Spirocyclic Motifs in Natural Products

Subjects: Chemistry, Organic

Contributor: Mikhail Krasavin , Chupakhin Evgeny , Olga Babich , Alexander Prosekov ,

Natural products play the central role in drug discovery due to their inherent biological activity and because have a wide span of structural diversity. Spirocyclic compounds have also occupied a special place in medicinal chemistry. Spirocycles are thought to possess a good balance of conformational rigidity and flexibility to be, on one hand, free from absorption and permeability issues characteristic of conformationally more flexible, linear scaffolds. On the other hand, spirocycles are more conformationally flexible compared to, for example, flat aromatic heterocycles and can adapt to many proteins as biological targets; thus, increasing the chances of finding bioactive hits. Spirocycles are distinctly three-dimensional and initial hits can be further optimized via manipulation of the molecular periphery whose three-dimensional positioning is well defined.

natural products spirocycles chemical diversity biological activity privileged structures

1. [2.4.0] Spirocyclic System

Spirocyclic motifs containing a cyclopropane unit were found in some sesquiterpenes (**5**–**7**) which were isolated from the essential oils of South-American *Schinus terebinthifolius* fruit [1].

In 2017, a novel condensed [2.4.0] spirocycle (**8**) was reported [2]. It was isolated and characterized among the secondary metabolites of the *Helminthosporium velutinum* plant and was named cyclohelminthol X. This compound was shown to inhibit the growth of a human colon adenocarcinoma (COLO201) cell line with moderate potency (IC50 = 16 μM), and, much more potently (IC50 = 0.35 μM)—leukemia HL60 cell line [2].

Bioassay-guided separation of *Valerianae Radix* plant extract led to the isolation and characterization of valtrate (**9**), which inhibited Rev protein mediated transport of HIV-1 from the nucleus to cytoplasm. This compound also inhibited p-24 production of HIV-1 virus without any notable cytotoxicity displayed against MT-4 cells. The presence of the chemically labile oxirane ring as part of the generalized [2.4.0] spirocyclic system is likely critical for the observed inhibition, as **9** was shown to covalently interact with cysteine [3].

2. [2.5.0] Spirocyclic System

This group of spirocyclic natural products is represented by sesquiterpenoids illudins M and S (**10** and **11**, respectively) isolated from fungi, including the highly poisonous Jack-o′-lantern mushroom *Omphalotus illudens*. Compound **11** is currently in Phase II clinical trials against ovarian, prostate, and gastrointestinal cancers.

Structurally analogous to illudins are sesquiterpenes **12**–**14** isolated from fungus *Agrocybe aegerita* [4] also containing a [2.5.0] spirocyclic system. These compounds displayed antifungal activity against *Candida albicans* and *Candida kefyr*.

An oxirane-bearing sesquiterpene (−)-ovalicin (**15**) also containing a [2.5.0] spirocyclic system was isolated from fungus *Pseudorotium ovalis Stolk* [5]. It—and the structurally similar monoester fumagillin (**16**) displayed potent antiparasitic activities and are generally devoid of toxicity [6]. For both compounds **15** and **16**, total syntheses have been reported [7].

A [2.5.0] spirocyclic system is recognizable in the structure of duocarmycin SA (**17**) and duocarmycin A (**18**)—new antitumor antibiotics isolated from *streptomyces* sp. [8].

3. [3.4.0] Spirocyclic System

This is an exceedingly rare type of spirocyclic motif encountered among natural products. The only compound reported in the literature to date containing such a *spirocyclic* system presented as a combination of a β-lactone and a pyrrolidine ring (**19**) was isolated from marine-derived Streptomyces strain collected in the southern area of the Korean Jeju Island [9]. This structurally intriguing compound displayed antibacterial activity.

4. [3.5.0] Spirocyclic System

The only spirocyclic combination of a four and six-membered rings represented in natural products is rather simple achiral 1-oxaspiro[3.5]nonan-7-ol substituted cleroindicin A (**20**) [10]. This compound was isolated from fungus *Clerodendrum japonicum*.

5. [3.7.0] Spirocyclic System

This intriguing spirocyclic combination of four and eight-membered rings is represented in only four closely-related sesquiterpene bis-lactones, **21**–**24**, isolated from poisonous plants in the Illicium genus grown in China [11]. These structures could also be viewed as possessing a [3.5.0] spirocyclic motif.

6. [4.4.0] Spirocyclic System

Besides the approved diuretic spironolactone (**2**, vide supra), heteroatom-containing [4.4.0] spirocyclic motifs are widely represented by various lactones.

The most structurally simple, naturally occurring spirocyclic lactone, 1,7-dioxaspiro[4.4.0]nonane or longianone (**25**) was isolated from higher fungi *Xylaria longiana* [12]. The absolute configuration of longianone was confirmed by stereoselective total synthesis [13]. Hyperolactones A (**26**) and C (**27**) isolated from *Hypericum chainens* plant [14]

displayed antiviral activity [15]. The Nicolaou group reported a photochemical, [2 + 2]-cycloaddition based synthesis of a library based on natural product biyouyanagin (**28**) which allowed revising its originally reported absolute configuration [16]. (+)-Crassalactone D (**29**) is a styryl-lactone isolated from the leaves of *Polyalthia crassa* plant which displayed cytotoxic properties [17]. Pyrenolide D (**30**) is a highly oxygenated tricyclic spirolactone isolated from phytopathogenic fungus *Pyrenophora teres*, also displaying potent cytotoxicity [18]. Sesequiterpene levantenolide (**31**) also contained a [4.4.0] spirocyclic lactone moiety; it was isolated from tobacco grown in Turkey [19]. It exerted potent suppression of cytokine cascades and can, therefore, be considered a lead for anti-inflammatory drug development [20]. Complex polycyclic alkaloids represented by compound **32** were isolated from *Stemona* genus shrubs. These compounds contain a basic cyclopenta[1,2-b]pyrrolo[1,2-a]azepine scaffold and display promising anti-cough medicinal properties [21].

