

Benzo-fused ten-membered ring meroterpenoids: sources, chemical diversity, biological activities, and biosynthesis

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ABSTRACT

Meroterpenoids, a class of hybrid natural products derived from both terpenoid and non-terpenoid biosynthetic pathways, serve as a prolific source of drug leads, because of their structural complexity and extensive bioactivities. Meroterpenoids have provided many clinical drugs or promising leads, such as mycophenolic acid (an immunosuppressant), territrem B (an acetylcholinesterase inhibitor), and pyripyropene A (a cholesterol acyltransferase-2 inhibitor). Recently, meroterpenoids featuring a benzo-fused ten-membered ring skeleton have attracted considerable attention for their unique scaffolds and diverse post-modifications. Bioactivity evaluations have revealed that nearly half of these compounds (32 of 66) exhibit cytotoxicity with half-maximal inhibitory concentrations below 10 μ M, and therefore have great potential as drug development candidates, particularly in cancer therapy. However, a systematic summary of this subclass remains lacking. Herein, we summarize benzo-fused ten-membered ring meroterpenoids reported between 1980 and 2024, including their sources, structural diversity, bioactivities, and biosynthetic pathways, to provide comprehensive insights to guide further studies on meroterpenoids.

Keywords: Benzo-fused ten-membered ring meroterpenoids, Structural diversity, Cytotoxic activity, Biosynthetic pathway, Natural product drug leads

1. INTRODUCTION

Meroterpenoids (MTs) are a class of natural products with molecular frameworks partially derived from terpenoids [1, 2]. Benzo-fused ten-membered-ring MTs are a subclass characterized by their rigid macrocyclic skeletons and extensive post-modifications, including oxidation, methylation, glycosylation, heterocyclic fusion, and photoinduced structural transformations [3-8]. These modifications markedly enrich the compounds' structural diversity and biological activities.

Several benzo-fused ten-membered-ring MTs have demonstrated promising anticancer potential [4, 9, 10]. For example, clavilactone D (**4**) has been identified as an effective inhibitor of the epidermal growth factor receptor (EGFR), a clinically validated target in multiple cancers, with a half-maximal inhibitory concentration (IC_{50}) of 5.5 μ M [9]. Its analog, clavilactone B (**2**), functions as a non-competitive EGFR inhibitor, thus offering a mechanism distinct from that of the ATP-competitive inhibitors commonly used in clinical practice [9, 11]. This mechanistic difference suggests potential for

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combination therapy to overcome resistance through synergistic targeting.

Accumulating evidence indicates that the compounds' biological activities are largely influenced by their post-modifications [12, 13]. Common modifiers such as oxidation enhance the cytotoxicity of certain compounds [14], whereas glycosylation is often associated with diminished cytotoxicity [7]. In addition, photoinduced structural transformations have been shown to influence cytotoxicity and have provided insights into the biosynthesis of related compounds [6]. However, the biological activities and preliminary structure-activity relationships have not been summarized.

Despite these compounds' promising pharmacological potential, the limited availability of natural sources remains a major challenge. These compounds are typically obtained in low yields, and overharvesting has prompted sustainability concerns [10, 15]. Although the total synthesis of several major clavilactones has been achieved [16, 17], chemical synthesis often poses an environmental burden, and the limited precision in structural control restricts scalability. Recently, biosynthetic approaches involving gene editing and metabolic engineering have emerged as promising options for sustainable and efficient production [18, 19]. In particular, the elucidation of the biosynthetic pathway of clavilactone A (**1**) has attracted widespread research attention [20]. To date, a systematic summary of the biosynthetic networks of these compounds has been lacking.

Therefore, in this review, we provide comprehensive insights into the sources, structural diversity, biological activities, and biosynthesis of benzo-fused ten-membered-ring MTs reported between 1980 and 2024, to provide a reference for future research and applications.

2. METHODS

To collect relevant academic literature, we initially searched for the keywords "meroterpenoid," "meroterpenoids," "hybrid terpenoid," "phenolic terpenoids," and "terpenoid benzoquinone" in the Web of Science, PubMed, and China National Knowledge Infrastructure electronic databases. We retrieved all publications on MTs from database inception to December 2024. All retrieved records were combined and manually deduplicated, thus resulting in 5493 candidate publications.

A second round of screening was then conducted. The inclusion criteria were as follows: (i) original research articles; (ii) articles describing compounds identified as MTs containing a benzo-fused ten-membered ring scaffold; and (iii) studies involving structural elucidation, bioactivity evaluation, and/or biosynthetic investigation. Reviews, conference abstracts, and patents were

excluded. Manual screening was independently performed by two authors. After application of the inclusion and exclusion criteria, a total of 31 publications were retained for this review.

3. SOURCES AND DISTRIBUTION

In 1980, wigandol, the first benzo-fused ten-membered-ring MT, was isolated from the Boraginaceae plant *Wigandia urens* by Gómez [21]. This natural product, characterized by its novel 6/10 bicyclic skeleton, attracted substantial attention from chemists and pharmacologists, and extensive studies were conducted on its isolation, structural characterization, biological activity, chemosynthesis, and biosynthesis [20, 22-24]. To date, 66 MTs with benzo-fused ten-membered ring skeletons have been reported, including natural products derived from plants and fungi, as well as derivatives obtained through chemosynthesis. Their names, molecular weights, molecular formulas, and sources are listed in Table 1.

The proportions and distributions of MTs from various sources are shown in Figure 1A and 1B. Most of these compounds (30 compounds, 43.18%) have been derived from fungi, including *Clitocybe clavipes* (20 compounds), *Lactarius flavidulus* (4 compounds), *Tricholoma terreum* (4 compounds), and *Resupinatus* sp. BCC84615 (2 compounds). Plant-derived MTs account for 31.06% (22 compounds); all these compounds originate from the Boraginaceae family, including *Arnebia euchroma* (19 compounds), *Cordia globifera* (3 compounds), *W. urens* (3 compounds), *Lithospermum erythrorhizon* (1 compound), and *Cordia glazioviana* (1 compound). In addition, 17 MTs (25.76%) were obtained through chemical modifications. These transformation products expand the compounds' availability and substantially enhance the structural diversity.

C. clavipes and *A. euchroma* are therefore the most prominent natural sources of benzo-fused ten-membered-ring MTs and have great potential for further research and development. Moreover, the combination of natural sources and chemically modified derivatives not only expands the accessible sources of MTs but also deepens understanding of their structure-activity relationships.

4. CHEMICAL DIVERSITY AND BIOLOGICAL ACTIVITY

The structural complexity of MTs is determined by hybrid terpenoid biosynthetic pathways [1]. This complexity derives from the rearrangement and cyclization processes within the terpenoid moiety, as well as diverse modifications of the non-terpenoid moiety [37]. Although benzo-fused ten-membered-ring MTs

Table 1 | Chemical information for MTs with benzo-fused ten-membered ring skeletons.

No.	Name	Molecular formula	Molecular weight	Sources	References
1	Clavilactone A	C ₁₆ H ₁₆ O ₅	311.0890 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i> / <i>A. euchroma</i>	[9, 13, 22, 25-27]
2	Clavilactone B	C ₁₆ H ₁₄ O ₅	309.28 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[9, 13, 22, 26]
3	Clavilactone C	C ₁₆ H ₁₆ O ₆	305 [M+H] ⁺ , CI-MS	<i>C. clavipes</i>	[22, 26]
4	Clavilactone D	C ₁₆ H ₁₅ NO ₅	302.1029 [M+H] ⁺ , ESI-MS	<i>C. clavipes</i>	[9, 26, 27]
5	Clavilactone E	C ₁₇ H ₁₈ O ₆	341.33 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[13, 26]
6	Clavilactone F	C ₁₆ H ₁₅ NO ₅	302.1025 [M+H] ⁺ , ESI-MS	<i>C. clavipes</i>	[27]
7	Clavilactone G	C ₁₆ H ₁₆ O ₆	303.0885 [M-H] ⁻ , ESI-MS	<i>C. clavipes</i>	[28]
8	Clavilactone H	C ₁₇ H ₁₈ O ₄	285.1132 [M-H] ⁻ , ESI-MS	<i>C. clavipes</i>	[13, 28]
9	Clavilactone I	C ₁₇ H ₁₈ O ₅	325.33 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[13, 28]
10	Clavilactone J	C ₁₆ H ₁₆ O ₆	327.0843 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[23]
11	Clavilactone K	C ₂₀ H ₂₃ NO ₆	372.1466 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[23]
12	Clavilactone L	C ₁₆ H ₁₇ NO ₅	326.0991 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[13]
13	Clavilactone M	C ₂₂ H ₂₅ NO ₁₀	464.1552 [M+H] ⁺ , ESI-MS	<i>C. clavipes</i>	[29]
14	Clavilactone N	C ₂₂ H ₂₅ NO ₁₀	486.1382 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[29]
15	Clavilactone O	C ₂₂ H ₂₅ NO ₁₀	486.1388 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[29]
16	Clavilactone P	C ₂₂ H ₂₅ NO ₁₁	502.1335 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[29]
17	Clavipine A	C ₂₀ H ₁₉ NO ₅	376.1153 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[27]
18	Clavipine B	C ₂₀ H ₁₉ NO ₅	376.1163 [M+Na] ⁺ , ESI-MS	<i>C. clavipes</i>	[27]
19	Clavipine C	C ₂₀ H ₁₉ NO ₄	338.1384 [M+H] ⁺ , ESI-MS	<i>C. clavipes</i>	[27]
20	Clavipyrine A	C ₂₀ H ₂₀ N ₂ O ₄	353.1505 [M+H] ⁺ , ESI-MS	<i>C. clavipes</i>	[8]
21	Terreumol A	C ₁₇ H ₂₀ O ₆	320.1258 [M] ⁺ , EI-MS	<i>T. terreum</i>	[3]
22	Terreumol B	C ₁₇ H ₂₀ O ₇	336.1216 [M] ⁺ , EI-MS	<i>T. terreum</i>	[3]
23	Terreum C	C ₁₇ H ₂₀ O ₅	304.1327 [M] ⁺ , EI-MS	<i>T. terreum</i>	[3]
24	Terreum D	C ₁₇ H ₂₀ O ₆	320.1258 [M] ⁺ , EI-MS	<i>T. terreum</i>	[3]
25	Flavidulol A	C ₁₇ H ₂₂ O ₂	259.1698 [M+H] ⁺ , FAB-MS	<i>L. flavidulus</i> / <i>W. urens</i> / <i>C. globifera</i>	[12, 30-32]
26	Flavidulol C	C ₃₄ H ₄₂ O ₄	514.3081 [M] ⁺ , EI-MS	<i>L. flavidulus</i>	[12, 31]
27	Flavidulol D	C ₃₅ H ₅₆ O ₃	524.4235 [M] ⁺ , EI-MS	<i>L. flavidulus</i>	[24]
28	ent-Clavilactone J	C ₁₆ H ₁₆ O ₆	305.1033 [M+H] ⁺ , ESI-MS	<i>Resupinatus</i> sp. BCC84615	[14]
29	ent-Clavilactone J quinone	C ₁₆ H ₁₄ O ₆	303.0862 [M+H] ⁺ , ESI-MS	<i>Resupinatus</i> sp. BCC84615	[14]
30	Arnebinol A	C ₁₆ H ₁₆ O ₄	271.0969 [M-H] ⁻ , ESI-MS	<i>A. euchroma</i>	[25, 33]
31	(+)-Arnebinol B	C ₁₆ H ₁₈ O ₃	259.1324 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[4, 7, 25, 33, 34]
32	(-)-Arnebinol B	C ₁₆ H ₁₈ O ₃	259.1324 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i> / <i>C. glazioviana</i>	[7, 34]
33	Arneuchrol B	C ₁₇ H ₂₂ O ₄	313.1412 [M+Na] ⁺ , ESI-MS	<i>A. euchroma</i>	[10]
34	3,4-Dimethoxy-(+)-arnebinol A	C ₁₈ H ₂₀ O ₅	317.1380 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
35	3,4-Dimethoxy-(+)-arnebinol B	C ₁₈ H ₂₂ O ₄	303.1588 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
36	Arnebinone B	C ₁₇ H ₁₈ O ₄	285.1125 [M-H] ⁻ , ESI-MS	<i>A. euchroma</i>	[4, 7, 25]
37	6S,11Z-2-methoxy-arnebinone B	C ₁₈ H ₂₀ O ₅	339.1361 [M+Na] ⁺ , ESI-MS	<i>A. euchroma</i> / <i>L. erythrorhizon</i>	[4, 35]

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Table 1 | (continued)

