

CYP1530	2	0.1
CYP1618	2	0.1
CYP181	2	0.1
CYP186	2	0.1
CYP194	2	0.1
CYP1995	2	0.1
CYP199	2	0.1
CYP2027	2	0.1
CYP211	2	0.1
CYP244	2	0.1
CYP253	2	0.1
CYP274	2	0.1
CYP1039	1	0.1
CYP1041	1	0.1
CYP1042	1	0.1
CYP1053	1	0.1
CYP1054	1	0.1
CYP1055	1	0.1
CYP1056	1	0.1
CYP1057	1	0.1
CYP1058	1	0.1
CYP1059	1	0.1
CYP1063	1	0.1
CYP1065	1	0.1
CYP1066	1	0.1
CYP1113	1	0.1
CYP112	1	0.1
CYP1151	1	0.1
CYP1193	1	0.1
CYP1194	1	0.1
CYP1196	1	0.1
CYP1207	1	0.1
CYP1215	1	0.1
CYP1222	1	0.1
CYP1223	1	0.1
CYP122	1	0.1
CYP123	1	0.1
CYP1248	1	0.1
CYP1274	1	0.1
CYP1339	1	0.1
CYP1373	1	0.1

CYP1385	1	0.1
CYP1392	1	0.1
CYP1418	1	0.1
CYP1422	1	0.1
CYP1424	1	0.1
CYP1457	1	0.1
CYP1459	1	0.1
CYP1469	1	0.1
CYP146	1	0.1
CYP1509	1	0.1
CYP151	1	0.1
CYP1694	1	0.1
CYP1722	1	0.1
CYP177	1	0.1
CYP1813	1	0.1
CYP2045	1	0.1
CYP206	1	0.1
CYP2108	1	0.1
CYP2189	1	0.1
CYP2238	1	0.1
CYP2266	1	0.1
CYP228	1	0.1
CYP2340	1	0.1
CYP246	1	0.1
CYP268	1	0.1
CYP282	1	0.1
CYP283	1	0.1
CYP298	1	0.1

Comparative analysis of P450 family dynamics between the genera *Streptomyces* and *Mycobacterium* revealed the presence of the highest number of P450 families and P450 subfamilies in *Streptomyces* species (Fig. 4.4). *Streptomyces* species have 144 P450 families and 377 P450 subfamilies compared to 77 P450 families and 132 P450 subfamilies identified in mycobacterial species (Fig. 4.4). *Streptomyces* species also have the highest number of new P450 families (66) and new P450 subfamilies (144) in their genomes compared to mycobacterial species (Fig. 4.4).

Interestingly, only two P450 families (CYP107 and CYP157) conserved in *Streptomyces* compared to mycobacterial species where 10 P450 families, namely CYP51, CYP123, CYP125, CYP130, CYP135, CYP136, CYP138, CYP140, CYP144 and CYP1128, were conserved (Parvez *et al.*, 2016).

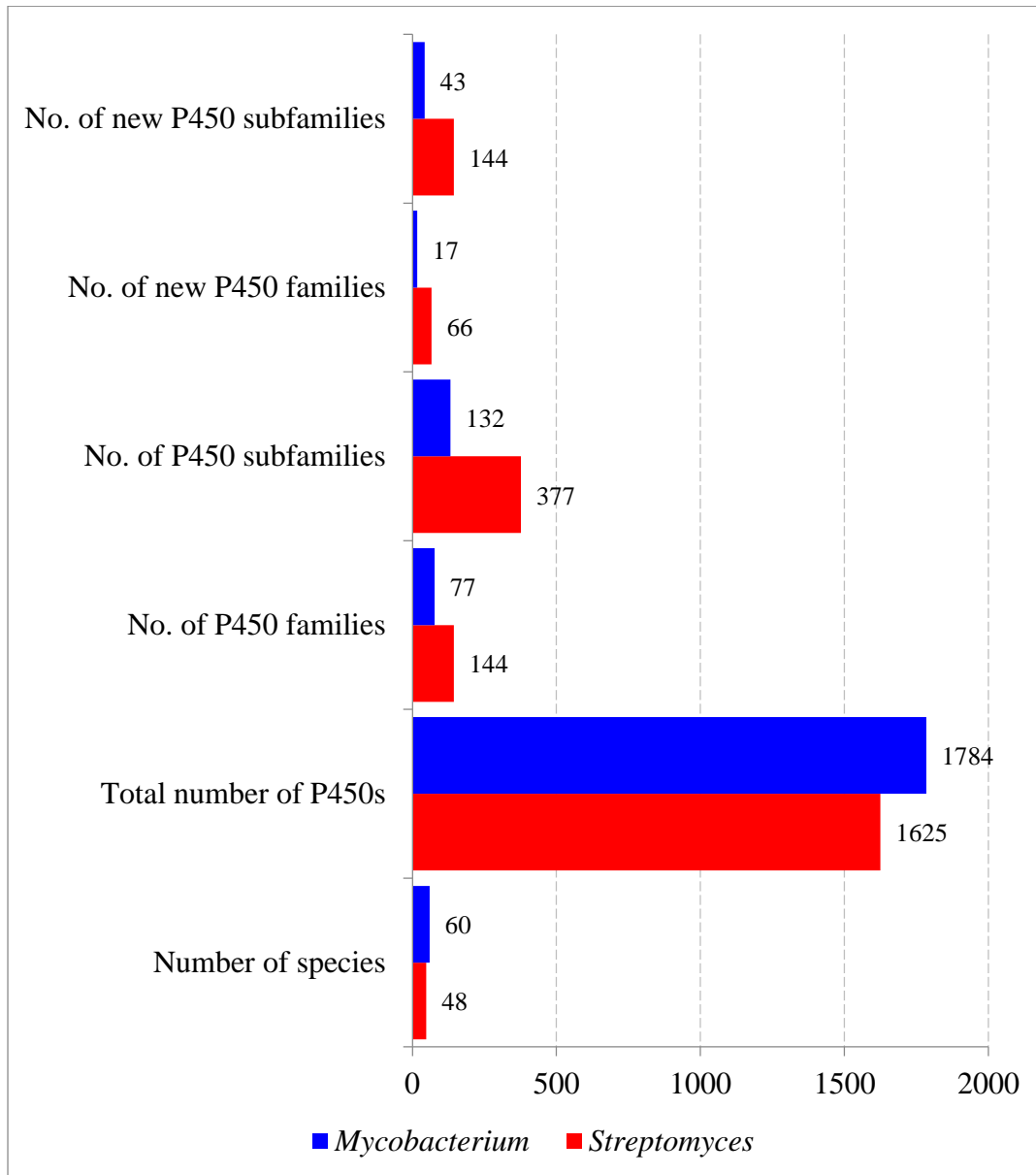


Figure 4. 4. Comparative analysis of key features of P450s between the genera *Streptomyces* and *Mycobacterium*. Y-axis indicates the count for each of the key features.

4.3 *Streptomyces* and *Mycobacterium* species show contrasting P450 profiles

Comparative analysis of P450 profiles between the genera *Streptomyces* and *Mycobacterium* revealed that species belonging to these genera have different P450 profiles with few similarities (Fig. 4.5). Despite both genera belonging to the same phylum, *Actinobacteria*, only 21 P450 families were found to be common and quite a large number of P450 families were found to be unique to *Streptomyces* (123 P450 families) and *Mycobacterium* (56 P450 families) (Fig. 4.5). In the 21 P450 families commonly found between the two genera, an interesting feature was observed in terms of the number of member P450s (Fig. 4.6). A significant difference in the number of member P450s in the commonly shared P450 families was observed between *Streptomyces* and *Mycobacterium* (Fig. 4.6). The P450 families CYP102, CYP105, CYP107, CYP147, CYP161 and CYP183 were highly populated in *Streptomyces* species, whereas the P450 families CYP108, CYP121, CYP123-CYP125, CYP130, CYP135, CYP136, CYP140, CYP143 and CYP268 were highly populated in mycobacterial species (Fig. 4.6).



Figure 4. 5. Comparative analysis of P450 families between *Streptomyces* and *Mycobacterium*. The numbers in parenthesis indicate the number of P450 families that are common and those that are unique to each genus.

