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REFERENCES

- Abdelfattah, M.S., Kharel, M.K., Hitron, J.A., Baig, I., and Rohr, J. (2008) Moromycins A and B, isolation and structure elucidation of C-glycosylangucycline-type antibiotics from *Streptomyces* sp. KY002. *J Nat Prod* **71**: 1569-1573.
- Adams, D.W., and Errington, J. (2009) Bacterial cell division: assembly, maintenance and disassembly of the Z ring. *Nat Rev Microbiol* **7**: 642-653.
- Adams, M.A., and Jia, Z. (2005) Structural and biochemical evidence for an enzymatic quinone redox cycle in *Escherichia coli*: identification of a novel quinol monooxygenase. *J Biol Chem* **280**: 8358-8363.
- Addinall, S.G., and Lutkenhaus, J. (1996) FtsZ-spirals and -arcs determine the shape of the invaginating septa in some mutants of *Escherichia coli*. *Mol Microbiol* **22**: 231-237.
- Aparicio, J.F., Caffrey, P., Gil, J.A., and Zotchev, S.B. (2003) Polyene antibiotic biosynthesis gene clusters. *Appl Microbiol Biotechnol* **61**: 179-188.
- Azumi, M., Ishidoh, K., Kinoshita, H., Nihira, T., Ihara, F., Fujita, T., and Igarashi, Y. (2008) Aurovertins F-H from the entomopathogenic fungus *Metarhizium anisopliae*. *J Nat Prod* **71**: 278-280.
- Bagchi, S., Tomenius, H., Belova, L.M., and Ausmees, N. (2008) Intermediate filament-like proteins in bacteria and a cytoskeletal function in *Streptomyces*. *Mol Microbiol* **70**: 1037-1050.
- Bailey, S. (1994) The ccp4 suite - programs for protein crystallography. *Acta Crystallogr D* **50**: 760-763.
- Balitz, D.M., O'Herron, F.A., Bush, J., Vyas, D.M., Nettleton, D.E., Grulich, R.E., Bradner, W.T., Doyle, T.W., Arnold, E., and Clardy, J. (1981) Antitumor agents from *Streptomyces anandii*: gilvocarcins V, M and E. *J Antibiot (Tokyo)* **34**: 1544-1555.
- 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 *Actinobacteria*. *Microbiol Mol Biol Rev* **80**: 1-43.

- Baugh, L., Phan, I., Begley, D.W., Clifton, M.C., Armour, B., Dranow, D.M., Taylor, B.M., Muruthi, M.M., Abendroth, J., Fairman, J.W., Fox, D., 3rd, Dieterich, S.H., Staker, B.L., Gardberg, A.S., Choi, R., Hewitt, S.N., Napuli, A.J., Myers, J., Barrett, L.K., Zhang, Y., Ferrell, M., Mundt, E., Thompkins, K., Tran, N., Lyons-Abbott, S., Abramov, A., Sekar, A., Serbzhinskiy, D., Lorimer, D., Buchko, G.W., Stacy, R., Stewart, L.J., Edwards, T.E., Van Voorhis, W.C., and Myler, P.J. (2015) Increasing the structural coverage of tuberculosis drug targets. *Tuberculosis (Edinb)* **95**: 142-148.
- Belyaeva, O.V., Wu, L.Z., Shmarakov, I., Nelson, P.S., and Kedishvili, N.Y. (2018) Retinol dehydrogenase 11 is essential for the maintenance of retinol homeostasis in liver and testis in mice. *J Biol Chem* **293**: 6996-7007.
- Bentley, S.D., Chater, K.F., Cerdeño-Tárraga, 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., Rabinowitsch, 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.
- Berendsen, H.J.C., Grigera, J.R., and Straatsma, T.P. (1987) The Missing Term in Effective Pair Potentials. *J Phys Chem-Us* **91**: 6269-6271.
- Berk, H., and Thauer, R.K. (1997) Function of coenzyme F420-dependent NADP reductase in methanogenic archaea containing an NADP-dependent alcohol dehydrogenase. *Arch Microbiol* **168**: 396-402.
- Berman, H., Henrick, K., and Nakamura, H. (2003) Announcing the worldwide Protein Data Bank. *Nat Struct Biol* **10**: 980-980.
- Bi, E.F., and Lutkenhaus, J. (1991) FtsZ ring structure associated with division in *Escherichia coli*. *Nature* **354**: 161-164.
- Bibb, M.J. (2005) Regulation of secondary metabolism in streptomycetes. *Curr Opin Microbiol* **8**: 208-215.
- Bilyk, O., Sekurova, O.N., Zotchev, S.B., and Luzhetskyy, A. (2016) Cloning and Heterologous Expression of the Grecoacycline Biosynthetic Gene Cluster. *PLoS One* **11**: e0158682.
- Bisson-Filho, A.W., Hsu, Y.P., Squyres, G.R., Kuru, E., Wu, F., Jukes, C., Sun, Y., Dekker, C., Holden, S., VanNieuwenhze, M.S., Brun, Y.V., and Garner, E.C. (2017) Treadmilling by FtsZ filaments drives peptidoglycan synthesis and bacterial cell division. *Science* **355**: 739-743.
- Blin, K., Pascal Andreu, V., de Los Santos, E.L.C., Del Carratore, F., Lee, S.Y., Medema, M.H., and Weber, T. (2019) The antiSMASH database version 2: a comprehensive resource on secondary metabolite biosynthetic gene clusters. *Nucleic Acids Res* **47**: D625-D630.
- Blount, J.F., Greeley, D.N., Maehr, H., Perrotta, A., Pitcher, R.G., Todaro, L., and Williams, T.H. (1985) Microbial products. VII. The relative configuration of actinomycete metabolite X-14881D. *J Antibiot (Tokyo)* **38**: 1270-1272.

- Borissow, C.N., Graham, C.L., Syvitski, R.T., Reid, T.R., Blay, J., and Jakeman, D.L. (2007) Stereochemical integrity of oxazolone ring-containing jadomycins. *Chembiochem* **8**: 1198-1203.
- Brown, A.S., Calcott, M.J., Owen, J.G., and Ackerley, D.F. (2018) Structural, functional and evolutionary perspectives on effective re-engineering of non-ribosomal peptide synthetase assembly lines. *Nat Prod Rep* **35**: 1210-1228.
- Bussi, G., Zykova-Timan, T., and Parrinello, M. (2009) Isothermal-isobaric molecular dynamics using stochastic velocity rescaling. *J Chem Phys* **130**.
- Celler, K., Koning, R.I., Koster, A.J., and van Wezel, G.P. (2013) Multidimensional view of the bacterial cytoskeleton. *J Bacteriol* **195**: 1627-1636.
- Celler, K., Koning, R.I., Willemse, J., Koster, A.J., and van Wezel, G.P. (2016) Cross-membranes orchestrate compartmentalization and morphogenesis in *Streptomyces*. *Nat Commun* **7**: ncomms11836.
- Challis, G.L. (2014) Exploitation of the *Streptomyces coelicolor* A3(2) genome sequence for discovery of new natural products and biosynthetic pathways. *J Ind Microbiol Biotechnol* **41**: 219-232.
- Chen, Y.H., Wang, C.C., Greenwell, L., Rix, U., Hoffmeister, D., Vining, L.C., Rohr, J., and Yang, K.Q. (2005) Functional analyses of oxygenases in jadomycin biosynthesis and identification of JadH as a bifunctional oxygenase/dehydrase. *J Biol Chem* **280**: 22508-22514.
- Chu, M., Yarborough, R., Schwartz, J., Patel, M.G., Horan, A.C., Gullo, V.P., Das, P.R., and Puar, M.S. (1993) Sch 47554 and Sch 47555, two novel antifungal antibiotics produced from a *Streptomyces* sp. *J Antibiot (Tokyo)* **46**: 861-865.
- Claessen, D., Rozen, D.E., Kuipers, O.P., Sogaard-Andersen, L., and van Wezel, G.P. (2014) Bacterial solutions to multicellularity: a tale of biofilms, filaments and fruiting bodies. *Nat Rev Microbiol* **12**: 115-124.
- Colis, L.C., Woo, C.M., Hegan, D.C., Li, Z., Glazer, P.M., and Herzon, S.B. (2014) The cytotoxicity of (-)-lomaiviticin A arises from induction of double-strand breaks in DNA. *Nat Chem* **6**: 504-510.
- Crawford, J.L., Lipscomb, W.N., and Schellman, C.G. (1973) The reverse turn as a polypeptide conformation in globular proteins. *Proc Natl Acad Sci U S A* **70**: 538-542.
- 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.
- Dann, M., Lefemine, D.V., Barbatschi, F., Shu, P., Kunstmann, M.P., Mitscher, L.A., and Bohonos, N. (1965) Tetrangomycin, a new quinone antibiotic. *Antimicrob Agents Chemother* **5**: 832-835.
- Darden, T., York, D., and Pedersen, L. (1993) Particle Mesh Ewald - an N.Log(N) Method for Ewald Sums in Large Systems. *J Chem Phys* **98**: 10089-10092.
- Davis, I.W., Leaver-Fay, A., Chen, V.B., Block, J.N., Kapral, G.J., Wang, X., Murray, L.W., Arendall, W.B., 3rd, Snoeyink, J., Richardson, J.S., and Richardson, D.C. (2007) MolProbity: all-atom contacts and structure validation for proteins and nucleic acids. *Nucleic Acids Res* **35**: W375-383.

