Review

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Future Medicinal Chemistry

Conformational restriction: an effective tactic in 'follow-on'-based drug discovery

The conformational restriction (rigidification) of a flexible ligand has often been a commonly used strategy in drug design, as it can minimize the entropic loss associated with the ligand adopting a preferred conformation for binding, which leads to enhanced potency for a given physiological target, improved selectivity for isoforms and reduced the possibility of drug metabolism. Therefore, the application of conformational restriction strategy is a core aspect of drug discovery and development that is widely practiced by medicinal chemists either deliberately or subliminally. The present review will highlight current representative examples and a brief overview on the rational design of conformationally restricted agents as well as discuss its advantages over the flexible counterparts.

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Background

Discovery of pharmacologically important leads and drug-like molecules with expected desired properties is the main aim of medicinal chemists. In general, the sources of new drugs can be roughly divided into three categories: existing drugs, screening against a biotarget and structure-based drug design. Overall, the discovery of innovative drug scaffolds by high-throughput screening and structure-based drug design is costly and time-consuming, and probably these newly emerging drugs can't outperform existing ones. As the saying goes, "the most fruitful basis of the discovery of a new drug is to start with an old drug" [1]. And indeed, among the different ways to accomplish new drugs, the application of 'follow-on'-based strategy has been, and continues to be, one of the most fruitful methodologies leading to promising bioactive molecules [2–5]. In recently published monographs, the general aspects of 'follow-on'-based strategy (also termed analogue-based drug discovery) are summarized and the various chemical approaches to making analogues are reviewed [3–5]. Generally speaking, drug molecules can be conceived as an assembly of scaffold and pharmacophore. To some extent, 'follow-on' approaches involve molecular operation of modifying or altering the scaffold of existing agents but maintaining the pharmacophore [2].

Advantages of the conformation restriction strategy

Notably, conformation restriction is a 'follow-on'-based strategy that has been widely used in modern drug design to obtain active and selective agents [6–8]. It is well-known that flexible ligands are considered to suffer an entropic penalty upon binding because of the freezing of rotatable bonds. From the perspective of drug design, the conformation restriction strategy may increase the potency by stabilizing a favorable binding conformation for better potency (therefore reducing the entropic penalty on binding to the target), and decrease degradation by blocking the metabolically labile sites by introducing a fused-ring structure or eliminating metabolized conformers, as well as improve isoforms selectivity towards one of the receptor subtypes or specificity by eliminating bioactive conformers that give undesired biological responses [9,10]. Besides, from the point of view of ligand efficiency, conformational control could be a very atom-efficient method for improving affinity that does not

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Key Terms

High-throughput screening: Commonly used method for experimentation especially used in drug discovery and relevant to the fields of biology and chemistry.

Structure-based drug design: Sometimes referred to as rational drug design, is the inventive process of finding novel medications based on the structural biology knowledge of a drug target.

Highly active antiretroviral therapy: Sometimes referred to as an anti-HIV 'cocktail', is currently the standard treatment for HIV infection by combination of several (three or more) antiretroviral medicines.

Drug resistance: Reduction in effectiveness of a compound in the antiviral, antimicrobial or anti-cancer drug research field.

Lipophilic efficiency: Sometimes referred to as ligand-lipophilicity efficiency, is a key parameter used in drug design and discovery to estimate the drug-likeness of bioactive compounds.

require additional interactions. For these advantages, conformationally restricted strategy has attracted considerable attention in novel drug design.

Applications of conformation-constrained strategy in drug discovery

To the best of our knowledge, the application of conformational constraint has not been reviewed presently. Therefore, in this manuscript we focus on the rational design of conformationally constrained analogues. It is intended to be illustrative rather than comprehensive, and the examples are chosen to convey the range of opportunities available in conformationally constrained approach and its contribution to new drug discovery.

Conformation-constrained design of anticancer agents

Worldwide, an estimated 24.6 million people are cancer patients [11]. Many approved drugs have exhibited severe toxicities that might limit their application, particularly in solid tumors. Therefore, continued efforts have been made on discovering novel, targeted therapies with potentially greater efficacy, isoform-specifity and lower toxicity for the treatment of cancer patients.

In this section, we will summarize the discovery of novel classes of anticancer agents based on the conformation-restriction strategy. The structures and chemical evolution of conformationally constrained anticancer agents are provided as a panorama in the **Supplementary Table 1**. Comparison of the activities between the parent compounds and conformationally constrained derivatives provided direct evidence for the hypothesis that the energetic benefit of rigidification of the pharmacophore is translated into the improved biological activities and/or enhanced pharmacokinetics, as well as optimized isoform selectivity towards binding with related targets.

It should be pointed out that, the class-selective or isoform-selective inhibitors are of great interest, not only as more effective chemotherapy with fewer side effects compared to pan-inhibitors, but also as tools for probing the biological functions of the isoforms.

Moreover, this conformational approach also led to a novel chemical patent space securing freedom of operation. The promising results warrant further development of these novel analogues to be potential clinical anticancer drugs.

Conformationally restricted agents for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is well known as one of the most common and severe neurodegenerative diseases in elderly individuals. Currently, the first-line treatments for AD include cholinergic (donepezil) and glutaminergic drugs (memantine) that have modest potency and poor tolerability [12–14]. Therefore, there is a need to discover novel and effective therapeutics with improved efficacy and tolerability, as well as new mechanism of action for the treatment of dementia based on drug-design strategy.

Rivastigmine (**1**) is an AChE inhibitor approved in 2000 for AD therapy. In the further modification process, compound **2**, bearing a sulfur-containing system, was designed as a conformationally restricted analogue of **1**. This compound showed higher efficacy, being 192-fold more potent than **1** (Figure 1) [15].

The function of β-secretase (BACE) inhibitors is a validated therapeutic strategy for AD treatment. To further improve the potency of BACE1 inhibitors, structure-based evolution combined with conformational constraint strategy of these lead compounds **3**, **5**, **7**, **9** and **11** was performed to facilitate access to the prime side of the BACE1 active site, which provided the discovery of the corresponding conformationally restricted analogues (such as 3-hydroxypyrrolidine **4** [16], imidazo[1,2-a]pyridine **6** [17], pyrrolidine **8** [18], bicyclic iminopyrimidinone **10** [19] and chiral cyclopropanes **12a-c** [20,21]; Figure 1).

Compound **6**, in particular, exhibited BACE1 inhibitory potency with an IC_{50} of 18 nM and displayed an EC_{50} for cell-based ELISA assay of 37 nM, as well as high affinity (K_i = 17 nM) and ligand efficiency of 1.7 kJ/mol [17]. The potency of pyrrolidine-based β-secretase inhibitor **8** was enhanced by four orders of magnitude from the high-throughput screening of lead **7** with accompanying improvement in physical properties [18]. Compound **10** was identi-

fied as an orally active, brain penetrant molecule that can lower amyloid-β (Aβ)40 in the plasma, cerebrospinal fluid and cortex of rats in a dose-dependent manner (Figure 1) [19].

Furthermore, γ-secretase modulators have emerged as a potential disease-modifying treatment for AD. The imidazole-containing benzimidazole **14** was identified as a γ-secretase modulators with low nanomolar activity *in vitro* and concomitant promising potency *in vivo* (mouse, rat and dog model) through a conformational lock of pyridine in lead compound **13** into bicyclic pyridone isostere (Figure 1) [22].

