



**HAL**  
open science

## Expanding the chemical diversity through microorganisms co-culture: Current status and outlook

Divya Arora, Prasoon Gupta, Sundeep Jaglan, Catherine Roullier, Olivier Grovel, Samuel Bertrand

### ► To cite this version:

Divya Arora, Prasoon Gupta, Sundeep Jaglan, Catherine Roullier, Olivier Grovel, et al.. Expanding the chemical diversity through microorganisms co-culture: Current status and outlook. *Biotechnology Advances*, 2020, 40, pp.107521. 10.1016/j.biotechadv.2020.107521 . hal-03015863

**HAL Id: hal-03015863**

**<https://hal.science/hal-03015863>**

Submitted on 22 Aug 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# 1 Expanding the Chemical Diversity through 2 Microorganisms Co-culture: Current Status 3 and Outlook

4 Divya Arora<sup>1,3,4</sup>, Praseon Gupta<sup>2,3</sup>, Sundeep Jaglan<sup>1,3</sup>, Catherine Roullier<sup>4</sup>, Olivier Grovel<sup>4</sup>,  
5 Samuel Bertrand<sup>4\*</sup>

6  
7 <sup>1</sup>Microbial Biotechnology Division, CSIR-Indian Institute of Integrative Medicine, Jammu-  
8 180001, India; <sup>2</sup>Natural Product Chemistry Division, CSIR-Indian Institute of Integrative  
9 Medicine, Jammu-180001, India; <sup>3</sup>Academy of Scientific and Innovative Research (AcSIR),  
10 Jammu Campus, Jammu – 180001, India; <sup>4</sup>Groupe Mer, Molécules, Santé-EA 2160, Faculté des  
11 Sciences pharmaceutiques et biologiques, Université de Nantes, 9 rue Bias, BP 53508, F-44035  
12 Nantes Cedex 01, France

13  
14 \*Corresponding Author: Samuel Bertrand, PhD

15 Groupe Mer, Molécules, Santé-EA 2160, Faculté des Sciences pharmaceutiques et biologiques,  
16 Université de Nantes, 9 rue Bias, BP 53508, F-44035 Nantes Cedex 01, France; Tel: +33 (0)2 51  
17 12 56 89; Correspondence: [samuel.bertrand@univ-nantes.fr](mailto:samuel.bertrand@univ-nantes.fr) (S. Bertrand)

18 1

## 19 **Abstract**

20 Natural products (NPs) are considered as a cornerstone for the generation of bioactive  
21 leads in drug discovery programs. However, one of the major limitations of NP drug discovery  
22 program is “rediscovery” of known compounds, thereby hindering the rate of drug discovery  
23 efficiency. Therefore, in recent years, to overcome these limitations, a great deal of attention has  
24 been drawn towards understanding the role of microorganisms’ co-culture in inducing novel  
25 chemical entities. Such induction could be related to activation of genes which might be silent or  
26 expressed at very low levels (below detection limit) in pure-strain cultures under normal  
27 laboratory conditions. In this review, chemical diversity of compounds isolated from microbial  
28 co-cultures, is discussed. For this purpose, chemodiversity has been represented as a chemical-  
29 structure network based on the “Tanimoto Structural Similarity Index”. This highlights the huge  
30 structural diversity induced by microbial co-culture. In addition, the current trends in microbial  
31 co-culture research are highlighted. Finally, the current challenges (1 - induction monitoring, 2 -  
32 reproducibility, 3 - growth time effect and 4 - up-scaling for isolation purposes) are discussed.  
33 The information in this review will support researchers to design microbial co-culture strategies  
34 for future research efforts. In addition, guidelines for co-culture induction reporting are also  
35 provided to strengthen future reporting in this NP field.

36 **Keywords:** Chemical diversity, Induction, Microbial co-culture

37

## 38 1. Introduction

39 Microorganisms have played a significant role as sources of specialized metabolites with a  
40 vast chemical diversity (Nai and Meyer, 2018). Currently, they are taking an even greater place  
41 in drug discovery programs due to the ease of sustainable microbial biomass production and  
42 resourcing through fermentation. However, as from other sources of natural products (NPs),  
43 chemists are currently struggling with the continuous rediscovery of known chemical entities  
44 (Gonzalez-Sabin, 2012). This is in contradiction with the high chemical diversity revealed by  
45 genome sequencing of microorganisms which revealed the huge difference between the number  
46 of NPs gene clusters present in such sequences with respects to the number of observed NPs  
47 produced in standard laboratory conditions (the latter being much less) (Pettit, 2011). To  
48 overcome such limitation, various approaches have been developed which could be considered  
49 as culture and non-culture-based strategies. The latter approaches (non-culture-based) are related  
50 to molecular biology and correspond to the specific engineering of organisms able to produce the  
51 desired molecules (*i.e.*, heterologous expression (Gomez-Escribano and Bibb, 2014),  
52 homologous activation (Zhang, B. et al., 2017), mutagenesis (Li et al., 2016)). Consequently,  
53 various culture-based strategies, such as the OSMAC approach (One Strain Many Compounds),  
54 epigenetic modification, co-culture, etc. have also been exploited to expand chemical diversity  
55 (Bode et al., 2002; Williams et al., 2008). In such cases, the presence of biological and chemical  
56 stimuli results in the biosynthesis of diverse NPs by unlocking cryptic pathway expression  
57 (Goodwin et al., 2015). Among these approaches, microbial co-culture, consists of growing  
58 multiple organisms together in a same confined environment has gained tremendous attention. It  
59 allows the microorganisms to initiate chemical interactions and results in the production of NPs  
60 that are not observed in pure-strain cultures such as pheromones, defence molecules or

61 metabolites related to symbiotic associations, therefore revealing hidden biosynthetic pathways  
62 (Harwani et al., 2018; Jones and Wang, 2018; Nai and Meyer, 2018; Tan et al., 2019;  
63 Tshikantwa et al., 2018). Such alteration in the specialized metabolisms can be attributed to  
64 alteration in core metabolisms by co-culture (Cheng et al., 2013; Nguyen et al., 2019). In  
65 addition, metabolite exchanges, metabolisation and/or detoxification of defence molecules  
66 (Shang et al., 2017; Vallet et al., 2017) may also occur yielding the induction of chemical  
67 novelty (Gebreselassie and Antoniewicz, 2015). Co-culture has demonstrated to significantly  
68 impact the metabolism of the involved microbial strains (Ponomarova and Patil, 2015). It can  
69 result in (a) yield enhancement, (b) *de novo* compound induction and (c) microorganisms  
70 pathways combination (Zhu et al., 2011). Nevertheless, from NPs chemist's perspective, this  
71 strategy is still random as only a few comparisons of the induced chemical diversity are  
72 available.

73 Up until recent years, the isolation and structural characterisation of compounds induced  
74 by co-culture were rather limited and highlighting common trends from such studies was a very  
75 complex challenge (Bertrand et al., 2014b). However, with the recent developments in analytical  
76 techniques (such as liquid chromatography coupled to high-resolution mass spectrometry),  
77 monitoring chemical induction became achievable (Bertrand et al., 2014b), leading very recently  
78 to more prolific studies exploring NPs "induction" by co-culture (Tasdemir, 2017). It is  
79 important to clearly define induction in that case; depending of the articles explored, induction  
80 can be understood as an increased in the content of a compound within the extract (which could  
81 be considered as) or the detection of a previously undetected metabolites (below detection limit  
82 when the organism is cultivated alone); both induction mechanisms are considered as up-  
83 regulation or *de novo* induction, respectively. Such induction may be the result of activation of

84 cryptic biosynthetic pathways (Schroeckh et al., 2009) or of the biotransformation by one of the  
85 microorganisms of compounds produced by the second one (Shang et al., 2017). In fact, even if  
86 inappropriate to describe the promotion of the formation of a novel compound, the term  
87 “induction” has been found in many articles related to co-cultures, even though the biochemical  
88 pathway activated was not described. Thus, using this term would be more in accordance with  
89 the different articles reviewed. From now in the manuscript, the define term “induction” in the  
90 fourth cases.

