

Supplementary Information

(Schemes S1-S4, Tables S1-S2, Figure S1, Lists S1-S2)

Antibiotics from insect-associated actinobacteria

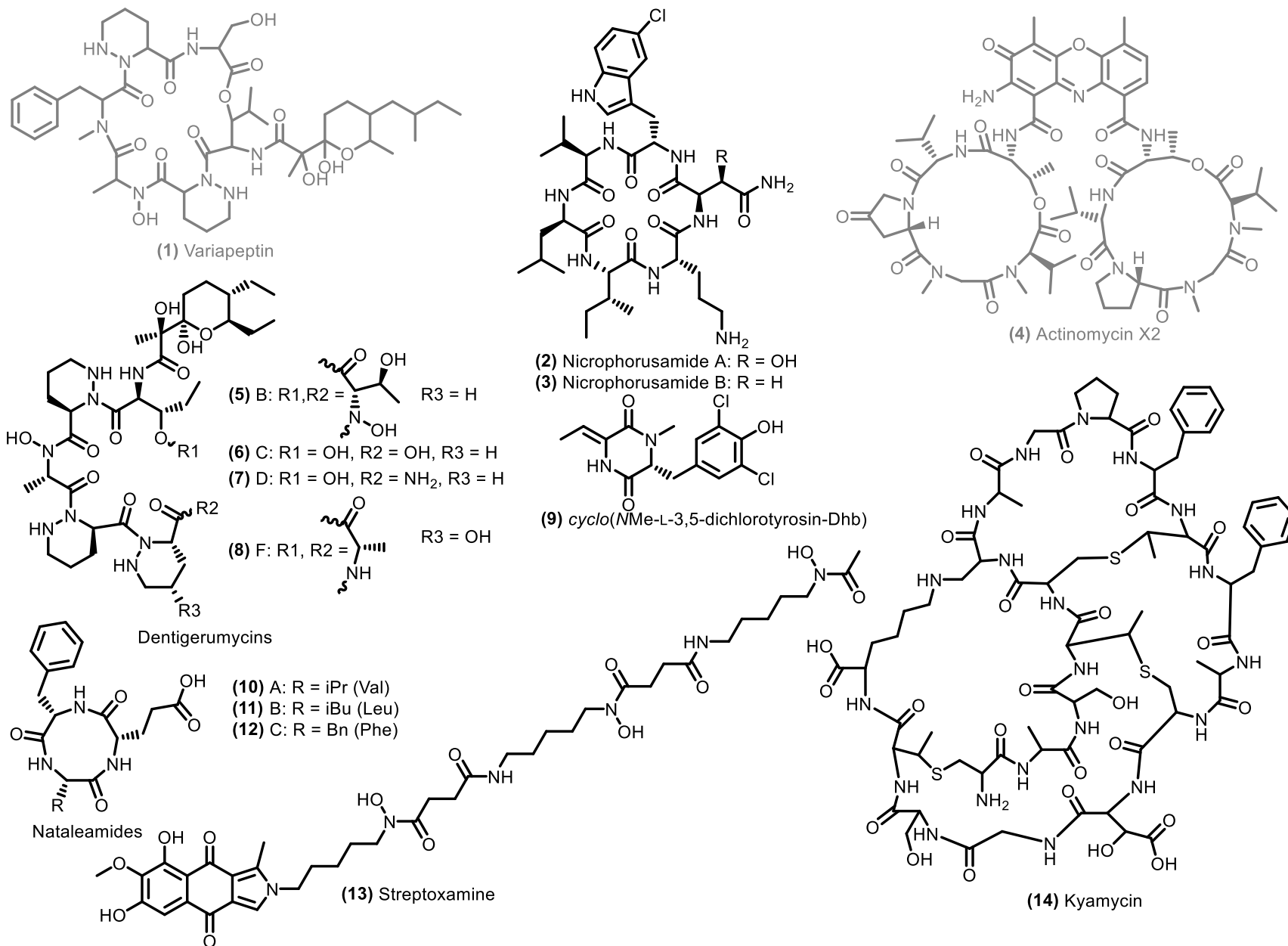
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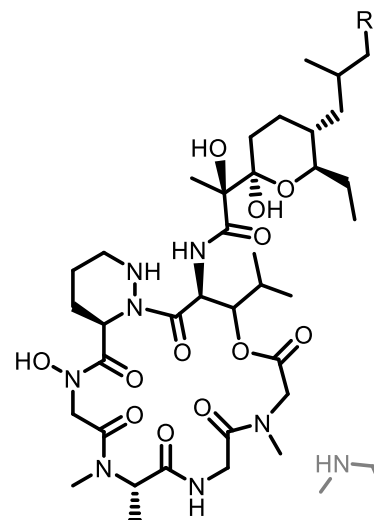
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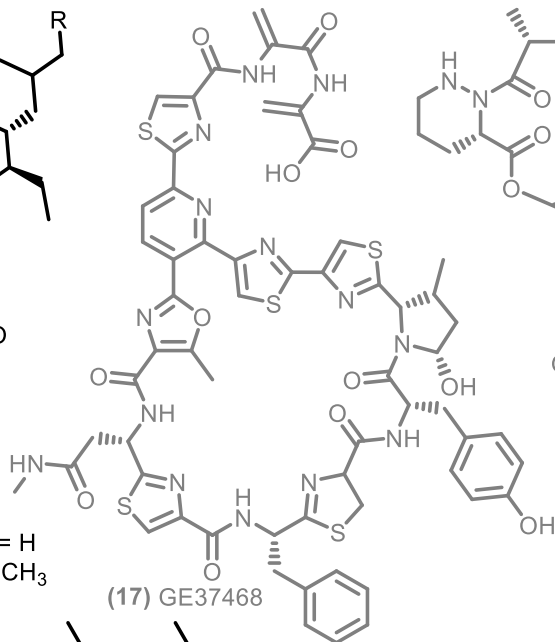
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SCHEME S1. PEPTIDE ANTIBIOTICS

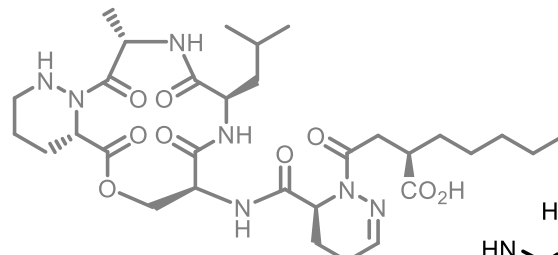




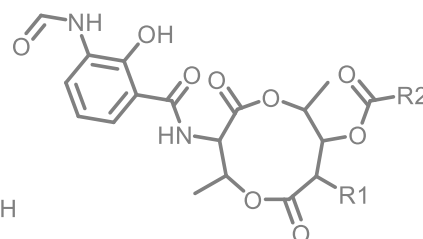
(15) Meliponamycin A: R = H
(16) Meliponamycin B: R = CH₃



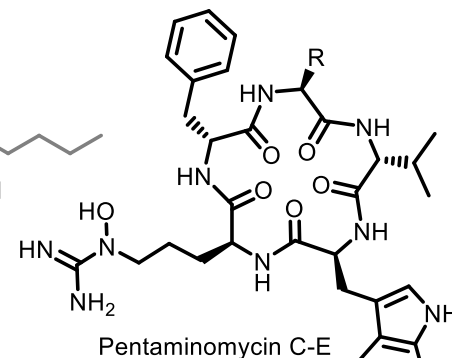
(17) GE37468



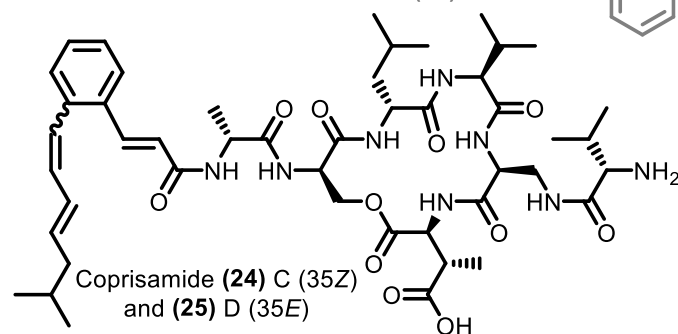
(18) Lydiamycin A



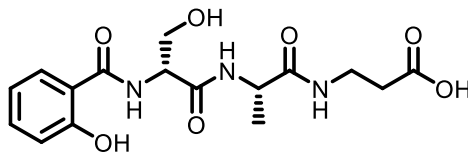
(19) Antimycin A complex
(R1, R2 - alkyls)



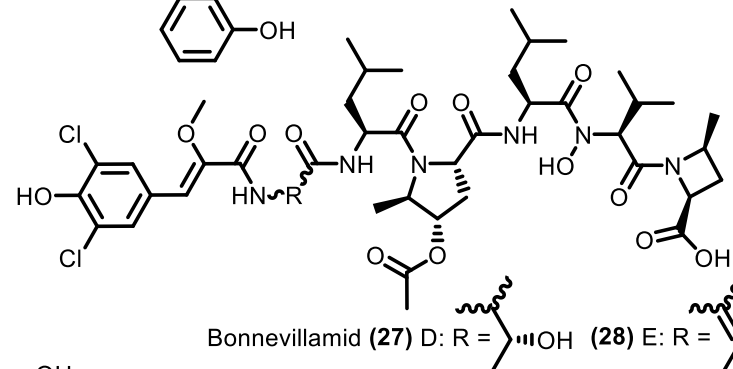
(20) C: R = *i*Bu (Leu)
(21) D: R = *i*Pr (Val)
(22) E: R = Bn (Phe)





