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Recent updates in click and computational chemistry for drug discovery and development

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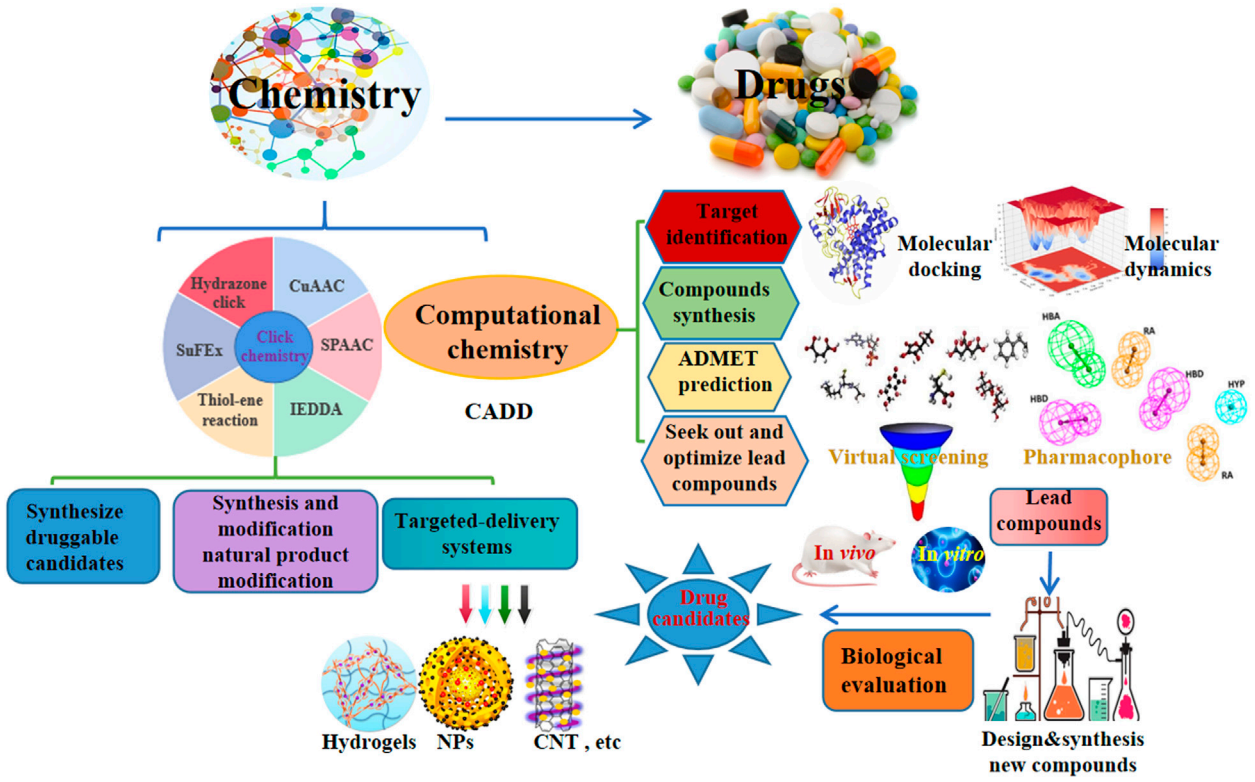
Drug discovery is a costly and time-consuming process with a very high failure rate. Recently, click chemistry and computer-aided drug design (CADD) represent popular areas for new drug development. Herein, we summarized the recent updates in click and computational chemistry for drug discovery and development including clicking to effectively synthesize druggable candidates, synthesis and modification of natural products, targeted delivery systems, and computer-aided drug discovery for target identification, seeking out and optimizing lead compounds, ADMET prediction as well as compounds synthesis, hopefully, inspires new ideas for novel drug development in the future.

KEYWORDS

click chemistry, computational chemistry, CADD, druggable candidates, drug development

