Universiteit
Leiden
The Netherlands

Exploring the chemical space of natural products from Streptomyces using multi-omics approaches

Nuñez Santiago, I.

Citation
Nuñez Santiago, I. (2025, April 16). *Exploring the chemical space of natural products from Streptomyces using multi-omics approaches*. Retrieved from https://hdl.handle.net/1887/4212242

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/4212242

Note: To cite this publication please use the final published version (if applicable).

List of publications

List of publications

Michiel T Uiterweerd*, **Isabel Nunez Santiago*,** Remco Havenith, Chao Du, Le Zhang, Helga van der Heul, Somayah Elsayed, Adri Minnaard, Gilles van Wezel. Biomimetic total synthesis and paired omics identify an intermolecular Diels-Alder reaction as the key step in lugdunomycin biosynthesis*. ChemRxiv*. (2024). 10.26434/chemrxiv-2024-d4qs8

Isabel Nuñez Santiago*, Nataliia V Machushynets*, Marija Mladic, Doris A van Bergeijk, Somayah S Elsayed, Thomas Hankemeier, Gilles P van Wezel. NanoRAPIDS as an analytical pipeline for the discovery of novel bioactive metabolites in complex culture extracts at the nanoscale. *Commun Chem* **7**, 71 (2024). https://doi.org/10.1038/s42004-024-01153-y

Doris A van Bergeijk, Somayah S Elsayed, Chao Du, **Isabel Nuñez Santiago**, Anna M Roseboom, Le Zhang, Victor J Carrión, Herman P Spaink, Gilles P van Wezel. The ubiquitous catechol moiety elicits siderophore and angucycline production in *Streptomyces*. Commun Chem **5**, 14 (2022). https://doi.org/10.1038/s42004-022-00632-4

Michiel T Uiterweerd**, Isabel Nuñez Santiago**, Helga van der Heul, Gilles P van Wezel, Adriaan J Minnaard. Iso-maleimycin, a Constitutional Isomer of Maleimycin, from *Streptomyces* sp. QL37. *Eur. J. Org. Chem*., 2020: 5145-5152. https://doi.org/10.1002/ejoc.202000767

References

References

Abraham, E.P., and Chain, E. (1988) An enzyme from bacteria able to destroy penicillin. 1940. *Rev Infect Dis* **10**: 677-678.

Akhter, N., Liu, Y., Auckloo, B.N., Shi, Y., Wang, K., Chen, J., Wu, X., and Wu, B. (2018) Stress-Driven Discovery of New Angucycline-Type Antibiotics from a Marine *Streptomyces pratensis* NA-ZhouS1. *Mar Drugs* **16**.

Akiyama, T., Harada, S., Kojima, F., Takahashi, Y., IMADA, C., OKAMI, Y., MURAOKA, Y., AOYAGI, T., and TAKEUCHI, T. (1998) Fluostatins A and B, New Inhibitors of Dipeptidyl Peptidase III, Produced by *Streptomyces* sp. TA-3391 I. Taxonomy of Producing Strain, Production, Isolation, Physico-chemical Properties and Biological Properties. *J Antibiot* **51**: 553-559.

Alam, K., Mazumder, A., Sikdar, S., Zhao, Y.M., Hao, J., Song, C., Wang, Y., Sarkar, R., Islam, S., Zhang, Y., and Li, A. (2022) *Streptomyces*: The biofactory of secondary metabolites. *Front Microbiol* **13**: 968053.

Albright, J.C., Henke, M.T., Soukup, A.A., McClure, R.A., Thomson, R.J., Keller, N.P., and Kelleher, N.L. (2015) Large-scale metabolomics reveals a complex response of *Aspergillus nidulans* to epigenetic perturbation. *ACS Chem Biol*: In press.

Aminov, R.I. (2010) A brief history of the antibiotic era: lessons learned and challenges for the future. *Front Microbiol* **1**: 134.

Apsel, B., Bender, J.A., Escobar, M., Kaelin Jr, D.E., Lopez, O.D., and Martin, S.F. (2003) General entries to C-aryl glycosides. Formal synthesis of galtamycinone. *Tetrahedron lett* **44**: 1075-1077.

Aron, A.T., Gentry, E.C., McPhail, K.L., Nothias, L.F., Nothias-Esposito, M., Bouslimani, A., Petras, D., Gauglitz, J.M., Sikora, N., Vargas, F., van der Hooft, J.J.J., Ernst, M., Kang, K.B., Aceves, C.M., Caraballo-Rodriguez, A.M., Koester, I., Weldon, K.C., Bertrand, S., Roullier, C., Sun, K., Tehan, R.M., Boya, P.C., Christian, M.H., Gutierrez, M., Ulloa, A.M., Tejeda Mora, J.A., Mojica-Flores, R., Lakey-Beitia, J., Vasquez-Chaves, V., Zhang, Y., Calderon, A.I., Tayler, N., Keyzers, R.A., Tugizimana, F., Ndlovu, N., Aksenov, A.A., Jarmusch, A.K., Schmid, R., Truman, A.W., Bandeira, N., Wang, M., and Dorrestein, P.C. (2020) Reproducible molecular networking of untargeted mass spectrometry data using GNPS. *Nat Protoc* **15**: 1954-1991.

Arora, D., Gupta, P., Jaglan, S., Roullier, C., Grovel, O., and Bertrand, S. (2020) Expanding the chemical diversity through microorganisms co-culture: Current status and outlook. *Biotechnol Adv* **40**: 107521.

Asnicar, F., Thomas, A.M., Beghini, F., Mengoni, C., Manara, S., Manghi, P., Zhu, Q., Bolzan, M., Cumbo, F., and May, U. (2020) Precise phylogenetic analysis of microbial isolates and genomes from metagenomes using PhyloPhlAn 3.0. *Nat Commun* **11**: 2500.

Atanasov, A.G., Zotchev, S.B., Dirsch, V.M., International Natural Product Sciences, T., and Supuran, C.T. (2021) Natural products in drug discovery: advances and opportunities. *Nat Rev Drug Discov* **20**: 200-216.

Audoin, C., Bonhomme, D., Ivanisevic, J., de la Cruz, M., Cautain, B., Monteiro, M.C., Reyes, F., Rios, L., Perez, T., and Thomas, O.P. (2013) Balibalosides, an original family of glucosylated sesterterpenes produced by the Mediterranean sponge Oscarella balibaloi. *Mar Drugs* **11**: 1477-1489.

Augustijn, H.E., Karapliafis, D., Joosten, K.M.M., Rigali, S., van Wezel, G.P., and Medema, M.H. (2024a) LogoMotif: A Comprehensive Database of Transcription Factor Binding Site Profiles in Actinobacteria. *J Mol Biol*: 168558.

Augustijn, H.E., Roseboom, A.M., Medema, M.H., and van Wezel, G.P. (2024b) Harnessing regulatory networks in Actinobacteria for natural product discovery. *Journal of industrial microbiology & biotechnology* **51**.

Autret, S., Nair, R., and Errington, J. (2001) Genetic analysis of the chromosome segregation protein Spo0J of Bacillus subtilis: evidence for separate domains involved in DNA binding and interactions with Soj protein. *Mol Microbiol* **41**: 743-755.

Avery, V.M., Camp, D., Carroll, A.R., Jenkins, I.D., and Quinn, R.J. (2010) The identification of bioactive natural products by high throughput screening (HTS).

Ayon, N.J. (2023) High-Throughput Screening of Natural Product and Synthetic Molecule Libraries for Antibacterial Drug Discovery. *Metabolites* **13**.

Baltz, R.H. (2008) Renaissance in antibacterial discovery from actinomycetes. *Curr Opin Pharmacol* **8**: 557-563.

Barbe, V., Cruveiller, S., Kunst, F., Lenoble, P., Meurice, G., Sekowska, A., Vallenet, D., Wang, T., Moszer, I., Medigue, C., and Danchin, A. (2009) From a consortium sequence to a unified sequence: the Bacillus subtilis 168 reference genome a decade later. *Microbiology* **155**: 1758-1775.

Barka, E.A., Vatsa, P., Sanchez, L., Gaveau-Vaillant, N., Jacquard, C., Meier-Kolthoff, J.P., Klenk, H.P., Clement, C., Ouhdouch, Y., and van Wezel, G.P. (2016) Taxonomy, physiology, and natural products of the Actinobacteria. *Microbiol Mol Biol Rev* **80**: 1-43.

Basch, H., and Gadebusch, H. (1968) In vitro antimicrobial activity of dimethylsulfoxide. *Appl Microbiol* **16**: 1953-1954.

Belknap, K.C., Park, C.J., Barth, B.M., and Andam, C.P. (2020) Genome mining of biosynthetic and chemotherapeutic gene clusters in *Streptomyces* bacteria. *Sci Rep* **10**: 2003.

Bentley, S.D., Chater, K.F., Cerdeno-Tarraga, A.M., Challis, G.L., Thomson, N.R., James, K.D., Harris, D.E., Quail, M.A., Kieser, H., Harper, D., Bateman, A., Brown, S., Chandra, G., Chen, C.W., Collins, M., Cronin, A., Fraser, A., Goble, A., Hidalgo, J., Hornsby, T., Howarth, S., Huang, C.H., Kieser, T., Larke, L., Murphy, L., Oliver, K., O'Neil, S., Rabbinowitsch, E., Rajandream, M.A., Rutherford, K., Rutter, S., Seeger, K., Saunders, D., Sharp, S., Squares, R., Squares, S., Taylor, K., Warren, T., Wietzorrek, A., Woodward, J., Barrell, B.G., Parkhill, J., and Hopwood, D.A. (2002) Complete genome sequence of the model actinomycete *Streptomyces coelicolor* A3 (2). *Nature* **417**: 141-147.

Bérdy, J. (2005) Bioactive microbial metabolites. *J Antibiot (Tokyo)* **58**: 1-26.

Bergmann, S., Schümann, J., Scherlach, K., Lange, C., Brakhage, A.A., and Hertweck, C. (2007) Genomics-driven discovery of PKS-NRPS hybrid metabolites from Aspergillus nidulans. *Nat Chem Biol* **3**: 213-217.

Bertrand, S., Bohni, N., Schnee, S., Schumpp, O., Gindro, K., and Wolfender, J.L. (2014) Metabolite induction via microorganism co-culture: a potential way to enhance chemical diversity for drug discovery. *Biotechnol Adv* **32**: 1180-1204.

Bibb, M.J. (2005) Regulation of secondary metabolism in streptomycetes. *Curr Opin Microbiol* **8**: 208-215.

Bitchagno, G.T.M., Nchiozem-Ngnitedem, V.-A., Melchert, D., and Fobofou, S.A. (2022) Demystifying racemic natural products in the homochiral world. *Nat Rev Chem* **6**: 806-822.

Blin, K., Medema, M.H., Kottmann, R., Lee, S.Y., and Weber, T. (2017) The antiSMASH database, a comprehensive database of microbial secondary metabolite biosynthetic gene clusters. *Nucleic Acids Res* **45**: D555-D559.

