

· 综述 ·

髓过氧化物酶抑制剂的研究进展

王玉婷, 秦亚娟, 厉廷有*

南京医科大学药学院, 江苏 南京 211166

[摘要] 髓过氧化物酶(myeloperoxidase, MPO)是血红素过氧化物酶-环氧化酶超家族的重要成员。MPO在多种炎症细胞,包括中性粒细胞、活化的小胶质细胞和单核/巨噬细胞等,以及星形胶质细胞和神经元中表达,在免疫监视和宿主防御机制中起着重要作用。然而,研究发现MPO的表达和活性的增加与包括帕金森病、阿尔茨海默病、脑卒中、心血管疾病等多种重大疾病的发生和进展相关。多年来,多家医药公司和科研单位在MPO抑制剂的研发中取得大量进展,文章综述了MPO蛋白的结构、催化机制、抑制剂的研发进展等,旨在为MPO抑制剂的研发提供参考。

[关键词] 髓过氧化物酶;蛋白结构;催化机制;可逆抑制剂;不可逆抑制剂

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Research progress on the development of myeloperoxidase inhibitors

WANG Yuting, QIN Yajuan, LI Tingyou*

School of Pharmacy, Nanjing Medical University, Nanjing 211166, China

[Abstract] Myeloperoxidase (MPO) is an important member of the haemoglobin peroxidase - cyclooxygenase superfamily. It is expressed in a variety of inflammatory cells, including neutrophils, activated microglia, monocytes/macrophages, as well as astrocytes and neurons, and plays an important role in immune surveillance and host defense mechanisms. However, studies have found that the increased expression and activity of MPO is associated with the development and progression of several major diseases, including Parkinson's disease, Alzheimer's disease, stroke, and cardiovascular disease. Over the years, several pharmaceutical companies and research institutes have made a lot of progress in the development of MPO inhibitors. This review mainly summarizes the structure of MPO protein, its catalytic mechanism and the progress of inhibitor development, aiming to provide a reference for the development of this enzyme inhibitors.

[Key words] myeloperoxidase; protein structure; catalytic mechanism; reversible inhibitor; irreversible inhibitor

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髓过氧化物酶(myeloperoxidase, MPO)是血红素过氧化物酶-环氧化酶超家族的重要成员。MPO在多种炎症细胞中表达,包括中性粒细胞、活化的小胶质细胞、单核/巨噬细胞、星形胶质细胞和神经元,在免疫监视和宿主防御机制中起着重要作用^[1]。多项研究表明,MPO在促进动脉粥样硬化和心血管疾病^[2]、肾小球肾炎、类风湿性关节炎^[3]、皮肤炎症和损伤^[4]、神经退行性疾病(如阿尔茨海默

病)^[5]、代谢综合征(如糖尿病)^[6]等疾病中起重要作用。本文综述了MPO的蛋白结构、催化机制、抑制剂的分类及其在临床试验中的应用。

1 MPO的蛋白结构

编码人类MPO的基因位于17号染色体的长臂上(片段q23.1),由11个内含子和12个外显子组成,大小约为11 kb^[7]。MPO基因的mRNA在成熟阶段的骨髓母细胞和前骨髓细胞表达,在完全分化的骨髓细胞中停止表达^[8]。成熟的MPO单体是一种功能性二聚体,由2个相同的糖基化单体 proMPO组