91         Some recent studies also demonstrate the possibility of co-cultivation of engineered  
92 microbial strains to access novel chemical diversity (Chen et al., 2019), or design  
93 biotechnological production strategy for known NPs (Jones and Wang, 2018; Roell et al., 2019;  
94 Wang et al., 2020). For example, Jones and colleagues have designed a specific *Escherichia coli*  
95 co-culture experiment between two specifically engineered strains for the production of  
96 flavonoids (Jones et al., 2016). While this approach is of considerable interest, from our  
97 perspective, it cannot really be considered as a strategy for the induction of microbial cryptic  
98 pathways. Furthermore, designing such stable microbial consortium for large scale production is  
99 still challenging (Stephens et al., 2019). This is particularly emphasized by the large possibility of  
100 microorganism interactions (Roell et al., 2019). Thus, currently, no generic models for  
101 biosynthetic pathway activation by co-culture exist.

102         In the microbial co-culture context, the metabolomics approach appears to be of great  
103 advantage to characterize the induction type (discussed in section 4). Metabolomics could be  
104 defined as a non-selective, universally applicable, comprehensive analytical approach for the  
105 identification and quantification of metabolites in a biological system (Wolfender et al., 2015). In  
106 NP research, metabolomics is considered as the large-scale analysis of metabolites of a given

107 organism during various physiological states which can be interpreted from a holistic manner  
108 (Sumner et al., 2003). However, only few papers have adopted this approach (Bertrand et al.,  
109 2013c; Bohni et al., 2016; Combès et al., 2012; Nguyen et al., 2019; Shen et al., 2019; Traxler et  
110 al., 2013; Wu et al., 2015; Xu et al., 2018), indicating that such strategy is not yet fully adopted  
111 in NPs chemistry.

112 This review covers all co-culture studies from 1994 to 2019 (to the best of our knowledge  
113 on July the 8<sup>th</sup> of 2019, Table S1). It reveals that the dawning era for the co-culture research has  
114 begun mainly from the year 2013. Thus, this corresponds to the improvement of analytical  
115 techniques, reaching their ability to accurately detect compounds within complex mixtures  
116 (Wolfender et al., 2015).

117 This review is an analysis of 82 articles demonstrating the induction 259 compounds *via*  
118 microbial co-culture. This review first presents the structural diversity of induced compounds  
119 based on a structural similarity clustering, followed by a discussion about observed current  
120 trends. Finally, the current challenges related to microbial co-culture experiments are highlighted  
121 to focus on some future directions that should be further explored from a NP chemist  
122 perspective.

## 123 **2. Expanding the chemical diversity**

124 The comparative analysis of chemical diversity induced through microbial co-culture is  
125 challenging and therefore, in this manuscript such diversity was explored in two different ways.  
126 First their physico-chemical properties (molecular weight and lipophilicity) were compared.  
127 Finally, structural diversity was explored constructing a structural similarity network based on  
128 "Tanimoto structure similarity index".

129           The comparison of physico-chemical properties of the 259 metabolites gives interesting  
130 insight into the chemical diversity of co-culture induced compounds. While molecular weight of  
131 compounds was ranging from 150 to 913 g/mol, most of them (more than 69%) were ranging  
132 from 200 to 450 g/mol (Figure 1A). This indicates that only a limited number of induced  
133 molecules corresponds to very large structures corresponding to complex biosynthesis pathways.  
134 A similar distribution was observed taking into account all reported NPs (Chen et al., 2018;  
135 Feher and Schmidt, 2003). Similarly, lipophilicity comparison indicates that AlogP ranges from -  
136 10.4 to 6.5, with about 56%, ranging from -1 to 1 (Figure 1B). AlogP represents an *in silico*  
137 evaluation of the logP value (logarithm of 1-octanol/water partition coefficient) (Ghose et al.,  
138 1998). Such medium lipophilicity (AlogP around 0) indicates rather hydrophilic molecules which  
139 possess at least reasonable water affinity to be excreted. Such property also makes them good  
140 candidates for inter-organisms' chemical communication. However, it is important to note that  
141 most of those compounds were obtained using conventional isolation strategies. Therefore, those  
142 convergent properties (close molecular weight and lipophilicity) may also reflect similar  
143 extraction and isolation procedures, in favour of the investigation of medium- and non-polar  
144 compounds, in the context of microbial co-culture. However, logP distribution centred around 0  
145 is not observed when all NPs are taken into account, in such cases logP is centred around 3.5  
146 (Chen et al., 2018). Thus, from a drug discovery perspective, most of the studies focusing on  
147 compounds induced during co-culture could be a good rationale to investigate future drug  
148 candidates possessing appropriate properties to be orally administered (Lipinski et al., 2012).  
149 This is a regularly observed trend observed in NP chemistry, where studies try to target  
150 isolation of the most druggable compounds (Harvey et al., 2015; Liu et al., 2017).

151



152 <<INSERT FIGURE 1 HERE>>

153

154 To explore further structural diversity induced by microbial co-cultures and therefore,  
155 highlight specific trends, a structural similarity network was constructed based on the “Tanimoto  
156 Structural Similarity Index” (see Supplementary Material, the network is also available in  
157 Cytoscape file format here [https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-](https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-culture-induced-compounds)  
158 [culture-induced-compounds](https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-culture-induced-compounds)) (Lo et al., 2016). Applying a threshold of 0.7 for the Tanimoto  
159 index clustered the 259 different structures into 9 clusters (Figure 1); such threshold being rather  
160 strict (O’Hagan et al., 2015). It is important to note that clustering of the structures based on  
161 Tanimoto Index did not always fit with biosynthetic considerations, but can reveal common  
162 structural features important for the physico-chemical properties of induced NPs which are  
163 discussed using clustering in this review. The major cluster (cluster 1) is composed of 137  
164 molecules from “Polyketides, Macrolides and Diterpenoids” classes. All 9 clusters are discussed  
165 in the manuscript.

166

167 <<INSERT FIGURE 2 HERE>>

168

## 169 **2.1.Non-nitrogenated induced compound clusters**

### 170 **2.1.1. Cluster 1 – Polyketides, Macrolides and Diterpenoids**

171 The major cluster (cluster 1) is composed of 137 structures described in a various co-  
172 culture articles. This cluster consists of polyketides, macrolides, some diterpenoids and

173 miscellaneous other poly-oxygenated structures. It is composed of compounds induced *via*  
174 bacterial co-culture (n=9), fungal co-culture (n=70) or during interaction between fungi and  
175 bacteria (n=59). For the better visualization of the various chemical groups, an exploded  
176 subnetwork has been constructed using a more restrictive Tanimoto Index limit of 0.8, which is  
177 shown in Figure 3.

178

179 <<INSERT FIGURE 3 HERE>>

180

181 Arora and colleagues have isolated one new polyketide blennolide K (**1**) from the co-  
182 culture of *Setophoma terrestris* and *Bacillus amyloliquifaciens* (Arora et al., 2018). Four new  
183 polyketides, penitalarins A, B, C and nafuredin B (**2-5**) were isolated by Zhang and colleagues  
184 from a co-culture of *Penicillium variable* and *Talaromyces aculeatus* (Zhang, Z. et al., 2017),  
185 from which only nafuredin B exhibited cytotoxic activity. König and colleagues isolated two  
186 new prenylated polyketides fumicycline A and B (**6-7**) from the co-culture of *Streptomyces*  
187 *rapamycinicus* and *Aspergillus fumigatus* (König et al., 2013). Chagas and colleagues have  
188 characterized five polyketides stemphyperlenol, alterperyleneol, altertoxin I, alternariol and  
189 alternariol monomethyl ether (**8-12**) from the co-culture of *Alternaria tenuissima* and *Nigrospora*  
190 *sphaerica*. Among these, stemphyperyleneol (**8**) was reported to be an antifungal compound  
191 (Chagas et al., 2013). Schroeckh and colleagues have reported four archetypal polyketides  
192 orsellinic acid, lecanoric acid, F-9775A and F-9775B (**13-16**) from the co-culture of  
193 *Streptomyces hygroscopicus* and *Aspergillus nidulans*. Among these, lecanoric acid (**14**) was  
194 found to be ATP synthesis inhibitor and F-9775A (**15**) and F-9775B (**16**) were anti-osteoporosis

