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REVIEW

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Small molecule modulators of IL-17A/IL-17RA: a patent review (2013-2021)

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ABSTRACT

Introduction: Interleukin-17A (IL-17A) is a well-established pro-inflammatory cytokine, which plays a pivotal role in immune and autoimmune diseases including psoriasis, asthma, psoriatic arthritis, and rheumatoid arthritis. Three currently approved monoclonal antibodies (mAbs) are in clinical practice for the treatment of multiple immune diseases. However, the disadvantages of the mAbs, such as non-oral administration, poor tissue penetration, lacking blood-brain barrier penetration, often long half-life times, narrow its application. Thus, intensive research is performed to discover potent small molecules, peptides, and macrocycles targeting the IL-17A/IL-17 RA protein–protein interaction (PPI) to modulate immune responses as an attractive approach for immunotherapy.

Areas covered: Small molecules, macrocycles, and peptides targeting IL-17A/IL-17RA PPI from 2013 to 2021.

Expert opinion: The rapid increase in the identification of small-molecule inhibitors of IL-17 should translate into a supplement of current biotherapeutics with mAbs. Potential advantages of small molecules over mAbs show room for clinical treatment improvement and new indication areas . An increasing number of patents and articles are recently published on small-molecule immunomodulators (SMIMs). Two compounds from Lilly and Leo Pharma are currently investigated in early clinical trials, followed by a Dice molecule. The outcome of these trials will influence future development of IL-17 inhibitors for treatment of inflammation-related diseases.

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KEYWORDS
IL17A; inflammation; macrocycle; small molecule; antagonist; drug

1. Introduction

The family of interleukin-17 (IL-17) cytokines, comprising IL-17A through IL-17 F, promotes the maintenance of both adaptive and innate immunity. The released cytokines act through their membrane-bound IL-17 receptor (IL-17R), a family of five receptors (IL-17RA through IL-17RE), and activating the IL-17 signal pathway [1,2]. Dysregulation expression of IL-17 may contribute to inflammatory and autoimmune diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, and multiple sclerosis (Figure 1) [3]. As such, they are highly interesting new therapeutic targets for inflammatory diseases [4].

Interleukin-17A (IL-17A) is the best investigated IL17 family member. It is well established as a pro-inflammatory cytokine, which plays a pivotal role in immune and autoimmune related diseases including psoriasis [5], asthma [6], psoriatic arthritis [7], and rheumatoid arthritis [8]. IL-17A forms homodimers or heterodimers with IL-17A or IL-17F and is a major cytokine mainly secreted from Th17 cells. It signals through its membrane-bound receptors, IL-17RA and IL-17RC, and modulates IL-17A signaling pathway and triggers multiple inflammatory and immune responses. Thus, IL-17A has emerged as a major topic of interest for treating inflammatory-associated diseases.

Antagonizing IL-17A/IL-17RA protein–protein interaction (PPI) was hypothesized to reduce overexaggerated inflammation in autoimmune diseases. There are several ways to block IL-17A signaling by targeting IL-17A proteins or receptors. Clinically, three monoclonal antibodies (mAbs) are already approved for different immunological diseases, secukinumab and ixekizumab target IL-17A while brodalumab targets IL-17RA (Table 1) [9]. Numerous clinical trials of anti-IL-17A and IL-17RA antibodies are currently in progress. IL-17A/IL-17RA directed biotherapeutics have achieved impressive successes in durable clinical treatment

of psoriasis, asthma, psoriatic arthritis, and rheumatoid arthritis. However, IL17A has also major implications in central nervous system neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and glaucoma [10,11]. However, mAbs have limited applications due to non-oral administration, poor tissue penetration, lacking blood-brain barrier penetration, often long half-life times, high cost-of-good, and most importantly being applicable only to extracellular targets [12]. For these reasons, the development of small-molecule modulators targeting IL-17A/IL-17RA is an emerging area, which potentially could considerably widening current indication areas. Small molecules, generally have a good tissue penetration with potentially higher efficacy and a tunable half-life time, and are orally bioavailable facilitating patient treatment. Herein we summarized patents and literature of non-mAb IL-17A inhibitors from 2013 to 2021.

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Article highlights

- IL-17/IL-17RA is a hot target for human immune therapy.
- A number of small-molecule IL-17/IL-17RA inhibitors have been identified.
- High-resolution cocrystals have been disclosed.
- A consensus approach to overcoming the shortcomings of mAbs.
- With these IL-17/IL-17RA inhibitors in phase I clinical trials, the outcome of these trials will likely influence future drug development in the immunotherapy of disease treatment.

This box summarizes key points contained in the article.

2. Structural information

The co-crystal structure of interleukin 17A in complex with IL-17RA receptor has been determined for the first time by Pfizer scientists Liu and colleagues in 2013 [13]. The mechanism of IL-17 receptors recognition is detailed in the paper. This complex shows the large buried surface area of IL-17A – IL-17RA of ~2000 Å^2. The overall interface between the two proteins is large, flat, and featureless, without deep binding pockets, resulting in numerous additive but weak polar and hydrophobic interactions and making the interface likely a challenging target for small molecules. Subsequently, Alfonso and his colleagues at Eli Lilly showed that the β-hairpin pocket is the binding site for Ensemble macrocycles through a combination of computational methods and hydrogen/deuterium exchange mass spectrometry (HDX-MS) experiments [14]. Based on further understanding of these studies, Pfizer scientists Liu and his colleagues firstly disclosed the co-crystal structures of interleukin 17A in complex with a small molecule and macrocycles in 2016 [15]. Inspired by the previous findings that an anti-IL-17A Fab stabilized the complex of the cytokine with a high-affinity peptide antagonist (HAP) [16], and based on disclosed inhibitors [16–18] exemplified by compound **1**, the first co-crystal structure of compound **1** with IL17A was achieved and shows that the binding site is a U shape pocket. Subsequently, Pfizer researchers designed

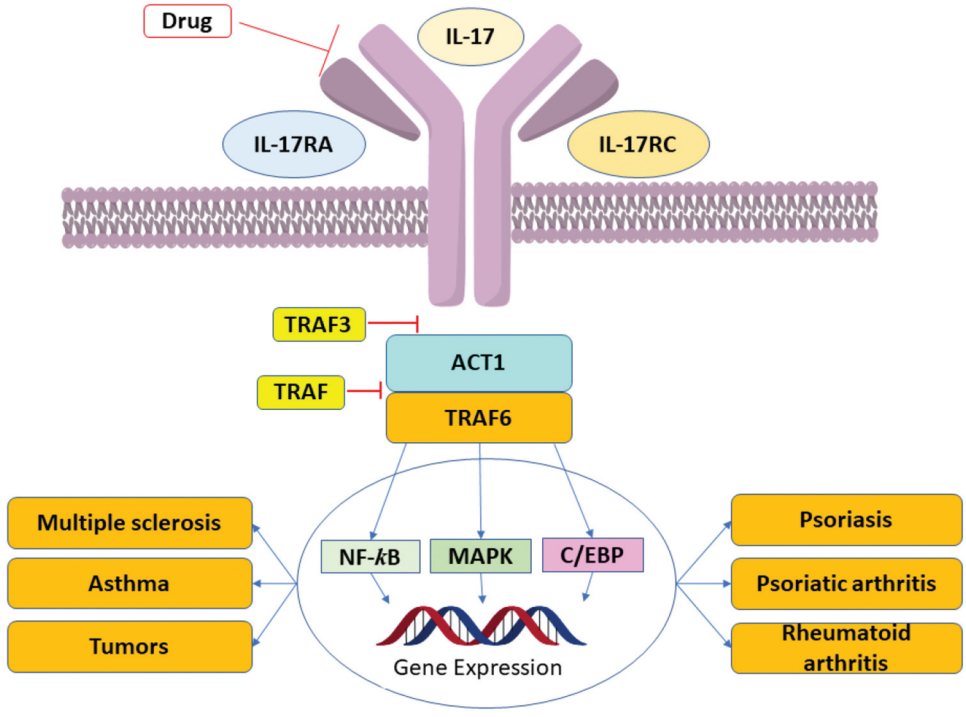


Figure 1. Effects of IL-17 under different disease conditions and IL-17 receptor mediated signaling.