- de Boer, P., Crossley, R., and Rothfield, L. (1992) The essential bacterial cell-division protein FtsZ is a GTPase. *Nature* **359**: 254-256.
- Demain, A.L. (2014) Importance of microbial natural products and the need to revitalize their discovery. *J Ind Microbiol Biotechnol* **41**: 185-201.
- Dewick, P.M. (2002) The biosynthesis of C5-C25 terpenoid compounds. *Nat Prod Rep* **19**: 181-222.
- Di Marco, A., Gaetani, M., Orezzi, P., Scarpinato, B.M., Silvestrini, R., Soldati, M., Dasdia, T., and Valentini, L. (1964) 'Daunomycin', a New Antibiotic of the Rhodomycin Group. *Nature* **201**: 706-707.
- Dickens, M.L., Ye, J.S., and Strohl, W.R. (1996) Cloning, sequencing, and analysis of aklaviketone reductase from *Streptomyces* sp strain C5. *J Bacteriol* **178**: 3384-3388.
- Distler, U., Kuharev, J., Navarro, P., Levin, Y., Schild, H., and Tenzer, S. (2014) Drift time-specific collision energies enable deep-coverage data-independent acquisition proteomics. *Nat Methods* **11**: 167-170.
- Donovan, C., and Bramkamp, M. (2014) Cell division in *Corynebacterineae*. *Front Microbiol* **5**: 132.
- Drautz, H., Zahner, H., Rohr, J., and Zeeck, A. (1986) Metabolic products of microorganisms. 234. Urdamycins, new angucycline antibiotics from *Streptomyces fradiae*. I. Isolation, characterization and biological properties. *J Antibiot (Tokyo)* **39**: 1657-1669.
- Dulmage, H.T. (1953) The Production of Neomycin by *Streptomyces fradiae* in Synthetic Media. *Appl Microbiol* **1**: 103-106.
- Dupuis, S.N., Veinot, T., Monro, S.M., Douglas, S.E., Syvitski, R.T., Goralski, K.B., McFarland, S.A., and Jakeman, D.L. (2011) Jadomycins derived from the assimilation and incorporation of norvaline and norleucine. *J Nat Prod* **74**: 2420-2424.
- El-Gebali, S., Mistry, J., Bateman, A., Eddy, S.R., Luciani, A., Potter, S.C., Qureshi, M., Richardson, L.J., Salazar, G.A., Smart, A., Sonnhammer, E.L.L., Hirsh, L., Paladin, L., Piovesan, D., Tosatto, S.C.E., and Finn, R.D. (2019) The Pfam protein families database in 2019. *Nucleic Acids Res* **47**: D427-D432.
- Elespuru, R.K., and Gonda, S.K. (1984) Activation of antitumor agent gilvocarcins by visible light. *Science* **223**: 69-71.
- Emsley, P., Lohkamp, B., Scott, W.G., and Cowtan, K. (2010) Features and development of Coot. *Acta Crystallogr D* **66**: 486-501.
- Erb, A., Luzhetskyy, A., Hardter, U., and Bechthold, A. (2009) Cloning and Sequencing of the Biosynthetic Gene Cluster for Saquayamycin Z and Galtamycin B and the Elucidation of the Assembly of Their Saccharide Chains. *Chembiochem* **10**: 1392-1401.
- Erickson, H.P., Taylor, D.W., Taylor, K.A., and Bramhill, D. (1996) Bacterial cell division protein FtsZ assembles into protofilament sheets and minirings, structural homologs of tubulin polymers. *Proc Natl Acad Sci U S A* **93**: 519-523.
- Eustaquio, A.S., Janso, J.E., Ratnayake, A.S., O'Donnell, C.J., and Koehn, F.E. (2014) Spliceostatin hemiketal biosynthesis in *Burkholderia* spp. is catalyzed by an iron/alpha-ketoglutarate-dependent dioxygenase. *Proc Natl Acad Sci U S A* **111**: E3376-3385.
- Evans, P.R., and Murshudov, G.N. (2013) How good are my data and what is the resolution? *Acta Crystallogr D* **69**: 1204-1214.

- Fan, K., Pan, G., Peng, X., Zheng, J., Gao, W., Wang, J., Wang, W., Li, Y., and Yang, K. (2012) Identification of JadG as the B ring opening oxygenase catalyzing the oxidative C-C bond cleavage reaction in jadomycin biosynthesis. *Chem Biol* **19**: 1381-1390.
- Fattorusso, E., and Tagliatalata-Scafati, O., (2007) *Modern alkaloids: Structure, isolation, synthesis and biology*. Wiley-VCH, Weinheim.
- Fedorushyn, M., Welle, E., Bechthold, A., and Luzhetskyy, A. (2008) Functional expression of the Cre recombinase in actinomycetes. *Appl Microbiol Biotechnol* **78**: 1065-1070.
- Feitelson, J.S., Malpartida, F., and Hopwood, D.A. (1985) Genetic and biochemical characterization of the *red* gene cluster of *Streptomyces coelicolor* A3(2). *J Gen Microbiol* **131**: 2431-2441.
- Feng, Z., Kim, J.H., and Brady, S.F. (2010) Fluostatins produced by the heterologous expression of a TAR reassembled environmental DNA derived type II PKS gene cluster. *J Am Chem Soc* **132**: 11902-11903.
- Fidan, O., Yan, R., Gladstone, G., Zhou, T., Zhu, D., and Zhan, J. (2018) New Insights into the Glycosylation Steps in the Biosynthesis of Sch47554 and Sch47555. *Chembiochem* **19**: 1424-1432.
- Filling, C., Berndt, K.D., Benach, J., Knapp, S., Prozorovski, T., Nordling, E., Ladenstein, R., Jornvall, H., and Oppermann, U. (2002) Critical residues for structure and catalysis in short-chain dehydrogenases/reductases. *J Biol Chem* **277**: 25677-25684.
- Fischer, C., Lipata, F., and Rohr, J. (2003) The complete gene cluster of the antitumor agent gilvocarcin V and its implication for the biosynthesis of the gilvocarcins. *J Am Chem Soc* **125**: 7818-7819.
- Flärdh, K. (2003) Growth polarity and cell division in *Streptomyces*. *Curr Opin Microbiol* **6**: 564-571.
- Flärdh, K., and Buttner, M.J. (2009) *Streptomyces* morphogenetics: dissecting differentiation in a filamentous bacterium. *Nat Rev Microbiol* **7**: 36-49.
- Flärdh, K., Richards, D.M., Hempel, A.M., Howard, M., and Buttner, M.J. (2012) Regulation of apical growth and hyphal branching in *Streptomyces*. *Curr Opin Microbiol* **15**: 737-743.
- Fleming, A. (1929) The antibacterial action of a *Penicillium*, with special reference of their use for the isolation of *B. influenzae*. *Brit J Exp Pathol* **10**: 226-236.
- Forget, S.M., Robertson, A.W., Overy, D.P., Kerr, R.G., and Jakeman, D.L. (2017) Furan and Lactam Jadomycin Biosynthetic Congeners Isolated from *Streptomyces venezuelae* ISP5230 Cultured with Nepsilon-Trifluoroacetyl-L-lysine. *J Nat Prod* **80**: 1860-1866.
- Fotso, S., Mahmud, T., Zabriskie, T.M., Santosa, D.A., and Proteau, P.J. (2008) Rearranged and unarranged angucyclinones from Indonesian *Streptomyces* spp. *J Antibiot (Tokyo)* **61**: 449-456.
- Fujii, I., and Ebizuka, Y. (1997) Anthracycline Biosynthesis in *Streptomyces galilaeus*. *Chem Rev* **97**: 2511-2524.
- Gerber, P.R., and Muller, K. (1995) MAB, a generally applicable molecular force field for structure modelling in medicinal chemistry. *J Comput Aided Mol Des* **9**: 251-268.
- Girard, G., Traag, B.A., Sangal, V., Mascini, N., Hoskisson, P.A., Goodfellow, M., and van Wezel, G.P. (2013) A novel taxonomic marker that discriminates between morphologically complex actinomycetes. *Open Biol* **3**: 130073.
- Gould, S.J. (1997) Biosynthesis of the Kinamycins. *Chem Rev* **97**: 2499-2510.

- Gould, S.J., Hong, S.T., and Carney, J.R. (1998) Cloning and heterologous expression of genes from the kinamycin biosynthetic pathway of *Streptomyces murayamaensis*. *J Antibiot (Tokyo)* **51**: 50-57.
- Grabley, S., Hammann, P., Hutter, K., Kluge, H., Thiericke, R., Wink, J., and Zeeck, A. (1991) Secondary metabolites by chemical screening. Part 19. SM 196 A and B, novel biologically active angucyclinones from *Streptomyces* sp. *J Antibiot (Tokyo)* **44**: 670-673.
- Grabley, S., Hammann, P., Raether, W., Wink, J., and Zeeck, A. (1990) Secondary metabolites by chemical screening: II. Amycins A and B two novel niphimycin analogs isolated from a high producer strain of elaiophycin and nigericin. *J Antibiot (Tokyo)* **43**: 639-647.
- Grantcharova, N., Lustig, U., and Flärdh, K. (2005) Dynamics of FtsZ assembly during sporulation in *Streptomyces coelicolor* A3(2). *J Bacteriol* **187**: 3227-3237.
- Grimm, A., Madduri, K., Ali, A., and Hutchinson, C.R. (1994) Characterization of the *Streptomyces peucetius* ATCC 29050 genes encoding doxorubicin polyketide synthase. *Gene* **151**: 1-10.
- Hale, C.A., and de Boer, P.A. (1997) Direct binding of FtsZ to ZipA, an essential component of the septal ring structure that mediates cell division in *E. coli*. *Cell* **88**: 175-185.
- Han, L., Yang, K., Ramalingam, E., Mosher, R.H., and Vining, L.C. (1994) Cloning and characterization of polyketide synthase genes for jadomycin B biosynthesis in *Streptomyces venezuelae* ISP5230. *Microbiology* **140** (Pt 12): 3379-3389.
- Harayama, S., Kok, M., and Neidle, E.L. (1992) Functional and evolutionary relationships among diverse oxygenases. *Annu Rev Microbiol* **46**: 565-601.
- 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.
- Henkel, T., and Zeeck, A. (1990) Derivatives of saquayamycins A and B. Regio- and diastereoselective addition of alcohols to the L-aculose moiety. *J Antibiot (Tokyo)* **43**: 830-837.
- Henrick, K., and Hirshberg, M. (2012) Structure of the signal transduction protein TRAP (target of RNAIII-activating protein). *Acta Crystallogr F* **68**: 744-750.
- Herschlag, D., and Natarajan, A. (2013) Fundamental Challenges in Mechanistic Enzymology: Progress toward Understanding the Rate Enhancements of Enzymes. *Biochemistry* **52**: 2050-2067.
- Hertweck, C. (2009) The biosynthetic logic of polyketide diversity. *Angew Chem Int Ed Engl* **48**: 4688-4716.
- Hertweck, C., Luzhetskyy, A., Rebets, Y., and Bechthold, A. (2007) Type II polyketide synthases: gaining a deeper insight into enzymatic teamwork. *Nat Prod Rep* **24**: 162-190.
- Herzon, S.B., and Woo, C.M. (2012) The diazofluorene antitumor antibiotics: structural elucidation, biosynthetic, synthetic, and chemical biological studies. *Nat Prod Rep* **29**: 87-118.
- Hess, B., Kutzner, C., van der Spoel, D., and Lindahl, E. (2008) GROMACS 4: Algorithms for highly efficient, load-balanced, and scalable molecular simulation. *J Chem Theory Comput* **4**: 435-447.