A [4.4.0] spirocyclic lactone moiety is found (in combination with a [2.4.0] spirocyclic oxirane) in limonoids **33**–**34**, which were recently isolated from *Trichilia connaroides*. For these compounds, some insights into a possible biosynthetic pathway have been provided. Likewise, these compounds were screened for various types of bioactivity and have been shown to inhibit NO production in a cellular model of inflammation (induced in RAW264.7 cell line with LPS) by 25.89% and 37.13% at 25 and 50 μM, respectively [22].

A very interesting class of natural products containing a [4.4.0] spirocyclic motif includes spiropseudoindoxyl alkaloids. Microbial transformation of the alkaloid mitragynine by the fungus *Helminthosporum* sp. was reported in 1974 to yield two major metabolites. The compounds were isolated from the biological milieu and their structures were elucidated as mitragynine pseudoindoxyl (**59**) and hydroxy mitragynine pseudoindoxyl (**60**) [23]. These compounds were later shown to possess opioid analgesic activity by exerting mu agonism and delta antagonism while not recruiting β-arrestin-2 [24].

The [4.4.0] spirocyclic pseudoindoxyl motif represents a rather common feature in indole alkaloids, as can be illustrated by such examples as fluorocurine (**61**) [25], several diketopiperazines isolated from holothurianderived fungus *Aspergillus fumigatus* (**62a**–**d**) [26], brevianamide B (**63**) [27], and rauniticine pseudoindoxyl (**64**) [28]

A structurally unique [4.4.0] spiroheterocyclic system is represented by a series of highly oxygenated lactone lactams (**65**–**69**) isolated from marine sediment-derived fungus Aspergillus sydowi D2–6. Compounds **65**–**69** were shown to inhibit growth of adenocarcinoma cell line A549 with an IC50 value of 10 μM [29].

A wide diversity of heterocyclic spirocyclic scaffolds all belonging to the generalized [4.4.0] system (**70**–**73**) have been isolated recently. Two regioisomeric phytoalexins—erucalexin (**70**) and its regioisomer (+)-1-methoxyspirobrassinin (**71**) were isolated from the wild crucifer *Erucastrum gallicum* [30].

Mycotoxins related to tryptoquialanine A (**71**) were isolated from *Penicillium* spp. and *Aspergillus clavatus* [31]. For tryptoquialanines, the biosynthetic pathway has been recently elucidated [15]. Another spirooxyindole lactone lactam compound **73** isolated from *Coix lachryma-jobi L.* has been recently reported and shown to possess activity against human lung cancer (A549) and colon carcinoma (HT-29 and COLO205) cell lines [32].

Secondary metabolite investigation of the liquid culture of entomogenous fungus *Isaria cateniannulata* led to the identification of a new spirocyclic compound **74** containing a 1,6-dioxaspiro[4.4]nonane moiety. The compound showed weak inhibitory activity against the HeLa cancer cell line [33].

Spirocyclic [4.4.0] tetrahydrofurans are featured in a series of twelve natural products **75a–l** dubbed bipolaricins. These compounds are ophiobolin-type tetracyclic sesterterpenes from a phytopathogenic *Bipolaris* sp. fungus. They were tested for HMGCoA reductase inhibition as well as anti-inflammatory and cytotoxic activities. The biological activity discovered provided the basis for considering these compounds as leads for antiinflammation and antihyperglycemic therapy developments [34].

An interesting type of [4.4.0] spirocyclic motif is present in fredericamycin A (**76**), an antitumor antibiotic produced by *Streptomyces griseus* ([35][36].

Spirolactones are the most widely represented motifs in the [4.4.0] spirocyclic systems, with over 20 examples discussed above. Spirocyclic lactams are exemplified by 10 natural products. However, [4.4.0] spirocyclic lactam lactones and spirooxyindoles are much less common in the natural products and are represented by only a handful of examples. In terms of biological activity, the current data are mostly limited to cytostatic and antibacterial properties. The natural products isolated within the last 1–2 years are poorly investigated with regard to their biological properties.

7. [4.5.0] Spirocyclic System

Secondary metabolite investigation of *Teucrium viscidum* led to the identification of a [4.5.0] spirocyclic compound (**77**) possessing a unique skeleton [37]. A skeleton of similar complexity had only been featured once in the literature three decades before that [38] .

The [4.5.0] spirocyclic motifs are featured in many natural terpenes. Recently, new spirocyclic triterpenoids **78**–**79** were isolated from *Leonurus japonicus frui.* These compounds displayed moderately potent (IC50 < 10 μM) growth inhibition of five human cancer cell lines (stomach cancer BGC-823 and KE-97, hepatocarcinoma Huh-7, Jurkat T-cell limphoblasts, and breast adenocarcinoma MCF-7) [39].

Another example of an all-carbon [4.5.0] spirocyclic system is provided by spirocarolitone (**80**), recently isolated from *Ruptiliocarpon caracolito* [40].

Structurally novel tricyclic-iridal triterpenoids belamcandanes A and B (**81** and **82**) were recently isolated from *Belamcanda chinensis* and shown to possess moderate hepatoprotective properties. A possible biosynthetic pathway has been proposed [41].

New biologically active sesquiterpenoids **83**–**85** possessing an all-carbon [4.5.0] spirocyclic system were isolated from rhizomes of *Acorus calamus*. Compound **83** exhibited weak hepatoprotective activities against APAP-induced

HepG2 cell damage [42].