Table 1. IL17 directed mAbs on the market and small molecules in clinical trials.

mAb[a]	Target	Indication	Development phase
Secukinumab (Novartis)	IL-17A	Plaque psoriasis Ankylosing spondylitis Rheumatoid arthritis	On the market
Ixekizumab (Lilly)	IL-17A	Plaque psoriasis	On the market
Brodalumab (Amgen)	IL-17RA	Plaque psoriasis	On the market
Small molecules[a]	Target	Indication	Development phase
S011806 (DICE Molecules)	IL-17A	psoriasis	Phase I
LY3509754 (Eli Lilly)	IL-17A	Psoriasis, Rheumatoid Arthritis, and Multiple Sclerosis	Phasel (suspended due to safety)
LEO 153339 (LEO Pharma)	IL-17A	psoriasis	Phase I

[a]Clinical trial information: https://clinicaltrials.gov/.

the potent macrocycles **2** and **3** and elucidated their high-resolution co-crystal structure with IL-17A as shown in Figure 2. For example, macrocycle **3** shows multiple interactions with its dimeric receptor, including hydrogen bonds (L97 and W67), hydrophobic interactions (main pocket: Y62, P63, W67, L97, and L112; subpocket: R114, E95, and L97) and stacking interactions (Y52 and L97) of the aromatic components of the macrocycle (Figure 2). Notably, the atoms of the spirocyclopentyl moiety are important activity elements in all active macrocycle series, which can be rationalized by the shape and electrostatic complementarity with the Lys114, Leu97 pocket. Simultaneously in surface plasmon resonance (SPR) and fluorescence resonance energy transfer (FRET) experiments, compound **2** and **3** not only showed desirable activities (SPR K_d < 200 nM; FRET IC_{50} < 35 nM) but also showed significant specificity for IL-17 F or IL-17RA, showing no measurable binding to IL-17 F or IL-17RA at concentrations up to 13.3 μM. Moreover, these compounds potently modulated IL-17A-stimulated production of the pro-inflammatory cytokine IL-8 (IC_{50} < 540 nM) in the psoriasis-relevant keratinocyte cellular assay. Furthermore, compound **3** did not inhibit the baseline IL-8 production of keratinocytes stimulated by TNF-α alone.

3. Patent review

3.1. Ensemble therapeutics corporation

Two patents to describe chemical matter inhibiting IL-17 has been disclosed by Ensemble Therapeutics Corporation in 2013 and 2015. Using DNA-encoded library (DEL) synthesis technology, a plentiful macrocycle library was developed for screening IL-17 inhibitors. Most macrocycles with general structure **1** (Figure 3) are claimed to have excellent binding to IL-17A [17,18]. These macrocycles mostly use –CH_2-(1,4-phenylene)– as a linker to connect the large cyclic amide ring and the aromatic motif. For example, compound **4** and its derivatives **5** and **6** were measured through enzyme-linked immunosorbent assay (ELISA), SPR assay, HT-

29 cell-based functional assay and a rheumatoid arthritis synovial fibroblast (RASF) cell assay. (Figure 3). Notably, macrocycle **4, 5**, and **6** were shown to bind to IL-17A with very good binding affinities K_d < 100 nM. Furthermore, the best compounds of these macrocycles have IC_{50} values of less than 1.0 μM in the HT-29 cell assay.

Workers from Ensemble Therapeutics Corporation also claimed linear peptides with general structure **2** (Figure 4) as modulator of IL-17/IL-17RA pathway in 2014 [19]. The inhibitory activity of exemplary compounds **7** and **8** was assessed by SPR and ELISA, and the K_d and the IC_{50} values of them were below 500 nM and below 100 nM, respectively. Interestingly, in the RASF cell assay, compound **8** showed significant improvement with EC_{50} < 1.0 μM.

3.2. UCB Biopharma Sprl

Based on the better understanding of intracellular signaling pathways and new hit finding technologies, especially the co-crystal structures of IL-17A and small molecules published by

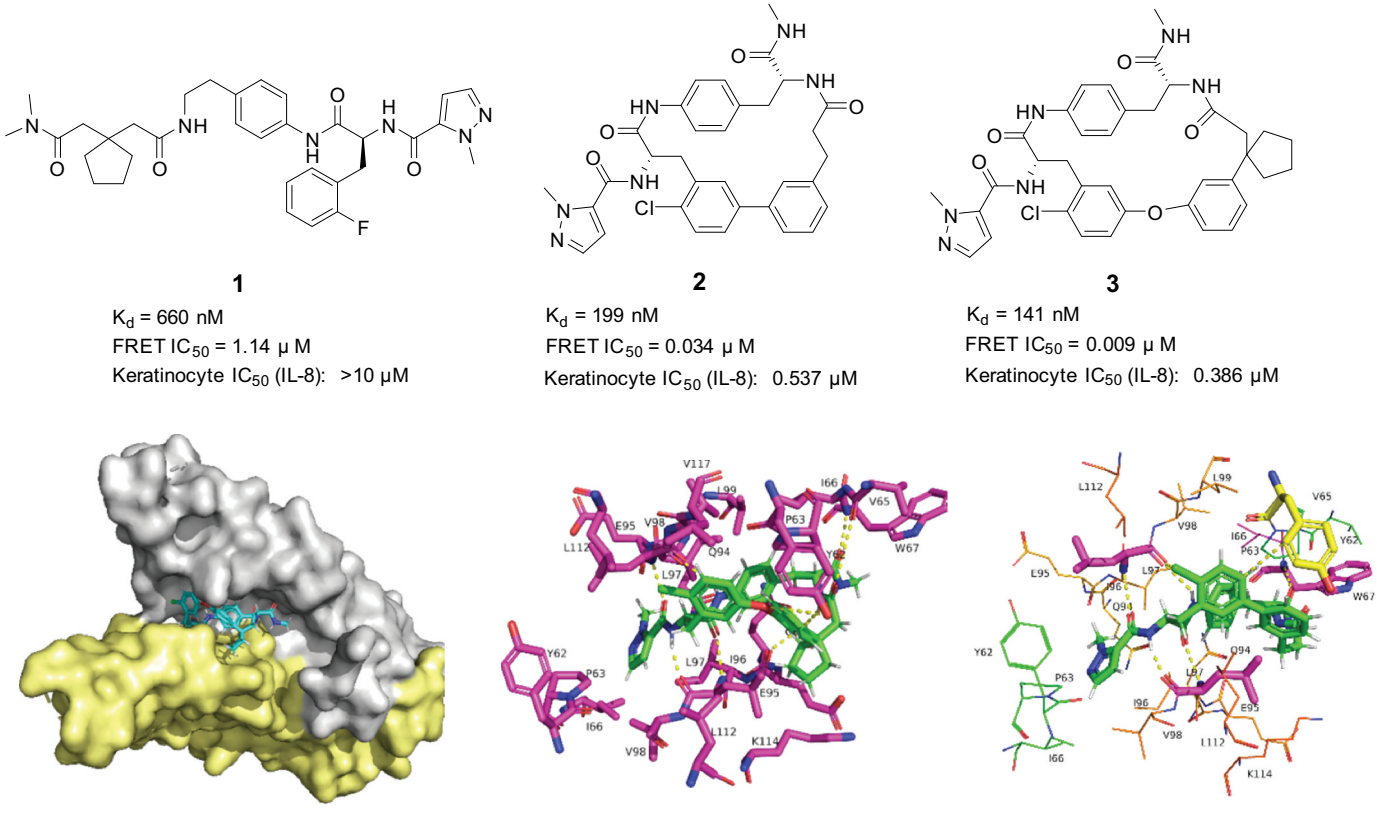


Figure 2. The examples of peptide and macrocycle and cocrystal structure of macrocycle **3** by Pfizer.

