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The chemical and biological properties of natural resorcylic acid lactones†

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Covering: 1953 to Feb 2025

Resorcylic acid lactones (RALs) represent a significant category of polyketides characterized by a β-resorcylate unit embedded in a macrolactone ring. Since the discovery of radicicol in 1953, over 300 natural RALs have been identified, showcasing remarkable structural diversity and a wide range of pharmacological activities, including antitumor, antimalarial, antifungal, and immunomodulatory effects. RALs target multiple molecular pathways, such as heat shock protein 90 (HSP90), WNT-5A, pyruvate dehydrogenase kinase 2 (PDK2), mitogen-activated protein kinase (MAPK), and peroxiredoxin 1 (PRDX1). Despite their promising pharmacological profiles, the clinical development of RALs has progressed at a sluggish pace. This review comprehensively catalogs all natural RALs reported to date, explores their bioactivity mechanisms, and critically assesses preclinical and clinical progress. By addressing gaps in mechanistic understanding and translational research, this work highlights the challenges in drug-like properties and clinical applicability, offering valuable insights for future RAL research.

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1. Introduction

Resorcylic acid lactones (RALs) are a distinct class of polyketide-derived natural products characterized by a β-resorcylate (2,4-

dihydroxybenzoic acid) core fused to a macrolactone ring.[1,2] As secondary metabolites produced by fungi, marine organisms, and plants, RALs exhibit remarkable structural diversity, arising from variations in macrolactone ring size (10- to 16-membered) and regioselective, site-specific oxidation. The discovery of radicicol in 1953 by Delmotte and colleagues from the fungus *Monocillium nordinii* marked the onset of RAL research,[3] with subsequent studies revealing its potency as an inhibitor of heat shock protein 90 (HSP90).[4–6] Over seven decades of investigation have unveiled more than 300 structurally distinct RALs, exhibiting a wide range of bioactivities, including antifungal,[7,8] cytotoxic,[9,10] antimalarial,[11] antiviral,[12] antiparasitic,[12] and immunosuppressive effects.[13] Notably, monocillins I–III are potent WNT-5A inhibitors;[14] radicicol binds to the ATP pocket of malaria parasite *Plasmodium* topoisomerase VIB and pyruvate dehydrogenase kinase 2 (PDK2);[15–17] hypothemycin derivatives containing a *cis*-enone are mitogen-activated protein kinase (MAPK) covalent inhibitors;[18–20] and pochonin D covalently targets peroxiredoxin 1 (PRDX1) to induce cuproptosis in triple-negative breast cancer.[21] The diverse pharmacological properties and broad range of biotargets make RALs valuable templates for drug discovery.

The RAL scaffold has driven decades of rational synthesis and structural optimization.[22,23] Nevertheless, the progress in clinical translation has paradoxically been sluggish. So far, a notable case has emerged: E6201, a derivative of LL-Z1640-2, demonstrated safety and initial efficacy in phase I trials for metastatic melanoma and phase II trials for psoriasis.[24] These clinical studies underscore the necessity of examining the translational challenges of RALs. While previous reviews have documented the structural diversity and bioactivities of RALs,[1,2,5,20,25,26] there remains a critical need for a systematic assessment of their drug-like properties and clinical limitations.

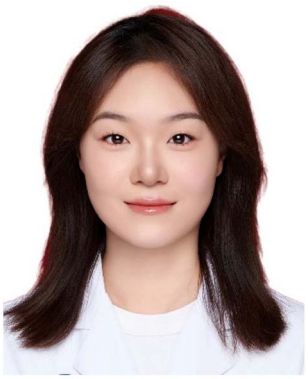
In this review, we present a comprehensive overview of the chemical structures and occurrence of all natural RALs reported since 1953, while also summarizing their bioactivities and potential applications in drug discovery. This work aims to address the gaps in previous reviews, particularly in mechanistic and translational research. Additionally, the review highlights the ongoing challenges in the field and provides valuable insights for future research on the RAL family.

2. Chemical diversity, classification, and occurrence of RALs

2.1. Chemical diversity and classification

Typically, RALs feature a 1,2,3,5-tetrasubstituted benzene ring with substitutions such as hydroxy, methoxy, or halogenated functional groups like chlorine and bromine. In some cases, pentasubstituted benzene rings with hydroxy, methoxy, or formyl groups are also observed. The lactone alcohol moiety generally includes a methyl group in most RALs, except for relgro-type RALs, which contain an aliphatic chain. Moreover, the lactone ring is usually decorated with a variety of functional groups, including *cis*- and *trans*-double bonds, hydroxy, methoxy, carbonyl, and epoxy groups.

Natural RALs are classified based on the size of their lactone ring into 10-membered (RAL_{10}), 12-membered (RAL_{12}), 13-membered (RAL_{13}), 14-membered (RAL_{14}), and 16-membered (RAL_{16}) (Fig. 1). Among them, RAL_{14} is the most common in nature, followed by RAL_{12}, while RAL_{10}, RAL_{13}, and RAL_{16} are relatively rare (Fig. 2). Additionally, RALs can be categorized



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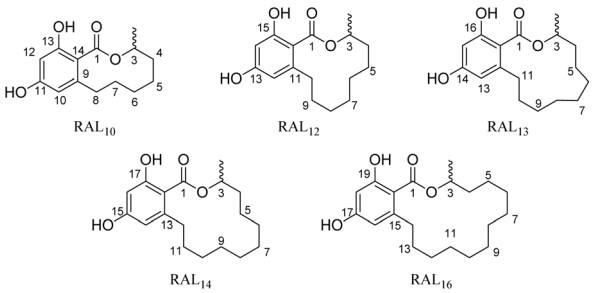

Fig. 1 The general structures and numbering systems of $RAL_{10, 12, 13, 14, 16}$.

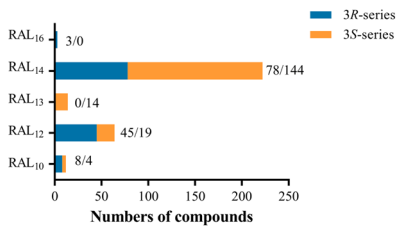

Fig. 2 The number of natural RALs reported until Feb. 2025.

based on the absolute configuration at the C-3 position. For RAL_{14}, those with a 3*R* configuration (radicicol-type) account for about half of those with a 3*S* configuration (hypothemycin-type). In contrast, for RAL_{12}, the 3*R*-series compounds outnumber the 3*S*-series by more than two to one. Importantly, we recommend that the research community adopt the unified numbering system presented in Fig. 1 for all newly discovered RALs, as it is essential for future comparative studies and data integration.

2.2. Occurrence and structural overview

By reviewing the original sources of natural RALs published up to February 2025 (Table S1†), an incomplete summary of fungal sources is provided in Fig. 3. Some studies used unidentified fungi, and early reports often lacked clear absolute configurations, making it impossible to trace their sources. RALs from fungi mainly come from genera such as *Ilyonectria*, *Fusarium*, *Paecilomyces*, *Penicillium*, *Podospora*, *Pochonia*, and *Lasiodiplodia*. Notably, *Lasiodiplodia*, a common pathogenic in tropical and subtropical regions, is a remarkable producer of RAL_{12}. We then classify the reported natural RALs into five subclasses: RAL_{10}, RAL_{12}, RAL_{13}, RAL_{14} and RAL_{16}, to discuss their isolation and chemical structures.

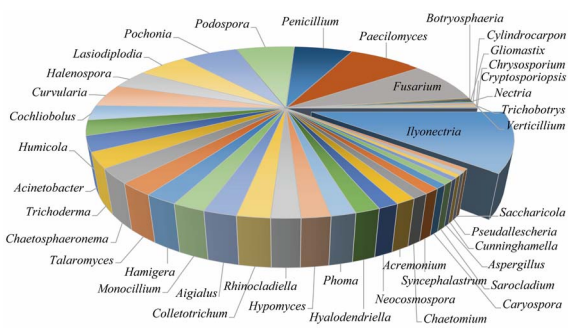

Fig. 3 The fungal sources of RALs published until Feb. 2025, divided by the genus.

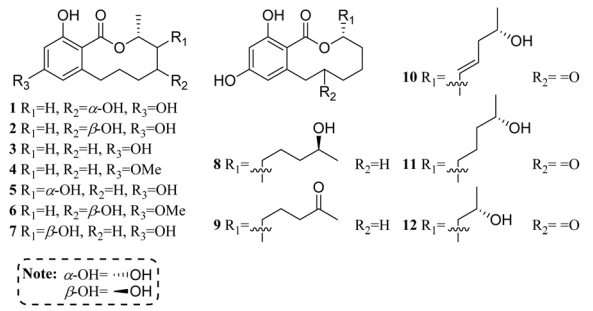

Fig. 4 Structures of RAL_{10}.

2.2.1. RAL_{10}. The first two 10-membered RALs, 3*R*, 5*R*-sonnerlactone (**1**, Fig. 4) and 3*R*, 5*S*-sonnerlactone (**2**), were originally isolated from a culture broth of an unidentified fungus, Zh6-B1, obtained from the bark of Chinese mangrove plant *Sonneratia apetala* in 2010.[27]

In 2018, Zhang *et al.* investigated the secondary metabolites of the endophytic fungus *Chaetosphaeronema hispidulum* from the desert plant *Bassia dasyphylla*, leading to the isolation of four new RAL_{10}, (*R*)-2,4-dihydroxy-7-methyl-7,8,9,10,11,12-hexahydro-6-oxa-benzocyclodecen-5-one (**3**) and hispidulactones A–C (**4–6**).[9] Among them, **3** displayed strong inhibitory effects against the seedling growth of *Arabidopsis thaliana*, the weed *Digitaria sanguinalis*, and *Echinochloa crusgalli*.[9] In 2020, further investigation of this fungus led to the identification of a new 12-membered lactone, hispidulactone F (**7**), along with three known analogs **1**, **2** and **5**.[28]

Relgro (**8**) and 10′-oxorelgro (**9**) are uncommon RAL_{10} with an aliphatic chain at C-3. Relgro (**8**) was first isolated from a seagrass-derived *Fusarium* sp. PSU-ES73 culture by Rukachaisirikul *et al.*,[29,30] while both **8** and **9** were later produced by another seagrass-derived fungus *Fusarium* sp. PSU-ES123 in 2016.[31] Their absolute configurations at C-3 were initially misassigned as *R*, while the first asymmetric total synthesis of **8** and **9** in 2019 confirmed their 3*S* configuration.[32] In 2021, our group obtained three new RAL_{10}, podospins A–C (**10–12**), from the solid rice-based culture of *Podospora* sp. G214, a plant-endophyte isolated from the root of *Sanguisorba officinalis* L.[13] Among them, **10** exhibited potent immunosuppressive activities against concanavalin A (ConA)-induced T cell proliferation with IC_{50} value of 10.6 μM, and lipopolysaccharide (LPS)-induced B cell proliferation with IC_{50} value of 10.3 μM.

2.2.2. RAL_{12}. (3*R*)-de-*O*-Methyllasiodiplodin (**13**, Fig. 5) and (3*R*)-lasiodiplodin (**14**) were first discovered from *Lasiodiplodia theobromae* in 1971.[33] Subsequently, **13** and/or **14** have been frequently obtained not only from various fungal genera, such as *Syncephalastrum*, *Fusarium*, *Trichoderma*, *Botryosphaeria* and *Chaetomium*,[34–38] but also from diverse plant genera, including

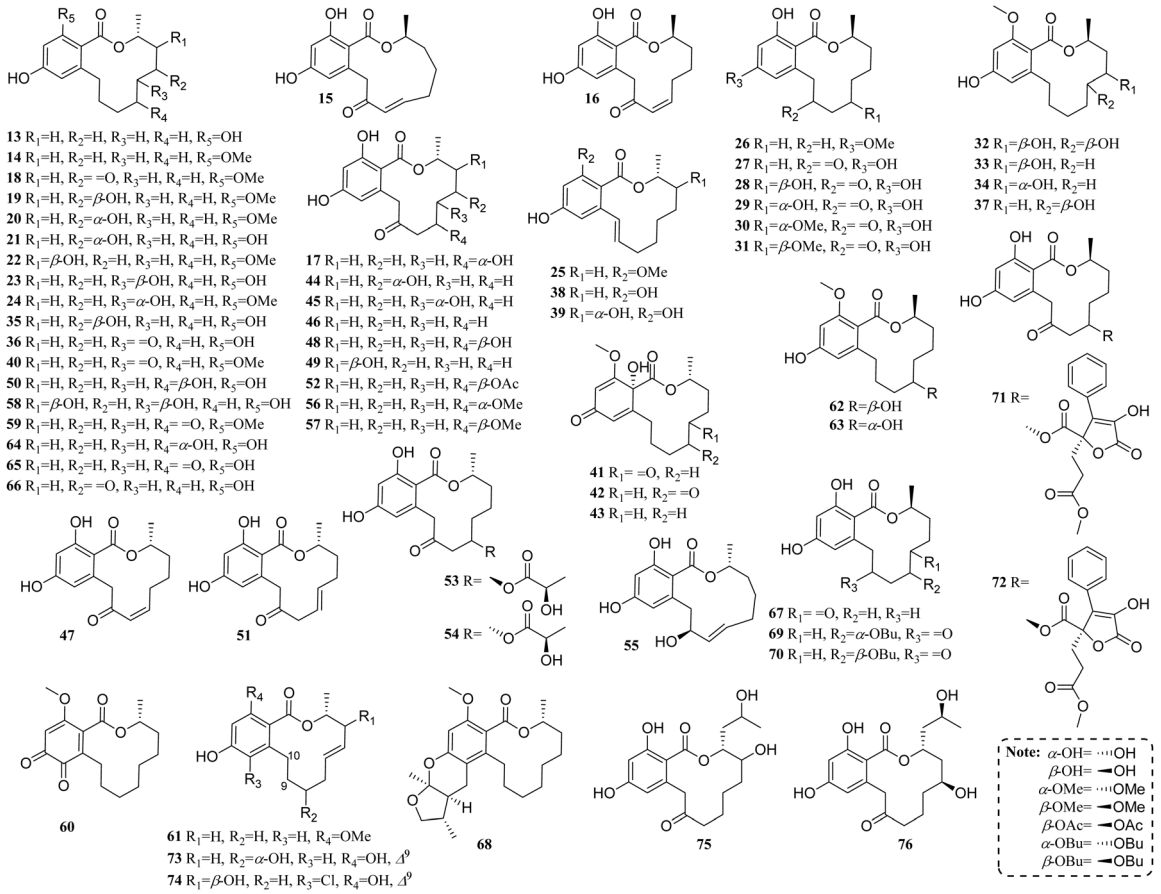

Fig. 5 Structures of RAL_{12}.