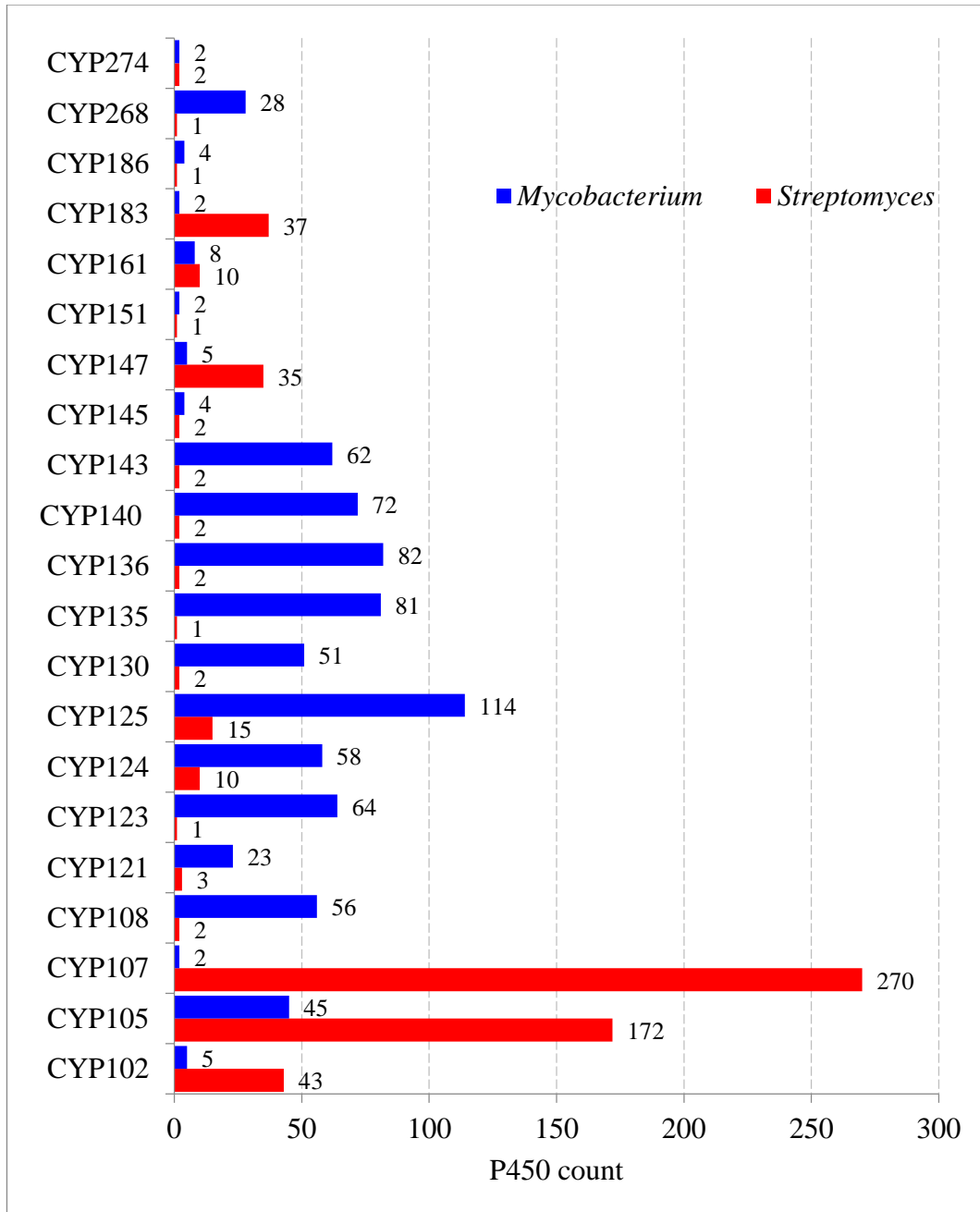


Figure 4. 6. Comparative analysis of member P450s in P450 families common between the genera *Streptomyces* and *Mycobacterium*. The numbers next to bars represent the number of P450s in the P450 family.

Differences were also observed in the number of dominant P450 families in the two genera (Fig. 4.7A and B). Only seven P450 families, namely CYP107, CYP105, CYP157, CYP154, CYP156, CYP147 and CYP183, contributed 62% of all P450s in *Streptomyces* species, whereas 15 P450 families, namely CYP125, CYP189, CYP150, CYP136, CYP135, CYP138, CYP140, CYP123, CYP143, CYP142, CYP144, CYP124, CYP108, CYP51 and CYP187, contributed 60% of all P450s in *Mycobacterium* (Fig. 4.7A and B). An interesting feature was that the percentage contribution of families was highest in *Streptomyces*, i.e. 23.4% by CYP107 and 13.8% by CYP105, compared to *Mycobacterium* P450 families, where the highest contribution was 6.4% by CYP125 (Fig. 4.7A and B). Furthermore, differences in P450 profiles between the two genera were observed in terms of type of dominant P450 families (Fig. 4.7A and B). A comparison of the dominant P450 families between the two genera revealed that none of the dominant P450 families was common between them (Figures 4.5 and 4.7 A and B).

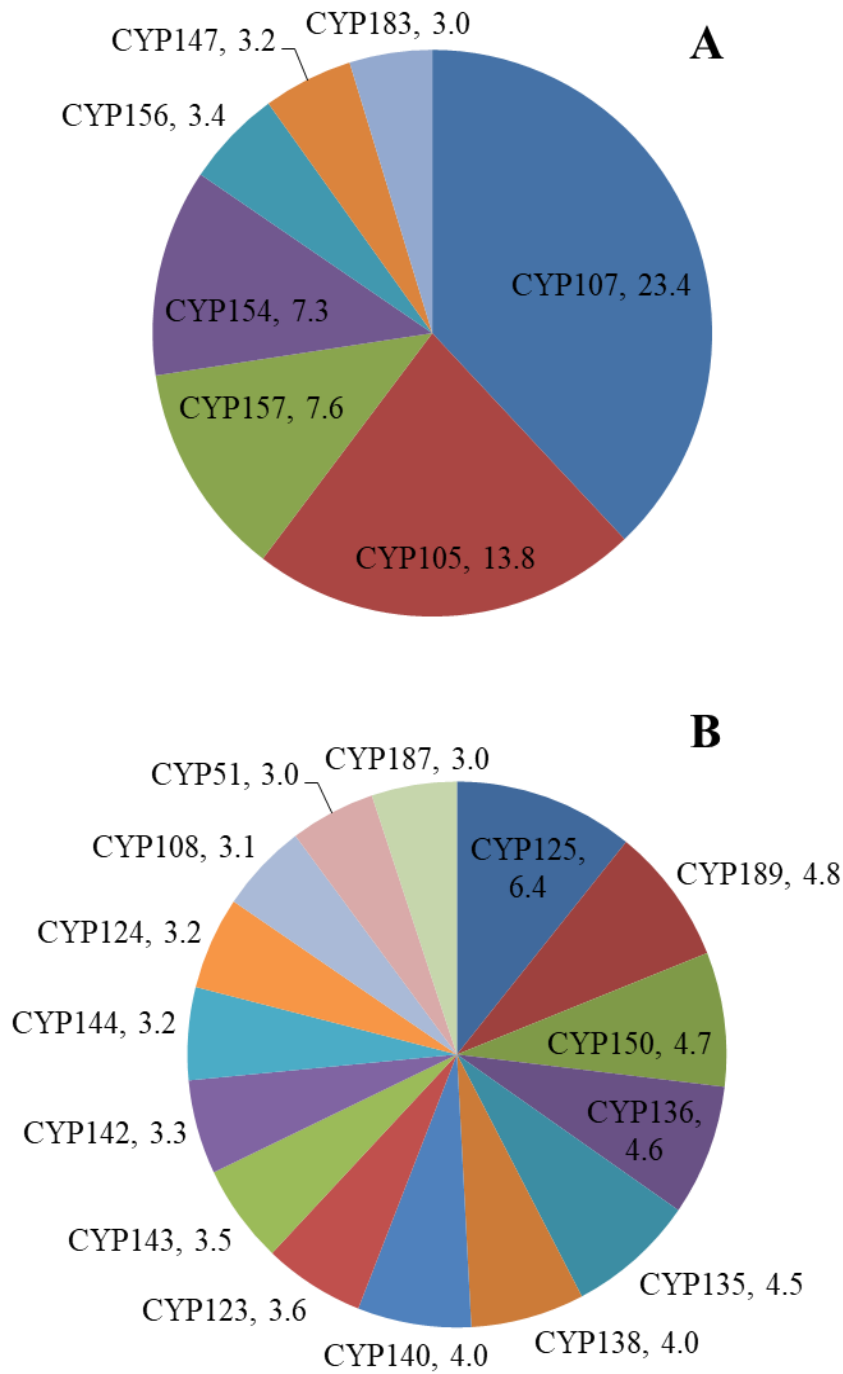


Figure 4. 7. Comparative analysis of dominant P450 families between the genera *Streptomyces* (A) and *Mycobacterium* (B). P450 families that are dominant in a genus are presented along with their

names and percentage contribution to the total number of P450s in a genus. A detailed analysis of the percentage contribution of each P450 family in *Streptomyces* species is presented in Table 4.5.

