•专题报道Ⅰ•

整合药物化学——药物发现中的新范式

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摘要: 新药研发是一项高投资、长周期、高风险的技术密集型产业。近年来, 随着组学技术、生物信息学、高通量与高内涵筛选、人工智能等现代学科的迅速发展, 小分子新药研发呈现出以“整合药物化学”为特征的药物发现新范式。本文总结并探讨了药物化学领域的交叉融合与整合创新。

关键词: 新药模式; 化学工具箱; 药物设计; 药物化学; 智能设计; 后期功能化

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Integrated medicinal chemistry: new modalities and methodologies in drug discovery

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Abstract: New drug research and development is a technology-intensive industry with high investment, high cycle and high risk. In recent years, with the rapid development of modern disciplines such as omics technology, bioinformatics, high-throughput and high-content screening, and artificial intelligence, the research and development of small-molecule drugs has presented a new paradigm characterized by "integrated medicinal chemistry". This review summarizes new enabling drug discovery technologies, the emergence of new subfields formed through integration innovations and practical chemistry toolbox in the field of medicinal chemistry.

Key words: new drug modality; chemistry toolbox; drug design; medicinal chemistry; smart design; late-stage functionalization

众所周知, 新药研发是一项高投资、长周期、高风险的技术密集型产业。在传统的药物研发范式中, 分子设计、合成和筛选各个环节的效率相对低下, 导致长期以来模拟创新成为我国重大新药创制中发现作用机制明确、结构新颖的先导化合物或候选药物的重要策略[1]。

近年来, 随着组学技术、生物信息学、分子生物学、人工智能等现代学科的迅速发展, 涌现出一些新的药物研发新策略与新技术, 基于靶标的合理药物设计、基于片段的药物设计、高通量虚拟筛选、高通量与高内涵筛选、动态组合化学、DNA编码库、定向进化等技术[2-9]。

“致广大而尽精微”, 这句话可以用来概括药物化学两方面的新进展。“致广大”方面, 现代有机合成化学的发展极大丰富了药物化学及化学生物学的“化学工具箱”, DNA编码库、高通量合成 (high-throughput synthesis)、超高通量虚拟筛选 (ultralarge virtual screening)、高通量蛋白结晶学 (high-throughput protein crystallography)、微量合成等技术可以快速实现数以亿计的化合物的合成与筛选[10,11]; “尽精微”方面, 随着“精

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准医疗”计划的启动, 当代药物设计也随之进入“精准”靶向药物分子设计时代[12]。基于靶标的合理药物设计及药物智能递送系统是精准药物设计的重要方面。靶标–配体精准相互作用为合理药物设计奠定了理论基础, 例如在药物设计中, 替换水分子、与水分子形成相互作用, 也成为化合物结构优化的有效方法[13]。

同时, 小分子新药研发呈现出以“整合药物化学”为特征的药物发现新范式[14]。例如, 在抗新冠病毒药物研发中, 药物化学、有机合成、计算化学、病毒学、分子生物学、结构生物学等学科的交叉与技术融通表现得淋漓尽致[15-17]: 基于晶体学的片段筛选 (crystallographic fragment screening)、高通量蛋白结晶学、共价结合药物、以核酸为靶标的药物设计、核酸降解 (ribonuclease targeting chimeras)、核酸适体、DNA 编码库、高通量合成、超高通量虚拟筛选、自由能微扰 (free-energy perturbation) 等技术的新应用方兴未艾; 表型筛选、老药新用等药物发现传统方法、变构结合与双靶标等药物优化经典策略以及生物无机化学、超分子化学等基础学科更是常用常新, 焕发出勃勃生机。

