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REVIEW

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Natural product-inspired strategies towards the discovery of novel bioactive molecules

Sunita Gagare[1,2*], Pranita Patil[2] and Ashish Jain[2,3]

Abstract

Background The intricate molecular frameworks of natural products with biological activity towards human targets offer academic and industrial chemists an important starting point for next generation drug discovery. With a focus on natural products for the production of diverse small-molecule libraries and the evaluation of uncharted chemical space, several strategies have emerged for achieving selective modulation of disease-associated targets. This review highlights some of the significant and more recent synthetic strategies inspired by naturally occurring molecular frameworks, aiming at the discovery and development of novel bioactive molecules. We underscore the potential of these innovative strategies with representative examples to forecast their role in addressing the enduring drug design challenge.

Main text In this review, we discuss these newer natural product-inspired synthetic approaches, among them diversity-oriented synthesis, biology-oriented synthesis, hybrid natural products, diverted total synthesis, pruning natural products, ring distortion of natural products and integrating natural product framework with a bioactive molecule. Selected representative examples associated with these strategies are given to demonstrate how they have been applied to afford desired bioactivity.

Conclusion This review elaborates several pioneering and emerging strategies inspired from natural product which allows access to the unexplored chemical space to identify novel molecules possessing noteworthy bioactivity. The corresponding examples highlight the success of these strategies in the discovery of novel bioactive molecules which can be further developed in drug discovery and can be novel probes for chemical biology. Although there are limited number of successful examples, the selectivity, activity, and efficacy associated with natural product-inspired molecules accentuate their importance.

Keywords Bioactive molecules, Natural products, Synthesis, Biomolecules, Pruning

Background

Continuing efforts towards the discovery of novel molecules to systematize and expand our knowledge and to understand the biological pathways and modify disease aetiology is of prime importance towards sustaining the quality and longevity of human life [1]. A total of 893 mammal- and pathogen-related molecular targets have been identified upon which marketed drugs act [2]. Meanwhile, the corresponding chemical space is estimated to comprise about 10^{60} drug-like structures/molecules that follow Lipinski's rule of five [3, 4]. Hence,

*Correspondence:
Sunita Gagare
sunita.gagare19@gmail.com
[1] Pharmaceutical Chemistry Department, Shri D. D. Vispute College of Pharmacy and Research Center, New Panvel, Maharashtra 410206, India
[2] Quality Assurance Department, Shri D. D. Vispute College of Pharmacy and Research Center, New Panvel, Maharashtra 410206, India
[3] Pharmacognosy and Phytochemistry, Shri D. D. Vispute College of Pharmacy and Research Center, New Panvel, Maharashtra 410206, India

although apparently important, it is very arduous to identify a new molecule out of this vast chemical space which specifically interacts with the defined molecular target [5].

In the early 2000s, combinatorial chemistry became a primary tool for drug discovery [6]. The idea of producing a large library of compounds that can be screened against numerous targets in a brief period of time seemed appealing to pharmaceutical companies and initiated significant industrial efforts [7]. Although substantial investment was made in relation to this concept, the overall success was less than anticipated with a few exceptions, such as the discovery of sorafenib, which is a multikinase inhibitor for the treating advanced renal cancer [8]. The constrained impact of this strategy can be attributed to the fact that molecules obtained by it were concentrated on a relatively small area of chemical space, and potential molecular diversity remained unexplored. Conversely, the chemical space occupied by natural products encompasses a vast chemical space [9].

For centuries, nature has been the source of medicinal compounds for the treatment of a wide spectrum of diseases [10]. The stunning structural and chemical diversity offered by natural products has revitalized, in multiple phases, the interest of medicinal chemists to take advantage of such chemotypes for drug discovery [11]. Natural products may differ significantly from easily accessible synthetic drug candidates [12]. They often feature versatile structural and physical properties such as a large number of stereogenic centres, sp^3-hybridized atoms and variable molecular mass as well as octanol–water partition coefficient. Moreover, they also tend to have a high oxygen content and to contain aliphatic ring systems and therefore display an intricate three-dimensional geometry [13]. Thus, the innovative design of a library of molecules based on natural product frameworks can in principle be propelled by applying specific strategies to synthesize arrays of novel bioactive compounds [14]. To achieve this goal, in the past two decades, several named concepts have been developed to address the unceasing drug discovery challenge [15]. In this review, we discuss these newer natural product-inspired synthetic approaches, among them diversity-oriented synthesis (DOS), biology-oriented synthesis (BIOS), hybrid natural products(HNPs), diverted total synthesis (DTS), pruning natural products (PNP), ring distortion of natural products(RDNPs) and integrating natural product framework with a bioactive molecule (iNPBM). Selected representative examples associated with these strategies are given to demonstrate how they have been applied to afford desired bioactivity.

Diversity-oriented synthesis (DOS)

Shortly after the period of thorough investigation of the potential of combinatorial chemistry, efforts were made towards increasing functional and structural diversity of the prepared compounds [16]. Generally speaking, diversity-oriented synthesis (DOS) was developed to rapidly generate libraries of compounds of high structural and skeletal variety [17]. DOS utilizes multicomponent reactions, complexity-generating transformations, stereoselective synthesis and branching pathways. It also includes so-called forward synthetic analysis in order to enter a comparatively large chemical space [18]. Typically, no more than five transformations, efficient as well as modular synthesis and scaffold diversity within the library of compounds are anticipated to provide novel hit compounds to accelerate drug discovery (Fig. 1) [19].

Generally, DOS was soon able to generate diverse libraries of compounds in a short span time; the molecules were screened across several targets randomly and were not directed towards specific biological targets or disease. In recent years, utilizing natural product frameworks as an origin or synthesis of a natural product-like DOS libraries has transformed the traditional DOS strategy. Natural product-based DOS library is more markedly directed towards a specific biological target. There must be, like in all cases of desired changes of the function of a protein or other target, a structural fit between the target and the modulating ligand. Identification of the binding site is helpful and crucial when it comes to narrowing the chemical space of the synthesized bioactive molecule [20]. The following are two representative examples of DOS modulating a specific biological target, as by disrupting protein–protein interaction and the discovery of new antibiotics to emphasize the potential of natural product-inspired diversity-oriented synthesis (DOS) as a dynamic tool for the discovery of novel bioactive molecules.

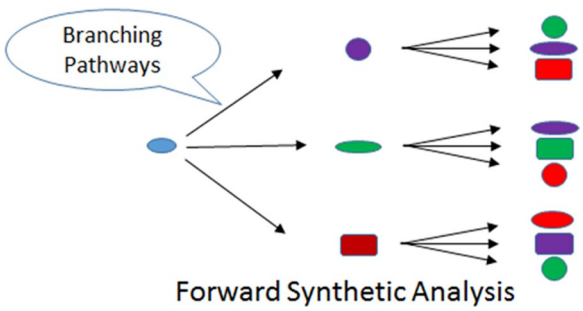


Fig. 1 Schematic representation of the concept of diversity-oriented synthesis. (To generate a small-molecule collection with a high degree of structural, and thus functional, diversity that interrogates large areas of chemical space simultaneously.) [16].

Many cell functions, physiological processes, and disease mechanisms comprise protein–protein interactions involving electrostatic interactions and other intermolecular forces. Thus, modulating protein–protein interaction is one of the attractive drug discovery concepts [21]. However, multiple binding sites, a high number of non-specific binding interactions and also a lack of generally applicable reliable screening assays make protein–protein interactions difficult basic strategy of drug discovery [22].

One such a protein–protein interaction pathway, named Hedgehog signalling pathway involving the protein *Sonic Hedgehog (Shh),* regulates cell proliferation as well as differentiation and is crucial for proper embryonic development. The Hedgehog signalling cascade is initiated by auto-cleavage of full-length Shh to an active N-terminal fragment (ShhN) upon its binding to 12-pass transmembrane receptor Patched (Patch1). It results into the reversal of the inhibitory effect on Smoothened (Smo) and releases Glioma (Gli) transcription factor. This mechanism regulates the transcription of gene Gli1 and Ptc1. The aberrant Shh pathway activity due to mutation of the gene is associated with the initiation of tumorigenesis [23]. The discovery of novel molecules which can modulate Shh signalling pathway have been proposed as one of the potential therapeutic strategy for treating the pancreatic cancer, basal cell carcinoma (BCC), medulloblastoma, prostate cancer and associated disorders (Fig. 2) [24, 25].

The bioactive, naturally occurring macrolactones such as pikromycin, erythromycin, enterobactin, and epothilones are known to act through changing different protein–protein interactions. Based on macrolactone framework **1**, Schreiber et al. synthesized a library of about 2070 small molecules (SM) and screened it for its binding with bacterially expressed protein—N-terminal sonic hedgehog protein (ShhN) to identify several new bioactive macrolactone structures (Fig. 3) [26]. Lead optimization on the initial hit compound **2** by ring contraction resulted in the identification of robotnikin (**3**), which displays strong and concentration-dependent inhibition of Gli expression with an EC_{50} value of 4 μM and EC_{max} reaching 91% (Fig. 3). This pronounced activity renders **3** a promising small-molecule probe of the Hedgehog signalling pathway [27].

In another notable example of utilizing natural product frameworks in DOS, Spring and coworkers have discovered new antibiotics against the methicillin-resistant *Staphylococcus aureus* (MRSA) [28]. Since discovery of Penicillin in the 1930s, antibiotics have revolutionized modern medicine and played in important role in improving the quality of life as well as the life expectancy [29].

However, over-prescription of antibiotics and their use without professional advice have given rise to drug-resistant microbes also termed 'superbugs' [30]. The alarming increase in resistance warrants immediate discovery of novel antibacterial compounds against multidrug-resistant bacteria such as MRSA [15, 31].

Spring and co-worker have synthesized a DOS library of about 242 molecules of 18 different natural product-like frameworks (**8**–**25**) from a solid-supported phosphonate (**4**) as a starting material [28]. Reaction of **4** with different aldehydes was done in step 1 to synthesize twelve different α,β-unsaturated acyl-imidazolidinones (Fig. 4). In the second step, pluripotent **5** is diversified via [3 + 2] cycloaddition, dihydroxylation, and [4 + 2]

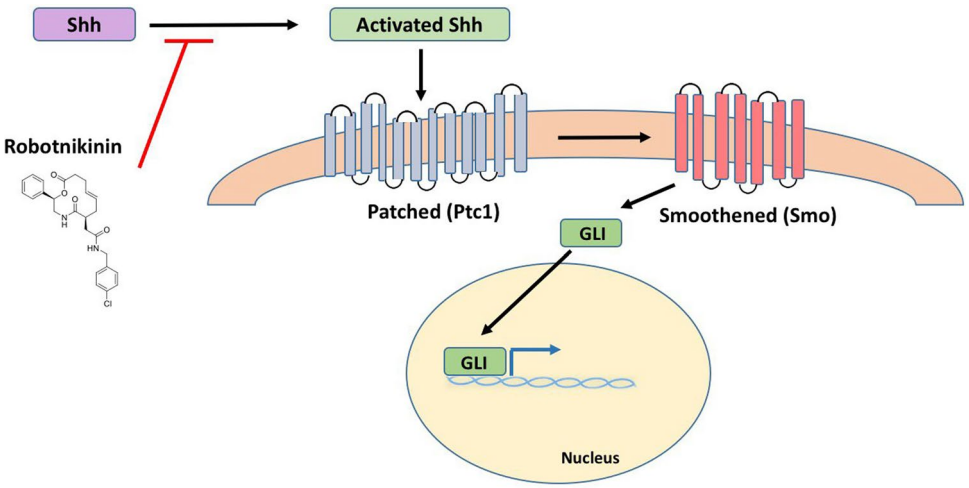


Fig. 2 Schematic diagram showing robotnikin inhibits the induction of the Shh pathway [25]. (Robotnikinin is a small molecule capable of binding to and inhibiting the activity of Sonic Hedgehog (Shh) signaling up stream of Smoothened)