Blin, K., Shaw, S., Augustijn, H.E., Reitz, Z.L., Biermann, F., Alanjary, M., Fetter, A., Terlouw, B.R., Metcalf, W.W., Helfrich, E.J.N., van Wezel, G.P., Medema, M.H., and Weber, T. (2023) antiSMASH 7.0: new and improved predictions for detection, regulation, chemical structures and visualisation. *Nucleic acids research* **51**: W46-W50.

Blin, K., Shaw, S., Kloosterman, A.M., Charlop-Powers, Z., van Wezel, G.P., Medema, M.H., and Weber, T. (2021) antiSMASH 6.0: improving cluster detection and comparison capabilities. *Nucleic Acids Res* **49**: W29-W35.

Bode, H.B., Bethe, B., Hofs, R., and Zeeck, A. (2002) Big effects from small changes: possible ways to explore nature's chemical diversity. *Chembiochem* **3**: 619-627.

Boger, D.L., Ledeboer, M.W., Kume, M., Searcey, M., and Jin, Q. (1999) Total synthesis and comparative evaluation of luzopeptin A– C and quinoxapeptin A– C. *J Am Chem Soc* **121**: 11375-11383.

Bosello, M., Robbel, L., Linne, U., Xie, X., and Marahiel, M.A. (2011) Biosynthesis of the siderophore rhodochelin requires the coordinated expression of three independent gene clusters in Rhodococcus jostii RHA1. *J Am Chem Soc* **133**: 4587-4595.

Braz, V.S., Melchior, K., and Moreira, C.G. (2020) Escherichia coli as a multifaceted pathogenic and versatile bacterium. *Front Cell Infect Microbiol* **10**: 548492.

Broberg, A., Menkis, A., and Vasiliauskas, R. (2006) Kutznerides 1– 4, Depsipeptides from the Actinomycete Kutzneria sp. 744 Inhabiting Mycorrhizal Roots of Picea a bies Seedlings. *J Nat Prod* **69**: 97-102.

Bunet, R., Mendes, M.V., Rouhier, N., Pang, X., Hotel, L., Leblond, P., and Aigle, B. (2008) Regulation of the synthesis of the angucyclinone antibiotic alpomycin in *Streptomyces ambofaciens* by the autoregulator receptor AlpZ and its specific ligand. *J Bacteriol* **190**: 3293-3305.

Bunet, R., Song, L., Mendes, M.V., Corre, C., Hotel, L., Rouhier, N., Framboisier, X., Leblond, P., Challis, G.L., and Aigle, B. (2011) Characterization and manipulation of the pathway-specific late regulator AlpW reveals *Streptomyces* ambofaciens as a new producer of kinamycins. *J Bacteriol* **193**: 1142-1153.

Caldeira, A.T., Santos Arteiro, J.M., Coelho, A.V., and Roseiro, J.C. (2011) Combined use of LC–ESI-MS and antifungal tests for rapid identification of bioactive lipopeptides produced by Bacillus amyloliquefaciens CCMI 1051. *Process Biochem* **46**: 1738-1746.

Carrión, V.J., Perez-Jaramillo, J., Cordovez, V., Tracanna, V., De Hollander, M., Ruiz-Buck, D., Mendes, L.W., van Ijcken, W.F., Gomez-Exposito, R., and Elsayed, S.S. (2019) Pathogen-induced activation of disease-suppressive functions in the endophytic root microbiome. *Science* **366**: 606-612.

Cautain, B., de Pedro, N., Schulz, C., Pascual, J., Sousa Tda, S., Martin, J., Perez-Victoria, I., Asensio, F., Gonzalez, I., Bills, G.F., Reyes, F., Genilloud, O., and Vicente, F. (2015) Identification of the Lipodepsipeptide MDN-0066, a Novel Inhibitor of VHL/HIF Pathway Produced by a New Pseudomonas Species. *PLoS One* **10**: e0125221.

Chemother, A. Abubacker, MN, Ramanathan, R., Senthil, KT, 2008, In vitro antifungal activity of Cassia alata Linn flower extract, Natural Product Radiance 7 (1): 6-9. Andrews, JM, 2001, Determination of minimum inhibitory concentrations, Journal of Antimicrobial Chemotherapy 48, Suppl. S1, 5-16. *J Antimicrob Chemother* **48**: 5-16.

Chen, J., Jia, Y., Sun, Y., Liu, K., Zhou, C., Liu, C., Li, D., Liu, G., Zhang, C., Yang, T., Huang, L., Zhuang, Y., Wang, D., Xu, D., Zhong, Q., Guo, Y., Li, A., Seim, I., Jiang, L., Wang, L., Lee, S.M.Y., Liu, Y., Wang, D., Zhang, G., Liu, S., Wei, X., Yue, Z., Zheng, S., Shen, X., Wang, S., Qi, C., Chen, J., Ye, C., Zhao, F., Wang, J., Fan, J., Li, B., Sun, J., Jia, X., Xia, Z., Zhang, H., Liu, J., Zheng, Y., Liu, X., Wang, J., Yang, H., Kristiansen, K., Xu, X., Mock, T., Li, S., Zhang, W., and Fan, G. (2024) Global marine microbial diversity and its potential in bioprospecting. *Nature* **633**: 371-379.

Cheng, K.C.-C., Cao, S., Raveh, A., MacArthur, R., Dranchak, P., Chlipala, G., Okoneski, M.T., Guha, R., Eastman, R.T., and Yuan, J. (2015) Actinoramide A identified as a potent antimalarial from titration-based screening of marine natural product extracts. *J Nat Prod* **78**: 2411-2422.

Chevrette, M.G., Gutierrez-Garcia, K., Selem-Mojica, N., Aguilar-Martinez, C., Yanez-Olvera, A., Ramos-Aboites, H.E., Hoskisson, P.A., and Barona-Gomez, F. (2020) Evolutionary dynamics of natural product biosynthesis in bacteria. *Nat Prod Rep* **37**: 566-599.

Chiang, Y.-M., Chang, S.-L., Oakley, B.R., and Wang, C.C. (2011) Recent advances in awakening silent biosynthetic gene clusters and linking orphan clusters to natural products in microorganisms. *Curr Opin Chem Biol* **15**: 137-143.

Chiang, Y.-M., Szewczyk, E., Davidson, A.D., Keller, N., Oakley, B.R., and Wang, C.C. (2009) A gene cluster containing two fungal polyketide synthases encodes the biosynthetic pathway for a polyketide, asperfuranone, in Aspergillus nidulans. *J Am Chem Soc* **131**: 2965-2970.

Chung, Y.R., Kim, C.H., Hwang, I., and Chun, J. (2000) Paenibacillus koreensis sp. nov., a new species that produces an iturin-like antifungal compound. *Int J Syst Evol Microbiol* **50 Pt 4**: 1495-1500.

Cornforth, D.M., and Foster, K.R. (2013) Competition sensing: the social side of bacterial stress responses. *Nat Rev Microbiol* **11**: 285-293.

Coy-Barrera, E., Ogungbe, I.V., and Schmidt, T.J. (2023) Natural Products for Drug Discovery in the 21st Century: Innovations for Novel Therapeutics. *Molecules* **28**.

Cragg, G.M., Newman, D.J., and Snader, K.M. (1997) Natural products in drug discovery and development. *J Nat Prod* **60**: 52-60.

Craig, M., Lambert, S., Jourdan, S., Tenconi, E., Colson, S., Maciejewska, M., Ongena, M., Martin, J.F., van Wezel, G., and Rigali, S. (2012) Unsuspected control of siderophore production by N-acetylglucosamine in streptomycetes. *Environ Microbiol Rep* **4**: 512-521.

Craney, A., Ozimok, C., Pimentel-Elardo, S.M., Capretta, A., and Nodwell, J.R. (2012) Chemical perturbation of secondary metabolism demonstrates important links to primary metabolism. *Chem Biol* **19**: 1020-1027.

Cruz-Morales, P., Vijgenboom, E., Iruegas-Bocardo, F., Girard, G., Yanez-Guerra, L.A., Ramos-Aboites, H.E., Pernodet, J.L., Anne, J., van Wezel, G.P., and Barona-Gomez, F. (2013) The genome sequence of *Streptomyces lividans* 66 reveals a novel tRNA-dependent peptide biosynthetic system within a metal-related genomic island. *Genome Biol Evol* **5**: 1165-1175.

Culp, E.J., Yim, G., Waglechner, N., Wang, W., Pawlowski, A.C., and Wright, G.D. (2019) Hidden antibiotics in actinomycetes can be identified by inactivation of gene clusters for common antibiotics. *Nat Biotechnol* **37**: 1149-1154.

da Silva, R.R., Wang, M., Nothias, L.-F., van der Hooft, J.J.J., Caraballo-Rodríguez, A.M., Fox, E., Balunas, M.J., Klassen, J.L., Lopes, N.P., and Dorrestein, P.C. (2018) Propagating annotations of molecular networks using in silico fragmentation. *PLoS Comput. Biol.* **14**: 1006089.

Dierkes, J., and Rücknagel, J. (2017) FAIR: Findable, Accessible, Interoperable, Reusable.

Djoumbou Feunang, Y., Eisner, R., Knox, C., Chepelev, L., Hastings, J., Owen, G., Fahy, E., Steinbeck, C., Subramanian, S., Bolton, E., Greiner, R., and Wishart, D.S. (2016) ClassyFire: automated chemical classification with a comprehensive, computable taxonomy. *J Cheminform* **8**: 61.

Du, Y.-L., He, H.-Y., Higgins, M.A., and Ryan, K.S. (2017) A heme-dependent enzyme forms the nitrogen–nitrogen bond in piperazate. *Nat Chem Biol* **13**: 836-838.

Dubey, R.K., Tripathi, V., Prabha, R., Chaurasia, R., Singh, D.P., Rao, C.S., El-Keblawy, A., Abhilash, P.C., Dubey, R.K., and Tripathi, V. (2020) Metatranscriptomics and metaproteomics for microbial communities profiling. *Environ Sci* **Unravelling the Soil Microbiome: Perspectives For Environmental Sustainability**: 51-60.

Duhrkop, K., Nothias, L.F., Fleischauer, M., Reher, R., Ludwig, M., Hoffmann, M.A., Petras, D., Gerwick, W.H., Rousu, J., Dorrestein, P.C., and Bocker, S. (2021) Systematic classification of unknown metabolites using high-resolution fragmentation mass spectra. *Nat Biotechnol* **39**: 462-471.

Duhrkop, K., Shen, H., Meusel, M., Rousu, J., and Bocker, S. (2015) Searching molecular structure databases with tandem mass spectra using CSI:FingerID. *Proc Natl Acad Sci U S A* **112**: 12580-12585.

Elsayed, S.S., van der Heul, H.U., Xiao, X., Nuutila, A., Baars, L.R., Wu, C., Metsä-Ketelä, M., and van Wezel, G.P. (2023) Unravelling key enzymatic steps in C-ring cleavage during angucycline biosynthesis. *Commun Chem* **6**: 281.