- Hochstein, F.A., Stephens, C.R., Conover, L.H., Regna, P.P., Pasternack, R., Gordon, P.N., Pilgrim, F.J., Brunings, K.J., and Woodward, R.B. (1953) The Structure of Terramycin^{1,2}. *J Am Chem Soc* **75**: 5455-5475.
- Holden, S.J., Pengo, T., Meibom, K.L., Fernandez Fernandez, C., Collier, J., and Manley, S. (2014) High throughput 3D super-resolution microscopy reveals *Caulobacter crescentus* in vivo Z-ring organization. *Proc Natl Acad Sci U S A* **111**: 4566-4571.
- Holm, L. (2019) Benchmarking fold detection by DaliLite v.5. *Bioinformatics*.
- Holmes, N.A., Walshaw, J., Leggett, R.M., Thibessard, A., Dalton, K.A., Gillespie, M.D., Hemmings, A.M., Gust, B., and Kelemen, G.H. (2013) Coiled-coil protein Scy is a key component of a multiprotein assembly controlling polarized growth in *Streptomyces*. *Proc Natl Acad Sci U S A* **110**: E397-406.
- Holzenkampfer, M., Walker, M., Zeeck, A., Schimana, J., and Fiedler, H.P. (2002) Simocyclinones, novel cytostatic angucyclinone antibiotics produced by *Streptomyces antibioticus* Tu 6040 II. Structure elucidation and biosynthesis. *J Antibiot (Tokyo)* **55**: 301-307.
- Hopwood, D.A. (1997) Genetic Contributions to Understanding Polyketide Synthases. *Chem Rev* **97**: 2465-2498.
- Hopwood, D.A., (2007) *Streptomyces in nature and medicine: the antibiotic makers*. Oxford University Press, New York.
- Hopwood, D.A., Malpartida, F., Kieser, H.M., Ikeda, H., Duncan, J., Fujii, I., Rudd, B.A.M., Floss, H.G., and Omura, S. (1985) Production of hybrid antibiotics by genetic-engineering. *Nature* **314**: 642-644.
- Hopwood, D.A., and Wright, H.M. (1983) CDA is a new chromosomally-determined antibiotic from *Streptomyces coelicolor* A3(2). *J Gen Microbiol* **129**: 3575-3579.
- Hornak, V., Abel, R., Okur, A., Strockbine, B., Roitberg, A., and Simmerling, C. (2006) Comparison of multiple amber force fields and development of improved protein backbone parameters. *Proteins* **65**: 712-725.
- Hoskisson, P.A., and van Wezel, G.P. (2019) *Streptomyces coelicolor*. *Trends Microbiol* **27**: 468-469.
- Huang, H., Yang, T., Ren, X., Liu, J., Song, Y., Sun, A., Ma, J., Wang, B., Zhang, Y., Huang, C., Zhang, C., and Ju, J. (2012) Cytotoxic angucycline class glycosides from the deep sea actinomycete *Streptomyces lusitanus* SCSIO LR32. *J Nat Prod* **75**: 202-208.
- Hutchinson, C.R., and Fujii, I. (1995) Polyketide synthase gene manipulation: a structure-function approach in engineering novel antibiotics. *Annu Rev Microbiol* **49**: 201-238.
- Hutchinson, E.G., and Thornton, J.M. (1994) A revised set of potentials for β -turn formation in proteins. *Protein Sci* **3**: 2207-2216.
- Igarashi, M., Watanabe, T., Hashida, T., Umekita, M., Hatano, M., Yanagida, Y., Kino, H., Kimura, T., Kinoshita, N., Inoue, K., Sawa, R., Nishimura, Y., Utsumi, R., and Nomoto, A. (2013) Waldiomycin, a novel Walk-histidine kinase inhibitor from *Streptomyces* sp. MK844-mF10. *J Antibiot (Tokyo)* **66**: 459-464.
- Ikeda, H., Ishikawa, J., Hanamoto, A., Shinose, M., Kikuchi, H., Shiba, T., Sakaki, Y., Hattori, M., and Ōmura, S. (2003) Complete genome sequence and comparative analysis of the industrial microorganism *Streptomyces avermitilis*. *Nat Biotechnol* **21**: 526-531.
- Jackson, D.R., Yu, X., Wang, G.J., Patel, A.B., Calveras, J., Barajas, J.F., Sasaki, E., Metsä-Ketelä, M., Liu, H.W., Rohr, J., and Tsai, S.C. (2016) Insights into complex oxidation during

- BE-7585A biosynthesis: structural determination and analysis of the polyketide monooxygenase BexE. *Acs Chem Biol* **11**: 1137-1147.
- Jacobsen, J.R., Hutchinson, C.R., Cane, D.E., and Khosla, C. (1997) Precursor-Directed Biosynthesis of Erythromycin Analogs by an Engineered Polyketide Synthase. *Science* **277**: 367-369.
- Jakeman, D.L., Farrell, S., Young, W., Doucet, R.J., and Timmons, S.C. (2005a) Novel jadomycins: incorporation of non-natural and natural amino acids. *Bioorg Med Chem Lett* **15**: 1447-1449.
- Jakeman, D.L., Graham, C.L., and Reid, T.R. (2005b) Novel and expanded jadomycins incorporating non-proteogenic amino acids. *Bioorg Med Chem Lett* **15**: 5280-5283.
- Jakimowicz, D., and van Wezel, G.P. (2012) Cell division and DNA segregation in *Streptomyces*: how to build a septum in the middle of nowhere? *Mol Microbiol* **85**: 393-404.
- Janso, J.E., Haltli, B.A., Eustaquio, A.S., Kulowski, K., Waldman, A.J., Zha, L., Nakamura, H., Bernan, V.S., He, H., Carter, G.T., Koehn, F.E., and Balskus, E.P. (2014) Discovery of the lomaiviticin biosynthetic gene cluster in *Salinispora pacifica*. *Tetrahedron* **70**: 4156-4164.
- Javidpour, P., Bruegger, J., Srithahan, S., Korman, T.P., Crump, M.P., Crosby, J., Burkart, M.D., and Tsai, S.C. (2013) The determinants of activity and specificity in actinorhodin type II polyketide ketoreductase. *Chem Biol* **20**: 1225-1234.
- Jornvall, H., Persson, B., Krook, M., Atrian, S., Gonzalez-Duarte, R., Jeffery, J., and Ghosh, D. (1995) Short-chain dehydrogenases/reductases (SDR). *Biochemistry* **34**: 6003-6013.
- Kabsch, W. (2010) Xds. *Acta Crystallogr D* **66**: 125-132.
- Kallio, P., Liu, Z., Mantsala, P., Niemi, J., and Metsä-Ketela, M. (2008a) A nested gene in *Streptomyces bacteria* encodes a protein involved in quaternary complex formation. *J Mol Biol* **375**: 1212-1221.
- Kallio, P., Liu, Z.L., Mantsala, P., Niemi, J., and Metsä-Ketelä, M. (2008b) Sequential action of two flavoenzymes, PgaE and PgaM, in angucycline biosynthesis: chemoenzymatic synthesis of gaudimycin C. *Chem Biol* **15**: 157-166.
- Kallio, P., Patrikainen, P., Suomela, J.P., Mantsala, P., Metsä-Ketela, M., and Niemi, J. (2011) Flavoprotein hydroxylase PgaE catalyzes two consecutive oxygen-dependent tailoring reactions in angucycline biosynthesis. *Biochemistry* **50**: 5535-5543.
- Kanehisa, M., and Sato, Y. (2020) KEGG Mapper for inferring cellular functions from protein sequences. *Protein Sci* **29**: 28-35.
- Kasus-Jacobi, A., Ou, J.F., Birch, D.G., Locke, K.G., Shelton, J.M., Richardson, J.A., Murphy, A.J., Valenzuela, D.M., Yancopoulos, G.D., and Edwards, A.O. (2005) Functional characterization of mouse RDH11 as a retinol dehydrogenase involved in dark adaptation *in vivo*. *J Biol Chem* **280**: 20413-20420.
- Katsuyama, Y., Sone, K., Satou, R., Izumikawa, M., Takagi, M., Fujie, M., Satoh, N., Shin-Ya, K., and Ohnishi, Y. (2016) Involvement of the Baeyer-Villiger Monooxygenase IfnQ in the Biosynthesis of Isofuranonaphthoquinone Scaffold of JBIR-76 and -77. *Chembiochem* **17**: 1021-1028.
- Keatinge-Clay, A.T. (2007) A tylosin ketoreductase reveals how chirality is determined in polyketides. *Chem Biol* **14**: 898-908.

- Keijser, B.J., Noens, E.E., Kraal, B., Koerten, H.K., and van Wezel, G.P. (2003) The *Streptomyces coelicolor* *ssgB* gene is required for early stages of sporulation. *FEMS Microbiol Lett* **225**: 59-67.
- Kelemen, G.H., Brian, P., Flärdh, K., Chamberlin, L., Chater, K.F., and Buttner, M.J. (1998) Developmental regulation of transcription of *whiE*, a locus specifying the polyketide spore pigment in *Streptomyces coelicolor* A3 (2). *J Bacteriol* **180**: 2515-2521.
- Kelleher, J.E., and Raleigh, E.A. (1991) A novel activity in *Escherichia coli* K-12 that directs restriction of DNA modified at CG dinucleotides. *J Bacteriol* **173**: 5220-5223.
- Kesenheimer, C., and Groth, U. (2006) Total synthesis of (-)-8-O-methyltetrangomycin (MM 47755). *Org Lett* **8**: 2507-2510.
- Kharel, M.K., Pahari, P., Lian, H., and Rohr, J. (2010) Enzymatic total synthesis of rabelomycin, an angucycline group antibiotic. *Org Lett* **12**: 2814-2817.
- 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.
- Khosla, C. (2015) Quo vadis, enzymology? *Nat Chem Biol* **11**: 438-441.
- Khosla, C., Gokhale, R.S., Jacobsen, J.R., and Cane, D.E. (1999) Tolerance and specificity of polyketide synthases. *Annu Rev Biochem* **68**: 219-253.
- Khosla, C., and Zawada, R.J. (1996) Generation of polyketide libraries via combinatorial biosynthesis. *Trends Biotechnol* **14**: 335-341.
- Kieser, T., Bibb, M.J., Buttner, M.J., Chater, K.F., and Hopwood, D.A., (2000) *Practical Streptomyces genetics*. John Innes Foundation, Norwich, U.K.
- Klinman, J.P. (2015) Dynamically Achieved Active Site Precision in Enzyme Catalysis. *Acc Chem Res* **48**: 449-456.
- Kobylyansky, A., Ostash, B., and Fedorenko, V. (2009) Heterologous cross-expression of oxygenase and glycosyltransferase genes in streptomycetes, producing angucyclic antibiotics. *Tsitol Genet* **43**: 55-62.
- Kolter, R., and van Wezel, G.P. (2016) Goodbye to brute force in antibiotic discovery? *Nat Microbiol* **1**: 15020.
- Koskiniemi, H., Metsä-Ketela, M., Dobritzsch, D., Kallio, P., Korhonen, H., Mantsala, P., Schneider, G., and Niemi, J. (2007) Crystal structures of two aromatic hydroxylases involved in the early tailoring steps of angucycline biosynthesis. *J Mol Biol* **372**: 633-648.
- Krissinel, E., and Henrick, K. (2007) Inference of macromolecular assemblies from crystalline state. *J Mol Biol* **372**: 774-797.
- Kulowski, K., Wendt-Pienkowski, E., Han, L., Yang, K.Q., Vining, L.C., and Hutchinson, C.R. (1999) Functional characterization of the *jadI* gene as a cyclase forming angucyclinones. *J Am Chem Soc* **121**: 1786-1794.
- Künzel, E., Faust, B., Oelkers, C., Weissbach, U., Bearden, D.W., Weitnauer, G., Westrich, L., Bechthold, A., and Rohr, J. (1999) Inactivation of the *urdGT2* Gene, Which Encodes a Glycosyltransferase Responsible for the C-Glycosyltransfer of Activated d-Olucose, Leads to Formation of the Novel Urdamycins I, J, and K. *J Am Chem Soc* **121**: 11058-11062.