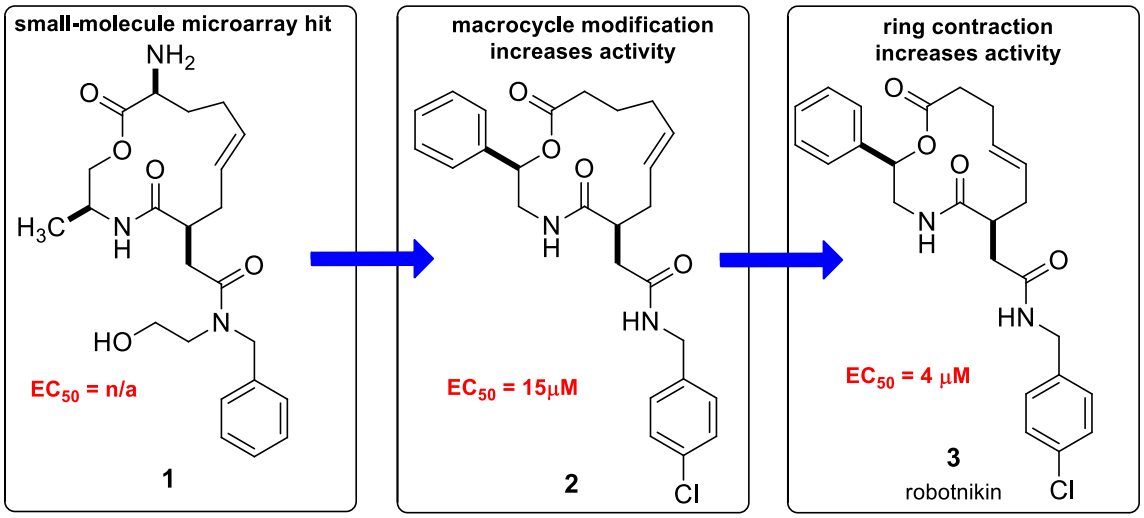


Fig. 3 Small-molecule modulators of Shh pathway discovered by DOS strategy with enhanced bioactivity

cycloaddition to generate further branch point substrates **7**–**9**. These molecules serve as intermediate compounds for the series of versatile organic reactions. Compounds **7** and **8** were further diversified into **10**–**13** and **14**/**15**; norbornene intermediate **9** was transformed into the five different scaffolds **16**–**20**. In step 4, further complexity and diversity was added to generate **21**–**25**. In the final step of purification, the compounds were hydrolysed from the silyl-polystyrene solid support resin and evaluated with regard to their *in vitro* bactericidal activity against two UK epidemic methicillin-resistant strains (EMRSA 15 and EMRSA 16) as well as three different strains of *S. aureus*: a methicillin-susceptible S. aureus (MSSA). In particular, they discovered three novel compounds (**26**–**28**) with growth inhibition against the three strains of *S. aureus*.

One compound named gemmacin (**26**) was found to be a broad-spectrum antibiotic to inhibit the Gram-positive bacteria and to exhibit lower cytotoxicity against human epithelial cells (Table 1).

Based on these two examples, one can see that diversity-oriented synthesis (DOS) of libraries of natural product (NP)-like molecules is capable of providing efficient skeletal diversity to explore biorelevant chemical space and opens a new direction for the discovery of bioactive molecules.

Hybrid natural products (HNP)

In developing potential therapeutics, it is important to limit the number of biologically inactive molecules; that is, synthetic efforts should ideally be focused and not produce irrelevant compounds. Taking advantage of the activity and specificity of known, naturally occurring systems, Tietze [32] and Mehta [33] have proposed the concept of hybrid natural products for drug discovery. In fact, in nature, there are several such naturally occurring natural product hybrids. One such an example is the indole alkaloid vincristine (**29**) which is used for the treatment of lymphatic leukaemia [34]. It is a hybrid of vindoline (**31**) [35], which belongs to the *Aspidosperma* alkaloid family and catharanthine (**30**) [36], which

(See figure on next page.)

Fig. 4 Library of 242 DOS compounds synthesized to study antibacterial activity [20]. Reagents and conditions: **a** LiBr, 1,8-diazabicyclo[5.4.0] undec-7-ene, R1 CHO, MeCN; **b** (R)-QUINAP, AgOAc, iPr2NEt, THF, 788Cl258C; **c** AD-mix, (DHQD)PHAL, THF/H2O (1:1); **d** chiral bis(oxazoline), Cu(OTf)2, 3 E M.S., CH2Cl2, C5H6; **e** R2 COCl, DMAP, pyridine, CH2Cl2; **f** R3 CHO, BH3·pyridine, MeOH; **g** SOCl2, pyridine, CH2Cl2, 40 8C; **h** R4 Br, Ag2O, CH2Cl2, 40 8C; **i** R5 C(O)R5, TsOH, DMF, 658C; **j** R6 CHO, TsOH, DMF, 65 8C; **k** NaN3, DMF, 1008C then dimethyl acetylenedicarboxylate, PhMe, 658C; **l** mCPBA, CH2Cl2 then MeOH, 658C; **m** CH2=CHCO2Bn, PhMe, 1208C, Grubbs II, CH2=CH2; **n** OsO4, NMO, CH3C(O)CH3/ H2O (10:1); **o** RNH2, Me2AlCl, PhMe 1208C; then NaH, R11X, DMF, THF; then PhMe, 1208C, Grubbs II, CH2=CH2; **p** NaIO4, THF/H2O (1:1); then R7 NH2, NaB(OAc)3H, CH2Cl2; **q** NaIO4, THF/H2O (1:1); then R8 NHR8, NaB(OAc)3H, CH2Cl2; **r** R9 CHO, DMF, TsOH, 60 8C; **s** R10C(O)R10, DMF, TsOH, 608C. DMF = N,N-dimethylformamide, THF = tetrahydrofuran, DMAP = N,N-dimethylaminopyridine, (DHQD)PHAL = hydroquinidine 1,4-phthalazinediyl diether, mCPBA = meta-chloroperbenzoic acid, Ts = para-toluenesulfonyl, Grubbs II = 1,3-(bis-(mesityl)-2-imidazolidinyl-idene) dichloro (phenylmethylene) (tricyclohexylphosphine) ruthenium, NMO = 4-methylmorpholine-N-oxide, OTf = CF3SO3, Bn = benzyl, QUINAP = 1-(2-diphenylphosphino-1-naphthyl)isoquinoline

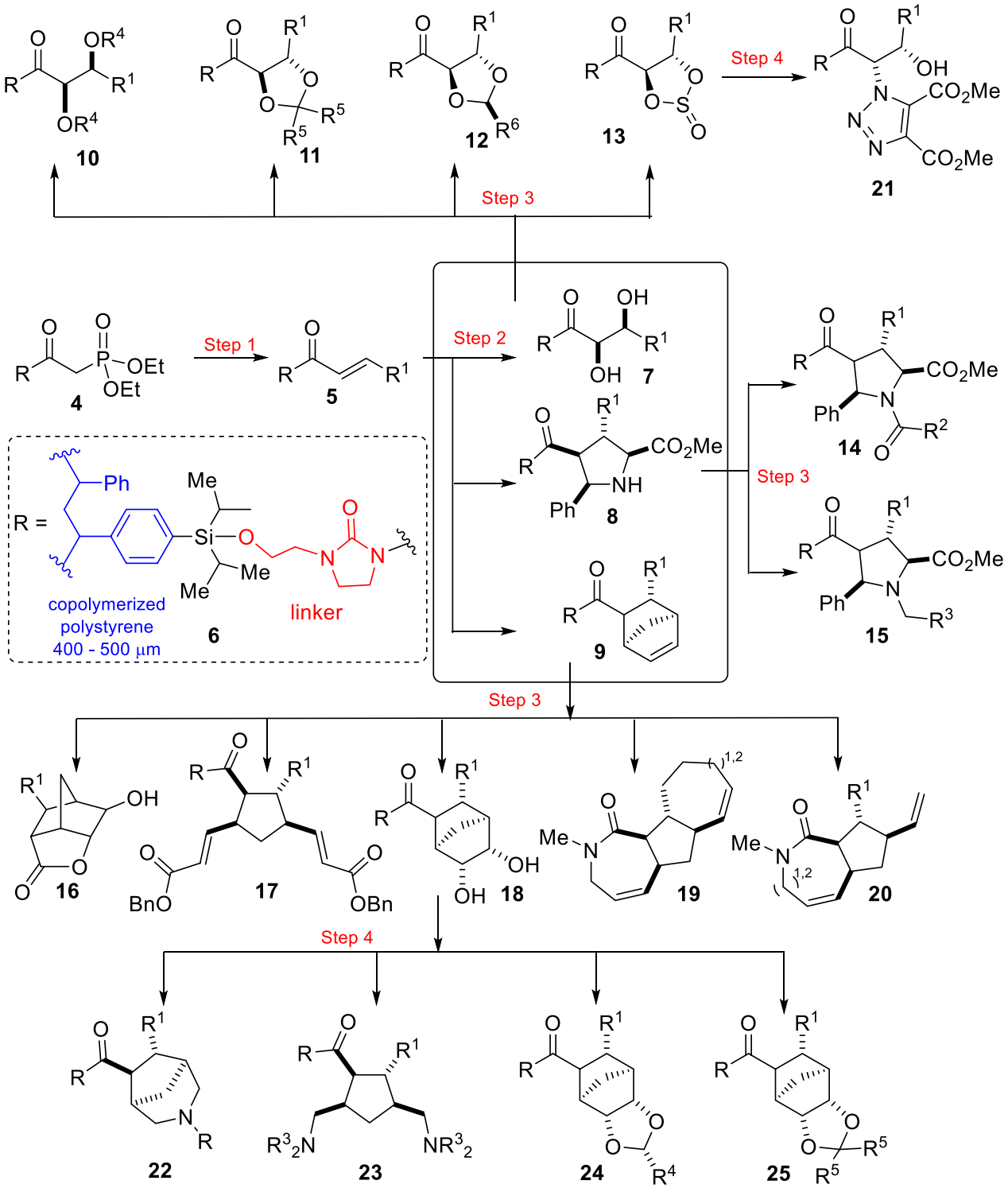
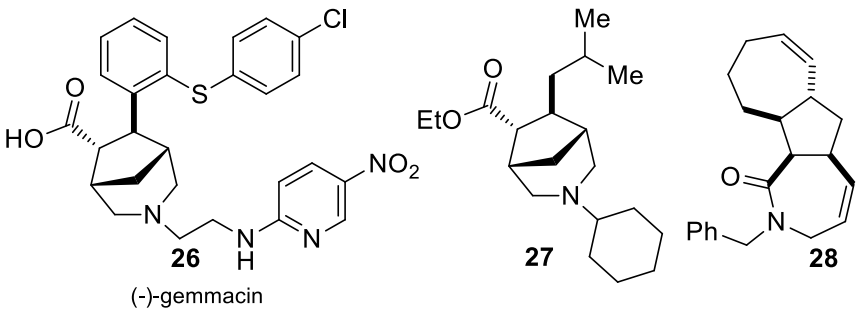


Fig. 4 (See legend on previous page.)

belongs to the *Iboga* class of alkaloids (Fig. 5). The individual monomers exhibit no significant activity, whereas **19** possesses pronounced bioactivity as well as specificity.

Generally speaking, artificially linking two or more natural products may result in the creation of hybrid molecules with improved bioactivity that differs from those

Table 1 Antibiotic activity of compounds synthesized from DOS strategy [20]



	MIC µg/mL		
	MSSA	EMRSA 15	EMRSA 16
(±)-gemmacin	2	16	32
(-)-gemmacin	ND	8	16
(+)-gemmacin	ND	16	32
(±)-**17**	16	16	>64
(±)-**18**	32	32	>64
etythromycin	0.5	>64	>64
oxacillin	0.5	>32	>32

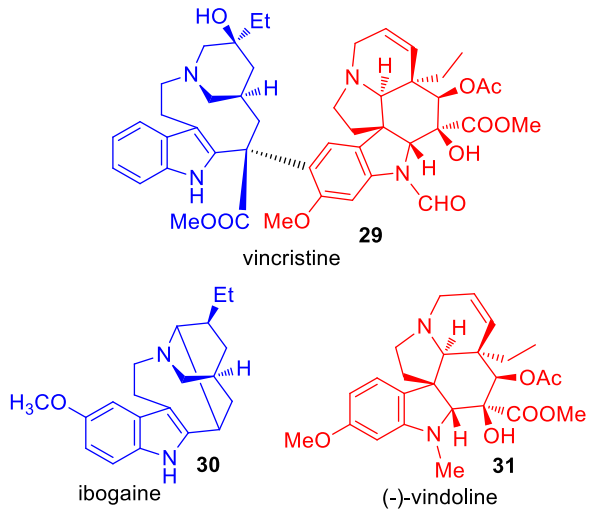


Fig. 5 Naturally occurring hybrid molecules. (Molecular structure of ibogaine, vindoline, vincristine). The structure of vincristine, two vinca alkaloids, are formed by two polycyclic moieties, namely vindoline (red) and catharanthine (blue). The catharanthine portion is also the basic motif found in the ibogaine molecule.)

