微量胺相关受体-1作为新兴药物靶点的研究进展与应用前景

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摘要: 微量胺相关受体-1 (trace amine-associated receptor 1, TAAR1) 是一种广泛分布于哺乳动物中枢神经系统的G蛋白偶联受体, 是调节单胺能和谷氨酸能系统的关键靶点, 在情绪、认知、奖赏及学习记忆等生理过程中发挥核心作用。近年来, 随着研究的深入, TAAR1的研究范畴已从最初的精神疾病领域, 迅速拓展至代谢综合征与免疫系统疾病, 展现出作为多疾病治疗靶点的巨大潜力。本文系统综述了TAAR1相关的信号通路及其在多种疾病中的关键作用, 重点探讨了TAAR1激动剂在精神分裂症、抑郁症、阿尔茨海默病、帕金森病、物质成瘾及2型糖尿病等疾病中的治疗机制与应用前景。此外, 本文还分析了TAAR1激动剂从基于天然配体的衍生化设计到基于结构生物学的理性设计的最新研发进展, 并展望了其与多靶点药物策略结合的未来发展方向, 以期为TAAR1靶向药物的开发与转化应用提供理论参考与研究思路。

关键词: 微量胺相关受体-1; 精神系统疾病; 信号通路; 微量胺相关受体-1激动剂; 合理药物设计

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Trace amine-associated receptor 1 as an emerging drug target: Research progress and therapeutic prospects

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Abstract: Trace amine-associated receptor 1 (TAAR1), a widely expressed G protein-coupled receptor in the mammalian central nervous system, serves as a key regulator of monoaminergic and glutamatergic systems and plays a pivotal role in physiological processes such as emotion, cognition, reward, and learning and memory. Recently, research on TAAR1 has expanded beyond its initial focus on psychiatric disorders to rapidly encompass metabolic syndrome and immune system diseases, revealing its considerable potential as a therapeutic target for multiple diseases. This review systematically summarizes TAAR1-associated signaling pathways and their critical roles in various diseases, with a particular emphasis on the therapeutic mechanisms and application prospects of TAAR1 agonists in schizophrenia, depression, Alzheimer's disease, Parkinson's disease, substance use disorder, and type 2 diabetes. Furthermore, this article examines recent advances in the development of TAAR1 agonists, spanning from derivatization tactics based on natural ligands to rational design guided by structural biology, and explores future research objectives, including multi-target drug strategies. The aim of this review is to provide a theoretical foundation and insights to support the development and translational application of TAAR1-targeted therapies.

Key words: trace amine-associated receptor 1; mental illness; signaling pathways; trace amine-associated receptor 1 agonist; rational drug design

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微量胺相关受体 (trace amine-associated receptors, TAARs) 是G蛋白偶联受体 (G protein-coupled receptors, GPCRs) 中一类特异性感知痕量胺的亚群[1-4], 在脊椎动物体内分布广泛, 但中枢神经系统中微量胺的内源性水平非常低 (比单胺神经递质低数百倍)。在人类基因中已鉴定出9种TAARs亚型, 其中微量胺相关受体-1 (trace amine-associated receptor 1, TAAR1) 是研究最为深入的亚型, 它是唯一不在嗅觉上皮表达的TAAR亚型。与其他亚型相比, 具有更广泛的组织分布和更复杂的生理功能[2]。TAAR1可在多巴胺能[5]、血清素能[6,7]和谷氨酸能[8]等多个区域表达, 参与调节奖励回路、边缘网络、认知过程和情绪状态[9-11], 对大脑功能调节具有重要意义。

当前研究焦点高度集中于TAAR1在神经精神疾病领域的治疗潜力, 尤其在精神分裂症 (schizophrenia, SCZ) 与物质使用障碍 (substance use disorders, SUD) 的病理机制干预中展现出突破性价值[12,13]。然而, 近年来随着研究深入, 发现TAAR1还在外周组织中分布, 如胰腺 (胰岛β细胞)、胃肠道、肾脏和免疫细胞等, 参与代谢综合征、免疫系统疾病和胃肠道功能的调控[14-16] (图1)。值得注意的是, 在代谢调控领域, TAAR1激动剂通过激活胰腺β细胞中的环磷腺苷−蛋白激酶A (cyclic adenosine monophosphate-protein kinase A, cAMP-PKA) 和环磷腺苷 (cyclic adenosine monophosphate-protein kinase A, cAMP) 直接激活交换蛋白依赖性信号传导增强葡萄糖刺激的胰岛素分泌, 同时通过cAMP-PKA通路促进cAMP反应元件结合蛋白磷酸化, 进而诱导下游靶基因胰岛素受体底物-2 (insulin receptor substrate-2, Irs-2) 的表达, 增强β细胞的增殖能力并抑制其凋亡。因此, 改善β细胞功能使得TAAR1成为2型糖尿病等代谢综合征的极富潜力的靶点[17]。TAAR1作为多疾病潜力靶点, 为了解神经精神疾病、代谢综合征等相关疾病的共病机制提供了新的视角。

鉴于TAAR1在多种疾病中的潜在作用, 因此对其进行系统分析具有重要意义。本文深入总结了TAAR1相关的体内信号通路及其与疾病的关联, 并对TAAR1激动剂的研究进展进行探讨。以期为推动TAAR1作为新兴药物靶点的基础研究与转化应用提供参考。

1 TAAR1涉及的信号通路

1.1 TAAR1与单胺系统

脑单胺包括常见生物胺和微量胺, 其活性异常与多种神经精神疾病相关, 在情绪、认知、奖赏和学习等方面发挥着至关重要的作用[18]。TAAR1神经解剖学分布与单胺系统高度重合, 广泛分布于哺乳动物脑内, 尤