The ethyl acetate soluble fraction of a MeOH extract of the dried stems and roots of Capsicum annum gave several new sesquiterpenoids, among which two [4.5.0] spirocyclic compounds termed canusesnols (**86**–**87**) were identified and evaluated for their cytotoxic activities [43].

Perhaps the most clinically advanced natural spirocyclic compound—spirocyclic benzofuran griseofulvin (**88**) isolated from *Penicillium griseofulvum* has been employed in clinical practice for therapy against ring worms [44] and was marketed by GlaxoSmithKline under the trade name Grisovin™ [45] .

Natural [4.5.0] spirocyclic lactones are characterized by a wide structural diversity and abundance of biological activities reported for them. These are exemplified by the mediator of mycoparasitism lambertollol C (**89**) [46], glycine-gated chloride channel receptor modulator (−)-ircinianin (**90**) [47], and terpenoid andirolactone (**91**) isolated from Cedrus libanotica [48].

Summarizing this Section, the scaffold diversity stemming from the general [4.5.0] spirocyclic framework is comparable to that of the [4.4.0] spirocyclic system discussed earlier.

8. [4.6.0] Spirocyclic System

As to the spirocyclic systems combining five and seven-memebred rings (the [4.6.0] spirocyclic system), spiro meroterpenoids spiroapplanatumines (**122**–**124**) isolated from the fruiting bodies of the fungus *Ganoderma applanatum* provide an eloquent example. Biological evaluation of the compounds disclosed that compound **124** inhibited JAK3 kinase with an IC50 value of 7.0 ± 3.2 μM [49].

In 2003, investigation of the neutral ether extracts of the fungus *Fomes cajanderi* led to the isolation of three novel ketal lactones named fomlactones A (**125**), B (**126**), and C (**127**). The compounds clearly possess a [4.6.0] spirocyclic lactone moiety. However, their biological potential remains to be investigated [50].

A very unique spirocyclic [4.6.0] framework formed by a spiro[benzofuranonebenzazepine] skeleton is featured in natural products (±)-juglanaloid A (**128a**–**b**) and (±)-juglanaloid B (**129a**–**b**). These benzazepine alkaloids were isolated from the bark of *Juglans mandshurica*. Remarkably, both racemic natural products were successfully resolved by chiral separation and absolute configurations were unambiguously assigned. These enantiopure versions were screened for their in vitro inhibitory activities against self-induced Aβ1-42 aggregation using the Thioflavin T (Th-T) assay using curcumin as a reference compound. The compounds demonstrated promise acting as inhibitors of amyloid β aggregation [51].

Furthermore, in the last 1–2 years there has been an avalanche of new [4.6.0] spirocyclic structures reported in the literature. For examples, lanostane-type spirolactone triterpenoids **130a**–**c** isolated from *Ganoderma applanatum*

were reported to possess anti-hepatic fibrosis activities [52]. Interestingly, an additional [4.5.0] and [2.5.0] spirocyclic motif is recognizable in compounds **130b** and **130c**, respectively.

Another recent example (reported in 2019) of a [4.6.0] spirocyclic system is provided by grayanane diterpenoid auriculatol A (**131**) isolated from leaves of Rhododendron auriculatum. This compound is the first example of a 5,20-epoxygrayanane diterpenoid bearing a 7-oxabicyclo[4.2.1]nonane motif and a*trans/cis/cis/cis*-fused 5/5/7/6/5 pentacyclic ring system. Auriculatol A showed analgesic activity in the acetic acid-induced writhing test [53].

Finally another [4.6.0] spirocyclic lactone, seconoriridone A (isolated as a 7:1 epimeric mixture of (**132a**) and (**132b**)) was isolated in 2019 from *Belamcanda chinensis*. Although no biological activity was reported for this intriguing molecular structure, a plausible biosynthetic pathway was proposed [54].

The [4.6.0] spirocyclic system is amply exemplified in the natural products domain by the gelsenium alkaloids—gelsebanine (**133**), 14α-hydroxyelegansamine (**134**), 14α-hydroxygelsamydine (**135**) [55], 14-acetoxygelsenicine (**136**), 14-acetoxy-15-hydroxygelsenicine (**137**), 14-hydroxy-19-oxogelsenicine (**138**), and 14-acetoxygelseligine (**139**) [56].

9. [4.7.0] Spirocyclic System

Spirocyclic natural products whose scaffolds contain rings larger than six-membered, e.g., [4.7.0] spirocyclic systems, are exceedingly rare. An eloquent example is provided by natural sugar-containing compounds phyllanthunin (**140**) recently isolated from an ethanol extract of the fruit of Phyllanthus emblica [57].

Additionally, remarkably illustrative of the presence of [4.7.0] spirocyclic motifs in natural products, are portimines A (**141**) and B (**142**) isolated from the marine benthic dinoflagellate Vulcanodinium rugosum collected from Northland, New Zealand [58][59]. In addition to a [4.7.0] spirocyclic system, these compounds also contain a [4.5.0] spirocycle. Portimine has also been shown to induce apoptosis and reduce the growth of a variety of cancer cell lines at low nanomolar concentrations

10. [5.5.0] Spirocyclic System

Among natural products containing a [5.5.0] spirocyclic motif, new spirocyclic chamigrane sesquiterpenes, merulinols B (**143**), C (**144**), E (**145**), and F (**146**) are notable examples. These compounds were isolated from basidiomycetous endophytic fungus XG8D associated with the mangrove Xylocarpus granatum [60]. The in vitro cytotoxicity of all compounds was evaluated against three human cancer cell lines, MCF-7, Hep-G2, and KATO-3. Compound **144** selectively displayed cytotoxicity against KATO-3 cells with an IC50 value of 35.0 μM.