下文基于几种代表性技术, 总结了药物化学中新策略与新技术的交叉融通, 并对药物化学中新的分支领域进行了分析 (图 1)。

1 整合药物化学: 药物化学新策略与新技术的交叉融通

1.1 蛋白降解 蛋白质水解靶向嵌合体 (proteolysis-targeting chimeras, PROTACs) 通过劫持内源性泛素–蛋白酶体系统来降解致病蛋白, 它已经成为化学生物学和药物发现中的一项变革性的技术, 广泛应用于抗肿瘤及其他疾病药物研发[18]。PROTAC 的优势包括: 事件驱动的活性、靶向不可成药蛋白、克服传统耐药等; 劣势包括透膜性、脱靶毒性等。最近也涌现出许多 PROTAC 技术的新概念: 共价结合型 PROTAC[19]、光控型 PROTAC[20-27]、多靶点型 PROTAC[28,29]、多价态结合型 PROTAC[30]、基于核酸适配的 PROTAC[31]、抗体偶联型 PROTAC[32-34]、自组装型 PROTAC[35]、半导体聚合物纳米型 PROTAC[36]、肿瘤微环境响应型聚合物化 PROTAC[37]等。此外, 点击化学[38]、微量合成[39,40]、高通量合成[41]等技术也应用于 PROTAC。同时 PROTAC 技术也应用于 G-四联体[42]、用于降解 RNA 结合蛋白或直接降解 RNA[43,44]。在抗病毒药物研发领域, PROTAC 也备受青睐[45,46]。继 PROTAC 降解致癌蛋白之后, 稳定抑癌蛋白的去泛素化酶靶向嵌合体 (deubiquitinase-targeting chimera, DUBTAC) 技术取得新进展[47,48]。DUBTAC 由靶标蛋白配体和去泛素化酶组成, 能够同时结合去泛素化酶以及靶蛋白, 通过抑制靶蛋白的多聚泛素化过程阻止靶蛋白被降解, 从而达到稳定靶蛋白的目的。

1.2 动态组合化学 动态组合化学是组合化学中的新方法, 它集合成与筛选为一体, 在动态组合化合物库中, 利用目标蛋白对反应性小分子片段的识别及诱导结合驱动作用, 进行配体组装, 选择性地获得与靶标蛋白存在强相互作用的优势分子, 在药物先导发现领域

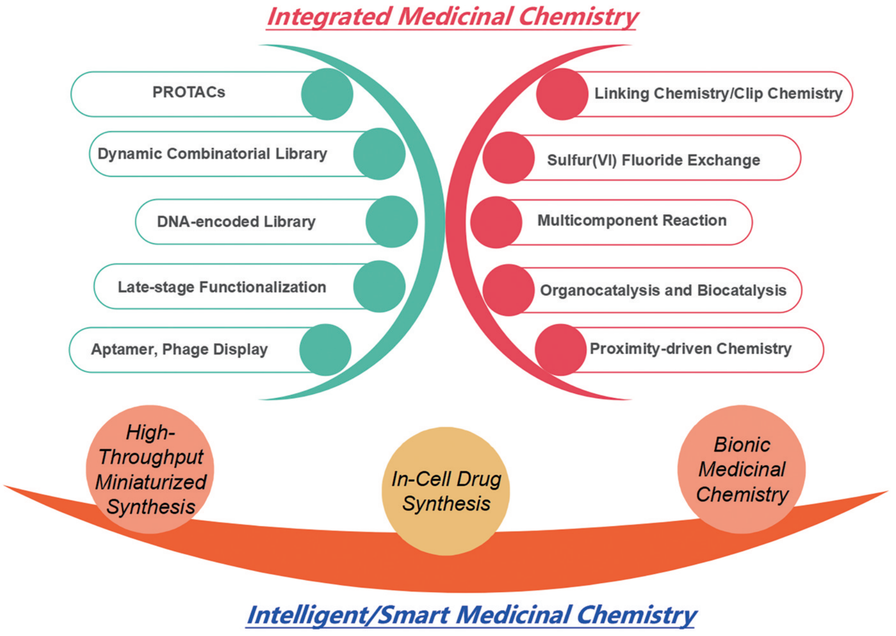

Figure 1 Overview of new enabling drug discovery technologies, the emergence of new subfields *via* integration innovations and practical chemistry toolbox in medicinal chemistry

具有广泛的应用前景[49-51]。在化学反应类型上, 动态组合化学除了最常使用的点击化学, 酰化反应[52]、多组分反应[53]也被普遍应用; 在技术融合方面, 计算机辅助药物设计也成功应用于动态组合化学[54]; 在应用场景方面, 动态组合化学目前已拓展到G-四连体配体的发现[55]、大分子肝素解毒剂的动态组合优化[56]及酶生成的适配体 (enzyme-generated aptamers, EGAs) 的蛋白质模板合成等[57]。动态组合化学能够靶向性地为生物大分子设计、合成和筛选其特异性配体, 极大地简化了药物的合成与筛选工作; 然而, 在应用动态组合化学方法时存在可逆共价反应或动态组合化学库筛选问题。