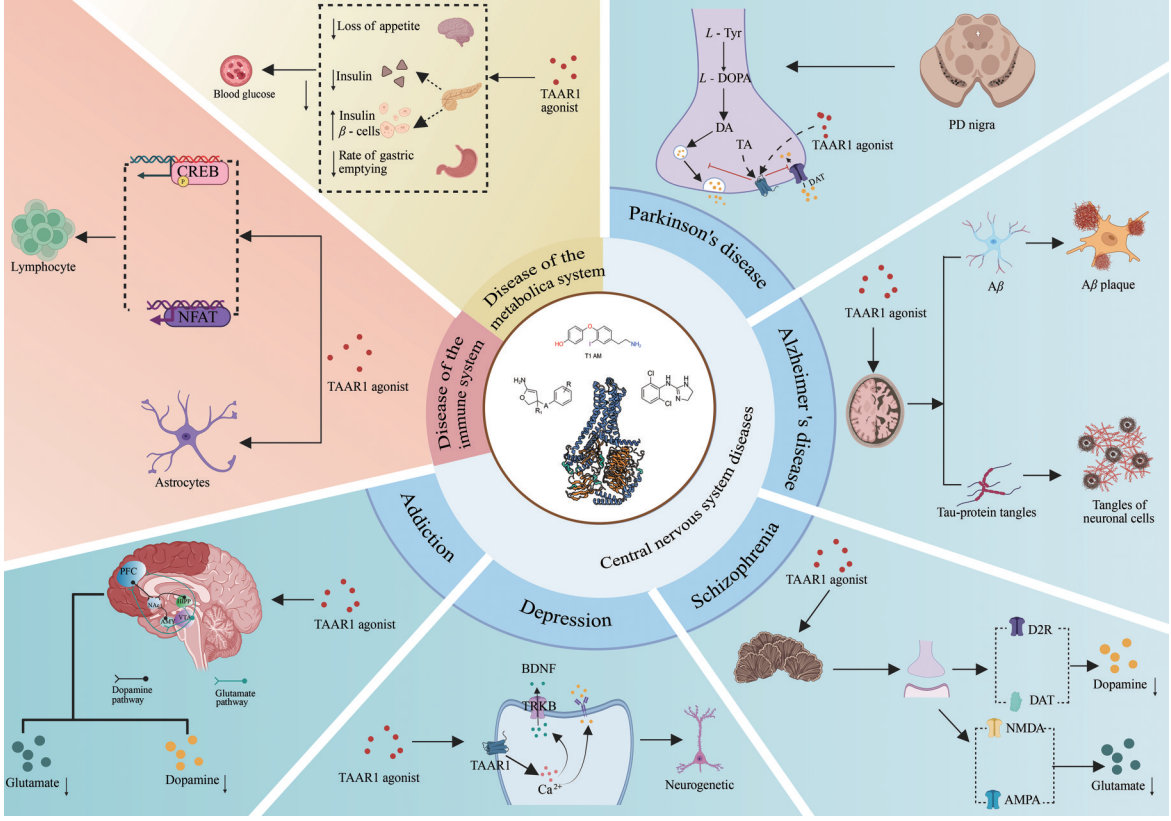


Figure 1 Role of TAAR1 in various diseases. TAAR1: Trace amine-associated receptor 1; Aβ: β-Amyloid protein; DA: Dopamine; NMDA: *N*-Methyl-*D*-aspartic acid receptor; AMPA: α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionicacid receptor

其在海马、杏仁核等边缘系统及腹侧被盖区、黑质、中缝核等富集单胺能神经元的脑区[1,11,19]。因此TAAR1和不同分子相互作用机制及下游信号通路的靶点得到广泛的关注 (图2)。

近年来研究表明, TAAR1可通过调节胞内信号通路影响单胺系统功能。TAAR1可通过激活Gαs蛋白来提高细胞内cAMP水平[1,2,20], 进而增加PKA和蛋白激酶C (protein kinase C, PKC) 的水平, 从而通过单胺转运蛋白磷酸化调节相应神经元的信号级联反应发挥一系列生理功能[21,22]。单胺转运蛋白是脑单胺能神经传递的重要调节因子, 参与突触间隙释放的单胺类神经递质的清除和神经信号的终止[23,24], TAAR1可通过与单胺转运蛋白和单胺自受体直接相互作用或与单胺能神经元建立细胞间通信调节单胺传递[25]。例如, 2008年Xie等[26]研究发现β-苯乙胺 (β-PEA) 激活TAAR1可通过与非单胺自受体相互作用对单胺转运蛋白摄取和排出功能的产生影响, 可能揭示痕量胺作用于大脑单胺能系统的主要机制。除通过激活Gαs蛋白外, TAAR1也通过β-抑制蛋白2 (β-arrestin2) 发出信号来调节单胺系统功能。Harmeier等[27]在2015年研究发现TAAR1和D2R的异二聚化提高了β-arrestin2向TAAR1的募集并激活Akt, 从而通过替代途径抑制糖原合成酶激酶-3β (glycogen synthase kinase-3β, GSK-3β), 这导致GSK-3β介导的如抑制多巴胺 (dopamine, DA) 依赖性运动活动行为减弱 (图2)。

1.2 TAAR1与谷氨酸系统

谷氨酸参与细胞存活、增殖和细胞内钙信号传导等细胞过程, 在哺乳动物中枢神经系统及皮肤和胰岛等非神经元外周细胞中表达[28-30]。2014年, Cisneros等[31]发现, 敲低TAAR1可显著增加谷氨酸清除率, 而甲基苯丙胺 (methamphetamine, METH) 可通过激活TAAR1, 引起人类星形胶质细胞内cAMP升高, 进而降低谷氨酸清除能力, 表明TAAR1与谷氨酸传递之间存在直接联系。

作为清除胞外谷氨酸、维持其浓度稳态的关键分子, 谷氨酸转运蛋白, 尤其是兴奋性氨基酸转运体-2 (excitatory amino acid transporter-2, EAAT-2) 在突触间隙中起主要作用, 负责清除约90%的细胞外谷氨酸[32]。而TAAR1可通过影响这类转运蛋白的功能调节谷氨酸水平, 如Ding等[33]在2017年发现DA可通过激活星形胶质细胞上的TAAR1受体下调EAAT2的表达 (图2), 从而抑制谷氨酸清除、导致细胞外谷氨酸蓄积; 随后, DA与谷氨酸协同作用, 通过激活神经元中的钙调神经磷酸酶−T细胞核因子 (calcineurin-nuclear factor of activated T cells, CaN-NFAT) 信号通路, 减少脑源性神经因子 (brain-derived neurotrophic factor, BDNF) 和神经营养因子-3等神经营养因子的生成, 最终引起记忆功能损害。