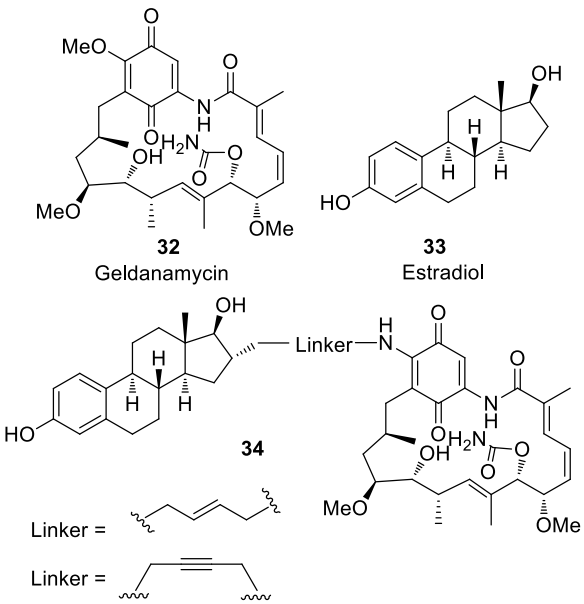


Fig. 6 Hybrid natural products synthesized from geldanamycin and estradiol

of its parent molecules. Based on this concept, natural product hybrid of geldanamycin (**32**) and estradiol (**33**) have been prepared and evaluated for its bioactivity, in particular, antimicrobial activity (Fig. 6). Compound **32** is an ansamycin antibiotic isolated from *Streptomyces hygroscopicus* and also effectively inhibits human epidermal growth factor receptor (HER2) kinases [37]. On the other hand, **33** induces selective degradation of certain

oestrogen receptors (ER) [38]. The estradiol-geldanamycin hybrid compounds **34** were found to be more selective than **32** in inhibiting HER2 and ER in breast cancer cell line MCF7 [39].

Many such natural product (NP) hybrids display exceedingly higher biological activity than their isolated parent natural molecules. Nonetheless, covalent linkage of two bioactive compounds does not necessarily lead to a overall improved desired properties. The oxindole containing natural product quinocarcin (**35**) [40] is isolated from *Streptomyces melunovinuceus*, displaying prominent antitumour activity [41]. It inspired Williams and coworkers to combine **35** with the natural product netropsin (**36**). However, the quinocarcin–netropsin hybrid **37** was found to display lower biological activity than its parent molecules (Fig. 7) [42].

The hybrid natural product is one of the newer natural product-inspired synthetic approaches, which can provide access to unique combinations of existing natural fragments. Although only a limited number of hybrid molecules have been synthesized to date, mainly for the development of new antibiotics and anticancer agents, the bioactivity associated with these hybrid molecules emphasizes the promising role of HNP for future drug discovery.

Biology-oriented synthesis (BIOS)

Combinatorial chemistry and DOS generate very large libraries to be screened against multiple different targets and hence potentially make the overall process highly expensive [43]. Therefore, to limit the number of molecules for biological studies, a unique structure-based approach named biology-oriented synthesis (BIOS) was introduced by Waldman and co-workers (Fig. 8) [44]. This approach takes into account the structural

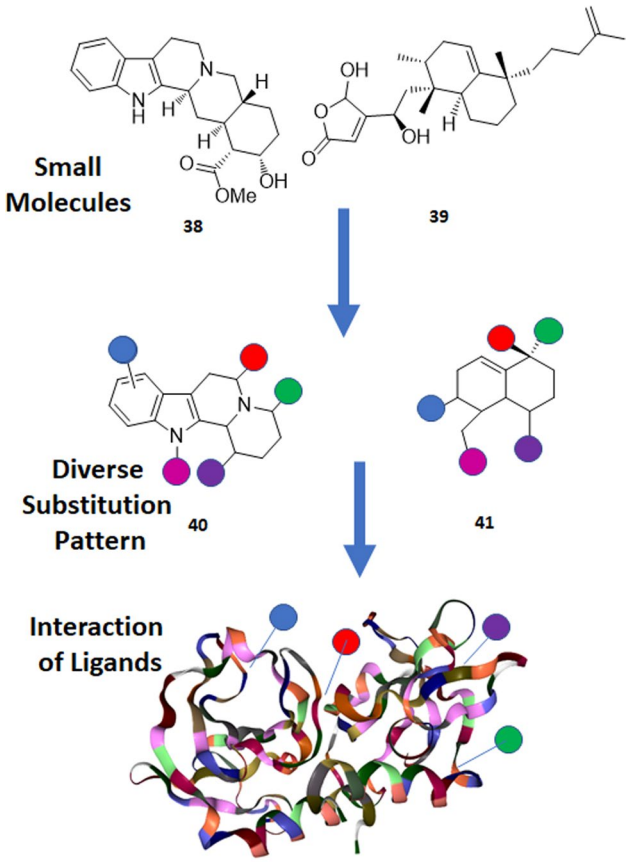


Fig. 8 Schematic representation of the concept of biology-oriented synthesis depicting scaffold-substituent analogy between small molecules and protein adapted from ref. 44 (https://doi.org/10.1002/anie.201007004) with permission). (The small-molecule scaffold determines the spatial orientation of the substituents, whereas the protein subfold arranges the amino acid side chains spatially. Binding occurs when compatible substituents match in their spatial positioning so they can interact.)

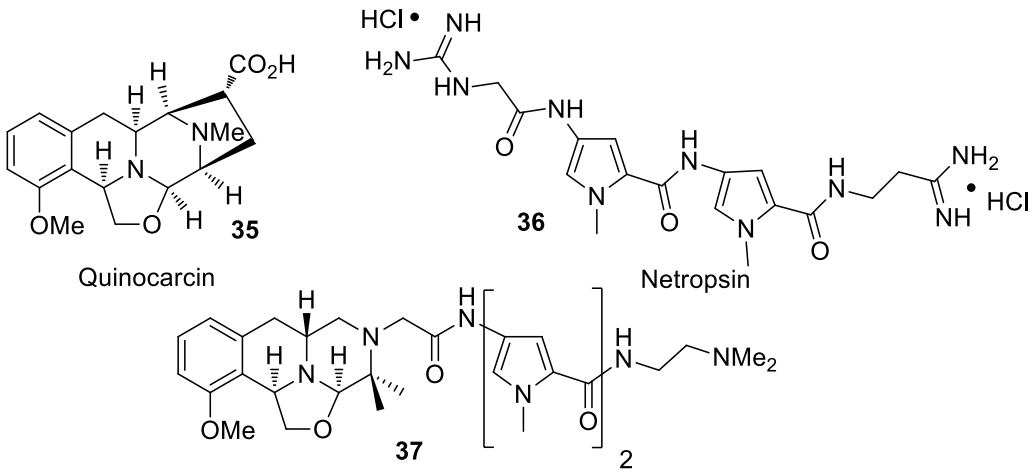


Fig. 7 Hybrid natural product synthesized from quinocarcin and netropsin

conservatism during evolution of the chemical space of target proteins and also natural products (NP) modulating them. The structural conservatism within protein families limits the number of small molecules and binding sites. The systematic structural analysis of proteins, namely 3D structure, sequence homology and classifying the small molecules which modulate them, is supposed to lead to the discovery of novel bioactive molecules. The applications lie, more generally speaking, in chemical biology as well as medicinal chemistry [45]. Waldmann and coworkers have invented a cheminformatics tool 'structural classification of natural products' (SCONP). Relatively complex natural products (such as **38** and **39**) are reduced to core scaffolds by holding bioactivity as a main guiding principle. Decorating the cores with new groups generates a so-called natural product structural tree, which is investigated in terms of target modulation and also further improved [46].

Thus, a library of a limited number of molecules (**40**,**41**) synthesized based on the BIOS concept may have added relevance to specified target/s and thus increases chances of displaying the desired bioactivity [47]. This BIOS strategy has been effectively applied for discovery of several novel bioactive molecules, as exemplified in the following [48].

The progressive degeneration of neuron and loss of neural activity is associated with many neurodegenerative disorders. Discovery of novel molecules which can promote neurite growth and restore neuronal viability or which can prevent neuronal decline is utmost important [49]. Towards the development of novel neurite growth-promoting compounds, Waldmann and coworkers have utilized the BIOS approach based on the iridoid scaffolds silphinene (**42**) as well as harpagide (**43**) and rhynchophylline (**44**), which belongs to the secoyohimbane class of compounds (Fig. 9) [50]. All of these are known to possess neurotropic and neuroprotective activity [51].

A library of 54 iridoid analogues (**48**) were synthesized by a [3+2] cycloaddition/Baeyer–Villiger oxidation sequence, and library of 56 secoyohimbane-related compounds (**52**) by enantioselective and organocatalysis. They were screened in phenotypic assays with respect to the modulation of neurite outgrowth. These assays were able to identify several new molecules (**53**–**56**) possessing growth-promoting properties, and which can be used as chemical probes for studying neurodevelopmental process (Fig. 9) [52].

The enzyme 11β-Hydroxysteroid dehydrogenase type 1 (11βHSD1) is NADPH-dependent enzyme which activates glucocorticoid hormones (GCs). Glucocorticoids regulate various physiological processes including glucose and lipid metabolism, and increased levels may result in various metabolic syndromes, such as hypertension, type 2 diabetes, and dyslipidemia [53]. Thus, selective inhibition of 11βHSD1 is an important strategy for the treatment of these syndromes [54]. The BIOS approach, by combining protein structure similarity clustering (PSSC) [55] and SCONP, was applied to the discovery of novel and selective 11βHSD1 inhibitors (Fig. 10) [56]. Analysis of PSSC of 11βHSD1 and dual specificity phosphatase (Cdc25 A) and acetylcholine esterase (AChE) revealed that the active site and position of the catalytic amino acid residue show very good overlap in these three proteins. Although the functions of 11βHSD1, Cdc25 A and AChE are different, the similarity of active sites indicates that the molecules which can modulate the Cdc25 A and AChE have the potential to modulate 11βHSD1. Generating PSSC analysis and SCONP analysis of related natural products can therefore lead to the identification of novel 11βHSD1 modulators [57]. Consequently, a SCONP tree was constructed by the software, based on the natural product dysidiolide (**57**) [58], which is known to inhibit Cdc25A, and glycyrrhetinic acid (**58**), which is a known 11bHSD ligand.

This analysis of multicyclic natural products led the researchers to identify decalin scaffolds **IV** and **VI**, which were presumed to be privileged cores associated with activity changes in 11βHSD1, Cdc25 A, and AChE. A natural product-inspired library of 483 compounds was synthesized and screened for their activity against 11βHSD1. Combining PSSC and SCONP led to the discovery of several new 11βHSD1 inhibitors **59**–**62**, acting at the nanomolar concentration level in vitro. Additionally **59** displays selective in vivo cellular inhibition of 11βHSD1 [46].

These representative examples emphasize the importance of the BIOS strategy in the efficient discovery of novel bioactive molecules [55].

Diverted total synthesis (DTS)

Danishefsky *et al.* purported a different concept 'diverted total synthesis', for discovery of novel bioactive compounds [59]. It is based on developing a smaller library of compounds by using and diverting the intermediates formed during the total synthesis of small-molecule natural products (SMNPs) [60]. Starting from building blocks **A**, the complexity and diversity associated with synthetic intermediates **B**, obtained during total synthesis of natural product (NP) **C** will allow access towards uncharted chemical space (Fig. 11). Such space would otherwise not be accessible due to limitations levied by biosynthetic pathways or by direct modification of parent natural products **C**.