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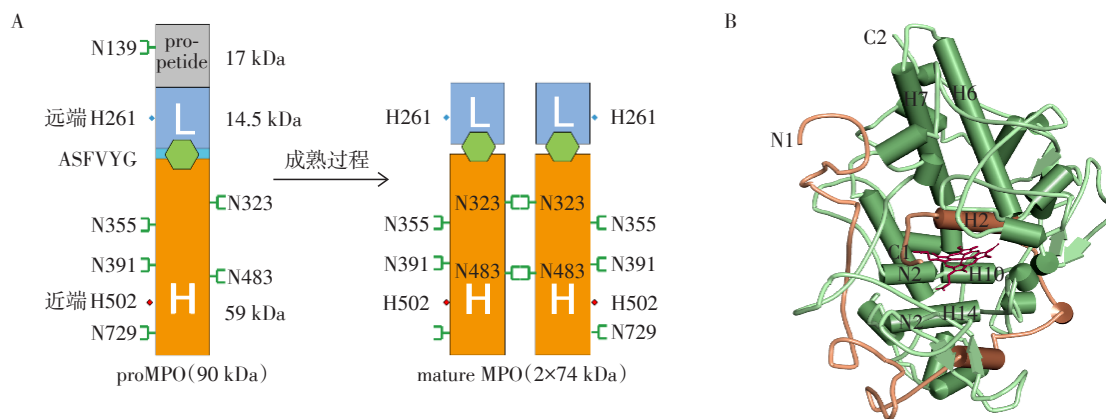
*通信作者(Corresponding author), E-mail: l_tingyou@njmu.edu.cn

成, 包含共价结合的血红素, 其中 proMPO 含有 1 个 14.5 kDa 轻肽(L 链)和 1 个 59 kDa 重肽(H 链), 2 个 H 链通过单个 Cys-319-Cys-319 键桥共价连接组成成熟的 MPO 二聚体(图 1A), proMPO 表现出与成熟 MPO 单体相同的特异性过氧化物酶活性^[9]。

每个 proMPO 单体都有 1 个含血红素的中心, 由 6 个 α 螺旋(H2、H6、H7、H9、H10 和 H14) 组成, 其中 5 个 α 螺旋来自重链, 1 个来自轻链, 棕色表示轻链, 绿色表示重链(图 1B)。重链的大部分折叠形成 5 个独立的结构域和 1 个围绕上述中心的开环。轻链包裹在分子表面, 位于其碳端的 α 螺旋(H2) 穿透 proMPO 的内部核心。其中 2 个较长的 α 螺旋(H6 和 H7) 由位于分子表面的短链连接, 形成具有大的疏水相互作用的中央核心。血红素口袋的远端表面由轻链的 H2 形成, 而近端表面由重链的螺旋 H9 和 H10 形成^[10]。

2 MPO 的催化机制

MPO 是血红素过氧化物酶-环氧化酶超家族的重要成员, 可以利用 H_2O_2 将卤离子(Cl^- 、 Br^- 、 I^-) 或假卤化离子(SCN^-) 分别催化产生次氯酸(hypochlorous acid, HClO)、次溴酸(hypobromous acid, HBrO)、次碘酸(hypoiodous acid, HIO) 或次硫氰酸(hypothiocyanous acid, HSCNO)。该酶能够催化两种类型的氧化还原反应, 卤化循环和过氧化物酶循环^[11]。卤化循环和过氧化物酶循环的第一步是相同的^[12]。在此步骤中, H_2O_2 与 native MPO($proFe^{3+}$) 反应, 形成 Compound I ($porFe^{3+}=O$)。Compound I 通过氧化卤离子生成 HClO(图 2)^[13]。Cl⁻ 作为血液中含量最丰富的卤化物, HClO 被确定为 MPO 与 H_2O_2 反应的主要产物。Compound I 还可以氧化多个有机和无机分子, 得到相应自由基以及酶的非活性形式 Com-



A: proMPO 和成熟 MPO 结构; B: MPO 单体结构示意图, 轻链和重链分别为棕色和绿色, 轻链末端标有 N1、C1, 重链末端标有 N2、C2。

图 1 MPO 的结构

Figure 1 Structures of MPO

ound II ($PorFe^{4+}-O$), 随后 Compound II 反应生成 native MPO。在这两步反应中, 由于 Compound II 生成 native MPO 是稳态催化过程中的限速步骤, 因此 Compound II 被认为一种更持久的中间体^[14]。

3 MPO 的抑制剂分类

MPO 抑制剂从抑制机制上可以分为: ①不可逆抑制剂, MPO 利用 H_2O_2 氧化不可逆抑制剂, 导致卤化循环中 HClO 的产生减少, 而 HClO 会氧化许多重要的生物大分子, 如巯基和硫醚分子、质膜三磷酸腺苷(adenosine-triphosphate, ATP)酶、胶原蛋白、抗坏血酸、蛋白质、核苷酸和 DNA 修复酶^[14], 以及氯化 DNA 碱基^[15]和氨基酸酪氨酸, 形成 MPO 氧化指纹生