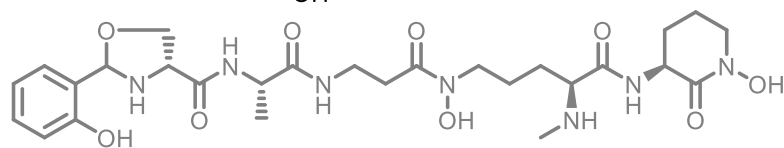
Coprisamide (24) C (35Z)
and (25) D (35E)



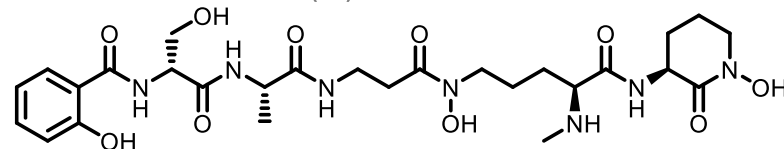
(26) Madurastatin G1



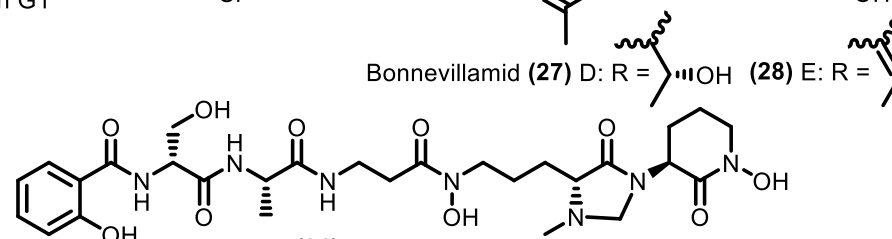
Bonnevilleamid (27) D: R =  OH (28) E: R = 



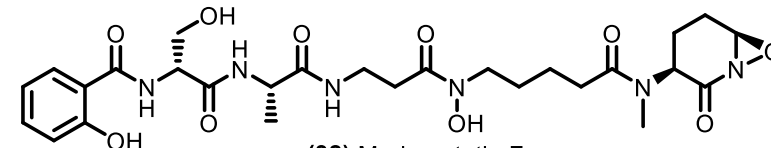
(29) Madurastatin A1



(30) Madurastatin A2

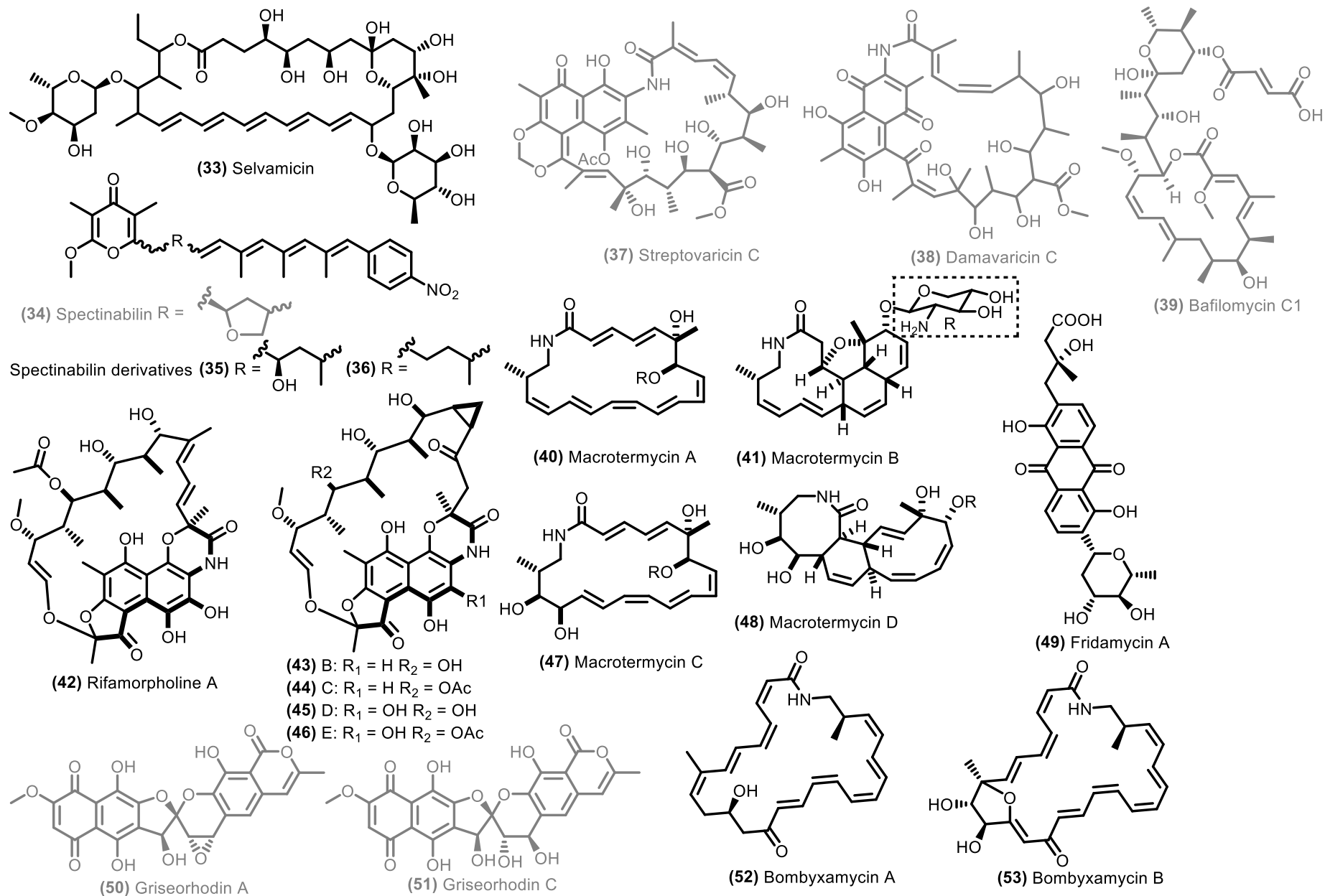


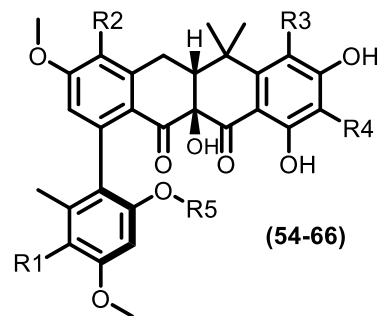
(31) Madurastatin E1



(32) Madurastatin F

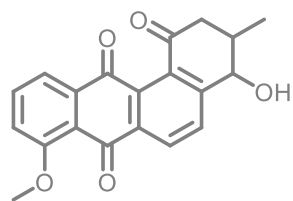
SCHEME S2. POLYKETIDE ANTIBIOTICS



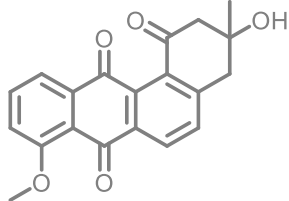


(54-66)

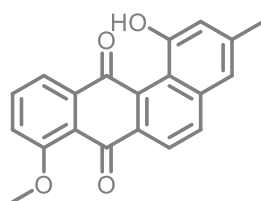
Formicamycin A R1 = H, R2 = Cl, R3 = H, R4 = H, R5 = CH₃
Formicamycin B R1 = Cl, R2 = Cl, R3 = H, R4 = H, R5 = H
Formicamycin C R1 = H, R2 = Cl, R3 = Cl, R4 = H, R5 = CH₃
Formicamycin D R1 = Cl, R2 = Cl, R3 = Cl, R4 = H, R5 = H
Formicamycin E R1 = Cl, R2 = Cl, R3 = Cl, R4 = H, R5 = CH₃
Formicamycin F R1 = Cl, R2 = Cl, R3 = H, R4 = Cl, R5 = CH₃
Formicamycin G R1 = H, R2 = Cl, R3 = H, R4 = Cl, R5 = CH₃
Formicamycin H R1 = Cl, R2 = H, R3 = Cl, R4 = Cl, R5 = CH₃
Formicamycin I R1 = Cl, R2 = Cl, R3 = Cl, R4 = Cl, R5 = H
Formicamycin J R1 = Cl, R2 = Cl, R3 = Cl, R4 = Cl, R5 = CH₃
Formicamycin K R1 = H, R2 = Cl, R3 = Br, R4 = Cl, R5 = CH₃
Formicamycin L R1 = Cl, R2 = Cl, R3 = Br, R4 = Cl, R5 = CH₃
Formicamycin M R1 = H, R2 = Br, R3 = H, R4 = H, R5 = CH₃