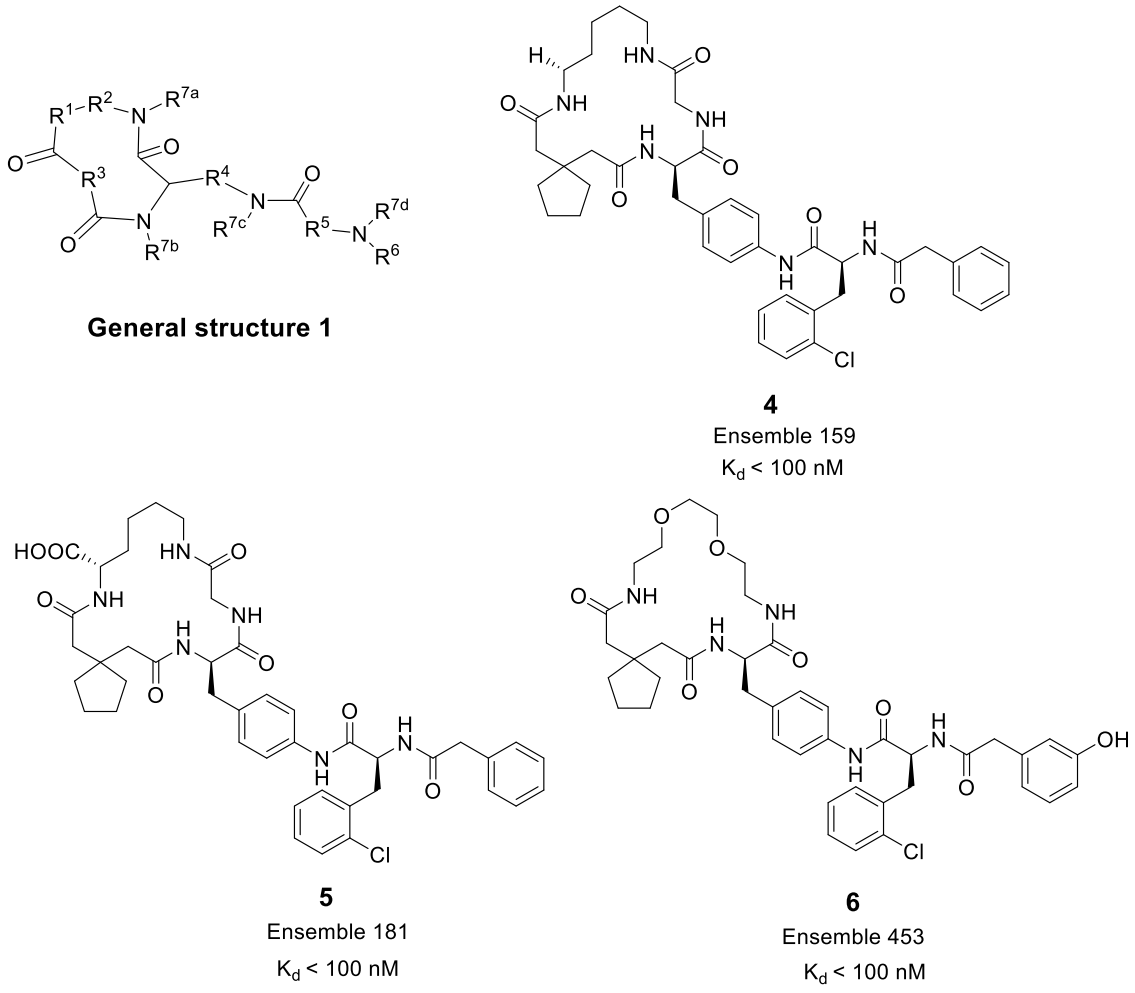


Figure 3. The general structure and examples of the macrocycles patented by Ensemble Therapeutics.

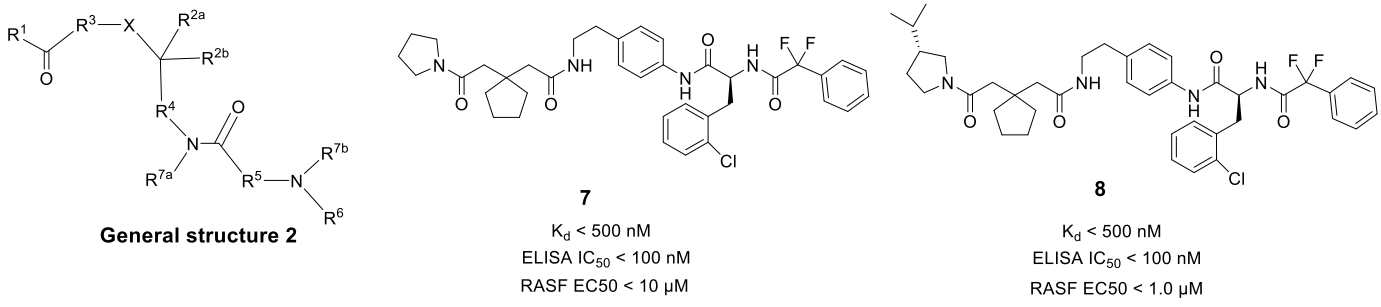
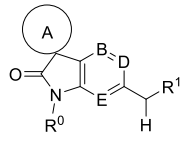


Figure 4. The general structure and examples of the linear peptide by Ensemble Therapeutics.

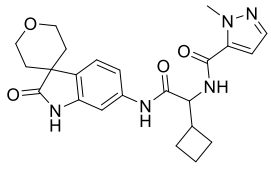
Pfizer scientists, the discovery of modulators of IL-17A is recently making major progress.

In the last 4 years, scientists at UCB Biopharma Sprl company have published 13 patent applications describing small-molecule IL-17A inhibitors. These compounds are claimed to be useful in modulating the human IL-17A activity and also be potentially used in combination with conventional biological therapies to treat and/or prevent various human ailments, such as inflammatory and autoimmune disorders.

The first patent, disclosed in 2018, describes a series of spirocyclic 2-oxoindoline derivatives with general structure **3** [20] that inhibit the IL-17/IL-17RA protein–protein interaction (PPI). Most spirocyclic oxoindolines were claimed, with a cycloalkyl ring **A** likely pointed toward the hydrophobic pocket, fused aromatic ring acting as the proposed binder and the 6-substituted amide group likely directed toward the inside pocket forming hydrogen bonds. Many of these compounds, tested by FRET assay and HDF (human dermal fibroblast) cell-line assay, show IC_{50} values in the range of 0.01 nM–10 μM (Figure 5). Subsequently, the second patent was reported by UCB Biopharma Sprl company chemists in 2019, including a series of substituted fused imidazole derivatives