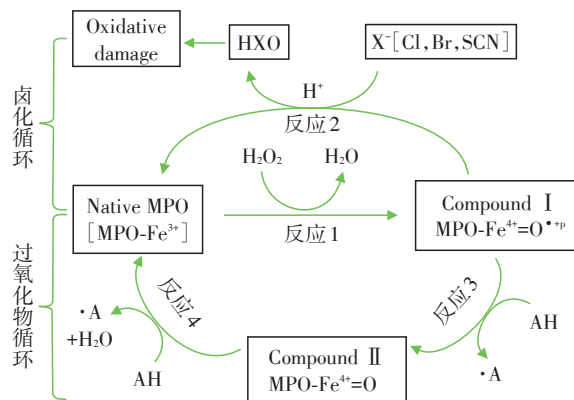


图 2 MPO 的卤化循环和过氧化物酶循环

Figure 2 Halogenation cycle and peroxidase cycle of MPO

物标志物 3-氯酪氨酸(3-chlorotyrosine, 3-ClTyr)^[16]。

3-ClTyr 作为一种生物标志物^[17],在动脉粥样硬化^[18]、心肌肥大^[19]和阿尔茨海默病^[20]患者中检测到水平升高。因此,不可逆 MPO 抑制剂通过减少 HClO 的生成,减少 3-ClTyr 的生成,从而抑制氧化应激,减少炎症发生^[21]。②可逆结合 MPO 活性位点的化合物,可逆抑制剂会占据结合 MPO 活性入口处的疏水远端血红素腔,与血红素配体的结合位点进行高亲和力 and 低解离率的相互作用,从而阻断 MPO 介导的卤化循环,抑制酶活性^[22]。③促进 Compound II 积累而不与活性位点结合的化合物,可以与 Cl⁻ 竞争并促进形成 Compound II 的合成,并且由于 Compound II

生成 native MPO 速度缓慢,从而造成 Compound II 积累,达到 MPO 抑制效果^[22]。

3.1 不可逆抑制剂

目前代表性的不可逆抑制剂主要有 Soubhye 等^[23]虚拟筛选得到的 MPO-in-28, Tong 等^[24]报道的含有酰肼结构的 4-氨基苯甲酸酰肼(4-aminobenzohydrazide, 4-ABAH)、阿斯利康主导研发的以 2-硫黄嘌呤作为核心基团的 AZD5904 和 AZD3241,以及辉瑞公司研发的含硫脲嘧啶骨架的 PF-06282999 和 PF-1355(图 3)。