Arnebia, *Anthocleista*, *Osbeckia*, *Areca*, *Durio*, *Cibotium*, *Macroptilium*, *Ficus*, *Abelmoschus*, *Illicium*, *Annona*, *Dendrobium*, *Pholidota*, *Euphorbia*, *Caesalpinia* and *Ampelopsis*.[39–55] The absolute configurations at C-3 of **13** and **14** were initially deduced to be *S*.[56,57] Later, some synthetic studies corrected the configurations at C-3 in both **13** and **14** to be *R*.[58–61] Compound **13** could inhibit the growth and survival of MCF-7 cells through the induction of apoptosis, with upregulation of apoptotic genes and downregulation of monocyte chemotactic protein (MCP)-3.[62,63] Additionally, it was reported as a potent inhibitor of pancreatic lipase, with an IC_{50} value of 4.7 μM.[64–66] In 2011, Jiang and coworkers synthesized **13** and discovered that it was a potent nonsteroidal antagonist of the mineralocorticoid receptor (MR), with IC_{50} value of 8.9 μM.[67] In 2013, the same group reported that **13** ameliorated the expression of obesity-related proinflammatory factors and lowered the blood glucose levels, suggesting its potential as a promising lead for diabetes-related metabolic dysfunction.[68] Additionally, **14** demonstrated significant antileukemic activity in P-388 lymphocytic leukemia.[56]

Trans- and *cis*-resorcylides (**15–16**), known for their plant growth inhibitory effects, were first isolated from a *Penicillium* species in 1978.[69] They have since been reported from *Penicillium* sp. SC2193 [70] and *Acremonium zeae*.[71] In 2017, **16** was obtained from a marine-derived fungus, *Talaromyces rugulosus*.[72] The 3*S*-configuration of these compounds was assigned on the basis of the chemical degradation and total synthesis.[69,73]

(3*R*, 7*S*)-7-hydroxydihydroresorcylide (**17**) was first isolated from the extract of *Penicillium* sp. SC2193 in 1997 [70] and later obtained from a sea sediment-derived fungus, *Penicillium* sp. TJ403-2, by Li *et al.* in 2020.[74] (3*R*)-5-oxo-lasiodiplodin (**18**), (3*R*, 5*S*)-5-hydroxylasiodiplodin (**19**), and (3*R*, 5*R*)-5-hydroxylasiodiplodin (**20**), were first isolated from the culture filtrate of the fungus *Lasiodiplodia theobromae* IFO 31059 by Matsuura *et al.* in 1998.[57] In 2000, the same group isolated (3*R*, 5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin (**21**), (3*R*, 4*S*)-4-hydroxylasiodiplodin (**22**), and (3*R*, 6*R*)-6-hydroxy-de-*O*-methyllasiodiplodin (**23**) from mycelium extracts of the same fungus.[75] In 2005, (3*R*, 6*S*)-6-hydroxylasiodiplodin (**24**) was isolated from *L. theobromae* Shimokita 2.[76] Later, **19** and **20** were also identified in *Lasiodiplodia* sp. ZJ-HQ_1 [77] and *Sarocladium kiliense*.[68] **18–24** exhibited weak potato micro-tuber-inducing activity *in vitro*.[57,75,76] And **20** demonstrated 100% lytic activity at a concentration of 10 μg mL^{-1} against the zoospore motility of the late blight phytopathogen *Phytophthora capsica*.[38]

In 2006, (*E*)-9-etheno-lasiodiplodin (**25**) was reported as a metabolite of an endophytic fungus No. ZZF36 from a brown alga *Sargassum* sp.[78] Later, it was also identified in the fungus *Lasiodiplodia* sp. ZJ-HQ_1.[77] In 2007, ozoroalide (**26**) was found from the roots of plant *Ozoroa insignis* Del. (*Heeria insignis*

Del.).[79] Purification of the extracts of *Ludwigia hyssopifolia* and fruits of *Capparis masaikai* also yielded **26**, which inhibited the growth of Hep-2 cell line (IC_{50} = 10.8 μg mL^{-1}) and induced apoptosis by regulating caspase-3.[80,81]

In 2008, dihydroresorcylide (**27**) and the isomers (3*S*, 7*R*)- and (3*S*, 7*S*)-7-hydroxydihydroresorcylide (**28–29**) were identified as metabolites of *Acremonium zeae*.[71,82] In 2017, *Gliomastix* sp. ZSDS1-F7, isolated from the sponge *Phakellia fusca* Thiele, was also found to produce **27**.[10] Additionally, **28**, **29**, **30** and **31** were reported from *Penicillium* sp.[70,74] and *Talaromyces rugulosus*.[72] The culture broth of the marine-derived fungus *Pseudallescheria ellipsoidea* F42-3 yielded two RAL_{12}: (5*S*, 6*S*)-dihydroxylasiodiplodin (**32**) and (5*S*)-hydroxylasiodiplodin (**33**).[83] **33** and its epimer (5*R*)-hydroxylasiodiplodin (**34**) were previously isolated from *Botryosphaeria rhodina* PSU-M114 in 2009 [84] and *Lasiodiplodia* sp. 318# in 2016.[85] Compound **34** has also been obtained from the co-cultivation of *Trichoderma* sp. and *Acinetobacter johnsonii* in 2017.[36]

In 2011, a chemical investigation of *Syncephalastrum racemosum* led to the isolation of (3*R*, 5*S*)-5-hydroxy-de-*O*-methyllasiodiplodin (**35**), (3*R*)-6-oxo-de-*O*-methyllasiodiplodin (**36**), along with **13**, **14** and **21**.[34] Compound **35**, a C-5 epimer of **21**, exhibited significant cytotoxic activities against cholangiocarcinoma, KKU-M139, KKU-M156, and KKU-M213 cell lines.[34] In 2013, a rice medium of *Sarocladium kiliense*, isolated from the gut of healthy *Apriona germari* (H_{OPE}), yielded (3*S*, 6*R*)-6-hydroxylasiodiplodin (**37**), **14**, and **19**.[68] In 2014, (*E*)-9-ethenode-*O*-methyl-lasiodiplodin (**38**) and (3*R*, 4*R*)-4-hydroxy-de-*O*-methyl-lasiodiplodin (**39**) were obtained from a culture of *L. theobromae*, an endophyte from the root tissues of *Mapania kurzii* (Cyperaceae).[86] A chemical investigation of the petroleum ether, chloroform, and EtOAc extracts of the stems of *Ficus auriculate* led to the isolation of (*R*)-6-oxolasiodiplodin (**40**) and ficusines A–C (**41–43**), with **41–43** possessing an uncommon quinone ring rather than a benzene ring.[47]

In 2015, an endophytic *Saccharicola bicolor* isolated from the root of *Bergenia purpurascens* provided two new RALs: 13-hydroxyhidroresorcylide (**44**) and 12-hydroxyhidroresorcylide (**45**).[87] Zhang *et al.* isolated (*R*)-dihydroresorcylide (**46**), (*R*)-*cis*-resorcylide (**47**), (10*R*, 14*R*)-10-hydroxydihydroresorcylide (**48**), and (13*S*, 14*R*)-13-hydroxydihydroresorcylide (**49**) from *Penicillium brocae* MA-192, which was collected from the fresh leaves of marine mangrove plant *Avicennia marina*.[88] Among them, **48** exhibited significant DPPH radical scavenging activity (IC_{50} = 14.4 μg mL^{-1}).[88] Compounds **46–49** were also isolated from *Penicillium* sp. (NO. SYP-F-7919) in 2016 by An *et al.*[83] Fractionation of *Fusarium solani* T-13 extract led to the isolation of **13** and 7-hydroxy-14-de-*O*-methyl-lasiodiplodin (**50**).[35] Shiono *et al.* explored the inhibitory effects of **13** and **50** on Ca^{2+}-signal transduction using the mutant yeast strain *Saccharomyces cerevisiae* (*zds1*Δ *erg3*Δ *pdr1/3*Δ: YNS17 strain). Among them, **13** showed significant doughnut-like phenotypes of growth-restoring activity at a concentration of 0.2 mg per spot.[35]

Penicillium sp. (no. SYP-F-7919), obtained from the rhizosphere soil of *Panax notoginseng*, was the source of the following RAL_{12}: penicimenolides A–E (**51–55**), (11*S*)- and (11*R*)-methoxyresorcylides (**56–57**), along with **46–49**.[70,83] Compounds **46–49** and **51–57** were evaluated for their cytotoxic activities against six human tumor cell lines (U937, MCF-7, A549, SH-SY5Y, HepG2 and SW480), of which **52–54** exhibited potent effects against U937 and MCF-7 cells with IC_{50} values ranging from 1.4 to 11.6 μM. In-depth investigation demonstrated that **52** induced apoptosis in MCF-7 cells by targeting mitogen-activated extracellular signal-regulated kinase 1/2 (MEK1/2) and extracellular signal-regulated kinase 1/2 (ERK1/2).[83] In addition, compounds **47** and **52–54** exhibited significant inhibitory effects against LPS-activated NO production with IC_{50} values ranging from 0.7 to 5.8 μM.[83]

In 2016, a new hydroxylasiodiplodin, (3*R*, 4*S*, 6*R*)-4,6-dihydroxy-de-*O*-methyllasiodiplodin (**58**), was discovered in the bark of *Cinnamomum cassia*.[89] Among two new RAL_{12} (**59** and **60**) isolated from the fungal strain *Lasiodiplodia* sp. 318#, **60** featured a unique *o*-benzoquinone ring fused with a 12-membered lactone moiety.[85] In 2017, further investigation of this fungus by the same group led to the isolation of **61**.[90] The investigation of *Strychnos angustiflora* Benth seeds, a medicinal plant from southern China, resulted in the isolation of (−)-(7*S*)-7-hydroxylasiodiplodin (**62**) and (+)-(7*R*)-7-hydroxylasiodiplodin (**63**).[91]

In 2017, (3*R*, 7*R*)-hydroxy-de-*O*-methyllasiodiplodin (**64**), along with (3*R*)-7-oxo-de-*O*-methyllasiodiplodin (**65**), (3*R*)-5-oxo-de-*O*-methyllasiodiplodin (**66**), and (3*S*)-6-oxo-de-*O*-methyl-lasiodiplodin (**67**), was produced through the co-cultivation of the mangrove endophytic fungus *Trichoderma* sp. 307 and the aquatic pathogenic bacterium *Acinetobacter johnsonii* B2 by Zhang *et al.*[36]

Lasiodiplactone A (**68**), a RAL_{12} fused with a pyran ring and a furan ring to form a unique 12/6/6/5 tetracyclic system, was obtained from the mangrove endophytic fungus *L. theobromae* ZJ-HQ_1.[92] This fungus produced normal RALs when cultured on autoclaved rice solid-substrate medium.[77] However, when grown on rice culture with 3% salinity, it may have activated silent gene clusters to produce **68**. Chen *et al.* evaluated the inhibitory activity of **68** against LPS-activated NO production, showing superior activity (IC_{50} = 23.5 μM) compared to the positive control, indomethacin.[92] (3*S*, 7*S*)-7-*O*-*n*-butylresorcylide (**69**), (3*S*, 7*R*)-7-*O*-*n*-butylresorcylide (**70**), and talarodilactones A–B (**71–72**), together with **16** and **28–31**, were characterized from the solid rice culture of a marine-derived fungus *Talaromyces rugulosus*.[72] Compounds **71** and **72** represent a new class of butenolide-resorcylide dimers, exhibiting potent cytotoxicity against the L5178Y mouse lymphoma cell line, while their monomeric building blocks were inactive.[72]

In 2019, monocillin VII-1 (**73**) was obtained from the bioactive extract of *Pochonia chlamydosporia* strain 170.[93] The original name of **73** was monocillin VII, which was the same as that of a RAL_{14} reported from a *Paecilomyces* species in 2017. To avoid confusion, it was renamed monocillin VII-1.[94] In 2020, our group discovered that the fungus *Ilyonectria* sp. sb65, isolated from soil near the fibrous root of *Schisandra bicolor* var. *tuberculate*, produced ilyoresorcy K (**74**), along with some RAL_{14} and RAL_{16}.[95] Compound **74** is the first RAL_{12} with a chlorine atom substituted on the benzene ring.