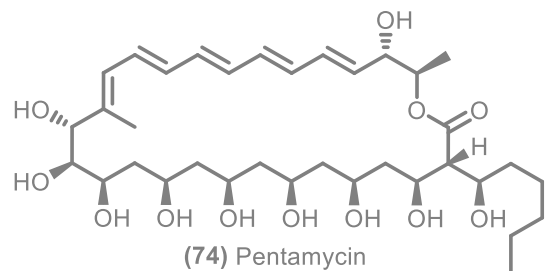
(68) Fugianmycin B



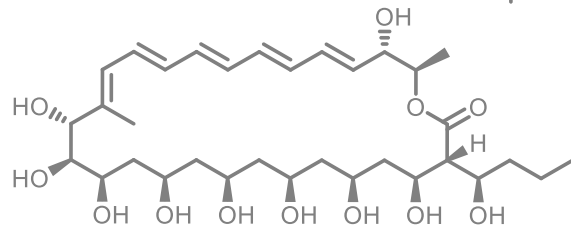
(69) 8-O-Methyltetrangomycin



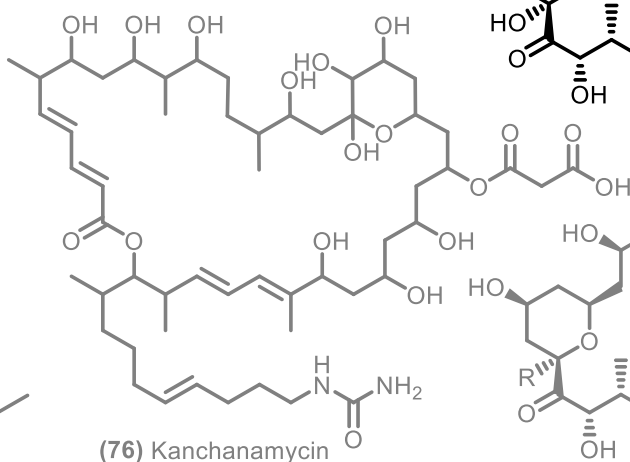
(70) 8-O-Methyltetrangulol



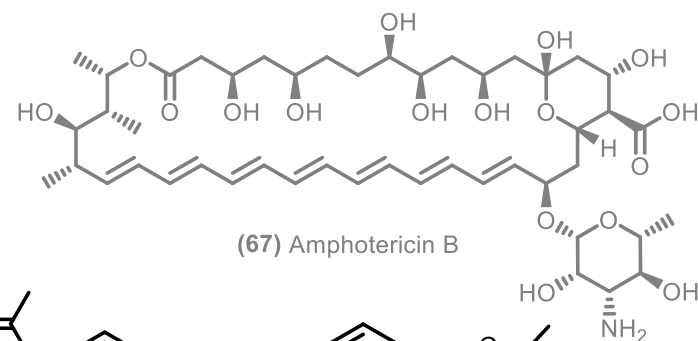
(74) Pentamycin



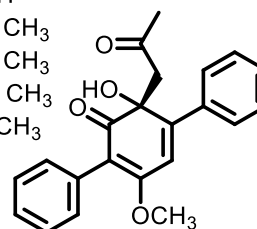
(75) 1',14-dihydroxyisochainin



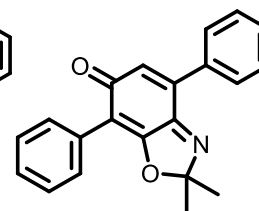
(76) Kanchanamycin



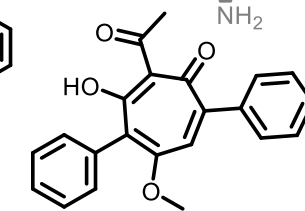
(67) Amphotericin B



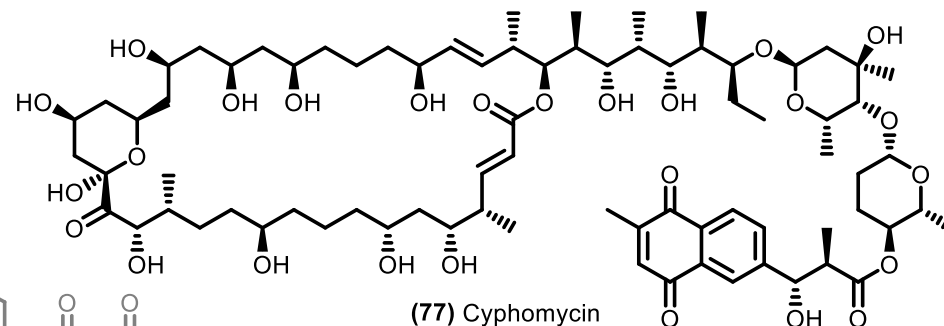
(71) Streptantibin A



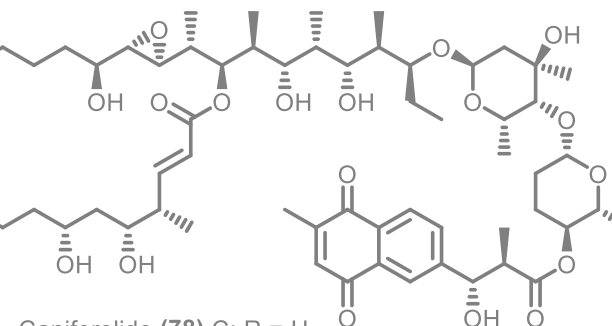
(72) Streptantibin B



(73) Streptantibin C

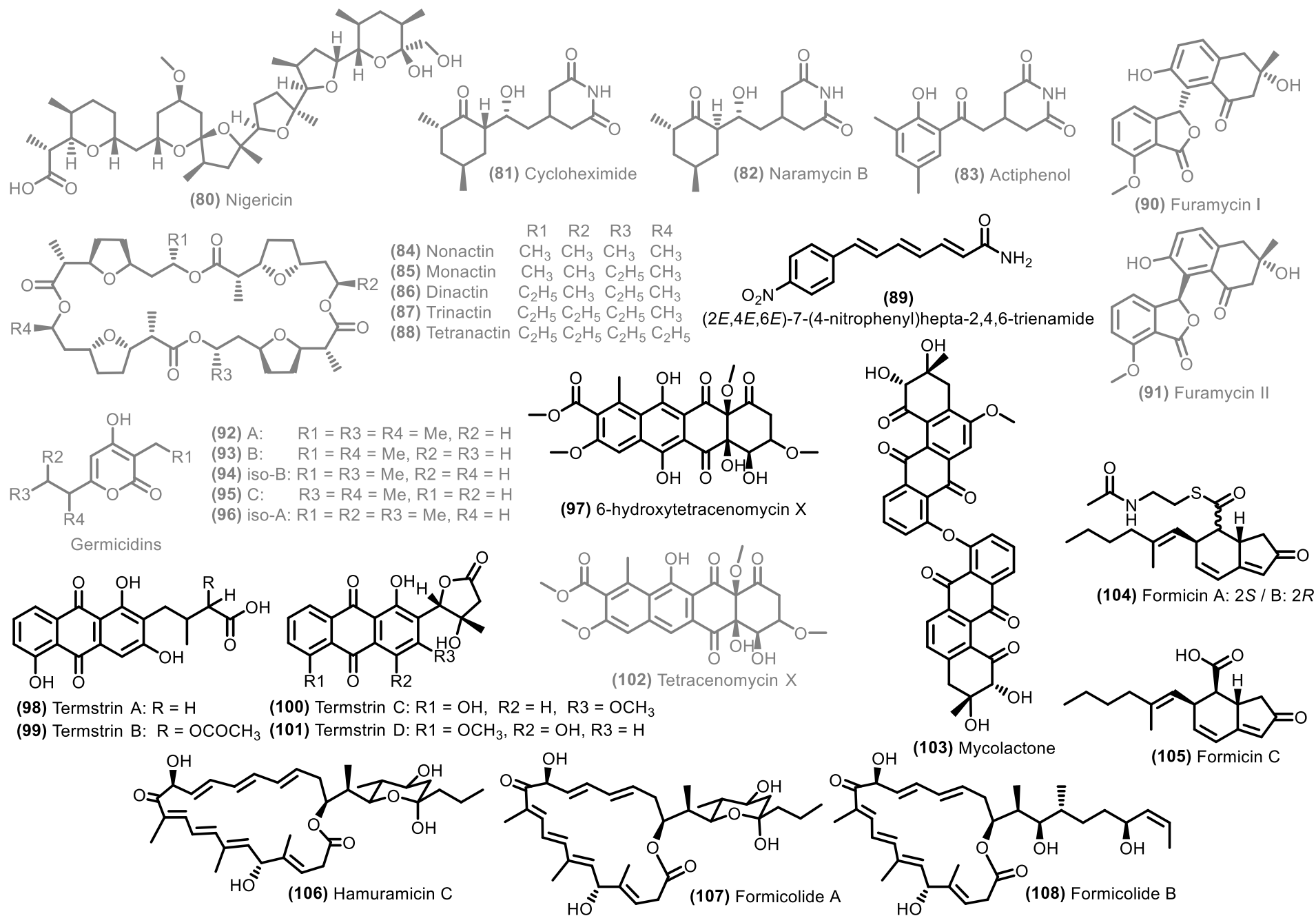


(77) Cyphomycin

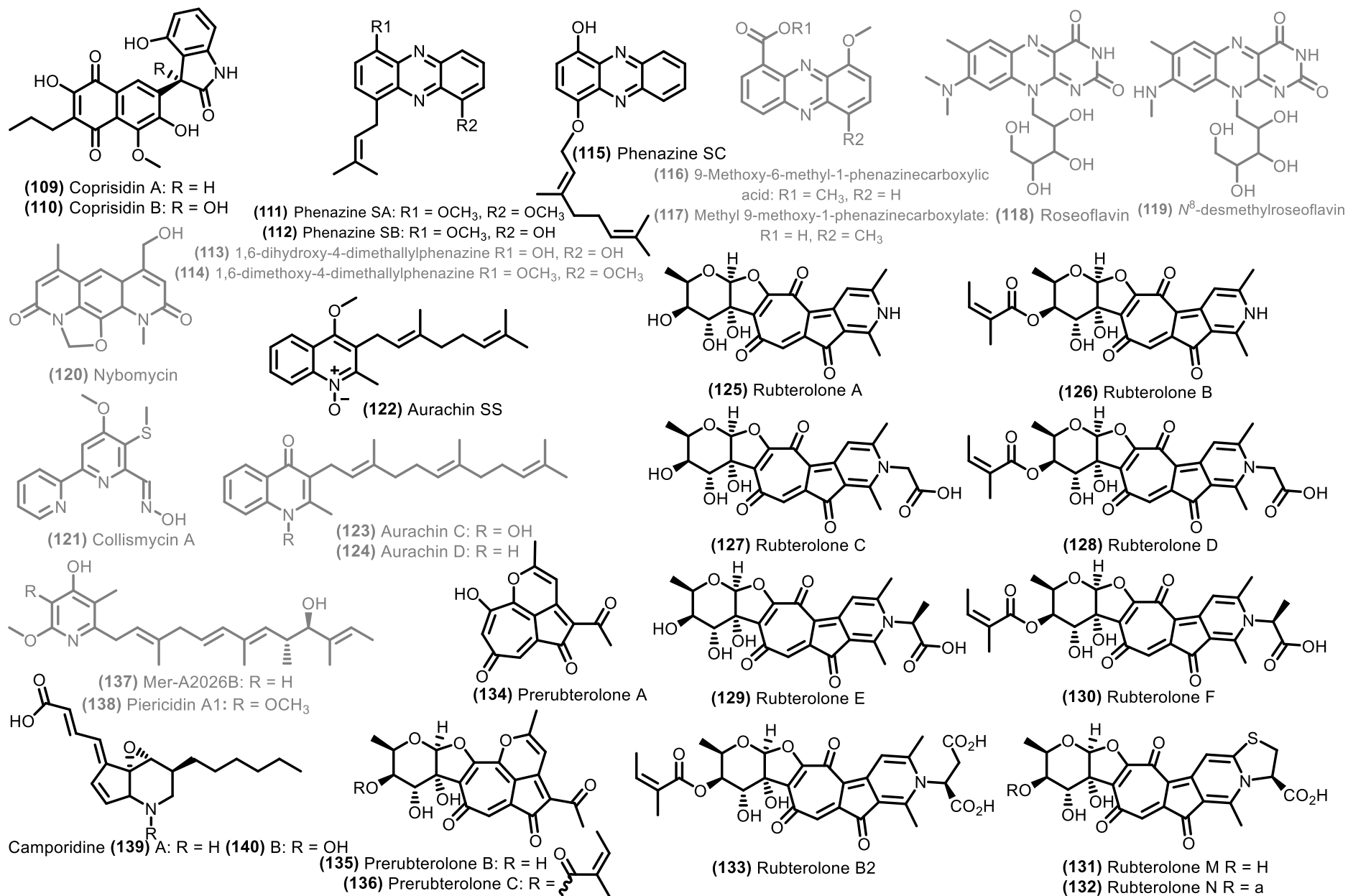


Caniferolide (78) C: R = H

(79) GT-35: R = OH



SCHEME S3. ALKALOID ANTIBIOTICS



SCHEME S4. OTHER ANTIBIOTICS

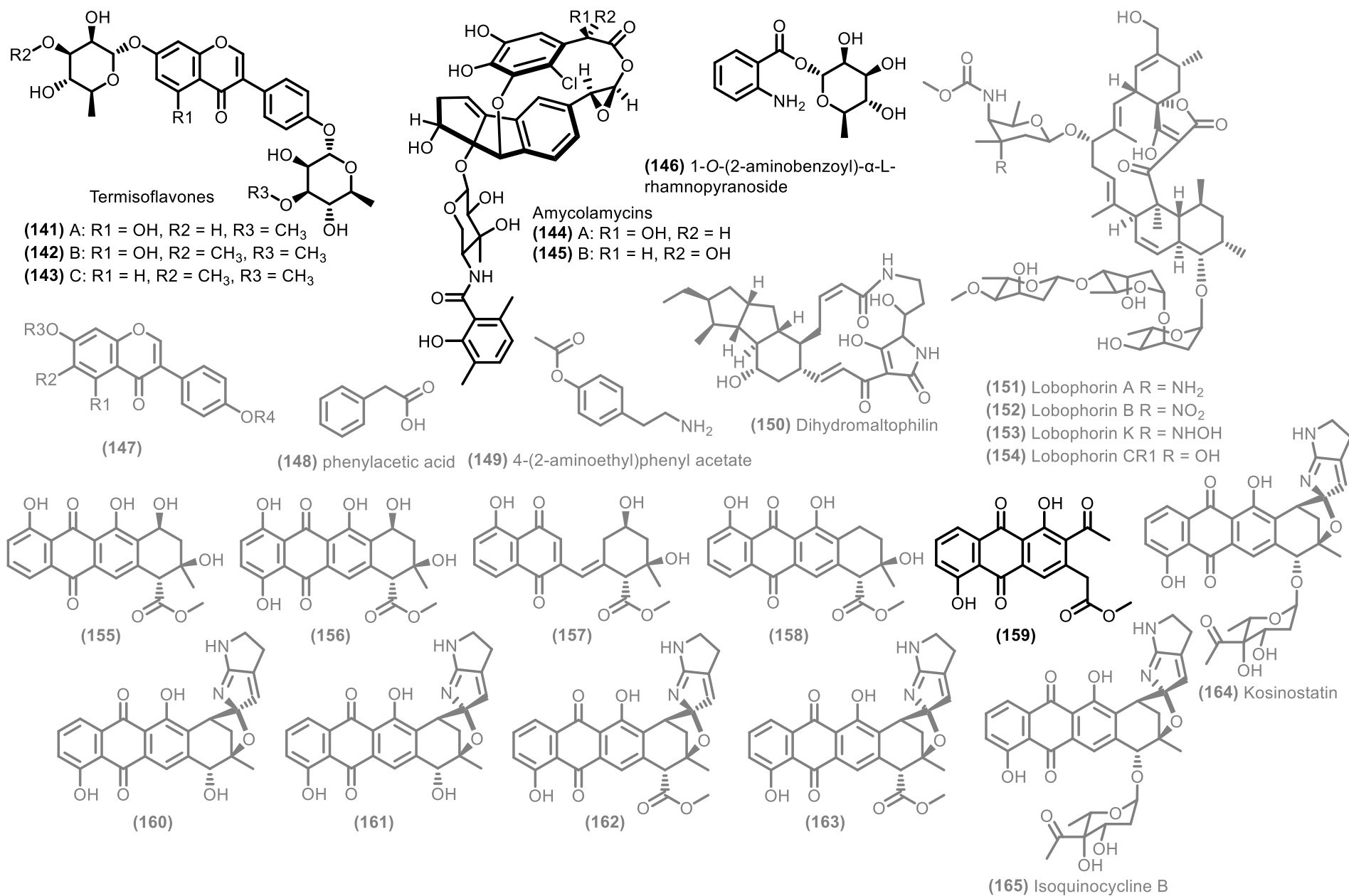


TABLE S1. SELECTED PUBLICATIONS

* See Table S2 for details

| Structure | Actinobacteria | Insect host | Isolation medium* | Activity/Ecological role | Location | Reference |
|---------------------------|---|--|--|---|--|-----------|
| (97), (102) | <i>Amycolatopsis camponoti</i> A23 | ant <i>Camponotus vagus</i> (worker) | AI (nystatin 250 mg, nalidixic acid 10 mg) | Tetracenomycin X and its new congener 6-hydroxytetracenomycin X have antimicrobial and cytotoxic activity. | Kasimovsky District (N 55.01138, E 41.73078), Ryazan region, Russia | [1] |
| (106) | <i>Streptomyces</i> sp. MBP16 | wasp <i>Vespa crabro flavofasciata</i> (gut) | A1 | Hamuramicin C demonstrated significant inhibitory activity against diverse human cancer cell lines (HCT116, A549, SNU-638, SK-HEP-1, and MDA-MB-231). | Gwanak Mountain, Seoul, Republic of Korea | [2] |