2017 年, Soubhye 等^[23]基于 MPO 活性位点结合

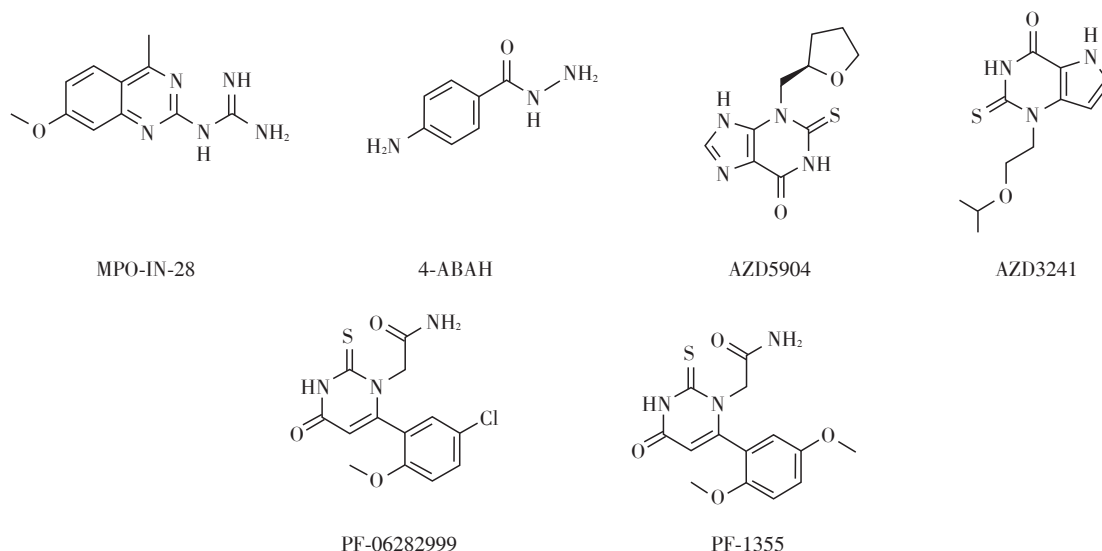


图3 代表性MPO不可逆抑制剂

Figure 3 Representative MPO irreversible inhibitors

的药效团建模,通过虚拟筛选得到了多个具有 MPO 抑制活性的化合物,其中 IC₅₀ 小于 1 μmol/L 的有 MPO-IN-28 (44 nmol/L)、hydralazine (0.9 μmol/L)、MPO-IN-42 (0.05 μmol/L)、MPO-IN-43 (0.35 μmol/L)、primaquine (0.3 μmol/L)、mefenamic acid (0.89 μmol/L)、MPO-IN-55 (0.13 μmol/L)。其中含有胍基结构的 MPO-IN-28 对 MPO 抑制活性最强。新冠病毒感染重症患者中,中性粒细胞 MPO 活性增加,促进内皮细胞糖复合物 (endothelial glycocalyx, EG) 降解,从导致内皮功能障碍,在体外新冠病毒感染原发性人主动脉内皮细胞中, MPO-IN-28 可以抑制 MPO 活性减少 EG 的降解^[25]。

4-ABAH 是 Kettle 等^[26]在 1995 年发现的含有酰肼结构的抑制剂,其对 MPO 具有选择性,不抑制过氧化氢酶或谷胱甘肽过氧化物酶, IC₅₀ 为 0.3 μmol/L。在动脉粥样硬化的动物模型中, 4-ABAH 可以通过

抑制 MPO 活性来保护血管,促进血管损伤后新生内膜形成^[27]。4-ABAH 还可以减弱由 MPO 介导的体外和体内促血管生成作用^[28]。

AZD5904 和 AZD3241 是由阿斯利康公司研发的以 2-硫黄嘌呤作为核心基团改造的抑制剂,与 MPO 进行共价结合,形成不可逆的抑制效果, IC₅₀ 值分别为 140 nmol/L 和 630 nmol/L^[29]。AZD5904 目前已经完成多发性硬化、慢性阻塞性肺疾病的 II 期临床试验。Ramachandre 等^[19]发现并证明 AZD5904 可以通过抑制心肌细胞中的 MPO 来缓解心肌肥厚症 (hypertrophic cardiomyopathy, HCM) 的舒张功能障碍。2019 年, AZD3241 获得了美国食品药品监督管理局 (Food and Drug Administration, FDA) 和欧盟欧洲药品管理局委员会的孤儿药认定。拜奥新医药公司 (Biohaven) 获得了该药的独家开发和推广使用权,改名为 BHV3241 缓释片,并于 2019 年 12 月完成