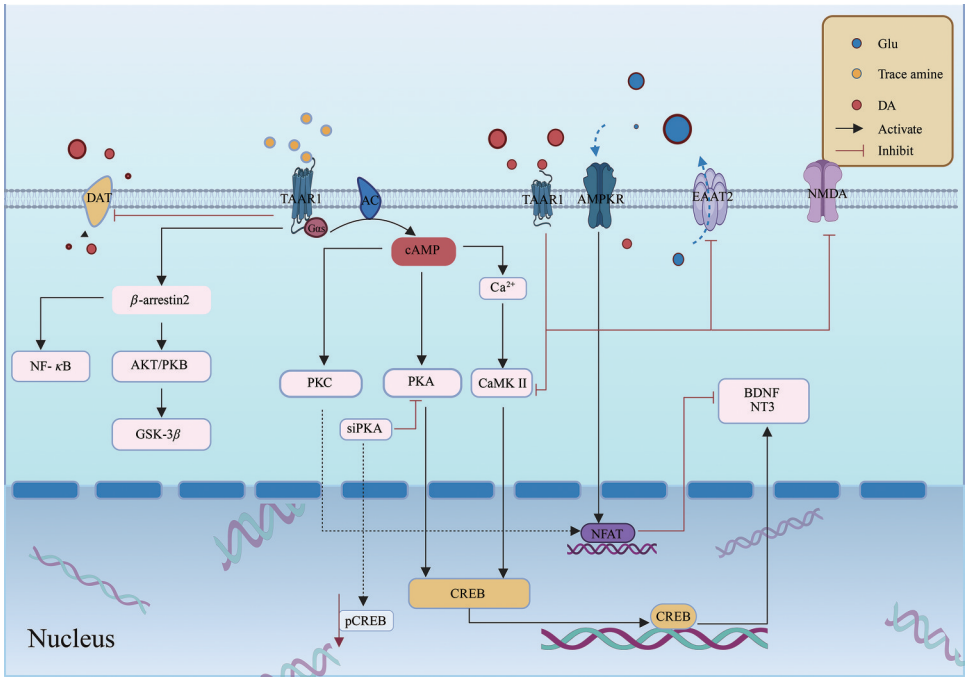


Figure 2 Regulation of TAAR1 on intracellular signaling pathway. PKA: Protein kinase A; PKC: Protein kinase C; NFAT: Nuclear factor of activated T cells; CREB: cAMP-response element binding protein; BDNF: Brain-derived neurotrophic factor; AMPK: AMP-activated protein kinase; NF-κB: Nuclear factor-κB; CaMKII: Calmodulin-dependent protein kinase II; NT3: Neurotrophin-3

2 TAAR1相关疾病

2.1 中枢神经系统性疾病中的TAAR1作用

2.1.1 精神分裂症 精神分裂症主要包括幻觉和妄想等阳性症状、社交退缩和快感缺乏等阴性症状及认知障碍3个主要症状特征[34,35]。目前其发病机制尚不明确, 但多巴胺功能亢进假说和基于*N*-甲基-*D*-天冬氨酸 (*N*-methyl-*D*-aspartic acid, NMDA) 受体的谷氨酸能信号传导功能减退的谷氨酸假说最为关键[36,37]。研究表明, TAAR1可通过调节多巴胺水平对治疗精神分裂症产生积极影响[38,39]。

传统抗精神病药物大多通过与D2R竞争性结合, 从而调节内源性多巴胺水平[40]。2014年, Leo等[5]发现TAAR1作用机制与其存在差异, 其主要与突触前多巴胺D2自身受体的异二聚化有关, 激活的TAAR1通过阻断酪氨酸羟化酶 (tyrosine hydroxylase, TH) 的磷酸化来增强D2R降低TH活性的能力, 从而减少左旋多巴的合成, 并提高D2R减少多巴胺释放的能力。此外, TAAR1激活可避免传统抗精神病药物引起的锥体外症状, 改善患者的治疗体验。2020年, Koblan等[41]进行了一项随机对照试验, 研究发现可激动TAAR1的ulotaront组和安慰剂组的不良事件发生率总体相似, 差异均低于2.5%, 且给药组和安慰剂组在锥体外系症状的患者百分比分别为3.3%和3.2%, 表明TAAR1激动剂具有较低的锥体外系症状风险。综上所述, TAAR1激动剂是一种新型治疗精神分裂症药物研究方向, 且无心脏代谢不良反应和因阻断D2信号传导而产生的一些不良反应。

2.1.2 阿尔茨海默病 阿尔茨海默病 (Alzheimer's disease, AD) 特征是记忆和认知能力逐渐丧失[42-44], 主要病理变化是由过度磷酸化的Tau蛋白形成的细胞内神经原纤维缠结和*β*淀粉样蛋白沉积物 (*β*-amyloid protein, A*β*) 组成的细胞外老年斑块, 以及神经胶质细胞增殖伴有神经元丢失[45,46]。TAAR1激动剂在各种行为实验研究中显示具有促认知作用。如Wu等[47]在2022年测试了TAAR1激动剂RO5263397在雄性小鼠对短期记忆的影响实验中, RO5263397显著增加了对新物体的探索时间 (0.03 mg·kg^{-1}: t_{23} = 2.15; 0.1 mg·kg^{-1}: t_{19} = 2.16); 同时, 在长期新物体识别测试中, RO5263397也增加了对新目标的探索时间 (t_{16} = 2.17), 进一步支持TAAR1激动剂具有促认知功能, 为记忆障碍治疗提供潜在靶点。

GSK-3*β*是与Tau蛋白异常磷酸化密切相关的主要激酶, 它能够促进Tau蛋白的错误折叠和聚集, 形成神经纤维缠结[48]。2015年, Harmeier等[27]研究发现TAAR1和D2R的异二聚化提高了*β*-arrestin2向TAAR1的募集并激活Akt, 从而抑制GSK-3*β*, 使GSK-3*β*介导的行为减弱, 可能对Tau蛋白异常磷酸化产生影响。认知功能受损还与NMDA受体功能障碍有关[49,50], 2022年, Leo等[51]研究发现TAAR1激动剂RO5256390可以增加细胞表面NMDA谷氨酸受体的表达, 并在体外抵消其A*β*诱导的减少。次年, Polini等[52]研究发现T1AM对A$\beta_{25\text{-}35}$诱导的小胶质细胞毒性具有保护作用, 10 μmol·L^{-1} T1AM可使A*β*损伤的HMC3细胞存活率从50%恢复至85%。此外, 2024年, Imbriglio等[53]发现TAAR1激活可以增强PFC的大脑活动, 而PFC是一个在执行功能和工作记忆中起着至关重要作用的区域。目前关于TAAR1对AD作用仍在研究中, 需要更多的证据来支持TAAR1调节剂在AD治疗中的作用。

2.1.3 帕金森综合征 帕金森综合征 (Parkinson's disease, PD) 主要表现为运动迟缓、静息性震颤和姿势不稳等典型运动症状, 以及睡眠障碍、情绪障碍和自主神经功能障碍等非运动症状[54,55], 其标志性病理涉及*α*-突触核蛋白的异常积累和黑质中多巴胺能神经元的进行性丧失[56,57]。早在2015年, Alvarsson等[58]研究表明TAAR1可增强多巴胺能神经元的变性, 并减弱纹状体中对左旋多巴和突触前和突触后谷氨酸神经传递的行为反应, 与TAAR1-KO小鼠相比, 野生型 (wild type, WT) 小鼠纹状体内给予6-羟多巴胺 (6-hydroxydopamine, 6-OHDA) 后多巴胺能标志物的损失减少; 相反, TAAR1激动剂RO5166017加重了WT小鼠中由纹状体内6-OHDA诱导的变性, 支持TAAR1与PD病理生理学和潜在管理的相关性。