- Laskowski, R.A., Macarthur, M.W., Moss, D.S., and Thornton, J.M. (1993) Procheck - a program to check the stereochemical quality of protein structures. *J Appl Crystallogr* **26**: 283-291.
- Leach, B.E., Calhoun, K.M., Johnson, L.E., Teeters, C.M., and Jackson, W.G. (1953) Chartreusin, a New Antibiotic Produced by *Streptomyces chartreusis*, a New Species. *J Am Chem Soc* **75**: 4011-4012.
- Lee, W.C., Reniere, M.L., Skaar, E.P., and Murphy, M.E. (2008) Ruffling of metalloporphyrins bound to IsdG and IsdI, two heme-degrading enzymes in *Staphylococcus aureus*. *J Biol Chem* **283**: 30957-30963.
- Lewis, P.N., Momany, F.A., and Scheraga, H.A. (1973) Chain reversals in proteins. *Biochim Biophys Acta* **303**: 211-229.
- Liebschner, D., Afonine, P.V., Baker, M.L., Bunkoczi, G., Chen, V.B., Croll, T.I., Hintze, B., Hung, L.W., Jain, S., McCoy, A.J., Moriarty, N.W., Oeffner, R.D., Poon, B.K., Prisant, M.G., Read, R.J., Richardson, J.S., Richardson, D.C., Sammito, M.D., Sobolev, O.V., Stockwell, D.H., Terwilliger, T.C., Urzhumtsev, A.G., Videau, L.L., Williams, C.J., and Adams, P.D. (2019) Macromolecular structure determination using X-rays, neutrons and electrons: recent developments in Phenix. *Acta Crystallogr D* **75**: 861-877.
- Liu, T., Fischer, C., Beninga, C., and Rohr, J. (2004) Oxidative rearrangement processes in the biosynthesis of gilvocarcin V. *J Am Chem Soc* **126**: 12262-12263.
- Liu, X., Biswas, S., Berg, M.G., Antapli, C.M., Xie, F., Wang, Q., Tang, M.C., Tang, G.L., Zhang, L., Dreyfuss, G., and Cheng, Y. (2013) Genomics-Guided Discovery of Thailanstatins A, B, and C As Pre-mRNA Splicing Inhibitors and Antiproliferative Agents from *Burkholderia thailandensis* MSMB43. *J Nat Prod* **76**: 685-693.
- Lluch-Senar, M., Querol, E., and Pinol, J. (2010) Cell division in a minimal bacterium in the absence of *ftsZ*. *Mol Microbiol* **78**: 278-289.
- Lorico, A., and Long, B.H. (1993) Biochemical characterisation of elsamicin and other coumarin-related antitumour agents as potent inhibitors of human topoisomerase II. *Eur J Cancer* **29**: 1985-1991.
- Lutkenhaus, J. (2007) Assembly dynamics of the bacterial MinCDE system and spatial regulation of the Z ring. *Annu Rev Biochem* **76**: 539-562.
- Luzhetskyy, A., and Bechthold, A. (2005) It works: combinatorial biosynthesis for generating novel glycosylated compounds. *Mol Microbiol* **58**: 3-5.
- Luzhetskyy, A., Taguchi, T., Fedoryshyn, M., Durr, C., Wohler, S.E., Novikov, V., and Bechthold, A. (2005) LanGT2 Catalyzes the First Glycosylation Step during landomycin A biosynthesis. *ChemBiochem* **6**: 1406-1410.
- Lyu, Z., Coltharp, C., Yang, X., and Xiao, J. (2016) Influence of FtsZ GTPase activity and concentration on nanoscale Z-ring structure *in vivo* revealed by three-dimensional Superresolution imaging. *Biopolymers* **105**: 725-734.
- MacKenzie, A.K., Kershaw, N.J., Hernandez, H., Robinson, C.V., Schofield, C.J., and Andersson, I. (2007) Clavulanic acid dehydrogenase: structural and biochemical analysis of the final step in the biosynthesis of the β -lactamase inhibitor clavulanic acid. *Biochemistry* **46**: 1523-1533.
- MacNeil, D.J., Gewain, K.M., Ruby, C.L., Dezeny, G., Gibbons, P.H., and MacNeil, T. (1992a) Analysis of *Streptomyces avermitilis* genes required for avermectin biosynthesis utilizing a novel integration vector. *Gene* **111**: 61-68.

- MacNeil, D.J., Occi, J.L., Gewain, K.M., MacNeil, T., Gibbons, P.H., Ruby, C.L., and Danis, S.J. (1992b) Complex organization of the *Streptomyces avermitilis* genes encoding the avermectin polyketide synthase. *Gene* **115**: 119-125.
- Maehr, H., Liu, C.M., Liu, M., Perrotta, A., Smallheer, J.M., Williams, T.H., and Blount, J.F. (1982) Microbial products. VI Five novel metabolites related to benz[a]anthracene from an unidentified actinomycete designated X-14881. *J Antibiot (Tokyo)* **35**: 1627-1631.
- Mahr, K., van Wezel, G.P., Svensson, C., Krengel, U., Bibb, M.J., and Titgemeyer, F. (2000) Glucose kinase of *Streptomyces coelicolor* A3(2): large-scale purification and biochemical analysis. *Anton Leeuw Int J G* **78**: 253-261.
- Maier, S., Pfluger, T., Loesgen, S., Asmus, K., Brotz, E., Paululat, T., Zeeck, A., Andrade, S., and Bechthold, A. (2014) Insights into the bioactivity of mensacarcin and epoxide formation by MsnO8. *Chembiochem* **15**: 749-756.
- Mao, X.M., Zhan, Z.J., Grayson, M.N., Tang, M.C., Xu, W., Li, Y.Q., Yin, W.B., Lin, H.C., Chooi, Y.H., Houk, K.N., and Tang, Y. (2015) Efficient Biosynthesis of Fungal Polyketides Containing the Dioxabicyclo-octane Ring System. *J Am Chem Soc* **137**: 11904-11907.
- Maplestone, R.A., Stone, M.J., and Williams, D.H. (1992) The evolutionary role of secondary metabolites — a review. *Gene* **115**: 151-157.
- Margolin, W. (2005) FtsZ and the division of prokaryotic cells and organelles. *Nat Rev Mol Cell Biol* **6**: 862-871.
- Martin, R., Sterner, O., Alvarez, M.A., de Clercq, E., Bailey, J.E., and Minas, W. (2001) Collinone, a new recombinant angular polyketide antibiotic made by an engineered *Streptomyces* strain. *J Antibiot (Tokyo)* **54**: 239-249.
- Martinez-Farina, C.F., and Jakeman, D.L. (2015) Jadomycins, put a bigger ring in it: isolation of seven- to ten-membered ring analogues. *Chem Commun (Camb)* **51**: 14617-14619.
- Matsumoto, A., and Hanawalt, P.C. (2000) Histone H3 and Heat Shock Protein GRP78 Are Selectively Cross-Linked to DNA by Photoactivated Gilvocarcin V in Human Fibroblasts. *Cancer Res* **60**: 3921-3926.
- McCarthy, A.A., Barrett, R., Beteva, A., Caserotto, H., Dobias, F., Felisaz, F., Giraud, T., Guijarro, M., Janocha, R., Khadrrouche, A., Lentini, M., Leonard, G.A., Marrero, M.L., Malbet-Monaco, S., McSweeney, S., Nurizzo, D., Papp, G., Rossi, C., Sinoir, J., Sorez, C., Surr, J., Svensson, O., Zander, U., Cipriani, F., Theveneau, P., and Mueller-Dieckmann, C. (2018) ID30B-a versatile beamline for macromolecular crystallography experiments at the ESRF. *J Synchrotron Radiat* **25**: 1249-1260.
- McCormick, J.R. (2009) Cell division is dispensable but not irrelevant in *Streptomyces*. *Curr Opin Microbiol* **12**: 689-698.
- McCormick, J.R., Su, E.P., Driks, A., and Losick, R. (1994) Growth and viability of *Streptomyces coelicolor* mutant for the cell division gene *ftsZ*. *Mol Microbiol* **14**: 243-254.
- McDaniel, R., Ebert-Khosla, S., Hopwood, D.A., and Khosla, C. (1995) Rational design of aromatic polyketide natural products by recombinant assembly of enzymatic subunits. *Nature* **375**: 549-554.
- McGowan, J.V., Chung, R., Maulik, A., Piotrowska, I., Walker, J.M., and Yellon, D.M. (2017) Anthracycline Chemotherapy and Cardiotoxicity. *Cardiovasc Drugs Ther* **31**: 63-75.