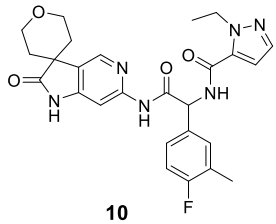


General structure 3



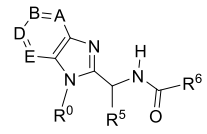
9

FRET 0.01 nM < IC_{50} < 10 μM

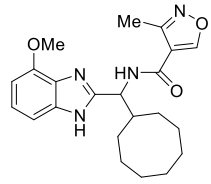


10

FRET 0.01 nM < IC_{50} < 10 μM

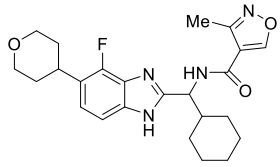


General structure 4



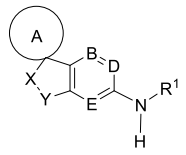
11

FRET 0.01 nM < IC_{50} < 10 μM

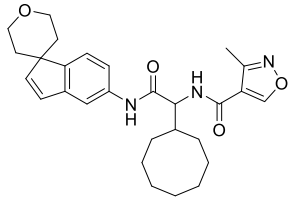


12

FRET 0.01 nM < IC_{50} < 10 μM

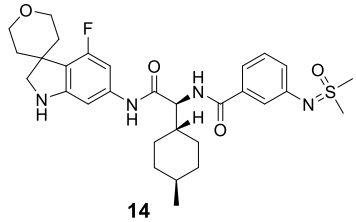


General structure 5



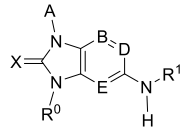
13

FRET 0.01 nM < IC_{50} < 10 μM

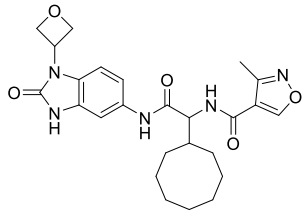


14

FRET 0.01 nM < IC_{50} < 10 μM

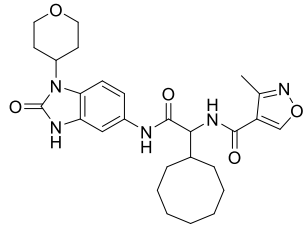


General structure 6



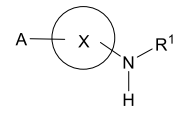
15

FRET 0.01 nM < IC_{50} < 10 μM

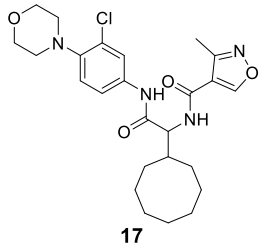


16

FRET 0.01 nM < IC_{50} < 10 μM

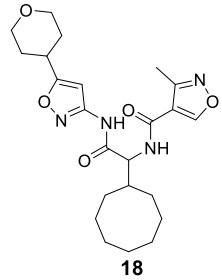


General structure 7



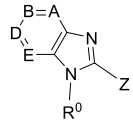
17

FRET 0.01 nM < IC_{50} < 10 μM

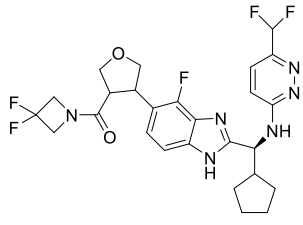


18

FRET 0.01 nM < IC_{50} < 10 μM

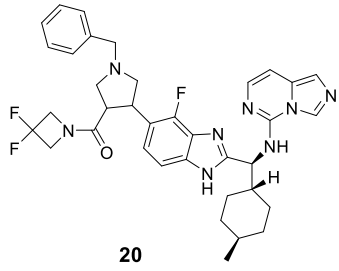


General structure 8



19

FRET 0.01 nM < IC_{50} < 10 μM



20

FRET 0.01 nM < IC_{50} < 10 μM

Figure 5. The general structure and examples of patented by UCB Biopharma Sprl.

with general structure **4** (Figure 5) [21]. An imidazole rings was used as an amide bond mimic, fused with the phenyl ring. Furthermore, the proposed substituents at R^5 for these compounds are likely conformation-preserving alkyl rings. The activities were measured by FRET and HDF, and exhibit IC_{50} values in the range of about 0.01 nM to about 10 μM, such as **11** and **12**.

Then, another six patents were disclosed in 2020 by UCB Biopharma Sprl researchers. Some of these compounds have very similar core scaffolds and also showed potent disruption between the IL-17A and soluble IL-17RA. General structures **5** [22] and **6** [23] are complementary to general structure **3**, as shown in Figure 5. The spirocyclic indolines were modified to obtain the general structure **5** of the spirocyclic indane analogs, and some representative examples such as compounds **13** and **14** showed desirable activities in the range of 0.01 nM to 10 μM as tested by FRET and HDF assays. Another general structure **6** of benzimidazol-2-one derivatives is formed by modifying general structure **3** by replacing the carbon in the fused 5-membered ring with nitrogen. This change not only expands the diversity of patents but also preserves the activity of compounds that bind to IL-17, such as example compounds **15** and **16**. The functionalized amine derivatives with general structure **7** [24], as shown in Figure 5, were designed as the promising antagonists. These amines with large alkyl rings inhibited the IL-17 and IL-17RA PPI with IC_{50} values between 0.01 nM and 10 μM (example **18** and **19**). A series of substituted fused bicyclic imidazole derivatives with general structure **8** [25] as shown in Figure 5, were modified from general structure **4**. Chemists payed more attention to the substitution of imidazole fused rings. For example, a substituted aliphatic ring was introduced as a substituent at the 5-position of benzimidazole. These compounds also modulated the IL-17/IL-17RA PPI with remarkable activities, for example compound **19** and **20** with IC_{50} values in the range of 0.1 nM–10 μM. Another series of fused bicyclic imidazole derivatives with general structure **9** (Figure 6) were also disclosed with another patent in 2020, including 4 H-imidazo[4,5-c]pyridin-4-one derivatives and analogues [26]. According to the FRET and HDF measurements, these novel inhibitors also were potent modulating the human IL-17A activity, for example compounds **21** and **22** gave IC_{50} values in the range of 0.1 nM–10 μM. The imidazopyridine derivatives with general structure **10** (Figure 6) were the last patent disclosed by UCB Biopharma Sprl chemists in 2020 [27]. This imidazopyridine scaffold is completely different from previously published fused imidazole cores. Importantly, it is not only expanding the molecular diversity but also keeps the activity competitive, for instance, the example compounds **23** and **24** with IC_{50} values from 0.1 nM to 10 μM.

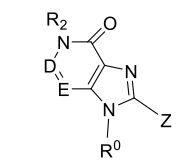
With more detailed study of IL-17A, another four patents were disclosed by the UCB Biopharma Sprl scientists in 2021. All compounds of these patents are difluorocyclohexyl derivatives with general structure **11** [28,29], **12** [30], **13** [31] as shown in Figure 6. These substituted difluorocyclohexyl compounds, derived from fused imidazole modulators, potently inhibit the ability of IL-17A to bind IL-17RA, as assessed by FRET and HDF assays. For example, these heterocyclic compounds with general structure **11** exhibit a pIC_{50} (pIC_{50} equals -log10[IC_{50}], in which IC_{50} is expressed as a molar concentration, higher pIC_{50} figure means more active compound) value of 5.0 or more, such as the pIC_{50} values of the example **25** and **26** are 8.83 and 8.30, respectively. Based on a difluorocyclohexyl core as a hinge-binding motif, compounds with general structure **12**, using the imidazole, triazole, tetrazole, and triazol[4,3-a]pyridine as functional groups, effectively inhibited the interaction of IL-17A and IL-17RA. For example, compounds **27** and **28** have IC_{50} values 1.0 nM and 2.0 nM, respectively. Interestingly, the best compounds with general structure **13** exhibit higher pIC_{50} than the compounds with the general structure **11**, such as compounds **29** and **30** have pIC_{50} values of 8.9 and 9.1, respectively.

3.3. Hitgen Inc

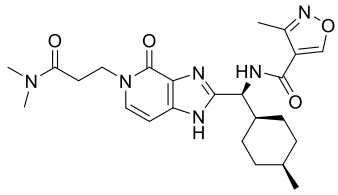
Over the last 3 years, the Chinese biotech company Hitgen Inc. has released many details of its research progress in discovering IL-17A modulators, especially in 2021, disclosing 10 patents. All of these reported inhibitors focus on the treatment of IL-17A mediated disease, including inflammation, autoimmune diseases, infectious diseases, cancer, and precancerous syndrome.

In these disclosed patents, most scaffolds appear to have a common imidazole core fused with a 5-substituted 6-membered ring. There are two types of core scaffolds in these published patents. All of these modulators were measured by ELISA assays and exhibited promising activity. Most modulators of the general structures **14** [32], **15** [33], **16** [34], **17** [35], **18** [36], **19** [37], **20** [38], **21** [39] and **22** [40] were claimed with the imidazole core fused to a 6-membered ring as shown in Figure 7 and Figure 8.