Therefore, molecules obtained by DTS might exhibit a upper order of complexity (**D**) or a lower order of

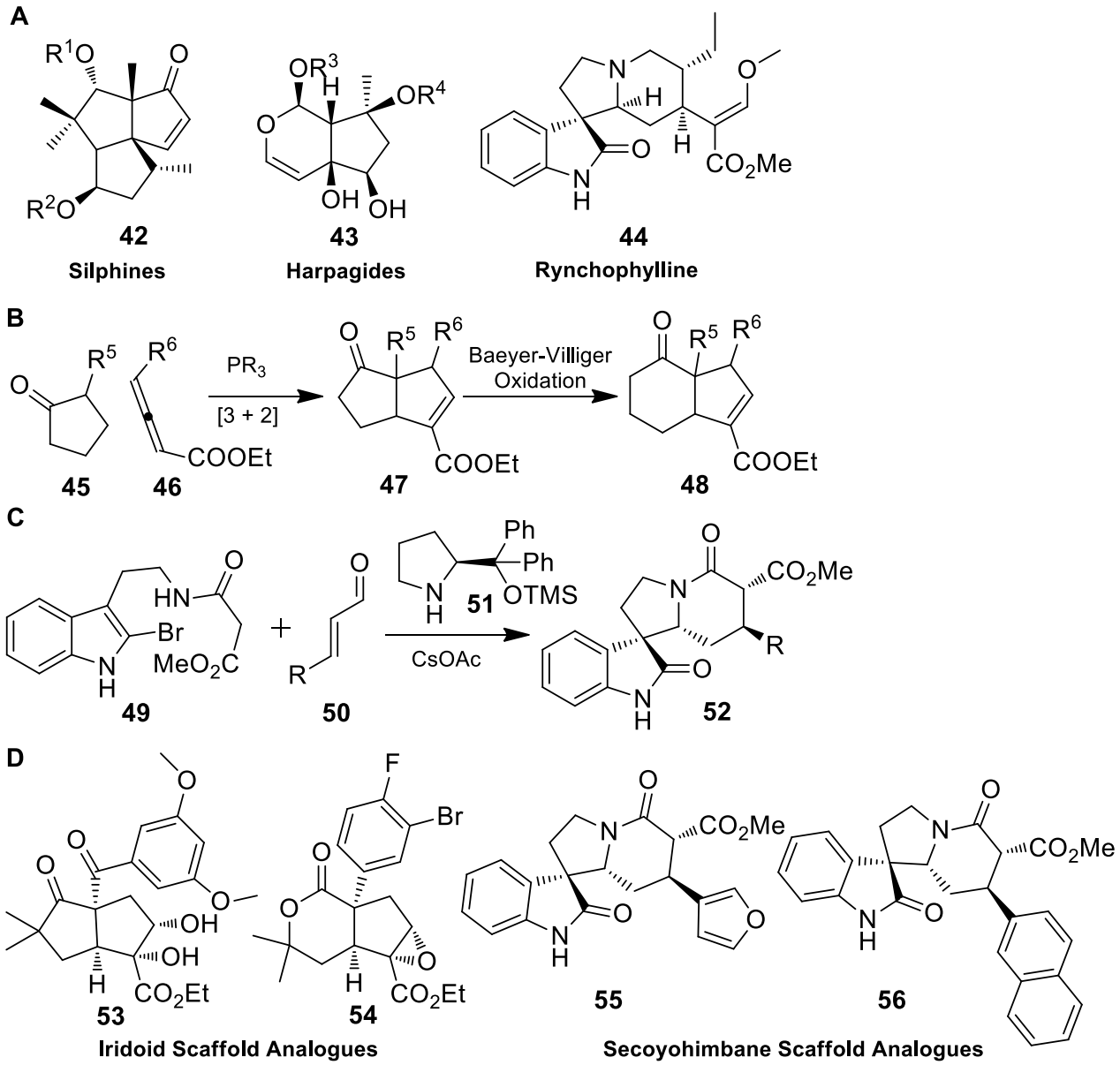


Fig. 9 Iridoid and secoyohimbane scaffold-inspired synthesis of BIOS library for discovery of neurite growth-promoting compounds

complexity (**E**) than **C.** These can be evaluated for their potential biological activity [61].

Such a library of compounds was produced by Danishefsky and coworkers based on the total synthesis of epothilone B (**63**) (Fig. 12). The natural product epothilone B is isolated from mycobacterium *Sorangium cellulosum* and found to exhibit strong in vitro cytotoxicity in multidrug-resistant (MDR) cell line by promoting stabilization of microtubule polymerization, thereby interrupting the cell division and apoptosis. However, in vivo studies revealed that epothilone B was highly toxic to mice, which inspires editing of the epothilone B framework to reduce its toxicity and increase the desired bioactivity. In the course of DTS, compound dEpoB (**64**), lacking the epoxy group, was made and shown to possess remarkably lesser toxicity as anticancer agent. Likewise, 9,10-dehydro-dEpoB (**65**) with added unsaturation was prepared and displayed improved survival rate in mice. Furthermore, fludelone (**66**) was obtained by installing a trifluoromethyl group, resulting more effective for tumour reduction in comparison with all the previous molecules. Eventually, alteration of the heterocyclic moiety leads to the identification of isofludelone (**67**), a

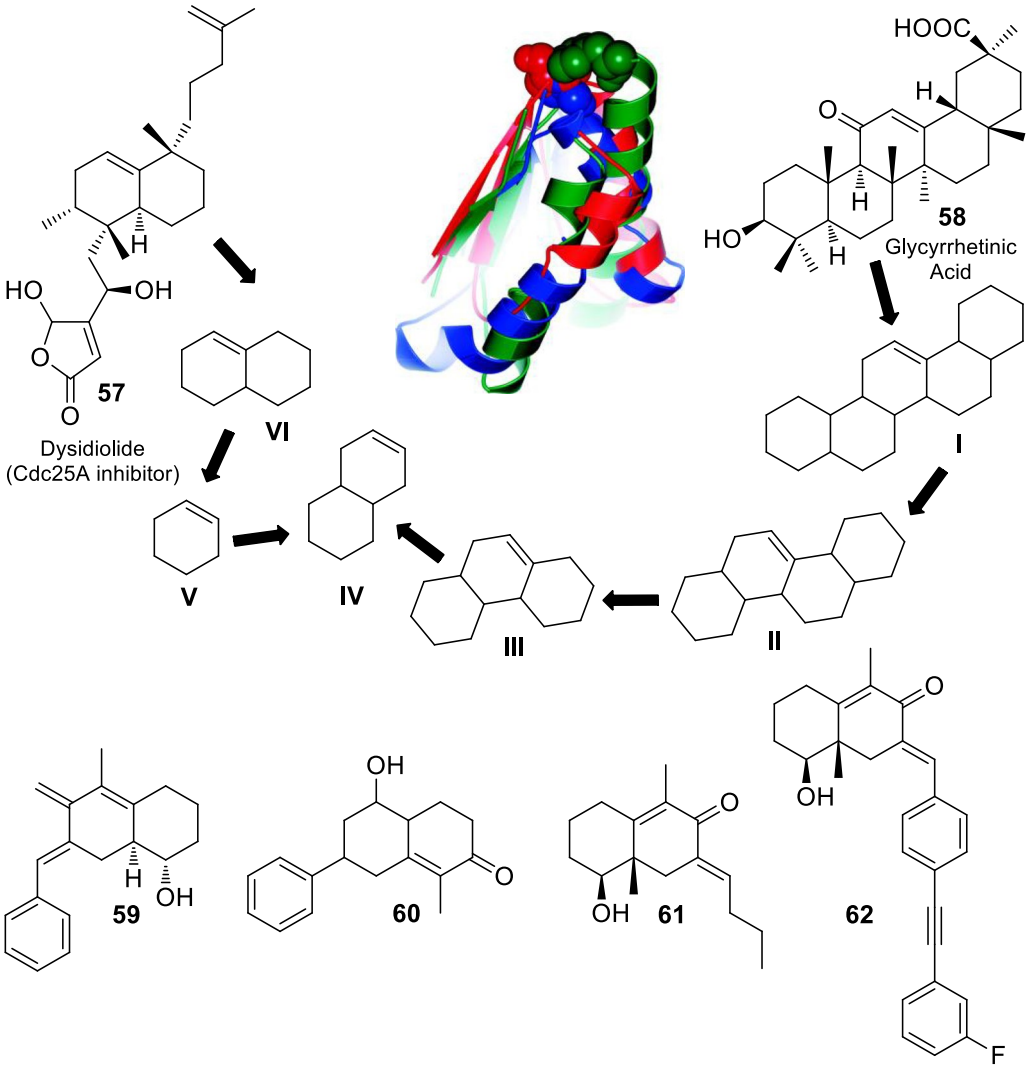


Fig. 10 SCONP analysis of natural products dysidiolide and glycyrrhetinic acid for identification of selective 11bHSD1 inhibitor using BIOS [44] and PSSC analysis of the superimposed catalytic sites of Cdc25A (red), 11_HSD1 (green), and AChE (blue) [46]

promising candidate intended for cancer treatment and currently under pre-clinical trials [59].

Pruning biomolecules and natural products (PBNP)

The structure of natural products (NPs) varies from simple frameworks to highly complex 3D architectures. The preparation of bioactive natural products with higher complexity poses a enormous challenge for the synthetic organic chemist. In the course of biosynthesis, the biochemical machinery can easily vary the substitution of the core structure in terms of side chains and functional groups, which can lead to different structures and activity of the natural product(s). In many cases, the simplified natural product framework retains substantial bioactivity [62]. Thus, pruning of biomolecules and natural products (PBNP) by systematic identification of the pharmacophore can address the synthetic challenge by reducing the number of chemical steps and may lead to the discovery of novel bioactive molecules [63]. To a certain extent, this approach is related to BIOS but relies primarily on cutting off substituents.

The discovery of eribulin (**69**) from the complex marine natural product halichondrin B (**68**) by Eisai Pharma and Kishi is a prominent example of PBNP for the discovery of anticancer drugs (Fig. 13). Halichondrin B (**68**) was isolated from marine-sponge *Halichondria Okadai*, which is a polyether macrolide [64]. During its total synthesis and biological evaluation, it was found that the right half of the molecule displays cell growth inhibition. The hydrolyzable ester functionality of **68** changed to a

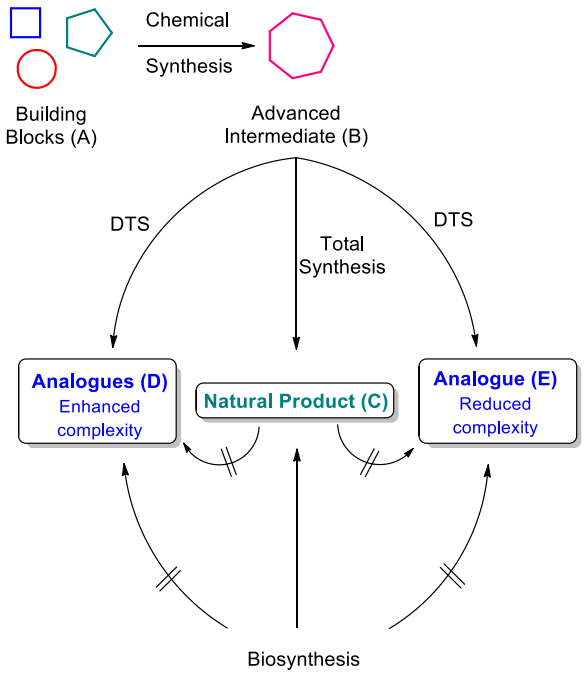


Fig. 11 Schematic representation of the concept of diverted total synthesis

non-hydrolyzable bioisostere enhanced the in vivo efficacy. Further synthetic efforts and clinical studies led to the identification of **69** for treating of late-stage breast cancer resistant to other anticancer drugs [65].

Another prominent example of PNBP is the discovery of novel migrastatin analogues. Migrastatin (**70**) is macrolactone isolated from *Streptomyces sp.* MK929-43F1 [66] which was found to inhibit cancer cell migration (Fig. 14). During its synthesis and bioevaluation, it was found that its truncated analogue **71** possesses increased activity as compared to the **70** and can be a promising candidate in cancer therapy to address metastasis (Fig. 14) [67].

Another example of PBNP is the development of antihypertensive agent rostafuroxin (**73**) (Fig. 15). The natural product ouabain (**72**) from the bark the tree of *Acokanthera ouabaio* is being used as an arrow poison by some of the African tribes. It was also found to be useful for the treatment of cardiac conditions. Ouabain binds to the plasma membrane and inhibits the Na+/K+ATPase in vivo. [68] However, it also has several side effects. The simplified analogue **73** was found to inhibit Na+/K+ATPase more selectively, without interacting with other receptors which regulate blood pressure; it is now being studied in clinical trials for treating hypertension [69].