- Mendez, C., and Salas, J.A. (2003) On the generation of novel anticancer drugs by recombinant DNA technology: the use of combinatorial biosynthesis to produce novel drugs. *Comb Chem High T Scr* **6**: 513-526.
- Metsa-Ketela, M., Palmu, K., Kunnari, T., Ylihonko, K., and Mantsala, P. (2003) Engineering anthracycline biosynthesis toward angucyclines. *Antimicrob Agents Chemother* **47**: 1291-1296.
- Minotti, G., Menna, P., Salvatorelli, E., Cairo, G., and Gianni, L. (2004) Anthracyclines: Molecular Advances and Pharmacologic Developments in Antitumor Activity and Cardiotoxicity. *Pharmacol Rev* **56**: 185-229.
- Mo, J., Ye, J., Chen, H., Hou, B., Wu, H., and Zhang, H. (2019) Cloning and identification of the Frigocyclinone biosynthetic gene cluster from *Streptomyces griseus* strain NTK 97. *Biosci Biotechnol Biochem* **83**: 2082-2089.
- Monahan, L.G., Robinson, A., and Harry, E.J. (2009) Lateral FtsZ association and the assembly of the cytokinetic Z ring in bacteria. *Mol Microbiol* **74**: 1004-1017.
- Montalbán-López, M., Scott, T.A., Ramesh, S., Rahman, I.R., van Heel, A., Viel, J.H., Bandarian, V., Dittmann, E., Genilloud, O., Goto, Y., Grande Burgos, M.J., Hill, C., Kim, S., Koehnke, J., Latham, J.A., Link, A.J., Martínez, B., Nair, S.K., Nicolet, Y., Rebuffat, S., Sahl, H.G., Sareen, D., Schmidt, E.W., Schmitt, L., Severinov, K., Süßmuth, R.D., Truman, A.W., Wang, H., Weng, J.K., van Wezel, G.P., Zhang, Q., Zhong, J., Piel, J., Mitchell, D.A., Kuipers, O.P., and van der Donk, W.A. (2020) New developments in RiPP discovery, enzymology and engineering. *Nat Prod Rep*: in press.
- Moore, B.S., and Hopke, J.N. (2001) Discovery of a New Bacterial Polyketide Biosynthetic Pathway. *Chembiochem* **2**: 35-38.
- Moore, B.S., and Piel, J. (2000) Engineering biodiversity with type II polyketide synthase genes. *Anton Leeuw Int J G* **78**: 391-398.
- Morimoto, M., Okubo, S., Tomita, F., and Marumo, H. (1981) Gilvocarcins, new antitumor antibiotics. 3. Antitumor activity. *J Antibiot (Tokyo)* **34**: 701-707.
- Motohashi, K., Izumikawa, M., Kagaya, N., Takagi, M., and Shin-ya, K. (2016) JBIR-76 and JBIR-77, modified naphthoquinones from *Streptomyces* sp. RI-77. *J Antibiot (Tokyo)* **69**: 707-708.
- Mukherjee, A., and Lutkenhaus, J. (1994) Guanine nucleotide-dependent assembly of FtsZ into filaments. *J Bacteriol* **176**: 2754-2758.
- Muleya, V., Hayeshi, R., Ranson, H., Abegaz, B., Bezabih, M.T., Robert, M., Ngadjui, B.T., Ngandeu, F., and Mukanganyama, S. (2008) Modulation of *Anopheles gambiae* Epsilon glutathione transferase activity by plant natural products *in vitro*. *J Enzyme Inhib Med Chem* **23**: 391-399.
- Murshudov, G.N., Vagin, A.A., and Dodson, E.J. (1997) Refinement of macromolecular structures by the maximum-likelihood method. *Acta Crystallogr D* **53**: 240-255.
- Nagasawa, T., Fukao, H., Irie, H., and Yamada, H. (1984) Sakyomicins A, B, C and D: new quinone-type antibiotics produced by a strain of *Nocardia*. Taxonomy, production, isolation and biological properties. *J Antibiot (Tokyo)* **37**: 693-699.
- Nakagawa, K., Hara, C., Tokuyama, S., Takada, K., and Imamura, N. (2012) Saprolymycins A–E, new angucycline antibiotics active against *Saprolegnia parasitica*. *J Antibiot (Tokyo)* **65**: 599-607.

- Nakano, H., Matsuda, Y., Ito, K., Ohkubo, S., Morimoto, M., and Tomita, F. (1981) Gilvocarcins, new antitumor antibiotics. 1. Taxonomy, fermentation, isolation and biological activities. *J Antibiot (Tokyo)* **34**: 266-270.
- 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.
- Noens, E.E., Mersinias, V., Traag, B.A., Smith, C.P., Koerten, H.K., and van Wezel, G.P. (2005) SsgA-like proteins determine the fate of peptidoglycan during sporulation of *Streptomyces coelicolor*. *Mol Microbiol* **58**: 929-944.
- Noens, E.E., Mersinias, V., Willemse, J., Traag, B.A., Laing, E., Chater, K.F., Smith, C.P., Koerten, H.K., and van Wezel, G.P. (2007) Loss of the controlled localization of growth stage-specific cell-wall synthesis pleiotropically affects developmental gene expression in an *ssgA* mutant of *Streptomyces coelicolor*. *Mol Microbiol* **64**: 1244-1259.
- Olano, C., Méndez, C., and Salas, J.A. (2010) Post-PKS tailoring steps in natural product-producing actinomycetes from the perspective of combinatorial biosynthesis. *Nat Prod Rep* **27**: 571-616.
- Oppermann, U., Filling, C., Hult, M., Shafqat, N., Wu, X., Lindh, M., Shafqat, J., Nordling, E., Kallberg, Y., Persson, B., and Jornvall, H. (2003) Short-chain dehydrogenases/reductases (SDR): the 2002 update. *Chem Biol Interact* **143-144**: 247-253.
- Ostash, B., Korynevskaya, A., Stoika, R., and Fedorenko, V. (2009) Chemistry and biology of landomycins, an expanding family of polyketide natural products. *Mini Rev Med Chem* **9**: 1040-1051.
- Ostash, B., Rix, U., Rix, L.L., Liu, T., Lombo, F., Luzhetskyy, A., Gromyko, O., Wang, C., Brana, A.F., Mendez, C., Salas, J.A., Fedorenko, V., and Rohr, J. (2004) Generation of new landomycins by combinatorial biosynthetic manipulation of the *IndGT4* gene of the landomycin E cluster in *S. globisporus*. *Chem Biol* **11**: 547-555.
- Oyola, R., Arce, R., Alegria, A.E., and Garcia, C. (1997) Photophysical Properties of Gilvocarcins V and M and Their Binding Constant to *Calf Thymus* DNA. *Photochem Photobiol* **65**: 802-810.
- Paananen, P., Patrikainen, P., Kallio, P., Mantsala, P., Niemi, J., Niiranen, L., and Metsä-Ketelä, M. (2013) Structural and functional analysis of angucycline C-6 ketoreductase LanV involved in landomycin biosynthesis. *Biochemistry* **52**: 5304-5314.
- Palmu, K., Ishida, K., Mantsala, P., Hertweck, C., and Metsä-Ketelä, M. (2007) Artificial reconstruction of two cryptic angucycline antibiotic biosynthetic pathways. *Chembiochem* **8**: 1577-1584.
- Pan, G., Gao, X., Fan, K., Liu, J., Meng, B., Gao, J., Wang, B., Zhang, C., Han, H., Ai, G., Chen, Y., Wu, D., Liu, Z.J., and Yang, K. (2017) Structure and Function of a C-C Bond Cleaving Oxygenase in Atypical Angucycline Biosynthesis. *Acs Chem Biol* **12**: 142-152.
- Pang, B., Qiao, X., Janssen, L., Velds, A., Groothuis, T., Kerkhoven, R., Nieuwland, M., Ovaa, H., Rottenberg, S., van Tellingen, O., Janssen, J., Huijgens, P., Zwart, W., and Neefjes,

- J. (2013) Drug-induced histone eviction from open chromatin contributes to the chemotherapeutic effects of doxorubicin. *Nat Commun* **4**: 1908.
- Parrinello, M., and Rahman, A. (1981) Polymorphic Transitions in Single-Crystals - a New Molecular-Dynamics Method. *J Appl Phys* **52**: 7182-7190.
- Patrikainen, P., Kallio, P., Fan, K., Klika, K.D., Shaaban, K.A., Mantsala, P., Rohr, J., Yang, K., Niemi, J., and Metsä-Ketela, M. (2012) Tailoring enzymes involved in the biosynthesis of angucyclines contain latent context-dependent catalytic activities. *Chem Biol* **19**: 647-655.
- Patrikainen, P., Niiranen, L., Thapa, K., Paananen, P., Tahtinen, P., Mantsala, P., Niemi, J., and Metsä-Ketela, M. (2014) Structure-based engineering of angucyclinone 6-ketoreductases. *Chem Biol* **21**: 1381-1391.
- Pende, N., Wang, J., Weber, P.M., Verheul, J., Kuru, E., Rittmann, S.K.R., Leisch, N., VanNieuwenhze, M.S., Brun, Y.V., den Blaauwen, T., and Bulgheresi, S. (2018) Host-Polarized Cell Growth in Animal Symbionts. *Curr Biol* **28**: 1039-1051 e1035.
- Peng, A., Qu, X., Liu, F., Li, X., Li, E., and Xie, W. (2018) Angucycline Glycosides from an Intertidal Sediments Strain *Streptomyces* sp. and Their Cytotoxic Activity against Hepatoma Carcinoma Cells. *Mar Drugs* **16**.
- Pfeifer, B.A., and Khosla, C. (2001) Biosynthesis of polyketides in heterologous hosts. *Microbiol Mol Biol Rev* **65**: 106-118.
- Pichoff, S., and Lutkenhaus, J. (2002) Unique and overlapping roles for ZipA and FtsA in septal ring assembly in *Escherichia coli*. *EMBO J* **21**: 685-693.
- Pichoff, S., and Lutkenhaus, J. (2005) Tethering the Z ring to the membrane through a conserved membrane targeting sequence in FtsA. *Mol Microbiol* **55**: 1722-1734.
- Pickens, L.B., and Tang, Y. (2009) Decoding and engineering tetracycline biosynthesis. *Metab Eng* **11**: 69-75.
- Piette, A., Derouaux, A., Gerkens, P., Noens, E.E., Mazzucchelli, G., Vion, S., Koerten, H.K., Titgemeyer, F., De Pauw, E., Leprince, P., van Wezel, G.P., Galleni, M., and Rigali, S. (2005) From dormant to germinating spores of *Streptomyces coelicolor* A3(2): new perspectives from the *crp* null mutant. *J Proteome Res* **4**: 1699-1708.
- Plocinski, P., Ziolkiewicz, M., Kiran, M., Vadrevu, S.I., Nguyen, H.B., Hugonnet, J., Veckerle, C., Arthur, M., Dziadek, J., Cross, T.A., Madiraju, M., and Rajagopalan, M. (2011) Characterization of CrgA, a new partner of the *Mycobacterium tuberculosis* peptidoglycan polymerization complexes. *J Bacteriol* **193**: 3246-3256.
- Prado, L., Fernandez, E., Weissbach, U., Blanco, G., Quiros, L.M., Brana, A.F., Mendez, C., Rohr, J., and Salas, J.A. (1999) Oxidative cleavage of premithramycin B is one of the last steps in the biosynthesis of the antitumor drug mithramycin. *Chem Biol* **6**: 19-30.
- Price, A.C., Zhang, Y.M., Rock, C.O., and White, S.W. (2004) Cofactor-induced conformational rearrangements establish a catalytically competent active site and a proton relay conduit in FabG. *Structure* **12**: 417-428.
- Rafanan, E.R., Jr., Le, L., Zhao, L., Decker, H., and Shen, B. (2001) Cloning, sequencing, and heterologous expression of the *elmGHII* genes involved in the biosynthesis of the polyketide antibiotic elloramycin from *Streptomyces olivaceus* Tu2353. *J Nat Prod* **64**: 444-449.
- Rahman, A., and Stilling, Fh (1971) Molecular Dynamics Study of Liquid Water. *J Chem Phys* **55**: 3336-+.