195 agents (Schroeckh et al., 2009). It is interesting to note that lecanoric acid (**14**) was first isolated  
196 from the lichen *Pseudocyphellaria crocata* (Maass, 1975) and also observed in many of such  
197 symbiotic organism (Ahmann and Mathey, 1967; Luo et al., 2009; van Herk and Aptroot, 2007).  
198 Interestingly, another orsellinic acid derivatives was isolated by Bertrand and colleagues and  
199 characterized as hydroxysulfoxy-2,2''-dimethylthielavin P (**17**) from the co-culture of  
200 *Trichophyton rubrum* and *Bionectria ochroleuca* (Bertrand et al., 2013c). Wang and colleagues  
201 isolated four phenolic polyketides alternariol, (9R, 14S)-epoxy-11-deoxyfunicone,  
202 deoxyfunicone and vermistatin (**11,18-20**) from the co-culture of *Streptomyces fradiae* 007 and  
203 *Penicillium* sp. WC-29-5, from which, (9R, 14S)-epoxy-11-deoxyfunicone (**18**) was found to be  
204 a previously unreported structure with moderate cytotoxic activity (Wang et al., 2014). Other  
205 similar phenolic polyketides lateropyrone (**21**), dihydrolateropyrone (**22**), fusatricinone A, B, C,  
206 D (**23-26**) were isolated from the co-culture of *Fusarium tricinctum* and *Streptomyces lividans*  
207 (Moussa et al., 2019). Other polyketides were also isolated from this latter co-culture,  
208 macrocarpon C (**27**), (-)-citreoisocoumarin (**28**), zearalenone (**29**), 7-hydroxy-2-(2-  
209 hydroxypropyl)-5-methylchromone (**30**, also named Aloesol). Among those induced compounds  
210 lateropyrone (**21**) and zearaleone (**29**) exhibited antibiotic activity (Kosawang et al., 2014; Ola et  
211 al., 2013), zearalenone (**29**) being a known mycotoxin with chronic estrogenic effects on  
212 mammals (Hueza et al., 2014; Kuiper-Goodman et al., 1987). Macrocarpon C (**27**) and (-)-  
213 citreoisocoumarin (**28**) were also isolated from the co-culture of *F. tricinctum* with the other  
214 bacteria *Bacillus subtilis* along with another isocoumarin derivative (-)-citreoisocoumarinol (**31**)  
215 (Ola et al., 2013). Another phenolic polyketide bikaverin (**32**) was highlighted by Maldi-MS  
216 imaging to only detected in the confrontation zone of *Fusarium fujikuroi* and *Ralstonia*  
217 *solanacearum* (Spraker et al., 2018).

218 Gordonic acid (**33**), which is an acyclic polyene polyketide, demonstrated weak  
219 antibacterial activity (Park et al., 2017). Resistomycin (**34**) and 2,5,6-trihydroxy-4,6-  
220 diphenylcyclohex-4-ene-1,3-dione (**35**) exhibited cytotoxic activity and correspond to  
221 pentacyclic or phenyl polyketide, respectively (Carlson et al., 2014; Xu et al., 2018). Other  
222 polyketides janthinopolyenemycin A and B (**36, 37**), possessing moderate anti-*candida* activity,  
223 were also reported to be induced during the co-culture of two strains of *Janthinobacterium* spp.  
224 (ZZ145 and ZZ148) (Anjum et al., 2018). Five perylene quinonoid polyketides were induced  
225 during the co-culture of *Shiraia* sp. *S9* and *Pseudomonas fulva* *SBI*. These correspond to the  
226 pigments hypocrellin A, C (**38, 39**) and elsinochrome A, B, C (**40-42**) which were evaluated as  
227 photosensitizers for photodynamic therapy (Ma et al., 2019).

228 This cluster was also composed of eight 16-atoms ring macrolides berkeleylactone A, B, C,  
229 D, E, F, G, H (**43-50**) isolated by Stierle and colleagues from the co-culture of *Penicillium*  
230 *fuscum* and *Penicillium camembertii/clavigerum*; three of them (**43, 45, 48**) exhibited cytotoxic  
231 activity (Stierle et al., 2017).

232 In addition, terpenes were also reported in this cluster. Cho and Kim have reported  
233 antifouling diterpene lobocompactol (**51**) from the co-culture of *Streptomyces cinnabarinus* and  
234 *Alteromonas* sp. (Cho and Kim, 2012). Oh and colleagues have reported the induction of four  
235 cytotoxic pimarane diterpenoids libertellenone A, B, C and D (**52-55**) from the co-culture of an  
236  $\alpha$ -proteobacterium (strain CNJ-328) and *Libertella* sp. (Oh et al., 2005). Zhang and colleagues  
237 isolated two sesquiterpenes microsphaeropsisin B (**56**) and C (**57**) by co-cultivation of  
238 *Trichoderma* sp. (Strain 307) with *Acinetobacter johnsonii* (Strain B2) (Zhang, L. et al., 2017).  
239 Microsphaeropsisin C (**57**) was having moderate  $\alpha$ -glucosidase inhibitory activity. Other  
240 sesquiterpenes melledonal A, C (**58, 59**) were induced by the co-culture of *Gloeophyllum*

241 *abietinum* and *Heterobasidion annosum* (Sonnenbichler et al., 1994), and isocaryophyllene,  $\alpha$ -  
242 humulene, cyclocaryophyllan-4-ol (**60-62**) by the co-culture of *Fusarium oxysporum* with  
243 *Serratia* sp. and *Achromobacter* sp. (Minerdi et al., 2009). Interestingly, those latter three  
244 compounds are volatile substances and represent rare examples of induction highlighted by gas  
245 chromatography coupled to MS. Zhou and colleagues isolated five new sesquiterpenes,  
246 nigirpexin A, B, C, D and nigrosirpexin A (**63-67**) from the co-culture of *Nigrospora oryzae* with  
247 *Irpex lacteus* (Zhou et al., 2018). All these latter compounds exhibited antifungal activity,  
248 nigrosirpexin A (**67**) being also an inhibitor of acetylcholinesterase.

249 The meroterpenoid austin (**68**) was reported to be induced during the co-culture of  
250 *Talaromyces purpurogenus* H4 and *Phanerochaete* sp. H2 and possesses moderate trypanocidal  
251 activity (do Nascimento et al., 2019).

252 Various citrinin analogues were reported to be induced during co-culture. Citrifelin A, B  
253 (**69-70**) were from the co-culture of the fungi *Penicillium citrinum* and *Beauveria felina* (Meng  
254 et al., 2015). Recently, Yang and colleagues reported the induction of citrinin (**71**) along with 10  
255 other analogues: seco-penicitrinol A (**72**), penicitrinol A and L (**73, 74**), penicitrinone A and F  
256 (**75, 76**), dihydrocitrinone (**77**) and decarboxydihydrocitrinone (**78**) during the interaction of  
257 *Penicillium citrinum* and *Aspergillus sydowii* (Yang et al., 2018). During this latter co-culture  
258 experiment, two other phenols were induced, called phenol A (**79**) and phenol A acid (**80**). From  
259 all those citrinin analogues only moderate antimicrobial activity was observed (Meng et al.,  
260 2015; Yang et al., 2018).

