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IL-8小分子调节剂的研究进展、挑战与未来展望

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摘　要

白介素(Interleukin, IL)家族是一类在免疫系统中发挥关键作用的细胞因子家族，其中IL-8 (CXCL8)作为核心ELR+ CXC趋化因子，不仅参与调节中性粒细胞趋化与活化，还广泛参与炎症性疾病进展与肿瘤微环境塑造，现有靶向IL-8及其受体CXCR1/CXCR2的生物大分子药物已展现出一定的治疗潜力。尽管CXCR1与CXCR2具有高度序列同源性，且其与IL-8的蛋白相互作用界面复杂，开发选择性小分子调节剂面临较大挑战，但近年来基于变构机制的多种小分子抑制剂已取得重要突破。越来越多的成功案例表明，靶向趋化因子受体胞内变构位点的小分子策略是可行的。因此，CXCR1/2小分子调节剂的研发已引起广泛关注。在本篇文章中，我们系统讨论了IL-8/CXCR1/2信号轴的结构基础与生物学功能，并列举了代表性的选择性CXCR2抑制剂和CXCR1/2双受体抑制剂，总结其发现历程、结构优化策略及临床试验进展，同时还展望了下一代抑制剂的开发方向与临床应用潜力。

关键词

白介素8，G蛋白偶联受体1/2，小分子调节剂，变构抑制剂，免疫调节

Research Progress, Challenges, and Future Perspectives of Small-Molecule Modulators Targeting IL-8

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Abstract

The interleukin (IL) family comprises a group of cytokines that play pivotal roles in the immune system. Among them, IL-8 (CXCL8), a prototypical ELR$^+$ CXC chemokine, not only regulates neutrophil chemotaxis and activation but is also extensively involved in the progression of inflammatory diseases and the shaping of the tumor microenvironment. Existing biologics targeting IL-8 and its receptors CXCR1/CXCR2 have demonstrated certain therapeutic potential. Although the high sequence homology between CXCR1 and CXCR2, together with the complex protein-protein interaction interface with IL-8, poses significant challenges for the development of selective small-molecule modulators. Recent years have witnessed important breakthroughs in the discovery of various small-molecule inhibitors exploiting allosteric mechanisms. Accumulating successful cases indicate that small-molecule strategies targeting the intracellular allosteric sites of chemokine receptors are feasible. Consequently, the research and development of small-molecule modulators of CXCR1/2 have attracted considerable attention. In this review, we systematically discuss the structural basis and biological functions of the IL-8/CXCR1/2 signaling axis, highlight representative selective CXCR2 inhibitors and dual CXCR1/2 inhibitors, summarize their discovery history, structural optimization strategies, and clinical trial progress, and also provide perspectives on the future development directions and clinical application potential of next-generation inhibitors.

Keywords

Interleukin-8, G Protein-Coupled Receptor 1/2, Small-Molecule Modulators, Allosteric Inhibitors, Immune Regulation

1. IL-8 结构与生物功能

中性粒细胞作为固有免疫系统的核心效应细胞，其生物学功能的精细调控在炎症性疾病与肿瘤微环境塑造中具有双重意义[1] [2]。在骨髓中，粒细胞集落刺激因子(Granulocyte Colony Stimulating Factor, G-CSF)受体通过调控中性粒细胞的终末分化实现免疫稳态[3]，成熟的中性粒细胞经趋化因子定向迁移至炎症部位的过程即为趋化过程[4]。这一过程既是宿主防御的关键环节，也可能因过度活化导致组织损伤[5]。值得注意的是，中性粒细胞可通过释放中性粒细胞胞外陷阱(Neutrophil Extracellular Traps, NETs)及血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)，直接参与肿瘤转移与免疫逃逸[6]-[8]，这使其成为免疫调节治疗的重要靶标。