No.	Name	Molecular formula	Molecular weight	Sources	References
38	Arnebinone B derivative	C ₃₂ H ₃₂ O ₆	513.2419 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[4]
39	Arnebinone D	C ₁₇ H ₁₆ O ₆	317.10165 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[6, 7]
40	(+)-Arnebinone E	C ₁₇ H ₁₆ O ₅	301.10681 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[6, 7]
41	(-)-Arnebinone E	C ₁₇ H ₁₆ O ₅	301.10681 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[6, 7]
42	Arnebic acid A	C ₁₆ H ₁₆ O ₅	289.1072 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[5]
43	Arnebic acid B	C ₁₆ H ₁₆ O ₆	305.1017 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[5]
44	9β-Hydroxy-(+)-arnebinol B-1-O-β-D-glucopyranoside	C ₂₂ H ₂₈ O ₉	437.18143 [M+H] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
45	9β-Hydroxy-(-)-arnebinol B-1-O-β-D-glucopyranoside	C ₂₂ H ₂₈ O ₉	459.16260 [M+Na] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
46	9α-Hydroxy-3-methoxy-(+)-arnebinol B-1-O-β-D-glucopyranoside	C ₂₃ H ₃₀ O ₁₀	489.17282 [M+Na] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
47	9α-Hydroxy-3-methoxy-(+)-arnebinol B-4-O-β-D-glucopyranoside	C ₂₃ H ₃₀ O ₁₁	489.17297 [M+Na] ⁺ , ESI-MS	<i>A. euchroma</i>	[7]
48	Globiferin	C ₁₆ H ₁₈ O ₂	265.1203 [M+Na] ⁺ , ESI-MS	<i>C. globifera</i>	[30]
49	Wigandol	C ₁₈ H ₂₂ O ₃	286 [M] ⁺ , EI-MS	<i>W. urens/C. globifera/L. flavidulus</i>	[21, 30-32, 36]
50	Globiferin 1,4-quinol derivative	C ₁₆ H ₂₀ O ₂	245.1541 [M+H] ⁺ , ESI-MS	<i>Chemically modified derivatives</i>	[30]
51	Methyl flavidulol A	C ₁₈ H ₂₄ O ₂	272 [M] ⁺ , EI-MS	<i>Chemically modified derivatives</i>	[12, 31]
52	Flavidulol A dihydro derivative	C ₁₇ H ₂₄ O ₂	260.1773 [M] ⁺ , EI-MS	<i>Chemically modified derivatives</i>	[12]
53	Flavidulol A tetrahydro derivative	C ₁₇ H ₂₆ O ₂	262.1929 [M] ⁺ , EI-MS	<i>Chemically modified derivatives</i>	[12]
54	Acetyl flavidulol A	C ₁₉ H ₂₄ O ₃	300 [M] ⁺ , EI-MS	<i>Chemically modified derivatives</i>	[12, 31]
55	Dimethyl clavilactone A	C ₁₈ H ₂₀ O ₅	317 [M+H] ⁺ , CI-MS	<i>Chemically modified derivatives</i>	[9, 22]
56	Globiferin O-diacetate derivate	C ₂₀ H ₂₄ O ₄	351.1564 [M+Na] ⁺ , ESI-MS	<i>Chemically modified derivatives</i>	[21, 30]
57	Clavilactone A diacetyl derivative	C ₂₀ H ₂₀ O ₇	373 [M+H] ⁺ , CI-MS	<i>Chemically modified derivatives</i>	[22, 26]
58	Flavidulol C acetyl derivative	C ₃₈ H ₄₆ O ₆	598 [M] ⁺ , EI-MS	<i>Chemically modified derivatives</i>	[31]
59	Arnebinone B derivative	C ₁₇ H ₁₆ O ₄	285.11191 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
60	Arnebinone B derivative	C ₁₇ H ₁₆ O ₄	285.11191 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
61	Arnebinone B derivative	C ₁₇ H ₁₆ O ₄	285.11185 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
62	Arnebinone B derivative	C ₁₇ H ₁₆ O ₄	285.11185 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
63	Arnebinone B derivative	C ₁₇ H ₁₈ O ₄	287.12762 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
64	Arnebinone B derivative	C ₁₇ H ₁₈ O ₄	287.12762 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
65	Arnebinone B derivative	C ₁₇ H ₁₈ O ₄	287.12756 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]
66	Arnebinone B derivative	C ₁₇ H ₁₈ O ₄	287.12756 [M+H] ⁺ , ESI-MS	<i>Photoreaction products</i>	[6]

ESI-MS: Electrospray ionization mass spectrometry; EI-MS: Electron ionization mass spectrometry; CI-MS: Chemical ionization mass spectrometry; FAB-MS: Fast atom bombardment mass spectrometry.

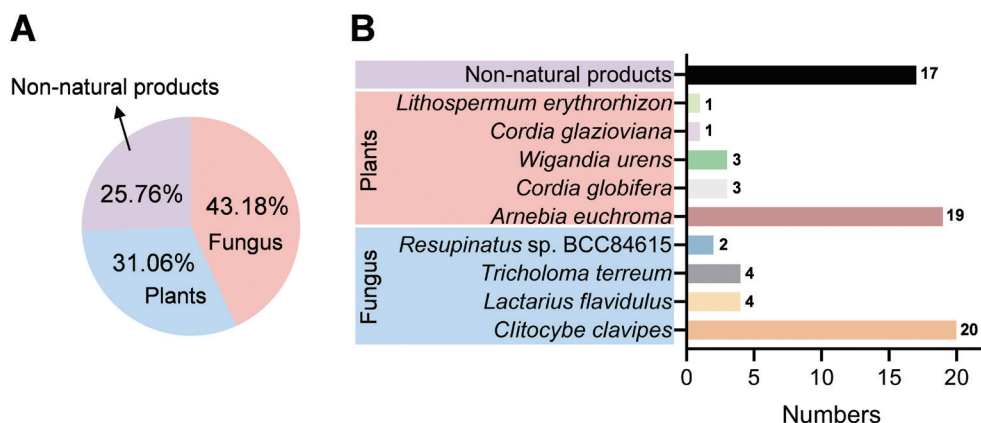


Figure 1 | Sources and distribution of MTs with benzo-fused ten-membered ring skeletons.

(A) sources of MTs (the overlapping MTs that occur in both plants and fungi were evenly divided (50% each) for calculation). (B) Distribution of MTs.

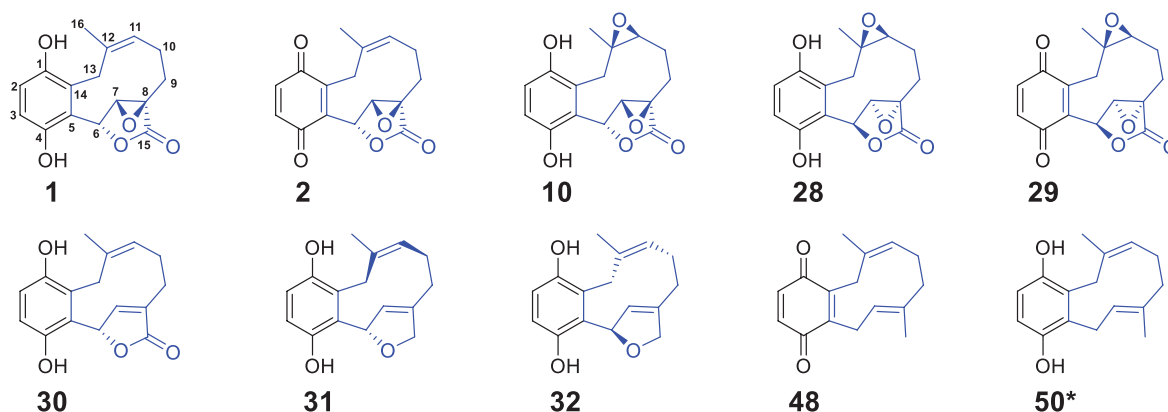


Figure 2 | Typical 6/10 bicyclic skeleton MTs. Blue represents the terpenoid moiety, and asterisk indicates chemically modified derivatives.

share a common core skeleton, each compound exhibits unique structural features, such as ring fusion patterns, post-modifications, and degrees of oxidation, which are closely associated with their diverse biological activities [3, 4, 8, 27]. This inherent chemical diversity not only reflects biosynthetic plasticity but also underpins the functional versatility of these compounds. Herein, we categorize the structural features of benzo-fused ten-membered-ring MTs, with a particular focus on the 6/10 bicyclic and 6/10/5 tricyclic skeletons, and discuss how these structural features correlate with the compounds' biological functions.

4.1 MTs with typical 6/10 bicyclic and 6/10/5 tricyclic skeletons

MTs bearing classic 6/10 bicyclic and 6/10/5 tricyclic skeletons are the fundamental structural types within this class. Their biological activities vary considerably

depending on ring fusion patterns and the degree of oxidation.

Globiferin (**48**), isolated from *C. globifera*, and its chemically modified derivative (**50**), both featuring the typical 6/10 bicyclic skeleton, have been reported [30, 31] (Figure 2). Both compounds contain a rigid ten-membered ring, bearing *para*-benzoquinone (**48**) and hydroquinone (**50**) in non-terpenoid moieties, respectively [30]. The cytotoxicity of globiferin (**48**) has been evaluated in the NCI-H187 cell line and *Plasmodium falciparum*, and shown IC_{50} values of 0.5 and 2.1 $\mu\text{g/mL}$, respectively [30] (Table 2).

Eight MTs (**1**, **2**, **10**, **28**, **29**, **30**, **31**, **32**) exhibit a more complex 6/10/5 tricyclic skeleton [7, 13, 14, 23, 25, 33] (Figure 2). Among them, (+)-arnebinol B (**31**), isolated from *A. euchroma*, exhibits approximately twice the cytotoxic potency of its enantiomer (**32**) in HCT-8, PANC-1, HGC-27, HepG2, and PC9 cell lines (Table 2),

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Table 2 | Cytotoxicity and antitumor activity of MTs with benzo-fused ten-membered ring skeletons.

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
1	MG-63	IC ₅₀ = 7.67 μM	IC ₅₀ = 12.31 μM (cisplatin)	[25]
	SNU387	IC ₅₀ = 13.70 μM	IC ₅₀ = 6.39 μM (cisplatin)	
	MGC-803	IC ₅₀ = 50.46 ± 4.26 μM	IC ₅₀ = 7.96 ± 1.27 μM (cisplatin)	[13]
	HeLa	IC ₅₀ = 43.13 ± 0.42 μM	IC ₅₀ = 2.7 ± 0.04 μM (cisplatin)	
	A549	IC ₅₀ = 24.17 ± 0.92 μM	IC ₅₀ = 10.83 ± 0.72 μM (cisplatin)	[10]
	MDA-MB-231	IC ₅₀ = 0.18 μM	IC ₅₀ = 0.48 μM (paclitaxel)	
	A431	Not determined		[9]
	IGROV-1	Not determined		
	SKOV-3	Not determined		
	NIH ^{PTC1}	IC ₅₀ = 2 μM		
	NIH ^{H-RAS}	IC ₅₀ = 2.8 μM		
	NIH ^{HER1}	ND		
	EGF-R	IC ₅₀ = 26 μM		
	Ret/ptc1	IC ₅₀ = 10.2 μM		
	v-Abl	Not determined		
	p34cdc2	Not determined		
	HepG2	IC ₅₀ = 32.14 ± 1.52 μM	IC ₅₀ = 7.68 ± 0.35 μM (cisplatin)	[27]
	A549	IC ₅₀ > 50 μM	IC ₅₀ = 10.83 ± 0.72 μM (cisplatin)	
	GES-1	IC ₅₀ > 100 μM	IC ₅₀ = 38.69 ± 0.86 μM (cisplatin)	
2	MGC-803	IC ₅₀ = 25.16 ± 0.83 μM	IC ₅₀ = 7.96 ± 1.27 μM (cisplatin)	[13]
	HeLa	IC ₅₀ = 28.34 ± 0.76 μM	IC ₅₀ = 2.7 ± 0.04 μM (cisplatin)	
	A549	IC ₅₀ = 19.18 ± 0.15 μM	IC ₅₀ = 10.83 ± 0.72 μM (cisplatin)	[9]
	A431	IC ₅₀ = 3.6 ± 1.31 μM		
	IGROV-1	IC ₅₀ = 6.1 ± 1.66 μM		
	SKOV-3	IC ₅₀ = 21.9 ± 10 μM		
	NIH ^{PTC1}	IC ₅₀ = 2 μM		
	NIH ^{H-RAS}	IC ₅₀ = 1.3 μM		
	NIH ^{HER1}	Not determined		
	EGF-R	IC ₅₀ = 27 μM		
	Ret/ptc1	IC ₅₀ = 7.7 μM		
	v-Abl	IC ₅₀ = 67.5 μM		
	p34 ^{cdc2}	IC ₅₀ = 120 μM		
4	HepG2	IC ₅₀ = 9.32 ± 0.74 μM	IC ₅₀ = 7.68 ± 0.35 μM (cisplatin)	[27]
	A549	IC ₅₀ = 24.17 ± 0.92 μM	IC ₅₀ = 10.83 ± 0.72 μM (cisplatin)	
	GES-1	IC ₅₀ = 38.13 ± 1.29 μM	IC ₅₀ = 38.69 ± 0.86 μM (cisplatin)	[9]
	A431	IC ₅₀ = 0.1 ± 0.05 μM		
	IGROV-1	IC ₅₀ = 0.8 ± 0.22 μM		
	SKOV-3	IC ₅₀ = 1 ± 0.44 μM		

Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
	NIH ^{PTC1}	IC ₅₀ = 0.1 µM		
	NIH ^{H-RAS}	IC ₅₀ = 0.2 µM		
	NIH ^{HER1}	IC ₅₀ = 0.02 µM		
	EGF-R	IC ₅₀ = 5.5 µM		
	Ret/ptc1	IC ₅₀ = 2.8 µM		
	v-Abl	IC ₅₀ = 81.3 µM		
	p34cdc2	IC ₅₀ = 128 µM		
	EGF-R	IC ₅₀ = 5 µM		[26]
5	MGC-803	IC ₅₀ = 76.25 ± 3.31 µM	IC ₅₀ = 7.96 ± 1.27 µM (cisplatin)	[13]
	HeLa	IC ₅₀ = 80.36 ± 0.71 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	
	A549	IC ₅₀ = 33.26 ± 0.72 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
6	HepG2	IC ₅₀ = 26.45 ± 0.84 µM	IC ₅₀ = 7.68 ± 0.35 µM (cisplatin)	[27]
	A549	IC ₅₀ = 18.22 ± 1.35 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
	GES-1	IC ₅₀ = 33.27 ± 2.11 µM	IC ₅₀ = 38.69 ± 0.86 µM (cisplatin)	
7	HeLa	IC ₅₀ > 100 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	[28]
	SGC-7901	IC ₅₀ = 62.2 ± 0.4 µM	IC ₅₀ = 1.1 ± 0.05 µM (cisplatin)	
	SHG-44	IC ₅₀ > 100 µM	IC ₅₀ = 1.8 ± 0.03 µM (cisplatin)	
8	HeLa	IC ₅₀ = 23.5 ± 0.4 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	[4]
	SGC-7901	IC ₅₀ = 14.5 ± 1.2 µM	IC ₅₀ = 1.1 ± 0.05 µM (cisplatin)	
	SHG-44	IC ₅₀ = 53.9 ± 2.4 µM	IC ₅₀ = 1.8 ± 0.03 µM (cisplatin)	
	MGC-803	IC ₅₀ = 38.23 ± 1.28 µM	IC ₅₀ = 7.96 ± 1.27 µM (cisplatin)	[13]
	HeLa	IC ₅₀ = 23.5 ± 0.4 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	
	A549	IC ₅₀ = 26.13 ± 0.52 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
9	MGC-803	IC ₅₀ > 100 µM	IC ₅₀ = 7.96 ± 1.27 µM (cisplatin)	[13]
	HeLa	IC ₅₀ > 100 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	
	A549	IC ₅₀ = 85.16 ± 0.33 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
	HeLa	IC ₅₀ > 100 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	[28]
	SGC-7901	IC ₅₀ = 84.2 ± 3.1 µM	IC ₅₀ = 1.1 ± 0.05 µM (cisplatin)	
	SHG-44	IC ₅₀ > 100 µM	IC ₅₀ = 1.8 ± 0.03 µM (cisplatin)	
10	HGC-27	IC ₅₀ = 56.6 ± 1.34 µM	IC ₅₀ = 8.9 ± 0.2 µM (cisplatin)	[23]
11	HGC-27	IC ₅₀ = 33.5 ± 0.65 µM	IC ₅₀ = 8.9 ± 0.2 µM (cisplatin)	[23]
12	MGC-803	IC ₅₀ = 11.76 ± 0.13 µM	IC ₅₀ = 7.96 ± 1.27 µM (cisplatin)	[13]
	HeLa	IC ₅₀ = 14.6 ± 0.7 µM	IC ₅₀ = 2.7 ± 0.04 µM (cisplatin)	
	A549	IC ₅₀ = 16.83 ± 0.41 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
13	HeLa	IC ₅₀ = 22.8 ± 0.9 µM	IC ₅₀ = 2.4 ± 0.02 µM (cisplatin)	[29]
	SGC-7901	IC ₅₀ = 53.5 ± 1.2 µM	IC ₅₀ = 2.0 ± 0.04 µM (cisplatin)	
	SHG-44	IC ₅₀ > 100 µM	IC ₅₀ = 1.5 ± 0.03 µM (cisplatin)	

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Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
14	HeLa	IC ₅₀ = 19.7 ± 1.1 µM	IC ₅₀ = 2.4 ± 0.02 µM (cisplatin)	[29]
	SGC-7901	IC ₅₀ = 38.4 ± 0.8 µM	IC ₅₀ = 2.0 ± 0.04 µM (cisplatin)	
	SHG-44	IC ₅₀ = 29.5 ± 0.8 µM	IC ₅₀ = 1.5 ± 0.03 µM (cisplatin)	
15	HeLa	IC ₅₀ = 55.2 ± 0.9 µM	IC ₅₀ = 2.4 ± 0.02 µM (cisplatin)	[29]
	SGC-7901	IC ₅₀ = 34.8 ± 1.3 µM	IC ₅₀ = 2.0 ± 0.04 µM (cisplatin)	
	SHG-44	IC ₅₀ = 35.8 ± 1.0 µM	IC ₅₀ = 1.5 ± 0.03 µM (cisplatin)	
16	HeLa	IC ₅₀ = 44.5 ± 0.7 µM	IC ₅₀ = 2.4 ± 0.02 µM (cisplatin)	[29]
	SGC-7901	IC ₅₀ = 47.9 ± 1.6 µM	IC ₅₀ = 2.0 ± 0.04 µM (cisplatin)	
	SHG-44	IC ₅₀ > 100 µM	IC ₅₀ = 1.5 ± 0.03 µM (cisplatin)	
17	HepG2	IC ₅₀ = 4.28 ± 0.26 µM	IC ₅₀ = 7.68 ± 0.35 µM (cisplatin)	[27]
	A549	IC ₅₀ = 7.49 ± 0.41 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
	GES-1	IC ₅₀ = 10.97 ± 0.36 µM	IC ₅₀ = 38.69 ± 0.86 µM (cisplatin)	
18	HepG2	IC ₅₀ = 11.07 ± 0.63 µM	IC ₅₀ = 7.68 ± 0.35 µM (cisplatin)	[27]
	A549	IC ₅₀ = 14.2 ± 0.28 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
	GES-1	IC ₅₀ = 26.51 ± 1.20 µM	IC ₅₀ = 38.69 ± 0.86 µM (cisplatin)	
19	HepG2	IC ₅₀ = 19.36 ± 1.24 µM	IC ₅₀ = 7.68 ± 0.35 µM (cisplatin)	[27]
	A549	IC ₅₀ = 13.13 ± 0.97 µM	IC ₅₀ = 10.83 ± 0.72 µM (cisplatin)	
	GES-1	IC ₅₀ = 27.02 ± 0.75 µM	IC ₅₀ = 38.69 ± 0.86 µM (cisplatin)	
20	U118-MG	24 h IC ₅₀ = 15.94 µM		[8]
		48 h IC ₅₀ = 6.53 µM		
	U373-MG	24 h IC ₅₀ = 14.07 µM		
21		48 h IC ₅₀ = 8.11 µM		[3]
	HL-60	IC ₅₀ = 4.0 µM	IC ₅₀ = 1.1 µM (cisplatin)	
	SMMC-7721	IC ₅₀ = 11.3 µM	IC ₅₀ = 6.7 µM (cisplatin)	
	A-549	IC ₅₀ = 4.2 µM	IC ₅₀ = 6.0 µM (cisplatin)	
	MCF-7	IC ₅₀ = 16.1 µM	IC ₅₀ = 15.4 µM (cisplatin)	
23	SW480	IC ₅₀ = 14.2 µM	IC ₅₀ = 16.3 µM (cisplatin)	[3]
	HL-60	IC ₅₀ = 5.6 µM	IC ₅₀ = 1.1 µM (cisplatin)	
	SMMC-7721	IC ₅₀ = 24.7 µM	IC ₅₀ = 6.7 µM (cisplatin)	
	A-549	IC ₅₀ = 16.4 µM	IC ₅₀ = 6.0 µM (cisplatin)	
	MCF-7	IC ₅₀ = 24.6 µM	IC ₅₀ = 15.4 µM (cisplatin)	
24	SW480	IC ₅₀ > 40 µM	IC ₅₀ = 16.3 µM (cisplatin)	[3]
	HL-60	IC ₅₀ = 17.8 µM	IC ₅₀ = 1.1 µM (cisplatin)	
	SMMC-7721	IC ₅₀ = 14.9 µM	IC ₅₀ = 6.7 µM (cisplatin)	
	A-549	IC ₅₀ = 6.5 µM	IC ₅₀ = 6.0 µM (cisplatin)	
	MCF-7	IC ₅₀ = 21.0 µM	IC ₅₀ = 15.4 µM (cisplatin)	
	SW480	IC ₅₀ = 21.1 µM	IC ₅₀ = 16.3 µM (cisplatin)	

Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
25	Mouse lymphocytes (con A induced)	IC ₅₀ = 8.9 µg/mL		[12]
	Mouse lymphocytes (LPS induced)	IC ₅₀ = 6.7 µg/mL		
26	Mouse lymphocytes (con A induced)	IC ₅₀ = 36.3 µg/mL		[12]
	Mouse lymphocytes (LPS induced)	IC ₅₀ = 28.3 µg/mL		
28	L929	IC ₅₀ = 2.1 µM	IC ₅₀ = 4.7×10 ⁻⁴ µM (epothilone B)	[14]
	KB 3.1	IC ₅₀ = 6.7 µM	IC ₅₀ = 3.4×10 ⁻⁵ µM (epothilone B)	
	A431	IC ₅₀ = 3.5 µM	IC ₅₀ = 5.1×10 ⁻⁵ µM (epothilone B)	
	A549	IC ₅₀ = 19 µM	IC ₅₀ = 6.7×10 ⁻⁵ µM (epothilone B)	
	MCF-7	IC ₅₀ = 1.9 µM	IC ₅₀ = 3.0×10 ⁻⁵ µM (epothilone B)	
	PC-3	IC ₅₀ = 18 µM	IC ₅₀ = 9.5×10 ⁻⁵ µM (epothilone B)	
	SK-OV-3	IC ₅₀ = 47 µM	IC ₅₀ = 2.6×10 ⁻⁴ µM (epothilone B)	
29	L929	IC ₅₀ = 6 µM	IC ₅₀ = 4.3×10 ⁻⁴ µM (epothilone B)	[14]
	KB 3.1	IC ₅₀ = 22 µM	IC ₅₀ = 7.3×10 ⁻⁵ µM (epothilone B)	
	A431	IC ₅₀ = 6.5 µM	IC ₅₀ = 6.5×10 ⁻⁵ µM (epothilone B)	
	A549	IC ₅₀ = 57 µM	IC ₅₀ = 5.3×10 ⁻⁵ µM (epothilone B)	
	MCF-7	IC ₅₀ = 4.2 µM	IC ₅₀ = 8.3×10 ⁻⁵ µM (epothilone B)	
	PC-3	IC ₅₀ = 19 µM	IC ₅₀ = 2.8×10 ⁻⁴ µM (epothilone B)	
	SK-OV-3	IC ₅₀ = 30 µM	IC ₅₀ = 1.8×10 ⁻⁴ µM (epothilone B)	
30	MG-63	IC ₅₀ = 9.44 µM	IC ₅₀ = 12.31 µM (cisplatin)	[25]
	SNU387	IC ₅₀ = 10.22 µM	IC ₅₀ = 6.39 µM (cisplatin)	
31	MG-63	IC ₅₀ = 21.71 µM	IC ₅₀ = 12.31 µM (cisplatin)	[25]
	SNU387	IC ₅₀ = 20.16 µM	IC ₅₀ = 6.39 µM (cisplatin)	
	HCT-8	IC ₅₀ = 9.4 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ = 37 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 35 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ = 20 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ = 27 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	SMMC-7721	IC ₅₀ = 72.21 ± 4.99 µM	IC ₅₀ = 8.96 ± 0.57 µM (cisplatin)	[4]
	HepG2	IC ₅₀ = 36.97 ± 3.71 µM	IC ₅₀ = 5.66 ± 0.499 µM (cisplatin)	
	QGY-7703	IC ₅₀ = 51.05 ± 4.86 µM	IC ₅₀ = 6.71 ± 0.612 µM (cisplatin)	
	HepG2/ADM	IC ₅₀ > 100 µM	IC ₅₀ = 27.96 ± 1.89 µM (cisplatin)	
	HCT116	IC ₅₀ = 9.4 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ > 50 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 35 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 20 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 27 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
32	RAW 264.7	IC ₅₀ = 71.66 ± 15.44 µM		[34]