261 Various other compounds exhibiting at least moderate antimicrobial activity are associated  
262 with this cluster, such as actinorhodin (**81**) (Mavituna et al., 2016; Traxler et al., 2013), BE-  
263 31405 (**82**) (Nonaka et al., 2015), the mycoalexin *O*-methylmellein (**83**) (Glauser et al., 2009),

264 the xanthone derivative 8-hydroxy-3-methyl-9-oxo-9*H*-xanthene-1-carboxylic acid methyl ether  
265 (**84**) (Li et al., 2011), the benzaldehyde derivative ethyl 5-ethoxy-2-formyl-3-hydroxy-4-  
266 methylbenzoate (**85**) (Wang, J. et al., 2013) and the cytotoxic benzophenone pestalone (**86**)  
267 (Cueto et al., 2001). 5-Formylsalicylic acid (**87**) (Keilhofer et al., 2018) was found to be a  
268 potential virulence factor of fungal plant pathogens. Three  $\gamma$ -butyrolactones chojalactone A, B, C  
269 (**88-90**) with moderate cytotoxicity were reported to be induced in co-culture of *Streptomyces* sp.  
270 CJ5 and *Tsukamurella pulmonis* TP-B0596 (Hoshino et al., 2015b). Phytopathogen dependent  
271 NPs harzianolide (**91**), sorbicillinol (**92**) and T39 butenolide (**93**) were isolated from the co-  
272 culture of *Moniliophthora roreri* and *Trichoderma harzianum* (Tata et al., 2015). Interestingly,  
273 harzianolide (**91**) is able to promote plant growth in tomato models (Cai et al., 2013). Similarly,  
274 other butenolide ( $\gamma$ -butyrolactones) chaetobutenolides A, B, C and WF-3681 methyl ester (**94-**  
275 **97**) were isolated from the co-culture of *Chaetomium* sp. with *Pseudomonas aeruginosa*  
276 (Ancheeva et al., 2017). Similarly, small butyrolactones isobutyrolactone II (**98**), 4-*O*-  
277 demethylisobutyrolactone II (**99**) were isolated from the interactions of *Aspergillus terreus* with  
278 *Bacillus* sp. strains (Chen et al., 2015). It is important to pinpoint this particular induction of  
279 butyrolactones as they are well known compounds involved in interspecies communication,  
280 especially in quorum-sensing mechanisms in bacteria (Niu et al., 2016).

281 Other compounds possessing polar head along with an alkyl side chain are also present in  
282 this cluster, such compounds may be expected to also be involved in interspecies  
283 communication, even though no information is available. Penixylarins A, B, C, D (**100-103**), 1,3-  
284 dihydroxy-5-(12-hydroxyheptadecyl)benzene (**104**) and 1,3-dihydroxy-5-(12-  
285 sulfoxyheptadecyl)benzene (**104**) were induced during the co-culture of *Penicillium crustosum*  
286 PRB-2 and *Xylaria* sp. HDN13-249 (Yu, G. et al., 2019). Among those compounds, penixylarins

287 B, C (**101**, **102**), 1,3-dihydroxy-5-(12-hydroxyheptadecyl)benzene (**104**) and 1,3-dihydroxy-5-  
288 (12-sulfoxyheptadecyl)benzene (**105**) exhibit moderate antibacterial activity and penixylarin C  
289 (**102**) potential antituberculosis effect. Two other compounds possess a similar scaffold:  
290 phexandiol A, B (**106-107**). They are produced during the interaction between *Phoma* sp.  
291 YUD17001 and *Armillaria* sp. 2TG-2016, however, no antimicrobial nor cytotoxic activities  
292 were observed (Li et al., 2019). Another example lies in the induction of the pyran derivative  
293 chaunopyran A (**108**) during the co-culture of *Chaunopycnis* sp. CMB-MF028 and *Trichoderma*  
294 *hamatum* CMB-MF030 (Shang et al., 2017). An unusual dimer of such scaffold is also induced  
295 during the interaction between *Penicillium pinophilum* FKI-5653 and *Trichoderma harzianum*  
296 FKI-5655, it corresponds to stromemycin (**109**) (Nonaka et al., 2011). This interaction also  
297 yields the induction of secopenicillide C (**110**), penicillide (**111**, also called Vermixocin A) and  
298 MC-141 (**112**).

299 Five azaphilones nigbeauvin A, B, C, D, E (**113-117**) were isolated by Zhang and  
300 colleagues (Zhang et al., 2018). Nigbeauvin A (**113**) has nitric oxide (NO) inhibitory activity and  
301 antibacterial activity, while nigbeauvin B (**114**) has only NO inhibitory activity. (3R)-5-oxo-de-  
302 *O*-methyllasiodiplodin (**118**) and (3R, 7R)-7-hydroxy-de-*O*-methyllasiodiplodin (**119**) were  
303 reported, from the co-culture of a *Trichoderma* sp. strain with *Acinetobacter johnsonii*, to have  
304 the  $\alpha$ -glucosidase inhibitory activity (Zhang, L. et al., 2017). Akone and colleagues isolated six  
305 compounds: shikimeran A, bipherin A, chorismeron, serkydayn, isosulochrin, protocatechuic  
306 acid methyl ester (**120-125**) from the co-culture of *Chaetomium* sp. with bacteria (Akone et al.,  
307 2016). Serkydayn (**123**) has moderate antibacterial activity and cytotoxic activity.

308 It is important to emphasise the case of the induction of the triterpene ergosterol (**126**) from  
309 the co-culture of two *Aspergillus* sp. strains (Zhu et al., 2011). This compound is known to have

310 a key role in fungal membrane integrity (Abe and Hiraki, 2009) and also possesses  
311 antiproliferative activity on cancer cells (Li et al., 2015; Ory et al., 2019).

312 In the co-culture studies, some compounds were reported without activities such as (E)-2-  
313 (3-hydroxyprop-1-en-1-yl)-phenol (**127**) (Wu et al., 2015), the furanone derivatives  
314 sclerotiorumin A, B (**128**, **129**) (Bao et al., 2017), the coumarin derivative 7-( $\gamma,\gamma$ -  
315 dimethylallyloxy)-6-hydroxy-4-methylcoumarin (**130**) (Wang et al., 2015), the shikimic acid  
316 derivatives chaetisochorismine (**131**), shikimeran B (**132**) (Ancheeva et al., 2017), the chromone  
317 7-methoxy-2,3-dimethylchromone-4-one (**133**) (Yu, M. et al., 2019) and the sesquiterpenoid  
318 naphthoquinone debromomarinone (**134**) (Khalil et al., 2019).

319 Additional compounds (2E,4E)-3-(2-carboxy-1-hydroxyethyl)-2,4-hexadienedioic acid  
320 (**135**) (Wu et al., 2015), oosponol (**136**), oospoglycol (**137**) (Sonnenbichler et al., 1994) were  
321 also attached to this network.

### 322 **2.1.2. Cluster 2 – Linear polyketides, Oxylipins and Fatty acids**

323 The second cluster (Cluster 2) is composed of 16 compounds reported in seven different  
324 articles, corresponding to linear polyketides, oxylipins and fatty acids (Figure 2).

325 A large variety of microorganisms have shown to specifically produce linear polyketides,  
326 fatty acids and their oxidation products oxylipins in response to mixed cultures. Kossuga and  
327 colleagues have reported two linear polyketides (Z) 2-ethylhex-2-enedioic acid (**138**) and (E) 4-  
328 oxo-2-propylideneoct-7-enoic acid (**139**) from the co-culture of two marine-derived  
329 *Penicillium* sp. Ma(M3)V and *Trichoderma* sp. Gc(M2)1. Wrede and colleagues generated an  
330 efficient system for lipid production, harvesting micro-algal cells and waste water treatment by  
331 co-cultivation of *Aspergillus fumigatus* and microalgae. Their co-cultivation demonstrated



332 synergistic and additive effects on lipid yield, wastewater bioremediation efficiency and biomass  
333 production. The co-culture produced palmitic acid, stearic acid, oleic acid and linoleic acid (**140-**  
334 **143**), which can be developed as a renewable source of biofuels (Wrede et al., 2014). Do  
335 Nascimento and colleagues studied the effect of co-culture of bacteria on the growth promotion  
336 of microalgae (Do Nascimento et al., 2013). They characterized an  $\omega$ 3 fatty acid, stearidonic acid  
337 (**144**) from the co-culture of *Rhizobium* strain 10II and *Ankistrodesmus* sp. strain SP2-15.  
338 Combès and colleagues investigated the co-culture potential of phytopathogen *Fusarium*  
339 *oxysporum* and endophytic fungus *Paraconiothyrium variabile* for the production of oxylipins  
340 13-oxo-9,11-octadecadienoic acid (**145**), 13-hydroperoxy-9,11-octadecadienoic acid (**146**) and  
341 reported their role in the regulation of development processes and also in the mycotoxin  
342 beauvericin production regulation in *F. oxysporum* (Combès et al., 2012). It is interesting to note  
343 that such oxylipins related compounds are regularly linked to interspecies communication  
344 (Wasternack and Feussner, 2018) as it was the case for butyrolactones from Cluster 1.