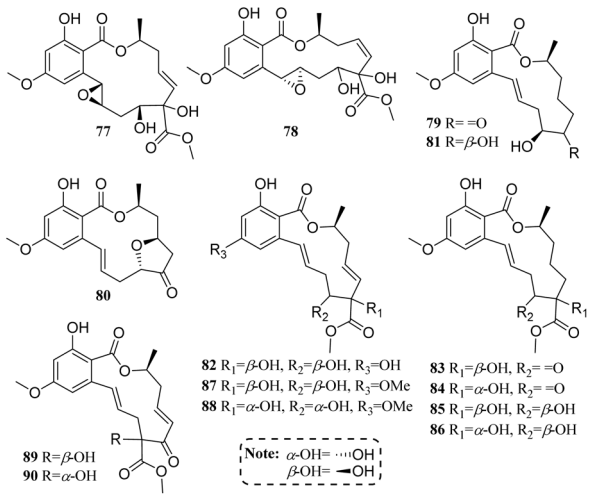

Fig. 6 Structures of RAL_{13}.

In 2022, a new RAL_{12}, colletoresorcylic lactone (**75**), was isolated from a halophyte-associated fungus, *Colletotrichum gloeosporioides* JS0419.[96] This is the first RAL_{12} with a propyl group at C-3, instead of a methyl group. In 2025, cochliomycin H (**76**) was isolated from the sponge-derived fungus *Curvularia* sp. ZYX-Z-4, showing neuroprotective effect on the H_2O_2-injured SH-SY5Y cells.[97]

2.2.3. RAL_{13}. In 2009, two rearranged 13-membered RALs (**77** and **78**, Fig. 6) were isolated from the marine mangrove fungus *Aigialus parvus* BCC 5311.[98] In 2022, our group conducted further chemical investigation on *Podospora* sp. G214, which led to the discovery of twelve undescribed RAL_{13}, podomycins A–L (**79–90**).[99] Compounds **80**, **84**, **86**, **88** and **90** displayed immunosuppressive activities against T cell proliferation with IC_{50} values of 14.5–21.9 μM, and B cell proliferation with IC_{50} values of 22.3–36.5 μM. Further mechanism of action research demonstrated that **84** distinctly induced apoptosis in activated T cells *via* MAPKs/AKT pathway.[99]

2.2.4. RAL_{14}. Radicicol (**91**, Fig. 7), the first naturally occurring RAL, was initially isolated in 1953 from *Monocillium nordinii* as a potent antibiotic and named monorden.[3] In 1964, it was re-identified as a mild tranquilizer from *Nectria radicicola* following a structural revision and renamed radicicol.[100] In 1987, Cutler *et al.* cultured *Neocosmospora tenuicristata* on shredded wheat medium, producing a large quantity of **91** and defining its stereochemistry through single crystal X-ray diffraction. This stereochemistry was later confirmed by the first total synthesis in 1992.[101,102] Radicicol has since been found in various fungi, such as *Cylindrocarpon radicicola*,[103] *Penicillium luteo-aurantium*,[104] *Verticillium chlamydosporium*,[105] *Humicola* sp. FO-2942,[106] *Chaetomium chiversii*,[107] *Pochonia chlamydosporia* TF-0480,[108] *Trichobotrys effuse*,[109] *Neocosmospora* sp. (UM-031509),[110] and *Ilyonectria* sp. sb65.[95] It exhibits various bioactivities, including antifungal,[7,8] antimalarial,[111] anti-inflammatory,[112] and inhibition of oncogene signal transduction.[113,114] In addition, radicicol has gained significant attention for its potent and selective inhibition of HSP90.[115,116]

In 1980, five new 14-membered RALs, named monocillins I–V (**92–96**) and **91**, were produced from the liquid culture of *Monocillium nordinii*, a mycoparasite of pine stem rusts.[117] Those monocillins were later found in diverse fungal species, including *Paecilomyces* sp. SC0924,[94] *Colletotrichum graminicola*,[8] and *Paraphaeosphaeria quadriseptata*.[107,118] Notably, monocillin I (**92**) identified as an HSP90 inhibitor, similar to **91**.[107] In 1998, a new antifungal monorden analog (**97**) was produced by the mycoparasite *Humicola fuscoatra* NRRL 22980, which was isolated from an *Aspergillus flavus* sclerotium in a cornfield near

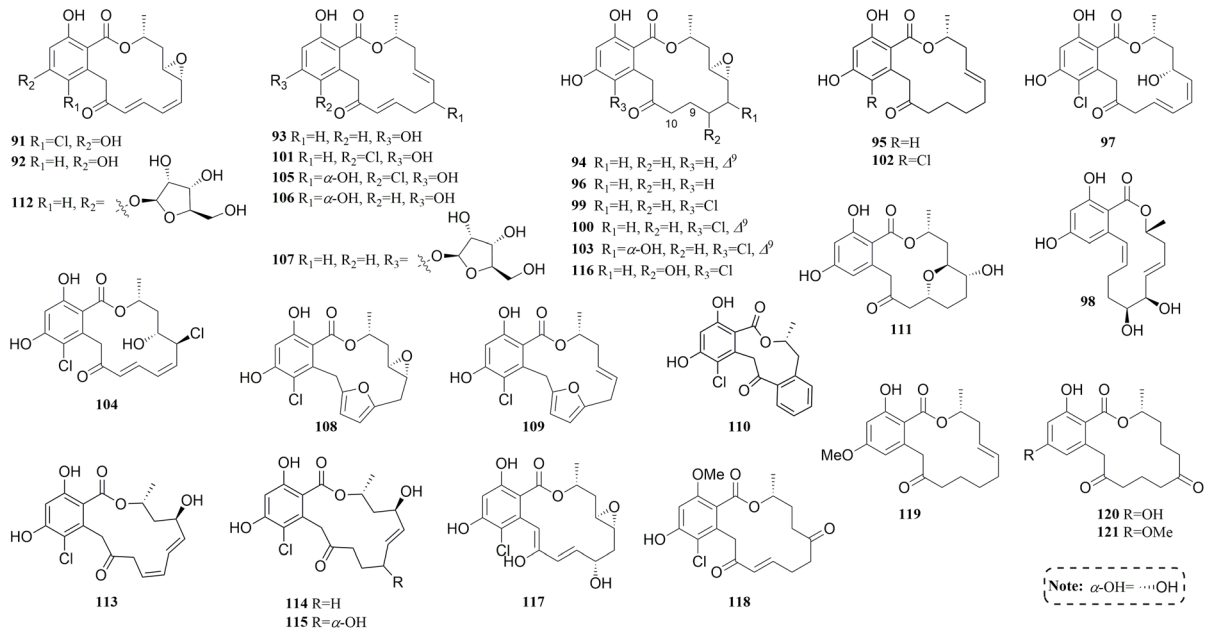

Fig. 7 Structures of radicicol-type RAL_{14} **91–121**.

Tifton, GA.[7] In 2009, Shinonaga *et al.* also obtained **97** from the culture broth of *Pochonia chlamydosporia* var. *chlamydosporia* and determined its stereochemistry.[108]

In 2002, aigialomycin E (**98**) was obtained from a mangrove fungus *Aigialus parvus* BCC 5311.[119] In 2003, monordens B–E (**99–102**) and **91** were derived from the amidepsine-producing *Humicola* sp. FO-2942. Among them, **91** and **102** exhibited antifungal activity specifically against *Aspergillus niger*, while all compounds induced cell cycle arrest at G1 and G2/M phases in Jurkat cells at 30 μM.[106] In the same year, Hellwig *et al.* reported the investigation of *Pochonia chlamydosporia* var. *catenulata* strain P 0297, leading to the discovery of pochonins A–E (**100**, **103**, **104**, **101**, **105**). This fungus also produced pochonin F (**106**) and monocillin II glycoside (**107**) when grown in bromide-containing culture media.[12] The configurations of C-6 in **104** and C-7 in **105–106** were established by total syntheses.[120,121] A cellular replication assay against HSV1 showed that **100**, **103**, **104** and **105** exhibited antiviral activities, with IC_{50} ranging from 1.5 to 10 μM.[12] Additionally, compound **100** exhibited selective antiparasitic activity against *Eimeria tenella*.[12]

A strain of *Pochonia chlamydosporia* TF-0480 was investigated and yielded pochonins G–P (**108–117**).[108,122] Most of these compounds inhibited WNT-5A expression. In 2012, chemical analysis of the fungus *Cryptosporiopsis* sp. strain CAFT122-1 resulted in the isolation and characterization of cryptosporiopsin A (**118**),[123] which exhibited motility inhibitory and lytic activities against zoospores of the grapevine downy mildew pathogen *Plasmopara viticola*, and also displayed significant inhibitory activity against *Pythium ultimum*, *Aphanomyces cochlioides*, and *Rhizoctonia solani*.[123]

In 2013, chromatographic fractionation of extracts from *Neocosmospora* sp. (UM-031509) led to neocosmosins A–C (**119–121**).[110] Among them, **121** showed good binding affinity for the human opioid receptors, suggesting that this class of compounds could serve as potential leads for the development of psychotropic drugs.[110] In 2014, bioassay-guided isolation of a marine-derived *Humicola fuscoatra* yielded three new RALs, radicicols B–D (**122–124**, Fig. 8), and several known RALs, including **91**, **103**, **104** and **115**.[124]

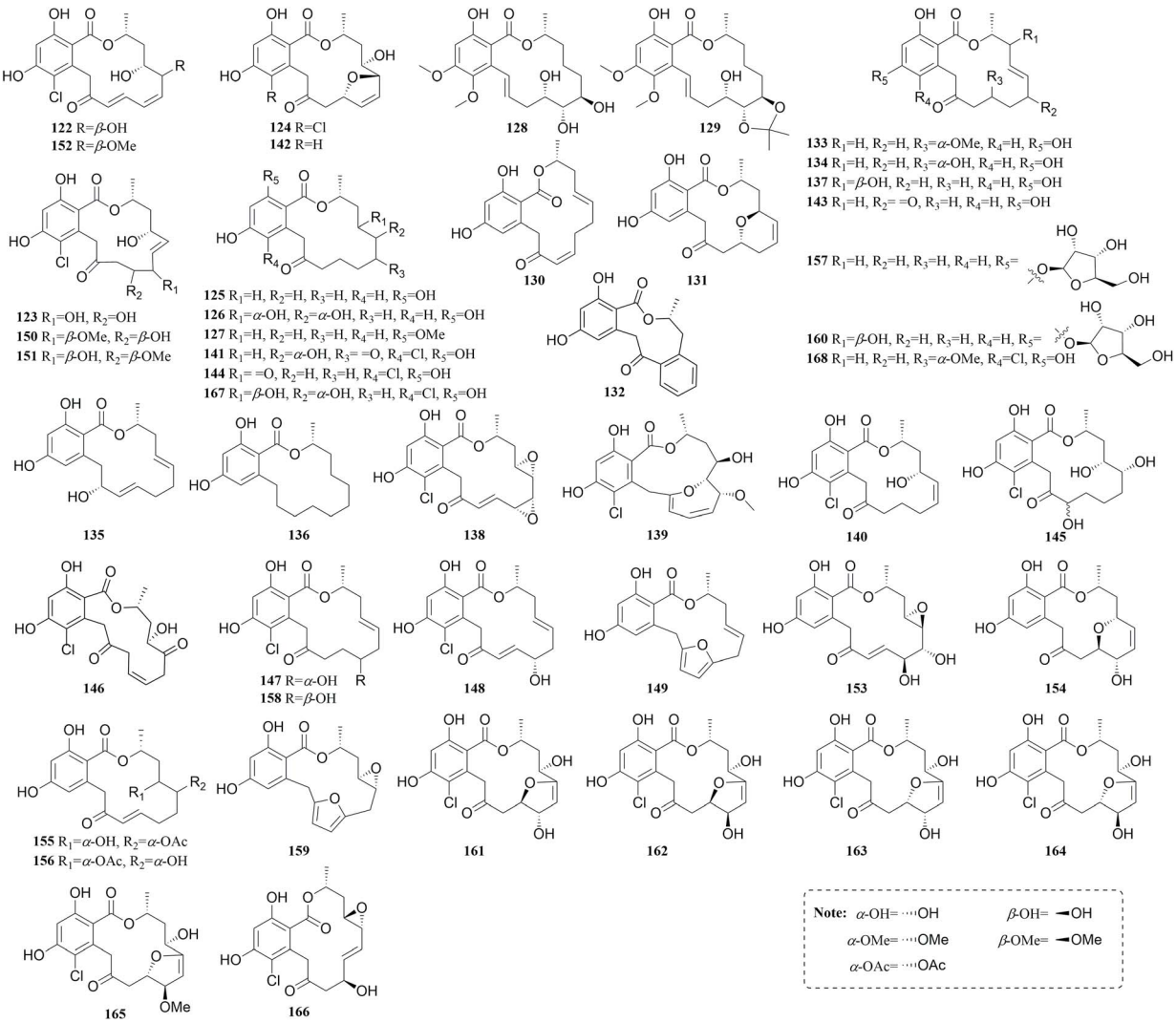

Fig. 8 Structures of radicicol-type RAL_{14} **122–168**.