Such truncated or simplified natural product obtained by PBNP will also not only help to gain insight into the role of the natural product during its evolution and biological processes but also directs the discovery of novel modulators of the biological targets.

Ring distortion of natural products (RDNP)

In order to rapidly generate a novel library of drug-like small molecules from a natural product with relatively high structural and complexity, Hergenrother has reported a 'ring distortion strategy'. In this approach, natural products with of a given framework, such as the 5,6,6-fused tricyclic system **74**, are converted into different core scaffolds by applying a minimum number of steps (Fig. 16). In this process, a distinct series of molecules is synthesized by taking inspiration from the biosynthetic pathway, which often creates diverse compounds from a common intermediate [70]. The ring distortion approach involves chemoselective transformations such as ring cleavage, expansion, fusion, as well as rearrangement, leading to systematically altered scaffolds such as **75**–**78** [71]. This strategy was exhibited for the production of different analogues of three readily available natural products, namely gibberellic acid (**79**), adrenosterone (**80**), and quinine (**81**) (Fig. 17). The RDNP produced 19, 18, and 12 diverse compounds, respectively, from these natural products.

These compounds were studied by cheminformatics techniques for correlation between structural features and potential biological activity [72]. The detailed results of bioactivity studies have not been disclosed yet.

Indole-containing compounds are abundant in nature, interacting with numerous biological targets and therefore displaying diverse biological activity. The alkaloid yohimbine (**82**), isolated from the bark of *Pausinystalia johimbe*, is known to inhibit the α2-adrenergic receptor (Fig. 18). This readily available natural product, which contains a complex multicyclic structure with a fused indole system, was the starting point for an extended RDNP study to rapidly generate a library of 70 diverse and complex compounds. The yohimbine ring distortion (RDNP) library was screened for bioactivity in processes linked inhibition to cancer, inflammation, and against pathogenic bacterial strains, whereby several hit compounds were identified (Fig. 19). One of the compounds, **83**, was found to exhibit promising anti-inflammatory as well as hypoxia-inducible factors to display (HIF)-dependent anticancer activity [73]. Furthermore, the compounds **84** and **85** were found to be activators of the Nrf2-ARE pathway. The transcription factor Nrf2 (Nuclear erythroid 2-related factor 2) selectively binds to antioxidant responsive element (ARE). Activation of Nrf2/ARE signalling pathway generally protects mammalian cells from impending oxidative stress-induced cell death. Thus, compounds which have ability to modulate

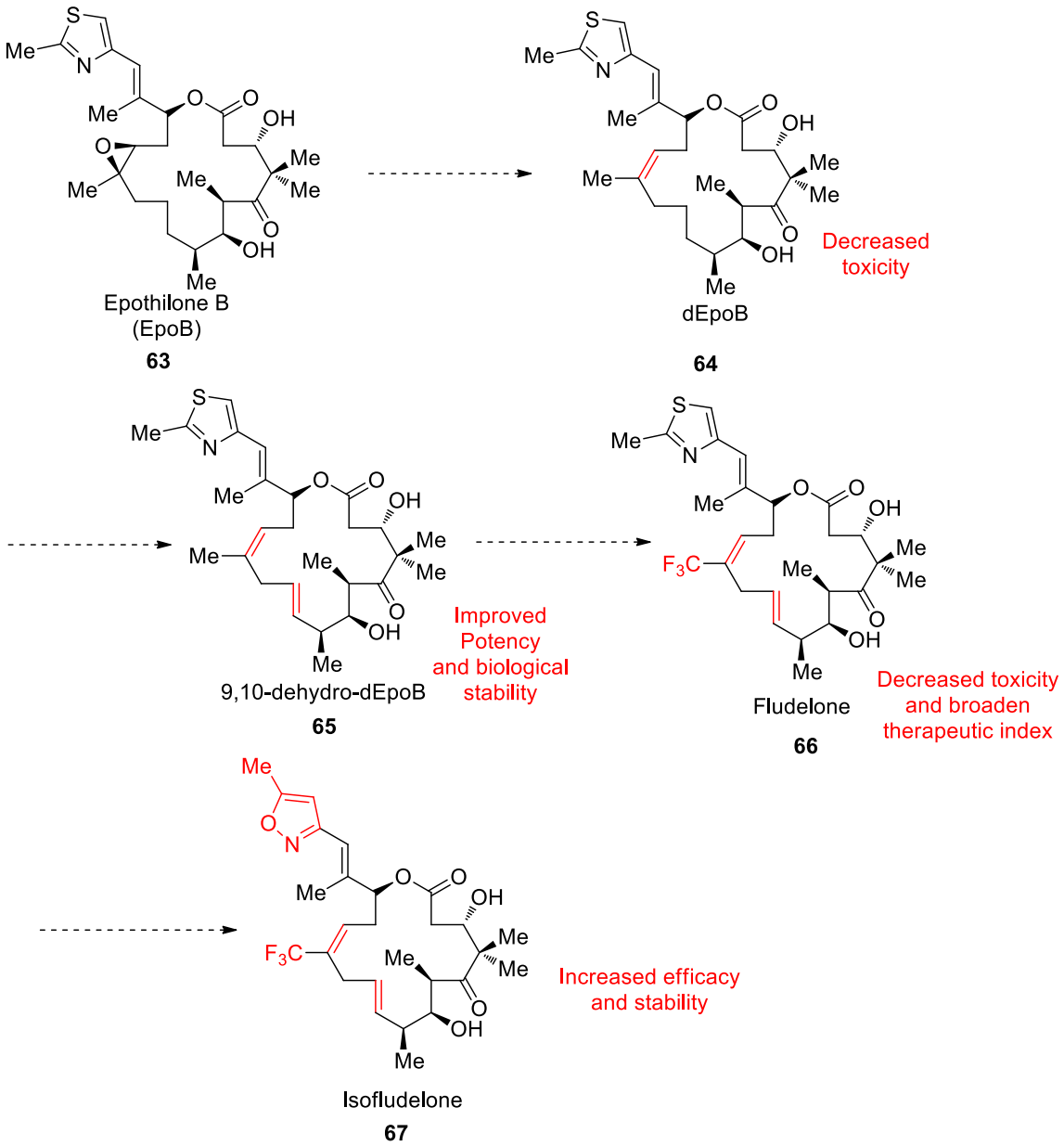


Fig. 12 Discovered novel anticancer compounds from the diverted total synthesis of Epothilone B with modulating the bioactivity

Nrf2/ARE can be prophylactive agents against cancer [74].

Conversely, Nrf2/ARE inhibitors render cancers cells more susceptible to chemotherapy. The compounds **86**–**88** were found to be selective inhibitors of Nrf2/ARE [75].

Although the availability of pure natural products isolated from natural resources limits the scope of RDNP, the systematic application of this strategy offers a convenient approach towards expanding biorelevant chemical space.

Integrating natural product framework with bioactive molecules (*i*NPBM)

Pandey et al. have introduced a distinct methodology of integrating natural product framework with synthetic bioactive molecules (*i*NPBM) [76]. This concept takes into consideration that increased bioactivity may result from the designed structural combination of a natural product with a synthetic pharmacophore. Schematically, this is exemplified in Fig. 20; a natural product framework (**A**), that possess limited biological activity against specified target, is integrated with a synthetic

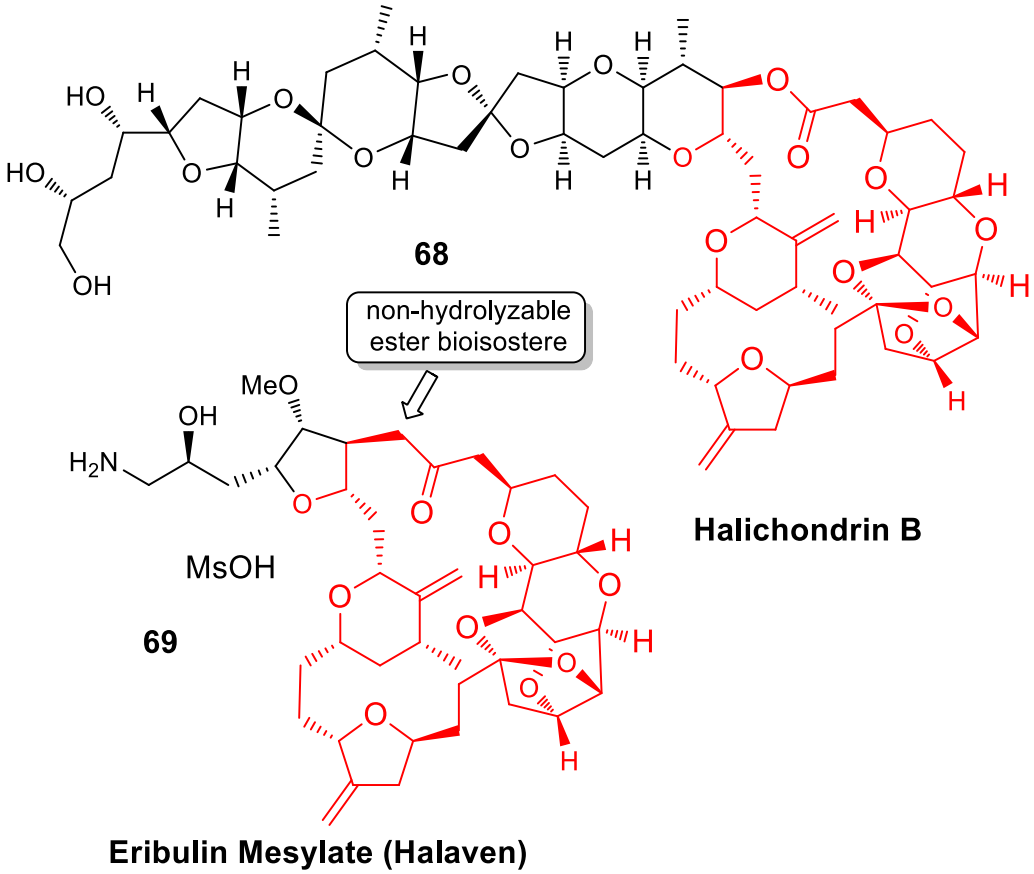


Fig. 13 Pruning of natural product halichondrin B for the discovery of anticancer drug halaven

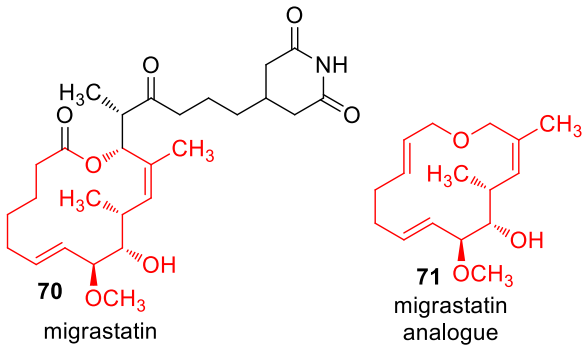


Fig. 14 Discovery of novel migrastatin analogue by pruning of natural product

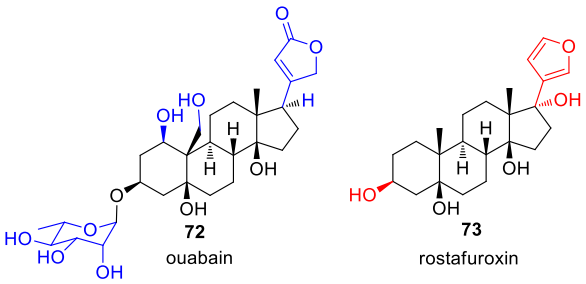


Fig. 15 Pruning of natural product ouabain for the discovery of hypertension drug

bioactive molecule (**B**), featuring one common structural motif, to afford the integrated molecules (**C** and **D**).

The resulting molecules ideally combine the bioactivity as well as selectivity of both molecules to exhibit highly enhanced therapeutic activity in comparison with their parent compounds.