4.4 Predicted functions of *Streptomyces* P450s

Functional analysis of P450s based on characterised homolog P450s from other microorganisms and P450s from *Streptomyces* species (Rudolf *et al.*, 2017) revealed that most of the *Streptomyces* P450s were involved in secondary metabolite production (Table 4.6). This strongly supports the concept that these *Streptomyces* P450s play a key role in the production of chemically diverse secondary metabolites, as a large number of P450 families were found in 48 *Streptomyces* species. Detailed analysis of P450 functions according to general functions and specific functions at P450 family and P450 subfamily level is presented in Tables 4.6 and Tables 4.7, respectively. The P450 family CYP180 was found to be part of a gene cluster that produces geosmin (Lamb *et al.*, 2003). Among the P450 families involved in secondary metabolite production, 88 P450 families are uniquely present in *Streptomyces* species compared to mycobacterial species (Fig. 4.5 and Tables 4.6 and 4.7). P450 families, namely CYP105, CYP107, CYP161, and CYP183, which are highly populated in *Streptomyces* species compared to mycobacterial species (Fig. 4.7), were found to be involved in secondary metabolite production (Tables 4.6 and 4.7). This strongly suggests that these P450 families have been populated in *Streptomyces* species owing to their importance and necessity in secondary metabolite production. Therefore, the diversity among these P450 families, judged by the large number of P450 subfamilies, presumably serves to increase the resultant chemical diversity further across different *Streptomyces* species. It is well established that P450s are one of the key enzymes contributing to the diversity of secondary metabolites in organisms (Greule *et al.*, 2018). In contrast to the P450 families highly populated in *Streptomyces* species, P450 families that are highly populated

in mycobacterial species such as CYP125, CYP124, CYP108, CYP140 and CYP268 (Fig. 4.7B) are involved in steroid (cholesterol) and hydrocarbon (lipids, alkenes, long chain acetate and ketone) hydroxylation (Fig. 4.7B and Table 4.6), suggesting that these P450 families possibly help mycobacterial species to assimilate the host compounds. It is noteworthy that results from this study revealed that some of these P450 families are rarely (CYP125 and CYP140) or never (CYP268) part of secondary metabolite BGCs in mycobacterial species (Tables 4.6 and 4.7).

Table 4. 6. Functional analysis of P450s. Functional analysis of P450s in Table 4.6 is presented at family level. Functional analysis of specific family members of the *Streptomyces* species is presented in Table 4.7.

P450 family	General function	References
Functional analysis of <i>Streptomyces</i> P450s		
CYP102	Fatty acid hydroxylation	(Lamb <i>et al.</i> , 2010)
CYP105	Biotransformation or degradation of xenobiotics, and biosynthesis of secondary metabolites	(Li <i>et al.</i> , 2013, Moody and Loveridge, 2014)
CYP107	Biosynthesis of secondary metabolites	(Sherman <i>et al.</i> , 2006)
CYP113	Biosynthesis of secondary metabolites	(Zhang <i>et al.</i> , 2013)
CYP122	Metabolism of terpenoids and polyketides	(Chen <i>et al.</i> , 2012)
CYP158	Biosynthesis of secondary metabolites (flaviolin]	(Zhao <i>et al.</i> , 2012a, Zhao <i>et al.</i> , 2007)

CYP154	Production of secondary metabolites and hydroxylation of steroids	(Cheng <i>et al.</i> , 2010, Podust <i>et al.</i> , 2004, Podust <i>et al.</i> , 2003)
CYP170	Biosynthesis of secondary metabolites	(Moody <i>et al.</i> , 2012, Takamatsu <i>et al.</i> , 2011, Zhao <i>et al.</i> , 2009)
CYP1048 & CYP264	Production of phytotoxins	(Healy <i>et al.</i> , 2000, Yu <i>et al.</i> , 2013)
CYP161	Biosynthesis of secondary metabolites	(Kelly <i>et al.</i> , 2010)
CYP151 & CYP248	Biosynthesis of secondary metabolites	(Zocher <i>et al.</i> , 2011)
CYP163	Biosynthesis of secondary metabolites	(Haslinger <i>et al.</i> , 2014)
CYP129 & CYP131	Biosynthesis of secondary metabolites	(Dickens <i>et al.</i> , 1997, Jaffrezou <i>et al.</i> , 1996, Walczak <i>et al.</i> , 1999)
CYP162	Biosynthesis of secondary metabolites	(Xie <i>et al.</i> , 2007)
CYP245 & CYP244	Biosynthesis of secondary metabolites	(Huang, 2003, Molnár <i>et al.</i> , 1996)
CYP183	Biosynthesis of secondary metabolites	(Quaderer <i>et al.</i> , 2006)
Functional analysis of P450s from other microorganisms		
CYP121	Synthesis of mycocyclosin, a natural product	(Belin <i>et al.</i> , 2009)
CYP125	Cholesterol oxidation	(McLean <i>et al.</i> , 2009, Ouellet <i>et al.</i> , 2010)
CYP124	Cholesterol and lipids hydroxylation	(Johnston <i>et al.</i> , 2009)
CYP152	Alkene production	(Belcher <i>et al.</i> , 2014)

CYP108	Terpineol hydroxylation	(Hasemann <i>et al.</i> , 1994)
CYP116	Degradation of toxic compounds (herbicides and alkyl aryl ethers)	(Çelik <i>et al.</i> , 2006, Warman <i>et al.</i> , 2012)
CYP140	Mycolactone toxin synthesis	(Mve-Obiang <i>et al.</i> , 2005)
CYP165& CYP146	Secondary metabolite production (vancomycin biosynthesis)	(Cryle <i>et al.</i> , 2010, Pylypenko <i>et al.</i> , 2003)
CYP199	Oxidation of benzoic acid derivatives	(Bell <i>et al.</i> , 2008, Bell <i>et al.</i> , 2012)
CYP268	Hydroxylation of long chain branched acetate and ketone	(Child <i>et al.</i> , 2018)

Table 4. 7. Functional analysis of P450s. Functional analysis of P450s was presented at P450 subfamily level with respect to *Streptomyces* species.