Highly oxygenated acylphloroglucinol, hyperbeanol C (**147**), was isolated from the methanol extract of Hypericum beanie [61]. This compound contains an all-carbon [5.5.0] spirocyclic system, spiro[5.5.0]undec-2-ene-1,5-dione . The cytotoxicity of **147** against the cancer cell lines HL-60, SMMC-7721, PANC-1, MCF-7, K562, and SK-BR-3 was

tested using the methyl thiazol tetrazalium (MTT) method with cis-platinum as the positive control. It exhibited modest cytotoxicity against K562 cells with an IC50 16.9 μM.

Remarkable presentation of the (R)-1,7-dioxaspiro[5.5] undecane framework is found in nor-spiro-azaphilones, thielavialides A−D (**148**–**151**), and bis-spiro-azaphilone, thielavialide E (**152**) together with bis-spiro-azaphilone pestafolide A (**153**). All these compounds were isolated from the endophytic fungal strain, Thielavia sp. PA0001, occurring in the healthy leaf tissue of aeroponically grown *Physalis alkekengi* [62].

A very similar [5.5.0] spirocyclic moiety can be found in the structure of pteridic acids C and F (**154** and **155**, respectively) isolated in 2017 from a culture broth of the marine-derived actinomycete *Streptomyces* sp. SCSGAA 0027. While these compounds were seen as potential leads for antibacterial drug discovery, their extensive testing for antimicrobial activity against two gorgonian pathogenic fungal strains *Aspergullus versicolor* SCSGAF 0096 and *Aspergullus sydowii* SCSGAF 0035; a human pathogenic fungal strain *Candida albicans* SC5314; and two bacterial strains *Escherichia coli* and *Bacillus subtilis*, showed that the compounds had only a weak antimicrobial activity [63].

A unique [5.5.0] spirocyclic skeleton formed by a hexahydropyran and a pyrrolo[2,1-c]morpholine moieties is found in pollenopyrroside A (**156**) and B (**157**) isolated from bee-collected *Brassica campestris* pollen. The Chinese team who reported these natural products in 2010 also proposed a biosynthetic pathway that involves a reaction of 3-deoxy-d-fructose and 5-oxymethyl-2-formyl-pyrrole as the key step. Biological testing of these aldehyde compounds using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method revealed that they possess no cytotoxicity against A549, Bel7420, BGC-823, HCT-8, and A2780 cancerous cell lines at 10 μg/mL [64].

Another unique [5.5.0] spirocyclic skeleton is noteworthy. Two structurally unique spirocyclic alkaloids **158** and **159** were isolated in 2007 from the halotolerant B-17 fungal strain of *Aspergillus variecolo*. Both compounds possessed an intriguing spirocyclic piperazin-2,5-dione moiety and exhibited cytotoxic properties [65].

Remarkably, in 2018, a very similar spirocyclic piperazin-2,5-dione variecolortin B (**160**) was isolated from the marine-derived fungus *Eurotium sp.* SCSIO F452. The compound exhibited different antioxidative and cytotoxic activities. Interestingly, the same species gave rise to a compound possessing an even more seldomly-occurring spirocyclic moiety; namely, [5.6.0] (vide infra) [66].

The [5.5.0] spirocyclic system occurs very prominently in bioactive meroterpenoids **161a**–**e** and **162a**–**d** isolated in 2019 from mangrove-derived fungus *Penicillium* sp.. Several of these compounds showed growth inhibition activity against newly hatched larvae of Helicoverpa armigera Hubner with IC50 values ranging from 50 to 200 μg/mL, and some notable activity against *Caenorhabditis elegans* [67].

Workers of the ant *Carebarella bicolor* collected in Panama were found to contain the histrionicotoxin class of alkaloids with unusual 2,7-disubstituted-1-azaspiro[5.5]undecanol structures **163a**–**i**[68].

11. [5.6.0] Spirocyclic System

An interesting group of natural products representative of this spirocyclic system are periplosides (**164**), a spiro-orthoester group-containing pregnane-type glycosides discovered in the course of phytochemical investigation of the root bark of *Periploca sepium*. The [5.6.0] spirocyclic orthoester core is distinctly modified with a steroid unit on one hand (R^1) and with an oligosaccharide moiety on the other (R^2). The compounds were evaluated for their inhibitory activities against the proliferation of T-lymphocytes. As a result, one specific compound (periploside C), the most abundant glycoside containing a spiro-orthoester moiety found in the plant, exhibited the most favorite selective index value (SI = 82.5). The inhibitory activity and the SI value appear to depend on the constitution of the saccharide chain [69].

The remarkable, from a structural perspective, spirolide G (**165**), was isolated from Danish strains of toxigenic dinoflagellate *Alexandrium ostenfeldii*. The toxicological profile of this compound was evaluated [70]. Interestingly, in addition to the spirocyclic [5.6.0] moiety in question, spirolide G (**165**) contains two others; namely, a [4.4.0] and a [4.5.0] motif .

Referring back to the chemical investigation of the marine-derived fungus *Eurotium* sp. SCSIO F452 discussed above in connection with compounds belonging to the [5.5.0] spirocyclic system, an intriguing [5.6.0] spirocyclic compound **166** was also isolated from the same species [66]. This is one species giving rise to a diversity of spirocyclic frameworks, underscoring the significance of spirocycles in the natural product realm. One particular example of such spirocycle diversity derived from a single organism is discussed in Section 13 below.