In addition, 5-HT(6) receptor is also demonstrated to be an important target for AD therapy. Several structurally restricted derivatives are reported as highly potent and selective antagonists of 5-HT(6) receptors. For instance, SB-742,457 (**15**) is a selective 5-HT(6) receptor blocker with memory, cogni-

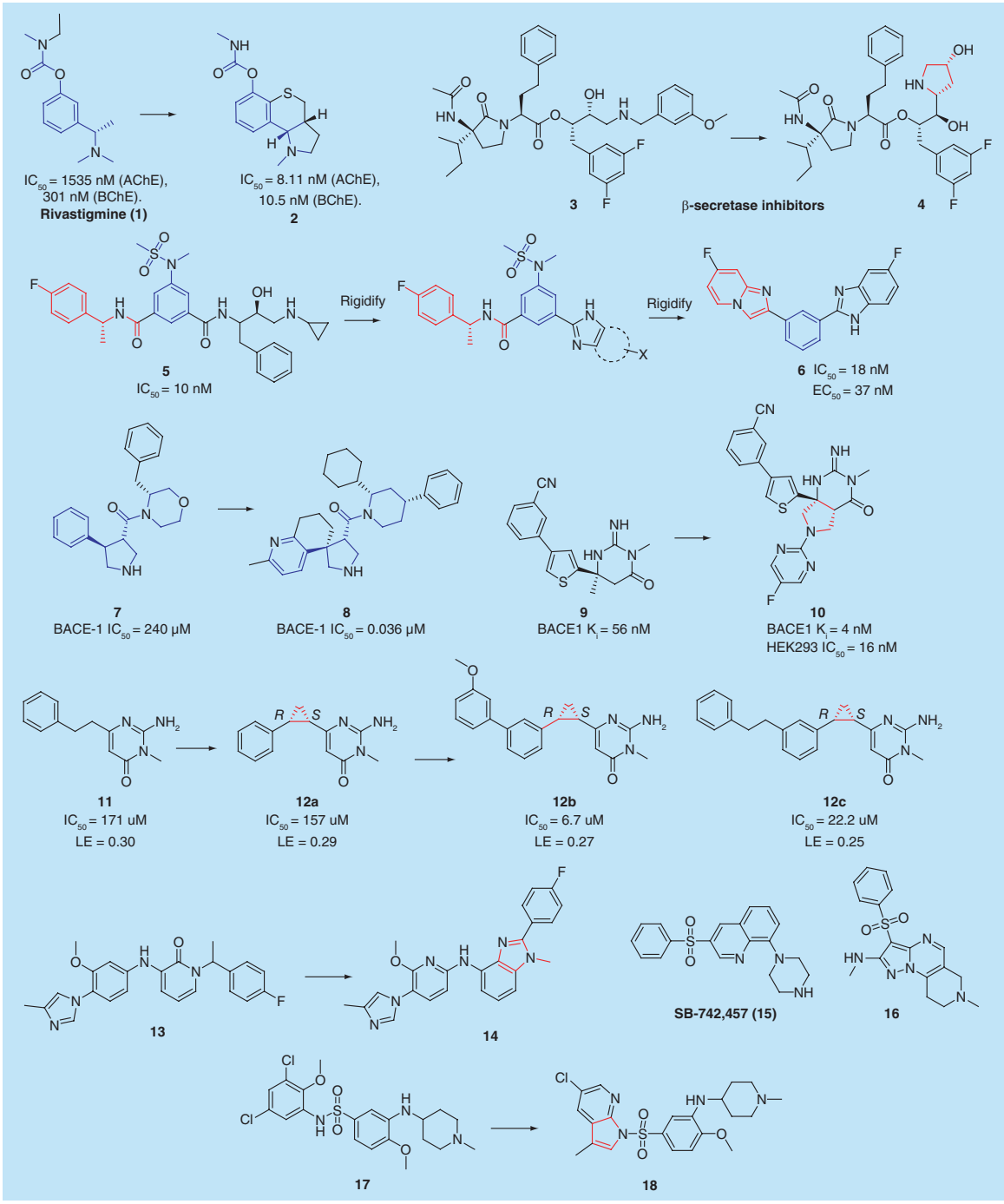

Figure 1. Design of conformationally restricted agents for the treatment of Alzheimer's disease.

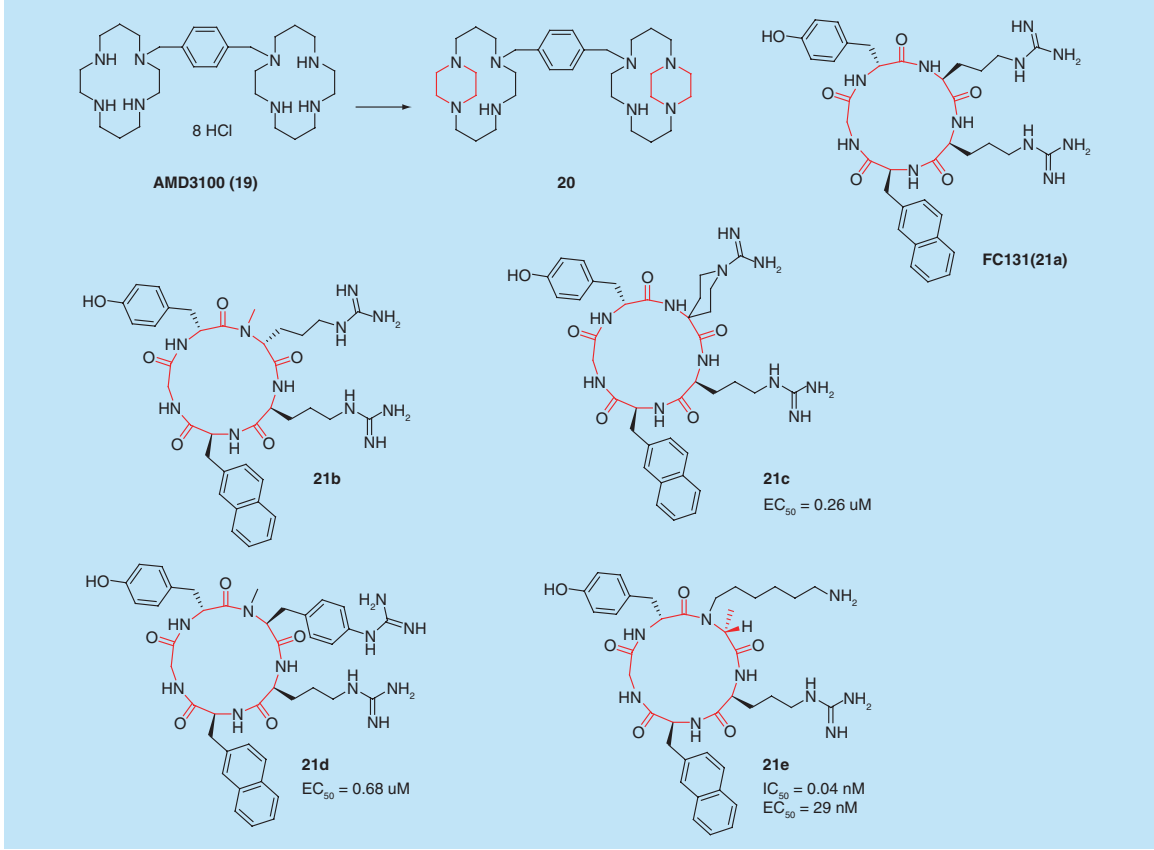

Figure 2. Design of conformationally restricted chemokine (C-X-C motif) receptor type 4 antagonists.

tion and learning-enhancing effects. Currently, it has demonstrated preliminary efficacy in Phase II clinical trials by GlaxoSmithKline [23]. 3-(phenylsulfonyl)pyrazolo[1,5-a]pyrido[3,4-e]pyrimidine (**16**) showed robust 5-HT(6) blocking activity (IC_{50} = 1.8 nM as compared with IC_{50} = 6.16 μM for 5-HT(2B) receptors) and extremely low hERG potassium channel blocking potency (IC_{50} = 54.2 μM), which can be considered to be another favorable candidate for further investigation [24].