1.3 DNA编码库 DNA编码库 (DNA-encoded library, DEL) 是近二十几年出现的一种用于发现先导化合物的新技术。DNA编码化学库中的小分子以共价键方式与DNA标签偶联, 赋予其独特的DNA分子编码。该技术可以构建规模非常庞大的组合化合物库, 通过对蛋白质靶标亲和筛选及高通量测序解码, 从而高效、快捷地发现高亲和力配体。它克服了传统化合物库高通量筛选中需要合成成千上万化合物, 且测试与靶蛋白的亲和力工作量巨大的缺点[58]。近期的新进展主要体现在: 除了基于靶标亲和力的筛选, DEL已经应用于表型筛选[59]; 已经发展了在细胞原生环境中针对蛋白质靶标筛选DEL的新技术[60-62]。在化学反应类型上, 多组分反应[63]、点击化学[64]、C-H活化反应[65]等已经用于DEL的构建。此外, 自组装[66]、动态组合化学[67-71]、机器学习等技术[72]也与DEL进行了技术整合。

1.4 药物后期功能化 (后修饰) 后期功能化 (late-stage-functionalization, LSF) 是指在最后的合成阶段进行官能团转化, 是药物发现中一种非常重要的技术[73]。其优点是可以在保持活性药物母核的同时进行结构修改, 使化合物性质发生变化、用这种方法更容易、更高效地发现新药。后期功能化与高通量合成[74]、微量组合合成[75]联合运用, 可大大提高化合物库的多样性与筛选的效率。但是在更广泛的底物范围内进一步提高反应的可靠性并建立方法预测不同基团的反应性和选择性仍有很大需要提高的空间。

1.5 其他技术的整合 共价抑制剂通过共价键与靶蛋白结合并对其产生抑制作用。其在疾病治疗中的优势也逐渐显现, 成为当前药物研发的热点[76]。共价结合已与PROTAC及噬菌体展示技术[77]紧密结合。核酸适配体因其低免疫原性、易于合成和高特异性结合亲和力等显著特性而被广泛用于很有前途的靶向递送技术。多价相互作用与核酸适配体结合, 进一步增强了亲和力[78]。此外, 分子片段组装[79,80]、整合型分子产生策略[81]、双共价结合[82]及配位-共价双结合 (catch and anchor approach)[83]等整合型药物发现思路也见诸报道。

2 药物化学新分支领域

2.1 微量药物化学 现代创新药物研发中, 化合物库的质量直接影响着整个研发的成功与否。因此, 如何快速构建数目庞大、结构多样的高质量化合物库是药物发现中的关键环节。微量合成技术的快速发展, 大大提高了构建高质量化合物库及发现先导化合物的效率, 且显著降低了试剂和溶剂的消耗, 契合绿色化学的理念[84-93]。

微量合成构建化合物库最常用的反应是一价铜离子催化的[3+2]Huisgen环加成点击化学 (copper-catalyzed alkyene-azide cycloaddition reaction, CuAAC)[94,95]。例如, 本团队将基于CuAAC点击化学微量合成的片段组装用于磷酸酶及HIV逆转录酶抑制剂的发现[96-98]; 研究者[99]通过原位点击化学反应合成体系 (*in situ* click chemistry system) 和细菌体外转录/翻译活性测试体系建立了合成/活性测试一体化的新型高通量药物筛选平台, 并据此发现了多个具有抗MRSA生物活性的细菌核糖体小分子抑制剂; 也有研究者将基于CuAAC点击化学微量合成用于GLS1荧光探针的发现、表征及在变构抑制剂高通量筛选中[100]。

与金属催化的生物正交点击反应相比, 无金属点击反应更具有生物相容性, 没有金属催化剂诱导的毒性[101]。鉴于此, Yao课题组[102]将无铜催化点击化学微量合成用于PARP14抑制剂的发现。此外, 酰化反应[103]、Suzuki-Miyaura偶联反应[104]、硒化反应[105]、多组分反应[106]等也成功实现微量化。

微量反应所使用的器材包括96孔微孔板、微阵列 (microarray)[102,107]、液滴微阵列 (droplet-microarray)[108,109]。此外, 微流控技术作为一项革命性的技术, 为微量合成及高通量筛选提供了新的机会[110]。