The planar structures of nordinone (**125**) and nordinonediol (**126**) were first reported by Ayer *et al.* in 1987 as metabolites from the liquid culture of *Monocillium nordinii*.[125] In 2014, the biosynthesis of **125** was achieved through heterologous production in *Saccharomyces cerevisiae*, and it was renamed lasicicol due to the prior use of the name "nordinone" for a steroid.[126,127] In 2015, lasicicol (**125**) and a new RAL_{14} derivatives (**127**) were isolated from *Lasiodiplodia* sp. ZJ-HQ1.[77] In addition, **127** was obtained from a mangrove endophytic fungus of the same species in 2016.[85] Compound **125** displayed moderate cytotoxicity against rat pituitary adenoma GH3 and rat prolactinoma MMQ cells, with IC_{50} values of 12.3 and 10.1 μM, respectively.[36,90]

Two new RAL_{14} with a 3*R*-configuration, hyalodendriellins C and E (**128** and **129**), were isolated from *Hyalodendriella* sp. Ponipodef12.[128] Compound **128** displayed moderate larvicidal activity against the fourth-instar larvae of the mosquito *Aedes aegypti*, with an LC_{50} value of 117.5 μg mL^{-1}. In 2017, monocillins VI–VII, dechloropochonin I, 4′-methoxymonocillin IV, 4′-hydroxymonocillin IV and 2′α-hydroxymonocillin II (**130–135**), together with **91–95** and **101**, were characterized from the solid-state fermentation of *Paecilomyces* sp. SC0924, a hypocrealean fungal strain isolated from soil.[94] Among them, **135** was synthesized by Shinonaga's group in 2009 as part of a search for WNT-5A expression inhibitors.[14] Compounds **130** and **133** exhibited antifungal activity against the phytopathogenic fungus *Peronophythora litchi*, with IC_{50} values of 9.2 and 19.3 μM, respectively.[94] In 2001, Bracher *et al.* described an enantiodivergent approach to the two enantiomers of zearalane *via* macrolactonization of (*S*)-2,4-dibenzyloxy-6-(10-hydroxyundecyl)benzoic acid using either Gerlach's modification of the Corey lactonization or a Mitsunobu lactonization.[129] Later, (*R*)-zearalane (**136**), with cytotoxic activity, was isolated from a mangrove endophytic fungus, *Lasiodiplodia* sp. 318#.[90]

In 2019, a new 14 membered monocillin analogue (**137**), a metabolite of *Pochonia chlamydosporia* strain 170, was found to exhibit modest antibacterial activity.[93] Since its name (monocillin VI) had already been assigned to **130**, it was renamed monocillin VI-1 for clarity. The antibacterial activities of **93**, **95**, **96**, **101**, **114**, and **137** were measured against *Xanthomonas campestris* pv. *campestris* by Qin *et al.* using a 2-fold liquid dilution series. All RAL_{14} showed modest antibacterial activities.[93]

In 2020, our group obtained eight new RAL_{14}, named ilyoresorcys C–J (**138**, **137**, **139–144**), from *Ilyonectria* sp. sb65.[95] In 2022, a new RAL_{14}, named radicicol E (**145**), was isolated from *Ilyonectria mors-panacis* DAOMC 251601.[130] In the same year, eleven new radicicol-type RALs, namely ilyomycins A–K (**146–156**), were identified by our group from the strain sb65.[131] Compounds **155** and **156** were a pair of inseparable regioisomers resulting from intramolecular transacetylation. Among these compounds, **148**, **152**, **153**, and **155**/**156** displayed immunosuppressive activities against T cell proliferation with IC_{50} values ranging from 1.2 to 21.7 μM, and B cell proliferation with IC_{50} values ranging from 1.1 to 20.1 μM. Further study revealed that ilyomycin C (**148**) exerted anti-proliferative effect on T lymphocytes through HSP90 inhibition.[131]

In 2023, colletogloeolactones A and B (**157** and **158**), and six known compounds (**93**, **97**, **107**, **113**, **124** and **135**), were identified from the endophytic fungus *Colletotrichum gloeosprioides* JS0419.[132] Compounds **93** and **107** showed potent anti-inflammatory activity in LPS-activated RAW 264.7 cells by inhibiting the synthesis of pro-inflammatory cytokines.

In 2024, ilyomycin L (**159**) was isolated from the fermentation of the soil-derived fungus *Ilyonectria* sp. DWS906.[133] A chemical study of the nematicidal biocontrol fungus *Pochonia chlamydosporia* PC-170 led to discovery of monocillin VI glycoside (**160**), along with **93**, **101**, **107**, **130**, and **157**.[134] The three glycosylated RALs, **160**, **157** and **107**, exhibited nematicidal activity against *Meloidogyne incognita* with LC_{50} values of 94, 152 and 64 μg mL^{-1}, respectively. In 2025, eight new RALs, ilyolactones A–H (**161–168**), were isolated from the plant endophytic *Ilyonectria* sp. FL-710.[21] All isolates were evaluated for cytotoxicity in six human cancer cell lines, and the result showed that the α,β-unsaturated ketone group was crucial for the antitumor activity of RALs.

Zearalenone (**169**), the first-discovered RAL of the hypothemycin-type (Fig. 9), was isolated from *Gibberella zeae* in 1962.[135] It is a widely distributed nonsteroidal estrogenic mycotoxin, produced by various *Fusarium* species. Although its acute toxicity is low, **169** can cause estrogenic symptoms, including vulvovaginitis, uterine enlargement, prolonged or interrupted oestrus, and infertility.[136] It also has genotoxic, cytotoxic, immunotoxic, and hepatonephrotoxic properties.[137–142] After **169**, 5-formylzearalenone (**170**), 7′-dehydrozeraralenone (**171**), 8′-hydroxyzearalenone (**172**), and 8′-*epi*-hydroxyzearalenone (**173**) were subsequently identified in *Gibberella zeae* in 1972.[143] Compound **171** exhibited higher cytotoxicity than **169**, while **169** and **172** had protective effects against INS-1 832/13 pancreatic β-cells, with the EC_{50} values of 6.1 and 13.1 μM, respectively.[31] Subsequently, more zearalenone congeners were identified from *Fusarium* species, such as 6′,8′-dihydroxyzearalene (**174**) in 1976,[144] epimers of 3′-hydroxyzearalenone (**175** and **176**) in 1980,[145] *cis*-zearalenone (**177**), four stereoisomers of zearalenol (**178–181**), zearalanone (**182**), and α- and β-zearalanol (**183–184**) in 1985.[146] Among them, *trans*-α-zearalenol (**179**) was found to be more oestrogenic than *trans*-β-zearalenol (**181**) and **169**, highlighting the significant impact of the hydroxy group orientation on oestrogenic activity.[147] In 2015, Drzymala *et al.* compared the estrogenicity of **169**, **177**, **178**, and **180–184**, and put forward that the transition from *trans* to *cis* configuration did not notably affect estrogenicity.[148]

The isolation and characterization of LL-Z1640-1 to 4 (**185–188**) from an unidentified fungus were first reported in 1978.[149] Although structurally related to **169**, compounds **185–188** did not exhibit anabolic or estrogen-like activities. Subsequent biological studies and the synthesis of **186**, also known as (5*Z*)-7-oxozeaenol, have revealed that it acts as an inhibitor of ERK2 and transforming growth factor-β-activated kinase 1 (TAK1).[150–154]

Zeaenol (**189**) was found to be produced by *Curvularia lunata* during chemical studies on aversion-antagonism.[155] In 1999, (5*E*)-7-oxozeaenol (**190**) and 5,6-dihydo-5-methoxy-7-oxozeaenol (**191**) were purified from the fermentation of *Xenova*

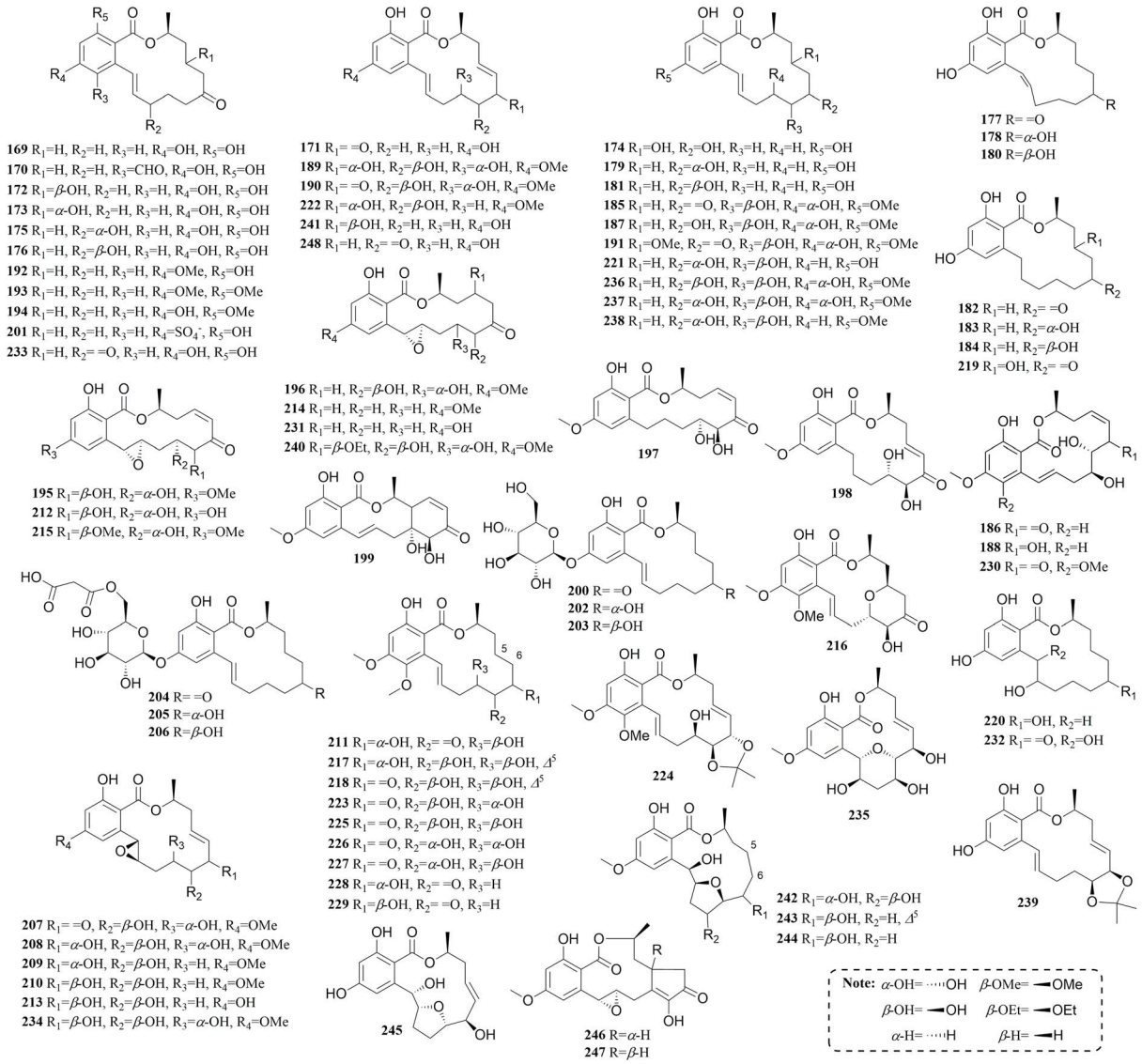

Fig. 9 Structures of hypothemycin-type RAL_{14} **169–248**.

fungus 20416, *Curvularia lunata*.[156] And 14-methoxyzearalenone (**192**) was isolated from an *Ascochyta* spp. (Xenova fungus 24518).[156] In 1988, 2,4-dimethoxyzearalenone (**193**) and 2-methoxyzearalenone (**194**) were obtained from the cultures of the fungus *Cunninghamella bainieri*.[157]

Two antibiotics, hypothemycin (**195**) and 7′,8′-dihydrohypothemycin (**196**), were originally isolated from *Hypomyces trichothecoides*.[11,158] Later, **195** was found in other fungal genera, such as *Coriolus versicolor* and *Aigialus parvus*, exhibiting antifungal, antimalarial, and cytotoxic activities.[119,159] Compound **195** was identified as an MEK inhibitor with IC_{50} value of 15 nM.[160] In 1999, L-783, 277 (**197**) was isolated from a *Phoma* sp. strain derived from the fruit body of *Helvella acetabulum*. It was a highly potent and irreversible MEK inhibitor with an IC_{50} value of 4 nM.[160] Its *trans*-isomer, L-783, 290 (**198**), showed a significantly reduced inhibitory effect on MEK (IC_{50} = 300 nM). In 2020, the successful asymmetric total syntheses of **197** and **198** were reported by Chakraborty *et al.*[161] Another MEK inhibitor, Ro 09-2210 (**199**), was isolated from fungal broth FC2506 and was found to effectively block T cell activation and/or proliferation, inhibiting IL-2 secretion.[162]

A significant amount of **169** was found in *Fusarium* cultures as zearalenone-14-β-D-glucopyranoside (**200**) or zearalenone-14-*O*-sulfate (**201**).[163–165] Subsequent studies confirmed that **200** was cleaved during digestion in swine, releasing its oestrogenic precursor, **169**.[166] In addition, compounds **179**, **181**, and their respective glucosides (**202**, **203**) were detected in maize cell cultures treated with **169** in 1999.[167] In 2006, Berthiller *et al.* treated *Arabidopsis thaliana* seedlings with 50 μM **169**, and then both the liquid media and plant extracts were analyzed by LC-MS/MS, leading to the detection of malonylglucosides (**204**–**206**), along with **169**, **179**, **181**, **200**, **202**, and **203**.[168] The author proposed a biotransformation pathway for **169** in *Arabidopsis thaliana*, covering both phase I and II metabolism. The occurrence of malonylglucosides and disaccharides suggested that they derive from the respective monoglucosides.