在趋化因子系统中，IL-8 (CXCL8)作为典型的 ELR$^+$ CXC 趋化因子(N 端含 Glu-Leu-Arg 特征基序)，通过激活 G 蛋白偶联受体 CXCR1/CXCR2 调控中性粒细胞迁移。该分子通过单体-二聚体动态平衡机制实现功能调控，两种构象在慢性阻塞性肺疾病、炎症性肠病等病理过程中均表现出生物活性[9] [10]。结构生物学研究表明，CXCL8 与 CXCR1/2 的细胞外区域结合后可激活 G 蛋白介导的信号转导通路，最终激活 MAPK/PI3K/PLC 信号级联通路，从而导致中性粒细胞向炎症部位趋化(图 1)。尽管 CXCR1 与 CXCR2 具有 76%的序列同源性，且对 CXCL8 的亲和力相当($K_d \approx 4$ nM) [11] [12]，但二者在配体选择性上存在显著差异：CXCR2 可广泛识别 CXCL1-3、5-7 等 ELR$^+$趋化因子，而 CXCR1 仅与这些配体微弱结合。这种

功能分化的结构基础可能源于第二个细胞外环区域的序列差异，即 C 端胞内域与 N 端胞外域[13] [14]，这也解释了为何多数变构抑制剂对 CXCR2 表现出更高选择性。基于此分子特征，开发 CXCR1/2 双重抑制剂或亚型选择性调节剂已成为干预病理性中性粒细胞浸润的重要策略。

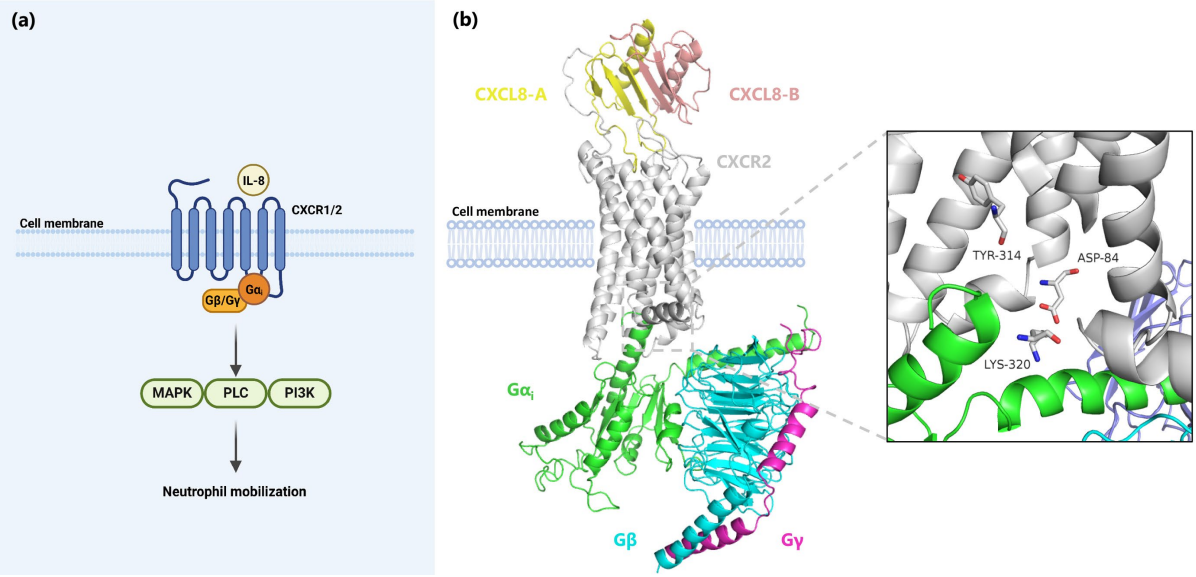

Figure 1. Signaling pathway and crystal structure of IL-8. (a) IL-8 signaling pathway. IL-8 binds to CXCR1/2, activating heterotrimeric G proteins, leading to the release of α and β subunits of Gα_i, thereby activating downstream MAPK, PLC, and PI3K signaling pathways to regulate neutrophil migration. (b) Crystal structure of the CXCL8 dimer/CXCR2/G Protein complex (PDB 6LFM) with CXCL8-A, CXCL8-B, CXCR2, Gα_i, Gβ and Gγ respectively shown in yellow, pink, grey, green, cyan and magenta, and critical residues of CXCR2 are represented by grey.