在技术整合方面, 微量合成与蛋白质晶体学 (protein crystallography, PX)[111]、声液滴喷射 (acoustic droplet ejection)[112,113]、后期功能化[114]等实现了整合创新。

2.2 细胞原位药物化学 药物与生物分子的相互作用必须在生物细胞环境中才有意义, 因此在细胞原位环境中通过生物正交反应获得药物分子, 可以克服传统药物筛选难以兼顾透膜性等理化性质的缺陷; 化疗作为一种应用广泛的癌症治疗方法, 目前仍存在不良反应大、耐药性和继发性转移等问题。鉴于此, 近年来研究者致力于开发在靶细胞部位被激活或合成的药物系统, 可以降低药物毒性。

众所周知, 成药性高的小分子药物分子质量在500 Da以下, 但是PROTAC由于片段的累加, 分子质量

往往高达1 000 Da及以上, 导致多数PROTAC存在细胞膜通透性差的缺陷。鉴于此, Astex制药公司开发了基于小分子前体的胞内降解分子 (in-cell click-formed proteolysis targeting chimera, CLIPTAC)[115]。四嗪标记的沙利度胺衍生物和反式环辛烯标记的CRBN E3配体两种小分子片段先后入胞后, 基于四嗪和反式环辛烯间的加成反应在细胞内形成完整的PROTAC分子。实验结果显示, CLIPTACs能够在HeLa、A375及HCT116等细胞系中成功诱导BRD4与ERK1/2的降解。与传统PROTAC相比, CLIPTAC不仅能明显改善细胞透膜性与溶解度, 且无需优化连接链, 降解不同的目标蛋白只需更换蛋白配体部分即可, 更加灵活便捷。

干扰细胞内蛋白−蛋白相互作用是阐明信号网络和开发新治疗方法的重要途径。然而, 设计具有结合大界面所需的多官能团、高透膜性的分子仍然具有挑战性。Ohkanda课题组[116]为发现能抑制14-3-3介导相互作用的小分子, 根据动态组合化学的理念, 利用羟胺−醛偶联反应在细胞环境中合成了二萜肽偶联物。随后, 其他课题组报道了在红细胞中通过蛋白模板诱导的动态组合化学合成bCAII配体[117]、在细胞中发现耐红霉素金葡菌核糖体配体的例子[118]。2020年, Alfonso课题组[119]报道了将A549活细胞作为动态组合化学的模板, 通过胺与醛的动态缩合反应获得了对细胞外基质的糖胺聚糖具有较强选择性结合的配体。

在靶细胞部位激活或合成药物系统研究方面, 曲晓刚团队[120]设计合成了一类原位合成的双功能药物, 可以实现AD治疗的自触发和自调节。由铜积累的β-淀粉蛋白 (Aβ) 斑块催化CuAAC反应, 激活荧光团并进行分子合成。在活细胞、转基因AD模型秀丽线虫CL2006及三转基因AD小鼠的大脑切片中均有效果。

CuAAC中Cu (I) 的毒性、低效的催化活性及现有催化剂缺乏细胞特异性靶向性, 阻碍了其在生命体系中的实际应用。鉴于此, 曲晓刚团队[121]设计了一种Cu/Zn双金属有机框架材料 (metal organic framework, MOF)。纳米粒子被癌细胞吸收后, 会在溶酶体的酸性微环境中释放铜离子, 这不仅为催化生物正交反应CuAAC提供了基础, 而且保证了生物安全性。此外, 该团队利用生物相容性非均相铜纳米催化剂在近红外 (NIR) 照射下的光动力和光热效应对CuAAC反应进行了双重促进[122], 还开发了一种基于DNA的生物相容性、高效、精确靶向的生物正交纳米催化剂, 并证明了该系统在哺乳动物中的安全性和有效性[123]。

目前临床使用的金属抗癌药靶向性较差、不良反应较大, 且长期使用容易产生耐药性。鉴于此, 研究者受生物学中“合成致死”概念的启发, 提出了“生物正交催化致死” (bio-orthogonally catalyzed lethality) 策略, 即, 根据在肿瘤组织中铜物种的含量远高于正常组织的特点, 这些铜物种可以作为催化剂, 以肿瘤细胞为抗癌药“制造工厂”, 将两种无毒性的药物前体Ru-N3和rhein-alkyne合成为高活性肿瘤靶向药物Ru-rhein, 产率高于80%。实现了对癌细胞及荷瘤小鼠肿瘤的选择性杀伤, 在正常细胞中, 几乎不发生上述反应, 对正常组织无毒副作用[124]。