Introduction

Click chemistry, an efficient chemo-selective synthesis method for coupling molecular fragments under mild reaction conditions, mainly includes Cu-catalyzed azide-alkyne cycloaddition reaction (CuAAC), strain-promoted azide-alkyne cycloaddition reaction (SPAAC), thiol-ene reaction, inverse electron demand Diels–Alder reaction (IEDDA), hydrazone click chemistry and the newly emerging sulfur fluoride exchange (SuFEx) reaction, has been a hot research topic in the field of chemistry since it was first reported in 2001 (Zhang et al., 2021a; Ashe, 2022). Computer-aided drug design (CADD) has attracted a lot of attention for its potential to accelerate and reduce the cost of the drug development process (Wu et al., 2020). In addition, natural products provide a variety of lead compounds and novel drugs, are worthy of further development. Furthermore, early and late-stage development of new drugs may be slowed down by problems such as poor target selectivity or side effects, toxicity, resistance, inappropriate physicochemical and pharmacokinetic properties. Therefore, we summarized the recent applications of click and computational chemistry in drug development such as click to effectively synthesize druggable candidates, synthesis and modification of natural products, targeted delivery systems including hydrogels, nanoparticles (NPs), carbon nanotubes (CNT), etc, and computer-aided drug discovery including molecular docking and molecular dynamics to identify target, virtual screening (VS.) and pharmacophore to found and optimize lead compounds, ADMET prediction as well as compounds synthesis, which are making a splash in new drug development, hopefully, providing new insights for the discovery of new drug from click and computational chemistry.



GRAPHICAL ABSTRACT

Click chemistry

Click to efficiently synthesize druggable candidates

The transformation of the active compound skeleton is a magic weapon for researchers to break through patent restrictions and improve the activity of compounds in the development of new drugs. Copper-catalyzed 1,3-dipolar cycloaddition (CuAAC) to form 1,2,3-triazoles is the most popular reaction in click chemistry. Recently, 1,2,3-triazole backbones with hydrogen bonds, moderate dipole moments and enhanced water solubility had been widely used to generate drug candidates of anti-tumor (Brown et al., 2022; Elganzory et al., 2022; Mohammed et al., 2022; Oekchuae et al., 2022; Oliveira et al., 2022; Mironov et al., 2023), anti-seizure (Bhattacherjee et al., 2022), anti-diabetic (Dhameja et al., 2022), anti-parasitic (Aljohani et al., 2022), anti-bacterial (Daher et al., 2022; Mokariya et al., 2022; Nsira et al., 2022) and anti-viral (Kutkat et al., 2022; Tatarinov et al., 2022) *via* CuAAC click chemistry (Figure 1A).

Synthesis and modification of natural products

Natural products have provide abundant resources for drug discovery. Recently, click chemistry had been adopted for synthesis and modification of natural products, for instances, SPAAC was used to modularly generate Bcl-xL inhibitor (Brauer et al., 2022), adjust PEG chain length and targeting moiety to further improve half-life as well as targeting IL-4 to arthritic joint (Figure 1B) (Spieler et al., 2020). It was reported that poly (globalide-co-ε-caprolactone) could be functionalized with N-acetylcysteine side chains *via* thiol-ene reaction (Guindani et al., 2019). Furthermore, IEDDA could be used to introduce aromatic heterocycles (Figure 1C) (Xu et al., 2020) and triazines (Zhang et al., 2021b). Similarly, the synthetic efficiency of biosynthesis of anti-fungal drug candidate Ilicicolin H increased 3×10^5 times *via* IEDDA (Figure 1D) (Zhang et al., 2019). Moreover, 5-fluorouracil-coumarin conjugation (Figure 1E) as anti-cancer drug candidate (ópez et al., 2022) and pH responsive doxorubicin delivery polymers nano-particles (Wallat et al., 2018) for treatment of breast and ovarian cancer were generated by modification of natural products *via* CuAAC. In addition, quercetin-gold quantum dots for adenocarcinoma treatment (Pansare et al., 2022) and chondroitin sulfate-multiarmed PEG hydrogels for skin tissue engineering (Sousa et al., 2022) had been developed by modification of natural products (Figure 1F).

Targeted delivery systems

Existing drugs may have dis-advantages such as low selectivity, long synthetic routes, poor stability and side effects, thence the development of targeted delivery systems make great sense. Recently click-generated hydrogels had broad applications in the fields of anti-tumor (Ali et al., 2022; Bonardd et al., 2022), wound repair (Basurto et al., 2022) and long term regeneration therapy (Jang et al., 2021) *via* IEDDA, CuAAC,thiol-ene reaction, and SuFEx, respectively. Biomimetic stiffening of cell-laden hydrogels *via* sequential thiol-ene and hydrazone click reactions (Chang et al.,