In 2019, Hitgen Inc chemists disclosed the imidazole derivatives with general structure **14** that inhibit IL-17A/IL-17RA PPI with exemplary promising IC_{50} values less than 250 nM. Subsequently, a class of ((methyl)pyrazolecarboxamido) methylbenzimidazoles with general structure **15** was disclosed by Hitgen Inc in 2021. These compounds (examples **33, 34**) are characterized with the IC_{50} values in the range of 1.0–100 μM as immunomodulators, which are useful for the inhibiting IL-17A. A series of (benzimidazolyl)(cyclobutylmethyl) acetamides with general structure **16** was reported by researchers from Hitgen Inc as shown in Figure 7. These compounds are more potent IL-17A/IL-17RA inhibitors (compounds **35, 36** IC_{50} < 100 nM) compared to their previously reported inhibitors. The general structure **17** for one series of these compounds was also disclosed by Hitgen Inc as immunomodulator and used for treating IL-17A-mediated diseases. Some representative examples with IC_{50} values of less than 100 nM are shown in Figure 7. Another class of ((methyl) pyrazolecarboxamido)methylbenzimidazoles with general structure **18** was disclosed by Hitgen Inc binding to IL-17A as promising inhibitors. Potentially to lock in the bound conformation, a cyclization strategy between the ring A and the R_3 was used among compounds of general structure **17** to form the derivatives of general structure **18** as shown in Figure 7. The best compounds with novel structure also have IC_{50} values below 100 nM for targeting IL-17A (example compounds **39** and **40**). Chemists at Hitgen Inc. reported a class of

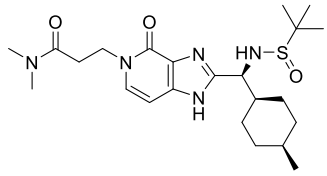


General structure 9



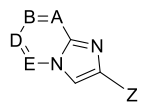
21

FRET 0.01 nM < IC_{50} < 10 μM

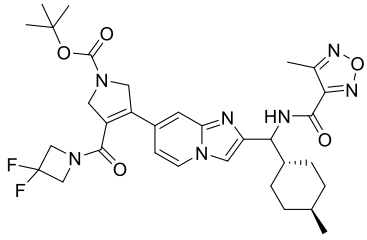


22

FRET 0.01 nM < IC_{50} < 10 μM

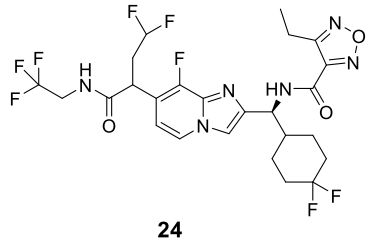


General structure 10



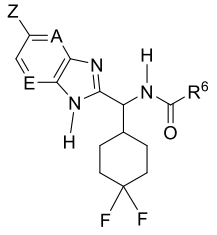
23

FRET 0.01 nM < IC_{50} < 10 μM

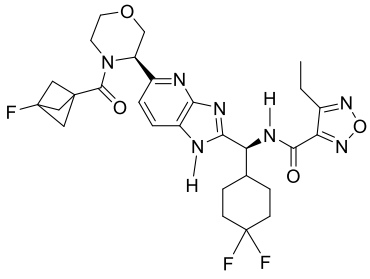


24

FRET 0.01 nM < IC_{50} < 10 μM

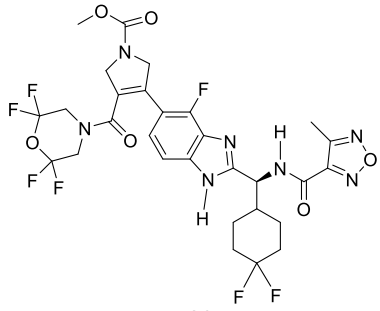


General structure 11



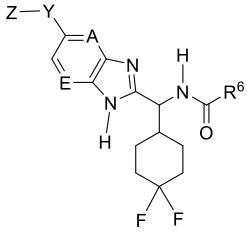
25

pIC_{50} = 8.83

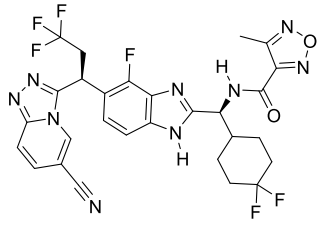


26

pIC_{50} = 8.30

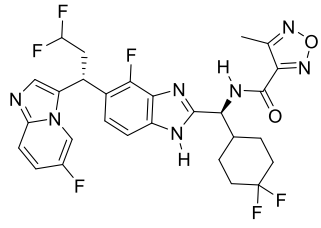


General structure 12



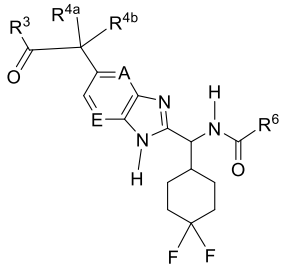
27

IC_{50} = 1.0 nM

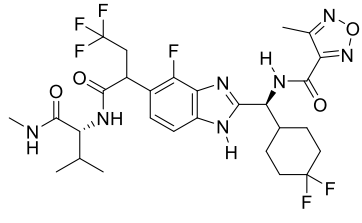


28

IC_{50} = 2.0 nM

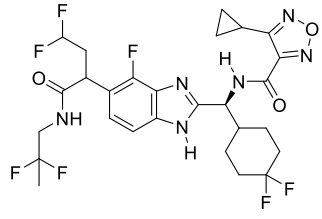


General structure 13



29

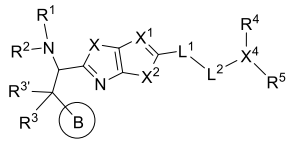
pIC_{50} = 8.9



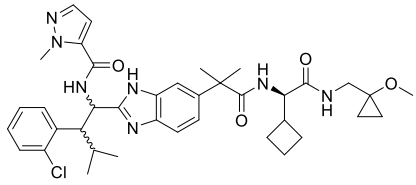
30

pIC_{50} = 9.1

Figure 6. The general structure and examples of patented by UCB Biopharma Sprl.