345 A series of polyhydroxylated fatty acids and esters: phomester A, B, (E)-5,9-  
346 dihydroxydodec-6-enoic acid (**147-149**), were isolated from the co-culture of *Phoma* sp.  
347 YUD17001 and *Armillaria* sp. 2TG-2016 (Li et al., 2019). Similarly, polyhydroxylated alkyl  
348 chain were also induced during the co-culture of *Trametes robiniophila* Murr and *Pleurotus*  
349 *ostreatus*. These correspond to postrediene A, B, C (**150-152**) and were not reported with any  
350 promising activities (Shen et al., 2019).

351 Furthermore, the tricarboxylic fatty acid bongkreic acid (**153**) was also produced by the  
352 bacteria *Burkholderia gladioli* when co-cultured with the fungus *Rhizopus microsporus*.  
353 Interestingly, this highly toxic compound possesses fungal growth inhibition properties, leading  
354 to assume its putative role in the co-culture (Ross et al., 2014).

## 355 **2.2.Non-alkaloidic nitrogenated induced compound clusters**

### 356 **2.2.1. Cluster 3 – Cyclic peptides, diketopiperazines and related compounds**

357 This cluster 3 consists of 60 compounds from 18 different co-culture articles (Figure 2).

358 Guo and colleagues isolated pseudoxyllallemycin A-F (**154-159**), cyclized tyrosine-  
359 containing non-ribosomal tetrapeptides, from the co-culture extract of *Pseudoxyllaria* sp. and  
360 *Microtermes* sp. Pseudoxyllallemycin A, B, C, D (**154-157**) were reported to possess  
361 antimicrobial activity, antiproliferative and cytotoxic properties, while pseudoxyllallemycin E  
362 and F (**158, 159**) were inactive (Guo et al., 2016). Other cyclic polypeptides were also observed  
363 to be induced and possess antimicrobial activity. Cyclo-(L-leucyl-trans-4-hydroxy-L-prolyl-D-  
364 leucyl-trans-4-hydroxy-L-proline) (**160**), cyclo-(D-proline-L-tyrosine-L-proline-L-tyrosine)  
365 (**161**) and cyclo-(glycine-L-phenylalanine-L-proline-L-tyrosine) (**162**) were observed in the co-  
366 culture of *Phomopsis* sp. K38 and *Alternaria* sp. E33 (Huang et al., 2014; Li et al., 2014). The  
367 mixed fermentation of *Umezawaea* sp. RD066910 and *Tsukamurella pulmonis* TP-B0596  
368 yielded the production of umezawamide A, B (**163, 164**) (Hoshino et al., 2018b), of *Emericella*  
369 sp. and *Salinispora arenicola* provided emericellamides A, B (**165, 166**) (Oh et al., 2007),  
370 *Fusarium tricinctum* with *Streptomyces lividans* or *Bacillus subtilis* yielded fusaristatin A (**167**)  
371 (Moussa et al., 2019; Ola et al., 2013), and *Aspergillus flavipes* and *Streptomyces* sp. activate the  
372 production of rosellichalasin (**168**), aspochalasin E, P, H, M (**169-172**) and 19,20-dihydro-  
373 aspochalasin D (**173**) (Yu et al., 2016). Finally, the co-culture of unidentified fungi induces the  
374 production of (–)-byssochlamic acid imide (**174**) (Ding et al., 2017).

375 Various diketopiperazines were induced during co-culture. Khalil and colleagues reported  
376 the induction of the bacteriostatic cyclo-(L-phenylalanine-trans-4-hydroxy-L-proline) (**175**)

377 during the co-culture of *Streptomyces* sp. and *Aspergillus* sp. (Khalil et al., 2019). Rateb and  
378 colleagues isolated antiparasitic diketopiperazines brevianamide F (**176**), spirotryprostatin A  
379 (**177**), 6-methoxy spirotryprostatin B (**178**), fumitremorgin B, C (**179**, **180**), 12,13-dihydroxy-  
380 fumitremorgin C (**181**), verruculogen (**182**) from the co-culture of *Streptomyces bullii* and  
381 *Aspergillus fumigatus* (Rateb et al., 2013). From this co-culture they also reported the induction  
382 of 11-*O*-methylpseurotin A (**183**) and 11-*O*-methylpseurotin A<sub>2</sub> (**184**); this latter compound  
383 exhibiting antiparasitic activity. Other diketopiperazines notoamide C, D, F, M, Q (**185-189**), (-  
384 )-notoamide B (**190**), 17-*epi*-notoamide Q (**191**), dehydronotoamide C (**192**), 17-  
385 hydroxynotoamide D (**193**), 17-*O*-ethylnotoamide M (**194**), 10-*O*-ethylnotoamide R (**195**),  
386 sclerotiamide (**196**), 10-*O*-ethylsclerotiamide (**197**), 10-*O*-acetylsclerotiamide (**198**) were  
387 produced during the interaction between *Aspergillus sulphureus* and *Isaria felina* (Afiyatulloev et  
388 al., 2018).

389 In addition, aspergicin (**199**) from the co-culture of two *Aspergillus* sp. strains (Zhu et al.,  
390 2011), *N*-demethylphiosetin (**200**), pallidorosetin A, B (**201**, **202**) from the co-culture of  
391 *Saccharopolyspora erythraea* and *Fusarium pallidroseum* (Whitt et al., 2014) and niizalactam  
392 A, B, C (**203-205**) from the co-culture of *Streptomyces* sp. NZ-6 and *Tsukamurella pulmonis* TP-  
393 B0596 (Hoshino et al., 2015a) were reported as induced.

394 Five nitrogenated compounds were distantly attached to this cluster. Among all compounds  
395 from this cluster, one was reported in two different articles. The pyrrol derivative  
396 undecylprodigiosin (**206**) was reported induced in two bacterial mixed fermentation involving  
397 *Streptomyces Coelicolor* with either *E. coli* (Mavituna et al., 2016) or *Coralloccoccus coralloides*  
398 (Schäberle et al., 2013). Prodiginine (**207**), a very similar compound was induced during the  
399 interaction of *Streptomyces coelicolor* and actinomycete strain (Traxler et al., 2013). Those red

400 pigments prodiginins are known to exhibit a wide range of activity: immunosuppressive,  
401 anticancer and antibacterial (Hu et al., 2016). It was demonstrated that such compounds could be  
402 up-regulated by extracellular cell–cell signaling (quorum sensing) due to the presence of  $\gamma$ -  
403 butyrolactones (Williamson et al., 2006). Additionally, the aminoglycosides rhodostreptomycin  
404 A, B (**208, 209**) were reported from the mixed fermentation of *Rhodococcus fascians* and  
405 *Streptomyces padanus* (Kurosawa et al., 2008). Moreover, complex nitrogenated fatty acids were  
406 also attached to this network. They correspond to borrelidin J and K (**210, 211**) produced during  
407 the interaction between *Streptomyces rochei* MB037 and *Rhinoctadiella similis* 35 (Yu, M. et al.,  
408 2019). Interestingly, borrelidin J (**210**) possesses antibacterial activity against methicillin-  
409 resistant *Staphylococcus aureus* at a low  $\mu$ M range. Additional compounds heronapyrrole B  
410 (**212**) (Khalil et al., 2019) and phomester C (**213**) (Li et al., 2019) was also attached to this  
411 network. Finally, the induction of taxol (**214**) from the co-culture of *Paraconiothyrium* SSM001  
412 with other fungal strains (Soliman and Raizada, 2013) is particularly interesting. This  
413 corresponds to the “re-discovery” of a very well-known anticancer drug first isolated from *Taxus*  
414 *baccata*, which in fact was produced by endophytic fungi instead of the plant itself.