基于微针透皮贴剂技术, 研究者开发了一种能够实现化疗药增效减毒的生物正交催化贴剂 (bioorthogonal catalytic patch)。该贴剂以聚乙烯醇为基质, 微针中掺杂着二氧化钛纳米片和催化剂钯纳米粒。当生物正交催化贴剂贴在黑色素瘤周围皮肤时, 微针中的钯纳米粒通过钯催化的化学断键反应能够把经血液循环到达肿瘤区域的多柔比星前药原位激活为多柔比星。这种“守株待兔”的策略能实现肿瘤部位的药物分子的富集, 有望降低催化剂和化疗药的毒性[125]。此外, 钯催化的化学断键反应还应用于5-氟尿嘧啶前体药物的设计[126]。Bradley课题组[127]使钯催化剂被脑胶质母细胞瘤细胞特异性摄取, 首次通过钯催化的原位合成及化学断键反应这两种完全不同的机制在细胞内同时合成了两种不同的抗癌药物, 提高了治疗效果。

尽可能减少对正常组织的毒性是实现有效的抗癌光动力治疗的基本要求, 这就需要在体内外实现具有癌细胞特异性甚至癌细胞器特异性的光敏剂合成或递送, 但是目前仍存在一定挑战。在此背景下, 研究者报道了一种由癌细胞激活合成具有聚集诱导发光性能的高效线粒体靶向型光敏剂的策略[128], 即在癌细胞中谷胱甘肽还原产生的Cu (I) 的催化下, 通过点击反应将含有炔及叠氮的惰性前体在体内产生光敏剂。在光照射下, 靶向线粒体的光敏剂发出明亮的红色荧光, 有效地产生$^1O_2$, 用于图像引导的癌细胞杀灭。

当前, 细胞微环境 (酸度、活性氧和酶过表达) 响应型自组装或化学断键前药[129-134]、外源过渡金属离子催化型[135-140]及外部光 (含X-射线) 催化型“化学断键”前药[141-143]是当前细胞原位药物发现的主要形式。

嵌合抗原受体 (chimeric antigen receptor, CAR) T细胞是癌症治疗的重大突破, 其中患者的T细胞被设计成识别肿瘤抗原, 从而激活局部细胞毒性免疫反应。然而, CAR-T细胞治疗目前仅限于B细胞癌, 其有效性受到抗原阴性肿瘤细胞的耐药性、肿瘤微环境中的免疫抑制、最终T细胞免疫功能衰竭和频繁的严重毒性的阻碍。为了克服这些问题, 美国纪念斯隆−凯特琳癌症中心的研究人员开发了一种可以表达特定酶的新型CAR-T细胞。当前体药物被注射到血液中, 进入体内

循环, 由CAR-T细胞产生的酶就如同一把“剪刀”, 在肿瘤部位原位激活 (化学断键) 释放出前体药物的活性部分。这种模块化的平台能够结合靶向细胞和小分子疗法来治疗癌症和其他各种疾病[144]。

2.3　仿生药物化学　仿生递送是基于天然成分创建药物载体, 并借助体内固有路径靶向递送药物。其优势是能够克服体内复杂环境和多重屏障, 并且具有较高的成药性。例如, 应用白蛋白载药体系成功研发出抗艾滋病药物[145]。此外, 溶瘤病毒、微针给药、生物催化等均是人们向自然学习而获得的药物发现技术。最近文献报道了特异性针对癌细胞直接输送蛋白质 (药物) 的细菌 (沙门氏菌) 递送系统[146]、用于mRNA的细胞质传递的病毒模拟细胞膜包覆纳米颗粒[147]、病毒衣壳作为药物传递的新型纳米材料[148]、通过表面聚糖修饰发挥抗SARS-CoV-2作用的细胞纳米海绵[149]等。随着对生物体系的深度认识, 越来越多的“仿生学”理念被应用于小分子药物的递送或结构优化, 称之为“仿生药物化学”。