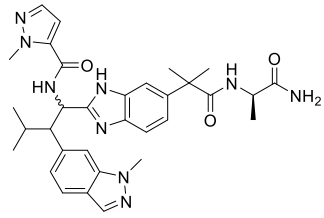


General structure 14



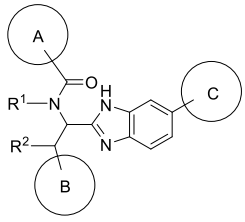
31

ELISA IC_{50} < 250 nM

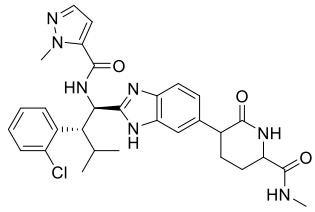


32

ELISA IC_{50} < 250 nM

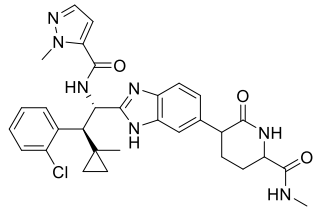


General structure 15



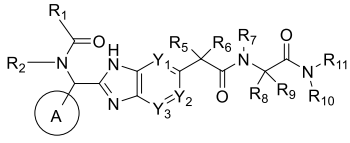
33

ELISA 1.0 μM < IC_{50} < 100 μM

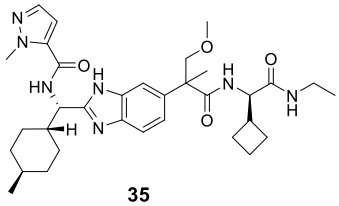


34

ELISA 1.0 μM < IC_{50} < 100 μM

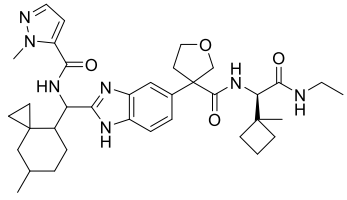


General structure 16



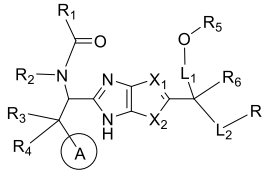
35

ELISA IC_{50} < 100 nM

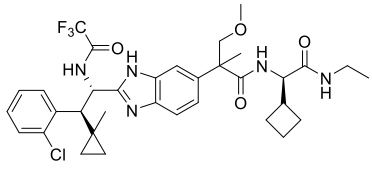


36

ELISA IC_{50} < 100 nM

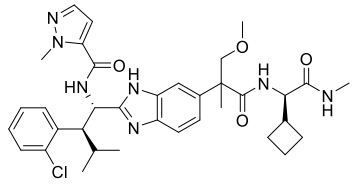


General structure 17



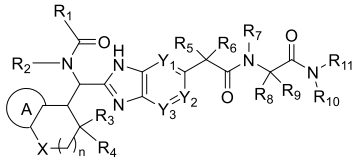
37

ELISA IC_{50} < 100 nM

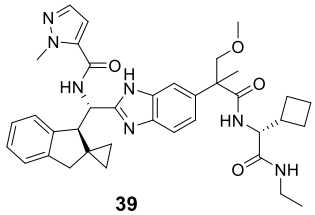


38

ELISA IC_{50} < 100 nM

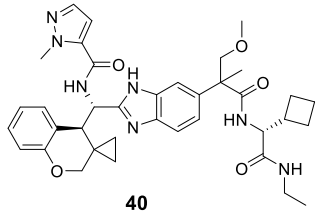


General structure 18



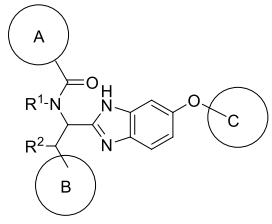
39

ELISA IC_{50} < 100 nM

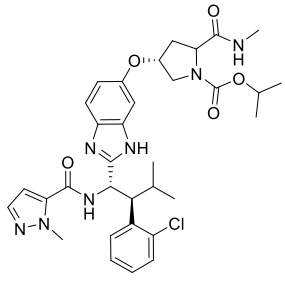


40

ELISA IC_{50} < 100 nM

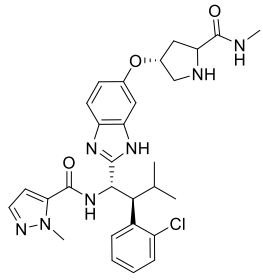


General structure 19



41

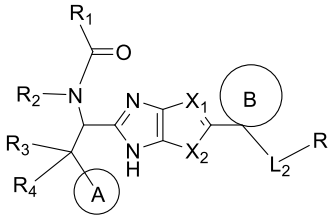
ELISA 100 nM < IC_{50} < 1.0 μM



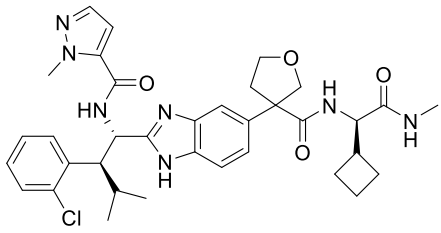
42

ELISA 100 nM < IC_{50} < 1.0 μM

Figure 7. The general structure and examples of patented by Hitgen Inc.

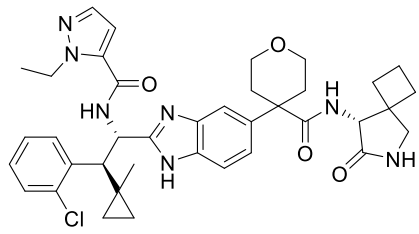


General structure 20



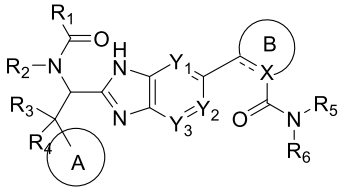
43

ELISA IC_{50} < 100 nM

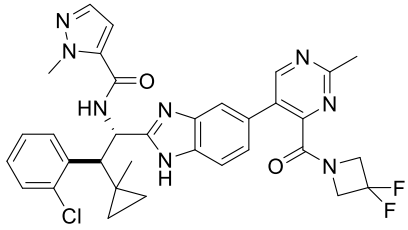


44

ELISA IC_{50} < 100 nM

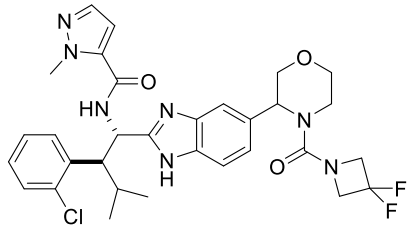


General structure 21



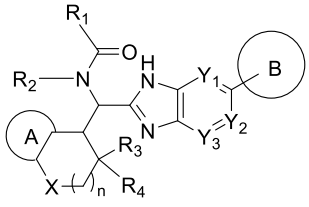
45

ELISA 100 nM < IC_{50} < 1.0 μM

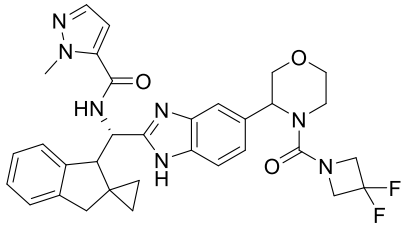


46

ELISA 100 nM < IC_{50} < 1.0 μM

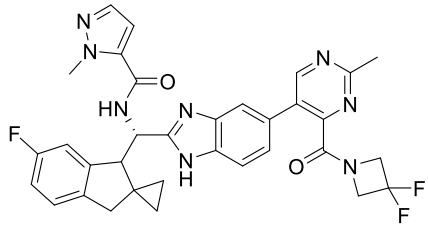


General structure 22



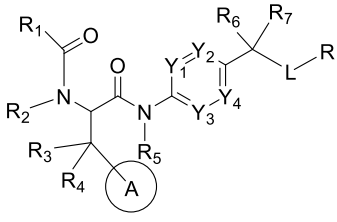
47

ELISA 100 nM < IC_{50} < 1.0 μM

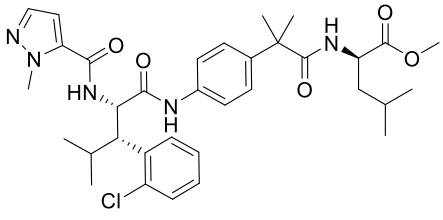


48

ELISA 100 nM < IC_{50} < 1.0 μM

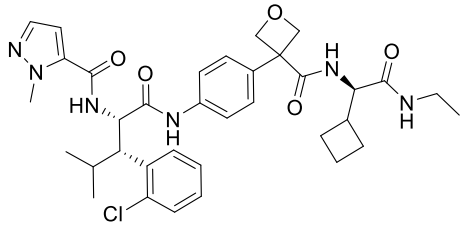


General structure 23



49

ELISA 1.0 μM < IC_{50} < 100 μM



50

ELISA 1.0 μM < IC_{50} < 100 μM

Figure 8. The general structure and examples of patented by Hitgen Inc.

(benzimidazole)oxypyrrolidines with general structure **19** in 2021 as the modulators for IL-17A related-disease. The claimed compounds **41** and **42** of general structures **19** showed activity (IC_{50}) in the range of 0.01–1.0 μM. In order to lock the sidechain conformation, a ring is introduced at the carbon between the phenyl ring and the amide to form the derivatives of general structures **20** as shown in Figure 8. Compounds with general structures **21** and **22**, directed used hetero ring to lock the conformation, are also potent inhibitors for IL-17A/IL-17RA PPI, exemplary promising compounds **45** and **47** exhibit IC_{50} values in the range of 0.01–1.0 μM.

Hitgen Inc disclosed their latest patent with the general structure **23** (Figure 8) in 2021 [41]. Guided by the ring-opening strategy, a para-substituted aromatic ring scaffold acts as a linker to replace the imidazole ring. However, these