- Ramachandran, G.N., Ramakrishnan, C., and Sasisekharan, V. (1963) Stereochemistry of polypeptide chain configurations. *J Mol Biol* **7**: 95-&.
- Ramirez-Diaz, D.A., Garcia-Soriano, D.A., Raso, A., Mucksch, J., Feingold, M., Rivas, G., and Schwill, P. (2018) Treadmilling analysis reveals new insights into dynamic FtsZ ring architecture. *PLoS Biol* **16**: e2004845.
- Ramond, E., Maclachlan, C., Clerc-Rosset, S., Knott, G.W., and Lemaitre, B. (2016) Cell Division by Longitudinal Scission in the Insect Endosymbiont *Spiroplasma poulsonii*. *mBio* **7**.
- Rappsilber, J., Mann, M., and Ishihama, Y. (2007) Protocol for micro-purification, enrichment, pre-fractionation and storage of peptides for proteomics using StageTips. *Nat Protoc* **2**: 1896-1906.
- Rice, L.B. (2008) Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. *J Infect Dis* **197**: 1079-1081.
- Rigali, S., Nothaft, H., Noens, E.E.E., Schlicht, M., Colson, S., Müller, M., Joris, B., Koerten, H.K., Hopwood, D.A., Titgemeyer, F., and Van Wezel, G.P. (2006) The sugar phosphotransferase system of *Streptomyces coelicolor* is regulated by the GntR-family regulator DasR and links N-acetylglucosamine metabolism to the control of development. *Mol Microbiol* **61**: 1237-1251.
- 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 Rep* **9**: 670-675.
- Rix, U., Fischer, C., Remsing, L.L., and Rohr, J. (2002) Modification of post-PKS tailoring steps through combinatorial biosynthesis. *Nat Prod Rep* **19**: 542-580.
- Rix, U., Zheng, J., Remsing Rix, L.L., Greenwell, L., Yang, K., and Rohr, J. (2004) The Dynamic Structure of Jadomycin B and the Amino Acid Incorporation Step of Its Biosynthesis. *J Am Chem Soc* **126**: 4496-4497.
- Robert, F., and Brakier-Gingras, L. (2001) Ribosomal protein S7 from *Escherichia coli* uses the same determinants to bind 16S ribosomal RNA and its messenger RNA. *Nucleic Acids Res* **29**: 677-682.
- Robertson, A.W., Martinez-Farina, C.F., Smithen, D.A., Yin, H., Monro, S., Thompson, A., McFarland, S.A., Syvitski, R.T., and Jakeman, D.L. (2015) Eight-membered ring-containing jadomycins: implications for non-enzymatic natural products biosynthesis. *J Am Chem Soc* **137**: 3271-3275.
- Rodriguez, E., and McDaniel, R. (2001) Combinatorial biosynthesis of antimicrobials and other natural products. *Curr Opin Microbiol* **4**: 526-534.
- Rohr, J. (1989) Urdamycins, new angucycline antibiotics from *Streptomyces fradiae*. VI. Structure elucidation and biosynthetic investigations on urdamycin H. *J Antibiot (Tokyo)* **42**: 1482-1488.
- Rohr, J., Beale, J.M., and Floss, H.G. (1989) Urdamycins, new angucycline antibiotics from *Streptomyces fradiae*. IV. Biosynthetic studies of urdamycins A-D. *J Antibiot (Tokyo)* **42**: 1151-1157.
- 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.

- Rohr, J., Zeeck, A., and Floss, H.G. (1988) Urdamycins, new angucycline antibiotics from *Streptomyces fradiae*. III. The structures of urdamycins C and D. *J Antibiot (Tokyo)* **41**: 126-129.
- Rossiter, S.E., Fletcher, M.H., and Wuest, W.M. (2017) Natural Products as Platforms To Overcome Antibiotic Resistance. *Chem Rev* **117**: 12415-12474.
- Rudd, B.A.M., and Hopwood, D.A. (1979) Genetics of Actinorhodin Biosynthesis by *Streptomyces coelicolor* A3(2). *Microbiology* **114**: 35-43.
- 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.
- Sasaki, E., Ogasawara, Y., and Liu, H.W. (2010) A biosynthetic pathway for BE-7585A, a 2-thiosugar-containing angucycline-type natural product. *J Am Chem Soc* **132**: 7405-7417.
- Schafer, M., Stevenson, C.E.M., Wilkinson, B., Lawson, D.M., and Buttner, M.J. (2016) Substrate-assisted catalysis in polyketide reduction proceeds via a phenolate intermediate. *Chem Biol* **23**: 1091-1097.
- Schlimpert, S., Wasserstrom, S., Chandra, G., Bibb, M.J., Findlay, K.C., Flärdh, K., and Buttner, M.J. (2017) Two dynamin-like proteins stabilize FtsZ rings during *Streptomyces* sporulation. *Proc Natl Acad Sci U S A* **114**: E6176-E6183.
- Schuttelkopf, A.W., and van Aalten, D.M. (2004) PRODRG: a tool for high-throughput crystallography of protein-ligand complexes. *Acta Crystallogr D* **60**: 1355-1363.
- Schwarzer, P., Wunsch-Palasis, J., Bechthold, A., and Paululat, T. (2018) Biosynthesis of Rishirilide B. *Antibiotics (Basel)* **7**.
- Schwedock, J., McCormick, J.R., Angert, E.R., Nodwell, J.R., and Losick, R. (1997) Assembly of the cell division protein FtsZ into ladder-like structures in the aerial hyphae of *Streptomyces coelicolor*. *Mol Microbiol* **25**: 847-858.
- Sciara, G., Kendrew, S.G., Miele, A.E., Marsh, N.G., Federici, L., Malatesta, F., Schimperna, G., Savino, C., and Vallone, B. (2003) The structure of ActVA-Orf6, a novel type of monooxygenase involved in actinorhodin biosynthesis. *EMBO J* **22**: 205-215.
- Scott, J.S., Bowker, S.S., Deschoolmeester, J., Gerhardt, S., Hargreaves, D., Kilgour, E., Lloyd, A., Mayers, R.M., McCoull, W., Newcombe, N.J., Ogg, D., Packer, M.J., Rees, A., Revill, J., Schofield, P., Selmi, N., Swales, J.G., and Whittamore, P.R. (2012) Discovery of a potent, selective, and orally bioavailable acidic 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) inhibitor: discovery of 2-[[(3S)-1-[5-(cyclohexylcarbamoyl)-6-propylsulfany]pyridin-2-yl]-3-piperidyl]acetic acid (AZD4017). *J Med Chem* **55**: 5951-5964.
- Scott, T.A., and Piel, J. (2019) The hidden enzymology of bacterial natural product biosynthesis. *Nat Rev Chem* **3**: 404-425.
- Selengut, J.D., and Haft, D.H. (2010) Unexpected abundance of coenzyme F(420)-dependent enzymes in *Mycobacterium tuberculosis* and other actinobacteria. *J Bacteriol* **192**: 5788-5798.
- Sen, B.C., Wasserstrom, S., Findlay, K., Soderholm, N., Sandblad, L., von Wachenfeldt, C., and Flärdh, K. (2019) Specific amino acid substitutions in beta strand S2 of FtsZ cause spiraling septation and impair assembly cooperativity in *Streptomyces* spp. *Mol Microbiol* **112**: 184-198.
- Sezaki, M., Kondo, S., Maeda, K., Umezawa, H., and Ohno, M. (1970) The structure of aquayamycin. *Tetrahedron* **26**: 5171-5190.