Conformational design was also performed to improve the ligand binding efficiency of compound **17**, which culminated in the discovery of piperidin-4-yl amino aryl sulfonamide **18** as an orally active and brain penetrant 5-HT(6) receptor selective antagonist. It was selected for further development for its overall profiles (Figure 1) [25].

Conformationally restricted HIV inhibitors

The human immunodeficiency virus type 1 (HIV-1) is the main cause of AIDS. Although a large number of approved drugs are used in highly active antiretroviral therapy, such as IN inhibitors, protease inhibitors, nucleoside or non-nucleoside RT inhibitors (NRTI/NNRTI), entry or fusion inhibitors, the emergence of the drug resistance severely limits their clinical effect. Thus, the development of novel classes of drugs for the treatment of HIV-1 infection is urgently needed [26].

Chemokine (C-X-C motif) receptor type 4 antagonists

Bis-azamacrocyclic compound AMD3100 (**19**) has been regarded as a highly effective antagonist of the chemokine (C-X-C motif) receptor type 4 (CXCR4). The two azamacrocyclic rings have shown to interact with aspartate residues on the receptor via electrostatic and hydrogen bonding interactions [27].

Design and validation of new azamacrocyclic AMD3100 analogues with locked configurations were performed to afford optimized interactions with the CXCR4 receptor, lastly to increase the potency of the new candidates relative to AMD3100 [28]. Notably, the zinc(II) complex of compound **20** (Figure 2) in solution was proved to adopt only one favorable binding configuration, and demonstrated high inhibition against HIV infection *in vitro* [28].

Meanwhile, several conformationally constrained cyclopentapeptide CXCR4 antagonists **21a-e** were rationally designed [29–32]. Especially, the binding affinity of compound **21e** was 1500-fold higher than that of AMD3100. The information provided by these

cyclopentapeptides will be very valuable in the exploitation of novel peptidomimetic-based CXCR4 antagonists (Figure 2) [31,32].

C-C chemokine receptor type 5 antagonists

C-C chemokine receptor type 5 (CCR5) is a tractable target for anti-HIV therapeutic intervention [33]. In the development of a small-molecule CCR5 antagonist, the conformational constrain-based design was adopted with aim to fix the basic motif into a desired orientation for effective binding with CCR5. These effects afforded novel CCR5 antagonists, such as imidazolone **23** [34], **24** [35], **26**, **27** [36], and 1,3,4-trisubstituted pyrrolidine **29** [37], which have the potential to be promising candidates for future development. It's worth mentioning that, to some extent, the discovery of approved drug maraviroc (**31**) was also benefited from contributions of the conformational constrain approach (Figure 3) [38].

HIV IN inhibitors

L-870810 (**32**) was an early IN inhibitor that once entered the clinical trials [39]. It was known to exist in dynamic equilibria between two rotational isomers: conformer A and B, attributed to rotation around the amide bond (Figure 4). Conformer B was postulated as the active form for metal coordination (Figure 5), to overcome the rotational barrier, conversion from A to B will cost approximately 5 kcal/mol. Therefore, the active binding conformation may be difficult to access due to this energetic barrier.

With aim to prepay the conformational penalty in binding to IN, conformationally locked scaffolds were proposed. For instance, rigidified tricyclic derivatives

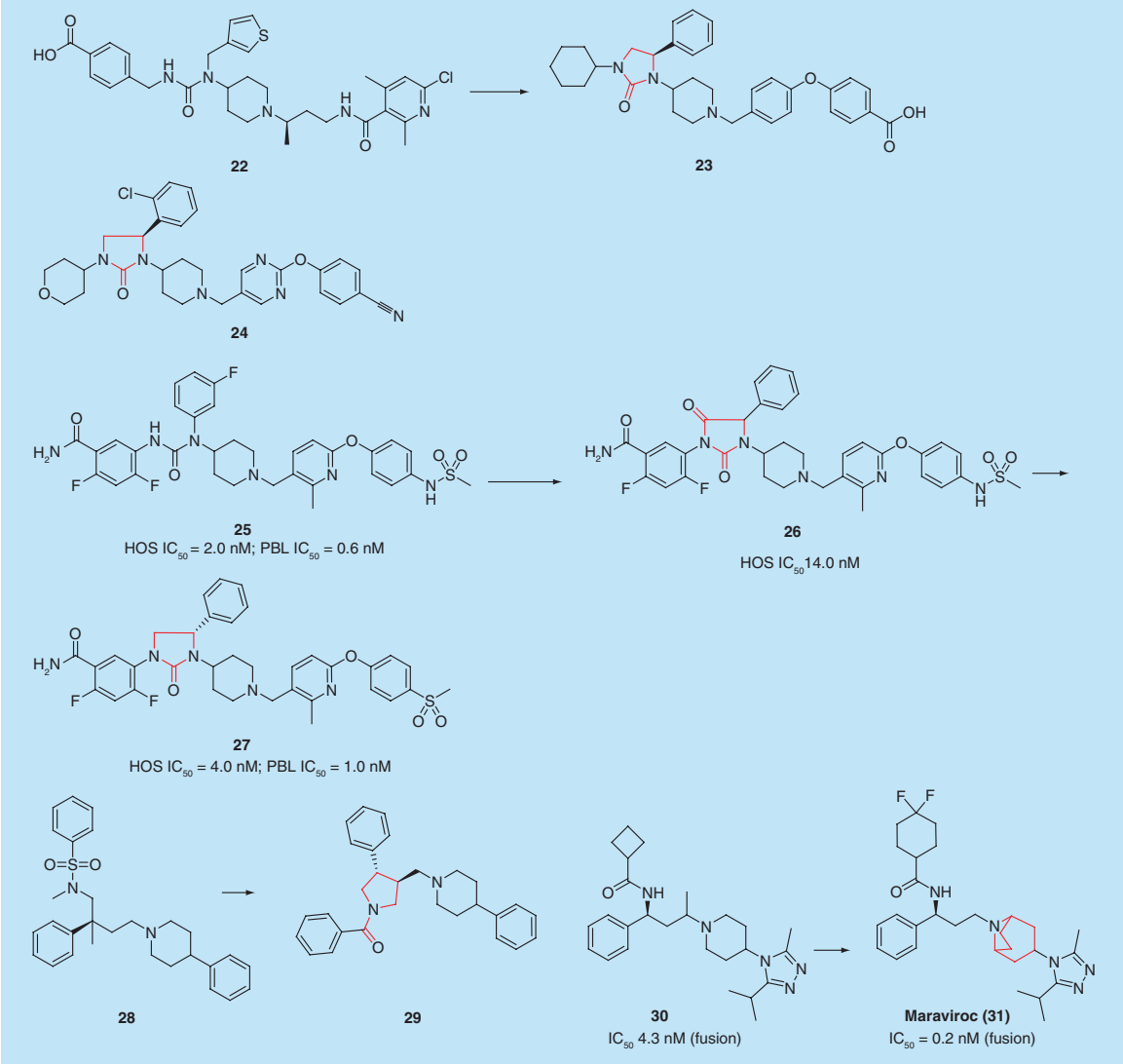

Figure 3. Design of conformationally restricted C-C chemokine receptor type 5 antagonists.
HOS: Human osteosarcoma cell line.