| no compounds | <i>Brachybacterium phenoliresistens</i> MO and <i>Microbacterium</i> sp. | ant <i>Messor orientalis</i> | G1 (160 mg/L cycloheximide, 50 mg/L of nalidixic acid) | Antifungal activity against <i>Peronophythora litchi</i> , <i>Rhizoctonia solani</i> , <i>Colletotrichum siamense</i> . | Wujiaqu, Xinjiang, China | [3] |
| no compounds | <i>Streptomyces</i> sp. W7 | undefined termites | G1 (50 mg/L of bichromate) | <i>Streptomyces</i> sp. W7 had strong inhibitory activity against plant pathogenic fungi <i>C. musae</i> , <i>C. cassiicola</i> , <i>P. aphanidermatum</i> , with strong antibacterial persistence and antibacterial stability. | Tropical plants garden of Chinese Academy of Tropical Agricultural Sciences in Haikou, Hainan, China | [4] |
| (26), (29-32) | <i>Actinomadura</i> sp. RB99 (in co-culture with <i>Pseudoxylaria</i> sp. X802) | (previously described) | (previously described) | Madurastatins act as a siderophores. | (previously described) | [5] |
| no compounds | <i>Streptomyces</i> sp. ACZ2-27 and ASC3-2 | bee <i>Apis andreniformis</i> | Cz and SCN (nalidixic acid and nystatin 25 mg) | Streptomycetes show antimicrobial activity against black rot pathogen (<i>Xanthomonas campestris</i> pv. <i>campestris</i> , by streak method). | The local villages in Mae-rim district, Chiang Mai province, Thailand | [6] |
| NH ₃ (ammonia) | <i>Streptomyces</i> sp. Av25_4 | ant <i>Acromyrmex volcanus</i> (cuticle) | AI | <i>Streptomyces</i> sp. Av25_4 overproduces ammonia (up to 8 mM) which completely inhibited the growth of <i>E. weberi</i> due to its strong basic pH. Additionally, other symbionts from different <i>Acromyrmex</i> ants inhibited <i>E. weberi</i> by production of ammonia. The waste of ca. one third of | Gamboa, Panama | [7] |