Erb, A., Krauth, C., Luzhetskyy, A., and Bechthold, A. (2009) Differences in the substrate specificity of glycosyltransferases involved in landomycins A and E biosynthesis. *Appl Microbiol Biotechnol* **83**: 1067-1076.

Ernst, M., Kang, K.B., Caraballo-Rodriguez, A.M., Nothias, L.F., Wandy, J., Chen, C., Wang, M., Rogers, S., Medema, M.H., Dorrestein, P.C., and van der Hooft, J.J.J. (2019) MolNetEnhancer: Enhanced Molecular Networks by Integrating Metabolome Mining and Annotation Tools. *Metabolites* **9**.

Fan, K., and Zhang, Q. (2018) The functional differentiation of the post-PKS tailoring oxygenases contributed to the chemical diversities of atypical angucyclines. *Synth Syst Biotechno* **3**: 275-282.

Felnagle, E.A., Jackson, E.E., Chan, Y.A., Podevels, A.M., Berti, A.D., McMahon, M.D., and Thomas, M.G. (2008) Nonribosomal peptide synthetases involved in the production of medically relevant natural products. *Mol Pharm* **5**: 191-211.

Fernandez-Moreno, M.A., Caballero, J.L., Hopwood, D.A., and Malpartida, F. (1991) The act cluster contains regulatory and antibiotic export genes, direct targets for translational control by the bldA tRNA gene of *Streptomyces*. *Cell* **66**: 769-780.

Filioti, J., Spiroglou, K., and Roilides, E. (2007) Invasive candidiasis in pediatric intensive care patients: epidemiology, risk factors, management, and outcome. *Intensive Care Med* **33**: 1272-1283.

Fotso, S., Mahmud, T., Zabriskie, T.M., Santosa, D.A., and Proteau, P.J. (2008) Rearranged and unrearranged angucyclinones from Indonesian *Streptomyces* spp. *J Antibiot (Tokyo)* **61**: 449-456.

Gavriilidou, A., Kautsar, S.A., Zaburannyi, N., Krug, D., Müller, R., Medema, M.H., and Ziemert, N. (2021) A global survey of specialized metabolic diversity encoded in bacterial genomes. *BioRXiv*: 2021.2008.2011.455920.

Geers, A.U., Buijs, Y., Strube, M.L., Gram, L., and Bentzon-Tilia, M. (2022) The natural product biosynthesis potential of the microbiomes of Earth–Bioprospecting for novel anti-microbial agents in the meta-omics era. *CSBJ* **20**: 343-352.

Genilloud, O. (2012) Current challenges in the discovery of novel antibacterials from microbial natural products. *Recent Pat Antiinfect Drug Discov* **7**: 189-204.

Genilloud, O. (2014) The re-emerging role of microbial natural products in antibiotic discovery. *AVL* **106**: 173-188.

Genilloud, O., Gonzalez, I., Salazar, O., Martin, J., Tormo, J.R., and Vicente, F. (2011) Current approaches to exploit actinomycetes as a source of novel natural products. *Journal of industrial microbiology & biotechnology* **38**: 375-389.

Gilchrist, C.L., and Chooi, Y.-H. (2021) Clinker & clustermap. js: Automatic generation of gene cluster comparison figures. *Bioinformatics* **37**: 2473-2475.

Gomez-Escribano, J.P., Song, L., Fox, D.J., Yeo, V., Bibb, M.J., and Challis, G.L. (2012) Structure and biosynthesis of the unusual polyketide alkaloid coelimycin P1, a metabolic product of the cpk gene cluster of *Streptomyces coelicolor* M145. *Chem Sci* **3**: 2716-2720.

Gomez-Escribano, J.P., and Bibb, M.J. (2011) Engineering *Streptomyces* coelicolor for heterologous expression of secondary metabolite gene clusters. *Microb Biotechnol* **4**: 207-215.

Gramajo, H.C., Takano, E., and Bibb, M.J. (1993) Stationary-phase production of the antibiotic actinorhodin in *Streptomyces coelicolor* A3 (2) is transcriptionally regulated. *Mol Microbiol* **7**: 837-845.

Gregory, M.A., Till, R., and Smith, M.C. (2003) Integration site for *Streptomyces* phage ϕBT1 and development of site-specific integrating vectors. *J. Bacteriol* **185**: 5320-5323.

Gubbens, J., Wu, C., Zhu, H., Filippov, D.V., Florea, B.I., Rigali, S., Overkleeft, H.S., and van Wezel, G.P. (2017) Intertwined Precursor Supply during Biosynthesis of the Catecholate-Hydroxamate Siderophores Qinichelins in *Streptomyces* sp. MBT76. *ACS Chem Biol* **12**: 2756-2766.

Gubbens, J., Zhu, H., Girard, G., Song, L., Florea, B.I., Aston, P., Ichinose, K., Filippov, D.V., Choi, Y.H., Overkleeft, H.S., Challis, G.L., and van Wezel, G.P. (2014) Natural product proteomining, a quantitative proteomics platform, allows rapid discovery of biosynthetic gene clusters for different classes of natural products. *Chem Biol* **21**: 707-718.

Hasebe, F., Matsuda, K., Shiraishi, T., Futamura, Y., Nakano, T., Tomita, T., Ishigami, K., Taka, H., Mineki, R., Fujimura, T., Osada, H., Kuzuyama, T., and Nishiyama, M. (2016) Amino-group carrier-protein-mediated secondary metabolite biosynthesis in *Streptomyces*. *Nat Chem Biol* **12**: 967-972.

Henkel, T., Rohr, J., Beale, J.M., and Schwenen, L. (1990) Landomycins, new angucycline antibiotics from *Streptomyces* sp. I. Structural studies on landomycins A-D. *J Antibiot (Tokyo)* **43**: 492-503.

Henrich, C.J., and Beutler, J.A. (2013) Matching the power of high throughput screening to the chemical diversity of natural products. *Nat Prod Rep* **30**: 1284-1298.

Hertlein, G., Seiffert, M., Gensel, S., Garcia-Gonzalez, E., Ebeling, J., Skobalj, R., Kuthning, A., Sussmuth, R.D., and Genersch, E. (2016) Biological Role of Paenilarvins, Iturin-Like Lipopeptide Secondary Metabolites Produced by the Honey Bee Pathogen Paenibacillus larvae. *PLoS One* **11**: e0164656.

Hertweck, C. (2009) The biosynthetic logic of polyketide diversity. *Angew Chem Int Ed Engl* **48**: 4688-4716.

Hiard, S., Maree, R., Colson, S., Hoskisson, P.A., Titgemeyer, F., van Wezel, G.P., Joris, B., Wehenkel, L., and Rigali, S. (2007) PREDetector: a new tool to identify regulatory elements in bacterial genomes. *Biochem Biophys Res Commun* **357**: 861-864.

Hopwood, D.A., (2007) *Streptomyces in nature and medicine: the antibiotic makers*. Oxford University Press.

Hosaka, T., Ohnishi-Kameyama, M., Muramatsu, H., Murakami, K., Tsurumi, Y., Kodani, S., Yoshida, M., Fujie, A., and Ochi, K. (2009) Antibacterial discovery in actinomycetes strains with mutations in RNA polymerase or ribosomal protein S12. *Nat Biotechnol* **27**: 462-464.

Hoshino, S., Wakimoto, T., Onaka, H., and Abe, I. (2015) Chojalactones A-C, cytotoxic butanolides isolated from *Streptomyces* sp. cultivated with mycolic acid containing bacterium. *Org Lett* **17**: 1501-1504.

Hoskisson, P.A., and Seipke, R.F. (2020) Cryptic or Silent? The Known Unknowns, Unknown Knowns, and Unknown Unknowns of Secondary Metabolism. *mBio* **11**.

Hou, Y., Braun, D.R., Michel, C.R., Klassen, J.L., Adnani, N., Wyche, T.P., and Bugni, T.S. (2012) Microbial strain prioritization using metabolomics tools for the discovery of natural products. *Anal Chem* **84**: 4277-4283.

Hover, B.M., Kim, S.-H., Katz, M., Charlop-Powers, Z., Owen, J.G., Ternei, M.A., Maniko, J., Estrela, A.B., Molina, H., and Park, S. (2018) Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-positive pathogens. *Nat Microbiol* **3**: 415-422.

Hsiao, N.H., Gottelt, M., and Takano, E. (2009) Chapter 6. Regulation of antibiotic production by bacterial hormones. *Methods Enzymol* **458**: 143-157.

Hulst, M.B., Grocholski, T., Neefjes, J.J.C., van Wezel, G.P., and Metsa-Ketela, M. (2022) Anthracyclines: biosynthesis, engineering and clinical applications. *Nat Prod Rep* **39**: 814-841.

Hutchings, M.I., Truman, A.W., and Wilkinson, B. (2019) Antibiotics: past, present and future. *Curr Opin Microbiol* **51**: 72-80.

Iacovelli, R., Bovenberg, R.A., and Driessen, A.J. (2021) Nonribosomal peptide synthetases and their biotechnological potential in Penicillium rubens. *Journal of industrial microbiology & biotechnology* **48**: kuab045.

Ikeda, H., Ishikawa, J., Hanamoto, A., Shinose, M., Kikuchi, H., Shiba, T., Sakaki, Y., Hattori, M., and Omura, S. (2003) Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis*. *Nat Biotechnol* **21**: 526-531.

Imhoff, J.F. (2016) New Dimensions in Microbial Ecology-Functional Genes in Studies to Unravel the Biodiversity and Role of Functional Microbial Groups in the Environment. *Microorganisms* **4**.

Jarmusch, A.K., Aron, A.T., Petras, D., Phelan, V.V., Bittremieux, W., Acharya, D.D., Ahmed, M.M., Bauermeister, A., Bertin, M.J., and Boudreau, P.D. (2022) A universal language for finding mass spectrometry data patterns. *BioRxiv*: 2022.2008. 2006.503000.

Jin, J., Yang, X., Liu, T., Xiao, H., Wang, G., Zhou, M., Liu, F., Zhang, Y., Liu, D., and Chen, M. (2018) Fluostatins M–Q featuring a 6-5-6-6 ring skeleton and high oxidized A-rings from marine *Streptomyces* sp. PKU-MA00045. *Mar Drugs* **16**: 87.

Kali, A. (2015) Antibiotics and bioactive natural products in treatment of methicillin resistant Staphylococcus aureus: A brief review. *Phcog Rev* **9**: 29.

Kalkreuter, E., Pan, G., Cepeda, A.J., and Shen, B. (2020) Targeting Bacterial Genomes for Natural Product Discovery. *Trends Pharmacol Sci* **41**: 13-26.

Kang, L., Song, Y., Mackelprang, R., Zhang, D., Qin, S., Chen, L., Wu, L., Peng, Y., and Yang, Y. (2024) Metagenomic insights into microbial community structure and metabolism in alpine permafrost on the Tibetan Plateau. *Nat Commun* **15**: 5920.

Katz, L., and Baltz, R.H. (2016) Natural product discovery: past, present, and future. *Journal of industrial microbiology & biotechnology* **43**: 155-176.