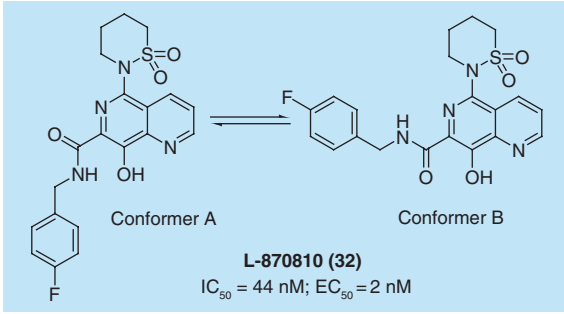

Figure 4. Two rotational isomers associated with rotation around the amide bond in IN inhibitor L-870810 (32).

34–36 were prepared to fix the metal chelation motif in the prototype compound **33** into a desired coplanar orientation for effective metal binding. And in consequence, compared with the potency of compound **33**, impact of conformation rigidity on activity of inhibitors toward HIV and IN is obvious (Figure 6) [40].

Besides, other geometrically or conformationally constrained analogues have also been reported, such as 6,7-dihydroxy-1-oxoisoindoline-4-sulfonamide **37** [41], pyrrolo[1,2-a]pyrazine-1(2*H*)-one **38** [42], macrocyclic derivatives **39** [43], carbazolone-containing α,γ-diketo acid **41** [44], cinnamoyl derivatives **43** [45,46] and bicyclic carbamoyl pyridone analogue **45** [47]. Especially, the chemical evolution of carbamoyl pyridone IN inhibitor **44** to bicyclic derivative dolutegravir (**45**) (which is currently in late state clinical evaluation) resulted in superior antiviral and pharmacokinetic profiles (Figure 6) [47].

Compared with the *N*-methyl hydroxamate **46**, the lipophilic efficiency of restricted rotamer *N*-hydroxydihydronaphthyridinone **47a** was substantially improved [48]. Another analogue PF-4776548 (**47b**) was identified as a promising candidate with high potency and excellent resistance profiles (Figure 6) [49]. These studies illustrated a viable protocol to discover IN inhibitors with enhanced potency.

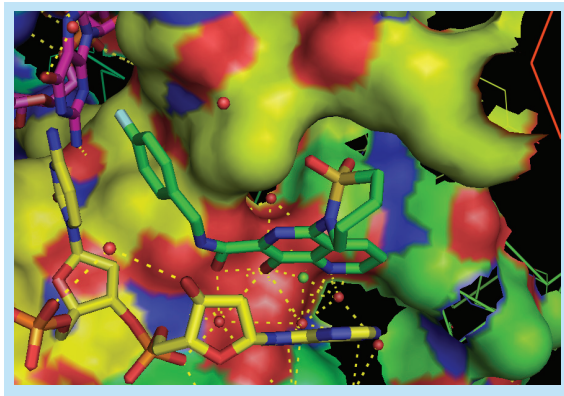

Figure 5. Crystal structure of the prototype foamy virus intasome in complex with magnesium and L-870810 (PDB code: 3OYF).

HIV protease inhibitors

Conformationally restricted sulfonamide **48** was found to be a potent HIV-1 protease inhibitor in Merck & Co. research team (Figure 7) [50,51]. x-ray crystallography demonstrated that the conformationally restricted sulfonamide can bind to a similar pocket in protease as approved drugs such as darunavir. Moreover, the stereochemistry of three asymmetric centers is also crucial to activity [51].

Conformationally locked nucleosides

The sugar rings of natural ribo- and deoxyribo-nucleosides can exist in dynamic equilibria between two main conformers: the South and North types. With aim to seek novel nucleosides endowed with potent bioactivities, conformationally restricted modifications of the sugar moieties in natural nucleosides have been performed [52], which resulted in the synthesis of hexahydroisobenzofuran nucleoside **49** (EC_{50} = 12.3 μM) [53], 3-oxabicyclo[3.2.0]heptane-typenucleoside **50** (Figure 8) [54]. Unfortunately, no impressive results have been observed.

HIV NNRTIs: conformationally restricted factors that contribute to the preferential 'butterfly-like' shape

From the literature survey, despite the chemical diversity of HIV-1 NNRTIs, they assume a common butterfly-like conformation [55–59]. As illustrated in Figure 9, the 3D pharmacophore model of 'butterfly-like' NNRTIs is the spatial arrangement of key structural features: hydrophobic domain, hydrogen bond donor and acceptor. The hydrophobic domain fills the hydrophobic subpocket consisted of Y181, Y188, F227 and W229 (Figure 9). The hydrogen bond donor and acceptor can form key hydrogen bonds with the backbone carbonyl and imino atoms of K101 (or K103) residue (directly or via a structural H_2O molecule). These pharmacophore functionalities are maintained in a spatial arrangement suitable for the interaction within the binding pocket by the conformational restricted motif [55].

For most NNRTIs, it is possible to find out the intramolecular restricted factors that contribute to this preferential butterfly-like conformation, including the rigid heterocycles located in the 'body-linker' region, intramolecular hydrogen bond and stereochemical diversity-oriented conformational restriction (Figure 10). For instance, the following heterocycles were employed as conformation restricted motifs (Figure 10A): fused tricyclic platform in R82913 (**51**) [60], pyrimidine in TMC278 (**52**) [61], indole in IDX-899 (**53**) [62], triazole in RDEA-806 (**54**) [63], 2-oxo-pyrrolidine in *N*-aryl pyrrolidinone **55** [64] and indazole in **56** [65]. The intramolecular hydrogen bonds