- Shaaban, K.A., Srinivasan, S., Kumar, R., Damodaran, C., and Rohr, J. (2011a) Landomycins P-W, cytotoxic angucyclines from *Streptomyces cyanogenus* S-136. *J Nat Prod* **74**: 2-11.
- Shaaban, K.A., Stamatkin, C., Damodaran, C., and Rohr, J. (2011b) 11-Deoxylandomycinone and landomycins X-Z, new cytotoxic angucyclin(on)es from a *Streptomyces cyanogenus* K62 mutant strain. *J Antibiot (Tokyo)* **64**: 141-150.
- 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.
- Shapiro, L., McAdams, H.H., and Losick, R. (2009) Why and How Bacteria Localize Proteins. *Science* **326**: 1225-1228.
- Shen, B. (2003) Polyketide biosynthesis beyond the type I, II and III polyketide synthase paradigms. *Curr Opin Chem Biol* **7**: 285-295.
- Shen, B., and Hutchinson, C.R. (1993) Tetracenomycin F1 monooxygenase: oxidation of a naphthacene to a naphthacenequinone in the biosynthesis of tetracenomycin C in *Streptomyces glaucescens*. *Biochemistry* **32**: 6656-6663.
- Shen, B., and Hutchinson, C.R. (1994) Triple hydroxylation of tetracenomycin A2 to tetracenomycin C in *Streptomyces glaucescens*. Overexpression of the *tcmG* gene in *Streptomyces lividans* and characterization of the tetracenomycin A2 oxygenase. *J Biol Chem* **269**: 30726-30733.
- Smanski, M.J., Zhou, H., Claesen, J., Shen, B., Fischbach, M.A., and Voigt, C.A. (2016) Synthetic biology to access and expand nature's chemical diversity. *Nat Rev Microbiol* **14**: 135-149.
- Staunton, J., and Weissman, K.J. (2001) Polyketide biosynthesis: a millennium review. *Nat Prod Rep* **18**: 380-416.
- Strauss, M.P., Liew, A.T., Turnbull, L., Whitchurch, C.B., Monahan, L.G., and Harry, E.J. (2012) 3D-SIM super resolution microscopy reveals a bead-like arrangement for FtsZ and the division machinery: implications for triggering cytokinesis. *PLoS Biol* **10**: e1001389.
- Sun, C.H., Wang, Y., Wang, Z., Zhou, J.Q., Jin, W.Z., You, X.F., Gao, H., Zhao, L.X., Si, S.Y., and Li, X. (2007) Chemomicin A, a new angucyclinone antibiotic produced by *Nocardia mediterranei* subsp. *kanglensis* 1747-64. *J Antibiot (Tokyo)* **60**: 211-215.
- Süssmuth, R.D., and Mainz, A. (2017) Nonribosomal Peptide Synthesis-Principles and Prospects. *Angew Chem Int Ed Engl* **56**: 3770-3821.
- Swiatek, M.A., Tenconi, E., Rigali, S., and van Wezel, G.P. (2012) Functional analysis of the N-acetylglucosamine metabolic genes of *Streptomyces coelicolor* and role in control of development and antibiotic production. *J Bacteriol* **194**: 1136-1144.
- Takahashi, K., Yoshida, M., Tomita, F., and Shirahata, K. (1981) Gilvocarcins, new antitumor antibiotics. 2. Structural elucidation. *J Antibiot (Tokyo)* **34**: 271-275.
- Tang, M.C., Zou, Y., Watanabe, K., Walsh, C.T., and Tang, Y. (2017) Oxidative Cyclization in Natural Product Biosynthesis. *Chem Rev* **117**: 5226-5333.
- Terwilliger, T.C., Adams, P.D., Read, R.J., McCoy, A.J., Moriarty, N.W., Grosse-Kunstleve, R.W., Afonine, P.V., Zwart, P.H., and Hung, L.W. (2009) Decision-making in structure solution using Bayesian estimates of map quality: the PHENIX AutoSol wizard. *Acta Crystallogr D* **65**: 582-601.

- Thompson, C.J., Kieser, T., Ward, J.M., and Hopwood, D.A. (1982) Physical analysis of antibiotic-resistance genes from *Streptomyces* and their use in vector construction. *Gene* **20**: 51-62.
- Tibrewal, N., Pahari, P., Wang, G., Kharel, M.K., Morris, C., Downey, T., Hou, Y., Bugni, T.S., and Rohr, J. (2012) Baeyer-Villiger C-C bond cleavage reaction in gilvocarcin and jadomycin biosynthesis. *J Am Chem Soc* **134**: 18181-18184.
- Tibrewal, N., and Tang, Y. (2014) Biocatalysts for natural product biosynthesis. *Annu Rev Chem Biomol Eng* **5**: 347-366.
- Tietze, L.F., Stewart, S.G., Polomska, M.E., Modi, A., and Zeeck, A. (2004) Towards a total synthesis of the new anticancer agent mensacarcin: synthesis of the carbocyclic core. *Chemistry* **10**: 5233-5242.
- Tong, Y., Charusanti, P., Zhang, L., Weber, T., and Lee, S.Y. (2015) CRISPR-Cas9 Based Engineering of Actinomycetal Genomes. *ACS Synth Biol* **4**: 1020-1029.
- Traag, B.A., Seghezzi, N., Vijgenboom, E., and van Wezel, G.P. (2007) Characterization of the sporulation control protein SsgA by use of an efficient method to create and screen random mutant libraries in streptomycetes. *Appl Environ Microbiol* **73**: 2085-2092.
- Traag, B.A., and van Wezel, G.P. (2008) The SsgA-like proteins in actinomycetes: small proteins up to a big task. *Anton Leeuw Int J G* **94**: 85-97.
- Tsukuda, E., Tanaka, T., Ochiai, K., Kondo, H., Yoshida, M., Agatsuma, T., Saitoh, Y., Teshiba, S., and Matsuda, Y. (1996) EI-1507-1 and -2, novel interleukin-1 beta converting enzyme inhibitors produced by *Streptomyces* sp. E-1507. *J Antibiot (Tokyo)* **49**: 333-339.
- Tsyplik, O., Makitrynsky, R., Frensch, B., Zechel, D.L., Paululat, T., Teufel, R., and Bechthold, A. (2020) Oxidative Carbon Backbone Rearrangement in Rishirilide Biosynthesis. *J Am Chem Soc* **142**: 5913-5917.
- Tzagoloff, H., and Novick, R. (1977) Geometry of cell division in *Staphylococcus aureus*. *J Bacteriol* **129**: 343-350.
- 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.
- Ueberschaar, N., Xu, Z., Scherlach, K., Metsä-Ketelä, M., Bretschneider, T., Dahse, H.M., Görls, H., and Hertweck, C. (2013) Synthetic Remodeling of the Chartreusin Pathway to Tune Antiproliferative and Antibacterial Activities. *J Am Chem Soc* **135**: 17408-17416.
- Uiterweerd, M.T., Nuñez Santiago, I., 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*: in press.
- Vagin, A., and Teplyakov, A. (1997) MOLREP: an automated program for molecular replacement. *J Appl Crystallogr* **30**: 1022-1025.
- 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*.
- van der Donk, W.A. (2017) Introduction: Unusual Enzymology in Natural Product Synthesis. *Chem Rev* **117**: 5223-5225.

- 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., 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 Dissel, D., Claessen, D., and Van Wezel, G.P. (2014) Morphogenesis of *Streptomyces* in submerged cultures. *Adv Appl Microbiol* **89**: 1-45.
- van Raaij, M.J., Orriss, G.L., Montgomery, M.G., Runswick, M.J., Fearnley, I.M., Skehel, J.M., and Walker, J.E. (1996) The ATPase inhibitor protein from bovine heart mitochondria: the minimal inhibitory sequence. *Biochemistry* **35**: 15618-15625.
- van Wezel, G.P., and McDowall, K.J. (2011) The regulation of the secondary metabolism of *Streptomyces*: new links and experimental advances. *Nat Prod Rep* **28**: 1311-1333.
- van Wezel, G.P., van der Meulen, J., Kawamoto, S., Luiten, R.G., Koerten, H.K., and Kraal, B. (2000) *ssgA* is essential for sporulation of *Streptomyces coelicolor* A3(2) and affects hyphal development by stimulating septum formation. *J Bacteriol* **182**: 5653-5662.
- Vara, J., Lewandowska-Skarbek, M., Wang, Y.G., Donadio, S., and Hutchinson, C.R. (1989) Cloning of genes governing the deoxysugar portion of the erythromycin biosynthesis pathway in *Saccharopolyspora erythraea* (*Streptomyces erythreus*). *J Bacteriol* **171**: 5872-5881.
- Vicente, J., Stewart, A.K., van Wagoner, R.M., Elliott, E., Bourdelais, A.J., and Wright, J.L.C. (2015) Monacyclinones, New Angucyclinone Metabolites Isolated from *Streptomyces* sp. M7_15 Associated with the Puerto Rican Sponge *Scopalina ruetzleri*. *Mar Drugs* **13**: 4682-4700.
- Vijgenboom, E., Woudt, L.P., Heinstra, P.W., Rietveld, K., van Haarlem, J., van Wezel, G.P., Shochat, S., and Bosch, L. (1994) Three tuf-like genes in the kirromycin producer *Streptomyces ramocissimus*. *Microbiology* **140** (Pt 4): 983-998.
- Voitsekhovskaia, I., Paulus, C., Dahlem, C., Rebets, Y., Nadmid, S., Zapp, J., Axenov-Gribanov, D., Ruckert, C., Timofeyev, M., Kalinowski, J., Kiemer, A.K., and Luzhetskyy, A. (2020) Baikalomycins A-C, New Aquayamycin-Type Angucyclines Isolated from Lake Baikal Derived *Streptomyces* sp. IB201691-2A. *Microorganisms* **8**.
- Waksman, S.A. (1953) Streptomycin: Background, Isolation, Properties, and Utilization. *Science* **118**: 259-266.
- Walczak, R.J., Hines, J.V., Strohl, W.R., and Priestley, N.D. (2001) Bioconversion of the anthracycline analogue desacetyladiamycin by recombinant DoxA, a P450-monooxygenase from *Streptomyces* sp. strain C5. *Org Lett* **3**: 2277-2279.
- Walker, M., Pohl, E., Herbst-Irmer, R., Gerlitz, M., Rohr, J., and Sheldrick, G.M. (1999) Absolute configurations of Emycin D, E and F; mimicry of centrosymmetric space groups by mixtures of chiral stereoisomers. *Acta Crystallogr B* **55**: 607-616.
- Walsh, C. (2003) Where will new antibiotics come from? *Nat Rev Microbiol* **1**: 65-70.
- Walsh, C.T. (2015) A chemocentric view of the natural product inventory. *Nat Chem Biol* **11**: 620-624.
- Walsh, C.T., and Fischbach, M.A. (2010) Natural Products Version 2.0: Connecting Genes to Molecules. *J Am Chem Soc* **132**: 2469-2493.