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Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
34	HCT-8	IC ₅₀ = 26 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ = 43 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ = 6.5 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ = 17 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 11 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ = 6.1 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ = 20 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
35	HCT-8	IC ₅₀ > 50 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ > 50 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
36	MG-63	IC ₅₀ = 7.07 µM	IC ₅₀ = 12.31 µM (cisplatin)	[25]
	SNU387	IC ₅₀ = 6.90 µM	IC ₅₀ = 6.39 µM (cisplatin)	
	HCT-8	IC ₅₀ = 16 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ = 23 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 20 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ = 18 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ = 13 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	SMMC-7721	IC ₅₀ = 14.31 ± 0.71 µM	IC ₅₀ = 8.96 ± 0.57 µM (cisplatin)	[4]
	HepG2	IC ₅₀ = 11.08 ± 0.86 µM	IC ₅₀ = 5.66 ± 0.499 µM (cisplatin)	
	QGY-7703	IC ₅₀ = 9.63 ± 0.64 µM	IC ₅₀ = 6.71 ± 0.612 µM (cisplatin)	
37	HepG2/ADM	IC ₅₀ = 18.77 ± 1.23 µM	IC ₅₀ = 27.96 ± 1.89 µM (cisplatin)	[6]
	HCT116	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	
	U87-MG	IC ₅₀ = 23 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 20 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 14 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 13 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	[4, 35]
	SMMC-7721	IC ₅₀ = 6.40 ± 0.51 µM	IC ₅₀ = 8.96 ± 0.57 µM (cisplatin)	
	HepG2	IC ₅₀ = 3.86 ± 0.28 µM	IC ₅₀ = 5.66 ± 0.499 µM (cisplatin)	
	QGY-7703	IC ₅₀ = 3.43 ± 0.27 µM	IC ₅₀ = 6.71 ± 0.612 µM (cisplatin)	
	HepG2/ADM	IC ₅₀ = 11.31 ± 0.67 µM	IC ₅₀ = 27.96 ± 1.89 µM (cisplatin)	
38	SMMC-7721	IC ₅₀ = 10.04 ± 0.89 µM	IC ₅₀ = 8.96 ± 0.57 µM (cisplatin)	[4]
	HepG2	IC ₅₀ = 5.41 ± 0.51 µM	IC ₅₀ = 5.66 ± 0.499 µM (cisplatin)	

Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
39	QGY-7703	IC ₅₀ = 6.18 ± 0.47 µM	IC ₅₀ = 6.71 ± 0.612 µM (cisplatin)	[6]
	HepG2/ADM	IC ₅₀ = 31.50 ± 2.14 µM	IC ₅₀ = 27.96 ± 1.89 µM (cisplatin)	
	HCT116	IC ₅₀ = 21 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	
	U87-MG	IC ₅₀ = 20 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ > 50 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 25 µM	IC ₅₀ = 0.019 µM (paclitaxel)	[7]
	PC9	IC ₅₀ = 19 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ = 35 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	
	PANC-1	IC ₅₀ = 22 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 14 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
40	HepG2	IC ₅₀ = 33 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[6]
	PC9	IC ₅₀ = 19 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT116	IC ₅₀ = 13 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	
	U87-MG	IC ₅₀ = 20 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 7.2 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 4.3 µM	IC ₅₀ = 0.019 µM (paclitaxel)	[7]
	PC9	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ = 15 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	
	PANC-1	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 9.4 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
41	HepG2	IC ₅₀ = 4.3 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[7]
	PC9	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ = 14 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	
	PANC-1	IC ₅₀ = 7.5 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ = 3.5 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[5]
	PC9	IC ₅₀ = 5.9 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	A549	Not cytotoxic (at 20 µM)		
	A549	Not cytotoxic (at 20 µM)		
	A549	Not cytotoxic (at 20 µM)		
44	HCT-8	IC ₅₀ > 50 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
	HepG2	IC ₅₀ > 50 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
45	HCT-8	IC ₅₀ > 50 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	[7]
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	

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Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
46	HepG2	IC ₅₀ > 50 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[7]
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ > 50 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
47	HepG2	IC ₅₀ > 50 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[7]
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	HCT-8	IC ₅₀ > 50 µM	IC ₅₀ = 0.0042 µM (paclitaxel)	
	PANC-1	IC ₅₀ > 50 µM	IC ₅₀ = 0.0015 µM (paclitaxel)	
	HGC-27	IC ₅₀ > 50 µM	IC ₅₀ = 0.0018 µM (paclitaxel)	
48	HepG2	IC ₅₀ > 50 µM	IC ₅₀ = 0.0045 µM (paclitaxel)	[30]
	PC9	IC ₅₀ > 50 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
	Vero	IC ₅₀ > 50 µg/mL	IC ₅₀ = 0.4 µg/mL (ellipticine)	
	KB	IC ₅₀ > 20 µg/mL	IC ₅₀ = 0.2 µg/mL (ellipticine)	
	BC-1	IC ₅₀ > 20 µg/mL	IC ₅₀ = 0.2 µg/mL (ellipticine)	
51	NCI-H187	IC ₅₀ = 0.5 ± 0.04 µg/mL	IC ₅₀ = 0.3 µg/mL (ellipticine)	[12]
	<i>P. falciparum</i>	IC ₅₀ = 2.1 ± 0.5 µg/mL	IC ₅₀ = 0.0012 µg/mL (dihydroartemisinin)	
	Mouse lymphocytes (con A induced)	IC ₅₀ = 14.9 µg/mL		
	Mouse lymphocytes (LPS induced)	IC ₅₀ = 8.4 µg/mL		
	Mouse lymphocytes (con A induced)	IC ₅₀ = 12.4 µg/mL		
52	Mouse lymphocytes (LPS induced)	IC ₅₀ = 10 µg/mL		[12]
	Mouse lymphocytes (con A induced)	IC ₅₀ = 4.1 µg/mL		
53	Mouse lymphocytes (LPS induced)	IC ₅₀ = 3.2 µg/mL		[12]
	Mouse lymphocytes (con A induced)	IC ₅₀ = 11.2 µg/mL		
54	Mouse lymphocytes (LPS induced)	IC ₅₀ = 7.5 µg/mL		[12]
	Mouse lymphocytes (con A induced)	IC ₅₀ = 7.5 µg/mL		
55	A431	Inactive		[9]
	IGROV-1	Inactive		
	SKOV-3	Inactive		
	NIH ^{PTC1}	Inactive		
	NIH ^{H-RAS}	Not determined		
	NIH ^{HER1}	Not determined		
	EGF-R	Inactive		
	Ret/ptc1	Not determined		
	v-Abl	Not determined		
	p34cdc2	Not determined		
57	A431	IC ₅₀ = 15.8 ± 0.79 µM		[9]
	IGROV-1	IC ₅₀ = 22.4 ± 11.8 µM		
	SKOV-3	IC ₅₀ = 41.2 ± 13 µM		

Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
	NIH ^{PTC1}	Inactive		
	NIH ^{H-RAS}	Not determined		
	NIH ^{HER1}	IC ₅₀ = 8.3 µM		
	EGF-R	Inactive		
	Ret/ptc1	Inactive		
	v-Abl	Inactive		
	p34cdc2	Inactive		
59	HCT116	IC ₅₀ = 11 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 9.3 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 7.3 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 14 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 11 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
60	HCT116	IC ₅₀ = 7.6 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 8.6 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 10 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 15 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 39 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
61	HCT116	IC ₅₀ = 13 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 12 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 8.3 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 30 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 26 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
62	HCT116	IC ₅₀ = 11 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 6.1 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 4.4 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 14 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 38 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
63	HCT116	IC ₅₀ = 18 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 16 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 9.4 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 31 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 23 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
64	HCT116	IC ₅₀ = 16 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 20 µM	IC ₅₀ = 0.031 µM (paclitaxel)	
	BGC803	IC ₅₀ = 13 µM	IC ₅₀ = 0.015 µM (paclitaxel)	
	HepG2	IC ₅₀ = 37 µM	IC ₅₀ = 0.019 µM (paclitaxel)	
	PC9	IC ₅₀ = 19 µM	IC ₅₀ = 0.0025 µM (paclitaxel)	
65	HCT116	IC ₅₀ = 10 µM	IC ₅₀ = 0.0034 µM (paclitaxel)	[6]

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Table 2 | (continued)

No.	Cells/animals/enzymes	IC ₅₀	Positive control	References
	U87-MG	IC ₅₀ = 5.6 μ M	IC ₅₀ = 0.031 μ M (paclitaxel)	
	BGC803	IC ₅₀ = 8.2 μ M	IC ₅₀ = 0.015 μ M (paclitaxel)	
	HepG2	IC ₅₀ = 12 μ M	IC ₅₀ = 0.019 μ M (paclitaxel)	
	PC9	IC ₅₀ = 17 μ M	IC ₅₀ = 0.0025 μ M (paclitaxel)	
66	HCT116	IC ₅₀ = 9.4 μ M	IC ₅₀ = 0.0034 μ M (paclitaxel)	[6]
	U87-MG	IC ₅₀ = 4.1 μ M	IC ₅₀ = 0.031 μ M (paclitaxel)	
	BGC803	IC ₅₀ = 6.4 μ M	IC ₅₀ = 0.015 μ M (paclitaxel)	
	HepG2	IC ₅₀ = 12 μ M	IC ₅₀ = 0.019 μ M (paclitaxel)	
	PC9	IC ₅₀ = 12 μ M	IC ₅₀ = 0.0025 μ M (paclitaxel)	

Con A: Concanavalin A; LPS: Lipopolysaccharide.

thus indicating the critical role of stereochemistry in cytotoxic activity [7]. Six additional MTs (**1**, **2**, **10**, **28**, **29**, **30**) with a γ -lactone moiety have also been reported (Figure 2). Arnebinol A (**30**), isolated from *A. euchroma*, has IC₅₀ values of 9.44 and 10.22 μ M in MG-63 and SNU387 cell lines, respectively. The spontaneous or enzyme-mediated oxidation of both terpenoid and non-terpenoid moieties increases the compounds' structural diversity and contributes to variations in biological activity (**1**, **2**, **10**, **28**, **29**). Clavilactone A (**1**), identified as a cytochrome P450-mediated oxidative product of arnebinol A (**30**) bearing an additional epoxide group, has been reported in *C. clavipes* and *A. euchroma* [10, 13]. Cytotoxicity assays have indicated that this oxidative modification selectively enhances cytotoxicity in MG-63 cells but slightly decreases cytotoxicity in SNU387 cells (Table 2). Moreover, clavilactone A (**1**) exhibits superior cytotoxicity (IC₅₀ = 0.18 μ M) to paclitaxel (IC₅₀ = 0.48 μ M) in MDA-MB-231 cells [10, 25] (Table 2).

Comparative studies have indicated that oxidative modifications in various regions have differential effects on cytotoxic potency. Clavilactone B (**2**) and *ent*-clavilactone J quinone (**29**), reported in *C. clavipes* and *Resupinatus* sp. BCC84615, possess additional oxidative features not present in clavilactone A (**1**), including quinone groups (**2**, **29**) and an epoxide moiety (**29**) in their non-terpenoid and/or terpenoid regions [13, 14] (Figure 2). Cytotoxicity assays have revealed greater potency of clavilactone B (**2**) than clavilactone A (**1**) in National Institutes of Health 3T3 (NIH3T3) mouse fibroblasts expressing the oncogenes RET/PTC1 (NIH3T3PTC1) or H-RAS (NIH3T3^{H-RAS}), thus suggesting that oxidation in the non-terpenoid moiety might enhance cytotoxicity [9]. In contrast, *ent*-clavilactone J quinone (**29**) has lower cytotoxicity in A431 cells (IC₅₀ = 6.5 μ M) than clavilactone B (**2**) (IC₅₀ = 3.6 $\pm$ 1.31 μ M); therefore, further oxidation in the terpenoid region does not necessarily improve cytotoxic potential.

Similarly, clavilactone J (**10**) and *ent*-clavilactone J (**28**), reported in *C. clavipes* and *Resupinatus* sp. BCC84615, are oxidative derivatives of clavilactone A (**1**), both featuring an additional epoxide group in the terpenoid moiety (Figure 2). Among these, *ent*-clavilactone J (**28**, IC₅₀ = 19 μ M) has shown stronger cytotoxicity in A549 cells than clavilactone A (**1**, IC₅₀ = 24.17 $\pm$ 0.92 μ M). However, another cytotoxicity assay has indicated an IC₅₀ > 50 μ M for *ent*-clavilactone J (**28**) in A549 cells. Therefore, cytotoxicity comparisons should be conducted under more standardized and parallel conditions to minimize potential bias.