| | | | | | | |
|----------|---------------------------------|--|--|--|---|------|
| | | | | <i>Acomyrnex</i> and <i>Atta</i> leaf-cutting ant colonies was strongly basic due to ammonia (up to ca. 8 mM) suggesting its role in nest hygiene. <i>Escovopsis</i> is sensitive to ammonia in contrast to the garden fungus <i>L. gongylophorus</i> . | | |
| (27, 28) | <i>Streptomyces</i> sp. UTZ13 | beetle <i>Nicrophorus concolor</i> (exoskeleton) | A1+C | Bonnevillamides D and E reversed the fibril formation by inducing the monomerization of amyloid- β aggregates (anti-Alzheimer's activity). | Maebong Mountain, Seoul, Republic of Korea | [8] |
| (24, 25) | <i>Micromonospora</i> sp. UTJ3 | beetle <i>Silpha perforata</i> (gut) | PD | Coprisamides have weak activity against the <i>Mycobacterium tuberculosis</i> mc2 6230 strain and induce quinone reductase (QR) activity | Gwanak Mountain, Seoul, Republic of Korea | [9] |
| (74, 75) | <i>Streptomyces</i> sp. HF10 | termite <i>Macrotermes barneyi</i> (foregut) | PY-CMC | Two pentene macrolides (pentamycin and 1·14- dihydroxyisochainin) were firstly purified from <i>Streptomyces</i> strain HF10, both exhibiting higher activity against <i>Xylaria</i> sp. and <i>M. anisopliae</i> than cultivar <i>Termitomyces</i> . These results indicate that polyene-producing <i>Streptomyces</i> from the guts of <i>M. barneyi</i> have strong inhibition to competitor fungus and polyenes contribute to inhibitory effects on <i>Xylaria</i> sp. | Hunan (N 26.5800, E 112.9600), China | [10] |
| (103) | <i>Amycolatopsis</i> sp. HCa1 | grasshopper <i>Oxya chinensis</i> (gut) | no data | Mycolactone did not exhibited cytotoxic effects against the tested human carcinoma cell lines (cervical cancer cell line HeLa, gastric adenocarcinoma cell line SGC-7901 and lung adenocarcinoma cell line SPC-A-1) at concentration of 100 μ M. | Nanchang, Jiangxi Province, China | [11] |
| (77, 79) | <i>Streptomyces</i> sp. ISID311 | ant <i>Cyphomyrmex</i> sp. | Ch (40 mg nystatin, 50 mg cycloheximide) | Compounds displayed high antagonism against different strains of <i>Escovopsis</i> sp., pathogen fungi specialized to the fungus-growing ant system. Compounds also exhibited potent antiprotozoal activity against intracellular amastigotes of the human parasite <i>Leishmania donovani</i> . | campus of the University of São Paulo – Ribeirão Preto (S 21.167889, W 47.847083), Brazil | [12] |
| (84-88) | <i>Streptomyces</i> sp. M54 | wasp <i>Polybia plebeja</i> (pupae) | Ch | Growth inhibition bioassays show that this bacterium produces antimicrobial | Las Brisas Nature Reserve, Limón | [13] |

| | | | | | | |
|------------|--------------------------------------|---|---------------------------|---|---|------|
| | | | | compounds that are active against <i>Hirsutella citriformis</i> , a natural fungal enemy of its host, and the human pathogens <i>Staphylococcus aureus</i> and <i>Candida albicans</i> . Analyses through TLC-bioautography, LC–MS/MS and NMR allowed the identification of five macrocyclic ionophore antibiotics, with previously reported antibacterial, antitumor and antiviral properties. | Province, Costa Rica | |
| (118, 119) | <i>Streptomyces davaonensis</i> YH01 | termite <i>Odontotermes formosanus</i> (queen, cuticle) | G1 (100 mg cycloheximide) | Roseoflavin and its analog were isolated. The roseoflavin showed strong inhibition activities against gram-positive bacteria. | campus of Zhejiang Normal University (N 29.004825, E 119.498567), Jinhua, Zhejiang, China | [14] |
| (23) | <i>Pseudonocardia</i> spp. | ants Attini (<i>Trachymyrmex</i> , <i>Apterostigma</i> , <i>Acromyrmex</i>) | no data | A large systematic study of Brazilian nests led to the discovery of the widespread production of a potent but overlooked antifungal agent, which we named attinimicin, by nearly two-thirds of all <i>Pseudonocardia</i> strains from multiple sites in Brazil. Attinimicin shows iron-dependent antifungal activity against specific environmental fungal parasites but no activity against the fungal cultivar. Attinimicin showed potent <i>in vivo</i> activity in a mouse <i>Candida albicans</i> infection model comparable to clinically used azole-containing antifungals. <i>In situ</i> detection of attinimicin in both ant nests and on worker ants supports an ecological role for attinimicin in protecting the fungal cultivar from pathogens. The geographic spread of the attinimicin biosynthetic gene cluster in Brazilian <i>Pseudonocardia</i> spp. marks attinimicin as the first specialized metabolite from ant-associated bacteria with broad geographic distribution. | Anavilhanas National Park (Amazonas) and Itatiaia National Park (Rio de Janeiro), Brazil | [15] |
| (8) | <i>Pseudonocardia</i> sp. | ants <i>Trachymyrmex</i> sp. | no data | Dentigerumycin F was active against | Ducke Reserve, | [16] |

| | | | | | | |
|------------------------------|---|---|---|--|---|------|
| | ICBG1122 | | | <i>Escovopsis</i> sp. and <i>Candida albicans</i> K1 | Amazon Region, Brazil | |
| (104, 105) | <i>Streptomyces</i> sp. SFA33 | ant <i>Formica yessensis</i> | mK | Formicins A–C were discovered. Formicin A inhibited the growth of human triple-negative breast cancer cells. | Cheongnyang Mountain, Gwangju-si, Gyeonggi-do, Republic of Korea | [17] |
| no compounds (only putative) | <i>Streptomyces</i> spp. | beetle <i>Cerambyx welensii</i> (larvae, gut) | ISP2 and R2YE (nalidixic acid 25 mg, cycloheximide 50 mg) | 24 actinomycetes strains isolated from the intestinal tract and feces from larvae of the xylophagous coleopteran. 14 of the isolates produce antimicrobial molecules against the gram-positive bacteria <i>Micrococcus luteus</i> . | La Serrana (N 39.023, W 6.638722), Mérida, Spain | [18] |
| (19) | <i>Streptomyces albidoflavus</i> A10 | ant <i>Camponotus vagus</i> | AI (nystatin 250 mg, nalidixic acid 10 mg) | Strain A10 was found to exhibit pronounced antifungal properties, including activity against entomopathogenic fungi, especially against <i>Conidiobolus coronatus</i> and <i>Beauveria bassiana</i> . The antifungal substances were isolated and identified as antimycin-type compounds. | Kasimovsky District (N 55.01138, E 41.73078), Ryazan region, Russia | [19] |
| (20-22) | <i>Streptomyces</i> sp. GG23 | beetle <i>Tenebrio molitor</i> (gut) | SCN | Pentaminomycins C–E were isolated from the culture. Pentaminomycins C and D showed significant autophagy-inducing activities and were cytoprotective against oxidative stress in vitro. | Seoul Grand Park, Gwacheon-si, Gyeonggi Province, Republic of Korea | [20] |
| (18) | <i>Streptomyces</i> sp. GG23 (previously described) | (previously described) | (previously described) | Lydiamycin A displayed weak antituberculosis activity in vitro | (previously described) | [21] |
| (17) | <i>Pseudonocardia</i> spp. | ant <i>Trachymyrmex septentrionalis</i> (laterocervical plates) | Ch (nystatin 30 mg) | Among nine <i>Pseudonocardia</i> strain isolates six were found to produce thiopeptide antibiotic GE37468 (formerly known as an inhibitor of Gram-positive bacteria, e.g. <i>S.aureus</i> and <i>E.faecalis</i>) thus antagonizing their competitors, other strains of ant-associated <i>Pseudonocardia</i> (agar diffusion assay). The compound showed no inhibitory activity on strains <i>Candida albicans</i> SC5314 and <i>Trichoderma harzianum</i> T22, and neither on <i>Escovopsis</i> sp. | Centereach, New York, USA | [22] |
| (107, 108) | <i>Streptomyces</i> sp. BA01 | ant <i>Formica yessensis</i> (gut) | P (cycloheximide 100 mg) | Formicolides A and B showed antioxidative (quinone reductase assay) and | Namhansanseong, Gyeonggi-do, Republic | [23] |