The widely distributed five distinct human muscarinic receptors (M1-M5) belong to family of G-protein-coupled receptors (GPCR) and are proven to regulate numerous essential processes of the central and peripheral nervous system. Gephyrotoxin (**89**) is an alkaloid obtained from the frog *Dendrobates histrionicus* and exhibits mild-antimuscarinic activity (Fig. 21). For the discovery of novel muscarinic receptor modulators, this natural product gephyrotoxin was combined with isoindolines (**90**) [77] which display a wide spectrum of

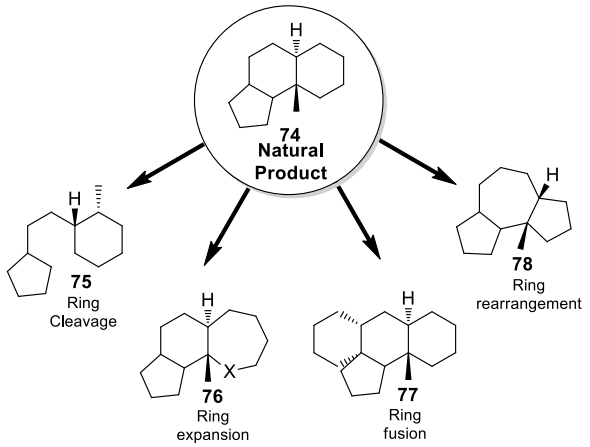


Fig. 16 Schematic representation of strategy ring distortion of natural product. (Ring-distortion reactions can be used readily to convert natural products into complex and diverse scaffolds.)

bioactivities. The presence of the common pyrrolidine ring was the basis for the design of integrated multicyclic molecules, such as **91** and **92**. A library of these integrated structures was synthesized and screened against various muscarinic receptors. A few of them turned out to be hit molecules featuring specific modulation of muscarinic receptor.

Compound **93** was found to be a potent M2 agonist with activity of < 4 nM and to be helpful in alleviating cognitive deficiency in a mouse model (Fig. 22) [78]. Moreover, compounds **94** and **95** are moderate and selective M2 agonists. On the other hand, compounds **96** and **97** act as selective M3 antagonist with activity of < 1 nM and might be further improved for treating respiratory disorders [79]. As illustrated by this study, the *i*NPBM approach suggests an unique strategy towards the discovery of receptor protein modulators alongside promising therapeutic implications.

Miscellaneous strategies

Waldmann and co-workers reported designed pseudo-natural products by using different combination of natural products and fragment-based compound development to afford novel performance-based diverse natural products displaying varying biological activity [80]. A natural product library of 244 member pseudo-natural products are designed by using indole-containing or chromanone containing fragments with natural product quinine, quinidine, sinomenine, and griseofulvin (**98–102** Fig. 23).

These fusion of NP fragments with different combinations provided pseudo-natural product compounds which spans over wide chemical space to display diverse bioactivity. The cheminformatic analysis suggests several compounds could exhibit both drug-like and natural product-like properties.

Recent updates

In additional example, Duttwyler and coworkers fused boron clusters with natural products to explore bioactivity of resultant natural product-boron cluster hybrids [81]. Stereoselective B-H activation was achieved to afford asymmetric boron cluster by fusing natural products camphanic acid and menthol **103–106** (Fig. 24). Several of resulting compound displayed excellent bactericidal properties against Gram-positive as well and Gram-negative bacterium strains with bioactivity up to 2-ug/Ml.

These results open up new space for the discovery of novel bioactive dodecaborate cages having diverse antimicrobial properties by fusing with suitable natural products (NP).

Zou and coworkers have recently reported efficient construction of 1,3-indanedione-based tetrahydroquinolines based on biology-oriented synthesis (BIOS). Spirocyclic tetrahydroquinoline and Spiroindane-1,3-dione were selected natural products for guiding the BIOS approach. Various 2-arylidene-1,3-indanediones reacted with different vinyl benzoxazinanones by using Pd catalyst to provide novel library of spirocyclic tetrahydroquinolines (Fig. 25).

Two of the synthesized products **114** and **115** display remarkable activity by inducing apoptosis in A549 human lung cancer cells [82].

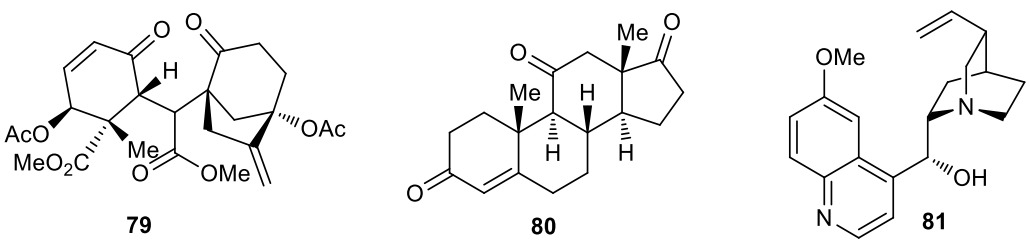


Fig. 17 Natural products for the synthesis of novel library of compounds by RDNP

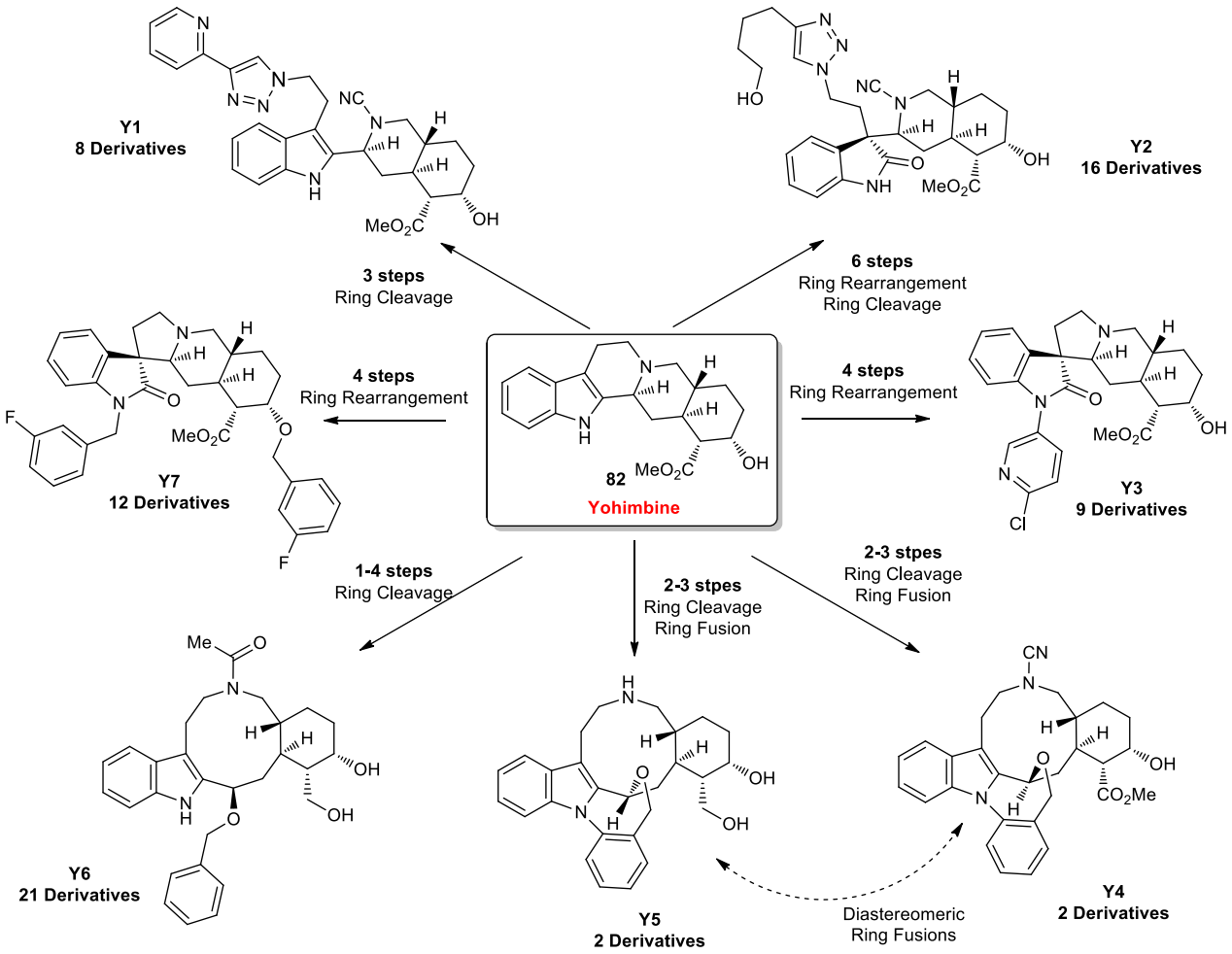


Fig. 18 Ring distortion of yohimbine for the discovery of novel bioactive molecules [75]

Natural products and molecular modelling for drug discovery

Bioactive natural products are vital starting points for crafting newer and improved analogues through advanced medicinal chemistry techniques like molecular modelling. Natural products and its analogues are rigorously studied through SAR analysis and molecular modelling to enhance potency, reduce toxicity, and optimize pharmacokinetics. Interactions with various ligands/target proteins are crucial in determining biological activity. The most promising analogues undergo synthesis and thorough evaluation via in vitro and in vivo assays, culminating in the development of optimized drug candidates. The overall process of molecular modelling involves in silico ligand construction and preparation, target preparation, docking, identification of hit molecule, and optimization of hits [83].

Software like Schrödinger, AutoDock Vina, Discovery Studio and optimization software such as Chimera, Chem 3D Ultra, and Avogadro are employed for molecular modelling. Initially, optimized 3D structures of ligands/targets in PDB format can be obtained from databases like PUBCHEM, while ZINC database provides access to structures of known natural products. In silico ligand construction involves geometry optimization to achieve minimal energy levels before docking. After energy minimization, the binding site for natural ligands within the target must be defined during target preparation. Subsequently, the 3D structures of natural products and their analogues are docked against the specified target using docking software to assess binding energy and analyse intermolecular binding interactions. The docking simulation results are then scrutinized to identify the top interactions. Based on interaction rankings, hit molecules exhibiting high affinity towards the target are identified. Further optimization of hit involves studying various analogues of hit molecules with improved drug-like properties using QSAR software, including stability, pharmacokinetic, and pharmacodynamic properties. Thus, molecular modelling enables the identification of

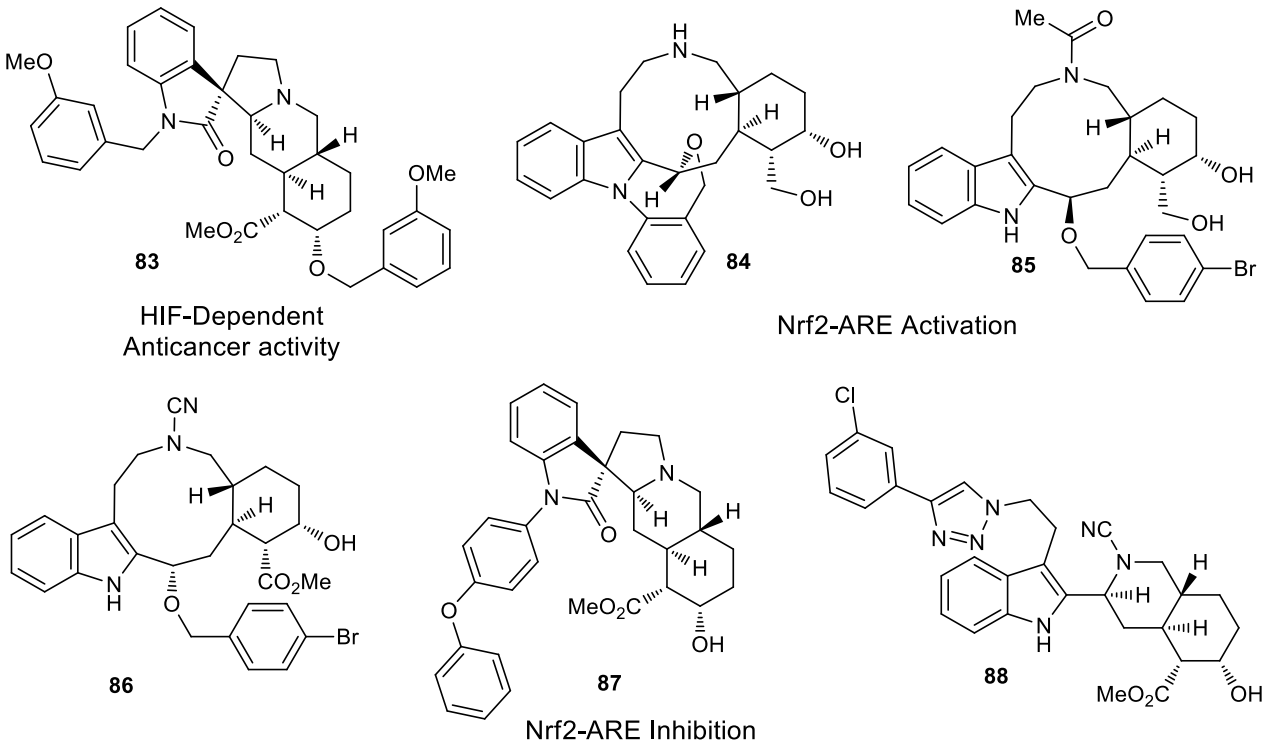


Fig. 19 Bioactive compounds from RDS of yohimbine

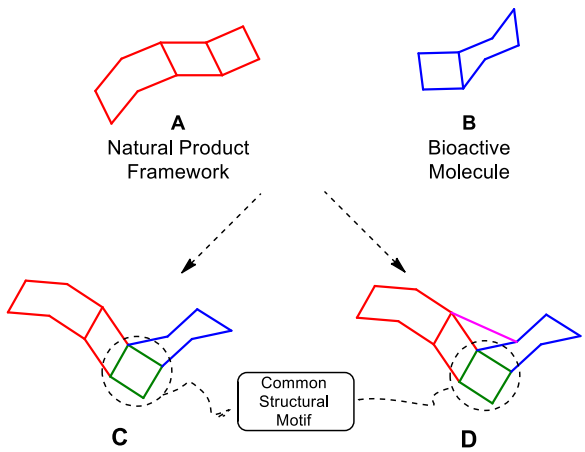


Fig. 20 Schematic representation of strategy integrating natural product and bioactive molecule for the discovery of novel bioactive molecules

potential hits for a target biological activity and facilitates establishing a robust structure–activity relationship (SAR) during lead optimization. This process effectively narrows down the pool of compounds for real testing through bioassays [84].