#### 415 **2.2.2. Cluster 4 – Other non-ribosomal peptides**

416 This cluster 4 consists of 5 peptides (Figure 2), either linear tetrapeptides or cyclic  
417 hexapeptides from two different co-culture articles. Wang and colleagues isolated depsipeptides  
418 subenniain A, B (**215, 216**) from the co-culture of *Fusarium tricinctum* and *Fusarium begonia*  
419 (Wang, J.-p. et al., 2013). In addition, enniatin A1, B, B1 (**217-219**) induced during the co-  
420 culture of *Fusarium tricinctum* with *Streptomyces lividans* or *Bacillus subtilis* (Moussa et al.,  
421 2019; Ola et al., 2013) was present in this cluster.

#### 422 **2.2.3. Clusters 5 and 6 – Miscellaneous Non-alkaloidic nitrogenated compound**

423 Two small clusters contain 16 compounds with at least one nitrogenated function. Those  
424 two clusters are less organized based on chemical structures of compounds as many are distantly  
425 attached together (Figure 2). This explains inconsistency of the clustered structures.

426 The first cluster is composed of 2-(carboxymethylamino) benzoic acid (**220**) isolated from  
427 the co-culture of *Fusarium tricinctum* and *Bacillus subtilis* (Ola et al., 2013) and bionectriamine  
428 A, B (**221, 222**) isolated from the co-culture of a *Bionectria* sp. strain with bacteria (Kamdem et  
429 al., 2018). In additions enacyloxin IIa, iso enacyloxin IIIa (**223, 224**) where reported from the  
430 interaction between *Burkholderia gladioli* and *Rhizopus microsporus* (Ross et al., 2014); only iso  
431 enacyloxin IIIa (**224**) exhibits antimicrobial activity.

432 The second cluster contains two compounds known to act as siderophores: desferrioxamine  
433 B (**225**) and coelichelin (**226**) induced during the co-culture of *Streptomyces coelicolor* and  
434 actinomycete (Traxler et al., 2013), thus responsible for iron scavenging in the environment and  
435 then supporting microbial growth (Bertrand et al., 2013a; Hider and Kong, 2010).The mixed  
436 fermentation of *Catenuloplanes* sp. RD067331 and *T. Pulmonis* yielded the production of  
437 catenulobactin A, B (**227, 228**) possessing iron-chelating and moderate cytotoxicity activity  
438 (Hoshino et al., 2018a). The peptides dentigerumycin E (**229**) exhibiting moderate antitumor  
439 activity was reported as induced during the co-fermentation of *Streptomyces* sp. strain *JB5* and  
440 *Bacillus* sp. (GN1) (Shin et al., 2018). Two additional compounds were reported alchivemycin A  
441 (**230**) and 11S-hydroxy-1-methoxyfusaricide (**231**) (Li et al., 2017) from the co-culture of  
442 *Tsukamurella pulmonis* with *Streptomyces endus* S-522 (Onaka et al., 2011) and of *Camporesia*  
443 *sambuci* FT1061 with *Epicoccum sorghinum* FT1062, respectively. This cluster is also  
444 composed of pyrazine alkaloids hydroxyaspergillin, neoaspergillic acid (**232, 233**) possessing  
445 cytotoxic and antibacterial activity respectively (Bao et al., 2017; Zhu et al., 2011). In addition,

446 an oxadiazine derivative sclerotiorumin C (**234**) issued from the combined culture of *Aspergillus*  
447 *sclerotiorum* and *Penicillium citrinum* (Bao et al., 2017) was also distantly associated with this  
448 cluster. Finally, one thiodiketopiperazine glionitrin A (**235**) was also present in this cluster. It  
449 was induced during the mixed fermentation of *Aspergillus fumigatus* with *Sphingomonas* sp., this  
450 compound exhibiting antimicrobial activity and cytotoxicity (Park et al., 2009).

## 451 **2.3. Alkaloidic induced compound clusters**

### 452 **2.3.1. Cluster 7 – Benzylamine Alkaloids**

453 A small cluster (Cluster 7) was observed covering nine structures from three different  
454 studies (Figure 2). Three structures were indolocarbazole alkaloids, a chemical family often  
455 isolated from actinomycetes (Cañedo Hernandez et al., 2000; Fu et al., 2012; Zhang et al., 2012).  
456 Hoshino and colleagues isolated a indolocarbazole alkaloids, arcyriaflavin A and E (**236**, **237**),  
457 together with BE-13793C (**238**) from the co-culture of *Streptomyces cinnamoneus* NBRC 13823  
458 and a mycolic acid-containing bacteria *Tsukamurella pulmonis* (Hoshino et al., 2015c);  
459 compounds **237** and **238** exhibiting moderate cytotoxic activity on P388 murine leukaemia cells.  
460 Feng and colleagues isolated marinamide (**239**) and its methyl ester (**240**) from the co-culture of  
461 two mangrove endophytic fungi (strain Nos. 3893 and 1924) (Zhu and Lin, 2006). One more  
462 compound, isolated from co-culture of the two sponge-associated actinomycetes  
463 *Actinokineospora* sp. EG49 and *Nocardiopsis* sp. RV163, is also associated with this cluster:  
464 5a,6,11a,12-tetrahydro-5a,11a-dimethyl[1,4]benzoxazino[3,2-*b*][1,4]benzoxazine (**241**) (Dashti  
465 et al., 2014).

466 Two additional compounds were distantly attached to this cluster: austramide (**242**) from  
467 the co-culture of *Aspergillus austroafricanus* with either *Bacillus subtilis* or *Streptomyces*

468 *lividans* (Ebrahim et al., 2016) and 1,6-dihydroxyphenazine (**243**) from the co-culture of  
469 *Actinokineospora* sp. EG49 with *Nocardiopsis* sp. RV163 (Dashti et al., 2014).

### 470 **2.3.2. Cluster 8 – Phenazine alkaloids**

471 This cluster 8 represents height phenazine compounds reported in three co-culture articles  
472 (Figure 2). Angell and colleagues isolated pyocyanin (**244**), which was overproduced in the co-  
473 culture of *Enterobacter* sp. Pup14A and *P. aeruginosa*, a well-known producer of such type of  
474 compounds (Angell et al., 2006). Pyocyanin (**244**) is reported to possess antimicrobial and  
475 cytotoxic activity (Jayaseelan et al., 2014). Such compounds are known for their toxic behaviour  
476 against many organisms. Therefore, their induction during micro-organisms co-cultures can be  
477 considered as a mechanism of defence of the bacteria. Interestingly, many fungi like *Aspergilli*  
478 possess specific detoxification mechanisms through phenazine specific biotransformation.  
479 Considering this, Moree and colleagues studied the production of different phenazines during the  
480 co-culture of *P. aeruginosa* and *A. fumigatus*, which led to the observation of the induction of  
481 some compounds and/or the appearance of biotransformed products, such as pyocyanin (**244**),  
482 phenazine-1-carboxamide (**245**), 1-hydroxyphenazine (**246**), phenazine-1-carboxylic acid (**247**),  
483 1-methoxyphenazine (**248**), phenazine-1-sulfate (**249**) and 5-*N*-methylated phenazine-1-  
484 carboxylic acid (**250**) (Moree et al., 2012). In this study, differences were clear between the  
485 “induction mechanisms” corresponding to biosynthesis activation and biotransformation. It is  
486 important to note that phenazines correspond to a class of compounds exhibiting a large variety  
487 of biological activity (Laursen and Nielsen, 2004). Dashti and colleagues isolated antibacterial  
488 and antiparasitic *N*-(2-hydroxyphenyl)-acetamide (**251**) from the co-culture of two actinomycetes  
489 *Actinokineospora* sp. EG49 and *Nocardiopsis* sp. RV163 (Dashti et al., 2014).

490 Fusaric acid (**252**) induced during the interaction between *Fusarium oxysporum* and  
491 *Sarocladium strictum* (Bohni et al., 2016) and quinomeran (**253**) from the co-culture of  
492 *Chaetomium* sp. with bacteria (Akone et al., 2016) were also present in this network.