Species name	CYP P450	Function	References
<i>Streptomyces coelicolor</i> A3(2)	CYP170A1	Catalyses the oxidation of epi-isozizaene to an epimeric mix of 5-albaflavenol	(Zhao <i>et al.</i> , 2009)
	CYP102B1	Fatty acid hydroxylase	(Lamb <i>et al.</i> , 2010)
	CYP105N1	Oxidase in coelibactin siderophore biosynthesis Monooxygenase involved in coelibactin synthesis	(Lim <i>et al.</i> , 2012, Zhao <i>et al.</i> , 2012a)
	CYP107U1	Putative steroid oxidase with role in sporulation and antibiotic synthesis	(Tian <i>et al.</i> , 2013)
	CYP154A1	Di-pentaenone cyclisation Involved in polyketide metabolism	(Podust <i>et al.</i> , 2004, Cheng <i>et al.</i> , 2010)

	CPY158A1 CYP158A2	C–C coupling in flaviolin polymerisation	(Zhao <i>et al.</i> , 2007, Zhao <i>et al.</i> , 2012b)
	CYP170A1	Two-step allylic oxidation of epi-isozizaene to albaflavenone in albaflavenone biosynthesis	(Zhao <i>et al.</i> , 2009)
	CYP154C1	12- and 14-carbon macrolactone monooxygenase e.g., narbomycin hydroxylase	(Podust <i>et al.</i> , 2003)
<i>Streptomyces avermitilis</i>	CYP102D1 C1- CYP105D6 C26- CYP105P1	Fatty acid hydroxylase	(Choi <i>et al.</i> , 2012, Xu <i>et al.</i> , 2010)
	CYP107W1	Oligomycin	(Han <i>et al.</i> , 2015)
	CYP105D6	C1-hydroxylation of filipin	(Xu <i>et al.</i> , 2010)
	CYP105D7	Filipin hydroxylase 1-deoxypentalenic acid hydroxylase	(Takamatsu <i>et al.</i> , 2011)
	CYP105P1	Filipin hydroxylation	(Xu <i>et al.</i> , 2010)
	CYP170A2	Two-step allylic oxidation of epi-isozizaene to albaflavenone	(Takamatsu <i>et al.</i> , 2011)
	CYP171A1	C6 and C8a avermectin algycone hydroxylation	(Lamb <i>et al.</i> , 2011)
	CYP183A	Pentalene hydroxylase	(Quaderer <i>et al.</i> , 2006)
	<i>Streptomyces scabiei</i>	CYP1048A1	Direct nitration of L-tryptophan with NO, O ₂ , redox partners, and NADPH Plays a novel catalytic role in the biosynthesis of a cyclic dipeptide phytotoxin Involved in the production of the plant toxin thaxtomin, responsible for potato common scab
CYP246A1		Thaxtomin phenylalanyl dihydroxylase in thaxtomin A biosynthesis	(Healy <i>et al.</i> , 2002)

<i>Streptomyces griseolus</i>	CYP105A1	Catalyses highly selective oxidations of diterpenoids Vitamin D3 hydroxylase involved in the conversion of vitamin D3 to its active form 1 α ,25-hydroxy vitamin D3	(Hayashi <i>et al.</i> , 2008, Janocha <i>et al.</i> , 2013, Sugimoto, 2008)
	CYP154C3	Catalyses monooxygenation reactions of a range of steroids	(Makino <i>et al.</i> , 2014)
<i>Streptomyces venezuelae</i>	CYP107L1	Involved in ring decoration of macrolide antibiotics Catalyses regioselective C-12 hydroxylation of narbomycin (the final step of pikromycin biosynthesis) 12- and 14- carbon macrolactone, e.g narbomycin and YC-17 hydroxylation	(Sherman <i>et al.</i> , 2006)
<i>Streptomyces natalensis</i>	CYP161A2 (PimD)	4,5-Desepoxypimaricin epoxidase in pimaricin biosynthesis	(Kelly <i>et al.</i> , 2010)
<i>Streptomyces thioluteus</i>	CYP151A (AurH)	Oxidation and ring formation to convert deoxyaureothin to aureothin	(Zocher <i>et al.</i> , 2011)
	CYP248A1	Aureothin synthase	(Zocher <i>et al.</i> , 2011)
<i>Streptomyces himastatinicus</i> ATCC 53653	CYP107B (HmtN)	γ -Hydroxylation of an unusual piperazine acid (Pip) motif in himastatin biosynthesis	(Zhang <i>et al.</i> , 2013)
<i>Streptomyces himastatinicus</i> ATCC 53653	HmtT	Regio- and stereospecific C2/C3 epoxidation of L-tryptophan indole ring and subsequent cyclisation forming hexahydropyrroloindole in himastatin biosynthesis	(Zhang <i>et al.</i> , 2013)
<i>Streptomyces</i> sp. Acta 2897	CYP163B3 (P450 Sky)	Three successive β -hydroxylations of separate PCP-bound L-amino acid precursors in skyllamycin biosynthesis	(Haslinger <i>et al.</i> , 2014, Uhlmann <i>et al.</i> , 2013)
<i>Streptomyces nodosus</i>	CYP161A3 (AmphL) CYP105H4 (AmphN)	Polyketide oxidative tailoring reactions	(Agarwal, 2006, Caffrey <i>et al.</i> , 2001)

<i>Streptomyces thermotolerans</i>	CYP107C1	C12-C13 epoxidation of carbomycin B to make carbomycin C	(Ashy <i>et al.</i> , 1980)
<i>Streptomyces bikiniensis</i>	ChmH1	C20 methyl macrolide hydroxylation	(Ward <i>et al.</i> , 2004)
<i>Streptomyces clavuligerus</i>	CYP105M1 (orf10)	Possible clavaminic acid derivative epoxidase	(Reading and Cole, 1977)
<i>Streptomyces</i> sp. strain C5	CYP129A2 (dox A) CYP131A2 (dnrQ)	C10,C13, C14 anthracycline glycine DNR precursor hydroxylations and likely aglycone core oxidation	(Dickens <i>et al.</i> , 1997, Jaffrezou <i>et al.</i> , 1996, Walczak <i>et al.</i> , 1999)
<i>Streptomyces graminofaciens</i>	GfsF	C8-9 macrolide epoxidation then C10 hydroxylation	(Kataoka <i>et al.</i> , 2000, Kudo <i>et al.</i> , 2010)
<i>Streptomyces tsukubaensis</i>	CYP122A4 (FkbD)	Four-electron C-9 FK506 precursor oxidation	(Chen <i>et al.</i> , 2012)
<i>Streptomyces pulveraceus</i>	FosK	C18 fostriecin hydroxylation	(Kong <i>et al.</i> , 2013, Liu <i>et al.</i> , 2013)
<i>Streptomyces himastatinicus</i>	CYP107B (HmtN) and HmtT and HmtS	Piperazic acid (Pip) motif γ -hydroxylation and C2/C3L-tryptophan epoxidation cyclisation to hexahydropyrroloindole and biaryl aromatic coupling of depsipeptide monomers	(LEET <i>et al.</i> , 1996, Ma <i>et al.</i> , 2011, Zheng <i>et al.</i> , 2013)
<i>Streptomyces tendae</i>	CYP162A1	Histidine β -hydroxylation to form nikkomycins X and I	(Lauer <i>et al.</i> , 2001, Xie <i>et al.</i> , 2007)
<i>Streptomyces spheroids</i>	CYP163A1 (NovI)	PCP-loaded tyrosine β -hydroxylation	(Chen and Walsh, 2001, Steffensky <i>et al.</i> , 2000)
<i>Streptomyces peucetius</i>	CYP105F2	Oleandomycin tailoring hydroxylation	(Rodriguez <i>et al.</i> , 1995, Shrestha <i>et al.</i> , 2008)
	CYP107A1	Catalyses the H ₂ O ₂ -mediated dealkylation of 7-ethoxycoumarin	(Niraula <i>et al.</i> , 2011)

<i>Streptomyces hygroscopicus</i>	CYP107G1 (rapN) CYP122A2 (rapJ) CYP122A3	C9, C26, C27 and C32 rapamycin macrolactone hydroxylation	(Huang, 2003, Molnár <i>et al.</i> , 1996)
<i>Streptomyces</i> sp. tp-a0274	CYP245A1 (StaP) and CYP244 A1 (StaN)	Aryl-aryl coupling of chromopyrrolic acid and C-N linkage of staurosporine aglycone	(Huang, 2003, Molnár <i>et al.</i> , 1996)
<i>Streptomyces griseochromogenes</i>	TauI/TmcR	C5 tautomycetin oxygenation	D. Kim <i>et al.</i> , 2012; F. Wang <i>et al.</i> , 2012
<i>Streptomyces fradiae</i>	CYP105L1 (TylH1,orf7), CYP113B1 (TylII), CYP154B1	Likely C23 methyl lactone ring oxidase (CYP105L1) and C20 methyl O-mycaminosyl-tylactone hydroxylation (CYP113B1)	(Fouces <i>et al.</i> , 1999, Merson-Davies and Cundiiffe, 1994)
<i>Streptomyces</i> sp. 307-9	TamI	C10 oxidation of tirandamycin C to E, then C11-12 epoxidation C18 hydroxylation	(Carlson <i>et al.</i> , 2010, Carlson <i>et al.</i> , 2011)
<i>Streptomyces albus</i>	CYP170B1	Produces albaflavenone from <i>epi</i> -isozizaene	(Moody <i>et al.</i> , 2012)