Very recently, Stefan Gahbauer and coworkers utilized computational design to discover potent inhibitors targeting the NSP3 macrodomain of SARS-CoV-2 with low- to sub-micromolar affinity. Ligands were designed by amalgamating small-molecule fragments and employing ultra-large library docking of 450 million molecules. In total, 160 ligands across 119 different scaffolds were identified, accompanied by the determination of 152 Mac1-ligand complex crystal structures. This approach led to the discovery of several selective and cell-permeable molecules, paving the way for developing novel antiviral therapeutics for SARS-CoV-2 (Fig. 26) [85].

Conclusions

Natural products (NPs) have always been a source of inspiration for designing novel drug-like molecules which largely relied on trial and errors assisted by serendipity. The systematic development of synthetic strategies based on logical hypothesis inspired from natural product has revived interest of medicinal chemists in utilizing them for innovative drug discovery. Recently, there has been major advancement in synthetic methodology with development of modern catalyst, advanced reagents which allows rapid derivatization of organic compounds. These coupled with contemporary development in computational tools for designing molecules, docking software, and biological screening allow swift detection of hit molecule for further drug development. This review elaborates several

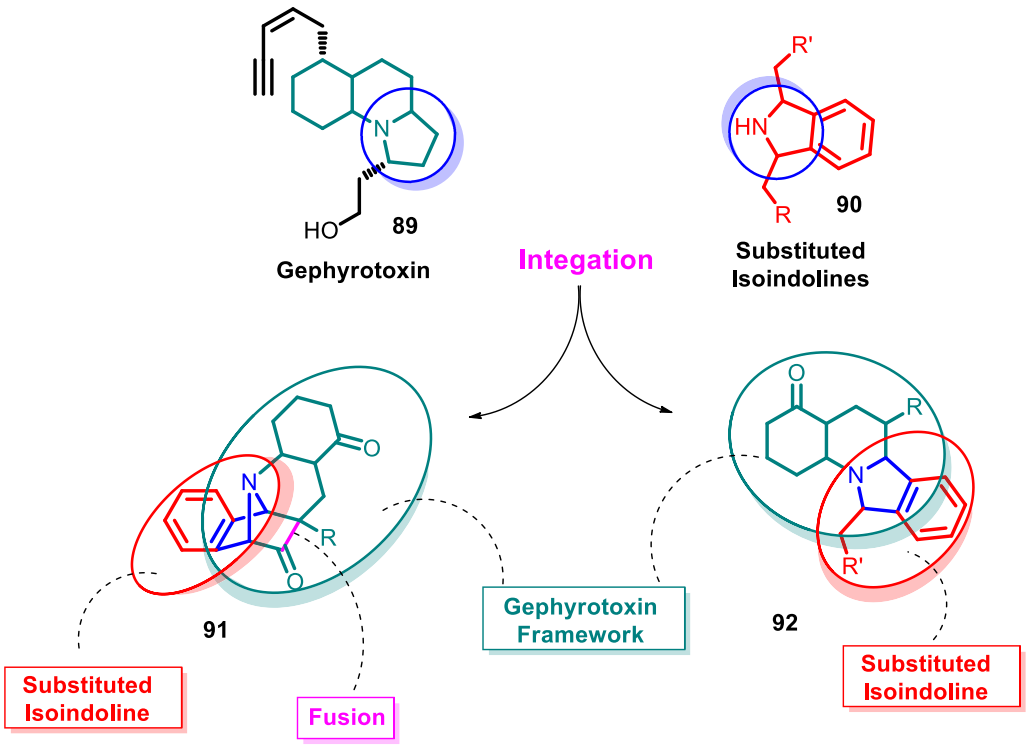


Fig. 21 Schematic representation of *i*NPBM strategy for identification of isoindolyl-gephyrotoxin frameworks for the discovery of novel muscarinic receptor modulators [76]

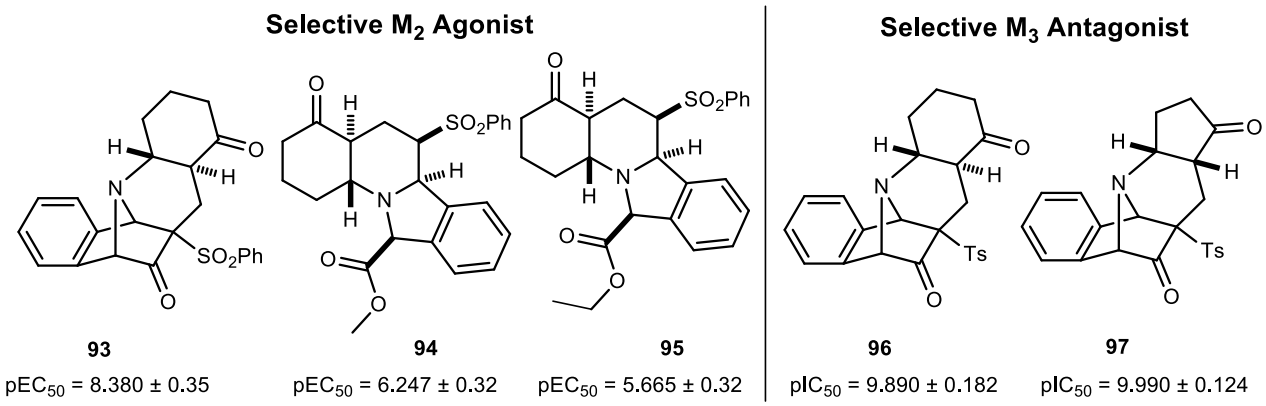


Fig. 22 Selective muscarinic receptor modulators discovered by iNPBM strategy

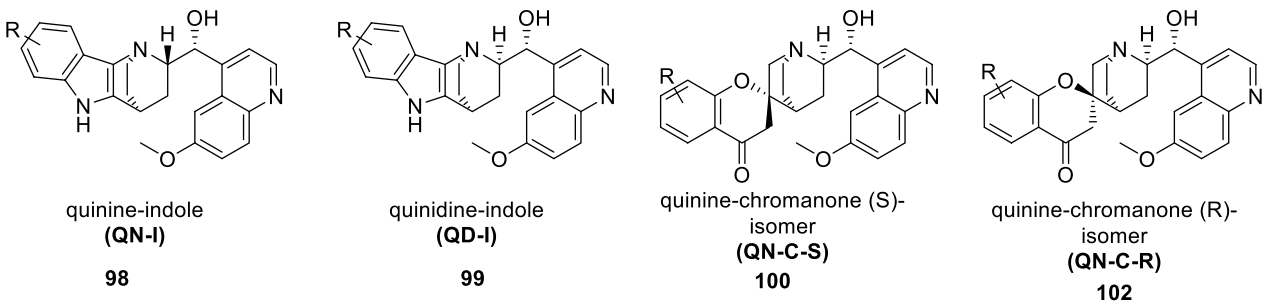


Fig. 23 Combination of indole and chromanone with natural product fragments of quinine and quinidine

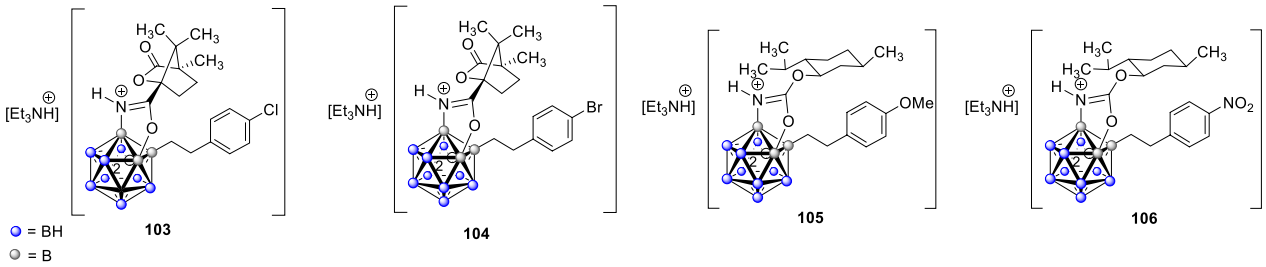


Fig. 24 Fusing natural product camphanic acid and menthol with boron clusters

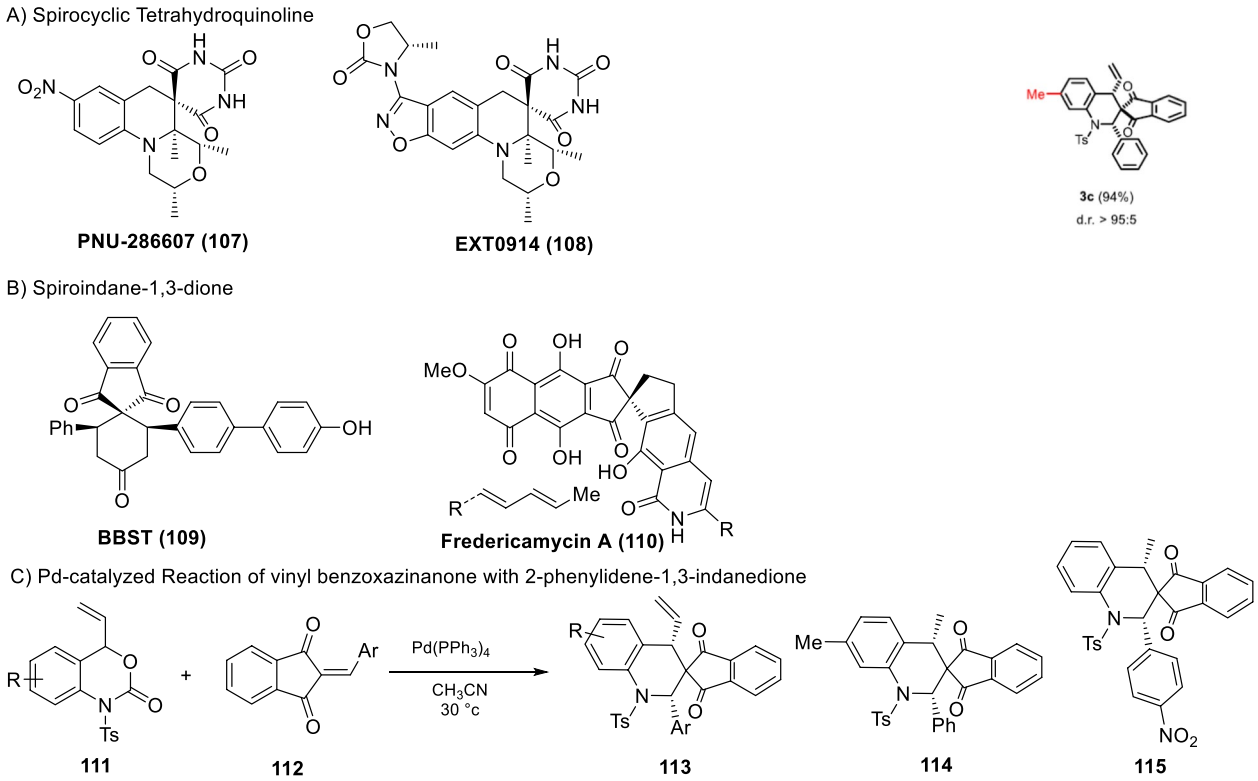


Fig. 25 1,3-Indanedione-based tetrahydroquinolines based on biology-oriented synthesis (BIOS)