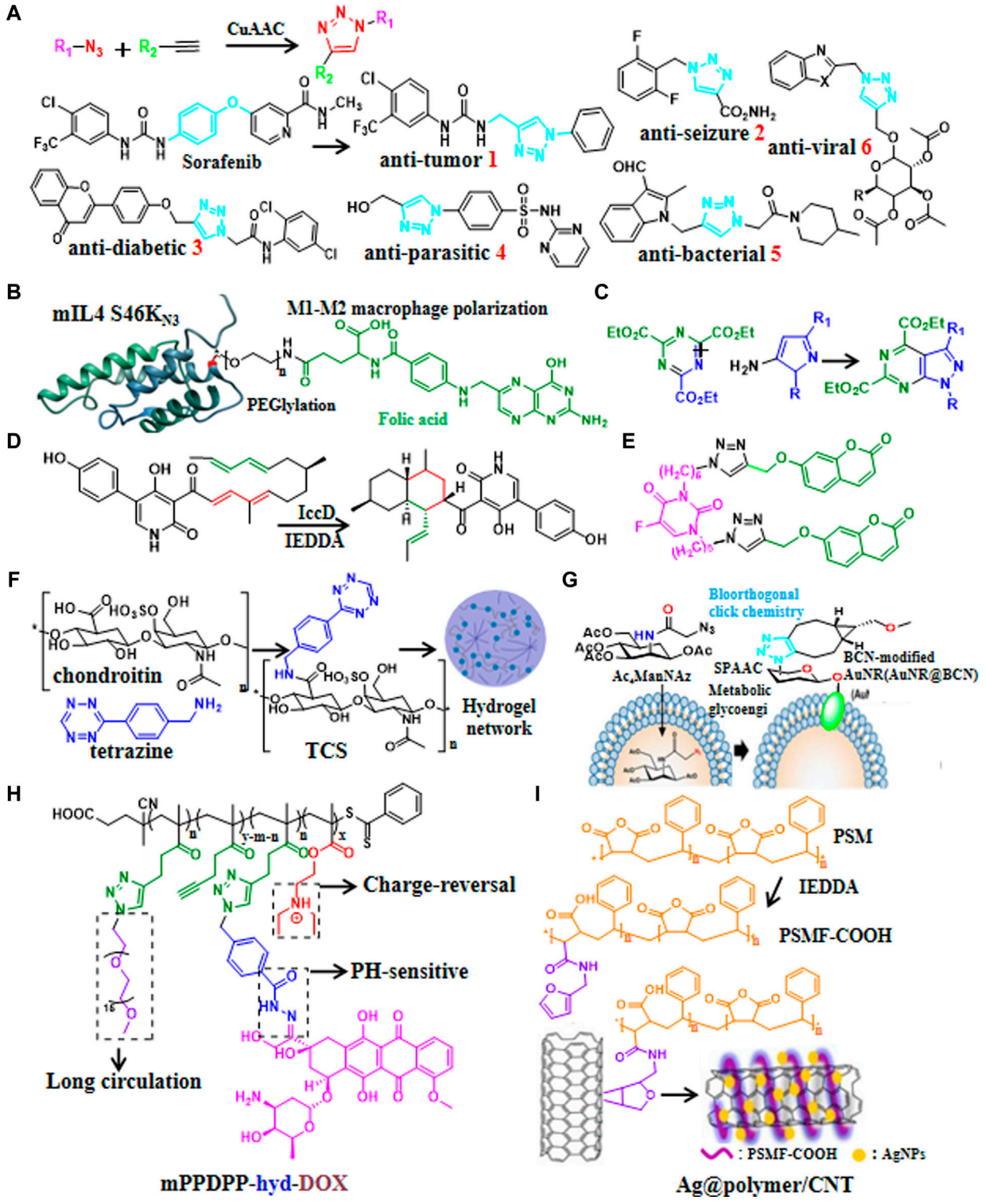


FIGURE 1
Recent updates in click chemistry for drug discovery and development. **(A)** Reaction formula of CuAAC and some recent applications of CuAAC for developing drug candidates containing 1,2,3-triazoles ring. **(B)** An example of natural product modification to improve half-life and target IL-4 to arthritic joint via SPAAC. **(C)** An example of introduction aromatic heterocycles via IEDDA. **(D)** An example of efficient synthesis of natural products via IEDDA. **(E)** An example of the generation of anti-cancer drug candidate by modification of the natural product coumarin via CuAAC. **(F)** Catalyst-free click chemistry to generate chondroitin sulfate-multiarmed PEG hydrogels for skin tissue engineering. **(G)** An example of the generation of MSCs-mediated deep tumor delivery of gold nanorod for anti-tumor therapy via SPAAC. **(H)** An example of polymer nanomicelle platform for cancer treatment via CuAAC. **(I)** An example of the generation of silver nanoparticle-supported polymer-encapsulated carbon nanotubes (CNTs) via IEDDA for nonenzymatic glucose sensing and antimicrobial activity applications.