A [5.6.0] spirocyclic moiety is recognizable in the new sesquiterpene dimer vieloplain G (**167**) isolated in 2019 from the roots of *Xylopia vielan*. This compound showed considerable cytotoxicity against DU145 cells with an IC50 value of 9.5 μM [71].old.

12. [6.6.0] Spirocyclic System

This type of spirocyclic framework is exceedingly rare in the natural product domain, with only one example of unique 1-oxaspiro[6.6]tridecane **168**, a spirocyclic nortriterpenoid Spiroschincarin A isolated from the fruit of *Schisandra incarnate* [72].

References

1. Richter, R.; von Reuß, S.H.; König, W.A. Spirocyclopropane-type sesquiterpene hydrocarbons from Schinus terebinthifolius raddi. Phytochemistry 2010, 71, 1371–1374.
2. Tanaka, S.; Honmura, Y.; Uesugi, S.; Fukushi, E.; Tanaka, K.; Maeda, H.; Kimura, K.; Nehira, T.; Hashimoto, M. Cyclohelminthol X, a hexa-substituted spirocyclopropane from Helminthosporium

velutinum yone96: Structural elucidation, electronic circular dichroism analysis, and biological properties. J. Org. Chem. 2017, 82, 5574–5582.

3. Murakami, N.; Ye, Y.; Kawanishi, M.; Aoki, S.; Kudo, N.; Yoshida, M.; Nakayama, E.E.; Shioda, T.; Koboyashi, M. New rev-transport inhibitor with anti-HIV activity from Valerianae Radix. Bioorg Med. Chem Lett. 2002, 12, 2807–2810.
4. Stransky, K.; Semerdžievab, M.; Otmara, M.; Procházkaa, Ž.; Buděšínskýa, M.; Ubika, K.; Kohoutováa, J.; Streinz, L. Antifungal antibiotic from the mushroom Agrocybe aegerita (BRIG.) SING. Collect. Czech. Chem. Commun. 1992, 57, 590–603.
5. Bollinger, P.; Sigg, H.P.; Weber, H.P. Die struktur von ovalicin. Helv. Chim. Acta. 1973, 56, 819–830.
6. Newman, D.J.; Cragg, G.M. Natural products of therapeutic importance. In Comprehensive Natural Products II; Liu, H.W., Mander, L., Eds.; Elsevier: Amsterdam, The Netherlands, 2010; pp. 623–650. ISBN 978-0-08-045382-8.
7. Yadav, J.S.; Reddy, P.N.; Reddy, B.V.S. Stereoselective total synthesis of (−) -ovalicin. Synlett 2010, 457–462.
8. Ichimura, M.; Ogawa, T.; Takahashi, K.-I.; Kobayashi, E.; Kawamoto, I.; Yasuzawa, T.; Takahashi, I.; Nakano, H. Duocarmycin SA, a new antitumor antibiotic from Streptomyces sp. J. Antibiot. (Tokyo) 1990, 43, 1037–1038.
9. Ko, K.; Lee, S.H.; Kim, S.H.; Kim, E.H.; Oh, K.B.; Shin, J.; Oh, D.C. Lajollamycins, nitro group-bearing spiro-β-lactone-γ-lactams obtained from a marine-derived Streptomyces sp. J. Nat. Prod. 2014, 77, 20999–22104.
10. Tian, J.; Zhao, Q.-S.; Zhang, H.-J.; Lin, Z.-W.; Sun, H.-D. New cleroindicins from Clerodendrum indicum. J. Nat. Prod. 1997, 60, 766–769.
11. Kouno, I.; Hashimoto, M.; Enjoji, S.; Takahashi, M.; Kaneto, H.; Yang, C.S. Isolation of neoanisatin derivatives from the pericarps of Illicium majus with other constituents. Chem. Pharm. Bull. 1991, 39, 1773–1778.
12. Edwards, R.L.; Maitland, D.J.; Oliver, C.L.; Pacey, M.S.; Shields, L.; Whalley, A.J. Metabolites of the higher fungi. Part 31.1 longianone, a C7H6O4 spirobicyclic lactone from the fungus Xylaria longiana (Rehm.). J. Chem. Soc. Perkin Trans. 1 1999, 715–719.
13. Perali, R.S.; Kalapati, S. First enantioselective total synthesis of (S)-(−)-longianone. Tetrahedron 2012, 68, 3725–3728.
14. Aramaki, Y.; Chiba, K.; Tada, M. Spiro-lactones, hyperolactone A-D from Hypericum chinense. Phytochemistry 1995, 38, 1419–1421.