4.5 References

- AGARWAL, P.K., AGARWAL, P., REDDY, M.K. AND SOPORY, S.K. (2006) Role of DREB transcription factors in abiotic and biotic stress tolerance in plants. *Plant Cell Reports*, 25(12), pp. 1263-1274.
- ASHY, M. A., ABD-EL-GALIL, M. K. & ABOU-ZEID, A.-Z. A. (1980) Carbomycin, a macrolide antibiotic. *Zentralblatt für Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene. Zweite Naturwissenschaftliche Abteilung: Mikrobiologie der Landwirtschaft, der Technologie und des Umweltschutzes*, 135(6), pp. 541-551. doi:10.1016/S0323-6056(80)80075-9.
- BELCHER, J., MCLEAN, K. J., MATTHEWS, S., WOODWARD, L. S., FISHER, K., RIGBY, S. E., NELSON, D. R., POTTS, D., BAYNHAM, M. T. & PARKER, D. A. (2014) Structure and biochemical properties of the alkene producing cytochrome P450 OleTJE (CYP152L1) from the *Jeotgalicoccus* sp. 8456 bacterium. *Journal of Biological Chemistry*, 289(10), pp. 6535-6550.
- BELIN, P., LE DU, M. H., FIELDING, A., LEQUIN, O., JACQUET, M., CHARBONNIER, J. B., LECOQ, A., THAI, R., COURÇON, M. & MASSON, C. (2009) Identification and structural basis of the reaction catalyzed by CYP121, an essential cytochrome P450 in *Mycobacterium tuberculosis*. *Proceedings of the National Academy of Sciences*, 106(18), pp. 7426-7431. doi:10.1073/pnas.0812191106.
- BELL, S. G., XU, F., FORWARD, I., BARTLAM, M., RAO, Z. & WONG, L. L. (2008) Crystal structure of CYP199A2, a para-substituted benzoic acid oxidizing cytochrome P450 from *Rhodospseudomonas palustris*. *Journal of Molecular Biology*, 383(3), pp. 561-574.
- BELL, S. G., YANG, W., TAN, A. B., ZHOU, R., JOHNSON, E. O., ZHANG, A., ZHOU, W., RAO, Z. & WONG, L. L. (2012) The crystal structures of 4-methoxybenzoate bound CYP199A2

and CYP199A4: structural changes on substrate binding and the identification of an anion binding site. *Dalton Transactions*, 41(28), pp. 8703-8714. doi: 10.1039/c2dt30783a.

CAFFREY, P., LYNCH, S., FLOOD, E., FINNAN, S. & OLIYNYK, M. (2001) Amphotericin biosynthesis in *Streptomyces nodosus*: deductions from analysis of polyketide synthase and late genes. *Chemistry & Biology*, 8(7), pp. 713-723.

CARLSON, J. C., FORTMAN, J., ANZAI, Y., LI, S., BURR, D. A. & SHERMAN, D. H. (2010) Identification of the tirandamycin biosynthetic gene cluster from *Streptomyces* sp. 307-9. *ChemBioChem*, 11, pp. 564-572. doi: 10.1039/c2dt30783a.

CARLSON, J. C., LI, S., GUNATILLEKE, S. S., ANZAI, Y., BURR, D. A., PODUST, L. M. & SHERMAN, D. H. (2011) Tirandamycin biosynthesis is mediated by co-dependent oxidative enzymes. *Nature Chemistry*, 3, pp. 628-633.

CDC (2017) Antibiotic/Antimicrobial resistance. Available at: <http://www.cdc.gov/drugresistance>: Center for Disease Control and Prevention. [24 January 2019].

ÇELİK, A., ROBERTS, G. A., WHITE, J. H., CHAPMAN, S. K., TURNER, N. J. & FLITSCH, S. L. (2006) Probing the substrate specificity of the catalytically self-sufficient cytochrome P450 RhF from a *Rhodococcus* sp. *Chemical Communications*, 0(43) pp. 4492-4494. doi: 10.1039/B609427A.

CHALLIS, D., YU, J., EVANI, U. S., JACKSON, A. R., PAITHANKAR, S., COARFA, C., MILOSAVLJEVIC, A., GIBBS, R. A. & YU, F. (2012) An integrative variant analysis suite for whole exome next-generation sequencing data. *BMC bioinformatics*, 13, pp. 8.

CHEN, D., ZHANG, Q., ZHANG, Q., CEN, P., XU, Z. & LIU, W. (2012) Improvement of FK506 production in *Streptomyces tsukubaensis* by genetic enhancement of the supply of unusual

polyketide extender units via utilization of two distinct site-specific recombination systems.

Applied Environmental Microbiology, 78(15), pp. 5093-5103.

CHEN, H. & WALSH, C. T. (2001) Coumarin formation in novobiocin biosynthesis: β -hydroxylation of the aminoacyl enzyme tyrosyl-S-NovH by a cytochrome P450 NovI. *Chemistry & Biology*, 8(4), pp. 301-312.

CHENG, Q., LAMB, D. C., KELLY, S. L., LEI, L. & GUENGERICH, F. P. (2010) Cyclization of a cellular dipentaenone by *Streptomyces coelicolor* cytochrome P450 154A1 without oxidation/reduction. *Journal of the American Chemical Society*, 132(43), pp. 15173-15175. doi: 10.1021/ja107801v.

CHILD, S. A., NAUMANN, E. F., BRUNING, J. B. & BELL, S. G. (2018) Structural and functional characterisation of the cytochrome P450 enzyme CYP268A2 from *Mycobacterium marinum*. *Biochemical Journal*, 475(4), pp. 705-722. doi: 10.1042/BCJ20170946.

CHOI, K. Y., JUNG, E., JUNG, D. H., PANDEY, B. P., YUN, H., PARK, H. Y., KAZLAUSKAS, R. J. & KIM, B. G. (2012) Cloning, expression and characterization of CYP102D1, a self-sufficient P450 monooxygenase from *Streptomyces avermitilis*. *The FEBS Journal*, 279(9), pp. 1650-1662. doi: 10.1111/j.1742-4658.2011.08462.x.

DICKENS, M. L., PRIESTLEY, N. D. & STROHL, W. R. (1997) In vivo and in vitro bioconversion of epsilon-rhodomyacinone glycoside to doxorubicin: functions of DauP, DauK, and DoxA. *Journal of Bacteriology*, 179(8), pp. 2641-2650.

FOUCES, R., MELLADO, E., DÍEZ, B. & BARREDO, J. L. (1999) The tylosin biosynthetic cluster from *Streptomyces fradiae*: genetic organization of the left region. *Microbiology*, 145 (Pt 4) (4), pp. 855-868.