2023年, Shum等[59]该研究通过利用*α*-突触核蛋白病体外和体内模型的多学科方法该研究表明揭示章鱼胺可保护神经元免受*α*-突触核蛋白神经变性, 重要的是, 章鱼胺可通过TAAR1-Orai1-Ca^{2+}-钙调神经磷酸素依赖性的方式介导星形胶质细胞中乳酸的产生, 从而促进有氧糖酵解来驱动大脑皮层中毒性星形胶质细胞转化为神经保护型的星形胶质细胞。PD的特征还包括嗅觉障碍等非运动功能障碍 (约90%的PD患者会出现嗅觉功能障碍)[60], Zhang等[61]在2024年提出了一种PD嗅觉功能障碍的替代机制, 表明沿嗅觉通路的大脑区域的神经元细胞凋亡和神经炎症是导致PD患者嗅觉障碍的原因, 而这种现象可能与这些区域TAAR1的减少有关。PD的病因复杂, 涉及遗传和环境因素及病理过程, 如线粒体功能障碍、溶酶体异常、突触损伤和神经炎症[62,63], 而TAAR1激动剂还可恢复NMDA受体膜表达以增强突触可塑性, 抑制小胶质细胞活化减轻神经炎症, 激活抗氧化通路保护多巴胺能神经元[51]。总之, 针对TAAR1在帕金森综合征药物开发和临床应用中具有较大的潜力, 但仍需进一步的临床试验和研

究来验证其疗效和安全性。

2.1.4 抑郁症 全世界有超过3亿人患有抑郁症, 而我国患抑郁症人数达9 500万, 每年大约40%自杀者罹患此症[64,65]。抑郁症以持续性情感与认知功能障碍为核心表现[66], 其发病机制的经典假设包括血清素能系统和单胺能神经系统功能不足、下丘脑−垂体−肾上腺轴失调、神经可塑性改变和神经免疫紊乱[67,68]。近年来, 多项研究表明TAAR1激动剂具有抗抑郁效果。例如, Ren等[69]发现ulotaront不仅能单独起效, 与低剂量度洛西汀联合使用后更是呈现出比单用度洛西汀(ED_{50} = 6.5 mg·kg^{-1}) 更强的剂量依赖性抗抑郁作用(ED_{50} = 3.8 mg·kg^{-1})。

BDNF降低会导致学习、记忆、计划和执行功能受损[70,71], 在2020年, Lee等[4]发现与对照神经元相比, 皮质酮 (corticosterone, CORT) 诱导的海马神经元中的BDNF、酪氨酸激酶受体B (tyrosine kinase receptor B, TrkB) 和环磷腺苷效应元件结合蛋白 (cAMP-response element binding protein, CREB) 的磷酸化水平分别下降24%、34%和61%, 而使用PEA可抑制这些物质水平降低, 表明PEA可能通过调节海马体中的BDNF/TrkB/CREB信号传导来改善抑郁样行为。同时, 在2024年, Zhang等[72]通过高尔基染色 (Golgi-Cox) 法发现, TAAR1的激活可减弱慢性社交挫败应激 (chronic social frustration stress, CSDS) 在齿状回细胞中诱导的结构可塑性的变化, 揭示RO5263397能够有效改善慢性应激导致的学习记忆功能障碍、成年神经发生受损、树突复杂性降低及齿状回颗粒细胞突触数量减少等不良效应。此外, TAAR1广泛分布于中枢神经系统, 尤其在前额叶皮层、海马体和杏仁核等情绪调节关键脑区中高度表达, TAAR1激动剂可能通过调节杏仁核突触可塑性发挥抗抑郁作用[73]。综上所述, 多项研究揭示了TAAR1激动剂具有作为新型抗抑郁药物的开发潜力。

2.1.5 物质成瘾 物质成瘾主要有精神兴奋剂、阿片类药物和酒精成瘾, 是一种慢性、易复发的脑部疾病, 与大脑奖赏系统的改变、神经突触可塑性及神经递质异常密切相关, 其中, 中脑边缘多巴胺系统被认为在物质成瘾过程中起着核心作用[74,75]。作为多巴胺能系统的调节剂, TAAR1已被证明在调节药物的奖励作用中发挥关键作用[76], 早在2014年Pei等[77]发现TAAR1激动剂RO5203648可在不改变DA半衰期的情况下阻止可卡因诱导的伏隔核DA溢出, 表明TAAR1可通过与多巴胺转运蛋白相互作用以外的机制调节可卡因诱导的DA溢出。随后, Liu等[78]在延长尼古丁自我给药的10天维持阶段中发现用RO5263397可使可卡因摄入量减少约50%, 表明TAAR1激活可调节尼古丁成瘾样行为。同时, TAAR1在中枢神经系统中的表达与大脑中的奖励回路重叠, 尤其是多巴胺能系统[79]。他们在另一项研究中通过将RO5166107显微注射到几个大脑区域, 发现内侧前额叶皮层的VTA[$F_{(3,20)}$ = 12.05]、伏隔核 (nucleus accumbens septi, NAc) 和前边缘皮质的TAAR1对可卡因寻求行为的恢复很重要, 而黑质和杏仁核中的TAAR1似乎对TAAR1介导可卡因寻求行为的恢复无明显影响, 表明中皮质边缘多巴胺能系统特定亚区域内的TAAR1在药物成瘾中起着关键作用[80]。

2.2 代谢综合征

代谢综合征 (metabolic syndrome, MetS) 是一种以腹部肥胖、胰岛素抵抗、高血压和高血糖为特征的病理状况[81,82]。临床前研究表明, TAAR1激动剂具有作为精神分裂症合并代谢综合征的新治疗选择。如2024年, Dedic等[83]发现与单纯停用致体重增加药物奥氮平相比 (停用7天后, 体重仅下降2%), TAAR1激动剂可更快、更显著地逆转奥氮平诱导的体重增加 (停用7天后, 体重下降7%), 表明TAAR1激动剂在改善血糖控制的同时, 可减轻体重并调节控制能量平衡和进食的神经回路, 从而改善啮齿动物代谢风险状况。