### 493 **2.3.3. Cluster 9 – Tryptamine and Pyrrole alkaloids**

494 One small cluster (Cluster 9) consisting of six compounds corresponded to two different  
495 articles (Figure 2). Yu and colleagues isolated and characterized algicidal *N*-acetyltryptamine  
496 (**254**), *N*-propanoyltryptamine (**255**), bacillamide A, B, C (**256-258**) from the liquid fermentation  
497 of *Streptomyces* sp. and *Bacillus mycoides* (Yu et al., 2015). Among all those tryptamine  
498 derivatives, only bacillamide A (**256**) exhibits algicidal activity (Wang et al., 2017). Bao and  
499 colleagues isolated 1-(4-benzyl-1H-pyrrol-3-yl)ethanone (**259**) from the liquid fermentation of  
500 *Aspergillus sclerotiorum* and *Penicillium citrinum* (Bao et al., 2017).

## 501 **3. Current trends in co-culture induction**

502 In terms of culture methods, out of 82 studies, 24 papers used solid medium, 59 studies  
503 used liquid fermentation (also called mixed fermentation). Among those, two studies used both  
504 strategies (Chagas et al., 2013; Sonnenbichler et al., 1989). Mapping such culture methods on the  
505 network (Fig. S1), it remains obvious that no clear relationship could be observed between  
506 induced structures and the culture method with two exceptions. The cluster 2 “linear polyketides,  
507 Oxylipins and Fatty acids” only contains compounds reported from liquid fermentation. The  
508 molecules present in cluster 3 “Cyclic peptides, diketopiperazines and related compounds” are  
509 also mostly obtained by liquid fermentation. Other cluster specific culture condition observed are  
510 too small and represent a too low number of articles to be able to give more general



511 consideration. Therefore, unless studies aim at inducing structures closely related to cluster 2 and  
512 3, both co-culture conditions should be evaluated.

513       Regarding microorganisms' combination, researchers have adopted different strategies.  
514 Microorganisms were chosen from a common ecological niche to reveal microbial community  
515 chemical interactions (Kuhlish and Pohnert, 2015). Alternatively, sometimes one considers that  
516 ecologically irrelevant interactions could stress the organisms even more (Bertrand et al., 2013b).  
517 Based on structural considerations, many teams had worked on inter-kingdom microbial  
518 interactions (*i.e.*, bacteria and fungus) to delineate the biological origin of *de novo*-induced  
519 isolated compounds based on biosynthetic differences (some key skeletons being only produced  
520 by specific kingdoms related biosynthetic pathways) (Ola et al., 2013).

521       The articles reporting compound inductions were compared based on the micro-organisms  
522 grown together (Figure 4). Interestingly, most of those microbial co-cultures were involving  
523 fungi (65 articles) followed by bacteria (47 articles). Only very few articles were using micro-  
524 algae (1 articles) which may be due to more difficult culture conditions. In addition, most articles  
525 (54 articles) reported kingdom specific co-cultures (fungus *vs.* fungus or bacteria *vs.* bacteria).  
526 Such observation may be mainly due to laboratory expertise in only one type of microorganisms.  
527 Thus, it is interesting to note that fungal and bacterial co-culture are mostly exploited as case  
528 studies for compound induction. Mapping such involved kingdom on the network (Fig. S2)  
529 obviously shows that, unfortunately, no relationship could be observed between induced  
530 structure and the organism kingdoms. Thus, up to the current knowledge, the reported structural  
531 diversity of induced compounds is still limited and more diversity is expected to be published in  
532 the near future.

533

534 <<INSERT FIGURE 4 HERE>>

535

536 In addition to co-culture involving bacteria and/or fungi, only very few studies explore  
537 other microbial sources. For example, only one used microalgae as indicated before (Wrede et  
538 al., 2014). However, in the near future, one can imagine to perform co-culture experiments with  
539 other microorganisms like amoeba (Zarei et al., 2019), or with plant, human and/or animal cells  
540 (Hara et al., 2018). Taking into account such possibilities, an improved chemical diversity should  
541 be accessible.

542

543 Finally, it remains important to highlight biological activity evaluated on the isolated  
544 compounds. However, it is important to note that in most studies, compounds were isolated for  
545 the first time in the studied microbial co-culture. Thus in that case, the biological evaluation was  
546 only reported in the article itself. This makes difficult to get a clear view of which biological  
547 activity to expect from such induced compounds. Interestingly, more than half of the compounds  
548 were reported without any activity (139 compounds), this corresponds to absence of biological  
549 evaluation but also to absence of biological activity (as many times, unfortunately, low activity  
550 values are not mentioned). Like in most NP studies, in the case of co-culture induced  
551 compounds, relevant biological activity reported were mostly antibacterial (37%), cytotoxic  
552 (35%) and antifungal (7%) (Figure 5 and figure S3 if moderate activity are taken into  
553 consideration). However, the proportion of antimicrobial activity represents 44% of the  
554 evaluated activity, and is largely, the most evaluated activity. This clearly indicates that NP  
555 chemists mostly expect to discover such activity of such induced compounds (Lodhi et al., 2018;

556 Netzker et al., 2018; Zhang and Straight, 2019). It is interesting to note other biological activity  
557 that could be related to interspecies interaction, with the presence of antifouling (Cho and Kim,  
558 2012), algicidal (Wang et al., 2017), phytotoxic compounds (Glauser et al., 2009), siderophores  
559 (Traxler et al., 2013) and plant growth promoters (Cai et al., 2013; Tata et al., 2015). But, yet, it  
560 remains unclear if this trend is real or an artefact of rationality, as this evaluation seems to be the  
561 first choice of investigators.

562

563 <<INSERT FIGURE 5 HERE>>

564

## 565 **4. Challenges of Co-Culture Strategies for Chemical Diversity**

### 566 **Enhancement**

567 The use of co-culture for induction of NPs is a very challenging process and various  
568 difficulties appears to all researchers working in this area. The challenges encountered from NP  
569 Chemist's point of view are: (1) how to observe the metabolic induction in co-culture? (2) how  
570 reproducible are such inductions? (3) what is the appropriate time to observe the induction? (4)  
571 are compound isolation and identification a challenging task?

572 These challenges are explained in detail as follow.

#### 573 **4.1.How to observe the metabolic induction in co-culture?**

574 One of the main challenge in co-culture chemical analysis, remains the monitoring of  
575 induction itself as well as chemical diversity evaluation. This is why, even if co-culture

576 experiments were already tested in the mid 80's (Tokimoto et al., 1987), a much larger number  
577 of articles have started to be published in the last ten years as better accurate and sensitive  
578 analytical techniques in NP research studies occurred (Bertrand et al., 2014b; Wolfender et al.,  
579 2019).

580 In the case of microbial co-culture, historically chemical induction was demonstrated using  
581 targeted strategy on known compounds (Tokimoto et al., 1987) using HPLC-UV detection for  
582 example. Nowadays, chemical profiling is mostly achieved by liquid chromatography coupled to  
583 high resolution mass spectrometry (LC-HRMS) or mass spectrometry imaging (MS-imaging)  
584 (Bertrand et al., 2014b). In the reported cases, NMR is mostly used to reveal core metabolism  
585 alterations, however providing information mostly about core metabolome alterations (Cheng et  
586 al., 2013; Martínez-Buitrago et al., 2019; Nguyen et al., 2019). Very recently, a 2D NMR  
587 fingerprint strategy (Buedenbender et al., 2018) has been reported to highlight metabolic  
588 alteration thus indicating the induction of polyketides, peptides and aromatic compounds base on  
589 specific observed resonances (Buedenbender et al., 2019). Untargeted approaches were proven to  
590 be more efficient, in particular when metabolomic strategies were employed. These latter  
591 strategies, by profiling various biological replicates, generate large datasets and thus need  
592 specific chemometric analyses to delineate chemical modifications attributed to each organism  
593 (Bertrand et al., 2014b; Geurts et al., 2017; Jansen et al., 2015; Wang and Bertrand, 2019). In  
594 this context, defining what is induction is already a complex question. It could be considered as  
595 “*de novo* induction” (not detected in pure strain culture) or “up-regulated” (detected at lower  
596 concentration in pure strain culture). Unfortunately, such a distinction has to be considered in  
597 regards to the analytical techniques used to highlight such induction. It is clear that detection  
598 limits for thin layer chromatography (TLC), HPLC-UV or UHPLC-MS are different. Therefore,

599 it remains complicated to conclude on general induction pattern when studies using TLC (Li et  
600 al., 2019) are compared with HPLC (Kossuga et al., 2013; Ma et al., 2019; Nonaka et al., 2015)  
601 or metabolomic driven LC-MS (Bertrand et al., 2013c; Bohni et al., 2016; Combès et al., 2012;  
602 Shen et al., 2019; Wu et al., 2015; Xu et al., 2018). However, in the future studies (or  
603 publication), the type in induction observed should be important to mention. This should further  
604 help to discuss chemical diversity in regards to induction type.