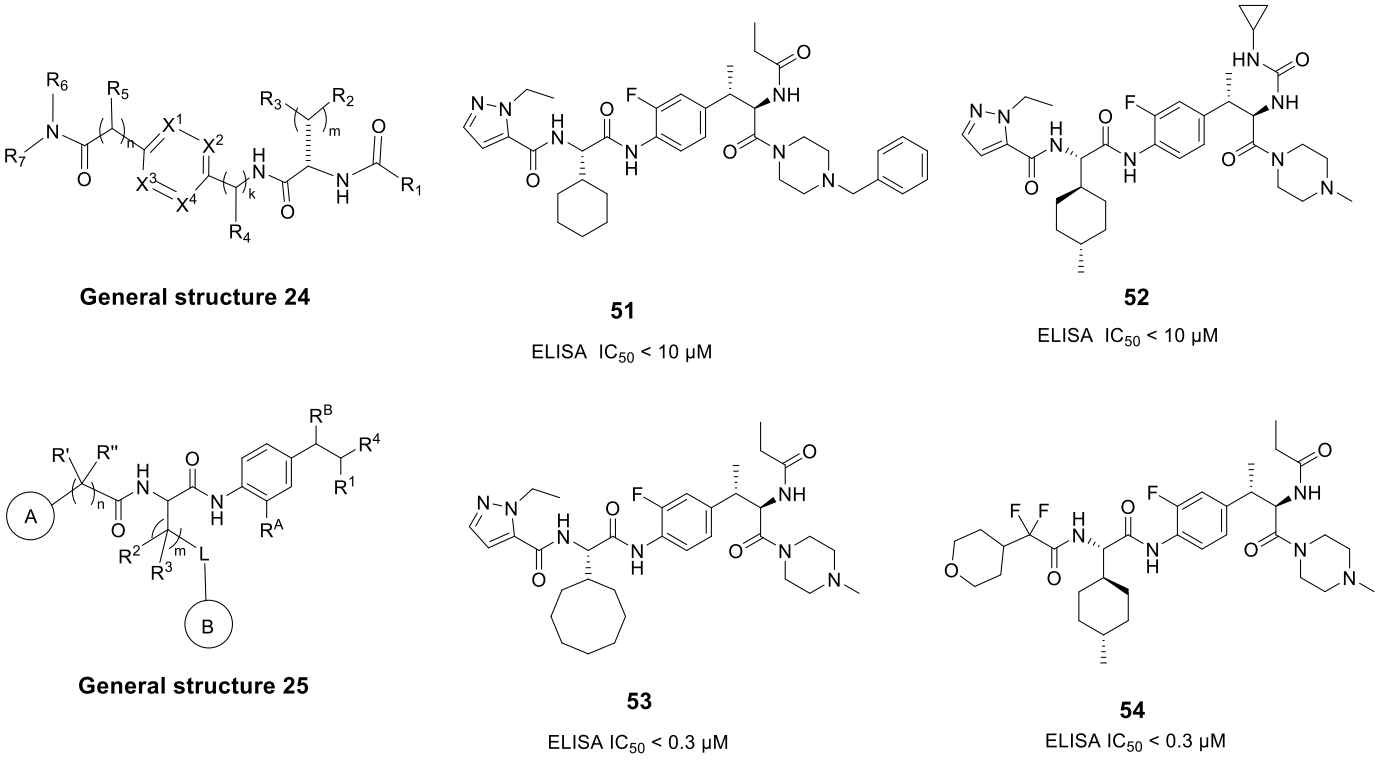


Figure 9. The general structure and examples of patented by Dice Alpha, Inc.

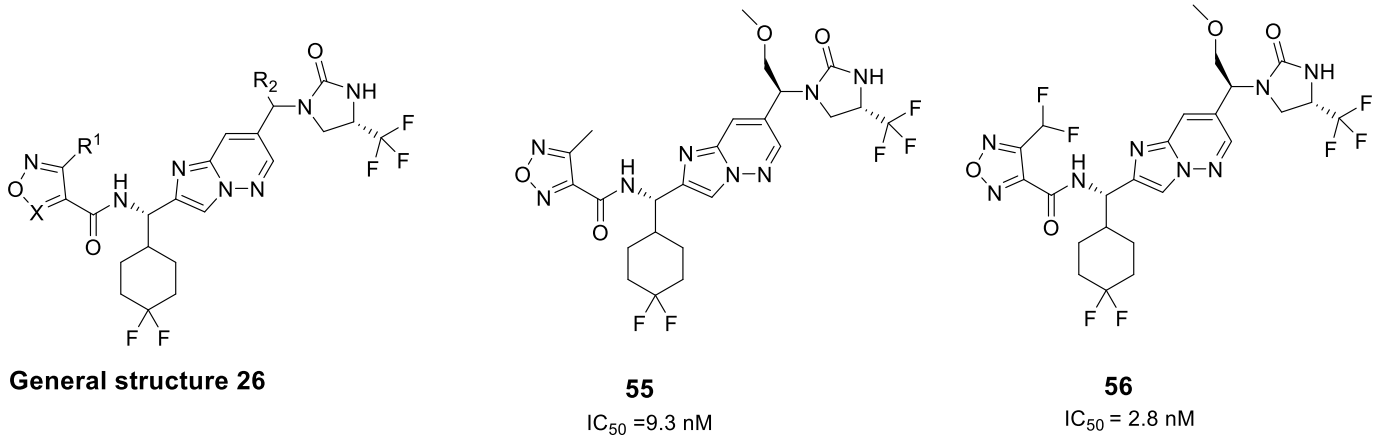
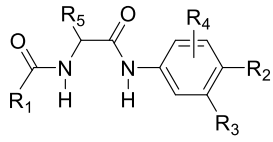


Figure 10. The general structure and examples of patented by Eli Lilly And Company.

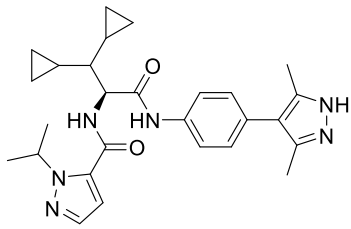
compounds have only moderate activity in binding to IL-17A. For example, compounds **49** and **50** have IC_{50} values in the range of 1.0 μM to 100 μM.

3.4. Dice Alpha, Inc

Dice Alpha, Inc. has disclosed two carboxamide derivative patents for targeting the IL-17A/IL-17RA PPI. The general structures **24** [42] and **25** [43] are shown in Figure 9, and the inhibition activity of these compounds was measured by IL-17A/A or IL-17A/F HEK-blue cell assay. The first patent, which disclosed in 2020, contains 419 compounds with the general structure **24** and many of these analogs are structurally related to general structure **23** derivatives. The promising compounds gave the IC_{50} values less than 10 μM, such as, compounds **50** and **51**. A second application claims compounds with the general structure **25** and exemplifies 810 IL-17A inhibitors in 2021. These compounds are complementary to the first application with more detailed research, and the best example compounds have IC_{50} values less than 0.3 μM. Based on their research, Dice Alpha, Inc has already started a Phase I clinical trial in 2022 (link).