Aigialomycins A–E (**207–210, 98**) and **195** were isolated from the mangrove fungus *Aigialus parvus* BCC 5311 in 2002.[119] Compounds **195** and **210** exhibited potent antimalarial activities against *Plasmodium falciparum*.[119] In 2002, chemical analysis of the fungal strain *Chrysosporium queenslandicum* IFM51121 resulted in the discovery of queenslandon (**211**).[169] Following this, several synthetic studies on **211** were reported.[170,171] Of the three new RALs (**212–214**) isolated from the fungal strains *Hypomyces subiculosus* DSM 11931 and DSM 11932, 4-*O*-demethylhypothemycin (**212**) exhibited potent and selective cytotoxicity against a panel of BRAF mutation human cell lines.[172] Compound **213**, later named 1′,2′-epoxy aigialomycin D, was also obtained from *Paecilomyces* sp. SC0924 and showed antifungal activity.[173] 5′-*O*-Methylhypothemycin (**215**) and **195** were isolated from a *Phoma* sp. from *Senecio kleinii* in Gomera.[174]

In 2007, an investigation of bioactive metabolites against plant-parasite nematodes from the freshwater fungus *Caryospora callicarpa* YMF1.01026 led to the isolation of caryospomycins A–C (**216–218**).[175] In 2008, 8′-hydroxyzearalanone (**219**) and 2′-hydroxyzearalanol (**220**) were isolated from the marine fungus *Penicillium* sp.[176] In the same year, 5′-hydroxyzearalenol (**221**) was identified as a new metabolite of the marine fungus *Fusarium* sp. 05ABR26.[177] A synthetic study on deoxy-aigialomycin C (**222**) used a diastereoselective ring closing metathesis macrocyclization protocol.[178] It was later reported as a natural product with potent antifouling activity, derived from the sea anemone-derived fungus *Cochliobolus lunatus*.[179]

Hamigeromycins A–G (**223–229**) and 89-250904-F1 (also named radicicol analogue A, **230**) were isolated from the soil fungus *Hamigera avellanea* BCC 17816.[180,181] Among these, only **230** exhibited moderate cytotoxicity against the KB, MCF-7 and NCI-H187 human cancer cell lines. In 2010, Pfeiffer *et al.* identified three new zearalenone congeners: zearalenone-11, 12-oxide (**231**), zearalenone-11,12-dihydrodiol (**232**), and 10-keto-zearalenone (**233**) from the fungus *Fusarium graminearum*.[182] In the same year, Xu *et al.* isolated paecilomycins A–B and E–F (**234–237**) from *Paecilomyces* sp. SC0924.[173,183] The structures of **236** and **237** were later revised in 2012 based on synthetic studies.[173,184,185] Further research in 2012 yielded paecilomycins G–I (**238–240**) and *trans*-7′,8′-dehydrozearalenol (**241**).[173] In 2013, Xu *et al.* isolated paecilomycins J–M (**242–245**), which contain a tetrahydrofuran ring from the same fungus,

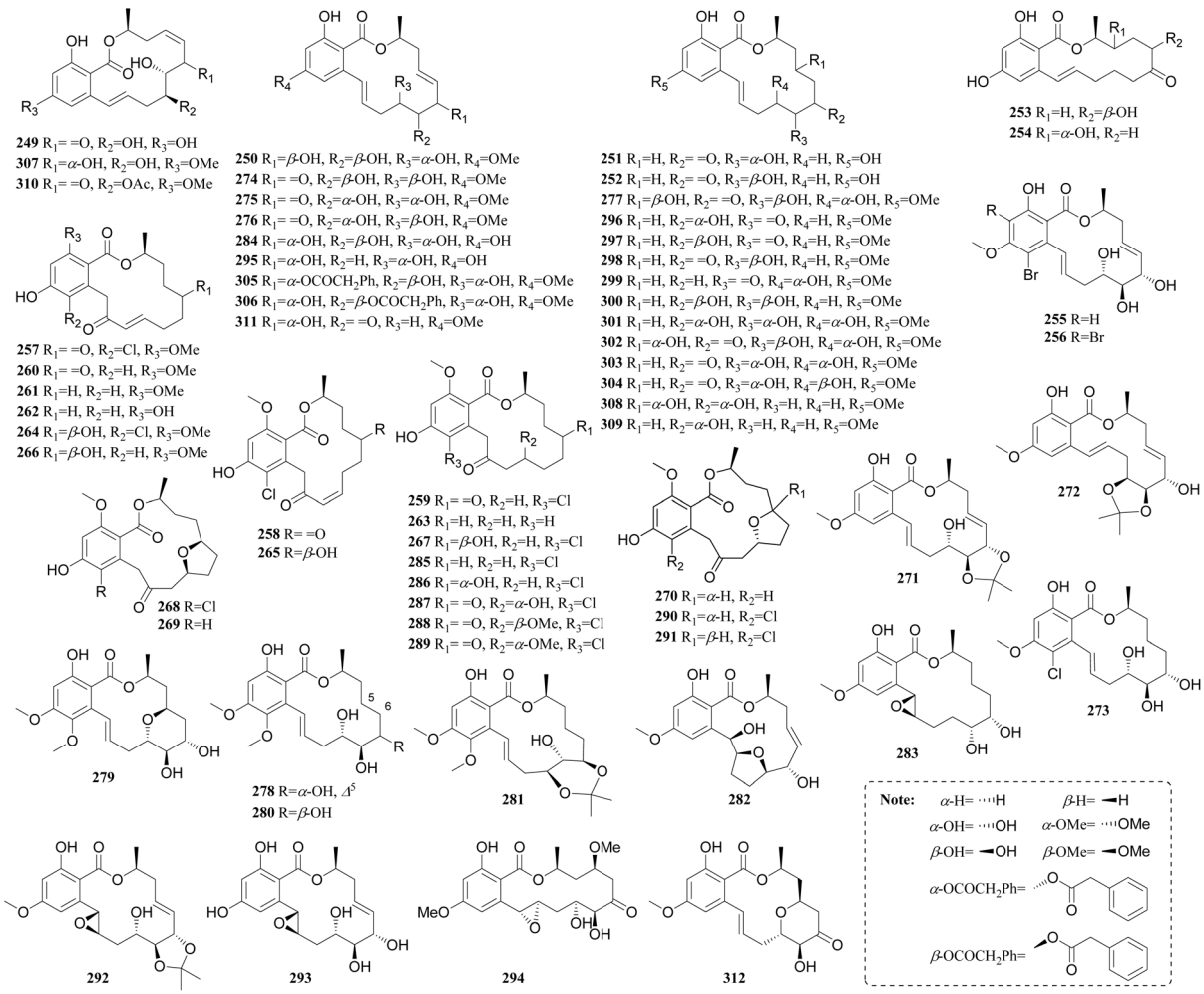

Fig. 10 Structures of hypothemycin-type RAL_{14} **249–312**.

with **245** exhibiting weak antifungal activity against *Peronophythora litchii*.[186,187] In 2017, additional fermentation of the strain SC0924 led to the isolation of paecilomycins N–P (**246–248**).[94] Compounds **246** and **247** featured a novel 6/11/5 ring system, which might derive from hypothemycin *via* a key Nazarov-type cyclization in the biogenetic pathway.

In 2011, 15-*O*-desmethyl-(5*Z*)-7-oxozeaenol (**249**, Fig. 10) and 7-*epi*-zeaenol (**250**) were isolated from a filamentous fungus, MSX 63935 (related to *Phoma* sp.), found in leaf litter collected in Nigeria, of which **249** displayed cytotoxic and submicromolar NF-κB inhibition activities.[188] In the same year, 5′-hydroxyzearalenone (**251**) was isolated from the seagrass-derived fungus *Fusarium* sp. PSU-ES73.[30] In 2016, the same group obtained its epimer, 5′β-hydroxyzearalenone (**252**), along with 7′β- and 9′α-hydroxyzearalenone (**253**, **254**) from another seagrass-derived fungus *Fusarium* sp. PSU-ES123.[31] In 2017, Thiraporn *et al.* synthesized **251** and **252** from commercially available materials, with **251** demonstrating potent cytotoxicity.[189]

In 2014, the first naturally occurring brominated RALs, 5-bromozeaenol (**255**) and 3,5-dibromozeaenol (**256**), were isolated from the fungal strain *Curvularia lunata* (TA26-46) treated with varying concentrations of sodium butyrate.[190] Additionally, 14 new greensporones (**257–270**) were isolated and characterized from a freshwater aquatic fungus *Halenospora* sp. found in a stream on the campus of the University of North Carolina.[191] Subsequently, Prabhu *et al.* reported that **257** and **259** induced mitochondrial-mediated apoptotic cell death in leukemic cells.[192,193]

Seven new RAL_{14}, named cochliomycins A–G (**271–277**), were isolated from the marine fungus *Cochliobolus lunatus*.[179,194,195] Compounds **271**, **274**, and **276** showed potent antifouling activity against the larval settlement of the barnacle *Balanus amphitrite*, with **271** also exhibiting antibacterial activity against *Staphylococcus aureus*. Meanwhile, **277** had potent antifouling activity against *Chlorella vulgaris*, *Chaetoceros socialis* and *Navicula exigua*, with EC_{50} values of 1.1, 0.9, and 0.6 μg mL^{-1}, respectively.

In 2016, a strain of *Hyalodendriella* sp. was investigated, resulting in the isolation of hyalodendriellins A–F (**278–279**, **128**, **280**, **129** and **281**).[128] Among them, **128** and **129** possessed a 3*R* configuration, while **278–281** were 3*S*-configurated. Compound **278** exhibited moderate activity against the nematodes *Caenorhabditis elegans* and *Meloidogyne incognita*, with LC_{50} values of 29.9 and 59.8 mM, respectively.[128] In 2017, paecilomycin N (**282**) and aigialomycin I (**283**) were isolated from the solid culture of the fungicolous *Hypomyces subiculosus*.[196] Since the name 'paecilomycin N' was already assigned to **246**, **282** was renamed paecilomycin N-1.

In 2018, a new phytotoxic and antifungal *O*-demethylated-zeaenol (**284**) was obtained from *Curvularia crepinii* QTYC-1, a fungus residing in the gut of *Pantala flavescens*.[197] In 2019, rhinoclactones A–E (**285–289**) were isolated from an endophytic fungus *Rhinocladiella similis* found in the desert plant *Agriophyllum squarrosum*.[198] In 2020, four RALs, including two new analogs rhinoclactones E–F (**290–291**) and two known ones **258** and **268**, were isolated from the same fungus.[199] Compounds **290** and **291** are a pair of stereoisomers with a unique furan ring fused to the macrolide ring.

Four new RALs, including 5α,6β-acetonide-aigialomycin B (**292**), 4-*O*-desmethyl-aigialomycin B (**293**), penochrochlactones C, D (**294** and **295**), were isolated from an endophytic fungus *Penicillium ochrochloron* SWUKD4.1850.[200] Penochrochlactone C (**294**) displayed moderate cytotoxicity against the HeLa tumor cells with an IC_{50} value of 9.7 μM. Additionally, compounds **293–295** exhibited moderate activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*, with MIC values from 9.7 to 32.0 μg mL^{-1}.

In 2021, our research group obtained nine new RAL_{14}, podospins D–L (**296–304**), along with some known ones, **185**, **190**, **196**, **210**, **275** and **276**, from the endophytic fungus *Podospora* sp. G214.[13] Most of these compounds exhibited potent immunosuppressive activities against ConA-induced T cell and LPS-induced B cell proliferation. Ascarpins A (**305**) and B (**306**), isolated from *Aspergillus* sp. ZJ-65, inhibited LPS-induced NO production in RAW 264.7 macrophages, with IC_{50} values 15.8 and 7.6 μM, respectively.[201]

In 2023, chemical epigenetic manipulation was applied to the zoanthid-derived fungus *Cochliobolus lunatus* (TA26-46) using a histone deacetylation modifier, nicotinamide, which resulted in the isolation of a new RAL named 7′(*Z*)-zeaenol (**307**) from the treated broth.[202] In 2024, chaetolactone A (**308**) and 4-methoxy-α-zearalenol (**309**), along with **169** and **179**, were obtained from the fermentation of a soil-derived fungus *Chaetosphaeronema* sp. SSJZ001.[203] Compound **169** showed weak cytotoxicity against A549, HO-8910, and MCF-7 cell lines, with IC_{50} values of 24.5, 34.3, and 28.6 μM, respectively.[203] Curvulomycins A–C (**310–312**) were identified by Xiaowei Luo's group from the coral-derived fungus *Curvularia lunata* GXIMD 02512.[204] Compounds **310** and **186** exhibited anti-proliferative effects against PC-3 and 22Rv1 prostate cancer cells, with IC_{50} values of 9.7 and 7.6 μM for PC-3 cells, and 6.0 and 3.2 μM for 22Rv1 cells, respectively. Moreover, compound **310** inhibited clonal cell colony and blocked the cell cycle, and induced apoptosis in both PC-3 and 22Rv1 cells.[204]

2.2.5. RAL_{16}. In 2020, our group discovered three new RAL_{16} (Fig. 11): ilyoresorcy A (**313**), atrop-ilyoresorcy A (**314**) and ilyoresorcy B (**315**) from the soil fungus *Ilyonectria* sp. sb65.[95] Compounds **313** and **314** shared identical planar structure and absolute configuration, but differed in conformation, giving rise to opposite Cotton effect at 212 nm in their CD spectra. The *in vitro* tests showed that **315** exhibited significant inhibition on both T and B cell proliferation.[95] Additionally, compounds **313–315** showed tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-resistance-overcoming ability when tested as potential TRAIL sensitizers in A549 cells.[95]

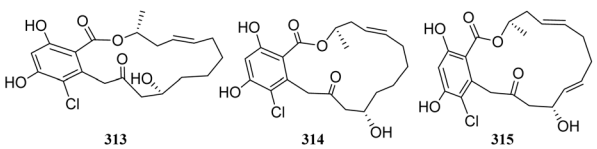

Fig. 11 Structures of RAL_{16}.