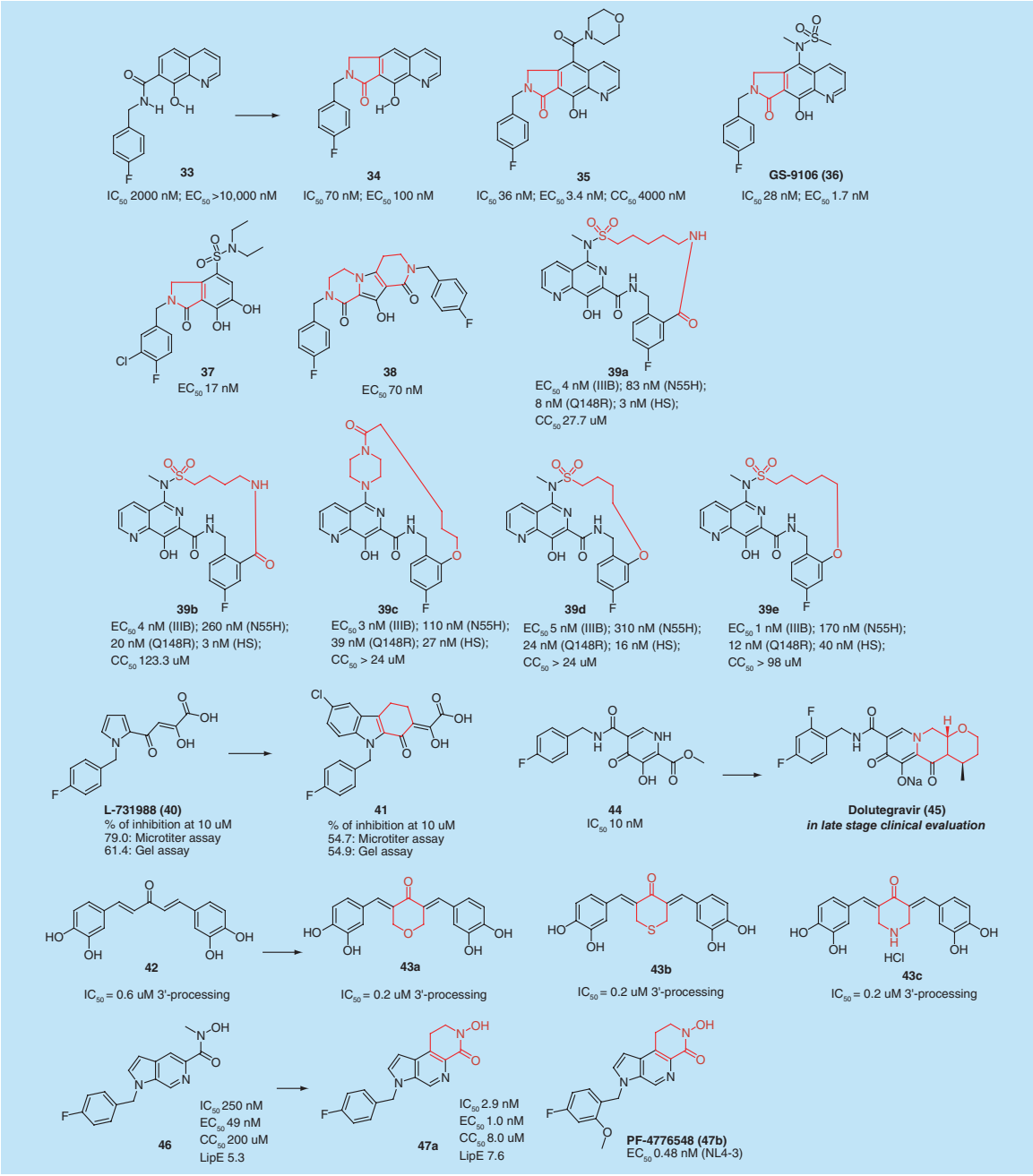

Figure 6. Design of conformationally restricted HIV IN inhibitors.

(Figure 10B) were found as the restricted factors in the structures of phenylethylthiazolylthiourea trovirdine (LY 300046·HCl; **57**) [66], MIV-150 (**58**) [67] and benzimidazolone **59** [68].

Incorporation of a chiral center into biologically active compounds might notably change their conformational behavior, which can be beneficial for the discovery of potential drug candidates. Herein, we will focus our remarks on the stereochemical diversity-oriented conformational restriction strategy.

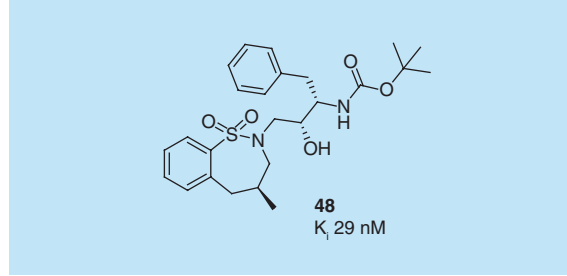

Figure 7. Structure of a conformationally restricted HIV-1 protease inhibitor.

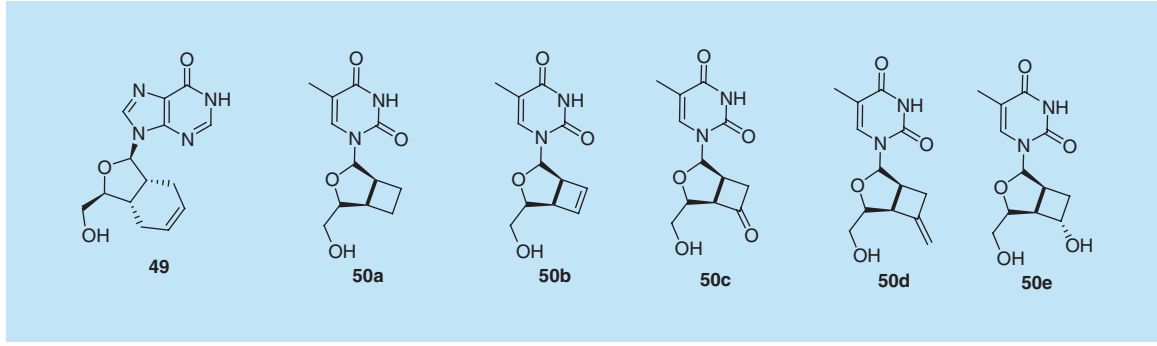

Figure 8. Structures of conformationally locked nucleosides.

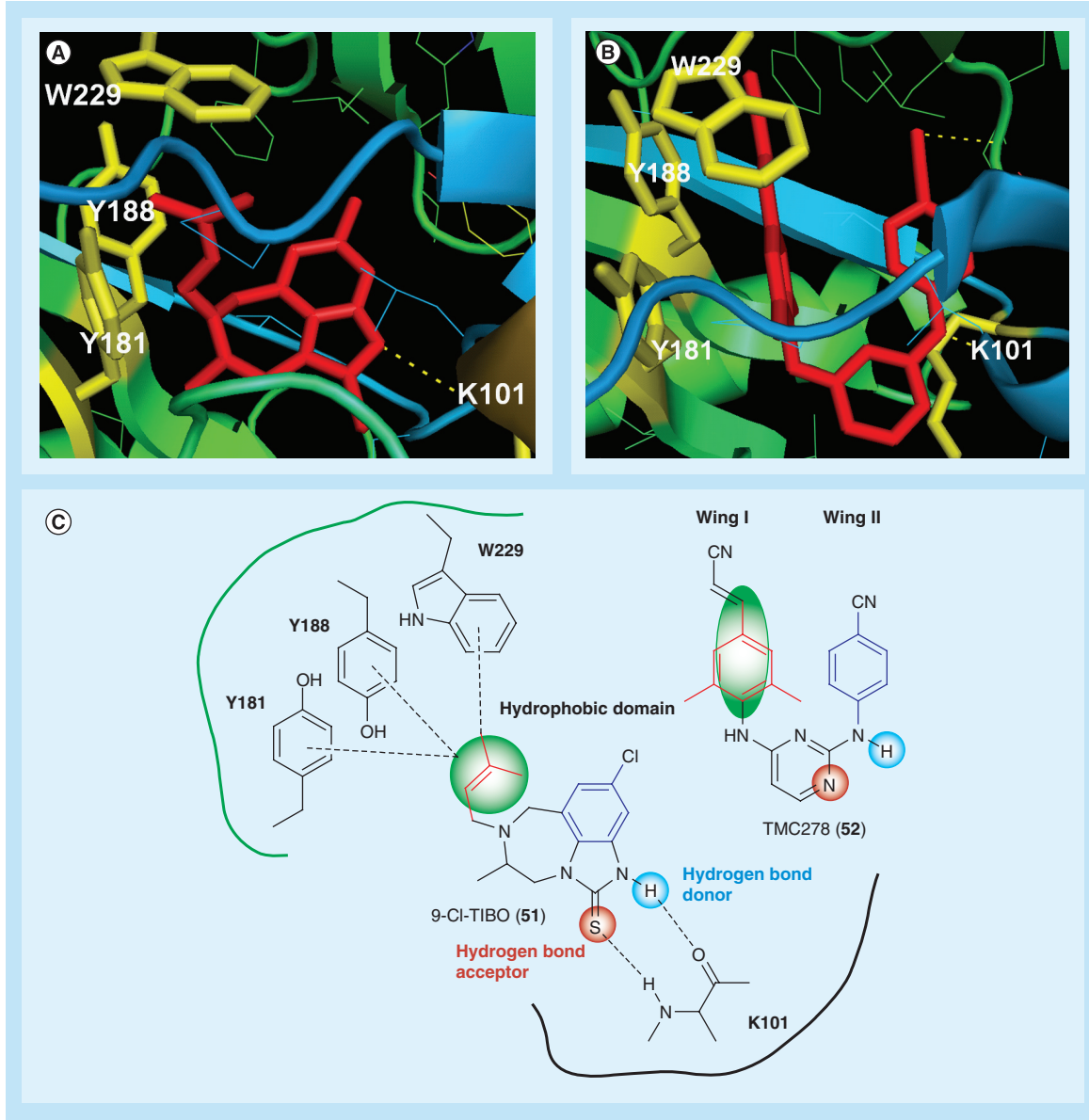

Figure 9. Binding modes of representative non-nucleoside RT inhibitors. (A) Co-crystal structure of 9-Cl-TIBO (red) in complex with RT (PDB code: 1TVR). **(B)** Co-crystal structure of TMC278 (red) in complex with RT (PDB code: 3MEE). These figures were generated using PyMOL [99]. **(C)** Positioning of non-nucleoside RT inhibitor binding into binding pocket by mapping of the pharmacophore points (exemplified by 9-Cl-TIBO and TMC278).