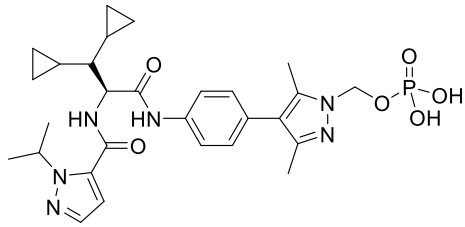


General structure 27



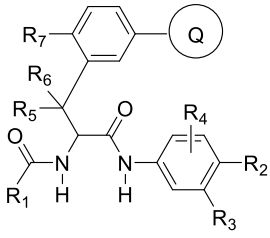
57

EC_{50} < 100 nM

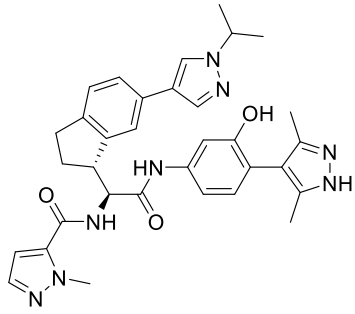


58

Prodrug

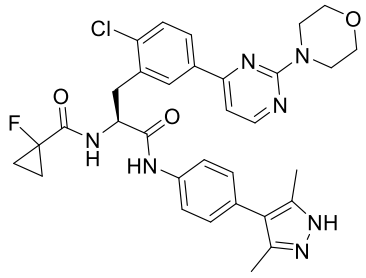


General structure 28



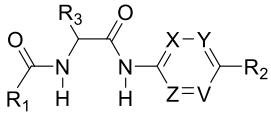
59

EC_{50} < 100 nM

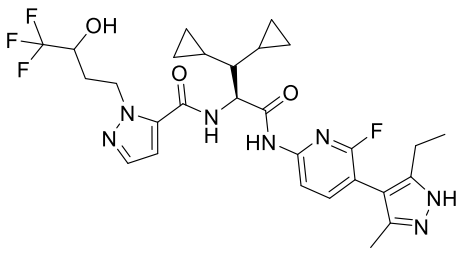


60

EC_{50} < 100 nM

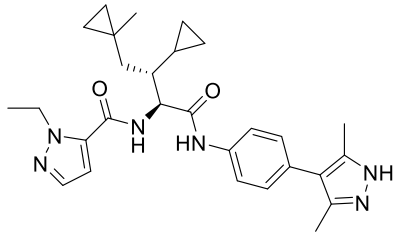


General structure 29



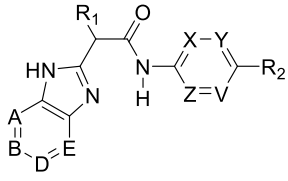
61

EC_{50} = 3.3 nM

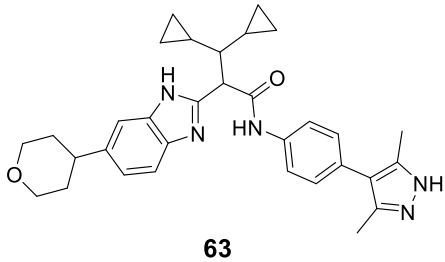


62

EC_{50} = 3.6 nM

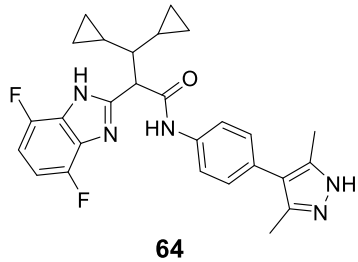


General structure 30



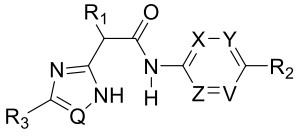
63

EC_{50} = 50 nM

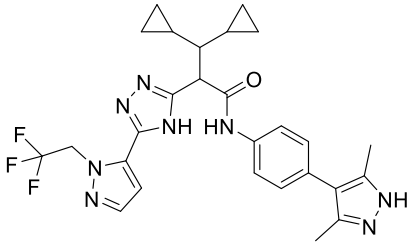


64

EC_{50} = 85 nM

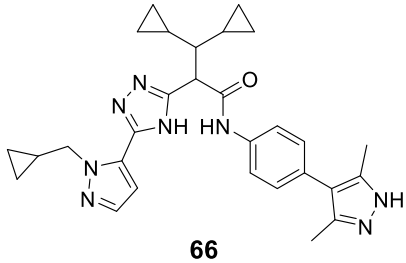


General structure 31



65

EC_{50} = 24 nM



66

EC_{50} = 22 nM

Figure 11. The general structure and examples of patented by Leo Pharma A/S.

3.5. Eli Lilly and Company

Researchers from Eli Lilly and Company described a series of potent imidazo[1,2-b]pyridazine derivatives with general structure **26** (Figure 10) in 2020 [44]. Compounds in this patent are claimed to treat certain symptoms of psoriasis, rheumatoid arthritis, or multiple sclerosis. These compounds utilize a difluorocyclohexyl-imidazopyridazinyl-imidazolidinone core and are very similar to compound **24** (Figure 6) reported by UCB Biopharma Sprl. This application only exemplifies 28 modulators and the inhibition activity of these compounds was measured by AlphaLISA assay as well as cell-based human IL-17A neutralization assay. The best compounds illustrate promising IC_{50} values in neutralizing human IL-17A-mediated signaling

in HT-29 cells, for example, compounds **55** and **56** are 9.3 nM and 2.8 nM, respectively. Importantly, Eli Lilly initiated a Phase I clinical trial (link) of compound **55** to study IL-17A-related diseases in 2021. But unfortunately, the clinical trial was suspended due to safety concerns.

3.6. Leo Pharma A/S

In 2020 and 2021, Leo Pharma A/S filed 5 patents for treating or ameliorating a variety of diseases, which involve up- or de-regulation of IL-17A, such as psoriasis, ankylosing spondylitis, and psoriatic arthritis. The disclosed general structures **27** [45], **28** [46], **29** [47], **30** [48], and **31** [49] are shown in Figure 11. The inhibition activity of these compounds was measured by IL-8 release assay in human epithelial keratinocytes adult, and some compounds had good EC_{50} values and good oral efficacy.

The amino-acid anilides and derivatives with general structures **27** [45] and **28** [46], which were published in 2020, are shown in Figure 11. Between these two disclosed patents, the general structure **28** uses bulky aromatic moiety at the position of the group R_5. Among these compounds, the most promising compounds have EC_{50} values in a range of less than 100 nM, such as **57, 58**, **59**, and **60**. Notably, the compound **57** showed a promising oral bioavailability in mouse and dog pharmacokinetic studies with 26% and 23% when dosed orally at 50 and 1 mg/kg, respectively. In addition, compound **58**, as a prodrug of compound **57**, showed a significantly higher pharmacokinetic profile than compound **57** in animal studies [45]. Subsequently, in order to expand the diversity of compounds, Leo Pharma A/S researchers disclosed a patent with general structure **29** in 2021, as shown in Figure 11 [47]. Substituting the benzene ring nucleus with a pyridine, pyrimidine, or pyridazine ring, these new compounds are not only structurally novel but also exhibit strong activities, such as compound **61** with an EC_{50} value of 3.3 nM. Finally, applying bioisosteric replacements, 1 H-imidazolyl, 1 H-1,2,4-triazolyl scaffolds with potentially better properties can replace the amide group. For example, the general structure **30** is claimed to use an aromatic 6-membered ring fused with imidazole to replace the amide bond (Figure 11) [48]. These compounds exhibit good activity, such as compounds **63** and **64** with EC_{50} values of 50 nM and 85 nM, respectively. In contrast, using 1 H-imidazolyl or 1 H-1,2,4-triazolyl scaffolds as linkers in the general structure **31** (Figure 11), the activity of the most promising compounds increased slightly, e.g. compounds **65** and **66** showed EC_{50} values of 24 nM and 22 nM, respectively. Compound **58**, as a prodrug, has entered a phase I clinical trial (link) for treatment of IL-17A-related diseases in 2021 [49].

4. Expert opinion

Currently, biotherapeutics of antibody therapy are leading the way in the treatment of IL-17-related diseases, three FDA approved monoclonal antibodies (mAbs) (secukinumab, ixekizumab, and brodalumab) have been made significant advances in the field of immunology therapy. However, these antibodies have a number of disadvantages as well, such as non-oral applications, poor tissue penetration, and long half-life times. In contrast, small-molecule modulators are highly suitable for oral administration as well as flexible treatment regimen to overcome drawbacks of mAbs for patient treating. Moreover, the small-molecule compounds may be safer due to the faster withdrawal rate of the drug should adverse events occur, and they also facilitate topical therapy. Hence, from a small-molecule perspective, IL-17A is of significant interest since it is pro-inflammatory cytokine playing a key role in pathogenic autoimmunity.

Although the co-crystal structure of IL-17A and IL-17RA were reported in 2013, targeting large featureless protein surfaces with small molecules remains a challenge for effective drug discovery. Fortunately, scientists at Pfizer reported co-crystal structures of small molecules in complex with IL-17A in 2016, and structure-based IL-17A/IL-17RA PPI drug discovery has burst out recently. Especially recently years, several companies have reported dozens of patents for small-molecule modulators for the treatment of IL-17A-related diseases. For example, UCB Biopharma Sprl company reported the spirocyclic and imidazole derivatives as the novel modulators of IL-17 in 13 patents. Hitgen Inc. company also disclosed a series of imidazole derivatives in 11 patents for the IL-17A treatment. Eli Lilly and LEO Pharma have initiated phase I clinical trials for treating IL-17A related disease, and DICE Molecules is also submitted an Investigational New Drug (IND) application.

Currently, patent protected small molecules antagonizing IL17a receptor interaction PPI are rather similar scaffolds, all build on a central bis amide motif or a bioisostere thereof. It can be speculated that all disclosed scaffolds have a similar binding mode to the interface of the IL-17a dimer involving four hydrogen bonds of the bisamide to the backbone of Leu97A and Leu97B. It remains to be seen if other fundamentally different classes of small molecules able to potently antagonize the IL17a receptor interaction PPI can be discovered.

Current discovery efforts should translate into an increase in the number of IL-17A inhibitors entering the clinic. This will lead to further insight into efficacy of IL-17A inhibitors as standalone and in combination with antibody therapies.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with

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Reviewer disclosures

One reviewer has consulted for Eli Lilly and Aclaris Therapeutics on some aspects of IL-17 signaling in the last 12 months. The remaining reviewers have no other relevant financial relationships or otherwise to disclose.

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