图 1. IL-8 的信号通路和晶体结构。(a) IL-8 信号通路：IL-8 与受体 CXCR1/2 结合触发异源三聚体 G 蛋白的激活，导致 Gα_i 释放 β 和 γ 亚基，从而激活下游 MAPK、PLC 和 PI3K 通路，调节中性粒细胞迁移；(b) CXCL8 dimer/CXCR2/G Protein 复合物晶体结构，其中 CXCL8-A, CXCL8-B, CXCR2, Gα_i, Gβ 和 Gγ 分别用黄色，粉色，灰色，绿色，青色和洋红色条带表示，关键氨基酸用灰色棒状结构表示(PDB:6LFM)

2. IL-8 小分子调节剂

2.1. CXCR2 选择性胞内变构抑制剂

1998 年，John 和同事通过高通量筛选发现二芳基脲类先导化合物 **1** (SK&F 83589，图 2(a)) [15]，经结构优化获得首个选择性 CXCR2 抑制剂 **2** (SB 225002，图 2(a))，能够以 IC_{50} = 22 nM 抑制 IL-8 与 CXCR2 结合且能够抑制 IL-8 介导的中性粒细胞趋化，显示出相较于 CXCR1 等其他七次跨膜蛋白(7-TMRs)的 150 倍选择性。基于此母核的磺胺类衍生物 **3** (SB-332235) [16] [17]、**4** (Danirixin) [18] [19]和 **5** (Elubrixin，图 2(a)) [20]通过引入磺胺基团显著改善代谢稳定性，其中 Elubrixin 在囊性纤维化 I 期临床试验中显示肺部中性粒细胞活化抑制效应(NCT00903201、NCT00551811) [21]，但溃疡性结肠炎 II 期研究因不明原因终止(NCT00748410)。Danirixin 开展了多项关于 COPD 和病毒性呼吸道感染的临床试验(NCT03250689、NCT02201303、NCT02453022、NCT03170232)，然而并没有显著减少 COPD 的标志物 neutrophil extracellular traps (NETs)的形成，因此 GSK 公司停止了 Danirixin 用于 COPD 的试验[22]。另外，SB-332235 虽没有进入临床，但也作为工具进行各种疾病机制的探索，其在神经炎症模型中展现出 NLRP3/NF-κB/Notch 通路多靶点抑制特性[23] [24]。这些研究数据提示，虽然磺酰胺类芳基脲小分子通过结构优化使体外活性和药代参数显著改善，但其对复杂病理网络中多靶点的协同调控能力仍显不足。