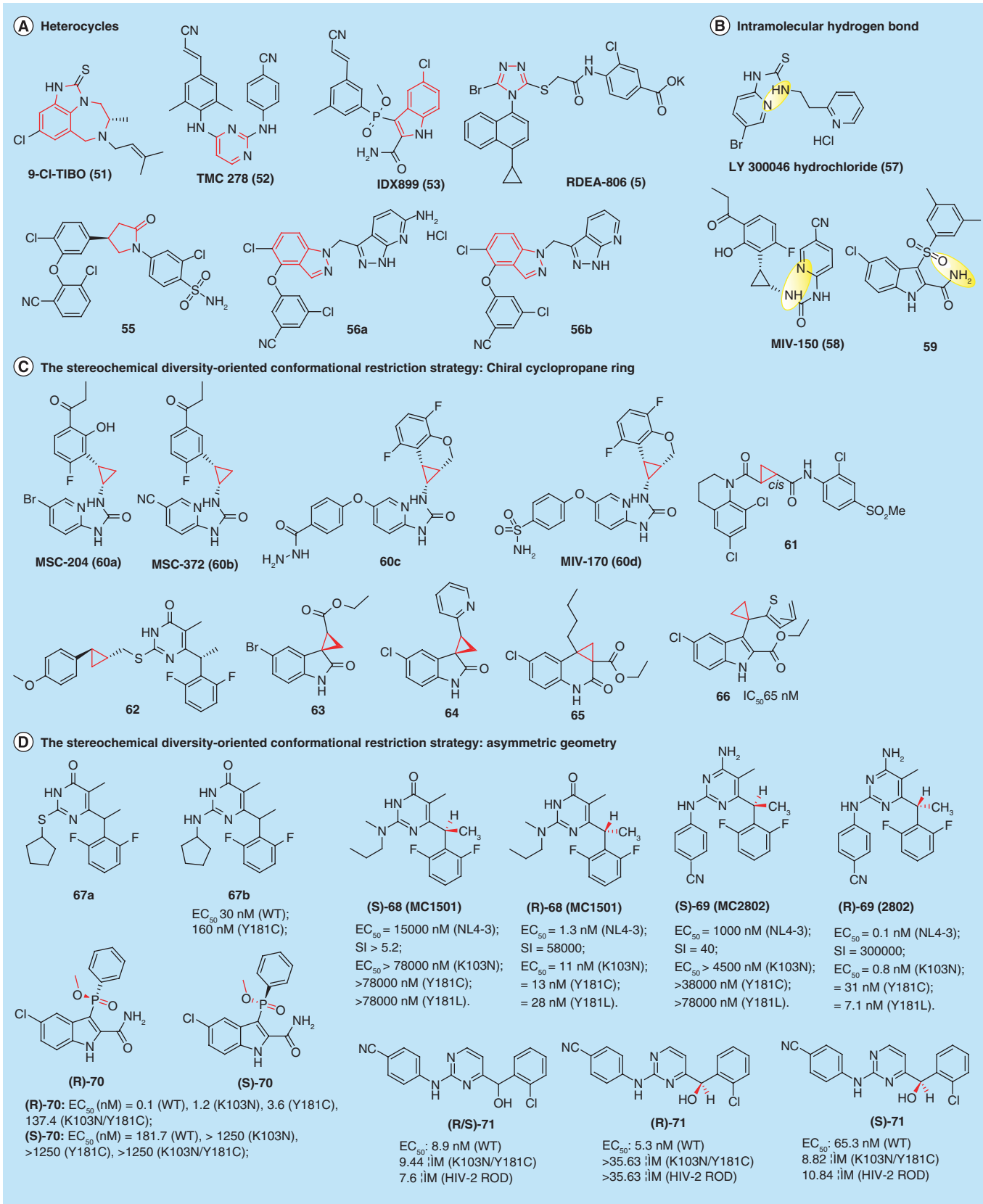

Figure 10. The intramolecular restricted factors that contribute to the preferential "butterfly-like" conformation in non-nucleoside RT inhibitors.

The introduction of suitable stereocenters in important pharmacophoric sites of promising NNRTI scaffolds could allow the emergence of a collection of enantiopure drugs with improved efficacy and potential usefulness in managing drug-induced mutations. Molecular modeling investigations pointed to the asymmetric geometry of the NNRTIs binding pocket, and experimental data proved that the regiochemistry and stereochemistry of NNRTIs can dramatically influence their anti-HIV activity [69].

Consequently, the introduction of a cyclopropane moiety in bioactive molecules offers increased conformational rigidity and a stereodiversified core, thus compounds consisting of a cyclopropane functionality have been reported to exhibit interesting biological properties [70]; many NNRTIs containing a chiral cyclopropane moiety as a structural unit were reported. Typically, the chiral cyclopropane ring-containing urea-phenethylthiazolylthiourea analogues **60a**,**b** [71], **60c** [72], **60d** [73], tetrahydroquinoline **61** [74], *S*-dihydroalkoxybenzyloxopyrimidine (DABO) **62** [75], oxindole **63** [76], **64** [77], quinolones **65** [78], and cyclopropyl indole **66** [79], demonstrated nanomolar activity against several clinically relevant mutants (Figure 10C).

Compounds **67a**,**b** are two novel conformationally constrained DABO derivatives, featuring two methyl groups at the benzylic carbon and at the pyrimidine 5-position. F_2-*S*-DABO derivative **67a** (IC_{50} = 5 nM, EC_{50} = 6 nM, CC_{50} > 200 μM) inhibited HIV-1 replication in MT-4 cells more actively than MKC-442 (by five times) and nevirapine (by 50-fold) [80]. F_2-NH-DABO derivative **67b** was also active against the Y181C variant (Figure 10d) [81]. Conformational analyses showed that the presence of two methyl groups would substantially reduce conformational freedom without compromising, in the *R* enantiomers, the capability of fitting into the NNRTIs binding pocket.

In addition, the *R* forms of *N*,*N*-DABO **68** (MC1501) and DABO-DAPY (diarylpyrimidines) hybrid **69** (MC2082) were more potent than their *S* counterparts and racemates. Interestingly, (*R*)-**69** displayed a faster binding to K103N RT with respect to wild-type (WT) RT, while (*R*)-**68** showed the opposite behavior [82]. The bioactivity data suggested that the stereochemistry (*R*/*S* enantiomer) in 3-aryl-phosphoindole **70** [83] and diarylpyrimidine CH(OH)-DAPY **71** [84], also has major effects on their binding affinities to RT (Figure 10D).