3. Method for determining configuration of RALs

The stereochemical elucidation of RALs is critical for understanding their biological activities. Below is a summary of the key methodologies employed to establish their configurations based on our previous work.

3.1. X-ray crystallography

Direct determination of absolute configuration by single crystal X-ray diffraction is considered the most reliable method. However, obtaining high-quality single crystals can be challenging for flexible RALs. In previous studies, we explored the effectiveness of the slow evaporation technique for crystallizing RALs. Specifically, RALs are completely dissolved in CH_2Cl_2-MeOH or MeOH-H_2O system, then the solution is transferred to a clean culture bottle and covered with perforated aluminum foil. Single crystals of RALs can be obtained by allowing solution to evaporate slowly.[13] Using this method, X-ray crystallography studies for **10–12**, **79**, **80**, **82–85**, **296**, **298**, and **300–302** were successfully conducted.[13,99] Additionally, introducing large chromophores like conjugated double bonds or aromatic rings into RALs promotes crystal growth and improves diffraction intensity.[99] For instance, the bromobenzoyl derivatives of **87** and **263** were more easily obtained as high-quality single crystals.[99,191]

3.2. Electronic circular dichroism spectroscopy

The Cotton effect observed around 266 nm, corresponding to the π–π^* excitation of the ester chromophore, is associated with the configuration of C-3 in RALs. By analyzing the electronic circular dichroism (ECD) spectra of both natural and synthetic RALs, we infer that for RALs possessing a methyl at C-3, the positive Cotton effect at 266 nm indicates a 3*R* configuration. However, for relgro-type RAL_{10} with a side chain connected to the lactone alcohol group, the positive Cotton effect at 266 nm reflects the α-orientation of the side chain, with the absolute configuration of the lactone alcohol depending on the priority of the substituents on the side chain.[9,27,31,32] Additionally, molybdenum- or rhodium-induced ECD experiments, along with ECD calculations, are widely used to elucidate the stereochemistry of chiral RALs.

3.3. Chemical reactions

In addition to determining the configurations of RALs through chemical comparison with known compounds, modified Mosher's method and acetonation are often used to determine the configuration of hydroxy-bearing RALs. The modified Mosher's method is a reliable approach for determining the absolute configuration of secondary alcohols and primary amines through calculating the chemical shift differences of the ester protons between the (*S*)- and (*R*)-2-methoxy-2-(trifluoromethyl) phenylacetic acid (MTPA) diastereoisomers.[205] The configurations of some RALs, such as compounds **86**, **154**, and **264–267**, have been clarified using the modified Mosher's method.[99,131,191] Furthermore, by reacting RALs containing vicinal-diol and -triol groups with 2,2-dimethoxypropane to form 5-membered or 6-membered oxygen rings, the relative configuration of these groups can be determined by analyzing the nuclear overhauser effect spectroscopy (NOESY) correlations of acetonide derivatives.[13] Additionally, a combination of acetonation, NOESY, and molybdenum-induced ECD can be employed for the stereochemical assignment of vicinal-diol and -triol within RALs.[13]

4. Biological activities and pharmacological mechanisms of RALs

As outlined in the previous section, a substantial array of RALs has been identified with diverse biological activities, including antitumor, antiparasitic, antivirus, immunomodulatory, and antifungal effects. In this section, we summarize the active compounds with IC_{50} or EC_{50} values below 10 μM, focusing specifically on their biological targets and molecular mechanisms (Fig. 12). Since Shilpa Kuttikrishnan *et al.* have comprehensively summarized the *in vitro* cytotoxic activities and anticancer mechanisms of RALs,[2] this review aims to supplement and update the latest anticancer research. The purpose of summarizing and discussing the biological targets of RALs is to highlight their critical biological functions and establish a foundational framework for future research in this area.

4.1. Antitumor activity and molecular targets

4.1.1. HSP90. HSP90 is a highly conserved molecular chaperone with an approximate molecular weight of 90 kDa.[206] It plays a critical role in regulating proteostasis under both physiological and stress conditions, participating in a variety of cellular processes, including apoptosis, cell cycle control, cell viability, DNA repair, and various signaling pathways.[207,208] HSP90 functions as a homodimer, with each monomer comprising an N-terminal domain (NTD), a middle domain linked to the NTD by a charged linker, and a C-terminal domain (CTD).[209] Adenosine triphosphate (ATP) binds to the highly conserved NTD, and its subsequent hydrolysis provides the energy necessary for client maturation.[210,211] The middle domain is essential for the recognition of clients and for interactions with co-chaperones, while the CTD is related to the dimerization.[210] Both N- and C-terminal inhibitors can disrupt the HSP90 chaperone cycle, making them promising candidates for cancer chemotherapies.

Numerous studies have demonstrated that, despite lacking structural similarity to ATP, radicicol (**91**) inhibits HSP90 by competitively binding to its N-terminal ATP-binding site in a lowest energy L-shaped conformation (Fig. 12A).[4–6] Importantly, radicicol (**91**) exhibits a stronger affinity for HSP90 (IC_{50} value: 19 nM) compared to geldanamycin (IC_{50} value: 1.2 μM),[212] and has been shown to induce apoptosis and subsequent death of cancer cells.[213–215] In addition to radicicol (**91**), other naturally occurring RALs, including monocillin I (**92**), pochonins A and D (**100** and **101**), have also been identified as HSP90 inhibitors, with IC_{50} values being 340 μM, 90 nM and 80 nM,

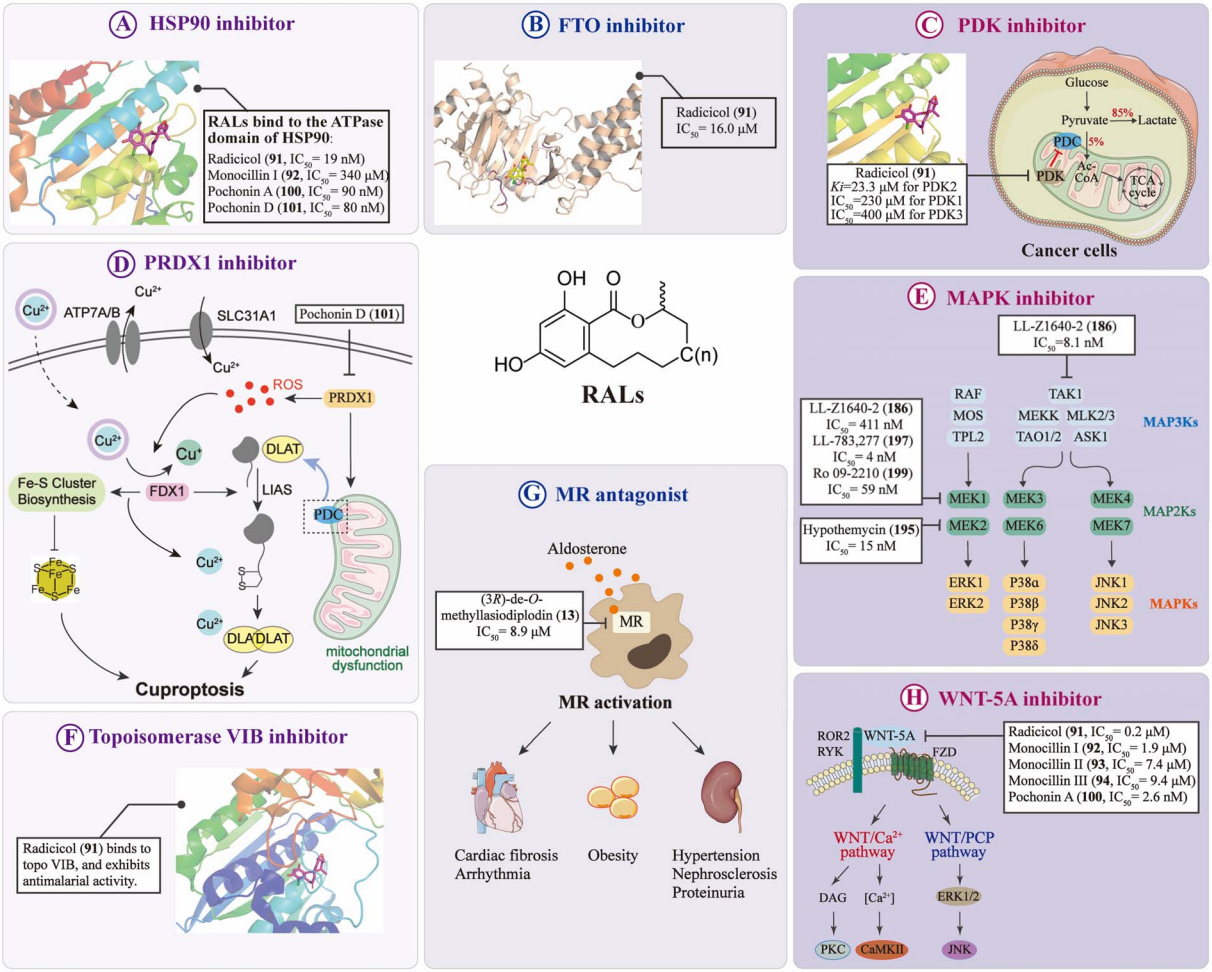

Fig. 12 The key biological targets of RALs. (A) Radicicol, monocillin I, pochonins A and D act as HSP90 inhibitors by competitively binding to its N-terminal ATP-binding site. (B) Radicicol is a potent inhibitor of FTO demethylase. The crystal structure shows that it adopts an L-shaped conformation in the FTO binding site. (C) Radicicol inhibits the activity of PDKs by competitively blocking ATP binding. (D) Pochonin D is a covalent inhibitor of PRDX1. (E) Hypothemycin-type RALs containing a *cis*-enone are covalent inhibitors of MAPK cascades. (F) Radicicol binds to the ATP binding pocket of topoisomerase VIB to inhibit ATP hydrolysis (PDB ID: 2HKJ). (G) (3*R*)-de-*O*-Methyllasiodiplodin is a potent nonsteroidal MR antagonist. (H) Radicicol, pochonin A and monocillins I–III are identified as the WNT-5A inhibitors using the QuantiGene assay. TPL2: tumor progression locus 2; MLK: mixed-lineage kinase; FZD: frizzled receptors; DAG: diacylglycerol; PCP: planar cell polarity; PKC: protein kinase C; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II.

respectively.[5,212] Further research on synthesis and structural–activity relationships (SAR) has underscored the significance of the *trans*-enone functionality, chlorination at the C14 position, and the modifications around the C5–C8 portion.[5]

4.1.2. Fat mass and obesity-associated protein. N6-methyladenosine (m^6A) represents the most prevalent internal modification of eukaryotic mRNA that affects RNA processing, stability, and translation. The fat mass and obesity-associated protein (FTO), identified as the inaugural RNA m^6A demethylase, has been associated with multiple types of cancer, particularly serving as an oncogene in acute myeloid leukemia.[216–218] In 2018, radicicol (**91**) was identified as a potent inhibitor of FTO demethylase, with an IC_{50} value of 16.0 μM.[219] Notably, the crystal structure demonstrates that radicicol adopts an L-shaped conformation in the FTO binding site, with the macrocyclic lactone plane positioned nearly perpendicular to the aromatic ring plane (Fig. 12B).[219] The discovery of radicicol as an FTO inhibitor opens the door for novel therapeutic strategies in leukemia treatment.