15. Gao, X.; Chooi, Y.H.; Ames, B.D.; Wang, P.; Walsh, C.T.; Tang, Y. Fungal indole alkaloid biosynthesis: Genetic and biochemical investigation of the tryptoquialanine pathway in Penicillium aethiopicum. J. Am. Chem. Soc. 2011, 133, 2729–2741.
16. Nicolaou, K.C.; Sanchini, S.; Sarlah, D.; Lu, G.; Wu, T.R.; Nomura, D.K.; Cravatt, B.F.; Cubitt, B.; de la Torre, J.C.; Hessell, A.J.; et al. Design, synthesis, and biological evaluation of a biyouyanagin compound library. PNAS 2011, 108, 6715–6720.
17. Tuchinda, P.; Munyoo, B.; Pohmakotr, M.; Thinapong, P.; Sophasan, S.; Santisuk, T.; Reutrakul, V. Cytotoxic styryl-lactones from the leaves and twigs of Polyalthia crassa. J. Nat. Prod. 2006, 69, 1728–1733.
18. Nukina, M.; Hirota, H. Pyrenolide D, a new cytotoxic fungal metabolite from Pyrenophora teres. Biosci. Biotechnol. Biochem. 1992, 56, 1158–1159.
19. González, A.G.; Francisco, C.G.; Freire, R.; Hernández, R.; Salazar, J.A.; Suárez, E.C. C12 stereochemistry of α- and β-levantenolide carbon-13 NMR spectra of labdanolic diterpenes. Tetrahedron Lett. 1976, 17, 1897–1898.
20. Kiem, P.V.; Anh, H.T.; Nhiem, N.X.; Minh, C.V.; Thuy, N.T.; Yen, P.H.; Hang, D.T.; Tai, B.H.; Mathema, V.B.; Koh, Y.S.; et al. Labdane-type diterpenoids from the Rhizomes of Hedychium coronarium inhibit lipopolysaccharide-stimulated production of pro-inflammatory cytokines in bone marrow-derived dendritic cells. Chem. Pharm. Bull. 2012, 60, 246–250.
21. Yang, X.-Z.; Zhu, J.-Y.; Tang, C.-P.; Ke, C.-Q.; Lin, G.; Cheng, T.-Y.; Rudd, J.A.; Ye, Y. Alkaloids from roots of Stemona sessilifolia and their antitussive activities. Planta Med. 2009, 75, 174–177.
22. An, F.-L.; Luo, J.; Li, R.-J.; Luo, J.-G.; Wang, X.-B.; Yang, M.-H.; Yang, L.; Yao, H.-Q.; Sun, H.-B.; Chen, Y.-J.; et al. Spirotrichilins A and B two rearranged spirocyclic Limonoids from Trichilia connaroides. Org. Lett. 2016, 18, 1924–1927.
23. Váradi, A.; Marrone, G.F.; Palmer, T.C.; Narayan, A.; Szabó, M.R.; Le Rouzic, V.; Grinnell, S.G.; Subrath, J.J.; Warner, E.; Kalra, S.; et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu agonism and delta antagonism, which do not recruit β-arrestin-2. J. Med. Chem. 2016, 59, 8381–8397.
24. Zarembo, J.E.; Douglas, B.; Valenta, J.; Weisbach, J.A. Metabolites of mitragynine. J. Pharm. Sci. 1974, 63, 1407–1415.
25. Hesse, M.; Philipsborn, W.V.; Schumann, D.; Spiteller, G.; Spiteller-Friedmann, M.; Taylor, W.I.; Schmid, H.; Karrer, P. Die Strukturen von C-Fluorocurin, C-Mavacurin und Pleiocarpamin. 57. Mitteilung über Curare-Alkaloide. Helv. Chim. Acta 1964, 47, 878–911.
26. Wang, F.; Fang, Y.; Zhu, T.; Zhang, M.; Lin, A.; Gu, Q.; Zhu, W. Seven new prenylated indole diketopiperazine alkaloids from holothurian-derived fungus Aspergillus fumigatus. Tetrahedron 2008, 64, 7986–7991.

27. Birch, A.J.; Wright, J.J. Studies in relation to biosynthesis—XLII: The structural elucidation and some aspects of the biosynthesis of the brevianamides-A and -E. Tetrahedron 1970, 26, 2329–2344.
28. Phillipson, J.D.; Supavita, N. Alkaloids of uncaria elliptica. Phytochemistry 1983, 22, 1809–1813.
29. Ren, H.; Liu, R.; Chen, L.; Zhu, T.; Zhu, W.M.; Gu, Q.Q. Two new hetero-spirocyclic γ-lactam derivatives from marine sediment-derived fungus Aspergillus sydowi D2–6. Arch. Pharm. Res. 2010, 33, 499–502.
30. Pedras, M.S.C.; Suchy, M.; Ahiahonu, P.W.K. Unprecedented chemical structure and biomimetic synthesis of erucalexin, a phytoalexin from the wild crucifer Erucastrum gallicum. Org. Biomol. Chem. 2006, 4, 691–701.
31. Ariza, M.R.; Larsen, T.O.; Petersen, B.O.; Duus, J.O.; Barrero, A.F. Penicillium digitatum metabolites on synthetic media and citrus fruits. J. Agric. Food. Chem. 2002, 50, 6361–6365.
32. Lee, M.; Lin, H.Y.; Cheng, F.; Chiang, W.; Kuo, Y. Isolation and characterization of new lactam compounds that inhibit lung and colon cancer cells from adlay (Coix lachryma-jobi L. var. ma-yuen Stapf) bran. Food. Chem. Toxicol. 2008, 46, 1933–1939.
33. Yang, X.L.; Li, Z.Z.; Zhang, S.; Yu, H.; Zhu, H.J.; Luo, D.Q. A new spirocyclic compound from the liquid culture of entomogenous fungus Isaria cateniannulata. J. Asian Nat. Prod. Res. 2012, 14, 1093–1096.
34. Liu, M.; Sun, W.; Shen, L.; Hao, X.; Al, A.; Weaam, H.; Lin, S.; Li, H.; Gao, W.; Wang, J.; et al. Bipolaricins A–I, ophiobolin-type tetracyclic sesterterpenes from a phytopathogenic Bipolaris sp. fungus. J. Nat. Prod. 2019, 82, 2897–2906.
35. Pandey, R.C.; Toussaint, M.W.; Stroshane, R.M.; Kalita, C.C.; Aszalos, A.A.; Garretson, A.L.; Wei, T.T.; Byrne, K.M.; Stroshane, R.M.; White, R.J. Fredericamycin A a new antitumor antibiotic. I. Production, isolation and physicochemical properties. J. Antibiot. (Tokyo) 1981, 34, 1389–1401.
36. Misra, R.; Pandey, R.C.; Silverton, J.V. Fredericamycin A, an antitumor antibiotic of a novel skeletal type. J. Am. Chem. Soc. 1982, 104, 4478–4479.
37. Li, Z.Y.; Qi, F.M.; Zhi, D.J.; Hu, Q.L.; Liu, Y.H.; Zhang, Z.X.; Fei, D.Q. A novel spirocyclic triterpenoid and a new taraxerane triterpenoid from Teucrium viscidum. Org. Chem. Front. 2017, 42–46.
38. Matsunaga, S.; Morita, R.; Ishida, T.; Inoue, M.; Shigi, M.; Miyamae, A. The structure of spirosupinanonediol, a triterpenoid bearing a novel skeletal system from Euphorbia supina. J. Chem. Soc. Chem. Commun. 1984, 1128–1129.
39. Ye, M.; Xiong, J.; Zhu, J.-J.; Hong, J.-L.; Zhao, Y.; Fan, H.; Yang, G.-X.; Xia, G.; Hu, J.-F. Leonurusoleanolides E–J, minor spirocyclic triterpenoids from Leonurus japonicus fruits. J. Nat.