Moreover, it should not been ignored that NNRTIs have inherent flexibility, helping to maintain activity against a wide range of resistance mutations. The compromise impartial match between conformational flexibility and restriction will determine the possibility of discovery bioactive molecules. Only when its bioactive conformation matches very well with the binding pocket, a drug molecule will display the highest potency.

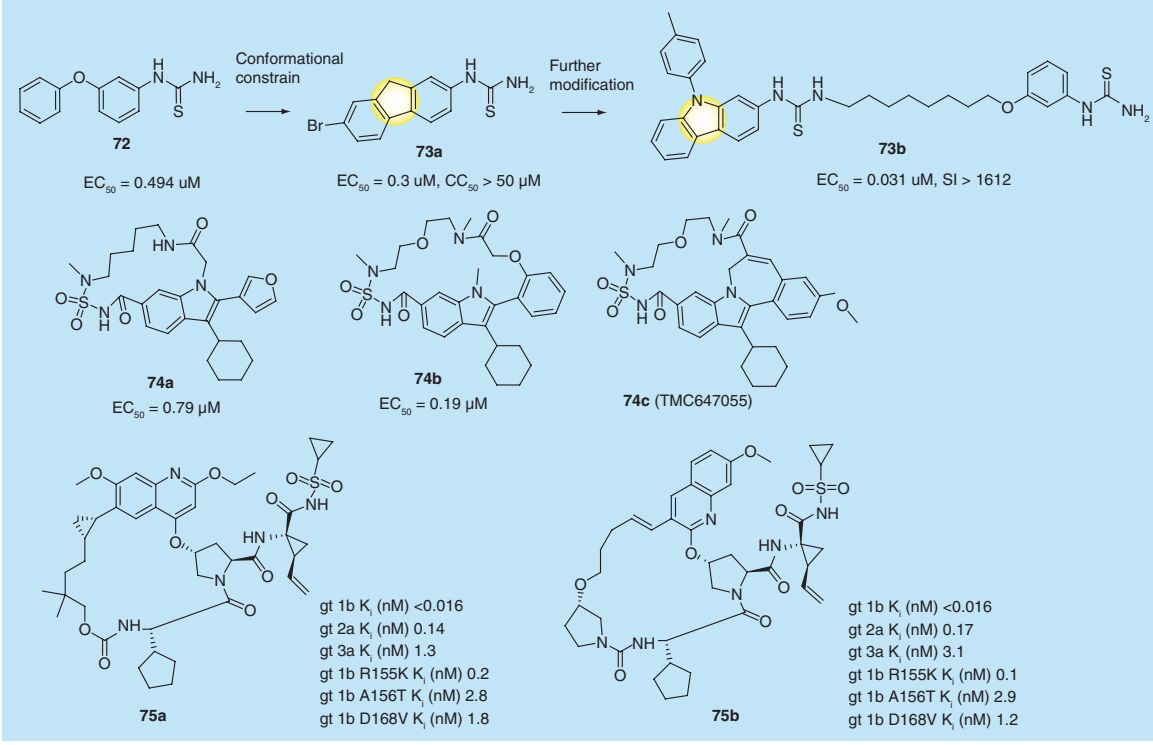

Figure 11. Structures of conformationally locked hepatitis C virus inhibitors. gt: Genotype.

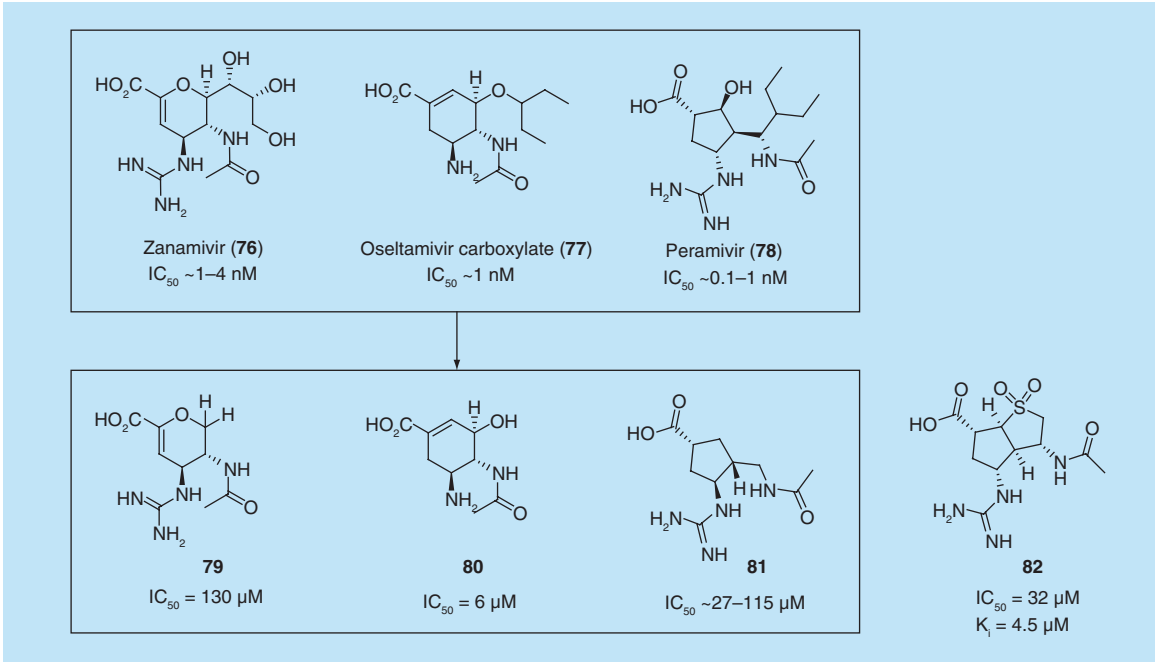

Figure 12. Schematic representation of the conformationally locked neuraminidase inhibitors.

Hepatitis C virus inhibitors

Hepatitis C virus (HCV) infection is a widespread disease affecting approximately 130–200 million people. The fluorene thiourea **73a**, a novel conformationally restricted analogue of anti-HCV hit molecule **72**, displayed better inhibitory activities in the cell-based subgenomic HCV replicon assay (EC_{50}= 0.3 μM, CC_{50} > 50 μM) and significantly improved pharmacokinetic properties [85–87]. In further modifications, a new carbazole derivative **73b** was found to possess higher anti-HCV activity (EC_{50} = 0.031 μM), lower cytotoxicity (CC_{50} >50 μM) and higher selectivity index (>1612) compared to its predecessors (Figure 11) [85–87].

In 2012, it was reported that several conformationally locked 1,6- and 2,6-macrocyclic HCV NS5b polymerase inhibitors **74a-c**, in which either the nitrogen or the phenyl group in the C2 position of the central indole nucleus is tethered to an acylsulfamide acid moiety, demonstrated enhanced anti-HCV potency and pharmacokinetic profile (Figure 11) [88,89].

In addition, a series of macrocyclic inhibitors of HCV NS3/4A protease containing cyclic constrained P2-P4 linkers have been identified and exhibited excellent potency against protease genotype 3a and genotype 1b R155K, A156T, A156V and D168V mutants while keeping high rat liver exposure (compound **75a,b**). The introduction of a variety of constrained ring systems into the P2–P4 linker yielded approximately 20-fold improvements in potency especially against genotype 1b A156 mutants (Figure 11) [90].