新药审评,2023年2月已经完成了Ⅲ期临床实验。

PF-06282999和PF-1355是Ruggeri等^[30]推出的硫脲嘧啶衍生物,通过共价、不可逆机制以时间依赖性抑制MPO活性,PF-06282999的 IC_{50} 值为 $1.9\ \mu\text{mol/L}$,PF-1355的 EC_{50} 值为 $1.47\ \mu\text{mol/L}$ 。研究发现动脉粥样硬化低密度脂蛋白受体小鼠模型中,PF-06282999可以促进动脉粥样硬化病变稳定和防止动脉粥样硬化斑块破裂^[31]。临床前研究表明,PF-06282999在小鼠、大鼠、狗和猴子体内吸收迅速且良好,口服生物利用度分别为100%、86%、75%和76%^[30]。评估健康成人受试者口服PF-06282999的安全性、耐受性和药代动力学的研究(NCT01626976)和在健康超重成人中的安全性、用量和效果的研究,以及测试PF-06282999对健康成人中咪达唑仑用量影响的研究(NCT01707082)已经完成I期临床研究。而由于对内毒素给药的安全性问题以及未来内毒素批次的可用性不确定,I期临床研究(NCT01965600)(用于评估研究药物对炎症标志物的影响)被终止。在此治疗过程中引发的主要不良反应为心动过速、发冷发热、肌痛头痛,其他不良反应有眼睛疼痛、皮炎多汗和恶心呕吐。2016年,Zheng等^[32]首次证明了PF-1355早期使用可以改善和重塑实验性心肌梗死后的心脏功能,具有对冠状动脉疾病(coronary artery disease, CAD)和缺血性心肌病中早期和后期心脏保护作用^[33],在心肌梗死及缺血再灌注损伤的模型中可以减少炎症和减缓

病情加重^[34]。在血管炎的小鼠模型中,口服PF-1355可降低疾病严重程度和炎症水平,减少水肿和中性粒细胞积累^[32]。

3.2 可逆性抑制剂

目前代表性的可逆抑制剂主要有含羟肟酸酯结构水杨基异羟肟酸(salicylhydroxamic acid, SHA)及其衍生物HX1^[35],天然产物异噻唑啉酮二葡萄糖苷(secoisolaricresinoldiglucoside, SDG)和N-乙酰赖氨酸-酪氨酸-半胱氨酸酰胺(N-acetyl lysyltyrosylcysteine amide, KYC)^[36](图4)。

SHA是含有羟肟酸酯结构的MPO抑制剂,最早由Forbes等^[37]发现,通过占据血红素结合口袋与MPO底物竞争的从而使酶可逆性失活, IC_{50} 为 $25\ \mu\text{mol/L}$ 。抑制剂的芳香环与血红素吡咯环在侧链之间的远端血红素口袋入口处的疏水区域结合。羟肟酸基团与远端组氨酸95和邻近的谷氨酰胺91酰胺基团都能形成氢键,但没有与血红素铁配位。SHA结合使3个水分子从远端血红素腔中移出,并使第4个水分子的位置发生小的移动。除此之外,复合物的活性位点区域和本地酶之间没有明显的构象差异^[38]。2013年,Forbes等^[39]基于SHA合成含有芳香基异羟肟酸酯结构的可逆性MPO抑制剂HX1、HX2、HX3,这3种化合物均具有高效的MPO抑制活性,其中HX1活性最强, IC_{50} 值为 $5\ \text{nmol/L}$ 。2018年,Forbes等^[39]开发了一种多底物的MPO抑制实验,进一步验证了HX1的高效力,筛选得到其他