In light of the cytotoxicity of clavilactone B (**2**) against tyrosine kinase-transformed cells, its mechanism of action has been further explored. Isotopically labeled ³²P has been used to assess the utilization of the phosphate donor ATP and the tyrosine-containing polymeric substrate poly (Glu₆ Ala₃ Tyr) in the EGFR kinase reaction [9] (Figure 3). Kinetic analysis has revealed a non-competitive inhibition pattern with respect to both ATP and the peptide substrate [9]. These findings suggest that clavilactone B (**2**) might serve as a complementary strategy for EGFR inhibitor development and might potentially be used in combination therapy with existing competitive EGFR inhibitors to mitigate drug resistance.

Beyond the typical ten-membered ring structure, a synthetic intermediate known as seco-clavilactone B has been found to decrease the ratio of filamentous actin to globular actin [38] (Figure 4). Further *in vitro* assays have demonstrated that seco-clavilactone B effectively inhibits actin polymerization and therefore has potential as a novel actin polymerization inhibitor [38].

Investigation of this compound's molecular mechanism of action through liquid chromatography-mass spectrometry analysis has revealed that seco-clavilactone B forms covalent bonds with threonine 5 and cysteine 285 of α -skeletal muscle actin [38]. However, because of the difficulty in obtaining active recombinant

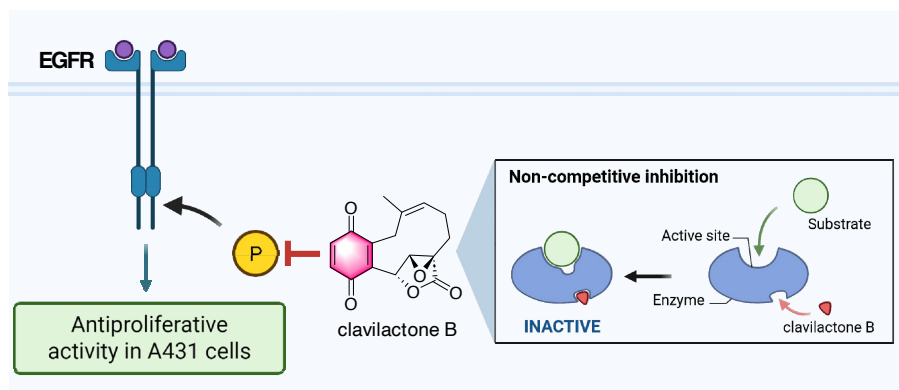


Figure 3 | Non-competitive inhibition by clavilactone B (2) of the utilization of the phosphate donor ATP or the tyrosine-containing polymer substrate poly(Glu₆ Ala₃ Tyr) in the EGFR kinase reaction (created in BioRender: www.biorender.com).

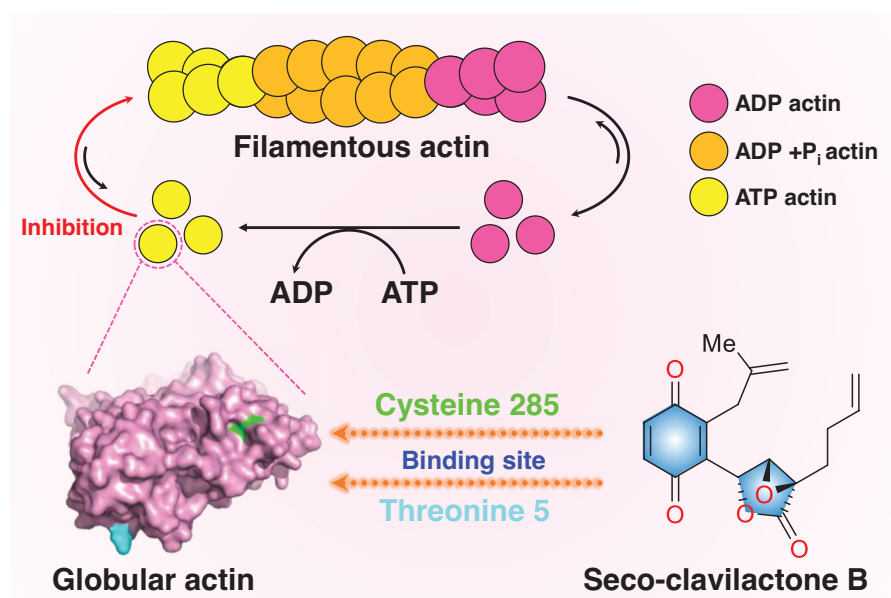


Figure 4 | Seco-clavilactone B functions as an actin polymerization inhibitor by binding cysteine 285 and threonine 5 of globular actin.

α -skeletal actin, the researchers expressed β -actin and three key mutants in *Escherichia coli* BL21: I5T (containing both threonine 5 and cysteine 285), C285S (lacking both residues), and I5T/C285S (lacking cysteine 285) [38]. Functional assays demonstrated that seco-clavilactone B decreased filamentous actin levels in wild-type β -actin, I5T, and I5T/C285S mutants, but not the C285S mutant [38]. Therefore, both threonine 5 and cysteine 285 are critical binding sites for the inhibitory effect of seco-clavilactone B on actin polymerization, and either site alone is sufficient to mediate this activity. These findings support its potential as a novel actin polymerization inhibitor.

Beyond their cytotoxic activity, the antimicrobial properties of seven MTs (1, 2, 28–31, 48) have been investigated (Table 3). Globiferin (48) exhibits potent inhibitory activity against *Mycobacterium tuberculosis* H37Ra, with a minimum inhibitory concentration (MIC) of 6.2 μ g/mL. Both clavilactone A (1) and clavilactone B (2) exhibit antifungal effects against *Cladosporium cladosporioides* and *Cladosporium cucumerinum*, whereas clavilactone B (2) shows a broader antimicrobial spectrum, inhibiting *Bacillus subtilis*, *Bacillus cereus*, *Sarcina lutea*, and *Saccharomyces cerevisiae* in disk diffusion assays. These results suggest that the highly oxidized quinone moiety in the

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Table 3 | Biological activity of MTs with benzo-fused ten-membered ring skeletons.

No.	Bioactivity	Cell lines/strains	MIC/MFC/IC ₅₀	Positive control	References
1	Anti-bacterial	<i>B. subtilis</i> (ATCC 6633)	100 µg disc ⁻¹		[22]
		<i>B. cereus</i> (ATCC 10702)	-		
		<i>S. lutea</i> (DMS 348)	-		
		<i>S. cerevisiae</i> (NCYC 729)	-		
	Anti-fungal	<i>Micrococcus lysodeikticus</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	[10]
		<i>Micrococcus luteus</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>Salmonella typhi</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>Alternaria longipes</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>S. aureus</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>C. cladosporioides</i>	50 µg disc ⁻¹		
		<i>C. cucumerinum</i>	50 µg disc ⁻¹		
		<i>Verticillium dahliae</i> Kleb	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ketoconazole)	
		<i>Colletotrichum acutatum</i> Simmonds	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>Cladosporium personatum</i>	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>Physalospora piricola</i> Nose	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>Fusarium oxysporum</i> f. sp. vesinfectum (Atk.) Snyder et Hansen	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
2	Anti-bacterial	<i>B. subtilis</i> (ATCC 6633)	50 µg disc ⁻¹		[22]
		<i>B. cereus</i> (ATCC 10702)	50 µg disc ⁻¹		
		<i>S. lutea</i> (DMS 348)	50 µg disc ⁻¹		
	Anti-fungal	<i>S. cerevisiae</i> (NCYC 729)	50 µg disc ⁻¹		
		<i>C. cladosporioides</i>	50 µg disc ⁻¹		
3	Anti-fungal	<i>C. cladosporioides</i>	50 µg disc ⁻¹		[22]
		<i>C. cucumerinum</i>	50 µg disc ⁻¹		
25	Anti-bacterial	<i>S. aureus</i> 209P	MIC = 6.2 µg/mL		[31]
		<i>B. subtilis</i> ATCC 6633	MIC = 6.2 µg/mL		
		<i>E. coli</i> NIHJ	MIC > 100 µg/mL		
	Anti-fungal	<i>Candida albicans</i> (50157)	MIC = 25 µg/mL		[31]
		<i>T. rubrum</i> sc.	MIC = 6.2 µg/mL		
		<i>T. mentagrophytes</i> sc.	MIC = 6.2 µg/mL		
28	Anti-bacterial	<i>B. subtilis</i>	MIC = 17 µg/mL	MIC = 8.3 µg/mL	[14]
		<i>Mycolicibacterium smegmatis</i>	No inhibition	MIC = 1.7 µg/mL	
		<i>S. aureus</i>	No inhibition	MIC = 1.7 µg/mL; MIC = 0.21 µg/mL	
		<i>Acinetobacter baumannii</i>	No inhibition	MIC = 0.26 µg/mL; MIC = 0.53 µg/mL	
		<i>Chromobacterium violaceum</i>	No inhibition	MIC = 0.42 µg/mL; MIC = 1.7 µg/mL	
		<i>E. coli</i>	No inhibition	MIC = 1.7 µg/mL	
		<i>Pseudomonas aeruginosa</i>	No inhibition	MIC = 0.42 µg/mL; MIC = 0.21 µg/mL	

Table 3 | (continued)

No.	Bioactivity	Cell lines/strains	MIC/MFC/IC ₅₀	Positive control	References
29	Anti-fungal	<i>Mucor hiemalis</i>	No inhibition	MIC = 4.2 µg/mL; MIC = 8.3 µg/mL	[14]
		<i>C. albicans</i>	No inhibition	MIC = 8.3 µg/mL	
		<i>Rhodotorula glutinis</i>	No inhibition	MIC = 2.1 µg/mL; MIC = 4.2 µg/mL	
		<i>Schizosaccharomyces pombe</i>	No inhibition	MIC = 4.2 µg/mL; MIC = 8.3 µg/mL	
		<i>Wickerhamomyces anomala</i>	No inhibition	MIC = 8.3 µg/mL	
	Anti-bacterial	<i>B. subtilis</i>	MIC = 67 µg/mL	MIC = 8.3 µg/mL	
		<i>M. smegmatis</i>	No inhibition	MIC = 1.7 µg/mL	
		<i>S. aureus</i>	MIC = 67 µg/mL	MIC = 1.7 µg/mL; MIC = 0.21 µg/mL	
		<i>A. baumannii</i>	No inhibition	MIC = 0.26 µg/mL; MIC = 0.53 µg/mL	
		<i>C. violaceum</i>	No inhibition	MIC = 0.42 µg/mL; MIC = 1.7 µg/mL	
		<i>E. coli</i>	No inhibition	MIC = 1.7 µg/mL	
		<i>P. aeruginosa</i>	No inhibition	MIC = 0.42 µg/mL; MIC = 0.21 µg/mL	
		Anti-fungal	<i>M. hiemalis</i>	MIC = 4.2 µg/mL; MIC = 8.3 µg/mL	
			<i>C. albicans</i>	MIC = 8.3 µg/mL	
			<i>R. glutinis</i>	MIC = 2.1 µg/mL; MIC = 4.2 µg/mL	
			<i>S. pombe</i>	MIC = 4.2 µg/mL; MIC = 8.3 µg/mL	
			<i>W. anomala</i>	MIC = 8.3 µg/mL	
30	Anti-fungal	<i>Aspergillus flavus</i> (100 mg/L)	MIC > 200 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	[33]
		<i>A. flavus</i> (200 mg/L)	MIC = 135 ± 4 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (400 mg/L)	MIC = 102 ± 5 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (800 mg/L)	MIC = 61.54 ± 3 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (1600 mg/L)	MIC = 33.9 ± 1.7 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (100 mg/L)	MFC > 200 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (200 mg/L)	MFC = 170 ± 3 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (400 mg/L)	MFC = 130 ± 4 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (800 mg/L)	MFC = 85.18 ± 2.9 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (1600 mg/L)	MFC = 41.4 ± 1.9 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
31	Anti-fungal	<i>A. flavus</i> (100 mg/L)	MIC > 200 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	[33]
		<i>A. flavus</i> (200 mg/L)	MIC = 120 ± 5 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (400 mg/L)	MIC = 89 ± 3 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (800 mg/L)	MIC = 49.21 ± 3.95 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (1600 mg/L)	MIC = 20.2 ± 2.4 mg/L	MIC = 0.05 ± 0.3 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (100 mg/L)	MFC > 200 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (200 mg/L)	MFC = 163 ± 4.31 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (400 mg/L)	MFC = 111 ± 3 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	
		<i>A. flavus</i> (800 mg/L)	MFC = 59.62 ± 2.43 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	

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Table 3 | (continued)

No.	Bioactivity	Cell lines/strains	MIC/MFC/IC ₅₀	Positive control	References
33	Anti-bacterial	<i>A. flavus</i> (1600 mg/L)	MFC = 30.8 ± 1.1 mg/L	MFC = 0.94 ± 0.15 mg/L (nystatin, 1 mg/L)	[10]
		<i>M. lysodeikticus</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>M. luteus</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>S. typhi</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>A. longipes</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
		<i>S. aureuse</i>	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ciprofloxacin)	
	Anti-fungal	<i>V. dahliae</i> Kleb	MIC > 100 µg/mL	MIC = 0.78 µg/mL (ketoconazole)	
		<i>C. acutatum</i> Simmonds	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>C. personatum</i>	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>P. piricola</i> Nose	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
		<i>F. oxysporum</i> f. sp. vesinfectum (Atk.) Snyder et Hansen	MIC > 100 µg/mL	MIC = 3.125 µg/mL (ketoconazole)	
48	Anti-bacterial	<i>M. tuberculosis</i> H ₃₇ Ra	MIC = 6.2 µg/mL	MIC = 0.0047 µg/mL (rifampicin)	[30]
				MIC = 0.05 µg/mL (isoniazid)	
				MIC = 2.5 µg/mL (kanamycin)	
	Anti-fungal	<i>C. albicans</i>	IC ₅₀ > 20 µg/mL	IC ₅₀ = 0.08 µg/mL (amphotericin B)	

MFC: Minimum fungicidal concentration.

non-terpenoid region plays a critical role in antimicrobial activity.