最近, 北京大学与南方医科大学团队合作研究根据多种白血病细胞具有特异性高表达CD71的广谱特点, 提出利用CD71配体铁蛋白颗粒 (Fn) 作为药物载体, 解决了Fn高效装载白血病治疗药物三氧化二砷的难题并实现了靶向递送, 显著抑制了多种白血病的发展[150]。此外, “木马”前药策略 (trojan horse prodrugs) 在抗病毒[151]及抗菌小分子药物[152-156]的修饰中受到人们的青睐。

内源性抗体是人类体内天然产生的抗体, 如抗2,4-二硝基苯 (2,4-dinitrophenyl, DNP) 和抗鼠李糖 (rhamnose, Rha) 抗体, 占人体血清蛋白含量的3%～8%。研究者运用小分子抗体募集策略 (antibody-recruiting small molecule, ARM) 利用人体中天然存在的内源性抗体DNP增强抗原呈递和介导免疫系统杀伤靶细胞的能力, 发现了基于内源性半抗原修饰的新型抗HIV[157]及抗流感化合物[158,159]。

近期, 研究者根据细胞膜的组成 (富含磷酯、胆固醇), 分别设计了抗HIV活性及药代动力学性质显著优化的替诺福韦脂质前药[160]、具有长效及抗耐药流感毒株活性的扎那米韦-胆固醇缀合物[161]。

最后, 不得不提的是, 早在2010年, 研究者利用细胞内的乙酰化过程, 设计合成了具有再循环再生机制的*S*-酰基-2-巯基苯甲酰胺硫酯类HIV-1核衣壳蛋白NCp7抑制剂[162]。该类分子具有化学计量学的优势 (substoichiometric inhibition), 与PROTAC及蛋白组装调控剂[163,164]具有类似性, 小分子均可以针对靶蛋白, 发挥“以一敌百”的功效。

3　药物化学中的“化学”——新“化学工具箱”浅析

毋庸置疑, 有机合成化学是药物化学的“基石”[165]。传统有机化学反应一直在药物化学中具有不可替代的作用, 且常用常新。近年来, 新链接化学、氟硫交换点击化学、多组分反应、化学断键反应、生物催化、有机催化、光控基团、细胞器定位基团、邻位诱导效应等普遍应用于当代药物发现及优化中。

3.1　新型链接化学　链接化学 (linking chemistry) 已成为药物化学中产生高效候选药物的有力工具。例如, 基于片段的药物发现提供了通过连接片段快速产生先导化合物的机会, 其成功实施依然需要借助于方便和高效的链接化学。

近期, Tang课题组[166]将酰肼-醛链接化学用于PROTAC分子的构建, 发现了雌激素受体降解剂。

硼酸介导的顺式二醇偶联 (dynamic covalent boronic ester) 是近年来应用最多的链接反应之一[167]。Giardina等[168]将44种硼酸和88种二醇衍生物通过该反应构建了含3 872种分子的组合库, 从中发现了几种对人*β*胰蛋白酶具有纳摩尔级抑制活性的分子, 活性比片段提高了100倍以上, 彰显了组合化学与链接化学联合应用的威力。该类反应也成功用于动态共价网络中, 研究分子行为与宏观性质的联系[169]。此外, 无铜催化的生物正交反应, 在药物发现及化学生物学领域均有广泛的应用。例如, Carlson课题组[170]利用逆电子需求Diels-Alder环加成反应开发了一种具有时空分辨率的新型活细胞荧光成像技术。

3.2　硫氟交换点击化学　硫 (VI) 氟交换反应 [sulfur (VI) fluoride exchange, SuFEx] 是一个新的点击化学类型[171,172], 在化学生物学领域有广泛应用[173-175], 也为选择性、快速和模块化合成功能分子开辟了一条途径。目前已应用于药物后期功能化[176,177]、高通量合成[178,179]、“反向药物发现” (inverse drug discovery)[180,181]、蛋白质共价药物[182,183]等。近期, SuFEx还演化出新的点击化学类型——硫三唑交换反应 (sulfur-triazole exchange, SuTEx)[184,185]。