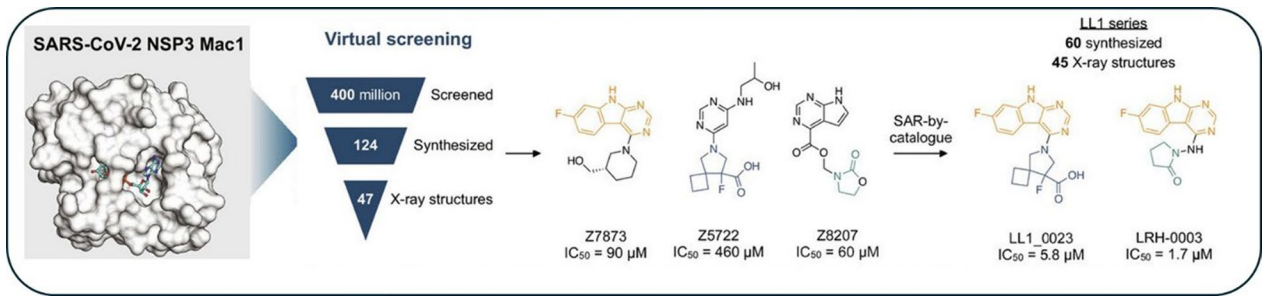


Fig. 26 Discovery of ligands that bind to the NSP3 macrodomain of SARS-CoV-2 (Mac1)

Table 2 Tabulated strategies and bioactive molecules discovered using the named strategy

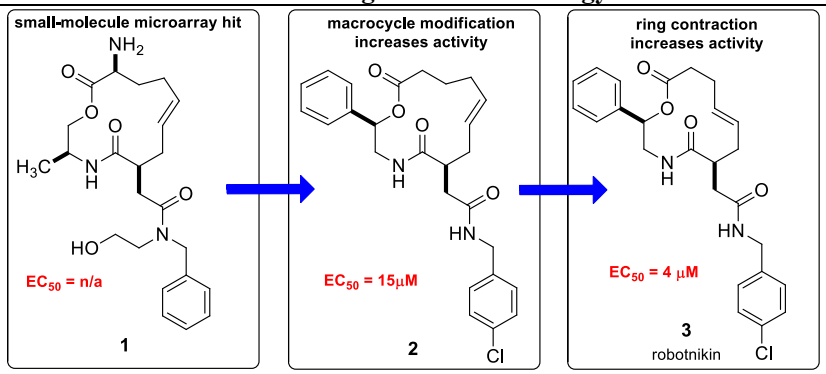
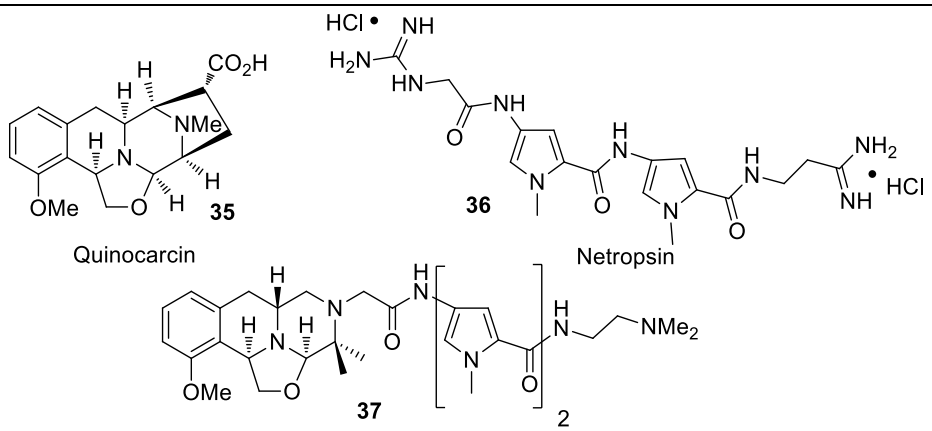
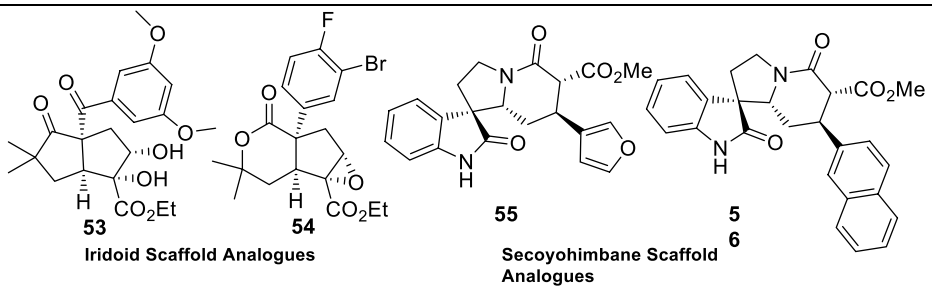
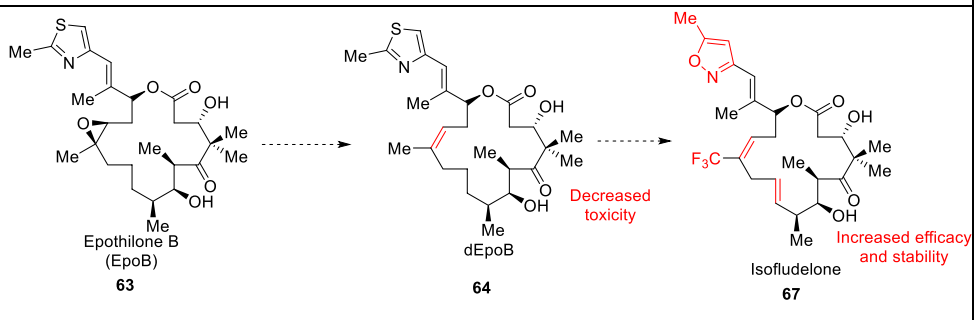
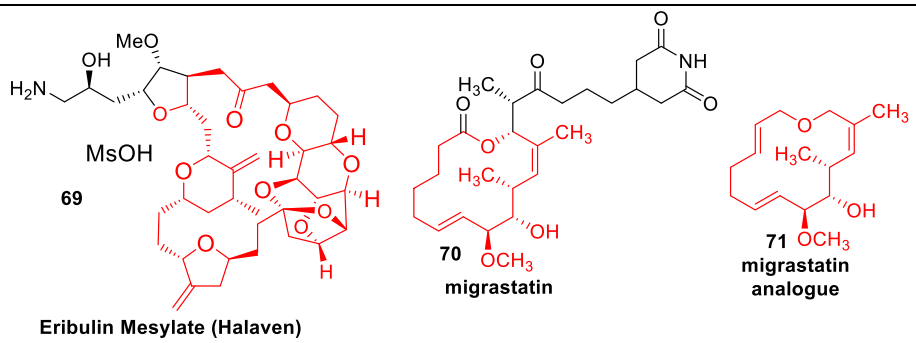
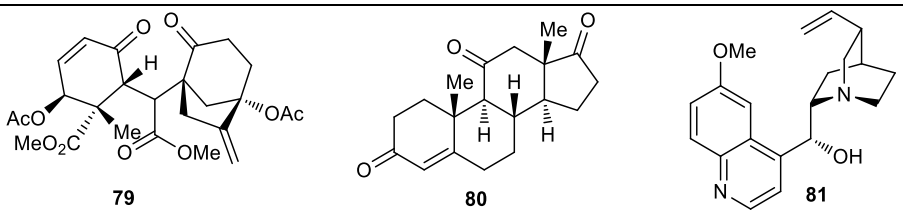
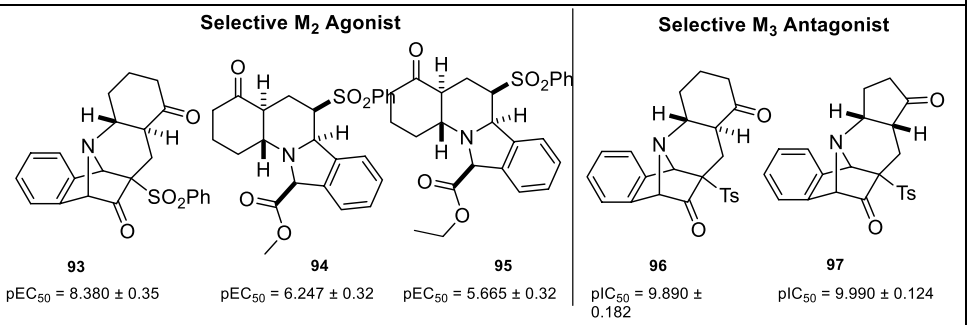
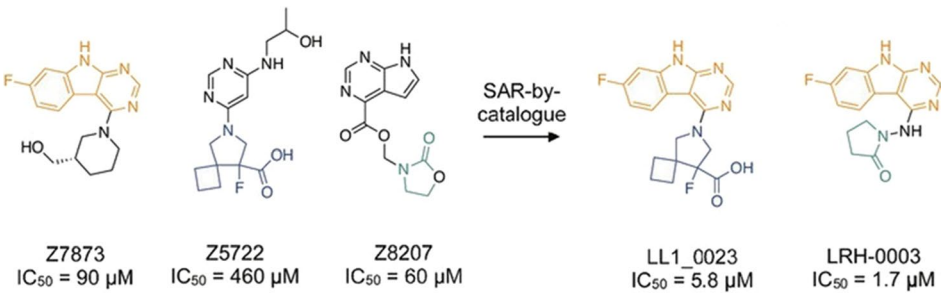
No.	Strategy	Bioactive molecules discovered using the named strategy
1	Diversity-oriented synthesis (DOS)	
2	Hybrid Natural Products (HNP)	
3	Biology-oriented Synthesis (BIOS)	
4	Diverted Total Synthesis (DTS)	

Table 2 (continued)

5	Pruning Biomolecules and Natural Products (PBNP)	
6	Ring Distortion of Natural Products (RDNP)	
7	Integrating natural product framework with bioactive molecules (*i*NPBM)	
8.	Molecular Modelling	

pioneering and emerging strategies inspired from natural product which allows access to the unexplored chemical space to identify novel molecules possessing noteworthy bioactivity (Table 2). The corresponding examples highlight the success of these strategies in the discovery of novel bioactive molecules which can be further developed in drug discovery and can be novel probes for chemical biology. Although there are limited number of successful examples, the selectivity, activity, and efficacy associated with natural product-inspired molecules accentuate their importance. Acknowledging the need for substantial further advancement, we anticipate that integrating natural product-inspired synthetic strategies with advance computational techniques involving molecular modelling will become a prevalent approach in modern drug discovery.

Abbreviations

ARE	Antioxidant responsive element
BCC	Basal cell carcinoma
BIOS	Biology-oriented synthesis
DOS	Diversity-oriented synthesis
DTS	Diverted total synthesis
ER	Oestrogen receptors
EMRSA	Epidemic methicillin-resistant strains
GCs	Glucocorticoid hormones
GPCR	G-protein-coupled receptors

HNPs	Hybrid natural products
HER2	Human epidermal growth factor receptor
11βHSD1	11β-Hydroxysteroid dehydrogenase type 1
iNPBM	Integrating natural product framework with a bioactive molecule
MRSA	Methicillin-resistant strains
MSSA	Methicillin-susceptible *S. aureus*
PDB	Protein data bank
NP	Natural product
PNP	Pruning natural products
QSAR	Quantitative structure–activity relationship
RDNPs	Ring distortion of natural products
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SM	Small molecules
ShhN	N-terminal sonic hedgehog protein
SCONP	Structural classification of natural products

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Author contributions
PP was involved in conceptualization, methodology, data curation, and drafting the paper; Dr SG was responsible for study, drafting the paper, and critical revision; Dr AJ contributed to data curation, conceptualization, and formal analysis; and all authors have read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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