糖尿病作为一种日益普遍的代谢性疾病, 影响着全球约3.82亿人, 预计到2035年将达到近6亿人[84,85], 其中由胰岛素分泌不足和胰岛素抵抗引起的2型糖尿病 (type 2 diabetes mellitus, T2DM) 占90%～95%[86,87]。2019年, Michael等[17]研究发现TAAR1可通过激活Gαs/AC/cAMP轴, 经PKA、Epac促葡萄糖刺激的胰岛素分泌 (glucose-stimulated insulin secretion, GSIS), 而腺苷酸环化酶 (adenyl cyclase, AC) 抑制剂MDL12和330A以及TAAR1拮抗剂EPPTB分别抑制该效应77%～82%、70%～82%; 还可调节cAMP介导钙信号结合钙调蛋白依赖性蛋白激酶II激活MAPK通路, 促β细胞增殖; 同时通过PKA磷酸化CREB, 使Irs-2上调50%以抗β细胞凋亡, 该研究揭示TAAR1是改善T2DM中β细胞功能的潜在靶点。

胰岛素抵抗是MetS及其相关疾病发病的核心机制, 而肥胖是这些疾病的主要表现[88]。2016年, Raab等[15]研究表明TAAR1在降低血糖的同时, 还可显著改善胰岛素抵抗, 餐后血浆胰岛素水平下降, 稳态模型评估胰岛素抵抗指数降低, 且伴随肝脏甘油三酯含量降低27%, 减轻脂毒性对胰岛素信号通路的干扰, 辅助缓解抵抗, 该效应具有TAAR1依赖性, 在TAAR1敲除小鼠中完全消失, 证实TAAR1激活是缓解胰岛素抵抗的关键机制之一。2023年, Zhai等[89]对胰岛素抵抗中的功能机制展开进一步研究, 结果表明: 肠道菌代谢所产生的色胺和苯乙胺通过TAAR1-ERK信号轴抑制代谢组

织的胰岛素诱导Akt磷酸化 (30%～40%), 而TAAR1拮抗剂EPPTB或ERK抑制剂可逆转上述胰岛素抵抗, 该研究表明TAAR1是肠道菌群介导胰岛素抵抗的关键分子。同时, 最近的研究揭示了DA在MetS发病机制中的重要性[90], 因此TAAR1还可能通过调节DA间接缓解胰岛素抵抗[91], 使得TAAR1成为治疗代谢综合征的一个极具潜力的新靶点。

2.3 免疫系统疾病

免疫系统由先天免疫系统和适应性免疫系统组成, TAAR1可通过调节包括T淋巴细胞、B细胞、巨噬细胞和单核细胞等多种免疫细胞对其进行调节[92-94]。如2023年, Barnes等[95]发现在小鼠外周骨髓来源巨噬细胞中, ATP (EC_{50} = 606.1 μmol·L^{-1}) 可诱导肿瘤坏死因子 (tumor necrosis factor, TNF) 分泌并引发糖酵解偏移, 而RO5256390可通过特异性抑制TNF分泌实现免疫功能调控, 且不会干扰IL-6表达、细胞活力与正常代谢过程。

TAAR1在免疫系统中的具体作用机制尚不完全清楚。其中, Panas等[96]在2012年通过Cignal^{TM} 45通路报告基因阵列来检测受体激活后上调的信号通路, 发现淋巴细胞激活后TAAR1的快速上调, 通过G蛋白偶联机制选择性地增强PKA和PKC的磷酸化水平, 特异性上调与免疫激活密切相关的CREB及NFAT信号通路活性。同时, 2020年, Bugda Gwilt等[97]提出TAAR1可通过调节神经内分泌系统间接影响免疫反应, 研究表明肠道微生物与饮食来源的微量胺可通过激活TAAR1, 调控免疫细胞信号通路、肠道屏障功能及炎症反应。

现有研究表明, TAAR1可能通过影响炎症细胞因子的产生在某些自身免疫性疾病中发挥作用。如2021年, Barnes等[98]发现多发性硬化 (multiple sclerosis, MS) 患者单核细胞中TAAR1 mRNA水平显著低于健康对照 (P = 0.042 4), 而MS患者外周血单核细胞中TAAR1 mRNA方差显著升高但均值无差异, 提示TAAR1可能参与MS神经炎症调控, 为MS提供潜在药理靶点。尽管目前对TAAR1与免疫系统的相互作用研究还相对较少, 但现有证据表明TAAR1可能在免疫调节、炎症反应和肿瘤免疫中发挥一定的作用。同时, TAAR1已被鉴定为多种癌症的一个潜在生物标志物和治疗靶点[96]。未来的研究可以进一步探索TAAR1在不同免疫细胞中的表达和功能, 阐明TAAR1参与免疫调节的具体分子机制, 并评估TAAR1作为免疫治疗靶点的潜力。

3 TAAR1激动剂的研究进展

3.1 基于天然配体的衍生化设计

目前新型TAAR1激动剂的发现利用已知多巴胺能、血清素能和肾上腺素能配体。其中化合物S18616 (图3) 被报道为有效的α_2-肾上腺素受体 (α_2-ADR) 激动剂和TAAR1激动剂, 但存在两大代谢缺陷: 一是N-去烷基化导致体内半衰期短; 二是其苯胺结构经氧化生成醌亚胺中间体, 引发谷胱甘肽加合, 存在潜在毒性风险[99]。S18616 (EC_{50} = 15 nmol·L^{-1}) 为螺环咪唑啉母核, 其刚性螺环结构易同时结合α_2-ADR与TAAR1, 目前对其改造核心是打开中心六元螺环, 构建2-氨基恶唑啉母核。如2011年, Revel等[100]在保留药效团 (芳香环与碱性头部) 的同时, 对连接区进行系统性改造设计选择性TAAR1激动剂化合物**1** (图3, EC_{50} = 59 nmol·L^{-1})。2016年, Galley等[101]又设计一系列2-氨基恶唑啉生物, 通过母核重构、连接区修饰、立体优化和芳环取代策略筛选出高效TAAR1激动剂化合物**2**和**3** (图3), 该研究表明化合物**2** (EC_{50} = 18 nmol·L^{-1}) 和**3** (EC_{50} = 31 nmol·L^{-1}) 较S18616的选择性均有所提高, 同时具有代谢稳定性。

2024年, Grossi等[102]通过分子建模研究对S18616衍生TAAR1激动剂的构效关系进一步完善, 研究结果表明: ① 恶唑啉核心和末端芳香环是关键药效团; ② TAAR1结合口袋的芳香残基 (Phe267/Phe268) 对配体芳环的取代基位置敏感, 优先选择邻位/间位疏水取代, 避免对位取代; ③ 去除苯环与恶唑啉环之间连接区, 活性仍保持在优效范围, 如化合物**4**, EC_{50} = 23 nmol·L^{-1} (图3), 说明连接区并非活性必需结构; ④ 甲氧基等极性修饰单独存在时会降低活性, 如化合物**5**, EC_{50} = 9 nmol·L^{-1} (图3)。该研究为后续筛选高选择性、跨物种活性的TAAR1激动剂提供了更精准的结构指导, 进一步完善以S18616为起点的TAAR1激动剂改造体系。