3.3　多组分反应　多组分反应 (multicomponent reactions, MCRs) 由于具有简便、经济、一步反应便能得到结构复杂多样的化合物等优点, 广泛用于大规模优化和筛选活性分子, 在动态组合化学[53]、DNA编码库[63]、微量合成[106]等技术中有成功应用。此外, 多组分反应还应用于硼酸类[186]、订书肽类化合物库[187]的构建, 并实现了与共价结合[188]、多价态结合思路[189]的整合创新。

3.4　有机催化与生物催化　自本世纪初, 不对称有机催化已经逐渐成为不对称催化领域中一个新的、最具活力的领域[190]。德国科学家本杰明•李斯特 (Benjamin List) 教授与美国科学家大卫•麦克米伦 (David MacMillan) 教授因在“不对称有机催化”上的突破性贡献, 获得2021年诺贝尔化学奖, 可以预计, 该类反应在今后会继续受到药物化学研究者的青睐。

在生物催化领域, 细胞色素P450能催化一系列C-H功能化反应, 例如C-H氨化反应[191], 可用于快速构建和后期修饰功能分子, 大大扩展优势结构的化学空间[192]。酶法药物合成方面, 近期, 不同课题组分别采用工程化胞苷脱氨酶[193]、工程化核糖体-1激酶[194]来生产抗SARS-CoV-2药物Molnupiravir及其关键中间体。

3.5 其他模块化反应 偶氮、硝基苯等光药物化学基本模块已经成功用于光控PROTAC[20-27]及化学生物学、智能前药的设计中。线粒体在调节癌细胞凋亡、代谢中发挥了重要作用, 因此线粒体靶向治疗策略在癌症治疗中具有广阔前途, 三苯基磷是典型的线粒体靶向基团[195,196]。利用化学断键反应 (又名生物正交断键反应、剪切反应、clip reactions) 研究生命科学 (在体蛋白质激活和调控工具) 及药物设计 (智能前药、细胞原位药物化学) 受到越来越多的关注[197]。

3.6 邻近驱动化学 酶的邻近效应为人们所熟知, 即在酶促反应中, 由于酶和底物分子之间的亲和性, 底物分子能向酶的活性中心靠近, 使得底物分子与酶活性中心的距离更近, 其有效浓度大大增加, 进而促进酶促反应的发生。与天然的酶邻近效应相似, 邻近驱动化学 (proximity-driven/directed chemistry) 基于配体-受体的相互作用, 或者其他化学生物学方法拉近生物正交反应基团 (或共价弹头) 的距离, 通过共价交联反应, 实现小分子合成或蛋白质共价标记[198-200]。邻近驱动化学是PROTAC、动态组合化学、细胞原位合成、反向药物发现及蛋白质共价药物的理论基础。形成了诱导接近药理学 (induced proximity pharmacology) 这一新的研究范式。

4 总结与展望

药物化学的重要环节是发现新分子结构, 要求药物化学研究者革新传统的“靶标-设计-合成-评价”的模式[201], 关注靶标及疾病的基础研究及药物化学新策略与新技术, 通过整合创新促进首创型新药创制; 例如相分离现象[202-204]、纳米酶[205,206]等新范式、新技术在抗病毒药物研发等领域中展示出广阔的应用前景。

同时, 药物研发要面向临床需求, 基于经典策略, 通过交叉融通解决新问题, 进行问题导向式研究与成果转化。例如, 核酸适体这一成熟技术仍在抗HIV及SARS-CoV-2药物领域普遍的应用[207-213], 定量构效关系 (quantitative structure-activity relationships, QSARs) 在RNA靶向药物中也有新应用[214]等, 这归因于问题与需求层出不穷, 经典方法与技术依旧历久弥新, 同时与时俱进、不断扬弃, 例如经典的类药5原则对以PROTAC为代表的双特异性分子不再适用, 高品质化合物库从强调结构多样性到体现立体性特征等[215]。

人工智能在新药研发领域中发挥着日益重要的作用。目前, 机器学习、深度学习、知识图谱等人工智能关键技术已广泛应用于蛋白结构预测、药物靶标预测、药物-靶标相互作用预测、药物合成路线设计、天然产物发掘、从头药物分子设计及药物ADMET预测等新药研发的各个环节[216-219]。可以预见, 以流动化学、微量合成为特征的自动合成技术 (automated synthesis) 与人工智能的深度融合[220-223], 将迎来智能药物化学 (intelligent medicinal chemistry) 新时代。

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