Influenza neuraminidase inhibitors

The neuraminidase inhibitors represent a class of multisubstituted compounds with powerful anti-influenza potency. Currently, various cyclic cores have been employed for the structural modifications, including

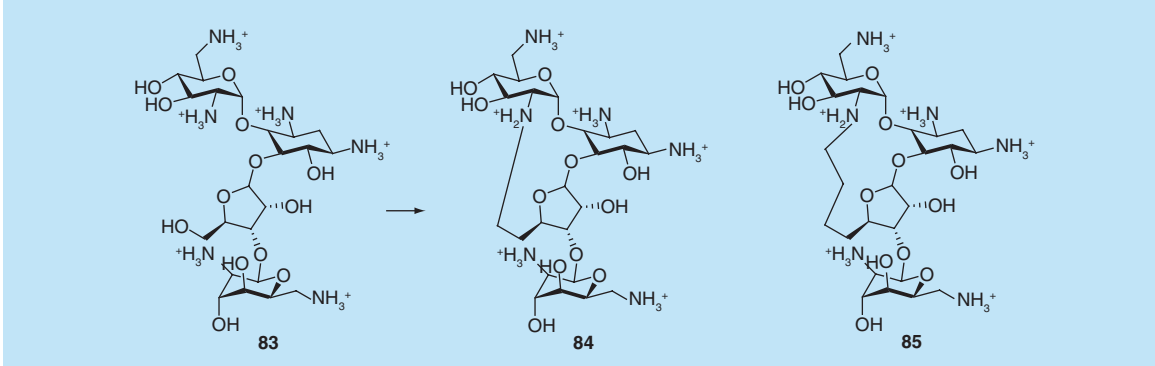

Figure 13. Schematic representation of the conformationally rigidified aminoglycosides.

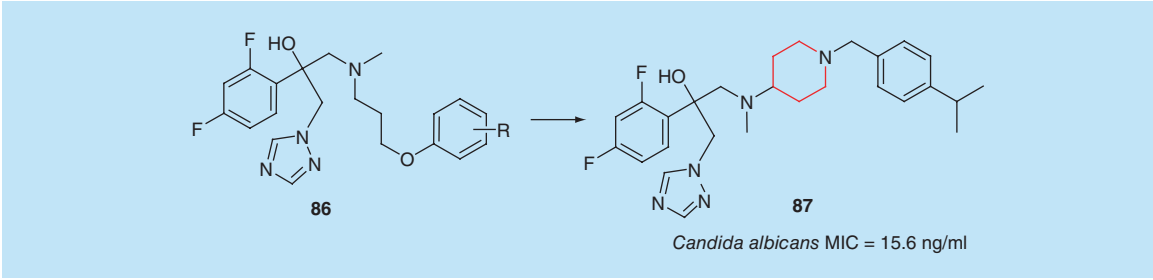

Figure 14. Design of a conformationally rigidified benzylpiperidine derivative as potent antifungal agent.
MIC: Minimum inhibitory concentration.

dihydropyrans (in zanamivir, **76**), cyclohexenes (in oseltamivir, 77), cyclopentanes (in peramivir, **78**), and tetrahydropyrroles and aromatic rings. Molecular modeling demonstrated that the central ring stays in the center of the binding pocket, anchoring the substituents in the scaffold into the optimal space for interactions with four subregions of the neuraminidase active site.

Based on the assumption that a bicyclic derivative, which locks this ring geometry in place, would have a reduced binding entropy and enhanced target selectivity, a new series of rigid, bicyclic inhibitors of influenza neuraminidase was prepared (Figure 12). Ultimately, the inhibition activity for racemic **82** is up to threefold lower than the activities reported for the side chain deleted derivatives of zanamivir and peramivir (**79** and **81**), thus, it appears likely that the rigidified bicyclic scaffold has shown its advantage (it is not proper to compare IC_{50} values from different experiments) [91].

Antibacterial & antifungal agents

On the base of biochemical mechanism for bacterial resistance, it should be feasible in theory to design a conformationally fixed oligosaccharide that still retains antibiotic potency but that is not susceptible to enzymatic inactivation. Consequently, several aminoglycoside compounds (**84 & 85**) locked in the ribosome-bound 'bioactive' conformation were synthesized (Figure 13). It was indicated that the conformational constraint had a modest effect on their binding with ribosomal RNA. In contrast, it probably displays a large effect on their enzymatic inactivation. Therefore, exploring the application of conformationally restricted aminoglycosides was regarded as a novel strategy to overcome bacterial resistance [92].

In 2010, taking **86** as lead compound, a series of novel conformationally locked triazole derivatives with benzylpiperidin-4-yl methyl amino side chains were reported as potent antifungal agents. In particular, compound **87** displayed higher antifungal activity against *Candida albicans* than fluconazole (Figure 14) [93].

Others examples using conformational restriction

Lastly but importantly, we will give a glance of other publications that have used the conformational restriction as a useful strategy for the discovery of bioactive small-molecule therapeutics (**Supplementary Table 2**). These publications exemplify how efficient ligands can be achieved by careful conformational control. Overall, the biological activity results of these molecules raveled that conformationally restricted agents were generally superior to their prototypes. Such compounds might be useful lead structures for the development of new drug candidates.

Besides, this concept has been also widely exploited with regard to the conformational constraint of peptides for various applications [94–96], including vaccines [97].

Future perspective

The design of efficient and specific ligands remains a key challenge in current drug discovery. The conformational restriction strategy was proven to be a robust and still underused method for developing specific ligands for physiological targets that are easier to synthesize or to avoid existing patent art.

Roughly speaking, finding conformationally restricted analogues to improve biological or physicochemical properties and to avoid patented structural features is not so easy. In every bioactive molecule, conformational restriction and freedom constitute two aspects of a contradiction, which are both opposite and unitary, also alive together. The new conformationally restricted scaffold should be of a similar volume and shape as the original structure and, where appropriate, make similar interactions with the binding site. Moreover, it should not be forgotten that exploitation of inhibitor conformational flexibility was considered as a powerful element of drug design, especially for the design of agents that will be active against mutant targets.

Understanding the detailed structural information about target–ligand interactions, chemical space around the target site and overall shape that have energetically accessible geometries is the molecular basis of designing conformationally restricted compounds with

higher potency. Concretely, optimizing the interactions with the conformationally flexible residues in the binding site of a receptor protein was considered to be an effective method to improve the drug potency [98].

In summary, the usage of conformational restriction strategy to navigate the available chemistry space and to afford chemically tractable compounds will continue to be important and innovative endeavors in medicinal chemistry.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.future-science.com/doi/full/10.4155/FMC.14.50

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Executive summary

Background

- The discovery of original drug scaffolds by high throughput screening and structure-based design approach has proved costly and time-consuming, and these newly emerging drugs might not be able to outperform the known ones.
- The application of 'follow-on'-based strategy continues to be one of the most effective the methodologies leading to promising drug candidates.

Advantages of the conformation restriction strategy

- It can increase the potency by reducing the entropic penalty on binding to the target and stabilizing a favorable binding conformation for better potency.
- It can decrease degradation by eliminating metabolized conformers or blocking the metabolically unstable positions by introducing a fused-ring structure.
- It can improve isoforms selectivity towards one of the receptor subtypes or specificity by eliminating bioactive conformers that give undesired biological effects.
- It is a very atom-efficient approach to improve affinity and ligand efficiency that does not require additional interactions.

Applications of conformation-constrained strategy in drug discovery

- This short overview is complete with many illustrative examples of drug/lead discovery using conformationally-restricted design from distinct therapeutic classes, including anticancer agents, Alzheimer disease therapeutic agents, HIV inhibitors, hepatitis C virus inhibitors, neuraminidase inhibitors, antibacterial and antifungal agents, and many others examples, which could stimulate medicinal chemists to take similar strategy in their project.

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