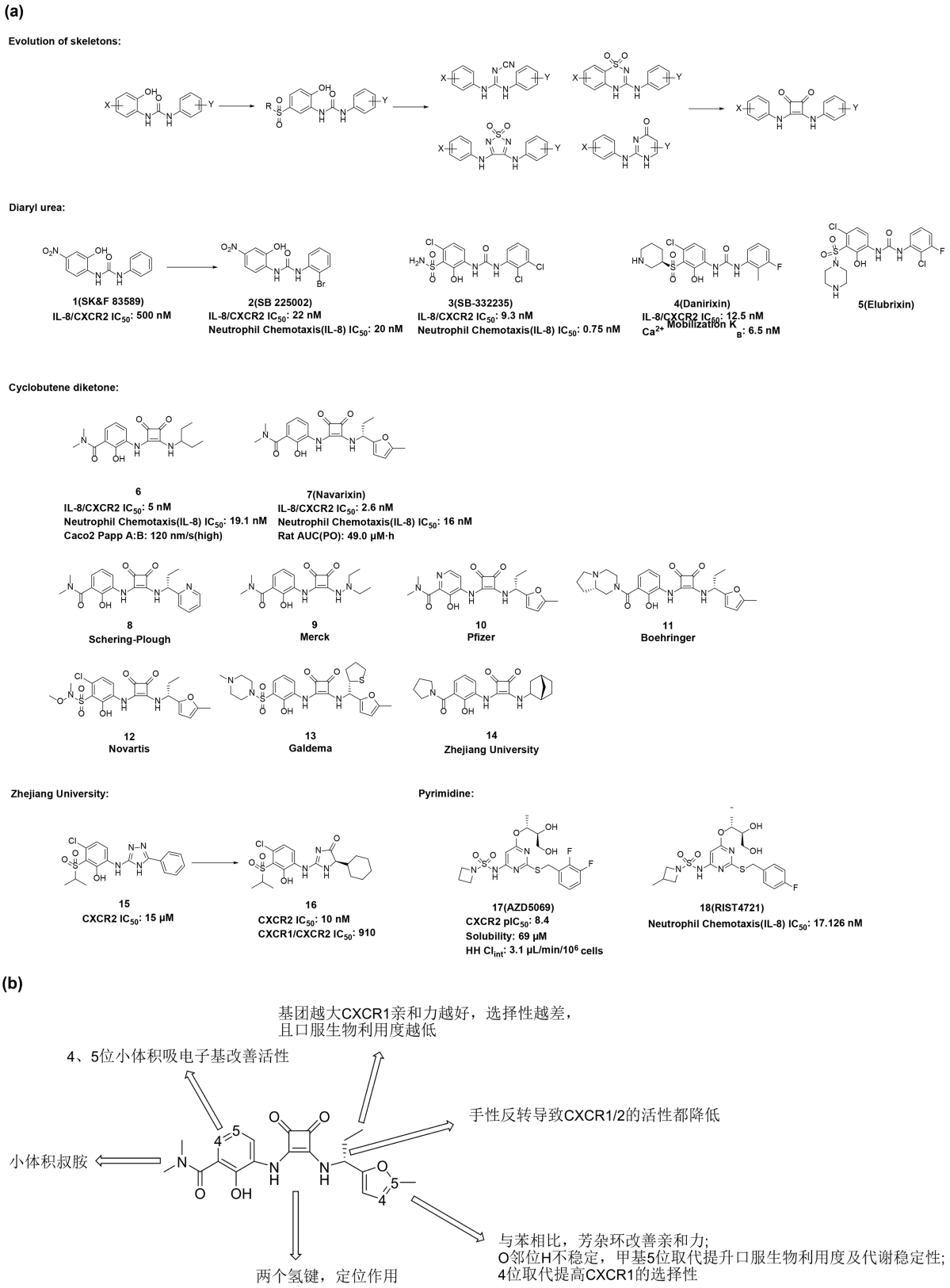

Figure 2. (a) Chemical structure of small molecules targeting CXCR2; (b) SAR of cyclobutenedione derivatives
图 2. (a) 靶向 CXCR2 的小分子结构；(b) 方酰胺类拮抗剂的 SAR

在二芳基脲骨架的优化过程中，研究者系统性地引入了二芳基胍、苯并噻二嗪、氨基嘧啶酮等生物电子等排体，通过维持关键氢键供体-受体特征的同时改善分子极性(图 2(a)) [25]-[31]。尽管脲基结构在药物化学中广泛应用，但其通常表现出溶解性低下和跨膜渗透性差，严重限制口服生物利用度[32]。为此，Merritt 和同事开发出环丁烯二酮类化合物作为创新性脲基等排体，其中化合物 **6** 表现出良好的活性及透膜性[33]。在化合物 **49** 的基础上，通过右侧脂肪链的立体化学修饰获得的小分子 **7** (Navarixin，图 2(a))，不仅维持强效抑制活性(IC_{50} = 2.6 nM)，其口服生物利用度在大鼠模型中也显著提升[34]。进一步研究发现，呋喃环 5 位甲基取代稳定代谢且 4 位烷基取代可提升 CXCR1 选择性[35]。其中，Navarixin 已完成治疗实体瘤、哮喘、银屑病的 II 期临床实验(NCT03473925、NCT00632502、NCT00688467、NCT00684593)，其荧光探针衍生物(Bianca 和同事，2023)通过引入荧光团(Fluorophore)，可实时表征配体与 CXCR2 变构口袋的结合，为 CXC 趋化因子受体细胞内变构拮抗剂的筛选和鉴定提供一种新的工具[36]。

基于此方酰胺骨架，Merck、Pfizer 等医药公司及研究机构公开了一系列衍生物(**8-14**, WO2010091543A1、WO2010131145A1 、 WO2010131146A1 、 WO2010131147A1 、 WO2012080456 、 WO2012080457 、WO2013030803A1、WO2013061002、WO2013061004、WO2013061005) [37] [38]，主要在左侧芳香区、右侧脂肪区及立体化学区进行改造(图 2(b))，这些系统性的结构修饰为开发新一代变构抑制剂提供了丰富的化学空间。