Kersten, R.D., and Dorrestein, P.C. (2009) Secondary metabolomics: natural products mass spectrometry goes global. *ACS Chem Biol* **4**: 599-601.

Kharel, M.K., Pahari, P., Shepherd, M.D., Tibrewal, N., Nybo, S.E., Shaaban, K.A., and Rohr, J. (2012) Angucyclines: Biosynthesis, mode-of-action, new natural products, and synthesis. *Nat Prod Rep* **29**: 264-325.

Kibret, M., Guerrero-Garzón, J.F., Urban, E., Zehl, M., Wronski, V.-K., Rückert, C., Busche, T., Kalinowski, J., Rollinger, J.M., and Abate, D. (2018) *Streptomyces* spp. from Ethiopia producing antimicrobial compounds: characterization via bioassays, genome analyses, and mass spectrometry. *Front Microbiol* **9**: 1270.

Kieser, T., (2000) *Practical Streptomyces genetics*.

Kim, H.W., Wang, M., Leber, C.A., Nothias, L.-F., Reher, R., Kang, K.B., Van Der Hooft, J.J., Dorrestein, P.C., Gerwick, W.H., and Cottrell, G.W. (2021) NPClassifier: a deep neural network-based structural classification tool for natural products. *J Nat Prod* **84**: 2795-2807.

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B.A., Thiessen, P.A., Yu, B., Zaslavsky, L., Zhang, J., and Bolton, E.E. (2022) PubChem 2023 update. *Nucleic Acids Res* **51**: D1373-D1380.

Kloosterman, A.M., Cimermancic, P., Elsayed, S.S., Du, C., Hadjithomas, M., Donia, M.S., Fischbach, M.A., van Wezel, G.P., and Medema, M.H. (2020) Expansion of RiPP biosynthetic space through integration of pan-genomics and machine learning uncovers a novel class of lantibiotics. *PLoS Biol* **18**: e3001026.

Kolter, R., and van Wezel, G.P. (2016) Goodbye to brute force in antibiotic discovery? *Nat Microbiol* **1**: 15020.

Komissarov, L., Ruger, R., Hellstrom, M., and Verstraelen, T. (2021) ParAMS: parameter optimization for atomistic and molecular simulations. *J Chem Inf Model* **61**: 3737-3743.

Koprowski, M., Bałczewski, P., Owsianik, K., Różycka-Sokołowska, E., and Marciniak, B. (2016) Total synthesis of (±)-epithuriferic acid methyl ester via Diels–Alder reaction. *Org Biomol Chem* **14**: 1822-1830.

Korynevska, A., Heffeter, P., Matselyukh, B., Elbling, L., Micksche, M., Stoika, R., and Berger, W. (2007) Mechanisms underlying the anticancer activities of the angucycline landomycin E. *Biochem Pharmacol* **74**: 1713-1726.

Krespach, M.K.C., Stroe, M.C., Netzker, T., Rosin, M., Zehner, L.M., Komor, A.J., Beilmann, J.M., Kruger, T., Scherlach, K., Kniemeyer, O., Schroeckh, V., Hertweck, C., and Brakhage, A.A. (2023) *Streptomyces* polyketides mediate bacteria-fungi interactions across soil environments. *Nat Microbiol* **8**: 1348-1361.

Krohn, K., and Baltus, W. (1988) Synthesis of rac- and ent-fridamycin E. *Tetrahedron* **44**: 49-54.

Laatsch, H., (2011) AntiBase 2011: the natural compound identifier. In.: Wiley-Vch, pp.

Lai, Z., Yu, J., Ling, H., Song, Y., Yuan, J., Ju, J., Tao, Y., and Huang, H. (2018) Grincamycins I - K, Cytotoxic Angucycline Glycosides Derived from Marine-Derived Actinomycete *Streptomyces lusitanus* SCSIO LR32. *Planta Med* **84**: 201-207.

Lawlor, E.J., Baylis, H.A., and Chater, K.F. (1987) Pleiotropic morphological and antibiotic deficiencies result from mutations in a gene encoding a tRNA-like product in *Streptomyces coelicolor* A3 (2). *Genes Dev* **1**: 1305-1310.

Lawson, A.J., Swienty-Busch, J., Géoui, T., and Evans, D., (2014) The Making of Reaxys—Towards Unobstructed Access to Relevant Chemistry Information. In: ACS Symp Ser. ACS, pp. 127-148.

Lazos, O., Tosin, M., Slusarczyk, A.L., Boakes, S., Cortés, J., Sidebottom, P.J., and Leadlay, P.F. (2010) Biosynthesis of the putative siderophore erythrochelin requires unprecedented crosstalk between separate nonribosomal peptide gene clusters. *Chem Biol* **17**: 160-173.

Ledford, H. (2015) Promising antibiotic discovered in microbial 'dark matter'. *Nature* **10**.

Lee, A.J., Reiter, T., Doing, G., Oh, J., Hogan, D.A., and Greene, C.S. (2022) Using genome-wide expression compendia to study microorganisms. *Comput Struct Biotechnol J* **20**: 4315-4324.

Lewis, K. (2013) Platforms for antibiotic discovery. *Nat Rev Drug Discov* **12**: 371-387.
Li, Q., Qin, X., Liu, J., Gui, C., Wang, B., Li, J., and Ju, J. (2016) Deciphering the biosynthetic origin of L-allo-isoleucine. *J Am Chem Soc* **138**: 408-415.
Ling, L.L., Schneider, T., Peoples, A.J., Spoering, A.L., Engels, I., Conlon, B.P., Mueller, A., Schäberle, T.F., Hughes, D.E., and Epstein, S. (2015) A new antibiotic kills pathogens without detectable resistance. *Nature* **517**: 455-459.
Lingham, R.B.H., A. H.; O'Brien, J. A., Sigmund; J. M., Sanchez, M.; Gagliardi; M. M., Heimbuch; B. K.; Genilloud, O.; Martin, I., Diez; M. T., Hirsch; C. F., Zink; D. L., Liesch; J. M., Koch; G. E., Gartner; S. E., Garrity; G. M.; Tsou, N. N.; Salituro, G. M. (1996) Quinoxapeptins: Novel Chromodepsipeptide Inhibitors of HIV-1 and HIV-2 Reverse Transcriptase I. The Producing Organism and Biological Activity. *J Antibiot* **49**: 253-259.
Liu, M., and Douthwaite, S. (2002) Resistance to the macrolide antibiotic tylosin is conferred by single methylations at 23S rRNA nucleotides G748 and A2058 acting in synergy. *Proc Natl Acad Sci U S A* **99**: 14658-14663.
Liu, Z., Zhao, Y., Huang, C., and Luo, Y. (2021) Recent advances in silent gene cluster activation in *Streptomyces*. *Front Bioeng Biotechnol* **9**: 632230.
Loureiro, C., Galani, A., Gavriilidou, A., Chaib de Mares, M., van der Oost, J., Medema, M.H., and Sipkema, D. (2022) Comparative Metagenomic Analysis of Biosynthetic Diversity across Sponge Microbiomes Highlights Metabolic Novelty, Conservation, and Diversification. *mSystems* **7**: e0035722.
Ludwig, M., Nothias, L.-F., Dührkop, K., Koester, I., Fleischauer, M., Hoffmann, M.A., Petras, D., Vargas, F., Morsy, M., and Aluwihare, L. (2019) ZODIAC: Database-independent molecular formula annotation using Gibbs sampling reveals unknown small molecules. *biorxiv*: 842740.
Ma, Y., Kong, Q., Qin, C., Chen, Y., Chen, Y., Lv, R., and Zhou, G. (2016) Identification of lipopeptides in Bacillus megaterium by two-step ultrafiltration and LC-ESI-MS/MS. *AMB Express* **6**: 79.
Machushynets, N.V., Elsayed, S.S., Du, C., Siegler, M.A., de la Cruz, M., Genilloud, O., Hankemeier, T., and van Wezel, G.P. (2022) Discovery of actinomycin L, a new member of the actinomycin family of antibiotics. *Sci Rep* **12**: 2813.
Machushynets, N.V., Wu, C., Elsayed, S.S., Hankemeier, T., and van Wezel, G.P. (2019) Discovery of novel glycerolated quinazolinones from *Streptomyces* sp. MBT27. *Journal of industrial microbiology & biotechnology* **46**: 483-492.
Mackelprang, R., Waldrop, M.P., DeAngelis, K.M., David, M.M., Chavarria, K.L., Blazewicz, S.J., Rubin, E.M., and Jansson, J.K. (2011) Metagenomic analysis of a permafrost microbial community reveals a rapid response to thaw. *Nature* **480**: 368-371.
Malmierca, M.G., Gonzalez-Montes, L., Perez-Victoria, I., Sialer, C., Brana, A.F., Garcia Salcedo, R., Martin, J., Reyes, F., Mendez, C., Olano, C., and Salas, J.A. (2018) Searching for Glycosylated Natural Products in Actinomycetes and Identification of Novel Macrolactams and Angucyclines. *Front Microbiol* **9**: 39.
Mao, D., Okada, B.K., Wu, Y., Xu, F., and Seyedsayamdost, M.R. (2018) Recent advances in activating silent biosynthetic gene clusters in bacteria. *Curr Opin Microbiol* **45**: 156-163.
Maskey, R.P., Helmke, E., and Laatsch, H. (2003) Himalomycin A and B: isolation and structure elucidation of new fridamycin type antibiotics from a marine *Streptomyces* isolate. *J Antibiot (Tokyo)* **56**: 942-949.
Matsuda, K., Hasebe, F., Shiwa, Y., Kanesaki, Y., Tomita, T., Yoshikawa, H., Shin-ya, K., Kuzuyama, T., and Nishiyama, M. (2017) Genome Mining of Amino Group Carrier Protein-Mediated Machinery: Discovery and Biosynthetic Characterization of a Natural Product with Unique Hydrazone Unit. *ACS Chem Biol* **12**: 124-131.

Medema, M.H., Blin, K., Cimermancic, P., De Jager, V., Zakrzewski, P., Fischbach, M.A., Weber, T., Takano, E., and Breitling, R. (2011) antiSMASH: rapid identification, annotation and analysis of secondary metabolite biosynthesis gene clusters in bacterial and fungal genome sequences. *Nucleic Acids Res* **39**: W339-W346.

Meredith, N.Y., Borsley, S., Smolyar, I.V., Nichol, G.S., Baker, C.M., Ling, K.B., and Cockroft, S.L. (2022) Dissecting solvent effects on hydrogen bonding. *Angew Chem Int Ed Engl* **61**: e202206604.

Metsä-Ketelä, M., Ylihonko, K., and Mäntsälä, P. (2004) Partial activation of a silent angucycline-type gene cluster from a rubromycin β producing *Streptomyces* sp. PGA64. *J Antibiot* **57**: 502-510.

Mir-Mohamad-Sadeghy, B., and Rickborn, B. (1983) Benzo [f] isobenzofuran. Mechanistic aspects of isobenzofuran formation from acetals and ortho esters. *J Org Chem* **48**: 2237-2246.