| | | | | | | |
|----------------|--|--|---|---|---|------|
| | | | | antiangiogenic (inhibition of capillary tube formation in human umbilical vein endothelial cells) activity, along with no anti-inflammatory activity (inducible nitric oxide synthase assay). | of Korea | |
| (15, 16) | <i>Streptomyces</i> sp. ICBG1318 | bee <i>Melipona scutellaris</i> (nurse bee) | Ch (cycloheximide 50 mg, nystatin 32 mg) | Meliponamycins A,B showed strong activity against the entomopathogen <i>Paenibacillus larvae</i> and human pathogens <i>Staphylococcus aureus</i> and <i>Leishmania infantum</i> . | Ribeirão Preto (S 21.150000, W 47.850000), São Paulo, Brazil | [24] |
| (98-101) | <i>Streptomyces</i> sp. BYF63 | termite <i>Odontotermes formosanus</i> | M3 (nystatin 75 mg, potassium dichromate 50 mg, nalidixic acid 25 mg) | Termistrins A, B and D exhibited antibacterial effect against <i>S. aureus</i> . Termistrin A exhibited moderate cytotoxic activity against the tumor cell lines A375 and MGC-803. | Jiangyin, Jiangsu, China | [25] |
| (89-91) | <i>Streptomyces</i> sp. 1H-XA2 | ant <i>Camponotus japonicus</i> (cuticle) | XA | Furamycins I and II have been reported to show strong antifungal activity. Polyene compound did not show any antifungal or antibacterial activity. Previous study showed that its structural analogs, trichostatin A and BL1521, could inhibit proliferation and induce apoptosis in neuroblastoma cells. | campus of Northeast Agriculture University (N 45.73333, E 126.71667), Harbin, Heilongjiang, China | [26] |
| (4), (121) | <i>Streptomyces globisporus</i> WA5-2-37 | cockroach <i>Periplaneta americana</i> (gut) | G1 | Actinomycin X2 and collismycin A showed strong inhibition of MRSA | Guangdong Provincial Center for Disease Control and Prevention, China | [27] |
| (81-83), (150) | <i>Streptomyces griseus</i> XylebKG-1 | beetle <i>Xyleborus saxesenii</i> (female) | Ch (cycloheximide 50 mg, nystatin 30 mg) | In this study we consistently isolated a single <i>Streptomyces</i> morphotype and phylotype from both <i>X. saxesenii</i> and <i>X. affinis</i> that inhibited the growth of the parasitic fungus <i>Nectria</i> sp., but not the mutualistic <i>Raffaelea sulphurea</i> , likely via the production of cycloheximide. Its ubiquity suggests that XylebKG-1 may be a defensive mutualist of these ambrosia beetles that inhibits the growth of all but a few fungi, including its mutualistic fungal food source. Dihydromaltophilin similarly | Southern Research Station in Pineville (N 31.333, W 92.400), Louisiana, USA | [28] |

| | | | | | | |
|---------------------------|--|--|--|---|--|------|
| | | | | inhibited both <i>Nectria</i> sp. and <i>R. sulphurea</i> . Naramycin B and Actiphenol were non-inhibitory under all conditions tested. | | |
| (92-96), (148, 149) | <i>Streptomyces</i> sp. N1508.10 | Undefined mud dauber wasp (cuticle) | G1 (6 mg potassium dichromate, 20 mg nalidixic acid) | Hexokinase II inhibitory activities of the compounds were evaluated for the first time. As a result, phenylacetic acid, 4-(2-aminoethyl)phenyl acetate, germicidin B, isogermicidin A, and germicidin C displayed significant inhibitory activity against hexokinase II. | Weihai, Shandong Province, China | [29] |
| (14) | <i>Saccharopolyspora</i> sp. KY21 | ant <i>Tetraponera</i> <i>penzigi</i> (cuticle) | no data | Kyamycin has a weak activity against <i>B. subtilis</i> EC1524 (MIC 128 ug/ml) | Ngong Hills (S 1.4491,E 36.6393), Kenya | [30] |
| (120) | <i>Streptomyces</i> sp. Pe6 | ant <i>Camponotus vagus</i> | G1 (nalidixic acid 10 mg, nystatin 250 mg) | Nybomycin has cytotoxic activity against human cell lines. | Bryansk Forest Nature State Biosphere Reserve (N 52.440009, E 34.126288), Bryansk region, Russia | [31] |
| S ₈ (sulphur) | <i>Streptomyces</i> <i>chartreusis</i> ICBG323 | ant <i>Mycocepurus</i> <i>goeldii</i> (exoskeleton of winged male) | Ch (cycloheximide 50 mg, nystatin 40 mg) | Sulphur has antifungal activity against <i>Escovopsis</i> sp. | Ribeirão Preto (W 47.848889, S 21.163889), São Paulo state, Brazil | [32] |
| (151-165) | <i>Streptomyces</i> sp. ICBG1323 <i>Micromonospora</i> sp. ICBG1321 | bee <i>Mellipona</i> <i>scutellaris</i> | Ch (cycloheximide 50 mg, nystatin 32 mg) | Lobophorins were active against the specialized pathogen of honey bees <i>Paenibacillus larvae</i> | Ribeirão Preto (S 21.150000, W 47.850000), São Paulo, Brazil | [33] |
| (80), (86), (137, 138) | <i>Streptomyces</i> sp. ICBG292 <i>Streptomyces</i> sp. ICBG233 <i>Streptomyces puniceus</i> ICBG378 (=AB10, previously described) | ants <i>Cyphomyrmex</i> sp. (workers, exoskeleton); <i>Atta</i> <i>sexdens</i> (workers, exoskeleton); <i>Atta</i> <i>rugosus rugosus</i> (previously described) | Ch (nystatin 40 mg, cycloheximide 50 mg) | Nigericin presented high activity against intracellular amastigotes of <i>L. donovani</i> (IC ₅₀ 0.129 ± 0.008 µM). <i>Streptomyces puniceus</i> ICBG378, isolated from workers of <i>Acromyrmex rugosus rugosus</i> , produced dinactin with potent anti- <i>L. donovani</i> activity against intracellular amastigotes (IC ₅₀ 0.018 ± 0.003 µM). All compounds were also active against some <i>Escovopsis</i> strains. Piericidins were also detected in ants' extracts by mass spectrometry, suggesting they are produced in the natural environment as defensive compounds | campus of the University of São Paulo – Ribeirão Preto (S 21.167889,W 47.847083), Brazil | [34] |

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| | | | | involved in the symbiotic interaction. | | |
| (52, 53) | <i>Streptomyces</i> sp. SD53 | silkworm <i>Bombyx mori</i> (larvae, gut) | A1+C (cycloheximide 100 mg) | Bombyxamycin A showed significant antibacterial and antiproliferative effects. | Boeun-eup, Boeun-gun, Chungcheongbuk-do, Republic of Korea | [35] |
| (49) | <i>Actinomadura</i> sp. RB99 (previously described) | (previously described) | (previously described) | Fridamycin A induced glucose uptake in 3T3-L1 cells by activating the AMP-activated protein kinase (AMPK) signaling pathway but did not affect adipocyte differentiation | (previously described) | [36] |
| (77) | <i>Streptomyces</i> sp. ISID311 | ant <i>Cyphomyrmex</i> sp. | HV or Ch (no additional data) (nystatin 20 mg, cycloheximide 10 mg) | Cyphomycin shows potent in vitro activity against both the ecologically relevant fungus-growing ant pathogen <i>Escovopsis</i> sp. and the resistant human pathogens <i>Aspergillus fumigatus</i> 11628 (triazole resistance), <i>Candida glabrata</i> 4720 (echinocandin resistance), and <i>C. auris</i> B11211 (echinocandin, triazole, and amphotericin B resistance) | no data | [37] |
| no compounds | <i>Streptomyces</i> spp. | bee <i>Tetragonisca angustula</i> | ISP3 and Ch agar (nalidixic acid 25 mg, cycloheximide or nystatin 50 mg) | Isolates showed antibacterial and antifungal activity. | La Selva Biological Station, Sarapiquí, Costa Rica | [38] |
| no compounds | <i>Streptomyces</i> spp. and <i>Microbacterium</i> sp. | ant <i>Acromyrmex coronatus</i> | SM3, TS, ISP2, ISP4, Ch (cycloheximide 50 mg, nalidixic acid 10 mg, novobiocin 10 mg, nystatin 50 mg) | Isolates showed insecticidal activity (against <i>Spodoptera frugiperda</i> larvae) | Escola Superior de Agricultura “Luiz de Queiroz” in Piracicaba, São Paulo, Brazil | [39] |
| (71-73) | <i>Streptomyces</i> sp. N1510.2 | wasp <i>Sceliphron madraspatanum</i> (larvae) | G1 (potassium dichromate 100 mg, nalidixic acid 20 mg) | Streptantibins A–C inhibited hexokinase II (HK2) activity and displayed antiproliferative activity against hepatoma carcinoma cells HepG-2, SMMC-7721 and plc-prf-5. | Dezhou, Shandong, China | [40] |
| (139-140) | <i>Streptomyces</i> sp. STA1 | ant <i>Camponotus kiusiuensis</i> (gut) | P (cycloheximide 100 mg) | Camporidine A displayed antimetastatic activity by suppression of cell invasion against the metastatic breast cancer cell line MDA-MB-231 and showed an anti-inflammatory effect by suppressing nitric oxide production induced by | Gwanak Mountain, Seoul, Republic of Korea, | [41] |