早期研究中，上述 CXCR2 小分子抑制剂的结合位点及作用模式尚不明确，研究者利用氨基酸的定点突变实验发现上述类型的小分子都结合在 CXCR2 的细胞内拮抗剂变构位点，与正构位点相距较远，其中 Lys320、Tyr341 和 Asp84 构成细胞内变构口袋的核心结合位点[39]-[43] (图 1(b))。且与竞争性机制相比，变构机制是直接抑制受体的功能，不依赖于与高浓度的竞争性底物进行竞争，阻断下游信号更加彻底[40] [44]。随后，Liu 等人揭示了环丁烯二酮类小分子与 CXCR2 细胞内变构口袋的结合模式：方酰胺骨架的两个氨基与 Asp84 形成氢键，起到定位作用，环丁烯二酮与 Lys320 和 Phe321 形成两个氢键，同时吡啶上的羟基和酮羰基提供额外两个氢键(图 3(a))，小分子通过此作用模式干扰了 CXCR2 与 $G\alpha_i$ 蛋白的结合，并限制了 CXCR2 的激活[13]。将上述代表性化合物与 CXCR2 进行虚拟对接：SB 225002 的脲母核与 Asp84 残基形成两个关键氢键，起到定位作用，其酚羟基与 Ser81 侧链建立第三个氢键，同时另一半部分的苯环与 Tyr314 具有 π-π 相互作用，共同稳定了抑制剂的变构结合构象(图 3(b))；基于此结合模式，Danirixin 通过引入磺酰胺基团与哌啶环额外提供两个氢键作用(图 3(c))。

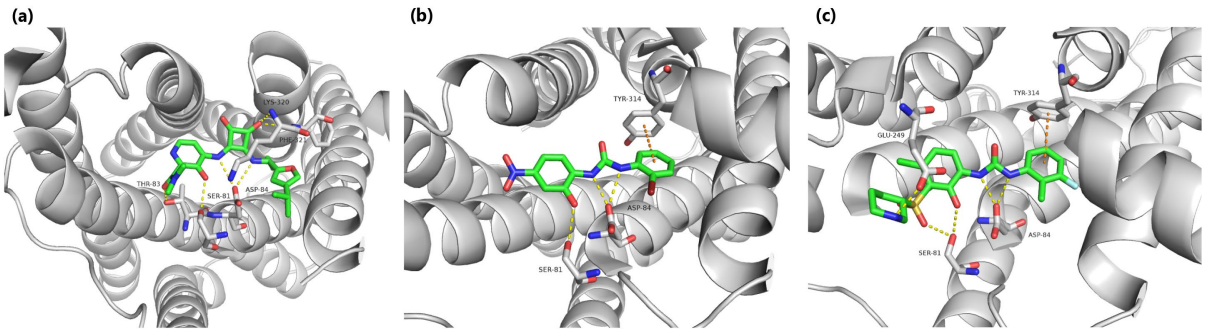

Figure 3. (a) Crystal structure of CXCR2 in complex with cyclobutenedione derivative (PDB 6LFL), small molecules and critical residues of CXCR2 are represented by green and grey tubes, respectively; (b) Virtual docking of SB225002 into CXCR2, π-π stacking is shown as orange dashed lines; (c) Virtual docking of Danirixin into CXCR2

图 3. (a) 方酰胺小分子与 CXCR2 的结合模式，小分子用绿色棒状表示，氢键相互作用用黄色虚线表示(PDB:6LFL)；(b) SB225002 与 CXCR2 的虚拟对接结合模式(PDB:6LFL)，π-π 相互作用用橙色虚线表示；(c) Danirixin 与 CXCR2 的虚拟对接结合模式(PDB:6LFL)

基于复合物晶体结构的精准解析，新一代小分子设计聚焦于核心骨架优化与变构口袋适配性改造。浙江大学团队通过理性设计策略，将先前研究的化合物 **15** 的三氮唑母核替换为对 CXCR2 更具选择性的咪唑酮母核，开发出 CXCR2 选择性抑制剂 **16** (CXCR1/CXCR2 IC_{50}: 910，图 2(a))。虚拟对接和分子动力学技术显示，**16** 通过苯酚羟基与 TM7 结构域 Lys320 形成氢键，而 CXCR1 上同一位置为 Asp，同时 **16** 限制了 CXCR2 激活过程中 TM3/6/7 的构象变化，而对 CXCR1 缺乏约束[29]，这解释了其高达 900 倍的选择性差异。