Mladic, M., Slagboom, J., Kool, J., Vonk, F.J., van Wezel, G.P., and Richardson, M.K. (2018) Detection and identification of antibacterial proteins in snake venoms using at-line nanofractionation coupled to LC-MS. *Toxicon* **155**: 66-74.

Mladic, M., Zietek, B.M., Iyer, J.K., Hermarij, P., Niessen, W.M.A., Somsen, G.W., Kini, R.M., and Kool, J. (2016) At-line nanofractionation with parallel mass spectrometry and bioactivity assessment for the rapid screening of thrombin and factor Xa inhibitors in snake venoms. *Toxicon* **110**: 79-89.

Mohimani, H., Gurevich, A., Mikheenko, A., Garg, N., Nothias, L.-F., Ninomiya, A., Takada, K., Dorrestein, P.C., and Pevzner, P.A. (2017) Dereplication of peptidic natural products through database search of mass spectra. *Nat Chem Biol* **13**: 30-37.

Monteiro, M.C., de la Cruz, M., Cantizani, J., Moreno, C., Tormo, J.R., Mellado, E., De Lucas, J.R., Asensio, F., Valiante, V., Brakhage, A.A., Latge, J.P., Genilloud, O., and Vicente, F. (2012) A new approach to drug discovery: high-throughput screening of microbial natural extracts against Aspergillus fumigatus using resazurin. *J Biomol Screen* **17**: 542-549.

Moon, K., Xu, F., and Seyedsayamdost, M.R. (2019a) Cebulantin, a Cryptic Lanthipeptide Antibiotic Uncovered Using Bioactivity-Coupled HiTES. *Angew Chem Int Ed Engl* **58**: 5973-5977.

Moon, K., Xu, F., Zhang, C., and Seyedsayamdost, M.R. (2019b) Bioactivity-HiTES Unveils Cryptic Antibiotics Encoded in Actinomycete Bacteria. *ACS Chem Biol* **14**: 767-774.

Morgan, K.D., Andersen, R.J., and Ryan, K.S. (2019) Piperazic acid-containing natural products: structures and biosynthesis. *Nat Prod Rep* **36**: 1628-1653.

Motamedi, H., Shafiee, A., and Cai, S.J. (1995) Integrative vectors for heterologous gene expression in *Streptomyces* spp. *Gene* **160**: 25-31.

Mullowney, M.W., Duncan, K.R., Elsayed, S.S., Garg, N., van der Hooft, J.J.J., Martin, N.I., Meijer, D., Terlouw, B.R., Biermann, F., Blin, K., Durairaj, J., Gorostiola Gonzalez, M., Helfrich, E.J.N., Huber, F., Leopold-Messer, S., Rajan, K., de Rond, T., van Santen, J.A., Sorokina, M., Balunas, M.J., Beniddir, M.A., van Bergeijk, D.A., Carroll, L.M., Clark, C.M., Clevert, D.A., Dejong, C.A., Du, C., Ferrinho, S., Grisoni, F., Hofstetter, A., Jespers, W., Kalinina, O.V., Kautsar, S.A., Kim, H., Leao, T.F., Masschelein, J., Rees, E.R., Reher, R., Reker, D., Schwaller, P., Segler, M., Skinnider, M.A., Walker, A.S., Willighagen, E.L., Zdrazil, B., Ziemert, N., Goss, R.J.M., Guyomard, P., Volkamer, A., Gerwick, W.H., Kim, H.U., Muller, R., van Wezel, G.P., van Westen, G.J.P., Hirsch, A.K.H., Linington, R.G., Robinson, S.L., and Medema, M.H. (2023) Artificial intelligence for natural product drug discovery. *Nat Rev Drug Discov* **22**: 895-916.

Murray, C.J., Ikuta, K.S., Sharara, F., Swetschinski, L., Aguilar, G.R., Gray, A., Han, C., Bisignano, C., Rao, P., and Wool, E. (2022) Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* **399**: 629-655.

Myers, O.D., Sumner, S.J., Li, S., Barnes, S., and Du, X. (2017) One step forward for reducing false positive and false negative compound identifications from mass spectrometry metabolomics data: new algorithms for constructing extracted ion chromatograms and detecting chromatographic peaks. *Anal Chem* **89**: 8696-8703.

Nanjundan, J., Ramasamy, R., Uthandi, S., and Ponnusamy, M. (2019) Antimicrobial activity and spectroscopic characterization of surfactin class of lipopeptides from Bacillus amyloliquefaciens SR1. *Microb Pathog* **128**: 374-380.

Navarro-Muñoz, J.C., Selem-Mojica, N., Mullowney, M.W., Kautsar, S.A., Tryon, J.H., Parkinson, E.I., De Los Santos, E.L.C., Yeong, M., Cruz-Morales, P., Abubucker, S., Roeters, A., Lokhorst, W., Fernandez-Guerra, A., Cappelini, L.T.D., Goering, A.W., Thomson, R.J., Metcalf, W.W., Kelleher, N.L., Barona-Gomez, F., and Medema, M.H. (2020) A computational framework to explore large-scale biosynthetic diversity. *Nat Chem Biol* **16**: 60-68.

Navon-Venezia, S., Kondratyeva, K., and Carattoli, A. (2017) Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. *FEMS Microbiol rev* **41**: 252-275.

Nazari, B., Kobayashi, M., Saito, A., Hassaninasab, A., Miyashita, K., and Fujii, T. (2012) Chitin-induced gene expression involved in secondary metabolic pathways in *Streptomyces coelicolor* A3 (2) grown in soil. *Appl Environ Microbiol* **79**: 707-713.

Nett, M., Ikeda, H., and Moore, B.S. (2009) Genomic basis for natural product biosynthetic diversity in the actinomycetes. *Nat Prod Rep* **26**: 1362-1384.

Newman, D.J., and Cragg, G.M. (2007) Natural products as sources of new drugs over the last 25 years. *J Nat Prod* **70**: 461-477.

Newman, D.J., and Cragg, G.M. (2016) Natural products as sources of new drugs from 1981 to 2014. *J Nat Prod* **79**: 629-661.

Nothias, L.-F., Petras, D., Schmid, R., Dührkop, K., Rainer, J., Sarvepalli, A., Protsyuk, I., Ernst, M., Tsugawa, H., Fleischauer, M., Aicheler, F., Aksenov, A.A., Alka, O., Allard, P.-M., Barsch, A., Cachet, X., Caraballo-Rodriguez, A.M., Da Silva, R.R., Dang, T., Garg, N., Gauglitz, J.M., Gurevich, A., Isaac, G., Jarmusch, A.K., Kameník, Z., Kang, K.B., Kessler, N., Koester, I., Korf, A., Le Gouellec, A., Ludwig, M., Martin H, C., McCall, L.-I., McSayles, J., Meyer, S.W., Mohimani, H., Morsy, M., Moyne, O., Neumann, S., Neuweger, H., Nguyen, N.H., Nothias-Esposito, M., Paolini, J., Phelan, V.V., Pluskal, T., Quinn, R.A., Rogers, S., Shrestha, B., Tripathi, A., van der Hooft, J.J.J., Vargas, F., Weldon, K.C., Witting, M., Yang, H., Zhang, Z., Zubeil, F., Kohlbacher, O., Böcker, S., Alexandrov, T., Bandeira, N., Wang, M., and Dorrestein, P.C. (2020) Feature-based molecular networking in the GNPS analysis environment. *Nat Methods* **17**: 905-908.

Noutsias, D., and Vassilikogiannakis, G. (2012) First total synthesis of paracaseolide A. *Org Lett* **14**: 3565-3567.

Nunez Santiago, I., Machushynets, N.V., Mladic, M., van Bergeijk, D.A., Elsayed, S.S., Hankemeier, T., and van Wezel, G.P. (2024) nanoRAPIDS as an analytical pipeline for the discovery of novel bioactive metabolites in complex culture extracts at the nanoscale. *Commun Chem* **7**: 71.

Nuutila, A., Xiao, X., van der Heul, H.U., van Wezel, G.P., Dinis, P., Elsayed, S.S., and Metsä-Ketelä, M. (2024) Divergence of Classical and C-Ring-Cleaved Angucyclines: Elucidation of Early Tailoring Steps in Lugdunomycin and Thioangucycline Biosynthesis. *ACS Chem Biol* **19**: 1131-1141.

O'Neill (2014) Antimicrobial Resistance: Tackling a Crisis for the Health and Wealth of Nations. *AMR review* **UK Review on Antimicrobial Resistance**.

Oka, M., Kamei, H., Hamagishi, Y., Tomita, K., Miyaki, T., Konishi, M., and Oki, T. (1990) Chemical and Biological Properties of Rubiginone, a Complex of New Antibiotics with Vincristine-Cytotoxicity. *J Antibiot* **43**: 967-976.

Okada, B.K., and Seyedsayamdost, M.R. (2017) Antibiotic dialogues: induction of silent biosynthetic gene clusters by exogenous small molecules. *FEMS Microbiol Rev* **41**: 19-33.

Ory, L., Nazih, E.H., Daoud, S., Mocquard, J., Bourjot, M., Margueritte, L., Delsuc, M.A., Bard, J.M., Pouchus, Y.F., Bertrand, S., and Roullier, C. (2019) Targeting bioactive compounds in natural extracts - Development of a comprehensive workflow combining chemical and biological data. *Anal Chim Acta* **1070**: 29-42.

Palazzotto, E., Tong, Y., Lee, S.Y., and Weber, T. (2019) Synthetic biology and metabolic engineering of actinomycetes for natural product discovery. *Biotechnol Adv* **37**: 107366.

Pang, Z., Lu, Y., Zhou, G., Hui, F., Xu, L., Viau, C., Spigelman, A.F., MacDonald, P.E., Wishart, D.S., Li, S., and Xia, J. (2024) MetaboAnalyst 6.0: towards a unified platform for metabolomics data processing, analysis and interpretation. *Nucleic Acids Res* **52**: W398-W406.

Park, S.R., Tripathi, A., Wu, J., Schultz, P.J., Yim, I., McQuade, T.J., Yu, F., Arevang, C.-J., Mensah, A.Y., and Tamayo-Castillo, G. (2016) Discovery of cahuitamycins as biofilm inhibitors derived from a convergent biosynthetic pathway. *Nat Commun* **7**: 10710.

Pathak, K.V., and Keharia, H. (2014) Identification of surfactins and iturins produced by potent fungal antagonist, Bacillus subtilis K1 isolated from aerial roots of banyan (Ficus benghalensis) tree using mass spectrometry. *3 Biotech* **4**: 283-295.

Paulus, C., Rebets, Y., Tokovenko, B., Nadmid, S., Terekhova, L.P., Myronovskyi, M., Zotchev, S.B., Ruckert, C., Braig, S., Zahler, S., Kalinowski, J., and Luzhetskyy, A. (2017) New natural products identified by combined genomics-metabolomics profiling of marine *Streptomyces* sp. MP131-18. *Sci Rep* **7**: 42382.

Pence, H.E., and Williams, A. (2010) ChemSpider: An Online Chemical Information Resource. *J Chem Educ* **87**: 1123-1124.