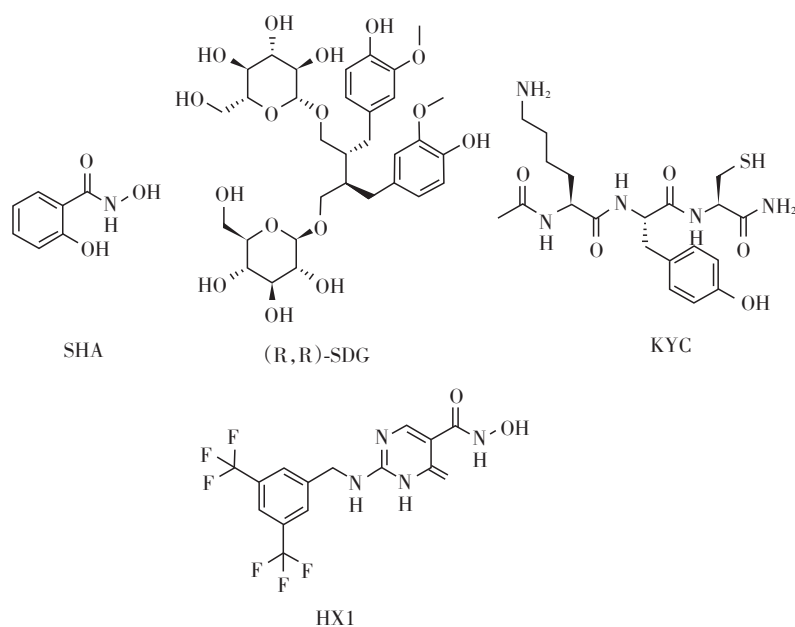


图4 代表性MPO不可逆抑制剂

Figure 4 Representative MPO irreversible inhibitors

MPO 抑制剂,抑制活性较好的有色胺(tryptophan)、4-溴苯胺和 BCH, IC_{50} 分别为 $0.5 \mu\text{mol/L}$ 、 $0.3 \mu\text{mol/L}$ 和 $0.2 \mu\text{mol/L}$ 。

SDG 是一种天然生物活性剂,具有很强的抗氧化和清除自由基[羟基、过氧化物和 2-2 二苯基胍(2-2 diphenyl hydrazyl, DPPH)]的特性^[40-41],还可以清除生理溶液辐射诱导的活性氯类化合物(active chlorine species, ACS)活性氯^[42]。SDG 通过与 MPO 活性位点近端结合,干扰 H_2O_2 进入 MPO 的活性位点而不影响 Cl^- 的进入,从而抑制 H_2O_2 依赖性的 MPO 活性^[42]; SDG 还可以清除抑制自由基 compound I^[43], 其 IC_{50} 为 $63.47 \mu\text{mol/L}$ 。

KYC 含有 Tyr、Lys 和 Cys 三肽,是一种强效、可逆、特异和无毒的 MPO 抑制剂^[44], 其 IC_{50} 为 $7 \mu\text{mol/L}$ 。Yu 等^[45]研究发现, KYC 治疗可明显减少大脑中动脉闭塞(middle cerebral artery occlusion, MCAO)小鼠大脑中的神经系统严重程度评分、梗死大小、IgG 外渗、中性粒细胞浸润、神经元损失、细胞凋亡和小胶质细胞/巨噬细胞激活,还可以促进体内 MPO 氧化指纹生物标志物 ClTyr 减少。

3.3 促进 compound II (PorFe⁴⁺-O) 累积的抑制剂

目前已知的促进 compound II 累积的抑制剂有 氨基苯酚、色胺、色氨酸及其类似物、吲哚(indole)及其类似物^[46](图 5)。2005 年, Camp 等^[47]发现褪黑素作为抗氧化剂和抗炎剂,可以抑制中性粒细胞中 MPO 活性,从而减轻 HClO 依赖性炎症组织损伤。2008 年, Galijasevic 等^[46]发现并验证色氨酸与褪黑素以类似形式抑制 MPO 活性,同时发现其补充剂可以作为抗抑郁药保持身体健康,缓解情绪不佳

和易被激怒,减少对碳水化合物的渴望,缓解慢性疼痛和躁狂行为症状,并使睡眠正常化。2009 年, Galijasevic 等^[46]发现叠氮化合物 4-胺-2, 2, 6, 6-四甲基二苯吡啶(4-amino-TEMPO)抑制 MPO 和中性粒细胞催化产生 HClO 的 IC_{50} 值分别为约 $1 \mu\text{mol/L}$ 和 $6 \mu\text{mol/L}$ 。