- Wang, B., Guo, F., Ren, J., Ai, G., Aigle, B., Fan, K., and Yang, K. (2015a) Identification of Alp1U and Lom6 as epoxy hydrolases and implications for kinamycin and lomaiviticin biosynthesis. *Nat Commun* **6**: 7674.
- Wang, B., Ren, J., Li, L., Guo, F., Pan, G., Ai, G., Aigle, B., Fan, K., and Yang, K. (2015b) Kinamycin biosynthesis employs a conserved pair of oxidases for B-ring contraction. *Chem Commun (Camb)* **51**: 8845-8848.
- Wang, G., Chen, J., Zhu, H., and Rohr, J. (2017a) One-Pot Enzymatic Total Synthesis of Presteffimycinone, an Early Intermediate of the Anthracycline Antibiotic Steffimycin Biosynthesis. *Org Lett* **19**: 540-543.
- Wang, L., White, R.L., and Vining, L.C. (2002) Biosynthesis of the dideoxysugar component of jadomycin B: genes in the *jad* cluster of *Streptomyces venezuelae* ISP5230 for L-digitoxose assembly and transfer to the angucycline aglycone. *Microbiology* **148**: 1091-1103.
- 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., Crüsemann, M., Boudreau, P.D., Esquenazi, E., Sandoval-Calderón, M., Kersten, R.D., Pace, L.A., Quinn, R.A., Duncan, K.R., Hsu, 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.A., Piel, J., Murphy, B.T., Gerwick, L., Liaw, C., Yang, Y., 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., Boya P, C.A., 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., Rodríguez, 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, P., Hong, G.J., Wilson, M.R., and Balskus, E.P. (2017b) Production of Stealthin C Involves an S-N-Type Smiles Rearrangement. *J Am Chem Soc* **139**: 2864-2867.
- Wang, W., Li, J., Li, H., Fan, K., and Liu, Y. (2019) Crystal structure of AlpK: An essential monooxygenase involved in the biosynthesis of kinamycin. *Biochem Biophys Res Commun* **510**: 601-605.
- Wang, X.K., and Jin, J.L. (2014) Crucial factor for increasing the conjugation frequency in *Streptomyces netropsis* SD-07 and other strains. *FEMS Microbiol Lett* **357**: 99-103.
- Wang, Y.S., Zhang, B., Zhu, J., Yang, C.L., Guo, Y., Liu, C.L., Liu, F., Huang, H., Zhao, S., Liang, Y., Jiao, R.H., Tan, R.X., and Ge, H.M. (2018) Molecular Basis for the Final Oxidative Rearrangement Steps in Chartreusin Biosynthesis. *J Am Chem Soc* **140**: 10909-10914.
- Weber, S., Zolke, C., Rohr, J., and Beale, J.M. (1994) Investigations of the biosynthesis and structural revision of landomycin A. *J Org Chem* **59**: 4211-4214.
- Weissman, K.J., and Leadlay, P.F. (2005) Combinatorial biosynthesis of reduced polyketides. *Nat Rev Microbiol* **3**: 925-936.

- Wenzel, S.C., and Müller, R. (2005) Recent developments towards the heterologous expression of complex bacterial natural product biosynthetic pathways. *Curr Opin Biotechnol* **16**: 594-606.
- Wildermuth, H., and Hopwood, D. (1970) Septation during sporulation in *Streptomyces coelicolor*. *J Gen Microbiol* **60**: 51-59.
- Willemse, J., Borst, J.W., de Waal, E., Bisseling, T., and van Wezel, G.P. (2011) Positive control of cell division: FtsZ is recruited by SsgB during sporulation of *Streptomyces*. *Genes Dev* **25**: 89-99.
- Willemse, J., and van Wezel, G.P. (2009) Imaging of *Streptomyces coelicolor* A3(2) with Reduced Autofluorescence Reveals a Novel Stage of FtsZ Localization. *PLoS ONE* **4**: e4242.
- Winkler, I., Winkelmann, E., Thomas, S., Manfred, R., Gerhard, J., and Matthias, H. (1990) Antiviral activity and pharmacokinetics of HOE 602, an acyclic nucleoside, in animal models. *Antivir Res* **14**: 61-73.
- Wright, L.F., and Hopwood, D.A. (1976) Identification of the Antibiotic Determined by the SCP1 Plasmid of *Streptomyces coelicolor* A3 (2). *Microbiology* **95**: 96-106.
- Wu, C., Du, C., Gubbens, J., Choi, Y.H., and van Wezel, G.P. (2015) Metabolomics-Driven Discovery of a Prenylated Isatin Antibiotic Produced by *Streptomyces* Species MBT28. *J Nat Prod* **78**: 2355-2363.
- 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. (2019) Lugdunomycin, an Angucycline-Derived Molecule with Unprecedented Chemical Architecture. *Angew Chem Int Ed Engl* **58**: 2809-2814.
- Wu, L.J., and Errington, J. (2011) Nucleoid occlusion and bacterial cell division. *Nat Rev Microbiol* **10**: 8-12.
- Wu, R., Skaar, E.P., Zhang, R., Joachimiak, G., Gornicki, P., Schneewind, O., and Joachimiak, A. (2005) *Staphylococcus aureus* IsdG and IsdI, heme-degrading enzymes with structural similarity to monooxygenases. *J Biol Chem* **280**: 2840-2846.
- Xu, D., Nepal, K.K., Chen, J., Harmody, D., Zhu, H., McCarthy, P.J., Wright, A.E., and Wang, G. (2018) Nocardiopeptidins A-C: New angucyclines with anti-MRSA activity isolated from a marine sponge-derived *Nocardiopepsis* sp. HB-J378. *Synth Syst Biotechnol* **3**: 246-251.
- Xu, Q., Traag, B.A., Willemse, J., McMullan, D., Miller, M.D., Elsliger, M.A., Abdubek, P., Astakhova, T., Axelrod, H.L., Bakolitsa, C., Carlton, D., Chen, C., Chiu, H.J., Chruszcz, M., Clayton, T., Das, D., Deller, M.C., Duan, L., Ellrott, K., Ernst, D., Farr, C.L., Feuerhelm, J., Grant, J.C., Grzechnik, A., Grzechnik, S.K., Han, G.W., Jaroszewski, L., Jin, K.K., Klock, H.E., Knuth, M.W., Kozbial, P., Krishna, S.S., Kumar, A., Marciano, D., Minor, W., Mommaas, A.M., Morse, A.T., Nigoghossian, E., Nopakun, A., Okach, L., Oommachen, S., Paulsen, J., Puckett, C., Reyes, R., Rife, C.L., Sefcovic, N., Tien, H.J., Trame, C.B., van den Bedem, H., Wang, S., Weekes, D., Hodgson, K.O., Wooley, J., Deacon, A.M., Godzik, A., Lesley, S.A., Wilson, I.A., and van Wezel, G.P. (2009) Structural and functional characterizations of SsgB, a conserved activator of developmental cell division in morphologically complex actinomycetes. *J Biol Chem* **284**: 25268-25279.
- Xu, Z., Jakobi, K., Welzel, K., and Hertweck, C. (2005) Biosynthesis of the antitumor agent chartreusin involves the oxidative rearrangement of an anthracyclic polyketide. *Chem Biol* **12**: 579-588.

- Yague, P., Willemse, J., Koning, R.I., Rioseras, B., Lopez-Garcia, M.T., Gonzalez-Quinonez, N., Lopez-Iglesias, C., Shliaha, P.V., Rogowska-Wrzesinska, A., Koster, A.J., Jensen, O.N., van Wezel, G.P., and Manteca, A. (2016) Subcompartmentalization by cross-membranes during early growth of *Streptomyces* hyphae. *Nat Commun* **7**: 12467.
- Yamashita, A., Kato, H., Wakatsuki, S., Tomizaki, T., Nakatsu, T., Nakajima, K., Hashimoto, T., Yamada, Y., and Oda, J. (1999) Structure of tropinone reductase-II complexed with NADP⁺ and pseudotropine at 1.9 Å resolution: implication for stereospecific substrate binding and catalysis. *Biochemistry* **38**: 7630-7637.
- Yan, X., Probst, K., Linnenbrink, A., Arnold, M., Paululat, T., Zeeck, A., and Bechthold, A. (2012) Cloning and heterologous expression of three type II PKS gene clusters from *Streptomyces bottropensis*. *Chembiochem* **13**: 224-230.
- Yang, C., Huang, C., Zhang, W., Zhu, Y., and Zhang, C. (2015) Heterologous Expression of Fluostatin Gene Cluster Leads to a Bioactive Heterodimer. *Org Lett* **17**: 5324-5327.
- Yang, K., Han, L., and Vining, L.C. (1995) Regulation of jadomycin B production in *Streptomyces venezuelae* ISP5230: involvement of a repressor gene, *jadR2*. *J Bacteriol* **177**: 6111-6117.
- Yang, X., Lyu, Z., Miguel, A., McQuillen, R., Huang, K.C., and Xiao, J. (2017) GTPase activity-coupled treadmilling of the bacterial tubulin FtsZ organizes septal cell wall synthesis. *Science* **355**: 744-747.
- Yanisch-Perron, C., Vieira, J., and Messing, J. (1985) Improved M13 phage cloning vectors and host strains: nucleotide sequences of the M13mp18 and pUC19 vectors. *Gene* **33**: 103-119.
- Yixizhuoma, Ishikawa, N., Abdelfattah, M.S., and Ishibashi, M. (2017) Elmenols C-H, new angucycline derivatives isolated from a culture of *Streptomyces* sp. IFM 11490. *J Antibiot (Tokyo)* **70**: 601-606.
- Zaffiri, L., Gardner, J., and Toledo-Pereyra, L.H. (2012) History of antibiotics. From salvarsan to cephalosporins. *J Invest Surg* **25**: 67-77.
- Zeng, T., Liu, Z., Liu, H., He, W., Tang, X., Xie, L., and Wu, R. (2019) Exploring Chemical and Biological Space of Terpenoids. *J Chem Inf Model* **59**: 3667-3678.
- Zhang, C., and Kim, S.H. (2000) The anatomy of protein β -sheet topology. *J Mol Biol* **299**: 1075-1089.
- Zhang, F., He, H.Y., Tang, M.C., Tang, Y.M., Zhou, Q., and Tang, G.L. (2011) Cloning and Elucidation of the FR901464 Gene Cluster Revealing a Complex Acyltransferase-less Polyketide Synthase Using Glycerate as Starter Units. *J Am Chem Soc* **133**: 2452-2462.
- Zhang, L., Willemse, J., Claessen, D., and van Wezel, G.P. (2016) SepG coordinates sporulation-specific cell division and nucleoid organization in *Streptomyces coelicolor*. *Open Biol* **6**: 150164.
- Zhang, Q., Peoples, A.J., Rothfeder, M.T., Millett, W.P., Pescatore, B.C., Ling, L.L., and Moore, C.M. (2009) Isofuranonaphthoquinone Produced by an Actinoplanes Isolate. *J Nat Prod* **72**: 1213-1215.
- Zhang, X., and Studier, F.W. (1997) Mechanism of inhibition of bacteriophage T7 RNA polymerase by T7 lysozyme. *J Mol Biol* **269**: 10-27.
- 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.
- Zhu, L., Ostash, B., Rix, U., Nur, E.A.M., Mayers, A., Luzhetskyy, A., Mendez, C., Salas, J.A., Bechthold, A., Fedorenko, V., and Rohr, J. (2005) Identification of the function of gene *IndM2* encoding a bifunctional oxygenase-reductase involved in the biosynthesis of the antitumor antibiotic landomycin E by *Streptomyces globisporus* 1912 supports the originally assigned structure for landomycinone. *J Org Chem* **70**: 631-638.