Pluskal, T., Castillo, S., Villar-Briones, A., and Oresic, M. (2010) MZmine 2: modular framework for processing, visualizing, and analyzing mass spectrometry-based molecular profile data. *BMC Bioinformatics* **11**: 395.

Prianichnikov, N., Koch, H., Koch, S., Lubeck, M., Heilig, R., Brehmer, S., Fischer, R., and Cox, J. (2020) MaxQuant software for ion mobility enhanced shotgun proteomics. *Mol Cell Proteomics* **19**: 1058-1069.

Priya, A., Alagumalai, A., Balaji, D., and Song, H. (2023) Bio-based agricultural products: a sustainable alternative to agrochemicals for promoting a circular economy. *RSC Sustainability* **1**: 746-762.

Products, D.o.N., Dictionary of Natural Products In: CHEMnetBASE. pp.

Raghavan, V., and Groisman, E.A. (2010) Orphan and hybrid two-component system proteins in health and disease. *Curr Opin Microbiol* **13**: 226-231.

Raju, R., Gromyko, O., Fedorenko, V., Luzhetskyy, A., and Müller, R. (2013) Oleaceran: A Novel Spiro [isobenzofuran-1, 2′-naptho [1, 8-bc] furan] Isolated from a Terrestrial *Streptomyces* sp. *Org Lett* **15**: 3487-3489.

Rateb, M.E., Hallyburton, I., Houssen, W.E., Bull, A.T., Goodfellow, M., Santhanam, R., Jaspars, M., and Ebel, R. (2013) Induction of diverse secondary metabolites in Aspergillus fumigatus by microbial co-culture. *Rsc Advances* **3**: 14444-14450.

Rigali, S., Anderssen, S., Naômé, A., and van Wezel, G.P. (2018) Cracking the regulatory code of biosynthetic gene clusters as a strategy for natural product discovery. *Biochem Pharmacol* **153**: 24-34.

Rigali, S., Titgemeyer, F., Barends, S., Mulder, S., Thomae, A.W., Hopwood, D.A., and Van Wezel, G.P. (2008) Feast or famine: the global regulator DasR links nutrient stress to antibiotic production by *Streptomyces*. *EMBO reports* **9**: 670-675.

Rivers, M.A., and Lowell, A.N. (2024) Expanding the Biosynthetic Toolbox: The Potential and Challenges of In Vitro Type II Polyketide Synthase Research. *SynBio* **2**: 85-111.

Rix, U., Wang, C., Chen, Y., Lipata, F.M., Remsing Rix, L.L., Greenwell, L.M., Vining, L.C., Yang, K., and Rohr, J. (2005) The oxidative ring cleavage in jadomycin biosynthesis: a multistep oxygenation cascade in a biosynthetic black box. *Chembiochem* **6**: 838-845.

Rodríguez-García, A., de La Fuente, A., Pérez-Redondo, R., Martín, J.F., and Liras, P. (2000) Characterization and expression of the arginine biosynthesis gene cluster of *Streptomyces* clavuligerus. *Journal of industrial microbiology & biotechnology* **2**: 543-550.

Rohr, J., Schoenewolf, M., Udvarnoki, G., Eckardt, K., Schumann, G., Wagner, C., Beale, J.M., and Sorey, S.D. (1993) Investigations on the biosynthesis of the angucycline group antibiotics aquayamycin and the urdamycins A and B. Results from the structural analysis of novel blocked mutant products. *J Org Chem* **58**: 2547-2551.

Rohr, J., and Thiericke, R. (1992) Angucycline group antibiotics. *Nat Prod Rep* **9**: 103-137.

Rohr, J., and Zeeck, A. (1987) Metabolic products of microorganisms. 240. Urdamycins, new angucycline antibiotics from *Streptomyces fradiae*. II. Structural studies of urdamycins B to F. *J Antibiot (Tokyo)* **40**: 459-467.

Romano, S., Jackson, S.A., Patry, S., and Dobson, A.D. (2018) Extending the "one strain many compounds" (OSMAC) principle to marine microorganisms. *Mar Drugs* **16**: 244.

Romero-Rodríguez, A., Maldonado-Carmona, N., Ruiz-Villafán, B., Koirala, N., Rocha, D., and Sánchez, S. (2018) Interplay between carbon, nitrogen and phosphate utilization in the control of secondary metabolite production in *Streptomyces*. *AVL* **111**: 761-781.

Rosen, P.C., and Seyedsayamdost, M.R., (2017) Though much is taken, much abides: finding new antibiotics using old ones. In.: ACS Publications, pp. 4925-4926.

Rosenblatt-Farrell, N. (2009) The landscape of antibiotic resistance. *Environ Health Perspect* **117**: A244-250.

Rückert, F., Aust, D., Böhme, I., Werner, K., Brandt, A., Diamandis, E.P., Krautz, C., Hering, S., Saeger, H.-D., and Grützmann, R. (2012) Five primary human pancreatic adenocarcinoma cell lines established by the outgrowth method. *J Surg Res* **172**: 29-39.

Rüger, R., Franchini, M., Trnka, T., Yakovlev, A., van Lenthe, E., Philipsen, P., van Vuren, T., Klumpers, B., and Soini, T., Amsterdam Modeling Suite (AMS version: 2021.107), Software for Chemistry & Materials SCM, Theoretical Chemistry, Vrije Universiteit, Amsterdam, The Netherlands. In., pp.

Ruiu, L. (2018) Microbial Biopesticides in Agroecosystems. *Agronomy* **8**: 235.

Rutledge, P.J., and Challis, G.L. (2015) Discovery of microbial natural products by activation of silent biosynthetic gene clusters. *Nat Rev Microbiol* **13**: 509-523.

Sahayasheela, V.J., Lankadasari, M.B., Dan, V.M., Dastager, S.G., Pandian, G.N., and Sugiyama, H. (2022) Artificial intelligence in microbial natural product drug discovery: current and emerging role. *Nat Prod Rep* **39**: 2215-2230.

Saldivar-Gonzalez, F.I., Aldas-Bulos, V.D., Medina-Franco, J.L., and Plisson, F. (2022) Natural product drug discovery in the artificial intelligence era. *Chem Sci* **13**: 1526-1546.

Salek, R.M., Steinbeck, C., Viant, M.R., Goodacre, R., and Dunn, W.B. (2013) The role of reporting standards for metabolite annotation and identification in metabolomic studies. *GigaScience* **2**.

Sánchez, S., Chávez, A., Forero, A., García-Huante, Y., Romero, A., Sánchez, M., Rocha, D., Sánchez, B., Avalos, M., and Guzmán-Trampe, S. (2010) Carbon source regulation of antibiotic production. *J Antibiot* **63**: 442-459.

Santos, J.D., Vitorino, I., de la Cruz, M., Diaz, C., Cautain, B., Annang, F., Perez-Moreno, G., Gonzalez, I., Tormo, J.R., Martin, J., Vicente, M.F., and Lage, O.M. (2020) Diketopiperazines and other bioactive compounds from bacterial symbionts of marine sponges. *AVL* **113**: 875-887.

Scherlach, K., and Hertweck, C. (2009) Triggering cryptic natural product biosynthesis in microorganisms. *Org Biomol Chem* **7**: 1753-1760.

Schröder, S., Maier, A., Schmidt, S., Mügge, C., and Tischler, D. (2024) Enhancing biocatalytical NN bond formation with the actinobacterial piperazate synthase KtzT. *J Mol Catal* **553**: 113733.

Schroeckh, V., Scherlach, K., Nützmann, H.-W., Shelest, E., Schmidt-Heck, W., Schuemann, J., Martin, K., Hertweck, C., and Brakhage, A.A. (2009) Intimate bacterial–fungal interaction triggers biosynthesis of archetypal polyketides in Aspergillus nidulans. *PNAS* **106**: 14558-14563.

Selegato, D.M., and Castro-Gamboa, I. (2023) Enhancing chemical and biological diversity by co-cultivation. *Front Microbiol* **14**: 1117559.

Seong, J., Shin, J., Kim, K., and Cho, B.-K. (2021) Microbial production of nematicidal agents for controlling plant-parasitic nematodes. *Process Biochem* **108**: 69-79.

Seyedsayamdost, M.R. (2014) High-throughput platform for the discovery of elicitors of silent bacterial gene clusters. *Proc Natl Acad Sci U S A* **111**: 7266-7271.

Seyedsayamdost, M.R., Traxler, M.F., Clardy, J., and Kolter, R., (2012) Old meets new: using interspecies interactions to detect secondary metabolite production in actinomycetes. In: Methods Enzymol. Elsevier, pp. 89-109.

Sezaki M Fau - Hara, T., Hara T Fau - Ayukawa, S., Ayukawa S Fau - Takeuchi, T., Takeuchi T Fau - Okami, Y., and Okami, Y. Studies on a new antibiotic pigment, aquayamycin.

Shaaban, K.A., Ahmed, T.A., Leggas, M., and Rohr, J. (2012) Saquayamycins G–K, Cytotoxic Angucyclines from *Streptomyces* sp. Including Two Analogues Bearing the Aminosugar Rednose. *J Nat Prod* **75**: 1383-1392.

Shaaban, K.A., Srinivasan, S., Kumar, R., Damodaran, C., and Rohr, J. (2011) Landomycins P-W, cytotoxic angucyclines from *Streptomyces cyanogenus* S-136. *J Nat Prod* **74**: 2-11.

Shakya, M., Lo, C.C., and Chain, P.S.G. (2019) Advances and Challenges in Metatranscriptomic Analysis. *Front Genet* **10**: 904.

Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N., Schwikowski, B., and Ideker, T. (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. *Genome Res* **13**: 2498-2504.

Shen, B. (2015) A New Golden Age of Natural Products Drug Discovery. *Cell* **163**: 1297-1300.

Shigihara, Y.K., Y.; Tamamura, T.; Homma, Y.; Isshiki, K.; Dobashi, K.; Naganawa, H.; Takeuchi, T. (1988) 6-Deoxy-8-O-methylrabelomycin and 8-O-methylrabelomycin from a *Streptomyces* species. *J Antibiot* **41**: 1260-1264.

Silver, L.L. (2011) Challenges of antibacterial discovery. *CMR* **24**: 71-109.

Singh, S.B. (2014) Confronting the challenges of discovery of novel antibacterial agents. *Bioorg Med Chem Lett* **24**: 3683-3689.

Sood, S., Steinmetz, H., Beims, H., Mohr, K.I., Stadler, M., Djukic, M., von der Ohe, W., Steinert, M., Daniel, R., and Muller, R. (2014) Paenilarvins: Iturin family lipopeptides from the honey bee pathogen Paenibacillus larvae. *Chembiochem* **15**: 1947-1955.

Soulountsi, V., Schizodimos, T., and Kotoulas, S.C. (2021) Deciphering the epidemiology of invasive candidiasis in the intensive care unit: is it possible? *Infection* **49**: 1107-1131.

Standard, B., (2006) British Standard BS EN ISO 20776–1:2006.7. In., pp.