Prod. 2014, 77, 178–182.

40. Asim, M.; Hussien, H.; Poveda, L.; Arnason, J.T.; Durst, T. Triterpenoids from the bark of Ruptiliocarpon caracolito. Phytochemistry 2010, 71, 1418–1422.
41. Ni, G.; Li, J.Y.; Mai, Z.P.; Yu, D.Q. Belamcandanes A and B, two unprecedented tricyclic-iridal triterpenoids from Belamcanda chinensis. Tetrahedron Lett. 2018, 59, 151–155.
42. Hao, Z.Y.; Liang, D.; Luo, H.; Liu, Y.F.; Ni, G.; Zhang, Q.J.; Li, L.; Si, Y.K.; Sun, H.; Chen, R.Y.; et al. Bioactive sesquiterpenoids from the rhizomes of Acorus calamus. J. Nat. Prod. 2012, 75, 1083–1089.
43. Kawaguchi, Y.; Ochi, T.; Takaishi, Y.; Kawazoe, K.; Lee, K.H. New sesquiterpenes from Capsicum annuum. J. Nat. Prod. 2004, 67, 1893–1896.
44. MacMillan, J. Griseofulvin. Part VII. Dechlorogriseofulvin. J. Chem. Soc. 1953, 1697–1702.
45. Petersen, A.B.; Rønnest, M.H.; Larsen, T.O.; Clausen, M.H. The chemistry of Griseofulvin. Chem. Rev. 2014, 114, 12088–12107.
46. Murakami, T.; Sasaki, A.; Fukushi, E.; Kawabata, J.; Hashimoto, M.; Okuno, T. Lambertellol C, a labile and novel biosynthetic congener of lambertellols A and B. Bioorg. Med. Chem. Lett. 2005, 15, 2587–2590.
47. Balansa, W.; Islam, R.; Fontaine, F.; Piggott, A.M.; Zhang, H.; Xiao, X.; Webb, T.I.; Gilbert, D.F.; Lynch, J.W.; Capon, R.J. Sesterterpene glycinyl-lactams: A new class of glycine receptor modulator from Australian marine sponges of the genus Psammocinia. Org. Biomol. Chem. 2013, 11, 4695–4701.
48. Avcibasi, H.; Anil, H.; Toprak, M. Four terpenoids from Cedrus libanotica. Phytochemistry 1987, 10, 2852–2854.
49. Luo, Q.; Di, L.; Dai, W.-F.; Lu, Q.; Yan, Y.-M.; Yang, Z.-L.; Li, R.-T.; Cheng, Y.-X. Applanatumin A, a New Dimeric Meroterpenoid from Ganoderma applanatum That Displays Potent Antifibrotic Activity. Org. Lett. 2015, 17, 1110–1113.
50. He, J.; Feng, X.Z.; Lu, Y.; Zhao, B. Fomlactones A−C, novel triterpene lactones from Fomes cajanderi. J. Nat. Prod. 2003, 66, 1249–1251.
51. Cheng, Z.-Y.; Du, Y.-Q.; Zhang, Q.; Lin, B.; Gao, P.-Y.; Huang, X.-X.; Song, S.-J. Two pairs of new alkaloid enantiomers with a spiro skeleton from the bark of Juglans mandshurica. Tetrahedron Lett. 2018, 59, 2050–2053.
52. Li, L.; Peng, X.-R.; Dong, J.-R.; Lu, S.-Y.; Li, X.-N.; Zhou, L.; Qiu, M.-H. Rearranged lanostane-type triterpenoids with anti-hepatic fibrosis activities from Ganoderma applanatum. RSC Adv. 2018, 8, 31287–31295.

53. Sun, N.; Zheng, G.; He, M.; Feng, Y.; Liu, J.; Wang, M.; Zhang, H.; Zhou, J.; Yao, G. Grayanane diterpenoids from the leaves of Rhododendron auriculatum and their analgesic activities. J. Nat. Prod. 2019, 82, 1849–1860.

54. Li, J.; Ni, G.; Liu, Y.; Mai, Z.; Wang, R.; Yu, D. Seconoriridone A: A C16-seco-noriridal Derivative with a 5/5/7 Tricyclic Skeleton from Belamcanda chinensisI. Tetrahedron Lett. 2019, 60, 900–905.

55. Xu, Y.-K.; Yang, S.-P.; Liao, S.-G.; Zhang, H.; Lin, L.-P.; Ding, J.; Yue, J.-M. Alkaloids from Gelsemium elegans. J. Nat. Prod. 2006, 69, 1347–1350.

56. Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. Isolation of gelsedine-type indole alkaloids from Gelsemium elegans and evaluation of the cytotoxic activity of gelsemium alkaloids for A431 epidermoid carcinoma cells. J. Nat. Prod. 2006, 69, 715–718.

57. Yang, C.B.; Zhang, F.; Deng, M.C.; He, G.Y.; Yue, J.M.; Lu, R.H. A new ellagitannin from the fruit of Phyllanthus Emblica L. J Chin Chem Soc. 2007, 54, 1615–1618.

58. Selwood, A.I.; Wilkins, A.L.; Munday, R.; Shi, F.; Rhodes, L.L.; Holland, P.T. Portimine: A bioactive metabolite from the benthic dinoflagellate Vulcanodinium rugosum. Tetrahedron Lett. 2013, 54, 4705–4707.

59. Fribley, A.M.; Xi, Y.; Makris, C.; Alves-de-Souza, C.; York, R.; Tomas, C.; Wright, J.L.; Strangman, W.K. Identification of portimine B, a new cell permeable spiroimine that induces apoptosis in oral squamous cell carcinoma. ACS Med. Chem. Lett. 2018, 10, 175–179.

60. Choodej, S.; Teerawatananond, T.; Mitsunaga, T.; Pudhom, K. Chamigrane sesquiterpenes from a basidiomycetous endophytic fungus XG8D associated with thai mangrove Xylocarpus granatum. Mar. Drugs 2016, 14, 132.

61. Chen, X.Q.; Li, Y.; Peng, L.Y.; He, J.; Wang, K.; Pan, Z.H.; Cheng, X.; Li, M.M.; Zhao, Q.S.; Xu, G. Spirocyclic acylphloroglucinol derivatives from Hypericum beanii. Chem. Pharm. Bull. 2011, 59, 1250–1253.

62. Wijeratne, E.M.K.; Espinosa-Artiles, P.; Gruener, R.; Gunatilaka, A.A.L. Thielavialides A–E, nor-spiro-azaphilones, and a bis-spiro-azaphilone from Thielavia sp. PA0001, an endophytic fungus isolated from aeroponically grown Physalis alkekengi. J. Nat. Prod. 2014, 77, 1467–1472.

63. Nong, X.H.; Wei, X.Y.; Qi, S.H. Pteridic acids C–G spirocyclic polyketides from the marine-derived Streptomyces sp. SCSGAA 0027. J. Antibiot. 2017, 70, 1047–1052.

64. Guo, J.G.; Feng, Z.F.; Yang, Y.J.; Zhang, Z.Z.; Zhang, P.C. Pollenopyrroside A and B, novel pyrrole ketohexoside derivatives from bee-collected Brassica campestris Pollen. Chem. Pharm. Bull. 2010, 58, 983–985.

65. Wang, W.L.; Zhu, T.J.; Tao, H.W.; Lu, Z.Y.; Fang, Y.C.; Gu, Q.Q.; Zhu, W.M. Three novel, structurally unique spirocyclic alkaloids from the halotolerant B-17 fungal strain of Aspergillus variecolor. Chem. Biodivers. 2007, 4, 2913–2919.
66. Zhong, W.; Wang, J.; Wie, X.; Chen, Y.; Fu, T.; Xiang, Y.; Huang, X.; Tian, X.; Xiao, Z.; Zhang, W.; et al. Variecolortins A–C, three pairs of spirocyclic diketopiperazine enantiomers from the marine-derived fungus Eurotium sp. SCSIO F452. Org. Lett. 2018, 20, 4593–4596.
67. Bai, M.; Zheng, C.-J.; Huang, G.-L.; Mei, R.-Q.; Wang, B.; Luo, Y.-P.; Zheng, C.; Niu, Z.-G.; Chen, G.-Y. Bioactive meroterpenoids and isocoumarins from the mangrove-derived fungus Penicillium sp. TGM112. J. Nat. Prod. 2019, 82, 1155–1164.
68. Jones, T.H.; Adams, R.M.M.; Spande, T.F.; Garraffo, H.M.; Kaneko, T.; Schultz, T.R. Histrionicotoxin alkaloids finally detected in an ant. J. Nat. Prod. 2012, 75, 1930–1936.
69. Wang, L.Y.; Qin, J.J.; Chen, Z.H.; Zhou, Y.; Tang, W.; Zuo, J.P.; Zhao, W.M. Absolute configuration of periplosides C and F and isolation of minor spiro-orthoester group-containing pregnane-type steroidal glycosides from Periploca sepium and their T-lymphocyte proliferation inhibitory activities. J. Nat. Prod. 2017, 80, 1102–1109.
70. Mackinnon, S.L.; Walter, J.A.; Quilliam, M.A.; Cembella, A.D.; LeBlanc, P.; Burton, I.W.; Hardstaff, W.R.; Lewis, N.I. Spirolides isolated from Danish strains of the toxigenic dinoflagellate Alexandrium ostenfeldii. J. Nat. Prod. 2006, 69, 983–987.
71. Xie, Y.; Zhong, X.; Xiao, Y.; Zhu, S.; Muhammad, I.; Yan, S.; Jin, H.; Zhang, W. Vieloplains A-G, seven new guaiane-type sesquiterpenoid dimers from Xylopia vielana. Bioorg Chem. 2019, 102891.
72. Song, J.; Liu, Y.; Zhou, M.; Cao, H.; Peng, X.G.; Liang, J.J.; Zhao, X.Y.; Xiang, M.; Ruan, H.L. Spiroschincarins A–E: Five spirocyclic nortriterpenoids from the fruit of Schisandra incarnate. Org. Lett. 2017, 19, 1196–1199.

Retrieved from https://encyclopedia.pub/entry/history/show/53583