在临床转化方面，Andrew 和同事基于先前筛选的嘧啶并噻唑类化合物(WO2010007427) [45] [46]采用单环化策略设计出化合物 **17** (AZD5069，图 2(a))通过嘧啶并噻唑母核的单环化设计，显著提升水溶性并降低肝细胞清除率[47]。该化合物已完成 I 期临床试验(NCT01480739)和针对慢性阻塞性肺疾病(COPD，NCT01233232)、支气管扩张症(NCT01255592)、无法控制的持续性哮喘(NCT01704495)和胰腺导管腺癌(NCT02583477)的 II 期临床试验[48]，目前正在进行治疗晚期实体瘤和复发性转移性头颈部鳞状细胞癌的临床试验(NCT02499328)。其衍生物 **18** (RIST4721，图 2(a))进一步优化药代特性，且与前述的 SB-656933 和 SCH527123 相比，RIST4721 不会抑制除趋化以外的其他正常功能。该化合物已经完成 I 期临床试验且在治疗掌跖脓疱病(PPP)的 IIa 期临床试验中表现良好[49]。

2.2. CXCR1/2 双受体变构抑制剂

作为趋化因子受体药物开发的前沿领域，CXCR1/2 双受体变构拮抗剂因其独特的治疗优势备受关注，能够在肿瘤免疫微环境调控、器官缺血再灌注损伤等病理过程中发挥核心作用。非甾体抗炎药(Non-steroidal Anti-inflammatory Drugs NSAIDs)的传统作用机制依赖于抑制环氧合酶(Cyclooxygenase, COX)发挥其抗炎作用，但 2001 年发现酮洛芬外消旋体可通过 COX 非依赖途径阻断 IL-8 诱导的多形核白细胞(Polymorphonuclear Leukocyte, PMN)趋化[50]。值得注意的是，虽其 R-和 S-异构体都抑制 IL-8 趋化性，但 R-酮洛芬在抑制 COX 方面的效果比 S-异构体差 100 倍，提示了构型特异性作用可能开辟新的治疗路径。基于此，Marcello 和同事通过分子对接模拟发现 R-酮洛芬与 CXCR1 的跨膜结构域形成变构结合，进而开发出选择性抑制剂 **19** (Repertaxin，图 4)，其通过与 CXCR1 螺旋 TM1,2,3,6 和 7 内的跨膜变构腔结合，虽然 Repertaxin 在 CXCR1 和 CXCR2 的结合位点高度同源，但异丁基特异性容纳在由 CXCR1 TM1 和 TM3 的四个残基组成的疏水口袋中，这种独特的相互作用模式使其对 CXCR1 的选择性达到 CXCR2 的 100 倍。在缺血再灌注损伤(Reperfusion Injury, RI)模型中，Repertaxin 能预防 PMN 的募集以及大大降低中性粒细胞肝脏浸润[51] [52]，且已经完成预防肺、胰岛、肾、肝等脏器移植后移植功能障碍的 III 期临床实验(NCT00224406、NCT01220856、NCT00248040、NCT03031470)。

进一步结构优化获得 **20** (Ladarixin，图 4)，构建的分子模型表明除了 Repertaxin 与 TM2 的 Lys99、TM3 的 Asn120、TM7 的 Glu291 形成的氢键外，其新引入的三氟甲磺酸基团与 TM1 的 Tyr46 形成额外氢键，此结论也与氨基酸突变实验结果一致[53]。在小鼠肝缺血和 RI 模型中，Ladarixin 同样可以预防 PMN 募集及减少肝组织损伤，该化合物已经开启延缓 1 型糖尿病(Type 1 Diabete, T1D)的 II 临床实验(NCT04628481)。