4.1.3. Pyruvate dehydrogenase kinase. In normal cells, pyruvate is converted to acetyl coenzyme A (Ac-CoA) catalyzed by the pyruvate dehydrogenase complex (PDC), which then enters the citric acid cycle to generate ATP.[220] However, cancer cells often rely on aerobic glycolysis rather than the mitochondrial oxidation of pyruvate.[220] Pyruvate dehydrogenase kinases (PDKs) regulate this glucose metabolism shift *via* inhibiting PDC activity through phosphorylation of specific serine residues.[221] Thus, inhibiting PDKs is a promising strategy in cancer treatment. In 2001, Tuganova *et al.* reported that radicicol (**91**) inhibits the activity of PDK2 by competitively blocking ATP binding, with an apparent inhibition constant (K_i) value of 23.3 μM (Fig. 12C).[17] In 2007, Kato *et al.* conducted a study

examining the inhibitory effects of radicicol on small ubiquitin modifier (SUMO)-tagged PDK1 and PDK3. Their findings revealed an IC_{50} value of 230 μM for the inhibition of PDK1 and an IC_{50} value of 400 μM for the inhibition of PDK3.[221] They also elucidated the crystal structure of the human PDK3-radicicol complex, revealing that radicicol inhibits kinase activity by interacting with the ATP-binding site of PDK3, in the same manner as it binds to HSP90.[221]

4.1.4. Peroxiredoxin 1. In 2025, Zhe Wang's research group obtained 24 RALs, including 9 previously unreported ones (**161–168**), from the endophyte *Ilyonectria* sp. FL-710.[21] Among them, pochonin D (**101**) demonstrated significant inhibition of triple-negative breast cancer (TNBC). *In vitro*, it showed dose- and time-dependent proliferation inhibition on TNBC cell lines (MDA-MB-231, 4T1, BT549, SUM159, and MDA-MB-157), with lower toxicity to normal breast cell MCF-10A. In animal models, pochonin D (**101**) suppressed the growth of TNBC xenograft tumors, reducing tumor volume without causing significant liver damage. Its activity was superior to that of first-line chemotherapy agents (*e.g.* 5-FU, cisplatin), highlighting its potential as a promising lead compound for TNBC therapy. Cuproptosis is a recently identified form of cell death driven by mitochondrial copper overload.[222] This process is characterized by the aggregation of lipoylated dihydrolipoamide *S*-acetyltransferase (DLAT), a critical component of PDC.[223,224] The resultant effects include irreversible mitochondrial dysfunction, loss of metabolic homeostasis, and ultimately, cell death. Unlike classical apoptosis, cuproptosis specifically targets cells reliant on oxidative phosphorylation, highlighting its unique mechanistic basis and therapeutic potential in malignancies with metabolic vulnerabilities. Zhe Wang *et al.* found that pochonin D (**101**) exhibited anti-TNBC activity by increasing intracellular copper content and triggering cuproptosis (Fig. 12D).[21] Mechanistically, it covalently binds to the Cys173 residue of peroxiredoxin 1 (PRDX1) with a higher affinity (K_d = 0.7 μM). This interaction inhibits PRDX1's peroxidase activity, leading to reactive oxygen species (ROS) accumulation, mitochondrial dysfunction, and subsequent cuproptosis. These findings highlight the novelty of RALs in inducing cuproptosis and being PRDX1 inhibitors.

4.1.5. Mitogen-activated protein kinase. Mitogen-activated protein kinase (MAPK) signaling is a critical pathway that operates downstream of sensors/receptors, linking extracellular stimuli to essential intracellular processes.[225,226] MAPK cascades (Fig. 12E) are initiated by the activation of MAPK kinase kinases (MAP3Ks), which phosphorylate and transmit signals to specific MAPK kinases (MAP2Ks). These, in turn, activate corresponding MAPKs by phosphorylating conserved threonine (Thr) and tyrosine (Tyr) residues on the MAPK.[227,228] There are three major subfamilies of MAPKs: extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK).[229] A variety of MAP3Ks, such as MAPK/ERK kinase kinases (MEKKs) and transforming growth factor β-activated kinase 1 (TAK1), are crucial for the activation of the latter two subfamilies.[228] Whereas, MAP3K RAF is specifically involved in the phosphorylation of MEK1/2, which subsequently phosphorylates ERK1/2 and facilitates its nuclear translocation.[230,231]

Hypothemycin-type RALs containing a *cis*-enone can react with the cysteine residue in the ATP-binding site of kinases through a Michael addition. These compounds act as multi-dimensional MAPK inhibitors, specifically targeting TAK1, MEK, ERK, and certain downstream substrates of ERK. For example, LL-Z1640-2 (**186**) is a selective and potent inhibitor of TAK1 with an IC_{50} value of 8.1 nM. Its inhibitory activity against MEK1 is reduced by 50 fold (IC_{50} = 411 nM), and it does not exhibit inhibitory effects on other kinases within MAPK cascades, such as MEKK1, apoptosis signal-regulating kinase 1 (ASK1), and MKK4.[154] Compound **186** has been shown to inhibit tumor progression in models of the bone-residing tumors, such as multiple myeloma and adult T-cell leukaemia/lymphoma.[232,233] In contrast, radicicol (**91**) and zearalenone (**169**) demonstrate negligible activity against TAK1.[154] Another *cis*-enone RAL, hypothemycin (**195**), acts as an irreversible inhibitor of MEK2 with an IC_{50} value of 15 nM. It disrupts the activation of p38 signaling cascade by inhibiting MEK3/6 and TAK1, as well as the JNK cascade through inhibition of MEK4/7.[19,20] Additionally, L-783, 277 (**197**) is a potent MEK1 inhibitor with an IC_{50} value of 4 nM, inhibiting the proliferation of human adrenocortical carcinoma H295R cells by binding to the ATP-binding sites of MEK1.[20,234] Furthermore, penicimenolide B (**52**) has been shown to induce apoptosis in breast cancer MCF-7 cells by targeting MEK1/2 and ERK1/2.[83]

4.2. Antiparasitic activity and molecular targets

4.2.1. Antimalarial activity. Some RALs have demonstrated potential antimalarial activity against *Plasmodium falciparum*. For instance, radicicol (**91**) exhibited high potency with an IC_{50} value of 0.01 μg mL^{-1}.[111] Hypothemycin (**195**) and its derivative 4-*O*-demethylhypothemycin (**212**) showed antimalarial activity against *P. falciparum* with IC_{50} values of 2.2 μg mL^{-1} and 3.0 μg mL^{-1}, respectively.[98,119] Furthermore, aigialomycin D (**210**) also displayed antimalarial activity with an IC_{50} of 6.6 μg mL^{-1}.[119] These results highlight the potential of RALs as leads for further development of antimalarial agents.

The malaria parasite *Plasmodium* topoisomerase VIB, localized in the organelle fraction, is considered as a promising target for the development of antimalarial drugs. In 2014, Chalapareddy *et al.* demonstrated that radicicol (**91**) specifically disrupted the mitochondrial replication of cultured *P. falciparum*, which correlated with an upregulation of topoisomerase VIB at both the transcript and protein levels.[235] Subsequent investigations revealed that *Plasmodium* topoisomerase VIB is capable of forming homodimers as well as topoisomerase VIB-VIA heteromers, the latter of which decatenates DNA in an ATP- and Mg^{2+}-dependent manner.[236] Furthermore, radicicol (**91**) not only binds to the ATP binding pocket of topoisomerase VIB (Fig. 12F) to competitively inhibit ATP hydrolysis with an IC_{50} value of approximately 100 μM,[15,16] but also inhibits the decatenation activity of the *Plasmodium* topoisomerase VIB-VIA complex,[236] suggesting that topoisomerase VIB represents a viable target for antimalarial intervention by radicicol.

4.2.2. Other antiparasitic activities. In 2003, Veronika Hellwig *et al.* assessed the antiparasitic efficacy of certain RALs

against economically important parasites, specifically *Eimeria tenella* and *Neospora caninum*, both of which are taxonomically related to *Plasmodium*. Among the compounds tested, pochonin A (**100**) showed moderate activity against *E. tenella*.[12] Subsequently, in 2021, a research team led by Xiaoyi Wei investigated the therapeutic potential of radicicol (**91**) against *Schistosoma japonicum*, a parasitic organism responsible for schistosomiasis, which poses a considerable threat to human health.[237] *In vitro* studies demonstrated that radicicol (10 μM) completely killed skin- and liver-stage schistosomula within 72 hours, outperforming praziquantel.[237] *In vivo*, it significantly reduced worm burdens and liver eggs by targeting migratory-stage schistosomula. Moreover, radicicol (**91**) damaged the tegument morphology and altered the motility of *S. japonicum* worms, indicating its potential as a promising candidate for the development of drugs targeting migratory-stage schistosomula.

4.3. Antivirus activity and molecular targets

In 2003, Marc Stadler's group evaluated the antiviral activities of **91**, **94**, **100**, **103**, **104**, **105**, and **106** against Herpes Simplex Virus 1 (HSV1) using the HSV1-F strain, and established the IC_{50} values for these RALs as follows: 0.2, 0.4, 2, 10, 6, 1.5 and 2 μM, respectively.[12] Song *et al.* investigated the antiviral efficacy of pochonin D (**101**) utilizing a murine model of human rhinovirus type 1B (HRV1B) infection. The administration of **101** resulted in a significant reduction in viral titers and a decrease in the infiltration of innate immune cells in the bronchoalveolar lavage following HRV1B infection.[238] Additionally, radicicol (**91**) was identified as a novel inhibitor of chikungunya virus (CHIKV) infection, an alphavirus transmitted by mosquitoes that causes a debilitating febrile illness marked by enduring muscle and joint pain, through a cytopathic effect-based high-throughput screening that utilized a library of highly purified compounds with defined chemical structures.[239] Sangwoo Nam and co-workers found that radicicol inhibited the early stages of the CHIKV replication cycle, specifically targeting its nonstructural proteins (nsPs).[239] Furthermore, it was found that HSP90β is essential for CHIKV replication and physically interacts with the MT-like domain located at the C-terminus of nsP2. Notably, mutations in CHIKV nsP2 cause resistance to radicicol (**91**) with decreased interaction with HSP90β, suggesting a specific antiviral mechanism of radicicol that disrupts targets the interaction between HSP90β and nsP2.[239] These findings indicate the antiviral potential of radicicol and its analogues.

4.4. Immunomodulatory activity

The MAPK pathway has emerged as a promising target for therapeutic intervention in the treatment of inflammatory and autoimmune diseases, attracting significant interest from both basic and clinical researchers.[228,240] As potent MAPKs inhibitors, certain RALs have demonstrated anti-inflammatory and immunosuppressive effects. For instance, LL-Z1640-2 (**186**) was shown to inhibit picryl chloride-induced ear swelling of mice[154] and mitigate joint inflammation and bone destruction in collagen-induced arthritis mice.[18] Hypothemycin (**195**) suppressed LPS-induced tumor necrosis factor-α production in macrophages through tristetraprolin-dependent downregulation of mRNA stability, which was at least partially mediated by blocking the activation of p38 and ERK.[241] Ro 09-2210 (**199**) exhibited antiproliferative effects on activated T cells by selectively blocking MEK1 (IC_{50} = 59 nM) and inhibited anti-CD3-induced peripheral blood T cell activation with an IC_{50} value of 40 nM.[162] Additionally, our group's previous studies reported that podospin A (**10**), LL-Z1640-1 (**185**), (5*E*)-7-oxozeaenol (**190**), cochliomycin D (**274**) and 7′,8′-dihydrohypothemycin (**196**) exhibited significant immunosuppressive effects against ConA-induced T cell proliferation with IC_{50} values ranging from 6.0 to 10.6 μM, and LPS-induced B cell proliferation, with IC_{50} values ranging from 6.2 to 10.3 μM.[13] Further studies revealed that podospin A (**10**) and podomycin F (**84**) could induce apoptosis of activated T cells *via* MAPKs/AKT pathway.[13,99] In addition to the hypothemycin-type RALs mentioned above, our team also identified that certain radicicol derivatives exhibited notable potency. Specifically, ilyoresorcys B and C (**315** and **138**) significantly suppressed T cell proliferation, with IC_{50} values of 4.1 and 1.9 μM, respectively.[95] These two compounds, along with iyoresorcy E (**138**), inhibited B cell proliferation with IC_{50} values of 9.8, 1.1 and 5.5 μM, respectively.[95] Similarly, ilyomycin C (**138**) displayed enhanced activity against T lymphocytes (IC_{50} = 1.2 μM), possibly through HSP90 inhibition.[131] These findings underscore the potential of RALs as immunomodulatory leads for therapeutic development.

4.5. Antifungal activities

In 2017, Xiaoyi Wei's research group evaluated the antifungal activities of several RALs against the phytopathogenic fungi *Peronophythora litchii* and *Fusarium verticillioides* using spore germination tests.[94] Among them, radicicol (**91**), monocillin I (**92**), monocillin II (**93**), monocillin VI (**130**), and hypothemycin (**195**) exhibited IC_{50} values of 1.4, 7.9, 9.8, 9.2 and 1.9 μM against *P. litchi*, respectively. Additionally, **91** and **195** also demonstrated antifungal activity against *F. verticillioides* with IC_{50} values of 8.0 and 1.1 μM, respectively.[94] Their group found that hypothemycin (**195**) significantly suppressed spore germination and mycelial growth of *P. litchi*, disrupted fungal cellular integrity, and suppressed peel browning in litchi fruit inoculated with *P. litchii* during storage,[242] demonstrating its strong *in vitro* and *in vivo* antifungal activity. Furthermore, de-*O*-methyllasiodiplodin (**13**) and penochrochlactone D (**295**) showed antifungal activities against *Staphylococcus aureus* with MIC of 6.5 and 9.7 μg mL^{-1}, respectively.[78,200] Radicicol (**91**) also exhibited pronounced antifungal activity against a wide variety of fungi, including *Phycotnyces blakesleennus*, *Fusarium avenaceum*, *Ceratocystis minor*, *Ceratocystis montia*, *Ceratocystis ulmi*, *Leptosphaeria maculans*, *Endocronartium harknessii*, *Pythium debaryanum*, *Rhizoctonia solani* and *Sclerotinia sclerotiorum*, *Coniophora puteana*, *Fomes pini*, *Merulius ambiguus*, *Schizophyllum commune*, and *Debaryomyces hansenii*.[103,117] Furthermore, zearalenone (**169**) exhibited significant inhibition of the plant pathogen *Pyricularia oryzae* (MIC = 6.2 μg mL^{-1}),[146] which affects rice, wheat, and other gramineous crops, leading to plant epidemic diseases.