- GREULE, A., STOK, J. E., DE VOSS, J. J., & CRYLE, M. J. (2018) Unrivalled diversity: The many roles and reactions of bacterial cytochromes P450 in secondary metabolism. *Natural Product Reports*, 35(8), pp. 757-791. doi: 10.1039/c7np00063d.
- HAN, S., PHAM, T.-V., KIM, J.-H., LIM, Y.-R., PARK, H.-G., CHA, G.-S., . . . KIM, D. (2015) Functional characterization of CYP107W1 from *Streptomyces avermitilis* and biosynthesis of macrolide oligomycin A. *Archives of Biochemistry and Biophysics*, 575, pp. 1-7. doi: 10.1016/j.abb.2015.03.025.
- HASEMANN, C. A., RAVICHANDRAN, K., PETERSON, J. A. & DEISENHOFER, J. (1994) Crystal structure and refinement of cytochrome P450 terp at 2.3 Å resolution. *Journal of Molecular Biology*, 236, pp. 1169-1185. doi: 10.1016/j.abb.2015.03.025.
- HASLINGER, K., BRIEKE, C., UHLMANN, S., SIEVERLING, L., SÜSSMUTH, R. D. & CRYLE, M. J. (2014) The structure of a transient complex of a nonribosomal peptide synthetase and a cytochrome P450 monooxygenase. *Angewandte Chemie International Edition*, 53(32), pp. 8518-8522. doi: 10.1002/anie.201404977.
- HAYASHI, K., SUGIMOTO, H., SHINKYO, R., YAMADA, M., IKEDA, S., IKUSHIRO, S., KAMAKURA, M., SHIRO, Y. & SAKAKI, T. (2008) Structure-based design of a highly active vitamin D hydroxylase from *Streptomyces griseolus* CYP105A1. *Biochemistry*, 47(46), pp. 11964-11972.
- HEALY, F. G., KRASNOFF, S. B., WACH, M., GIBSON, D. M. & LORIA, R. (2002) Involvement of a cytochrome P450 monooxygenase in thaxtomin A biosynthesis by *Streptomyces acidiscabies*. *Journal of Bacteriology*, 184(7), pp. 2019-2029.
- HEALY, F. G., WACH, M., KRASNOFF, S. B., GIBSON, D. M. & LORIA, R. (2000) The txtAB genes of the plant pathogen *Streptomyces acidiscabies* encode a peptide synthetase required

for phytotoxin thaxtomin A production and pathogenicity. *Molecular Microbiology*, 38(4), pp. 794-804.

HUANG, S., Bjornsti, M, A. & Houghton, P. J. (2003) Rapamycins: mechanism of action and cellular resistance. *Cancer Biology Therapy*, 2(3), pp. 222.

JAFFREZOU, J.-P., LEVADE, T., BETTAIEB, A., ANDRIEU, N., BEZOMBES, C., MAESTRE, N., VERMEERSCH, S., ROUSSE, A. & LAURENT, G. (1996) Daunorubicin-induced apoptosis: triggering of ceramide generation through sphingomyelin hydrolysis. *The EMBO Journal*, 15(10), pp. 2417-2424. doi: 10.1002/j.1460-2075.1996.tb00599.x.

JANOCHA, S., ZAPP, J., HUTTER, M., KLESER, M., BOHLMANN, J. & BERNHARDT, R. (2013) Resin acid conversion with CYP105A1: an enzyme with potential for the production of pharmaceutically relevant diterpenoids. *ChemBioChem*, 14(4), pp. 467-473. doi: 10.1002/cbic.201200729.

JAWALLAPERSAND, P., MASHELE, S. S., KOVAČIČ, L., STOJAN, J., KOMEL, R., PAKALA, S. B., . . . SYED, K. (2014) Cytochrome P450 monooxygenase CYP53 family in fungi: comparative structural and evolutionary analysis and its role as a common alternative anti-fungal drug target. *PLoS One*, 9(9), pp. e107209. doi: 10.1371/journal.pone.0107209.

JOHNSTON, J. B., KELLS, P. M., PODUST, L. M. & DE MONTELLANO, P. R. O. (2009) Biochemical and structural characterization of CYP124: A methyl-branched lipid ω -hydroxylase from *Mycobacterium tuberculosis*. *Proceedings of the National Academy of Sciences*, 106(49), pp. 20687-20692. doi: 10.1073/pnas.0907398106.

KATAOKA, T., YAMADA, A., BANDO, M., HONMA, T., MIZOUE, K. & NAGAI, K. (2000) FD-891, a structural analogue of concanamycin A that does not affect vacuolar acidification or

perforin activity, yet potently prevents cytotoxic T lymphocyte-mediated cytotoxicity through the blockage of conjugate formation. *Immunology*, 100(2), pp. 170.

KELLY, A., MCGEE, M., CREWS JR, D., SWEENEY, T., BOLAND, T. & KENNY, D. (2010) Repeatability of feed efficiency, carcass ultrasound, feeding behavior, and blood metabolic variables in finishing heifers divergently selected for residual feed intake. *Journal of Animal Science*, 88(1), pp. 3214-3225. doi: 10.2527/jas.2009-2700.

KGOSIEMANG, I. K. R., SYED, K., & MASHELE, S. S. (2014) Comparative genomics and evolutionary analysis of cytochrome P450 monooxygenases in fungal subphylum *Saccharomycotina*. *Journal of Pure and Applied Microbiology* 8 (Spl. edn. 2), pp. 291–302.

KONG, R., LIU, X., SU, C., MA, C., QIU, R. & TANG, L. (2013) Elucidation of the biosynthetic gene cluster and the post-PKS modification mechanism for fostriecin in *Streptomyces pulveraceus*. *Chemistry & Biology*, 20(1), pp. 45-54. doi: 10.1016/j.chembiol.2012.10.018.

KUDO, F., MOTEGI, A., MIZOUE, K. & EGUCHI, T. (2010) Cloning and characterization of the biosynthetic gene cluster of 16-membered macrolide antibiotic FD-891: involvement of a dual functional Cytochrome P450 monooxygenase catalyzing epoxidation and hydroxylation. *ChemBioChem*, 11(11), pp. 1574-1582. doi: 10.1002/cbic.201000214.

LAMB, D. C., IKEDA, H., NELSON, D. R., ISHIKAWA, J., SKAUG, T., JACKSON, C., . . . KELLY, S. L. (2003) Cytochrome P450 complement (CYPome) of the avermectin-producer *Streptomyces avermitilis* and comparison to that of *Streptomyces coelicolor* A3 (2). *Biochemical and Biophysical Research Communications*, 307(3), pp. 610-619. doi: 10.1016/S0006-291X(03)01231-2.

- LAMB, D. C., LEI, L., ZHAO, B., YUAN, H., JACKSON, C. J., WARRILOW, A. G., SKAUG, T., DYSON, P. J., DAWSON, E. S. & KELLY, S. L. (2010) *Streptomyces coelicolor* A3 (2) CYP102 protein, a novel fatty acid hydroxylase encoded as a heme domain without an N-terminal redox partner. *Applied Environmental Microbiology*, 76(6), pp. 1975-1980.
- LAMB, D. C., ZHAO, B., GUENGERICH, F. P., KELLY, S. L. & WATERMAN, M. R. (2011) *Genomics of Streptomyces cytochrome P450*; Norfolk, UK: Caister Academic Press.
- LAUER, B., RUSSWURM, R., SCHWARZ, W., KALMANCZHELYI, A., BRUNTNER, C., ROSEMEIER, A. & BORMANN, C. (2001) Molecular characterization of co-transcribed genes from *Streptomyces tendae* Tü901 involved in the biosynthesis of the peptidyl moiety and assembly of the peptidyl nucleoside antibiotic nikkomycin. *Molecular and General Genetics MGG*, 264(5), pp. 662-673.
- LAWRENCE, C., CLARK, M. & KING, R. (1990) Induction of common scab symptoms in aseptically cultured potato tubers by the vivotoxin, thaxtomin. *Phytopathology*, 80, pp. 606-608.
- LEET, J. E., SCHROEDER, D. R., GOLIK, J., MATSON, J. A., DOYLE, T. W., LAM, K. S., HILL, S. E., LEE, M. S., WHITNEY, J. L. & KRISHNAN, B. S. (1996) Himastatin, a new antitumor antibiotic from *Streptomyces hygrosopicus*. *The Journal of Antibiotics*, 49(3), pp. 299-311.
- LI, Z. Z., LI, X. F., YANG, W., DONG, X., YU, J., ZHU, S. L., LI, M., XIE, L. & TONG, W. Y. (2013) Identification and functional analysis of cytochrome P450 complement in *Streptomyces virginiae* IBL14. *BMC Genomics*, 14(1), pp. 130.
- LIM, Y.-R., HONG, M.-K., KIM, J.-K., DOAN, T. T. N., KIM, D.-H., YUN, C.-H., CHUN, Y.-J., KANG, L.-W. & KIM, D. (2012) Crystal structure of cytochrome P450 CYP105N1 from *Streptomyces coelicolor*, an oxidase in the coelibactin siderophore biosynthetic pathway.

Archives of Biochemistry and Biophysics, 528(2), pp. 111-117. doi: 10.1016/j.abb.2012.09.001.