3.4 作用机制不明的天然产物来源的 MPO 抑制剂

除了以上两类抑制剂外,也有一些作用机制不明的天然产物也表现出 MPO 抑制活性,如亚甲基小檗碱(demethyleberberine, DMB)、4-甲基七叶皂苷(4-methylscutellin, 4-ME)、N-甲基胞嘧啶(N-methylcytosine, NMC)等(图 6)。DMB 是一种天然线粒体靶向的抗氧化剂,具有阳离子和邻苯二酚结构^[48]。Chen 等^[49]发现在炎症性肠病(inflammatory bowel disease, IBD)中, DMB 可以降低 MPO 活性,显著缓解体重减轻,减少白细胞介素-6(interleukin-6, IL-6)和肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)等促炎细胞因子的产生,并抑制了核因子 κB (nuclear factor kappa-B, NF- κB)信号通路的激活从而抑制炎症反应。4-ME 是香豆素衍生物之一,具有很强的抗氧化和抗炎活性^[50]。Witaicenis 等^[51]证明在葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导的 IBD 模型中, 4-ME 可以降低 MPO 活性,降低了结肠 IL-6 的水平,并抵消了谷胱甘肽(glutathione, GSH)的消耗。NMC 是从紫薇和苦参的种子中提取的三环喹啉类生物碱,具有多种药理活性,如降血糖、镇痛和抗炎活性。DSS 诱导小鼠结肠炎模型中, NMC 可以有效抑制 MPO 活性的显著增加,减少局部炎症^[52]。

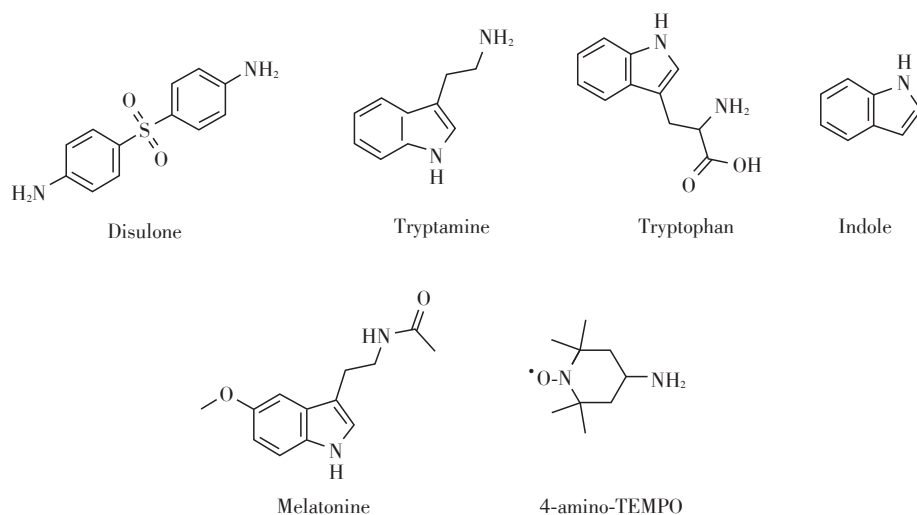


图5 促进化合物 II 积累的代表性 MPO 抑制剂

Figure 5 Representative MPO inhibitors that promote the accumulation of compound II

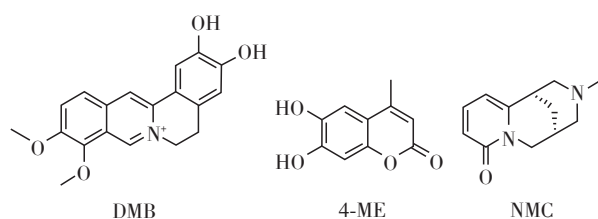


图6 作用机制不明的天然产物来源MPO抑制剂

Figure 6 MPO inhibitors representing a natural product source with an unclear mechanism of action

4 小结与展望

MPO抑制剂的研究是药物研发的热点。目前MPO不可逆抑制剂主要包括MPO-in-28^[23]、4-ABAH^[26]、AZD5904、AZD3241^[29]、PF-06282999^[30]和PF-1355等;可逆结合MPO活性位点的化合物包括SHA^[35]、SDG^[43]、KYC^[44]等;促进化合物II积累而不与活性位点结合的化合物包括色胺、色氨酸及其类似物、吲哚及其类似物等;作用机制不明确天然活性化合物包括DMB^[48]、4-ME、NMC^[52]等。这些抑制剂由于抑制了各种损伤中MPO的催化活性,在各种炎症疾病中均能起到促进恢复的作用,如动脉粥样硬化^[37]、心肌肥厚^[30]、缺血性脑卒中^[53]等。这些研究表明,MPO是具有很高研究价值的作用靶点,也进一步证明了针对MPO抑制机制进行药物开发的可行性。

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