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| | | | | lipopolysaccharide. | | |
| (111-117) | <i>Streptomyces</i> sp. NA04227 (previously described) | (previously described) | (previously described) | Compounds exhibited moderate AchE inhibitory activities, and Phenazine SC showed antimicrobial activities against <i>M. luteus</i> . | (previously described) | [42] |
| (10-12) | <i>Actinomadura</i> sp. RB99 | termite <i>Macrotermes natalensis</i> (worker, body surface) | Ch | Nataleamide C exhibited significant inhibitory effects on 3-isobutyl-1-methylxanthine (IBMX)-induced melanin production | Pretoria (S 25.729417, E 28.235806), South Africa | [43] |
| (68-70) | <i>Streptomyces capitiformicae</i> sp. 1H-SSA4 | ant <i>Camponotus japonicus</i> (head) | SSA (cycloheximide 50 mg, nalidixic acid 20 mg) | Angucycline antibiotics (8- <i>O</i> -methyltetrangulol, 8- <i>O</i> -methyltetrangomycin, fugianmycin B) exhibited activities against bacteria and cancer cells | Northeast Agricultural University, Harbin, Heilongjiang, China | [44] |
| (146) | <i>Streptomyces</i> sp. RB1 (previously described) | (previously described) | (previously described) | 1- <i>O</i> -(2-aminobenzoyl)- α -L-rhamnopyranoside ameliorated cisplatin-induced cytotoxicity to 80% of the control value at 25 μ M by blocking the MAPK signaling cascade. | (previously described) | [45] |
| (13) | <i>Streptomyces</i> sp. HKHCa2 | grasshopper <i>Oxya chinensis</i> | no data | Streptoxamine showed weak antibacterial activity against the gram-positive bacteria, <i>Staphylococcus aureus</i> and <i>Mycobacterium smegmatis</i> . | Haikou, China | [46] |
| no compounds | <i>Streptomyces lasii</i> 5H-CA11 | ant <i>Lasius flavus</i> (head) | Ch (cycloheximide 50 mg, nalidixic acid 20 mg) | Strain exhibited antifungal activity | Northeast Agriculture University, Harbin, Heilongjiang, China | [47] |
| (131-136) | <i>Actinomadura rubteroloni</i> RB29 (= <i>Actinomadura</i> sp.5-2) (previously described) | (previously described) | (previously described) | Rubterolones and related compounds have anti-inflammatory activity | (previously described) | [48] |
| (9) | <i>Actinomadura rubteroloni</i> RB29 (= <i>Actinomadura</i> sp.5-2) (previously described) | (previously described) | (previously described) | cyclo(NMe-L-3,5-dichlorotyrosin-Dhb) has antibacterial activity | (previously described) | [49] |
| (125-130) | <i>Actinomadura</i> sp. 5-2 (= <i>Actinomadura rubteroloni</i> RB29) | termite <i>Macrotermes natalensis</i> (gut) | Ch or MC (cycloheximide 50 mg) (no additional data) | Strain 5-2 (RB29) displayed weak antimicrobial activity against <i>B. subtilis</i> and moderate to good antifungal activity in co-cultivation assay. | Pretoria (S 25.743278, E 28.263333), South Africa | [50] |
| (122-124) | <i>Streptomyces</i> sp. | earwig <i>Forficula</i> | ISP4 (with | Compounds showed moderate activity | Qixia Mountain in the | [51] |

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| | NA04227 | <i>auricularia</i> | cycloheximide) | against Gram-positive bacteria | suburb of Nanjing, Jiangsu, China | |
| (67) | <i>Streptomyces amphotereticus</i> 1H-SSA8 | ant <i>Camponotus japonicus</i> (head) | SSA (cycloheximide 50 mg, nalidixic acid 20 mg) | Strain 1H-SSA8T showed broad-spectrum antifungal activity. The strain was found to produce amphotericin. | Northeast Agriculture University, Harbin, Heilongjiang, China | [52] |
| (76) | <i>Streptomyces lasiicapitis</i> 3H-HV17(2) | ant <i>Lasius fuliginosus</i> (head) | HV (cycloheximide 50 mg, nalidixic acid 20 mg) | Kanchanamycin is a potential antifungal agent. | Northeast Agriculture University, Harbin, Heilongjiang, China | [53] |
| (50, 51) | <i>Streptomyces puniceus</i> AB10 (= <i>Streptomyces puniceus</i> ICBG378) | ant <i>Atta rugosus rugosus</i> (worker) | Ch (nystatin 40 mg, cycloheximide 50 mg) | no data | campus of the University of São Paulo – Ribeirão Preto (S 21.167889, W 47.847083), Brazil | [54] |
| (54-66) | <i>Streptomyces formicae</i> KY5 | ant <i>Tetraponera penzigi</i> | no data | Novel pentacyclic polyketides are active against MRSA and VRE. The formicamycins are more potent than the previously reported and structurally related fasamycins. | Kenya (no additional data) | [55] |
| (39) | <i>Streptomyces</i> sp. 4231 | termite <i>Coptotermes formosanus</i> (fecal and wood material) | TFA (cycloheximide 100 mg) | The release of bafilomycin C1 by <i>Streptomyces</i> sp. 4231 induces the production of several defensive metabolites by <i>Trichoderma harzianum</i> WC13. | Broward County, Florida, USA | [56] |
| (2, 3) | <i>Microbacterium</i> sp. UTG9 | beetle <i>Nicrophorus concolor</i> (gut) | SC (cycloheximide 100 mg) | Nicrophorusamide A showed antibacterial activity against several gram-positive bacteria. | Maebong Mountain, Seoul, Republic of Korea | [57] |
| (40, 41), (47, 48) | <i>Amycolatopsis</i> sp. M39 | termite <i>Macrotermes natalensis</i> (worker) | MC | Macrotermycins A and C had antibacterial activity against human-pathogenic <i>Staphylococcus aureus</i> and, of greater ecological relevance, they also had selective antifungal activity against a fungal parasite of the termite fungal garden. | South Africa (no additional data) | [58] |
| (5-7) | <i>Streptomyces</i> sp. M41 | termite <i>Macrotermes natalensis</i> | no data | Dentigerumycins B-D were screened against a panel of gram-positive and gram-negative bacteria, yeast, and fungi, but no activity was detected. | no data | [59] |
| (144-145) | <i>Amycolatopsis</i> sp. HCa4 (previously described) | (previously described) | (previously described) | Amicolamycin A suppressed the proliferation of M231 cells by inducing apoptosis through activation of caspase-3. | (previously described) | [60] |
| (42-46) | <i>Amycolatopsis</i> sp. | locust <i>Locusta</i> | G1 | Compounds have activity against gram- | Zijing Mountain, | [61] |

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| | HCa4 | <i>migratoria</i> | | positive bacteria | Nanjing, China | |
| no compounds | <i>Streptomyces</i> spp. | beetle <i>Orthotomicus erosus</i> | Ch (cycloheximide 5 mg, nystatin 10 kU) | 11 <i>Streptomyces</i> spp. isolates with antifungal activity were collected from adult beetles that infest <i>Pinus</i> spp. | Lothair plantation, Mpumalanga Province, South Africa | [62] |
| no compounds | <i>Streptomyces</i> spp. | termites <i>Reticulitermes flavipes</i> , <i>Reticulitermes tibialis</i> (guts) | Ch (nystatin 43 mg, cyclohexamide 67 mg) | Actinobacteria expressed a diversity of antimicrobial characteristics against mold fungi and <i>Serratia marcescens</i> showed a broad range of antimicrobial activity in vitro (34 from 38 were active against 1 test-culture at least). | southern Wisconsin (Janesville, Muscoda, Hazel Green), USA | [63] |
| (1) | <i>Streptomyces</i> sp. IB2014/010-1 | caddisfly <i>Trichoptera</i> sp. (larvae) | MS or Cz (cycloheximide 50 mg, phosphomycin 100 mg) (no additional data) | Variapeptin is a hexadepsipeptide antibiotic with antibacterial activity of azinothricin family. | South Baikal near Listvyanka village (N 51.867936, E 104.829715), Irkutsk region, Russia | [64] |
| no compounds | <i>Pseudonocardia</i> spp. | ant <i>Acromyrmex echinator</i> (workers, laterocervical plates) | LB | Strains show antibacterial antagonistic activity. | Soberania National Park, Gamboa, Panama | [65] |
| (34, 35) | <i>Streptomyces</i> sp. 1H-GS5 | ant <i>Camponotus japonicus</i> (head) | no data | Spectinabiblin derivative 1 exhibited good cytotoxic activities. | Northeast Agricultural University, Harbin, Heilongjiang, China | [66] |
| (36-38) | <i>Streptomyces</i> sp. 1H-GS5 (previously described) | (previously described) | (previously described) | A new spectinabilin derivative showed cytotoxicity against human tumor cell lines. | (previously described) | [67] |
| (141-143), (147) | <i>Streptomyces</i> sp. RB1 | termite <i>Macrotermes natalensis</i> (worker, cuticle) | no data | <i>Streptomyces</i> sp. RB1 showed significant activity against <i>Staphylococcus aureus</i> and weak activity against human-pathogenic <i>Candida albicans</i> . Three new isoflavonoid glycosides, termisoflavones A–C, and eight isoflavonoids were isolated. None of the isolated compounds displayed antifungal or antimicrobial activities. | Pretoria, South Africa | [68] |
| (109, 110) | <i>Streptomyces drozdowiczii</i> SNU607 | beetle <i>Copris tripartitus</i> (gut) | P (cycloheximide 200 mg) | Coprisidin A was found to inhibit the action of Na ⁺ /K ⁺ -ATPase, and coprisidin B showed activity for the induction of NAD(P)H:quinone oxidoreductase 1 (NQO1). | Jeju Island (N 33.385359, E 126.732773), Republic of Korea | [69] |
| (33) | <i>Pseudonocardia</i> spp. | ants <i>Apterostigma</i> sp. | no data | Novel antifungal polyene | La Selva Biological Station, Costa Rica | [70] |