LIU, Z., ZHANG, W., HUANG, F., FENG, H., SHU, W., XU, X. & CHEN, Y. (2013) High throughput capture of circulating tumor cells using an integrated microfluidic system. *Biosensors and Bioelectronics*, 47, pp. 113-119. doi: 10.1016/j.bios.2013.03.017.

MA, J., WANG, Z., HUANG, H., LUO, M., ZUO, D., WANG, B., SUN, A., CHENG, Y. Q., ZHANG, C. & JU, J. (2011) Biosynthesis of Himastatin: assembly line and characterization of three Cytochrome P450 enzymes involved in the post-tailoring oxidative steps. *Angewandte Chemie International Edition*, 50(34), pp. 7797-7802. doi:10.1002/anie.201102305.

MAKINO, T., KATSUYAMA, Y., OTOMATSU, T., MISAWA, N. & OHNISHI, Y. (2014) Regio- and stereospecific hydroxylation of various steroids at the 16 α position of the D ring by the *Streptomyces griseus* cytochrome P450 CYP154C3. *Applied Environmental Microbiology*, 80(4), pp. 1371-1379.

MCLEAN, K. J., LAFITE, P., LEVY, C., CHEESMAN, M. R., MAST, N., PIKULEVA, I. A., LEYS, D. & MUNRO, A. W. (2009) The structure of *Mycobacterium tuberculosis* CYP125 molecular basis for cholesterol binding in a P450 needed for host infection. *Journal of Biological Chemistry*, 284(51), pp. 35524-35533.

MERSON-DAVIES, L. A. & CUNDIFFE, E. (1994) Analysis of five tyrosin biosynthetic genes from the tyllBA region of the *Streptomyces fradiae* genome. *Molecular Microbiology*, 13(2), pp. 349-355.

MOLNÁR, I., APARICIO, J. F., HAYDOCK, S. F., KHAW, L. E., SCHWECKE, T., KÖNIG, A., STAUNTON, J. & LEADLAY, P. F. (1996) Organisation of the biosynthetic gene cluster for

rapamycin in *Streptomyces hygroscopicus*: analysis of genes flanking the polyketide synthase. *Gene*, 169(1), pp. 1-7.

MOODY, S. C. & LOVERIDGE, E. J. (2014) CYP105-diverse structures, functions and roles in an intriguing family of enzymes in *Streptomyces*. *Journal of Applied Microbiology*, 117(6), pp. 1549-63.

MOODY, S. C., ZHAO, B., LEI, L., NELSON, D. R., MULLINS, J. G., WATERMAN, M. R., KELLY, S. L. & LAMB, D. C. (2012) Investigating conservation of the albaflavenone biosynthetic pathway and CYP170 bifunctionality in streptomycetes. *The FEBS Journal*, 279(9), pp. 1640-1649.

MVE-OBIANG, A., LEE, R. E., UMSTOT, E. S., TROTT, K. A., GRAMMER, T. C., PARKER, J. M., RANGER, B. S., GRAINGER, R., MAHROUS, E. A. & SMALL, P. (2005) A newly discovered mycobacterial pathogen isolated from laboratory colonies of *Xenopus* species with lethal infections produces a novel form of mycolactone, the *Mycobacterium ulcerans* macrolide toxin. *Infection and Immunity*, 73(6), pp. 3307-3312. doi: 10.1128/IAI.73.6.3307-3312.2005.

NELSON, D. R. (2006) *Cytochrome P450 Nomenclature, 2004 Cytochrome P450 protocols* Totowa, New Jersey: Humana Press.

NIRAULA, N. P., KANTH, B. K., SOHNG, J. K. & OH, T.-J. (2011) Hydrogen peroxide-mediated dealkylation of 7-ethoxycoumarin by cytochrome P450 (CYP107AJ1) from *Streptomyces peucetius* ATCC27952. *Enzyme and Microbial Technology*, 48(2), pp. 181-186. doi: 10.1016/j.enzmictec.2010.10.001.

OUELLET, H., GUAN, S., JOHNSTON, J. B., CHOW, E. D., KELLS, P. M., BURLINGAME, A. L., COX, J. S., PODUST, L. M. & DE MONTELLANO, P. R. O. (2010) *Mycobacterium*

tuberculosis CYP125A1, a steroid C27 monooxygenase that detoxifies intracellularly generated cholest-4-en-3-one. *Molecular Microbiology*, 77(3), pp. 730-742.

PARVEZ, M., QHANYA, L. B., MTHAKATHI, N. T., KGOSIEMANG, I. K. R., BAMAL, H. D., PAGADALA, N. S., ..THERON, C. W. (2016) Molecular evolutionary dynamics of cytochrome P450 monooxygenases across kingdoms: special focus on mycobacterial P450s. *Scientific Reports*, 6, pp. 33099.

PODUST, L. M., BACH, H., KIM, Y., LAMB, D. C., ARASE, M., SHERMAN, D. H., KELLY, S. L. & WATERMAN, M. R. (2004) Comparison of the 1.85 Å structure of CYP154A1 from *Streptomyces coelicolor* A3 (2) with the closely related CYP154C1 and CYPs from antibiotic biosynthetic pathways. *Protein Science*, 13(1), pp. 255-268. doi: 10.1110/ps.03384804.

PODUST, L. M., KIM, Y., ARASE, M., NEELY, B. A., BECK, B. J., BACH, H., SHERMAN, D. H., LAMB, D. C., KELLY, S. L. & WATERMAN, M. R. (2003) The 1.92-Å Structure of *Streptomyces coelicolor* A3 (2) CYP154C1 a new monooxygenase that functionalizes macrolide ring systems. *Journal of Biological Chemistry*, 278, pp. 12214-12221. doi: 10.1110/ps.03384804.

PYLYPENKO, O., VITALI, F., ZERBE, K., ROBINSON, J. A. & SCHLICHTING, I. (2003) Crystal structure of OxyC, a cytochrome P450 implicated in an oxidative C–C coupling reaction during vancomycin biosynthesis. *Journal of Biological Chemistry*, 278(47), pp. 46727-46733.

QHANYA, L. B., MATOWANE, G., CHEN, W., SUN, Y., LETSIMO, E. M., PARVEZ, M., . . . SYED, K. (2015) Genome-wide annotation and comparative analysis of cytochrome P450 monooxygenases in Basidiomycete biotrophic plant pathogens. *PLoS One*, 10(11), pp. e0142100.

- QUADERER, R., OMURA, S., IKEDA, H. & CANE, D. E. (2006) Pentalenolactone biosynthesis. Molecular cloning and assignment of biochemical function to PtlI, a cytochrome P450 of *Streptomyces avermitilis*. *Journal of the American Chemical Society*, 128(40), pp. 13036-7. doi: 10.1021/ja0639214.
- READING, C. & COLE, M. (1977) Clavulanic acid: a beta-lactamase-inhibiting beta-lactam from *Streptomyces clavuligerus*. *Antimicrobial Agents and Chemotherapy*, 11(5), pp. 852-857.
- RODRIGUEZ, A. M., OLANO, C., MÉNDEZ, C., HUTCHINSON, C. R. & SALAS, J. (1995) A cytochrome P450-like gene possibly involved in oleandomycin biosynthesis by *Streptomyces antibioticus*. *FEMS Microbiology Letters*, 127(1-2), pp. 117-120. doi: 10.1111/j.1574-6968.1995.tb07459.x.
- RUDOLF, J. D., CHANG, C.-Y., MA, M., & SHEN, B. (2017) Cytochromes P450 for natural product biosynthesis in *Streptomyces*: sequence, structure, and function. *Natural Product Reports*, 34(9), pp. 1141-1172. doi: 10.1039/c7np00034k.
- SHERMAN, D. H., LI, S., YERMALITSKAYA, L. V., KIM, Y., SMITH, J. A., WATERMAN, M. R. & PODUST, L. M. (2006) The structural basis for substrate anchoring, active site selectivity, and product formation by P450 PikC from *Streptomyces venezuelae*. *Journal of Biological Chemistry*, 281(36), pp. 26289-26297.
- SHRESTHA, P., OH, T.-J., LIOU, K. & SOHNG, J. K. (2008) Cytochrome P450 (CYP105F2) from *Streptomyces peucetius* and its activity with oleandomycin. *Applied Microbiology and Biotechnology*, 79(4), pp. 555.
- STEFFENSKY, M., MÜHLENWEG, A., WANG, Z.-X., LI, S.-M. & HEIDE, L. (2000) Identification of the novobiocin biosynthetic gene cluster of *Streptomyces spheroides* NCIB 11891. *Antimicrobial Agents and Chemotherapy*, 44(5), pp. 1214-1222.