3.2 基于精神疾病类药物3′-碘甲状腺原氨酸的衍生化设计

除单胺系统配体之外, 精神疾病类药物也被发现作为有效的TAAR1激动剂, 其中3′-碘甲状腺原氨酸 (3′-iodothyronamine, T1AM) 被发现为有效的TAAR1激动剂 (EC_{50} = 198 nmol·L^{-1})[103,104], 虽存在碘代毒性、代谢快、物种差异大等问题, 但其双芳环–醚键连接–乙胺侧链的核心结构为TAAR1激动剂设计提供研究思路。早在2006年, Hart等[105]通过合成大量T1AM衍生物发现甲状腺胺类化合物激活TAAR1存在明确结构要求: ① α位碱性氨基是必需基团, 替换为羟基会完全丧失活性; ② 氨基单甲基化可提升活性, 但更大烷基或双烷基化会显著降低活性; ③ 3位碘或甲基取代最优, 多碘取代则导致活性下降; ④ 4′-位为H时活性优于OH, 且大于OH的取代基会产生有害影响。为改善传统甲状腺胺类化合物代谢快及合成难等不足之处, 2015年, Chiellini等[104]将T1AM的双芳基醚键替换

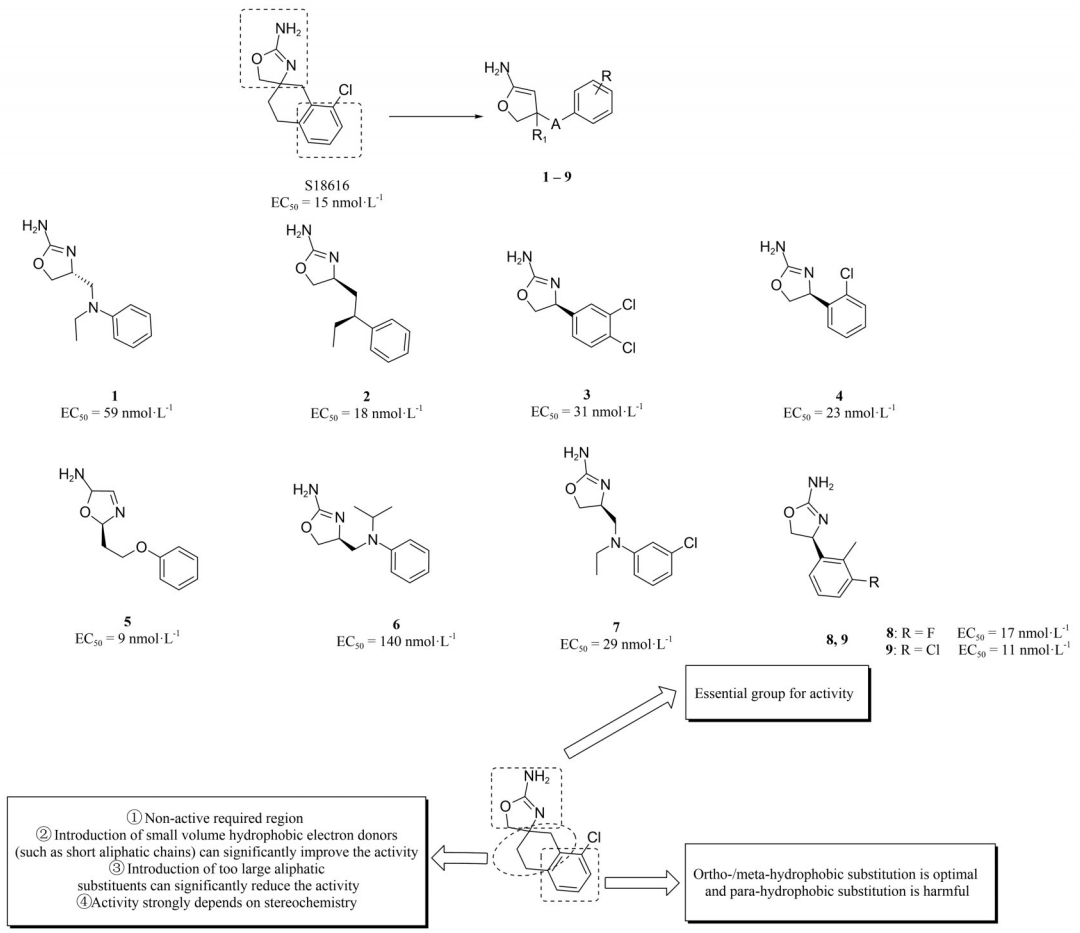


Figure 3 2-Aminooxazoline TAAR1 agonists

为亚甲基桥, 发现醚键并非活性必需如化合物**10** (图4, EC_{50} = 98 nmol·L^{-1}); 同时将易代谢的乙胺侧链替换为氨基乙氧基得到化合物**11** (图4, EC_{50} = 240 nmol·L^{-1})和化合物**12** (图4, EC_{50} = 1 700 nmol·L^{-1}); 此外缺失α位碱性氨基 (图4, 化合物**13**和**14**) 无明显活性, 这与Hart等[105]的研究一致, 也进一步表明碱性氨基和芳香环为活性必需基团。但化合物**11**具有心脏负性变力、血糖升高等不良反应, 可能是由于TAAR1 D284的负电荷与氧原子的相互作用可辅助D102/Y291形成“三角稳定结构”, 确保mTAAR1持续激活, 最终介导胞内cAMP升高所导致。因此, 2016年Chiellini等[106]在此基础上进一步优化, 通过将先导化合物**11**的氧乙胺侧链替换为乙基氨基 (图4, **16**, EC_{50} = 119 nmol·L^{-1}), 同时在该骨架的酚羟基 (图4, **18**, EC_{50} = 98 nmol·L^{-1}), 证实这两个化合物在体内可有效调节血糖, 在代谢紊乱等领域具有潜在治疗价值, 是重要的药用靶点。

3.3 靶向TAAR1激动剂

目前开发的大多数激动剂都存在选择性不足的问题, 近年来, 设计新型TAAR1靶向药物成为了研究新风向。2023年, Shang等[107]通过解析9个TAAR1-Gs/Gq复合物结构, 首次揭示TAAR1存在两个关键结合口袋: 伯胺识别口袋 (primary amine recognition pocket, PARP) 与第二结合口袋 (second combination pocket, SBP); 同时表明Gs/Gq双通路激动剂化合物**20** (图5)比单通路激动剂化合物**19**和**22** (图5) 对精神分裂症具有更好的疗效。同年, Xu等[108]通过分析TAAR1的分子识别和药理学机制进一步分析TAAR1与多种配体的结合方式揭示TAAR1的配体识别机制主要含1个保守主胺识别口袋PARP和3个扩展口袋、G蛋白选择性调控机制及人h/mTAAR1种属特异性差异, 证实TAAR1通过不同口袋适配多样配体, 为TAAR1靶向药物研发提供关键结构基础。两项研究表明PARP可用于保守的胺识别和受体激活, 而SBP部分特定残基可以调节信号偏好, 揭示了TAAR1受体中药物识别口袋的可塑性, 为设计新型靶向药物提供了新思路。