4.2 6/10 skeleton MTs with post-modifications

Beyond the basic 6/10 skeletons, post-modifications such as methylation, acetylation, and hydroxylation further enhance chemical diversity and modulate biological activities.

Fourteen 6/10 bicyclic MTs (21–27, 49, 51–54, 56, 58) have been reported to contain methyl (21–27, 51–54, 58), acetyl (49, 54, 56, 58), or stearyl (27) substitutions [3, 12, 24, 30, 31] (Figure 5). Notably, the ten-membered ring of wigandol (49) was initially proposed to possess a *trans, trans*-geometry but was later found to have a *cis, trans*-configuration through single-crystal X-ray analysis [30].

Flavidulol A (25), isolated from plants (*W. urens*/C. *globifera*) or fungi (*L. flavidulus*), together with its chemically modified derivatives 52 and 53, exhibits antiproliferative activity [12, 30]. These compounds share a methyl substitution at the C4 position of the non-terpenoid moiety and differ in the degree of saturation within the ten-membered ring [12]. Evaluation of their antiproliferative effects in mouse lymphocytes stimulated with lipopolysaccharide or concanavalin A has demonstrated IC₅₀ values of 3.2–12.4 µg/mL [12] (Table 2). Interestingly, although flavidulol A (25) and its derivatives (52, 53) feature a decrease in double bonds within the

ten-membered ring, they still retain notable antiproliferative activity, and the tetrahydro derivative (53) exhibits stronger cytotoxicity than flavidulol A (25) [12] (Table 2). Moreover, additional methylation (51) or acetylation (54) at the C1 position slightly decreases activity [12]. These findings suggest that neither double bonds in the ten-membered ring nor the methyl/acetyl substitution at C1 is essential for maintaining antiproliferative activity.

Beyond its cytotoxic effects, flavidulol A (25) has been evaluated for antimicrobial activity. This compound has potent inhibitory effects against four microbial strains (*Staphylococcus aureus* 209P, *B. subtilis* ATCC 6633, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*), with MIC values of 6.2 µg/mL [31] (Table 3).

Four MTs (21–24) exhibit a unique 6/10 fused pattern (Figure 5) observed only in *T. terreum* [3]. Cytotoxicity assays (Table 2) have revealed that terreum C (23) displays potent cytotoxicity in five cancer cell lines (HL-60, SMMC-7721, A-549, MCF-7, and SW480), particularly in HL-60 (IC₅₀ = 5.6 µM) [3]. Terreumol A (21), which contains an additional epoxide group at C6/C7, in contrast to terreum C (23), shows stronger cytotoxicity in the same five cell lines [3]. Terreum D (24), which, compared with terreum C (23), has an additional hydroxyl group at C8, has shown an increase in cytotoxicity in four cell lines (SMMC-7721, A-549, MCF-7, SW480), excluding

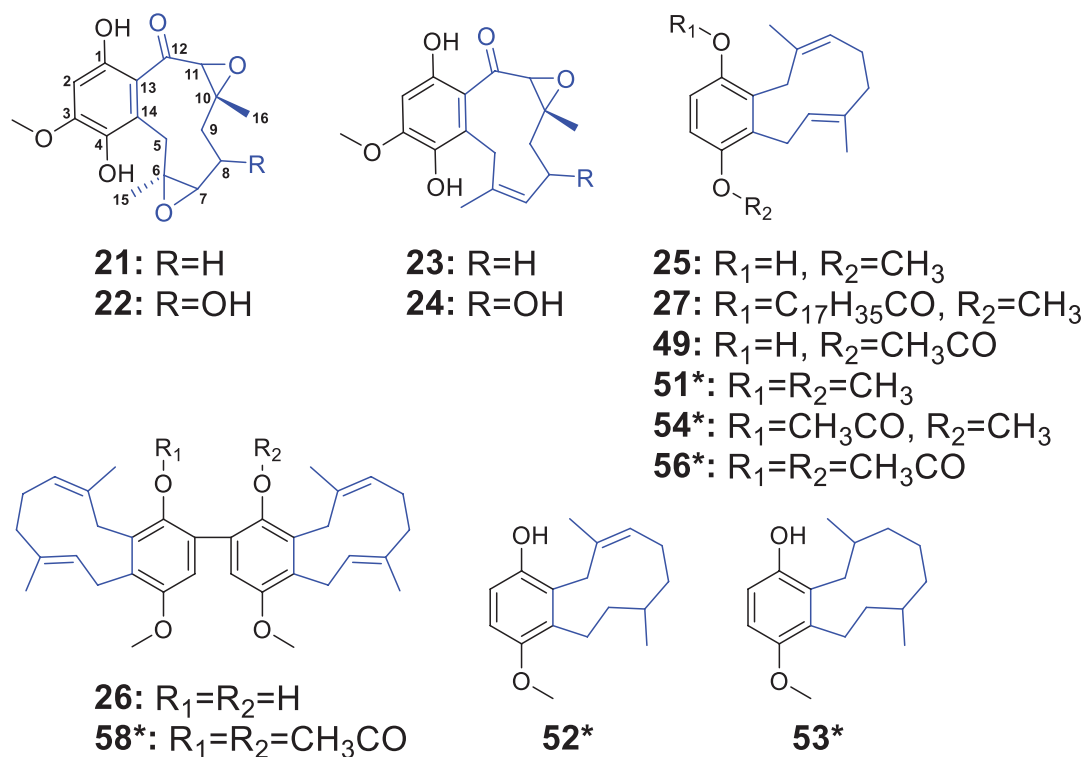


Figure 5 | 6/10 bicyclic skeleton MTs with post-modifications. Blue represents the terpenoid moiety, and asterisk indicates chemically modified derivatives.

HL-60 [3]. These findings suggest that both the distinctive fused ring structure and the degree of oxidation are crucial for modulating cytotoxic effects, and the additional hydroxyl group at C8 may enhance cytotoxicity.

4.3 6/10/5 skeleton MTs with post-modifications

The 6/10/5 tricyclic skeletons exhibit enhanced chemical complexity, characterized by diverse functional group modifications and higher oxidation states that contribute to various biological activities.

Eleven MTs (3, 5, 7–9, 11, 12, 34, 35, 55, 57) feature a typical 6/10/5 tricyclic skeleton with various substitutions, including methyl (8, 9, 35, 55), amino (12), hydroxyl (3, 7), methoxy (5, 34), acetyl (57), and isobutyramide groups (11) [7, 9, 13, 22, 23, 26, 28] (Figure 6). Clavilactone H (8), isolated from *C. clavipes*, has a γ -lactone structure and exhibits IC₅₀ values of 14.5–53.9 μ M against five human cancer cell lines, including HeLa, SGC-7901, SHG-44, MGC-803, and A549 [13, 28] (Table 2). Clavilactone L (12), also isolated from *C. clavipes*, bears an additional amino group at C3 that is absent in clavilactone H (8), and exhibits IC₅₀ values of 11.76–16.83 μ M in three cancer cell lines [13]. These findings suggest that amino substitution at C3 is a promising modification for anticancer drug development. However, other substitutions, including hydroxyl (34, 36), methoxy

(5, 34, 35), methyl (55), acetyl (57), isobutyramide (11), and epoxide (9), appear to have limited effects on cytotoxicity (Table 2).

Seven highly oxidized MTs (4, 6, 36, 37, 39–41) with quinone structures fused with either a furan ring (36, 37) or a γ -lactone ring (4, 6, 39–41) have been isolated from *A. euchroma* (36, 37, 39–41) and *C. clavipes* (4, 6) [7, 27, 35] (Figure 6). Arnebinone B (36) has been found to exhibit cytotoxicity across 16 cell lines, with IC₅₀ values of 6.9–23 μ M [4, 6, 7, 25] (Table 2). A structural comparison has revealed that 6S,11Z-2-methoxy-arnebinone B (37), which contains an additional methoxy group at C2, exhibits enhanced cytotoxicity, with IC₅₀ values of 3.43–11.31 μ M, particularly against liver cancer cells (HepG2) [35]. Mechanistic studies have shown that 6S,11Z-2-methoxy-arnebinone B (37) inhibits hepatoma cell proliferation by downregulating the mTOR signaling pathway and activating the intrinsic apoptotic pathway (Figure 7A), while simultaneously inhibiting epithelial-mesenchymal transition through reprogramming related gene expression [35] (Figure 7B).

Five MTs (4, 6, 39–41) contain a benzoquinone core fused to a ten-membered carbon ring and a γ -lactone, with methoxy (39–41) or amino (4, 6) substitutions [6, 7, 27]. Notably, the structural elucidation of

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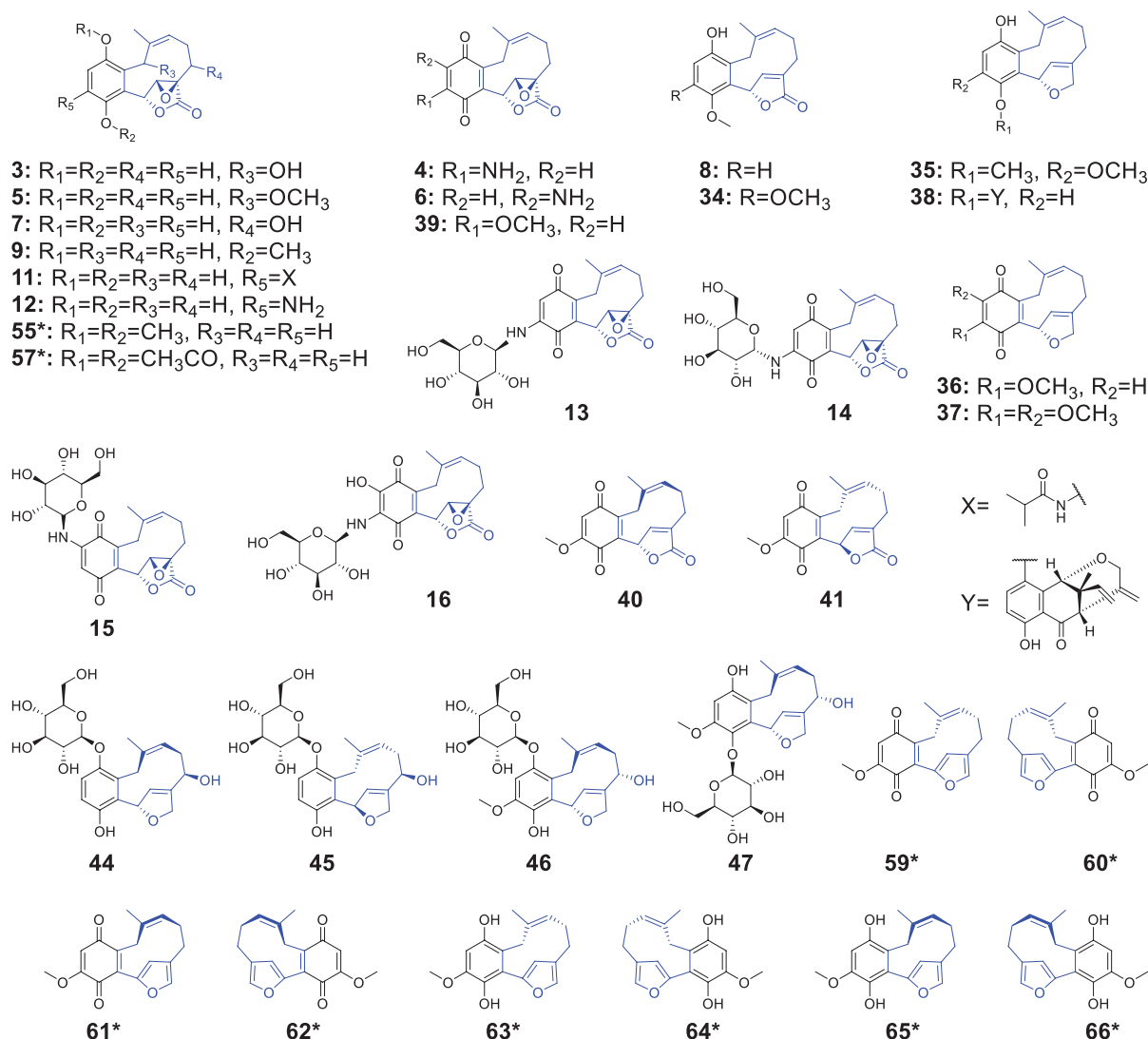


Figure 6 | 6/10/5 tricyclic skeleton MTs with post-modifications. Blue represents the terpenoid moiety, and asterisk indicates chemically modified derivatives.

clavilactone D (**4**) was initially incorrect and was subsequently corrected through total synthesis by Tadano's group [17].