在骨架创新方面，Celltech 和同事开发的烟酰胺类小分子 **21** (图 4)因酯前药特性导致在血浆内动力学层面面临挑战[54]，但后续研究者并没有放弃这一新型母核，通过将具有争议的酯部分替换为硼酸基团，特别的，引入硼酸基团后表现出对 CXCR1/2 双受体的有效抑制，这可能是发生了基于受体的硼介导的亲核加成反应。再引入三氟甲基降低硼酸易被氧化的风险从而提高代谢稳定性[55]，优化得到的 **22** (SX-682，图 4)已经完成与 Bintrafusp alfa (双靶点免疫检查点抑制剂)联合治疗晚期实体瘤的 I/II 期临床实验(NCT04574583)，**22** 可阻断 CXCR1/2 以减少肿瘤相关中性粒细胞浸润、解除免疫抑制，与免疫检查点抑

制剂联用能协同增强 T 细胞抗肿瘤效应，但存在潜在毒性，中性粒细胞过度抑制可能引发感染风险，可通过间歇给药、剂量梯度滴定管控，同时监测外周血中性粒细胞计数，保障联合用药安全。进一步的，其硫原子替换衍生物 **23** (SX-667，图 4)在大鼠嗜碱性白血病(Rat Basophilic Leukemia, RBL)细胞中展现出更强的 4 nM 级抑制活性，且能够抑制分离中性粒细胞中的钙通量[56]。值得注意的是，通过氨基酸定点突变实验证实这一类烟酰胺小分子也结合在细胞内的变构口袋，但与上述选择性 CXCR2 拮抗剂 SB225002 等不同的是，他们对 CXCR1/2 具有双重拮抗作用，这可能与结合的口袋不同有关。也有文献报道了另一类咪唑基嘧啶类[57]化合物与上述磺酸类选择性抑制剂不是竞争性结合 CXCR2 [42]，这表明细胞内存在不同的变构口袋，具体位置仍有待研究证实。

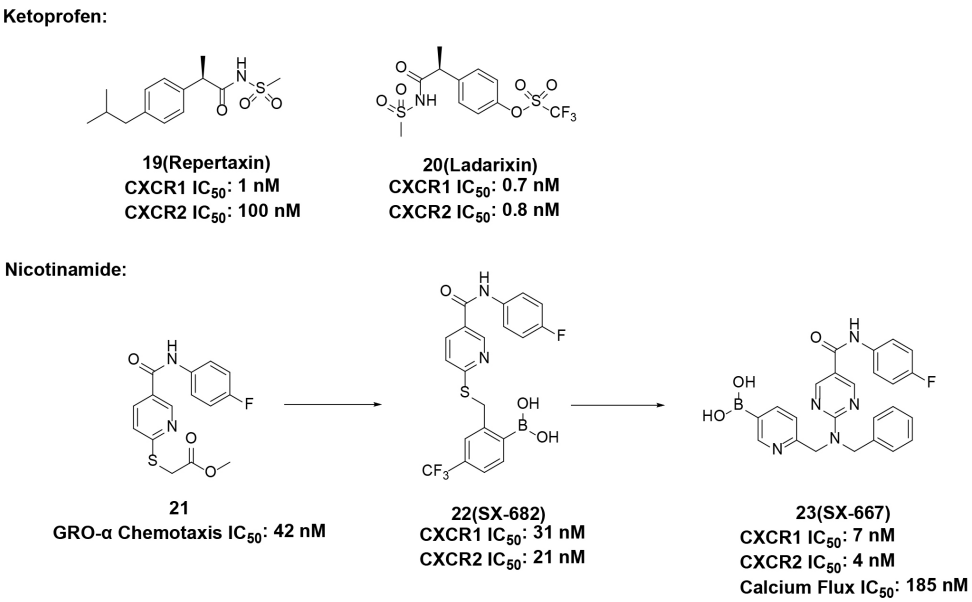

Figure 4. Chemical structure of small molecules targeting CXCR1/2
图 4. 靶向 CXCR1/2 的小分子结构

化合物 22 (SX-682)可阻断 CXCR1/2 以减少肿瘤相关中性粒细胞浸润、解除免疫抑制，与免疫检查点抑制剂联用能协同增强 T 细胞抗肿瘤效应。但存在潜在毒性，中性粒细胞过度抑制可能引发感染风险，可通过间歇给药、剂量梯度滴定管控，同时监测外周血中性粒细胞计数，保障联合用药安全。