Strohalm, M., Kavan, D., Novak, P., Volny, M., and Havlicek, V. (2010) mMass 3: a cross-platform software environment for precise analysis of mass spectrometric data. *Anal Chem* **82**: 4648-4651.

Sugiyama, R., Nishimura, S., Ozaki, T., Asamizu, S., Onaka, H., and Kakeya, H. (2015) 5-Alkyl-1,2,3,4-tetrahydroquinolines, new membrane-interacting lipophilic metabolites produced by combined culture of *Streptomyces* nigrescens and Tsukamurella pulmonis. *Org Lett* **17**: 1918-1921.

Świątek-Połatyńska, M.A., Bucca, G., Laing, E., Gubbens, J., Titgemeyer, F., Smith, C.P., Rigali, S., and van Wezel, G.P. (2015) Genome-wide analysis of in vivo binding of the master regulator DasR in *Streptomyces coelicolor* identifies novel non-canonical targets. *PLoS One* **10**: e0122479.

Swiatek, M.A., Tenconi, E., Rigali, S., and van Wezel, G.P. (2012a) Functional analysis of the N-acetylglucosamine metabolic genes of *Streptomyces coelicolor* and role in the control of development and antibiotic production. *J Bacteriol* **194**: 1136-1144.

Swiatek, M.A., Urem, M., Tenconi, E., Rigali, S., and van Wezel, G.P. (2012b) Engineering of N-acetylglucosamine metabolism for improved antibiotic production in *Streptomyces coelicolor* A3 (2) and an unsuspected role of NagA in glucosamine metabolism. *Bioengineered* **3**: 280-285.

T., F., (2019) MSc thesis, Leiden Universiy, the Netherlands. In., pp.

Tanaka, Y., Komatsu, M., Okamoto, S., Tokuyama, S., Kaji, A., Ikeda, H., and Ochi, K. (2009) Antibiotic overproduction by *rpsL* and *rsmG* mutants of various actinomycetes. *Appl Environ Microbiol* **75**: 4919-4922.

Te Velde, G.t., Bickelhaupt, F.M., Baerends, E.J., Fonseca Guerra, C., van Gisbergen, S.J., Snijders, J.G., and Ziegler, T. (2001) Chemistry with ADF. *J Comput Chem* **22**: 931-967.

Teijaro, C.N., Adhikari, A., and Shen, B. (2019) Challenges and opportunities for natural product discovery, production, and engineering in native producers versus heterologous hosts. *Journal of industrial microbiology & biotechnology* **46**: 433-444.

Terlouw, B.R., Biermann, F., Vromans, S.P.J.M., Zamani, E., Helfrich, E.J.N., and Medema, M.H. (2024) RAIChU: automating the visualisation of natural product biosynthesis. *J Cheminform* **16**: 106.

Terlouw, B.R., Blin, K., Navarro-Muñoz, J.C., Avalon, N.E., Chevrette, M.G., Egbert, S., Lee, S., Meijer, D., Recchia, M.J., and Reitz, Z.L. (2023) MIBiG 3.0: a community-driven effort to annotate experimentally validated biosynthetic gene clusters. *Nucleic acids research* **51**: D603-D610.

Tobia, D., Harrison, R., Phillips, B., White, T.L., DiMare, M., and Rickborn, B. (1993) Unusual stability of N-methylmaleimide cycloadducts: characterization of isobenzofuran retro-Diels-Alder reactions. *J Org Chem* **58**: 6701-6706.

Tomono, A., Tsai, Y., Yamazaki, H., Ohnishi, Y., and Horinouchi, S. (2005) Transcriptional control by A-factor of strR, the pathway-specific transcriptional activator for streptomycin biosynthesis in *Streptomyces griseus*. *J Bacteriol* **187**: 5595-5604.

Tsukahara, K., Toume, K., Ishikawa, N., Abdelfattah, M.S., and Ishibashi, M. (2015) Novel cytotoxic isobenzofuran derivatives from *Streptomyces* sp. IFM 11490. *Tetrahedron lett* **56**: 6345-6347.

Uchida, T., Imoto, M., Watanabe, Y., Miura, K., Dobashi, T., Matsuda, N., Sawa, T., Naganawa, H., Hamada, M., and Takeuchi, T. (1985) Saquayamycins, new aquayamycin-group antibiotics. *J Antibiot (Tokyo)* **38**: 1171-1181.

Uiterweerd, M.T., and Minnaard, A.J. (2022) Racemic Total Synthesis of Elmonin and Pratenone A, from *Streptomyces*, Using a Common Intermediate Prepared by peri-Directed C-H Functionalization. *Org Lett* **24**: 9361-9365.

Uiterweerd, M.T., Santiago, I.N., Havenith, R., Du, C., Zhang, L., van der Heul, H., Elsayed, S., Minnaard, A., and van Wezel, G. (2024) Biomimetic total synthesis and paired omics identify an intermolecular Diels-Alder reaction as the key step in lugdunomycin biosynthesis.

Uiterweerd, M.T., Santiago, I.N., van der Heul, H.U., van Wezel, G.P., and Minnaard, A.J. (2020) Iso-maleimycin, a Constitutional Isomer of Maleimycin, from *Streptomyces* sp. QL37. *Eur J Org Chem* **2020**: 5145-5152.

Urem, M., Świątek-Połatyńska, M.A., Rigali, S., and van Wezel, G.P. (2016) Intertwining nutrient-sensory networks and the control of antibiotic production in *Streptomyces*. *Mol Microbiol* **102**: 183-195.

van Bergeijk, D.A., Elsayed, S.S., Du, C., Nuñez Santiago, I., Roseboom, A.M., Zhang, L., Carrion, V.J., Spaink, H.P., and van Wezel, G.P. (2022) The ubiquitous catechol moiety elicits siderophore and angucycline production in *Streptomyces*. *Comms Chem* **5**: 14.

van Bergeijk, D.A., Terlouw, B.R., Medema, M.H., and van Wezel, G.P. (2020) Ecology and genomics of Actinobacteria: new concepts for natural product discovery. *Nat Rev Microbiol* **18**: 546-558.

van der Heul, H., (2022) Analysis of the angucycline biosynthetic gene cluster in *Streptomyces* sp. QL37 and implications for lugdunomycin production. In.: Leiden University, pp.

Van Der Heul, H.U., Bilyk, B.L., McDowall, K.J., Seipke, R.F., and Van Wezel, G.P. (2018) Regulation of antibiotic production in Actinobacteria: new perspectives from the post-genomic era. *Nat Prod Rep* **35**: 575-604.

van der Meij, A., Elsayed, S.S., Du, C., Willemse, J., Wood, T.M., Martin, N.I., Raaijmakers, J.M., and van Wezel, G.P. (2023) The plant stress hormone jasmonic acid evokes defensive responses in streptomycetes. *Appl Environ Microbiol* **89**: e0123923.

van der Meij, A., Worsley, S.F., Hutchings, M.I., and van Wezel, G.P. (2017) Chemical ecology of antibiotic production by actinomycetes. *FEMS Microbiol Rev* **41**: 392-416.

van Santen, J.A., Jacob, G., Singh, A.L., Aniebok, V., Balunas, M.J., Bunsko, D., Neto, F.C., Castano-Espriu, L., Chang, C., Clark, T.N., Cleary Little, J.L., Delgadillo, D.A., Dorrestein, P.C., Duncan, K.R., Egan, J.M., Galey, M.M., Haeckl, F.P.J., Hua, A., Hughes, A.H., Iskakova, D., Khadilkar, A., Lee, J.H., Lee, S., LeGrow, N., Liu, D.Y., Macho, J.M., McCaughey, C.S., Medema, M.H., Neupane, R.P., O'Donnell, T.J., Paula, J.S., Sanchez, L.M., Shaikh, A.F., Soldatou, S., Terlouw, B.R., Tran, T.A., Valentine, M., van der Hooft, J.J.J., Vo, D.A., Wang, M., Wilson, D., Zink, K.E., and Linington, R.G. (2019) The natural products atlas: an open access knowledge base for microbial natural products discovery. *ACS Cent Sci* **5**: 1824-1833.

Vara, J., Lewandowska-Skarbek, M., Wang, Y.-G., Donadio, S., and Hutchinson, C. (1989) Cloning of genes governing the deoxysugar portion of the erythromycin biosynthesis pathway in *Saccharopolyspora erythraea* (*Streptomyces erythreus*). *J Bacteriol* **171**: 5872-5881.

Vicente, F., Basilio, A., Platas, G., Collado, J., Bills, G.F., Gonzalez del Val, A., Martin, J., Tormo, J.R., Harris, G.H., Zink, D.L., Justice, M., Kahn, J.N., and Pelaez, F. (2009) Distribution of the antifungal agents sordarins across filamentous fungi. *Mycol Res* **113**: 754-770.

Wakefield, J., Hassan, H.M., Jaspars, M., Ebel, R., and Rateb, M.E. (2017) Dual induction of new microbial secondary metabolites by fungal bacterial co-cultivation. *Front Microbiol* **8**: 1284.

Wang, J., Zhang, R., Chen, X., Sun, X., Yan, Y., Shen, X., and Yuan, Q. (2020) Biosynthesis of aromatic polyketides in microorganisms using type II polyketide synthases. *Microb Cell Fact* **19**: 110.

Wang, M., Carver, J.J., Phelan, V.V., Sanchez, L.M., Garg, N., Peng, Y., Nguyen, D.D., Watrous, J., Kapono, C.A., Luzzatto-Knaan, T., Porto, C., Bouslimani, A., Melnik, A.V., Meehan, M.J., Liu, W.T., Crusemann, M., Boudreau, P.D., Esquenazi, E., Sandoval-Calderon, M., Kersten, R.D., Pace, L.A., Quinn, R.A., Duncan, K.R., Hsu, C.C., Floros, D.J., Gavilan, R.G., Kleigrewe, K., Northen, T., Dutton, R.J., Parrot, D., Carlson, E.E., Aigle, B., Michelsen, C.F., Jelsbak, L., Sohlenkamp, C., Pevzner, P., Edlund, A., McLean, J., Piel, J., Murphy, B.T., Gerwick, L., Liaw, C.C., Yang, Y.L., Humpf, H.U., Maansson, M., Keyzers, R.A., Sims, A.C., Johnson, A.R., Sidebottom, A.M., Sedio, B.E., Klitgaard, A., Larson, C.B., P, C.A.B., Torres-Mendoza, D., Gonzalez, D.J., Silva, D.B., Marques, L.M., Demarque, D.P., Pociute, E., O'Neill, E.C., Briand, E., Helfrich, E.J.N., Granatosky, E.A., Glukhov, E., Ryffel, F., Houson, H., Mohimani, H., Kharbush, J.J., Zeng, Y., Vorholt, J.A., Kurita, K.L., Charusanti, P., McPhail, K.L., Nielsen, K.F., Vuong, L., Elfeki, M., Traxler, M.F., Engene, N., Koyama, N., Vining, O.B., Baric, R., Silva, R.R., Mascuch, S.J., Tomasi, S., Jenkins, S., Macherla, V., Hoffman, T., Agarwal, V., Williams, P.G., Dai, J., Neupane, R., Gurr, J., Rodriguez, A.M.C., Lamsa, A., Zhang, C., Dorrestein, K., Duggan, B.M., Almaliti, J., Allard, P.M., Phapale, P*., et al.* (2016) Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. *Nat Biotechnol* **34**: 828-837.