Among these compounds, (+)-arnebinone E (**40**) and (–)-arnebinone E (**41**) have comparable cytotoxicity against HGC-27 and HepG2 cells, with IC_{50} values of 3.5–9.4 μM [7]. In contrast, enantiomeric differences have been observed in PC9 cells, with IC_{50} values of 9.3 and 5.9 μM [7], respectively, thereby suggesting a stereoselective cytotoxic effect against lung cancer cells.

Furthermore, eight phototransformation products (**59–66**) have been derived from arnebinone B (**36**) via irreversible proton transfer leading to a rearrangement of the double bond within the furan ring [6]. This

eco-friendly transformation method has expanded the chemical diversity of MTs, although structural instability (particularly in *p*-benzoquinone- $CH_2/CH-\pi$ groups) poses challenges in isolation and purification. Cytotoxicity testing has revealed that six products (**59–62**, **65**, **66**) display enhanced activity in U87-MG and BGC803 cell lines (IC_{50} of 4.4–39 μM), thereby providing valuable insights for MT modification [6].

In addition, eight glycosylated MTs have been reported, including four *O*-glycosides (**44–47**) from *A. euchroma* and four *N*-glycosides (**13–16**) from *C. clavipes* [7, 29]. Cytotoxicity assays have indicated that glycosylation attenuates the activity with respect to that of the corresponding aglycones (Table 2). Therefore,

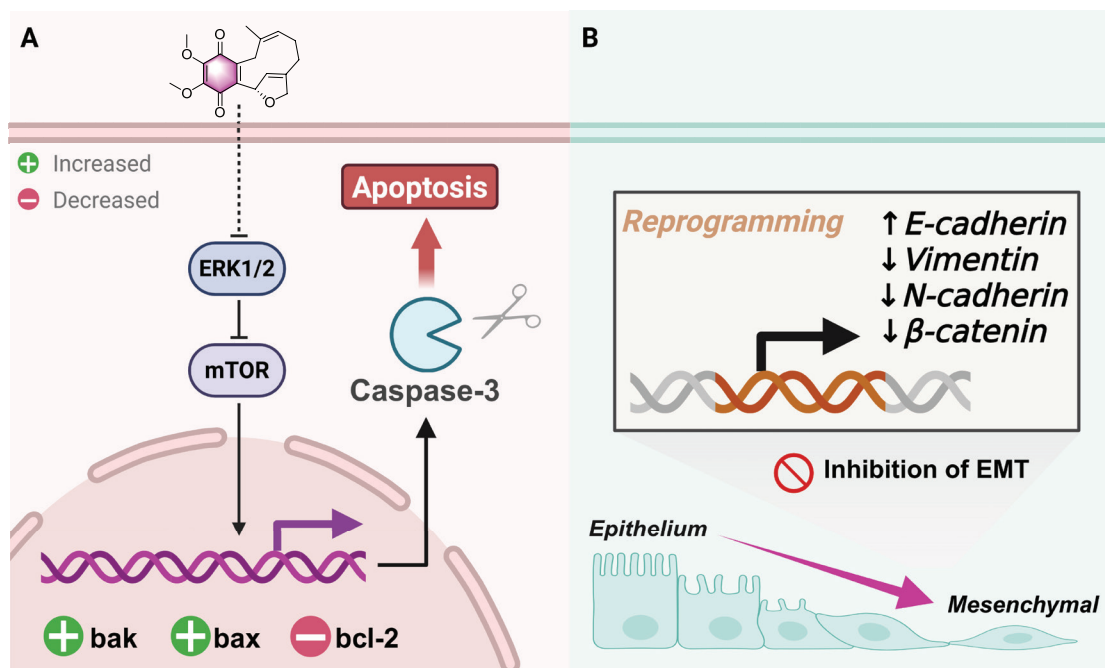


Figure 7 | Mechanisms of 6S,11Z-2-methoxy-arnebinone B (37) for liver cancer intervention (created in BioRender: www.biorender.com).

(A): Downregulation of the mTOR activation triggers apoptosis in SMMC-7721 and HepG2 cells by regulating the expression of apoptotic factors through the ERK1/2 pathway. (B): Suppression of epithelial-mesenchymal transition through the reprogramming of gene expression in SMMC-7721 and HepG2 cells.

glycosylation might be a strategy used by fungi and plants to modulate or mitigate self-toxicity.

Finally, an arnebinone B derivative (**38**) isolated from *A. euchroma*, which forms a rare complex MT through conjugation with other MT, exhibits cytotoxicity against HepG2 and QGY-7703 cells (IC_{50} = 5.41 and 6.18 μ M, respectively) [4].

4.4 MTs with complex ring fusion patterns

Beyond conventional structures, several MTs exhibit rare and unique fusion patterns, thus further enriching their structural and functional diversity. These patterns include fusion with a pyrrolo[1,2-*a*]imidazole ring, thus forming nitrogen-containing polycyclic compounds (clavipyrine A, **20**), as well as fusion with an azepine ring (**17–19**) or oxidation to other ring systems (**33**, **42**, **43**), thus resulting in uncommon structures [8, 27] (Figure 8).

Three MTs (**17–19**) isolated from *C. clavipes* possess similar ring fusion patterns but differ in the degree of oxidation in the terpenoid moiety. Evaluation of their cytotoxicity in three cell lines (HepG2, A549, and GES-1) has indicated IC_{50} values of 4.28–27.02 μ M [27] (Table 2). Structural comparisons have revealed that both the degree of oxidation and the ring fusion patterns are critical factors influencing cytotoxicity, although their precise structure-activity relationships require further investigation.

Moreover, the elevated cytotoxicity against cancer cells is accompanied by enhanced toxicity toward normal gastric mucosal epithelial cells (GES-1) [27]. Consequently, potential adverse effects must be carefully considered in the development of future anticancer agents (Table 2).

Clavipyrine A (**20**), isolated from *C. clavipes*, exhibits dynamic cytotoxicity against the human glioma cell lines U118-MG and U373-MG, with IC_{50} values of 6.53–15.94 μ M [8]. Moreover, the greater cytotoxicity observed at 48 hours than at 24 hours suggests a time-dependent cytotoxic effect [8]. Further mechanistic studies have revealed that clavipyrine A induces cancer cell apoptosis by inhibiting the JAK signaling pathway and enhancing SOCS1/3 expression through reprogramming [8] (Figure 9).

Beyond its cytotoxicity, the antimicrobial activity of arneuchrol B (**33**), an MT isolated from *A. euchroma*, has been evaluated against five bacterial and five fungal strains [10] (Table 3). However, the MIC values greater than 100 μ g/mL suggested insufficient antimicrobial activity.

5. BIOSYNTHESIS

A biosynthetic pathway of benzo-fused ten-membered-ring MTs was first proposed in 1994, in which the intermediate geranyl hydroquinone undergoes consecutive oxidative reactions, thus generating clavilactones [22].

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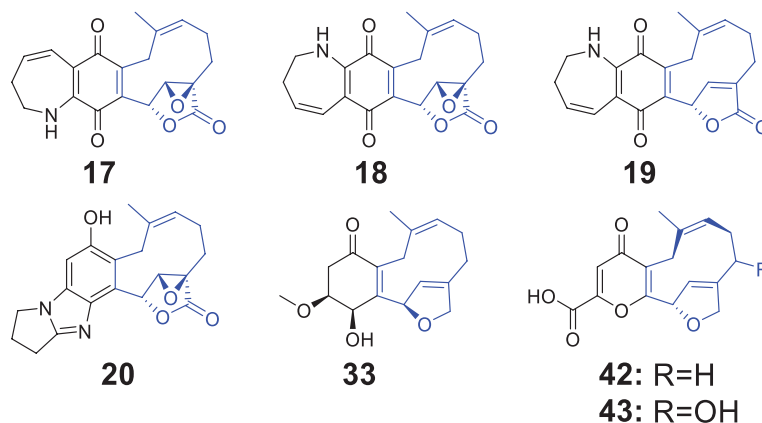


Figure 8 | 6/10/5 tricyclic skeleton MTs with complex ring fusion patterns. Blue represents the terpenoid moiety.

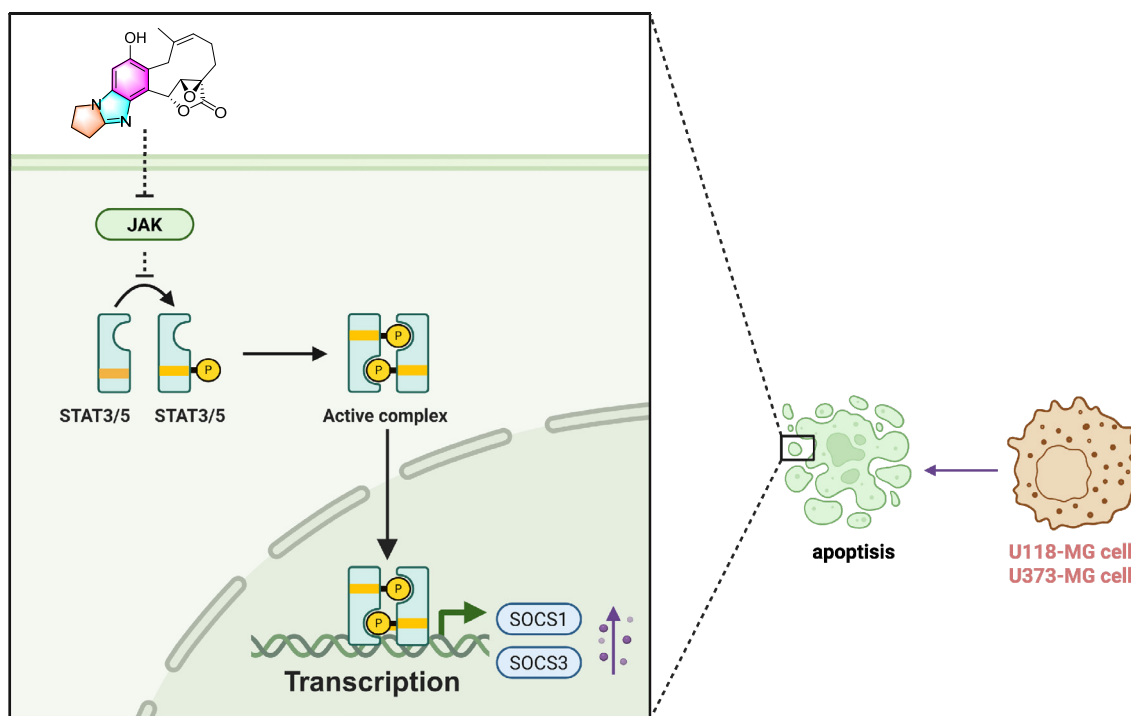


Figure 9 | Clavipyrine A (20) promotes cancer cell apoptosis by blocking the JAK/STAT pathway, thereby enhancing SOCS1/3 expression in U118-MG and U373-MG cells (created in BioRender: www.biorender.com).

However, the biosynthetic pathway of clavilactone A was not elucidated until 2024 [20], and the characterization of related pathways remains in its infancy, with many key post-modifications and regulatory mechanisms remaining to be uncovered. To address the limited availability of natural clavilactones and their derivatives, we summarize the key biosynthetic enzymes and

possible synthetic routes of clavilactones, to provide new insights into the biosynthesis of benzo-fused ten-membered-ring MTs.