CXCR1 与 CXCR2 的氨基酸序列具有高达 78%的相似性，主要差异集中在 N 端、C 端、第二个细胞外环和第四个跨膜结构域。虽然他们在结构上高度相似，但在各种生理和病理过程中起着不同的作用[58] [69]。CXCR2 在中性粒细胞中高表达，促进中性粒细胞的迁移和激活驱动炎症反应[60] [61]，同时可以上调 VEGF 和 MMP-9 促进肿瘤血管生成[8]；而 CXCR1 在急性细菌感染如肺炎中起关键作用，同时可以促进肿瘤相关中性粒细胞(TANs)的浸润，抑制抗肿瘤免疫[62] [63]。基于上述功能分化的治疗需求，开发高选择性抑制剂可以精确定位治疗需求，特别是在特定的炎症性疾病和癌症的治疗中，可以实现更高的治疗效果和更低的副作用风险。提高选择性的策略主要是精准靶向受体特异性结构域：借鉴其他 GPCR 小分子抑制剂的母核结构以提高结合能力，如 CCR7 的噻二唑二氧化物抑制剂等[64]，同时寻找新的提供选择性的关键氨基酸；开发正构位点，CXCR1 和 CXCR2 在 N 端的结构有细微差异，且其他具有类似结构的 GPCR 如 CXCR4、CCR7 等存在细胞外正构位点[65] [66]，故可以在此区域寻找是否有成药性的正构口袋。

3. 总结与展望

白介素作为细胞因子超家族的核心成员，在免疫调控、炎症反应及细胞间通讯中发挥着枢纽作用，其中 IL-8 通过激活 G 蛋白偶联受体 CXCR1/2，在中性粒细胞的定向迁移、炎症反应及肿瘤微环境塑造中发挥关键作用。当前，靶向 IL-8/CXCR1/2 信号轴的小分子调节剂研究已取得显著进展，变构抑制策略因其不依赖竞争内源性配体、信号阻断更彻底等优势，成为主流方向。然而，该领域仍面临若干关键挑战：一是 CXCR1 与 CXCR2 的高度同源性使得亚型选择性抑制剂的设计仍具难度，如何进一步提升抑制剂的亚型选择性、降低脱靶效应，仍是药物设计的核心难点；二是部分化合物(如 Danirixin、Elubrixin)在临床试验中因疗效不足或不明原因终止，提示体外活性与体内复杂病理环境之间存在差距；三是现有抑制剂主要集中于已知的胞内变构口袋且不同变构位点的功能差异仍需深入探索，同时新的结合位点(如正构位点或其他变构区域)仍有待挖掘。

未来，IL-8 小分子调节剂的研究可聚焦于以下方向：一是依托结构生物学与分子动力学技术，精准解析 CXCR1/CXCR2 的胞内变构口袋结构，为高选择性抑制剂的理性设计提供理论支撑，尤其可针对 CXCR1/CXCR2 的 N 端、第二个细胞外环等差异区域，探索成药性正构口袋的开发潜力；二是探索 CXCR1/2 在不同疾病背景下(如肿瘤免疫、自身免疫病、感染)的功能分化，开发更具适应症针对性的调节剂；三是持续优化药物分子结构，通过引入新型生物电子等排体、立体化学修饰等策略，改善药代动力学特性，解决水溶性、代谢稳定性等临床转化瓶颈；四是发展双功能分子以降解而非仅抑制受体，重点开发 CXCR1/2 靶向 PROTAC、分子胶与可逆共价抑制剂，利用胞内变构口袋实现高效降解或长效抑制，同时可结合 LYTAC/TransTAC 策略降解胞外 IL-8 与膜受体，突破传统 PROTAC 仅靶向胞内蛋白的局限，同时提升亚型选择性与肿瘤微环境特异性，实现更持久的调控效果；五是拓展药物的临床应用场景，深入探索小分子调节剂与免疫检查点抑制剂、化疗药物等的联合治疗方案，尤其在肿瘤免疫治疗、慢性炎症性疾病等领域，挖掘其协同调控潜力。总之，IL-8 小分子调节剂的持续优化与创新，将为炎症性疾病和肿瘤免疫治疗提供新的有效工具。

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