开发新型Gs/Gq双通路激动剂的研发已成为当下研究精神分裂症药物的研究焦点, 关键在于与$Ile103^{3.3}$、$Phe185^{ECL2}$、$Phe265^{6.52}$形成疏水相互作用。2024年, Zhou

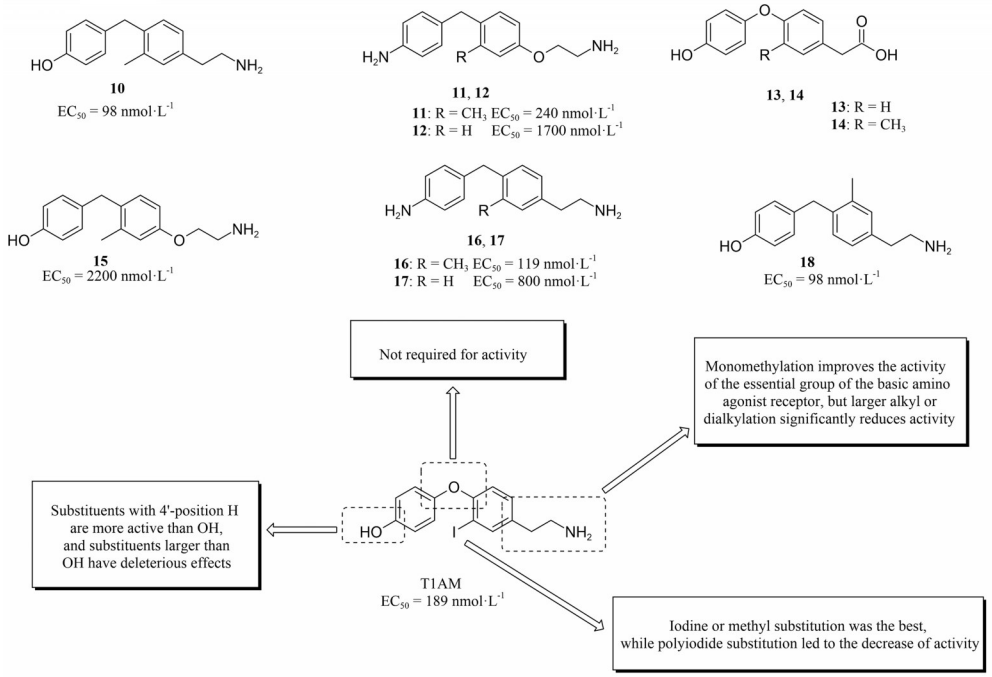


Figure 4 Thyroid amine analogue TAAR1 agonist. T1AM: 3′-Iodothyronamine

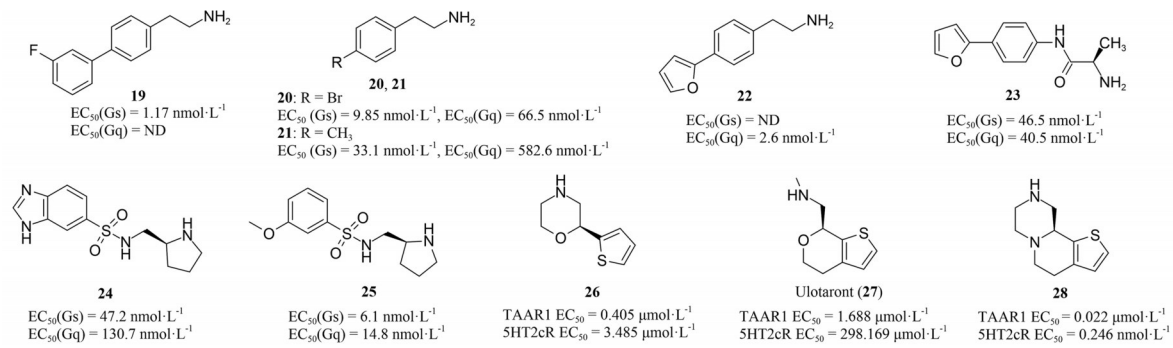


Figure 5 Targeted TAAR1 agonists. ND: Not detected

等[109]在研究中发现化合物**20**药物代谢动力学数据较差 ($T_{1/2}$ = 1.02 h, F = 1.26%), 因此, 该团队以Gq单通路激动剂化合物**22**为先导化合物, 通过结构修饰获得Gs/Gq双通路激动剂化合物**23** (图5, $EC_{50\text{-}Gs}$ = 46.5 nmol·L^{-1}; $EC_{50\text{-}Gq}$ = 40.5 nmol·L^{-1}), 在显著改善大鼠口服PK特性 ($t_{1/2}$ = 2.31 h, F = 39%) 的同时缓解SCZ中的认知障碍, 而不会诱发僵直症。2025年, Zhou等[110]又以化合物**24** ($EC_{50\text{-}Gs}$ = 47.2 nmol·L^{-1}, $EC_{50\text{-}Gq}$ = 130.7 nmol·L^{-1}) 为先导化合物, 以提高化合物对Gs/Gq激动活性及其水溶性为目的进行优化, 筛选出高效候选化合物**25** (图5, $EC_{50\text{-}Gs}$ = 6.1 nmol·L^{-1}, $EC_{50\text{-}Gq}$ = 14.8 nmol·L^{-1}), 该化合物具有良好水溶性 (pH = 7.4, 43.3 mg·mL^{-1})、代谢稳定性及口服生物利用度 (F = 13.45%)。

目前, 设计新型的TAAR1/5-HT双通路激动剂具有同时改善精神分裂症阳性和阴性症状的重要潜力。2023年, Wang等[111]通过计算机模拟筛选出的化合物**26** (图5, TAAR1 EC_{50} = 0.405 μmol·L^{-1}), 优于阳性对照化合物**27** (图5, TAAR1 EC_{50} = 1.688 μmol·L^{-1}); 重要的是, 对比传统治疗药物利培酮, 化合物**26** (F = 84.3%, $t_{1/2}$ = 161 min) 可弱激活5-HT$_1$AR/5-HT$_2$AR, 显著抑制小鼠精神分裂症样行为的同时无锥体外系症状。2025年, Lu等[112]基于TAAR1与5-HT$_{2C}$受体结合口袋的关键残基高度保守及二者激动剂的结构相似性设计出首个TAAR1/5-HT$_{2C}$R双激动剂**28** (TAAR1 EC_{50} = 0.022 μmol·L^{-1}; 5-HT$_{2C}$R EC_{50} = 0.246 nmol·L^{-1})。综上所述, 新型的TAAR1/5-HTR双通路激动剂为强效、安全的, 可作为精神分裂症治疗候选化合物。