The biosynthesis of clavilactones requires contributions from both terpenoid and non-terpenoid moieties [20, 39]. The terpenoid moiety is derived from the mevalonate and methylerythritol phosphate pathways,

whereas the non-terpenoid moiety originates from the phenylpropanoid pathway (in plants) [39]. The biosynthetic precursors geranyl diphosphate and *p*-hydroxybenzoic acid, generated *via* different metabolic pathways, are assembled into geranyl-*p*-hydroxybenzoic acid by UbiA membrane-bound aromatic prenyltransferases [40] (Figure 10). Oxidative decarboxylation of geranyl-*p*-hydroxybenzoic acid is considered a key step in the formation of geranyl hydroquinone. Interestingly, Yang et al. have identified an atypical *p*-hydroxybenzoic acid-type UbiA prenyltransferase (ClaS) from *C. clavipes*, which transfers geranyl diphosphate to hydroquinone instead of *p*-hydroxybenzoic acid [41]. A single point mutation (H73R) in ClaS fully switches its substrate preference from hydroquinone to *p*-hydroxybenzoic acid; therefore, histidine and arginine residues at the active site serve as gatekeepers for substrate specificity [41].

Genomic mining of *C. clavipes* has revealed a biosynthetic gene cluster encoding ClaS and seven cytochrome P450s, which are believed to be involved in clavilactone biosynthesis [20]. Functional analysis of these P450s has indicated that ClaR mediates the formation of the ten-membered ring *via* a diradical C-C coupling reaction [20]. After the construction of the 6/10 fused ring system, ClaT catalyzes stepwise oxidation and precisely regulates the formation of the α,β -epoxy- γ -lactone moiety [20].

Oxidative reactions also play major roles in the biosynthesis of clavilactone analogs [3, 14]. Clavilactone J, a highly oxidized derivative of clavilactone A (in the terpene moiety), is likely to be formed by further oxidation *via* a P450 enzyme [14]. In addition, oxidation of the non-terpene moiety involves primarily spontaneous oxidation of phenol into quinone, and contributes to the formation of globiferin, compound J, clavilactone B, and clavilactone J quinones [20]. The chemical diversity of the non-terpenoid moiety has been hypothesized to expand after quinone formation. For instance, clavilactone D might result from C-N bond cleavage of a quinone-amino acid conjugate, whereas the seven-membered rings in clavipines A–C are probably derived from rearrangements of similar conjugated intermediates [27].

Moreover, the biosynthetic pathway of nitrogen-containing polycyclic MTs, such as clavipyrine A, has been proposed to involve geranyl diphosphate transfer to *p*-aminobenzoic acid, followed by oxidative transformations yielding intermediates B and C [8]. Feeding [^{15}N]-labeled γ -aminobutyric acid to *C. clavipes* and subsequent high-resolution electrospray ionization mass spectrometry analysis have indicated that the pyrrole unit in clavipyrine A is derived from γ -aminobutyric acid [8].

Interestingly, our comparative analysis of chemical diversity suggested that MTs bearing a five-membered furan ring (31–33, 35–38, 42–47) were isolated from only plant sources, including *A. euchroma* and *C. glazioviana*, rather than fungal sources. Consequently, we hypothesize that plant-derived and fungal-derived MTs might

follow distinct biosynthetic pathways, as also observed in other natural products [42, 43]. Both shikonin and shikonofuran, the major components of *A. euchroma*, have been shown to be derived from the same precursor, geranyl hydroquinone, through a series of sequential steps. This precursor has also been identified in the biosynthesis of clavilactone A [39, 44]. Therefore, we speculate that clavilactones in *A. euchroma* might originate from a branch of the shikonin/shikonofuran biosynthetic pathway, although this hypothesis remains to be experimentally validated.

Beyond elucidating their biosynthetic pathways, enhancing MT production remains a key challenge. Advances in terpenoid synthetic biology have enabled heterologous production in *S. cerevisiae*, which has native terpenoid pathways and a mature genetic system [45–47]. The biosynthesis of these MTs involves assembly of these moieties. The fungal enzyme ClaS, which provides the most efficient approach for assembling terpenoid and non-terpenoid moieties, can directly transfer geranyl diphosphate to hydroquinone, whereas plant-derived AePGT/LePGT can transfer only geranyl diphosphate to *p*-hydroxybenzoic acid and therefore requires an additional decarboxylation and hydroxylation step [40, 41, 48]. This plant-specific step remains poorly characterized, and fungal enzymes currently serve as the only reference [49]. Therefore, using ClaS with hydroquinone feeding in *S. cerevisiae* is a practical strategy to efficiently produce the key precursor geranyl hydroquinone. This approach is cost-effective and metabolically efficient, because it uses inexpensive industrial substrates and minimizes enzymatic steps. Nevertheless, because hydroquinone is potentially cytotoxic to the host, fed-batch fermentation or optimized cultivation conditions are necessary to maintain safe substrate levels [50].

The terpenoid portion can be enhanced by engineering yeast pathways to boost mevalonate flux, thereby increasing isopentenyl diphosphate and dimethylallyl diphosphate supply for high geranyl diphosphate production, through a well-established strategy in *S. cerevisiae* [47, 51, 52]. After geranyl hydroquinone formation, a series of oxidations are catalyzed by P450 enzymes [20], whose suboptimal efficiency poses a major production bottleneck. The P450 ClaT requires the second electron transfer chain component, cytochrome b5, to function. Because b5 has been reported to exhibit substrate specificity in certain specialized metabolites, screening for the most suitable b5 and engineering the electron transfer chain are viable strategies to enhance P450 activity [53].

Finally, given the intrinsic cytotoxicity of these MTs, potential detrimental effects to hosts must also be considered. This challenge is often encountered in the heterologous production of bioactive natural products [54]. Consequently, various mitigation strategies, such as compartmentalization engineering, efflux engineering,

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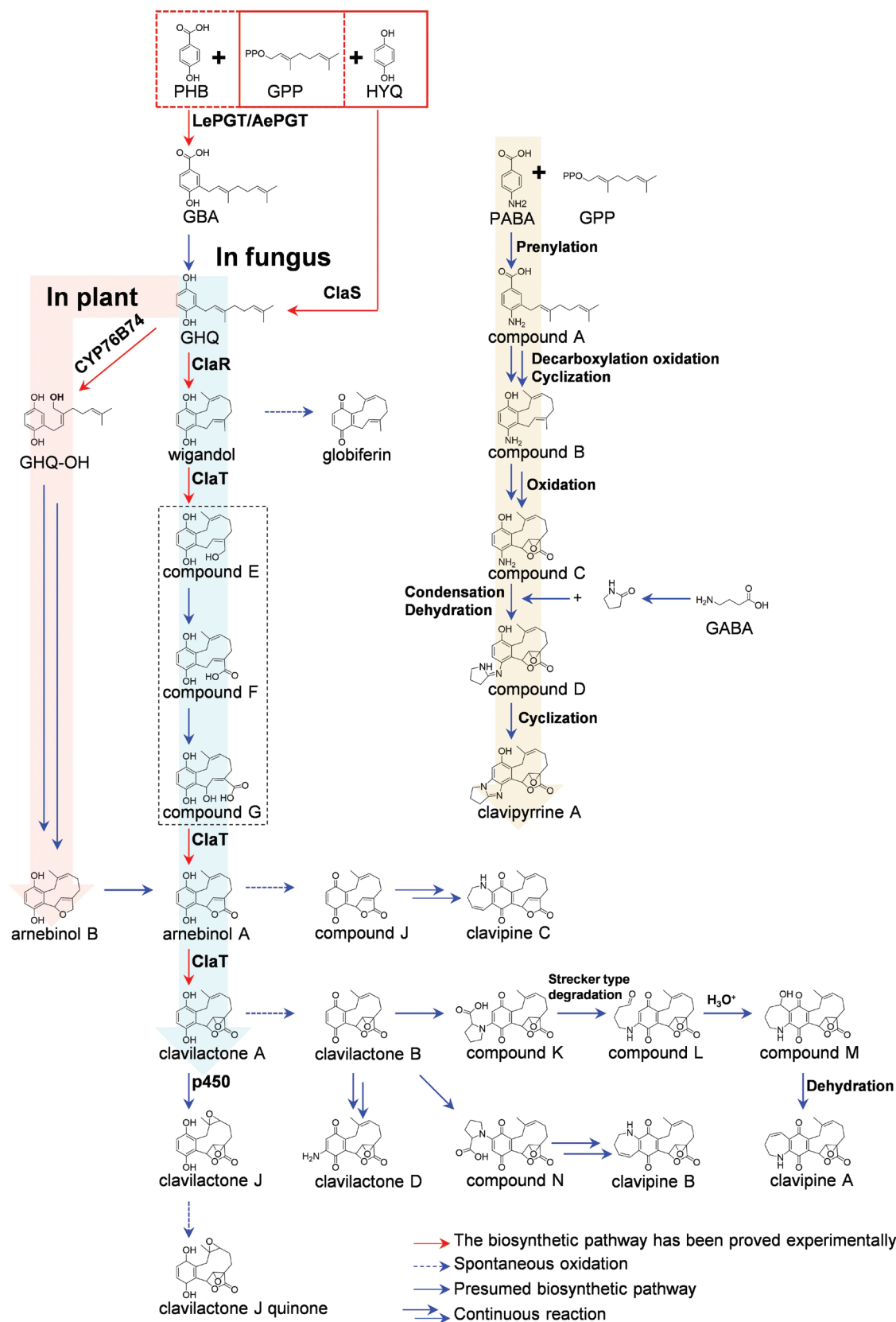


Figure 10 | Reconstruction of the biosynthetic pathway of clavilactones. Red solid arrows indicate experimentally validated steps; blue dashed arrows indicate spontaneous oxidation; blue solid arrows indicate proposed steps; and two arrows indicate multi-step reactions. PHB: *p*-hydroxybenzoic acid; GPP: geranyl diphosphate; HYQ: hydroquinone; GBA: geranyl hydroxybenzoic acid; GHQ: geranyl hydroquinone; PABA: *p*-aminobenzoic acid; GABA: gamma-aminobutyric acid.

adaptive evolution, and dynamic expression regulation, have been used to sustain cell growth and maintain metabolic balance [55-58].

6. PERSPECTIVES AND CONCLUSIONS

This review provided comprehensive insights into the chemical structures, sources, distribution, biological activities, and biosynthetic pathways of benzo-fused ten-membered-ring MTs. We summarized the structural diversity of these compounds and highlighted their significance in natural product chemistry and pharmacological research, particularly their potential in anticancer and antimicrobial therapy. On the basis of a classification of distinct ring architectures, such as the 6/10 bicyclic, 6/10/5 tricyclic, and other complex fused skeletons, we discussed the crucial role of structural modifications and oxidation in determining the biological activities of MTs.

Although substantial progress has been made, such as the complete elucidation of the biosynthetic pathway of clavilactone A, the study of MTs remains in early stages. Many aspects, including the roles of key enzymes, post-synthetic modifications, and regulatory mechanisms, require further investigation. Current research on plant and fungal sources, particularly *C. clavipes* and *A. euchroma*, has underscored their importance as natural reservoirs of MTs, and offered broad prospects for the discovery and utilization of novel compounds. Furthermore, the combination of chemical synthesis and structural modification has not only expanded the accessible sources of MTs but also promoted structural diversification, thereby opening new avenues for drug discovery.

Future research should focus on several key areas, including (1) further elucidation of the biosynthetic mechanisms of MTs, particularly potential branched pathways diverging from shikonin biosynthesis in plant sources; (2) investigation of how different oxidation states and modifications regulate biological activities, to uncover underlying mechanisms and molecular targets; (3) optimization of MT biosynthetic pathways through genome mining and enzyme engineering to enhance yield and structural diversity, thereby enabling improved bioactivity; and (4) exploration of the clinical potential of MTs, particularly for the treatment of cancer, infections, and other diseases.

In conclusion, benzo-fused ten-membered-ring MTs are a structurally complex and pharmacologically promising category of natural products with broad research and application potential. With continued advances in synthetic biology, metabolic engineering, and high-throughput drug screening, these compounds are poised to progress toward clinical development, thus providing a robust foundation for next-generation drug development.

ABBREVIATIONS

MTs: Meroterpenoids; EGFR: Epidermal growth factor receptor; IC₅₀: Half-maximal inhibitory concentration; MIC: Minimum inhibitory concentration; MFC: Minimum fungicidal concentration; NIH: National Institutes of Health.

AUTHOR CONTRIBUTIONS

Wenjie Luo and Ruishan Wang: Investigation, Writing—Original Draft. Danièle Werck-Reichhart and Kanade Tatsumi: Review and Editing. Changzheng Liu: Data Curation. Haodi Sun: Software. Sheng Wang and Lanping Guo: Supervision, Writing—Review & Editing, Project Administration, Funding Acquisition.

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CONFLICT OF INTEREST

The authors declare that they have no financial or personal conflicts of interest that could have influenced the research presented herein.

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