- SUGIMOTO, H. (2008) Crystal structure of *Streptomyces griseolus* CYP105A1 catalyzing vitamin D hydroxylation. *Vitamins*, 82, pp. 497-502.
- SYED, K., SHALE, K., PAGADALA, N. S., & TUSZYNSKI, J. (2014) Systematic identification and evolutionary analysis of catalytically versatile cytochrome P450 monooxygenase families enriched in model basidiomycete fungi. *PLos One*, 9(1), pp. e86683. doi:10.1371/journal.pone.0086683.
- TAKAMATSU, S., XU, L.-H., FUSHINOBU, S., SHOUN, H., KOMATSU, M., CANE, D. E. & IKEDA, H. (2011) Pentalenic acid is a shunt metabolite in the biosynthesis of the pentalenolactone family of metabolites: hydroxylation of 1-deoxypentalenic acid mediated by CYP105D7 (SAV_7469) of *Streptomyces avermitilis*. *The Journal of Antibiotics*, 64(1), pp. 65.
- TIAN, Z., CHENG, Q., YOSHIMOTO, F. K., LEI, L., LAMB, D. C. & GUENGERICH, F. P. (2013) Cytochrome P450 107U1 is required for sporulation and antibiotic production in *Streptomyces coelicolor*. *Archives of Biochemistry and Biophysics*, 530(2), pp. 101-107.
- UHLMANN, S., SÜSSMUTH, R. D. & CRYLE, M. J. (2013) Cytochrome P450sky interacts directly with the nonribosomal peptide synthetase to generate three amino acid precursors in skyllamycin biosynthesis. *ACS Chemical Biology*, 8(11), pp. 2586-2596. doi:10.1021/cb400555e.
- WALCZAK, R. J., DICKENS, M. L., PRIESTLEY, N. D. & STROHL, W. R. (1999) Purification, properties, and characterization of recombinant *Streptomyces* sp. strain C5 DoxA, a cytochrome P450 catalyzing multiple steps in doxorubicin biosynthesis. *Journal of Bacteriology*, 181(1), pp. 298-304.

- WARD, S. L., HU, Z., SCHIRMER, A., REID, R., REVILL, W. P., REEVES, C. D., PETRAKOVSKY, O. V., DONG, S. D. & KATZ, L. (2004) Chalcomycin biosynthesis gene cluster from *Streptomyces bikiniensis*: novel features of an unusual ketolide produced through expression of the chm polyketide synthase in *Streptomyces fradiae*. *Antimicrobial Agents and Chemotherapy*, 48(12), pp. 4703-4712.
- WARMAN, A. J., ROBINSON, J. W., LUCIAKOVA, D., LAWRENCE, A. D., MARSHALL, K. R., WARREN, M. J., CHEESMAN, M. R., RIGBY, S. E., MUNRO, A. W. & MCLEAN, K. J. (2012) Characterization of *Cupriavidus metallidurans* CYP116B1–A thiocarbamate herbicide oxygenating P450–phthalate dioxygenase reductase fusion protein. *The FEBS Journal*, 279(9), pp. 1675-1693.
- XIE, Z., NIU, G., LI, R., LIU, G. & TAN, H. (2007) Identification and characterization of sanH and sanI involved in the hydroxylation of pyridyl residue during nikkomycin biosynthesis in *Streptomyces ansochromogenes*. *Current Microbiology*, 55, pp. 537-542.
- XU, L.-H., FUSHINOBU, S., TAKAMATSU, S., WAKAGI, T., IKEDA, H. & SHOUN, H. (2010) Regio- and stereospecificity of filipin hydroxylation sites revealed by crystal structures of cytochrome P450 105P1 and 105D6 from *Streptomyces avermitilis*. *Journal of Biological Chemistry*, 285, pp. 16844-16853.
- YU, F., LI, M., XU, C., WANG, Z., ZHOU, H., YANG, M., CHEN, Y., TANG, L. & HE, J. (2013) Structural insights into the mechanism for recognizing substrate of the cytochrome P450 enzyme TxtE. *PLoS One*, 8, pp. e81526. doi: 10.1371/journal.pone.0081526.
- ZHANG, H., CHEN, J., WANG, H., XIE, Y., JU, J., YAN, Y. & ZHANG, H. (2013) Structural analysis of HmtT and HmtN involved in the tailoring steps of himastatin biosynthesis. *FEBS Letters*, 587(11), pp. 1675-1680. doi: 10.1016/j.febslet.2013.04.013.

- ZHAO, B., BELLAMINE, A., LEI, L. & WATERMAN, M. R. (2012a) The role of Ile87 of CYP158A2 in oxidative coupling reaction. *Archives of Biochemistry and Biophysics*, 518(2), pp. 127-132. doi: 10.1016/j.abb.2011.12.007.
- ZHAO, B., LAMB, D. C., LEI, L., KELLY, S. L., YUAN, H., HACHEY, D. L. & WATERMAN, M. R. (2007) Different binding modes of two flavin substrate molecules in cytochrome P450 158A1 (CYP158A1) compared to CYP158A2. *Biochemistry*, 46(30), pp. 8725-8733.
- ZHAO, B., LEI, L., VASSYLYEV, D. G., LIN, X., CANE, D. E., KELLY, S. L., YUAN, H., LAMB, D. C. & WATERMAN, M. R. (2009) Crystal structure of albaflavenone monooxygenase containing a moonlighting terpene synthase active site. *Journal of Biological Chemistry*, 284(52), pp. 36711-36719.
- ZHAO, B., MOODY, S. C., HIDER, R. C., LEI, L., KELLY, S. L., WATERMAN, M. R. & LAMB, D. C. (2012b) Structural analysis of cytochrome P450 105N1 involved in the biosynthesis of the zincophore, coelibactin. *International Journal of Molecular Sciences*, 13(7), pp. 8500-8513.
- ZHENG, R., CHEN, Z., CAI, C., WANG, X., HUANG, Y., XIAO, B. & SUN, G. (2013) Effect of biochars from rice husk, bran, and straw on heavy metal uptake by pot-grown wheat seedling in a historically contaminated soil. *BioResources*, 8(4), pp. 5965-5982.
- ZOCHER, G., RICHTER, M. E., MUELLER, U. & HERTWECK, C. (2011) Structural fine-tuning of a multifunctional cytochrome P450 monooxygenase. *Journal of the American Chemical Society*, 133(7), pp. 2292-2302.

CHAPTER 5

CONCLUSION AND FUTURE PERSPECTIVES

Adaptation is key for the survival of an organism. Organisms adapt to different ecological niches by changing their gene pool and thus changing their physiology to make them suitable for survival in the new environment. The effect of ecological niches or lifestyle on P450s' evolution in organisms such as animals, plants, fungi and oomycetes has been observed. In this study, for the first time, the influence of lifestyle on the evolution of P450s in a bacterial population has been presented. Ample evidence of the impact of lifestyle on shaping the P450 profile in species belonging to the genera *Streptomyces* and *Mycobacterium* is identified in the study. It is clear that different lifestyles influenced the P450 profiles in *Streptomyces* and *Mycobacterium*, hence the differences observed between the two genera in terms of number of P450s, P450 family and subfamily diversity, type of dominant and unique P450 families and differences in number of P450s in common P450 families. Furthermore, functional analysis of P450s suggests that in *Streptomyces*, P450s are destined for secondary metabolite production, whereas in *Mycobacterium* they are destined for utilisation of host lipids or synthesis of novel lipids. Future works involves assessing the physiological function of P450s in order to identify their role, if any, in the adaptation of *Streptomyces* species or mycobacterial species to different ecological niches.