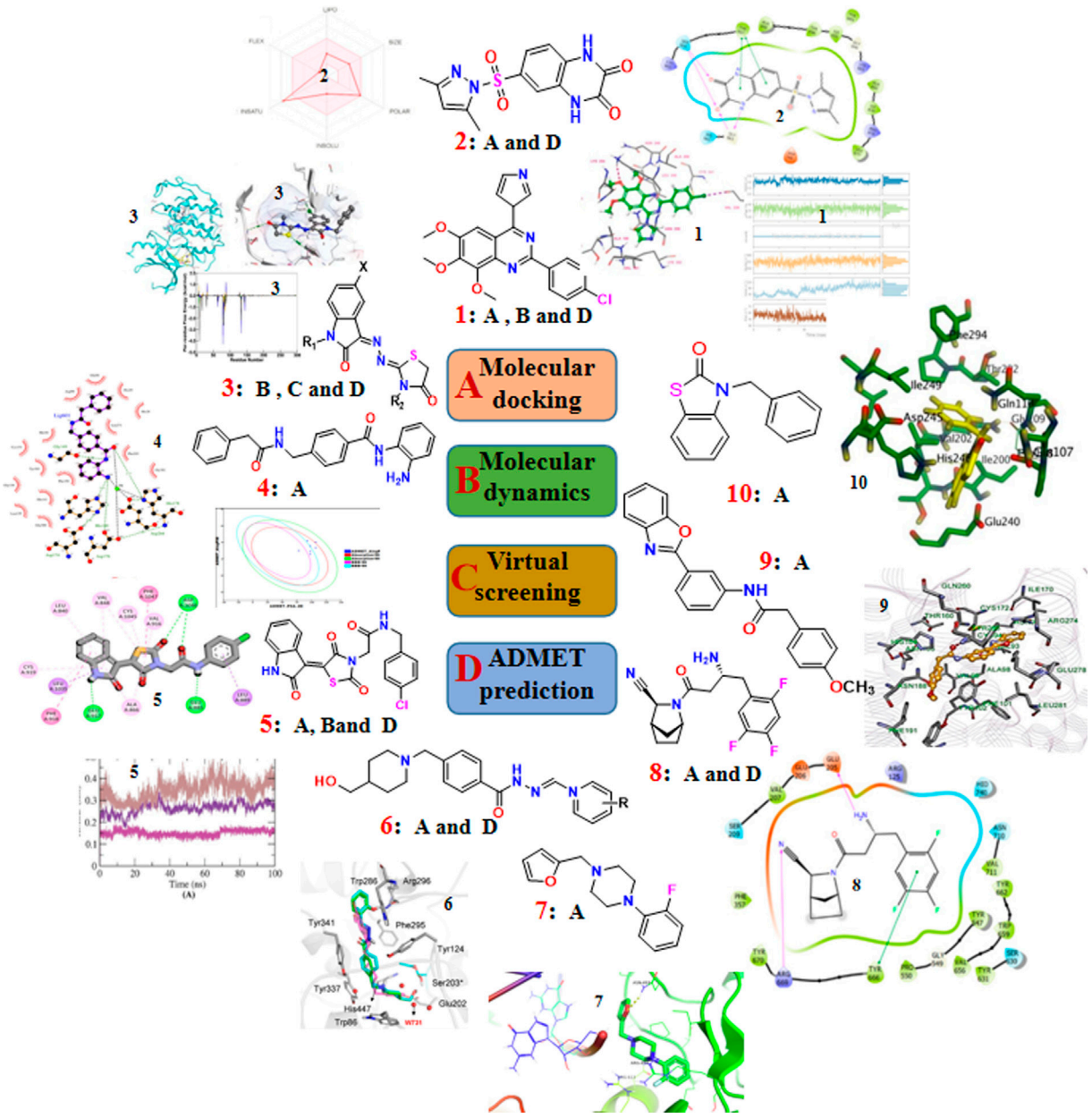


FIGURE 2
The recent updates of computational chemistry in target identification, lead compound discovery and ADMET prediction for drug development.