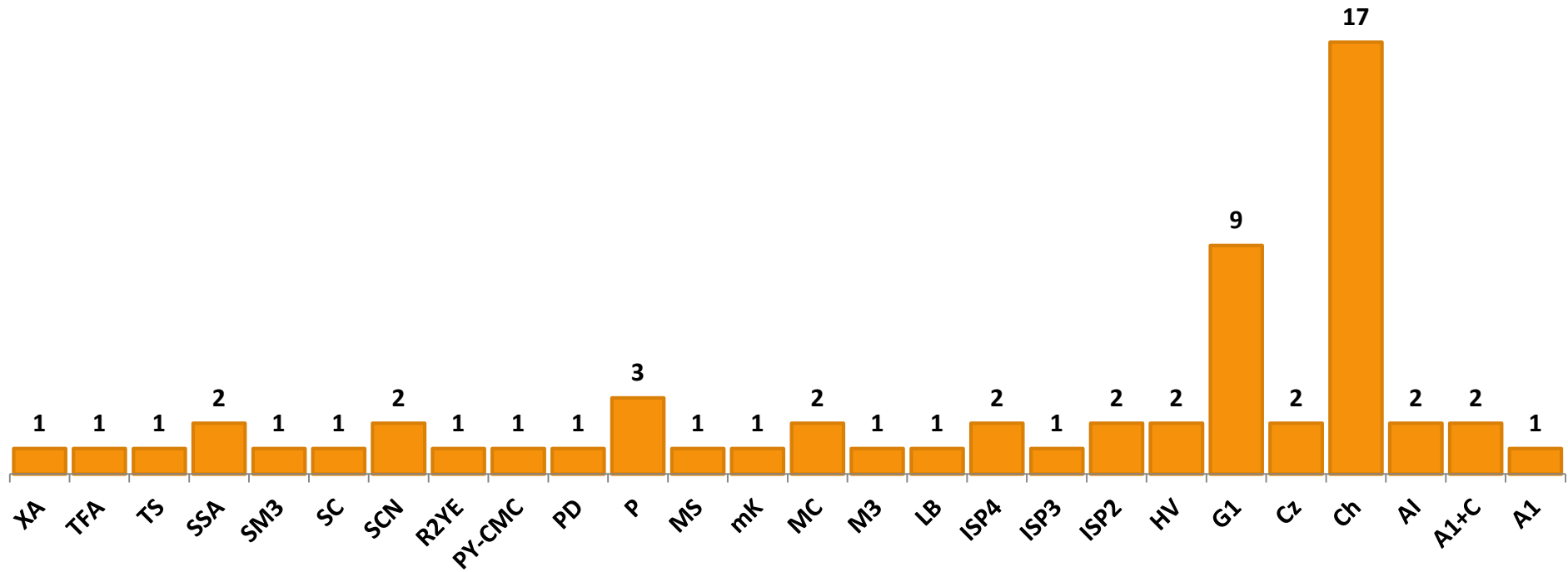
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|-----------------|--|--|--|--|--|------|
| no compounds | <i>Streptomyces formicae</i> 1H-GS9 | ant <i>Camponotus</i> <i>japonicus</i> (head) | G1 (cycloheximide 50 mg, nalidixic acid 20 mg) | Strain 1H-GS9T was found to have antifungal activity. | Northeast Agricultural University, Harbin, Heilongjiang, China | [71] |
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TABLE S2. MEDIA USED FOR ACTINOBACTERIA ISOLATION

| code | Full name, synonyms | Ingredients (per 1 L) | Reference |
|--------|--|--|------------------|
| A1 | DSMZ 1054 | soluble starch 10 g, yeast extract 4 g, peptone 2 g | [72] p.11 |
| A1+C | - | soluble starch 10 g, yeast extract 4 g, peptone 2 g, CaCO ₃ 1 g | [35] |
| AI | Actinomycete isolation medium, Streptomycete isolation medium | glycerol 5 g, sodium propionate 4 g, sodium caseinate 2 g, K ₂ HPO ₄ 0.5g, asparagine 0.1 g, MgSO ₄ ×7H ₂ O 0.1g, FeSO ₄ ×7H ₂ O 1 mg | [72] p.57 |
| Ch | Chitin medium | chitin 4 g; K ₂ HPO ₄ 0.7 g; KH ₂ PO ₄ 0.3 g; MgSO ₄ ×5H ₂ O 0.5 g; FeSO ₄ ×7H ₂ O 10 mg; ZnSO ₄ 1 mg; MnCl ₂ 1 mg | [73] |
| Cz | Czapek medium | sucrose 30 g, NaNO ₃ 3 g, K ₂ HPO ₄ 1 g, KCl 0.5 g, MgSO ₄ ×7H ₂ O 0.5 g, FeSO ₄ ×7H ₂ O 0.01 g | [72] p.479 |
| G1 | Gause medium #1, Gause synthetic medium, DSMZ 1048 | soluble starch 20 g, KNO ₃ 1 g, K ₂ HPO ₄ 0.5g, MgSO ₄ 0.5 g, NaCl 0.5 g, FeSO ₄ 0.01g | [72] p.719 |
| HV | Humic medium, Humic Acid-Vitamin medium | humic acid 1 g, Na ₂ HPO ₄ 0.5 g, KCl 1.71 g, MgSO ₄ ×7H ₂ O 0.05 g, FeSO ₄ ×7H ₂ O 0.01 g, CaCO ₃ 0.02 g, B-vitamins | [74] |
| ISP2 | International Streptomyces Project medium #2, Yeast extract-malt extract agar | yeast extract 4 g, malt extract 10 g, glucose 4 g | [75] |
| ISP3 | International Streptomyces Project medium #3, Oatmeal medium | oatmeal 20 g, trace elements | [75] |
| ISP4 | International Streptomyces Project medium #4, Starch ammonia medium, Inorganic salts-starch medium | soluble starch 10 g, K ₂ HPO ₄ 1 g, MgSO ₄ ×7H ₂ O 1.0 g, NaCl 1.0 g, (NH ₄) ₂ SO ₄ 2 g, CaCO ₃ 2 g, trace elements | [75] |
| LB | Lysogeny broth, Luria broth, Lennox broth, Luria-Bertani medium | tryptone 10 g, yeast extract 5 g, NaCl 10 g | [72] p.911 |
| M3 | - | monosodium citrate 0.12 g, citric acid monohydrate 0.12 g, NaNO ₃ 1.5 g, K ₂ HPO ₄ ×H ₂ O 0.4 g, MgSO ₄ ×7H ₂ O 0.1 g, CaCl ₂ ×H ₂ O 0.05 g, EDTA 0.02 g, Na ₂ CO ₃ 0.2 g | [76] |
| MC | Microcrystalline cellulose medium, Microcrystalline medium | microcrystalline cellulose 5 g | [77] |
| mK | modified K medium | yeast extract 4 g, malt extract 5 g, soytone 5 g, soluble starch 5 g, mannitol 5 g, glucose 2 g | [78] |
| MS | Mannitol-soy medium | soy flour 20 g; D-mannitol 20 g | [79] p.409 |
| P | Pure agar | no additives | - |
| PD | Potato-dextrose medium, Potato-glucose medium | infusion from 200 g of unpeeled potatoes, glucose 20 g | [72] p.1412 |
| PY-CMC | ATCC medium 1513, Peptone Yeast Extract Carboxymethyl Cellulose Medium | carboxymethyl cellulose 10 g, peptone 5 g, yeast extract 5 g, NaCl 5 g, KH ₂ PO ₄ 1 g, MgSO ₄ ×7H ₂ O 2 g, Na ₂ CO ₃ 10 g | [72] p.1451 |
| R2YE | R2 with yeast extract | sucrose 103 g, K ₂ SO ₄ 0.25 g, MgCl ₂ ×6H ₂ O 10.12 g, glucose 10 g, Difco Casaminoacids 0.1 g, yeast extract 5 g, KH ₂ PO ₄ 50 mg, CaCl ₂ ×2H ₂ O, L-proline, TES buffer, trace elements, NaOH | [79] p.408 |
| SCN | Starch-casein-nitrate medium | soluble starch 10 g, casein 0.3 g, KNO ₃ 2 g, MgSO ₄ ×7H ₂ O 0.05 g, K ₂ HPO ₄ 2 g, NaCl 2 g, CaCO ₃ 0.02 g, FeSO ₄ ×7H ₂ O 0.01 g | [72] p.1635-1636 |

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|-----|---|---|-------------|
| SC | Starch-casein medium | soluble starch 10 g, casein 1 g, K ₂ HPO ₄ 0.5 g | [80] |
| SM3 | <i>Amycolatopsis</i> selective medium #3 | glucose 10 g; peptone 5 g; tryptone 3 g; NaCl 5 g; supplemented with filter sterilised solutions of cycloheximide 50 mg, nalidixic acid 10 mg, novobiocin 10 mg and nystatin 50 mg | [81] |
| SSA | Sodium succinate-asparagine medium | asparagine 0.2 g; sodium succinate 1 g; CaCl ₂ ×2H ₂ O 0.2 g; FeSO ₄ ×7H ₂ O 1 mg; KCl 0.3 g; KH ₂ PO ₄ 0.9 g; K ₂ HPO ₄ ×3H ₂ O 0.6 g | [52] |
| TS | Trypticase soy medium, ATCC medium 18, Soybean-casein digest medium | pancreatic digest of casein 15 g, papaic digest of soybean meal 5 g, NaCl 5 g | [72] p.1825 |
| TFA | Termite faecal medium | ground carton material from a <i>Coptotermes formosanus</i> laboratory nest 60 g | [82] |
| XA | Xylan-arginine medium | xylan 2.5g, arginine 1 g, (NH ₄) ₂ SO ₄ 1 g, CaCl ₂ 2 g, K ₂ HPO ₄ 1 g, MgSO ₄ ×7H ₂ O 0.2 g, FeSO ₄ ×7H ₂ O 10 mg | [83] |

FIGURE S1. MEDIA USED FOR ACTINOBACTERIA ISOLATION



Labels in the histogram are identical to those in Table S2

LIST S1. REFERENCES FOR TABLES S1 AND S2

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LIST S2. EXCLUDED PUBLICATIONS

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3. Kim, K.H.; Ramadhar, T.R.; Beemelmans, C.; Cao, S.; Poulsen, M.; Currie, C.R.; Clardy, J. Natalamycin A, an Ansamycin from a Termite-Associated *Streptomyces* Sp. *Chem. Sci.* **2014**, *5*, 4333–4338, doi:[10.1039/C4SC01136H](https://doi.org/10.1039/C4SC01136H). (source - termite comb)
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