4.6. Other activities and molecular targets

4.6.1. Mineralocorticoid receptor and pancreatic lipase. Mineralocorticoid receptor (MR) is a member of the steroid nuclear receptor family, playing a crucial role in the regulation of fluid, electrolyte, and hemodynamic homeostasis through binding with steroidal ligands, primarily aldosterone and cortisol.[243] A number of preclinical investigations have demonstrated that MR is hyperactivated in individuals with diabetes, which contributes to the promotion of inflammatory and fibrotic processes within the kidney.[244] MR antagonists have shown beneficial effects in counteracting the alterations associated with obesity-related pro-inflammatory adipokines and in enhancing insulin sensitivity, thereby presenting a viable therapeutic approach for regulating obesity-related pathological processes.[245,246] Importantly, (3*R*)-de-*O*-methyllasiodiplodin (**13**), a RAL_{12}, has been identified as a potent nonsteroidal MR antagonist with an IC_{50} value of 8.9 μM (Fig. 12G).[67] It diminished aldosterone-induced MR transcriptional activity and significantly reduced blood glucose and glycosylated hemoglobin levels in db/db mice.[247] Furthermore, compound **13** also serves as a potent inhibitor of pancreatic lipase (PL), an enzyme critical for the effective digestion of triglycerides and a target for obesity treatment, with an IC_{50} value of 4.7 μM.[67]

4.6.2. WNT-5A. WNT-5A, a prototypical member of the non-canonical Wingless/integrase 1 (WNT) family, is highly conserved among species and plays key roles in various biological processes, ranging from embryonic morphogenesis to the maintenance of post-natal homeostasis.[248,249] In the context of hair growth, WNT-5A has been identified as a direct target of Notch signaling in dermal papilla cells, which are crucial for regulating the hair growth cycle through the modulation of proliferation and differentiation of follicular keratinocytes.[14] Additionally, WNT-$5A^{-/-}$ mice exhibit notable dermal papilla dysfunctions in E17.5 embryonic skin grafted onto nude mice, including impaired hair follicle-inductive capabilities, a reduction in hair follicle differentiation markers, and abnormal expression of cytokeratin 1.[250,251] In 2009, Hideki Shinonaga *et al.* measured the WNT-5A expression inhibitory activities of radicicol (**91**) and its analogues using the QuantiGene assay.[14] The IC_{50} values for radicicol (**91**), pochonin A (**100**), and monocillins I–III (**92–94**) were 0.2, 2.6, 1.9, 7.4, and 9.4 μM, respectively (Fig. 12H).[14] A series of chemical modifications revealed the SAR information of radicicol derivatives, leading to the identification of 6,7-dihydro-10α-hydroxyradicicol as a lead compound, which exhibited significant WNT-5A inhibition (IC_{50} value: 1.9 μM) and no cytotoxicity against dermal papilla cells.[14]

5. Application prospects and drug development challenges of RALs

5.1. Clinical progress of RAL derivatives

Inspired by the structure and bioactivity of RALs, a notable candidate E6201, derived from LL-Z1640-2 (**186**), has entered clinical studies. Although effective in inhibiting TAK1 (IC_{50} = 8.1 nM) and reducing inflammation in animal models, LL-Z1640-2 suffers from poor metabolic stability.[154] To address this issue, the Eisai Corporation made structural modifications to synthesize a metabolically stabilized analog, ER-803064, by adding a methyl group at C4, which prevents Michael nucleophiles from accessing the convex face of the *cis*-enone (Fig. 13).[252] Further optimization led to the creation of analogs with extended alkyl side chains at C15 containing N or O functional groups, which showed improved activity but low oral bioavailability in mice.[152] Shen *et al.* then designed analogs featuring a C14-C15 fused *N*-methylimidazole and simplified *N*-substituted side chains at C15, leading to the discovery of the ethyl-substituted derivative, E6201, a MEK inhibitor with good oral bioavailability and excellent anti-inflammatory effect.[253,254]

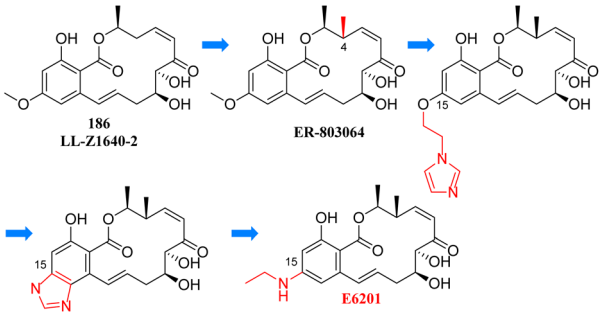

Fig. 13 The discovery of E6201.

So far, six clinical trials involving E6201 have been reported across various indications like malignant melanoma, acute myeloid leukemia, and psoriasis (Table 1). A phase I study involving subjects with advanced solid tumors (NCT00794781) determined the maximum tolerated dose, dose-limiting toxicities, safety profile, and established recommended dosing in patients with advanced solid tumours. The results indicated that intravenous administration of E6201 at 320 mg m^{-2} once weekly (qw; days 1 + 8 + 15 of a 28-day cycle) was generally well tolerated and clinically effective in patients with advanced solid tumours, including melanoma with brain metastases.[24] For BRAF V600-mutated metastatic melanoma with brain metastases, E6201 in combination with dabrafenib has been explored, though detailed results remain pending (NCT05388877). Moreover, topical E6201 gel has been evaluated in psoriasis vulgaris patients, with a 12-day randomized, blinded study demonstrating its efficacy and safety (NCT01268527). These trials collectively underscore E6201's diverse therapeutic potential and favorable safety profile across different administration routes and indications.

5.2. Drug development challenges

5.2.1. Poor pharmacokinetic properties. RALs frequently encounter pharmacokinetic challenges arising from their inherent physicochemical properties. Characterized by high molecular weights and limited aqueous solubility, many RALs exhibit suboptimal absorption profiles and erratic tissue distribution. These limitations are further exacerbated by rapid metabolic inactivation or enzymatic susceptibility, collectively diminishing their therapeutic potential despite promising *in*

Table 1 Clinical trials of E6201

Identification code	Clinical stage	Trial status	Indication	Trial start date	Trial completion date
NCT00794781	Phase I	Completed	Advanced solid tumors	Jun 22, 2008	Oct 15, 2015
NCT05388877	Phase I	Active, not recruiting	Malignant melanoma; brain metastases	Oct 20, 2022	Dec, 2026 (anticipated)
NCT03332589	Phase I	Terminated	Malignant melanoma; brain metastases	Jul 2, 2018	Oct 11, 2021
NCT02418000	Phase I/II	Terminated	Acute myeloid leukemia; myelodysplastic syndromes; chronic myelomonocytic leukaemia	Apr 10, 2015	Jun 8, 2017
NCT01268527	Phase II	Completed	Psoriasis vulgaris	Mar 15, 2010	Dec 11, 2010
NCT00539929	Phase II	Completed, not submitted	Chronic plaque psoriasis	Sep, 2007	Jul, 2008

vitro bioactivity. A paradigmatic example is radicicol (**91**), a potent HSP90 inhibitor demonstrating selective inhibition with an IC_{50} value of 20 nM.[4,6] However, its structural motifs, a reactive Michael acceptor and an epoxide moiety, render it prone to enzymatic degradation *in vivo*. This metabolic instability leads to precipitous clearance rates, undermining its robust *in vitro* efficacy and impeding clinical translation.[255,256] Pharmacokinetic analyses of LL-Z1640-2 (**186**) revealed analogous challenges, with a plasma half-life of only 61 minutes in murine models.[257] Further studies by Du *et al.* at the Eisai Corporation have clarified the rapid inactivation of RALs in both human and mouse microsomes and plasma, a phenomenon attributed to the *cis*-to-*trans* isomerization of enone in the presence of glutathione (GSH) and glutathione transferase (GST) in biological fluids.[252] This property of RALs limits systemic exposure and may exacerbate off-target effects. To circumvent these limitations, structural modifications have been employed, and stabilizing the *cis*-enone moiety has shown promise in enhancing metabolic stability.[152,252] Additionally, advanced liposomal encapsulation and nanoparticle-based delivery platforms demonstrate the capacity to modulate biodistribution patterns and prolong systemic exposure.[258,259] These approaches may synergistically address the intrinsic pharmacokinetic deficiencies of RALs while preserving their bioactive scaffolds.

5.2.2. Toxicity and adverse events. RALs and their synthetic derivatives exhibit a toxicity profile. For example, radicicol (**91**) and its synthetic derivatives exhibit strong affinity for HSP90 and significant antitumor activities, while the non-specific toxicity to normal cells limits their use *in vivo*.[256,260] Additionally, E6201, a potent inhibitor of MEK, demonstrated in clinical trials that dose-dependent adverse events (AEs) were predominantly manageable, though dose-limiting toxicities (DLTs) emerged at higher doses. The common AEs include maculopapular rash affecting the trunk and face (incidence 50–70%), pruritus (20–30%), diarrhea (40–60%), nausea/vomiting (30–50%), fatigue (35–55%), pyrexia (15–20%), and hypophosphatemia (10–15%) linked to MEK/ERK-mediated renal phosphate wasting. Severe DLTs include grade 3 rash (5–8%), hepatobiliary abnormalities with elevated transaminases (3–5%), grade 4 neutropenia (2–3%), and retinopathy. These findings highlight the need for further optimization to improve the selectivity and reduce the toxicity of RALs.

5.2.3. Difficulty of origin. Numerous RALs are obtained in trace amounts from slow-growing fungi, making large-scale extraction unfeasible. For instance, pochonins A and D (**100** and **101**), derived from *Pochonia chlamydosporia* var. *catenulata*, have been identified as potent HSP90 inhibitors with IC_{50} values of 90 nM and 80 nM respectively. However, producing just 1 g of these compounds requires the use of 500–1000 L of culture medium.[12,261,262] Such low yields underscore the difficulties associated with relying exclusively on natural sources for the synthesis of these valuable compounds. Furthermore, the intricate macrocyclic structure and stereochemical diversity of RALs further complicate synthesis efforts even further. Conventional total synthesis routes are frequently impeded by laborious multistep processes and suboptimal yields. For example, the first total synthesis of radicicol (**91**) was reported by Lampilas and Lett in 1992 with a total yield of less than 2%,[263] making it difficult to scale up for large-scale production. Although several modular synthesis strategies with good yields have been employed to synthesize important RALs, like pochonin A (**100**),[261] zearalenone (**169**),[264] LL-Z1640-2 (**186**),[265] and cochliomycin B (**272**),[266] efficiently synthesizing them through concise routes to extend the diversity of RALs remains challenging. The application of synthetic biology-driven approaches, such as heterologous expression, activation of silent biosynthetic gene clusters, and optimization of host strains, may provide a better solution to the limited availability of natural sources. In parallel, the investigation of efficient synthesis methodologies is crucial for addressing the challenges associated with the RALs production.

6. Conclusions and future perspective

In this review, a total of 315 naturally derived RALs, reported from 1953 to February 2025, are systematically summarized, focusing on their structures, isolation, and occurrence. These compounds are categorized into six subclasses based on the size of their lactone rings, with RAL_{14} being the most prevalent and RAL_{16} the least abundant. Additionally, the detailed analysis of their biological activities illustrates that RALs showcase remarkable pharmacological versatility, including antitumor, antimalarial, antivirus, antifungal, and immunomodulatory activities. Our in-depth examination of their mechanisms of action has revealed effects on key targets such as HSP90, FTO, PDK, PRDX1, MAPK, MR, and WNT-5A. Despite their promise, clinical translation remains hindered by certain limitations. This review also evaluates the clinical potential and challenges

of RALs, using E6201 as a representative example, and provides insights into optimizing their pharmacokinetic properties, reducing toxicity, and addressing production challenges.

The remarkable biological activities of RALs undoubtedly open the door for their future application as pharmaceuticals. Future research should focus on several key directions. First, in-depth research into their natural origin and mechanistic elucidation is imperative to establish the structure–bioactivity relationships of RALs and expand their functional potential. Second, leveraging modular synthesis to streamline the production of RALs and generate analogs with enhanced metabolic stability. Third, exploring nanoparticle-based systems to improve bioavailability and reduce off-target toxicity. Fourth, structure-based drug design, combined with computational methods and artificial intelligence-driven design, should be employed to develop novel derivatives with improved profiles. Finally, sustainable production methods, particularly synthetic biology approaches, should be developed to ensure efficient biosynthesis and reduce production costs, thereby supporting the broader application of RALs in drug discovery. By addressing these challenges, RALs may evolve into new therapeutics for cancer, infectious diseases, and autoimmune disorders, ultimately fulfilling their untapped potential in precision medicine.

7. Data availability

The data supporting this article have been included as part of the ESI.†

8. Author contributions

Ying Gao: data curation, investigation, visualization, writing – original draft. Wanpeng Li: data curation, investigation. Hanli Ruan: conceptualization, funding acquisition, writing – review & editing.

9. Conflicts of interest

There are no conflicts to declare.

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