2021). Furthermore, nanoscale covalent organic frameworks (COFs) (Guan et al., 2022), Nisin-shelled nanoemulsion (Hashad et al., 2022), and MSCs-mediated deep tumor delivery of gold nanorod (Figure 1G) (Yun et al., 2022) had been synthesized for anti-tumor therapy *via* thiol-ene reactions, SPAAC, and SPAAC, respectively. Moreover, pH-sensitive polysaccharide-gold nanorod conjugate (Hou et al., 2019) and polymer nanomicelle platform (Figure 1H) (Liao et al., 2021) were reported to treat cancers *via* hydrazone click reaction and CuAAC, respectively. In addition, silver nanoparticle-supported polymer-wrapped carbon nanotubes (CNT) (Cao et al., 2022) for non-enzymatic glucose sensing and antimicrobial applications (Figure 1I), COF-based nanoreactors for click-activated pro-drug delivery and precise anti-vascular therapy (Wang et al., 2022) had been synthesized *via* IEDDA, these click chemistry-based targeting strategies may find widespread application in drug delivery in the future.

Computational chemistry in drug discovery

To effectively and efficiently design and develop new drugs, computational methods had been applied for drug design including target identification, seeking out and optimizing lead compounds prediction of pharmacokinetic and toxicological properties as well as compound synthesis by molecular docking and molecular dynamics, virtual screening, pharmacophore and ADMET prediction. Novel quinazoline derivative **1** as tubulin

polymerization inhibitor (Dwivedi et al., 2022), PARP-1 inhibitor **2** (Syam et al., 2022), CDK2 inhibitor **3** (Qayed et al., 2022), HDAC-1-3 inhibitor **4** (Cheshmazar et al., 2022), VEGFR-2 inhibitor **5** (Taghour et al., 2022) were identified for cancer therapies. Furthermore, AChE inhibitor **6** (Macedo Vaz et al., 2022) for treatment of Alzheimer's disease and Mtb RNAP inhibitor **7** (Mekonnen Sanka et al., 2022) for antitubercular and antimicrobial treatment were deserve further study. Moreover, a lead compound **8** of DDP4 inhibitor (Maslov et al., 2022) and acetamide derivative **9** (Zhou et al., 2022) as P2Y14R antagonist were considered as drug candidates for treating type 2 diabetes and gout, respectively. Additionally, potential SARS-CoV-2 main protease inhibitor **10** (Dong et al., 2023) and carbazole alkaloids from Murraya koenigii (Wadanambi et al., 2023) were identified as a promising drug candidates for inhibiting coronavirus infection. Surprisingly, it had been reported a computationally guided asymmetric total synthesis of resveratrol dimers, which possessed a wide range of biological activities such as antioxidant, anti-tumor and cardiovascular activities (Nakajima et al., 2022), suggesting that computationally guided organic synthesis may be a powerful strategy to advance the chemistry of natural products (Figure 2).

Conclusion and prospects

In the review, we summarized recent updates in click chemistry for drug discovery and development, including chemical click synthesis of druggable candidates, synthesis and modification of natural products, targeted delivery systems. In addition, we introduced updated computational chemistry in drug discovery for target identification, discovery and optimization of lead compounds, compounds synthesis and prediction of pharmacokinetic and toxicological properties. Click chemistry is a very powerful tool in drug discovery, in which the synthesis of 1,2,3-triazole ring as a pharmacophore, bioisostere *via* CuAAC has great potential in the drug design for a variety of diseases, however, 1,2,3-triazole ring itself is not a commonly used pharmacophore, and it is rare in marketed drugs, indicating that the use of 1,2,3-triazole as drug molecules still has certain limitations. Furthermore, the CuAAC reaction introduces copper species into biological systems and organisms, leading to potential toxicity issues while many Cu chelation sites may inhibit catalyst activity. Moreover, Copper-free cycloaddition SPAAC reaction and IEDDA reaction have their own issues: for example, they are susceptible to side reactions with nucleophilic residues (e.g., thiol residues in glutathione), and the reactive (electrophilic) nature of the requisite cyclic alkynes/alkenes may result in poor regiospecificity. Although computer molecular docking and molecular dynamics have important applications for target identification, however, the protein used for molecular docking may have a huge unknown difference from the protein in the pathological state due to site mutation. Additionally, computational chemistry needs to be combined with more biological activity test and mechanism exploration. In a word, although click and computational chemistry have shortcomings, which still hold a great and unnegligible potential for drug discovery and development, hopefully, this review can stimulate new ideas for the development of drugs with high selectivity, low toxicity, good stability and their clinical application in the near future.

Author contributions

JC and XZ: Writing-original draft. XL and YZ: proof-reading and editing. XTL and others: data collection, the article was approved for submission by all authors.

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Conflict of interest

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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