Wang, T., and Hoye, T.R. (2015) Diels–Alderase-free, bis-pericyclic,[4+ 2] dimerization in the biosynthesis of (±)-paracaseolide A. *Nat Chem* **7**: 641-645.

Wang, W., Kim, S., Vu, T.H.N., Quach, N.T., Oh, E., Park, K.-H., Park, C., Cho, Y., Jang, H., and Roh, E. (2023) Bioactive Piperazic Acid-Bearing Cyclodepsipeptides, Lydiamycins E–H, from an Endophytic *Streptomyces* sp. Associated with Cinnamomum cassia. *J Nat Prod* **86**: 751-758.

Weber, T., Blin, K., Duddela, S., Krug, D., Kim, H.U., Bruccoleri, R., Lee, S.Y., Fischbach, M.A., Müller, R., and Wohlleben, W. (2015) antiSMASH 3.0—a comprehensive resource for the genome mining of biosynthetic gene clusters. *Nucleic Acids Res* **43**: W237-W243.

Wei, Z.-W., Niikura, H., Morgan, K.D., Vacariu, C.M., Andersen, R.J., and Ryan, K.S. (2022) Free piperazic acid as a precursor to nonribosomal peptides. *J Am Chem Soc* **144**: 13556-13564.

Wenzel, S.C., and Muller, R. (2005) Recent developments towards the heterologous expression of complex bacterial natural product biosynthetic pathways. *Curr Opin Biotechnol* **16**: 594-606.

Wersmeyer-Wenk, B., Zähner, H., Krone, B., and Zeeck, A. (1981) Metabolic products of microorganisms. 207 Haloquinone, a new antibiotic active against halobacteria I. Isolation, characterization and biological properties. *J Antibiot* **34**: 1531-1537.
Westhoff, S., Kloosterman, A.M., van Hoesel, S.F.A., van Wezel, G.P., and Rozen, D.E. (2021) Competition Sensing Changes Antibiotic Production in *Streptomyces*. *mBio* **12**.
Wietzorrek, A., and Bibb, M. (1997) A novel family of proteins that regulates antibiotic production in streptomycetes appears to contain an OmpR-like DNA-binding fold. *Mol Microbiol* **25**: 1181-1184.
Willey, J.M., and Gaskell, A.A. (2011) Morphogenetic signaling molecules of the streptomycetes. *Chem Rev* **111**: 174-187.
Wolf, F., Bauer, J.S., Bendel, T.M., Kulik, A., Kalinowski, J., Gross, H., and Kaysser, L. (2017) Biosynthesis of the β-Lactone Proteasome Inhibitors Belactosin and Cystargolide. *Angew Chem Int Ed Engl* **56**: 6665-6668.
Wong, F., Zheng, E.J., Valeri, J.A., Donghia, N.M., Anahtar, M.N., Omori, S., Li, A., Cubillos-Ruiz, A., Krishnan, A., Jin, W., Manson, A.L., Friedrichs, J., Helbig, R., Hajian, B., Fiejtek, D.K., Wagner, F.F., Soutter, H.H., Earl, A.M., Stokes, J.M., Renner, L.D., and Collins, J.J. (2024) Discovery of a structural class of antibiotics with explainable deep learning. *Nature* **626**: 177-185.
Wright, G.D. (2014) Something old, something new: revisiting natural products in antibiotic drug discovery. *Can J Microbiol* **60**: 147-154.
Wright, G.D. (2015) Solving the antibiotic crisis. *ACS Infect Dis* **1**: 80-84.
Wu, C., Du, C., Gubbens, J., Choi, Y.H., and van Wezel, G.P. (2015a) Metabolomics-Driven Discovery of a Prenylated Isatin Antibiotic Produced by *Streptomyces* Species MBT28. *J Nat Prod* **78**: 2355-2363.
Wu, C., Shang, Z., Lemetre, C., Ternei, M.A., and Brady, S.F. (2019a) Cadasides, calcium-dependent acidic lipopeptides from the soil metagenome that are active against multidrug-resistant bacteria. *J Am Chem Soc* **141**: 3910-3919.
Wu, C., van der Heul, H.U., Melnik, A.V., Lubben, J., Dorrestein, P.C., Minnaard, A.J., Choi, Y.H., and van Wezel, G.P. (2019b) Lugdunomycin, an angucycline-derived molecule with unprecedented chemical architecture. *Angew Chem Int Ed Engl* **58**: 2809-2814.
Wu, C., Zacchetti, B., Ram, A.F., van Wezel, G.P., Claessen, D., and Hae Choi, Y. (2015b) Expanding the chemical space for natural products by *Aspergillus-Streptomyces* co-cultivation and biotransformation. *Sci Rep* **5**: 10868.
Xiao, X., Elsayed, S.S., Wu, C., van der Heul, H.U., Metsa-Ketela, M., Du, C., Prota, A.E., Chen, C.C., Liu, W., Guo, R.T., Abrahams, J.P., and van Wezel, G.P. (2020) Functional and Structural Insights into a Novel Promiscuous Ketoreductase of the Lugdunomycin Biosynthetic Pathway. *ACS Chem Biol* **15**: 2529-2538.
Xu, F., Nazari, B., Moon, K., Bushin, L.B., and Seyedsayamdost, M.R. (2017) Discovery of a cryptic antifungal compound from *Streptomyces albus* J1074 using high-throughput elicitor screens. *J Am Chem Soc* **139**: 9203-9212.
Ye, Y.-f., Li, Q.-q., Fu, G., Yuan, G.-q., Miao, J.-h., and Lin, W. (2012) Identification of Antifungal Substance (Iturin A2) Produced by Bacillus subtilis B47 and Its Effect on Southern Corn Leaf Blight. *J Integr Agric* **11**: 90-99.
Yoon, V., and Nodwell, J.R. (2014) Activating secondary metabolism with stress and chemicals. *Journal of industrial microbiology & biotechnology* **41**: 415-424.
Zdouc, M.M., Bayona Maldonado, L.M., Augustijn, H.E., Soldatou, S., de Jonge, N., Jaspars, M., van Wezel, G.P., Medema, M.H., and van der Hooft, J.J. (2022) FERMO: a dashboard for streamlined rationalized prioritization of molecular features from mass spectrometry data. *bioRxiv*: 2022.2012. 2021.521422.

Zdouc, M.M., Iorio, M., Vind, K., Simone, M., Serina, S., Brunati, C., Monciardini, P., Tocchetti, A., Zarazua, G.S., Crusemann, M., Maffioli, S.I., Sosio, M., and Donadio, S. (2021) Effective approaches to discover new microbial metabolites in a large strain library. *Journal of industrial microbiology & biotechnology* **48**.

Zhang, C., and Seyedsayamdost, M.R. (2020) CanE, an Iron/2-Oxoglutarate-Dependent Lasso Peptide Hydroxylase from *Streptomyces* canus. *ACS Chem Biol* **15**: 890-894.

Zhang, J., Sun, Y., Wang, Y., Chen, X., Xue, L., Zhang, J., Zhu, X., Duan, Y., and Yan, X. (2021) Genome mining of novel rubiginones from *Streptomyces* sp. CB02414 and characterization of the post-PKS modification steps in rubiginone biosynthesis. *Microb cell fact* **20**: 1-14.

Zhang, J.H., Chung, T.D., and Oldenburg, K.R. (1999) A Simple Statistical Parameter for Use in Evaluation and Validation of High Throughput Screening Assays. *J Biomol Screen* **4**: 67-73.

Zhang, Y., Feng, L., Hemu, X., Tan, N.H., and Wang, Z. (2024) OSMAC Strategy: A promising way to explore microbial cyclic peptides. *Eur J Med Chem* **268**: 116175.

Zhao, S., Xia, Y., Liu, H., Cui, T., Fu, P., and Zhu, W. (2022) A cyclohexapeptide and its rare glycosides from marine sponge-derived *Streptomyces* sp. OUCMDZ-4539. *Org Lett* **24**: 6750-6754.

Zheng, C., Xie, T., He, H., and Gao, S. (2021) Asymmetric Total Synthesis of PD-116740. *Org Lett* **23**: 469-473.

Zheng, Q., Tian, Z., and Liu, W. (2016) Recent advances in understanding the enzymatic reactions of [4+ 2] cycloaddition and spiroketalization. *Curr Opin Chem Biol* **31**: 95-102.

Zhou, H., Wang, Y., Yu, Y., Bai, T., Chen, L., Liu, P., Guo, H., Zhu, C., Tao, M., and Deng, Z. (2012) A non-restricting and non-methylating Escherichia coli strain for DNA cloning and high-throughput conjugation to *Streptomyces coelicolor*. *Curr Microbiol* **64**: 185-190.

Zhu, H., Swierstra, J., Wu, C., Girard, G., Choi, Y.H., van Wamel, W., Sandiford, S.K., and van Wezel, G.P. (2014) Eliciting antibiotics active against the ESKAPE pathogens in a collection of actinomycetes isolated from mountain soils. *Microbiology* **160**: 1714-1725.

Zietek, B.M., Mladic, M., Bruyneel, B., Niessen, W.M.A., Honing, M., Somsen, G.W., and Kool, J. (2017) Nanofractionation platform with parallel mass spectrometry for identification of CYP1A2 inhibitors in metabolic mixtures. *SLAS Discov.* **23**: 283-293.

Curriculum Vitae

Curriculum Vitae

Isabel Núñez Santiago was born in Madrid, Spain. From an early age, she developed a strong interest in biology, particularly marine biology. However, due to her tendency to experience seasickness on boats, she decided to pursue a degree in Biología Sanitaria at the University of Alcalá de Henares, where she spent some of the most memorable years of her life.

In her fourth year, driven by a desire to explore new countries, she participated in an Erasmus exchange program in Leiden University, where she completed a minor in Molecular Biotechnology. During this time, she was introduced to the world of *Streptomyces* and had the opportunity to complete an internship in this field.

Following this experience, she enrolled in the Microbial Biotechnology and Health master's program at Leiden University. Her first internship allowed her to gain insight into natural products produced by streptomycetes, in the research group of Prof. Gilles van Wezel. For her second internship, she decided to move abroad again, joining the University of Cambridge to work on antimicrobial persisters in *E. coli* under the supervision of Dr. David Summers.

Her passion for *Streptomyces* remained strong, leading her to pursue a PhD in the research group of Prof. van Wezel. After the COVID-19 pandemic, during her third year of PhD and motivated by her enthusiasm for teaching and mentoring students, she decided to complete a distance master's degree in Education at the Universidad del Atlántico Medio. This additional qualification contributed to her to obtaining the University Teaching Qualification (BKO) during her PhD.

Currently, she works as a Lecturer and Project Manager at Leiden University.