3.4 其他TAAR1激动剂

2009年, Hu等[113]通过筛选咪唑啉类配体以寻找强

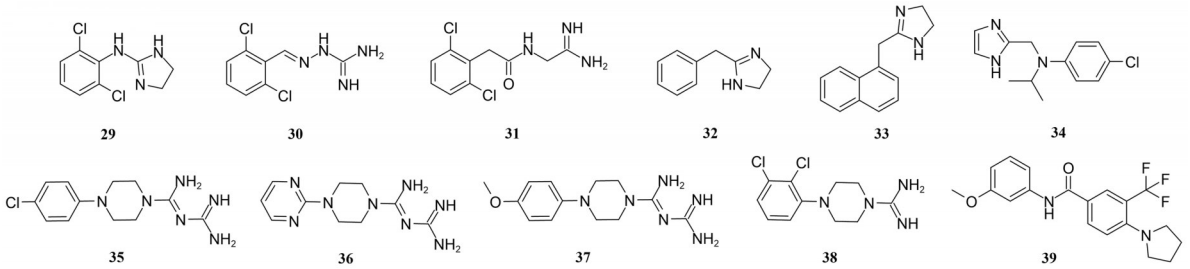


Figure 6 Structures of compounds **29**–**39**

效TAAR1激动剂, 最终发现高效候选化合物**29** (图6, cTAAR1 EC_{50} = 25 nmol·L^{-1}; TAAR1 $EC_{50\text{-mouse}}$ = 7 nmol·L^{-1})和化合物**30** (图6, cTAAR1 EC_{50} = 31 nmol·L^{-1}; $EC_{50\text{-mouse}}$ = 76 nmol·L^{-1}), 其中化合物**29**比较内源性配体PEA (cTAAR1 EC_{50} = 56 nmol·L^{-1}; $EC_{50\text{-mouse}}$ = 108 nmol·L^{-1})对小鼠TAAR1的活性提升约11倍, 且具有TAAR1特异性, 同时揭示人/小鼠TAAR1的显著物种差异, 为咪唑啉类TAAR1激动剂开发及物种差异研究提供关键依据。但在2012年, Galley等[114]研究发现咪唑啉类虽对TAAR1有一定激动活性, 但对α_2受体的活性普遍更强, 因此为提高对TAAR1的选择性将咪唑啉母核改为咪唑及*N*-丙基取代, 筛选出高效选择化合物**34** (图6, $EC_{50\text{-mouse}}$ = 23 nmol·L^{-1}, $EC_{50\text{-rat}}$ = 25 nmol·L^{-1}), 且具有良好口服生物利用度 (F_{mouse} = 86%, F_{rat} = 66%)。

2018年, Guariento等[115]通过cAMP-BRET活性测试发现2个mTAAR1选择性激动剂化合物**35** (图6, EC_{50} = 2.66 μmol·L^{-1})和化合物**36** (图6, EC_{50} = 9 μmol·L^{-1})以及1个hTAAR1选择性激动剂化合物**37** (图6, EC_{50} = 11.4 μmol·L^{-1}), 结合分子对接验证, 开发了首个双胍类物种选择性TAAR1激动剂, 揭示双胍类激动剂在mTAAR1与hTAAR1中的差异化结合模式。2020年, Francesconi等[116]通过母核精简策略解决双胍类激动剂在hTAAR1活性不足的问题, 其中化合物**38** (图6)表现最优 (hTAAR1 EC_{50} = 20 nmol·L^{-1})。

最早对于TAAR1激动剂的研究主要以内源性化合物为研究对象进行设计, 通常包含一个胺基结构, 这与TAAR1的内源性配体痕量胺的结构的特征相符。目前TAAR1中的配体偏倚为探索新的信号通路开辟了新的机会, 在信号传导机制 (Gq, Gs/Gq) 的重要性已经显现出来, 其对精神分裂症样模型小鼠具有潜在的治疗作用。同时TAAR1的PARP明显小于其他识别EAH的GPCR的PARP, 特别是Ile103、Pro183和Tyr287构成了配体口袋葫芦形状的"瓶颈", 这种特定的疏水性堆积可能会限制PARP的大小, 成为TAAR而非其他GPCR识别痕量胺的决定因素之一[107], 因此目前设计的TAAR1激动剂均属于低分子质量化合物 (< 400 kD)。

目前TAAR1激动剂仍存在选择性不足、代谢稳定性欠佳和个体差异大等不足, 需进一步优化结构以平衡活性、选择性与成药性。与TAAR1激动剂不同, 仅存在一种选择性高亲和力TAAR1拮抗剂EPPTB (图6, 化合物**39**), 可增加D2受体的激动剂效力, 同时降低D2脱敏率[117], 然而在治疗各类疾病方面的潜力尚未进行系统探索, 需在未来对其进行系统探索。

4 展望与挑战

TAAR1作为一类广泛分布于中枢及外周组织的G蛋白偶联受体, 在精神疾病、代谢综合征及免疫调节等多个疾病领域展现出巨大的治疗潜力。TAAR1激动剂通过调节单胺能系统、谷氨酸能系统及下游信号通路, 在精神分裂症、抑郁症、药物成瘾等神经精神疾病中表现出显著疗效, 并在代谢调控和免疫调节中发挥多重作用, 展现出作为多疾病干预靶点的广阔前景。然而, 尽管TAAR1激动剂在临床前研究中表现优异, 其临床转化仍面临诸多挑战。例如, 药物的物种差异性显著, 信号通路复杂且需精准调控, 生物利用度和药代动力学特性有待进一步提升, 长期用药的安全性及潜在不良反应仍需系统评估。

随着结构生物学和药物筛选技术的飞速发展, TAAR1激动剂的研发已从单一靶点筛选转向多通路/多靶点协同调控策略。特别是通过解析TAAR1与G蛋白的复合物结构, 揭示了其双结合口袋 (PARP与SBP)的构效关系与信号偏好机制, 为理性药物设计提供了关键结构基础。通过骨架修饰、官能团引入和分子优化, 进一步提高化合物的选择性、稳定性和脑渗透性, 有望推动TAAR1激动剂从临床前研究走向临床应用, 最终为精神系统疾病、代谢性疾病及免疫相关疾病患者带来新的治疗希望。

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