605 Alternatively, approaches based on MS-imaging were also successfully applied to co-  
606 culture, providing information about the spatial metabolite distribution and metabolisation  
607 (Moree et al., 2013; Tata et al., 2015). This alternative approach highlights metabolite located  
608 specifically in the microorganisms' interaction zone. It provides an interesting insight into  
609 microbial interaction mechanisms. Interestingly, both strategies are complementary in revealing  
610 the very complex nature of such co-culture induction.

#### 611 **4.2. How reproducible are such inductions?**

612 Intriguingly, only very few examples exist of in depth studies of compound induction  
613 mechanisms by co-culture. In addition, only rare cases report the reproduction of co-culture  
614 experiments. To the author knowledge, only the interaction of *B. obtusa* and *E. lata* was  
615 attempted two times highlighting similar induction pattern (Azzollini et al., 2018; Glauser et al.,  
616 2009). In addition, some articles report the use of closely related organisms with the induction of  
617 identical compounds, such as *F. tricinctum* with different bacteria (*S. lividans* or *B. subtilis*)  
618 yielded macrocarpon C (**27**), (-)-citreoisocoumarin (**28**), fusaristatin A (**168**), enniatin A1, B and  
619 B1 (**217-219**) induction (Moussa et al., 2019; Ola et al., 2013).

620 One reason may be the focus of NP-chemists on discovering new chemical entities, which  
621 yield to model change once structures are finally published. However, a second reason lays in the  
622 difficulties encountered when reproducing a co-culture experiment is attempted. As many  
623 parameters should be taken into consideration for microbial growth, some of them could be  
624 complicated to fully control, such as the history of inoculum for the producing cultures (number  
625 of pre-culture and/or pre-culture treatment) (Imhoff, 2016). This may explain such difficulties  
626 and thus the low number reproduced studies.

627 Unfortunately, to the best of our knowledge, no studies report difficulties to reproduce  
628 previous experiments in order to study in-depth microbial interaction mechanisms or optimisation  
629 of co-culture conditions for compound production.

### 630 **4.3. What is the appropriate time to observe the induction?**

631 The NP biosynthesis is a very dynamic process, and recent studies have revealed that  
632 specialized metabolites may be produced at every stage of microbial growth (Roullier et al.,  
633 2016). Thus, in the context of microbial co-culture, such study conditions are much more  
634 complex. Unfortunately, only few studies exist on the impact of time on co-culture induction  
635 (Arora et al., 2019; Azzollini et al., 2018; Bertrand et al., 2014a). For example, the study of  
636 *Aspergillus sclerotiorum* and *Xylaria psidii* shows antimicrobial activity induction only at a  
637 specific culture time (Arora et al., 2019). Similarly, the metabolic study through time of a  
638 *Fusarium* sp. strain with *A. clavatus* Sin141 clearly shows the dynamic nature of compound  
639 induction, with some of them being induced only at specific growth time (Bertrand et al., 2014a;  
640 Geurts et al., 2017).

641 Therefore, to get an exhaustive view of compound induction in a specific co-culture  
642 experiment, it remains crucial to use sensitive analytical techniques and to explore the influence  
643 of time. The analysis of such temporal data can be clearly eased by metabolomic approach  
644 (Geurts et al., 2017; Roullier et al., 2016). Using such strategy, should drastically improve  
645 induction observation and avoid (or decrease) irreproducibility of microbial co-culture  
646 experiment, as demonstrated in the *B. obtusa* and *E. lata* co-culture (Azzollini et al., 2018;  
647 Glauser et al., 2009).

#### 648 **4.4. Are compound isolation and identification a challenging task?**

649 Metabolomic approaches, as described previously, also help to evaluate the chemical  
650 diversity of the compounds induced during microbial interactions. High mass and spectral  
651 accuracy information provided by high-resolution mass spectrometry used either in LC-MS or  
652 imaging-MS strategies, allow the dereplication (also called annotation) of compounds of interest  
653 (Wolfender et al., 2019). The identification of the highlighted metabolites based only on the MS  
654 data represents the most challenging step (Bertrand et al., 2014b) because it is a very time  
655 consuming work and, as reported, co-culture-induced metabolites display a lower database hit  
656 rate in comparison to constitutively produced compounds (Bertrand et al., 2013b). Therefore,  
657 such strategies can highlight reported and unreported compounds revealing chemical novelty  
658 within induced compounds. As a complementary approach to traditional dereplication strategy,  
659 MS/MS spectral similarity networking (Allegra T. et al., 2019; Wang et al., 2016) (also called  
660 Molecular Network) represents a very promising approach to reveal the structural relationship  
661 between constitutive and induced compounds. Thus, it can highlight structurally analogous  
662 metabolites based on similar fragmentation patterns yielding sometimes the identification of a  
663 large number of analogous compounds (Oppong-Danquah et al., 2018; Traxler et al., 2013).

664           Once unreported compound is highlighted, a real challenge consists in isolating it for  
665 further identification. Some studies reported the isolation of major induced compound from a  
666 very limited amount of raw material (Bertrand et al., 2013c; Bohni et al., 2016), however, to  
667 purify and identify minor induced compound a large amount of extract remains necessary.  
668 Obtaining such quantity could become a great challenge, especially if reproducibility of  
669 microbial co-culture is limited. Bertrand and collaborators reported difficulties observed in  
670 upscaling from 2-cm- to 15-cm-diameters Petri dishes the co-culture of *Fusarium* sp. strain with  
671 *A. clavatus* (Bertrand et al., 2014a). In their example, some highlighted induced compounds  
672 disappeared after up-scaling, particularly early induced ones.

673           Instead of multiplying the number of replicates to get more chances to obtain appropriate  
674 starting material, in some studies, pure-strain culture conditions were evaluated focusing on  
675 finding easier solution to access to co-culture induced compounds. Some successful examples  
676 exist, with the addition of epigenetic modifiers (Akone et al., 2016) or one of the organisms  
677 extract or sterilized organisms (Akone et al., 2016; Ancheeva et al., 2017; El-Sayed et al., 2019;  
678 Liang et al., 2019; Rateb et al., 2013). Strategies modifying one of the microorganisms of the co-  
679 culture setup may also provide improved production and should be eventually tested (Boruta et  
680 al., 2019). Yet, not enough cases are reported to provide a general strategy to access such  
681 compounds of interest, and research in this direction should be continued.

682           Even if many successful examples of compound isolation were reported in the literature,  
683 the compound isolation and identification remains a challenging task, in particular in the case of  
684 induction of minor compounds.



## 685 5. Conclusion

686 This review provides a comprehensive analysis of NPs induced in microbial co-culture  
687 with a specific focus on their chemical structure. As general trends, the induced structures were  
688 clustered into 9 significant clusters which can be organized in three groups corresponding to  
689 “Non-nitrogenated compounds” (clusters 1-2), “non-alkaloidic nitrogenated compounds” (cluster  
690 3-6), “alkaloidic compounds” (clusters 7-9). This shows that very large variety of structures are  
691 induced; even though rather focused physico-chemical properties were observed. Therefore, co-  
692 culture can be a promising strategy for the specific production of some valuable NPs and  
693 induction of new ones. Among all those compounds, it is interesting to note that many of them  
694 exhibit antimicrobial activity, which can indicate that they have a specific role in interspecies  
695 microbial interaction. This is further pointed out by the induction of small molecule related to  
696 microbial communication, such as butyrolactones (Ancheeva et al., 2017; Chen et al., 2015;  
697 Hoshino et al., 2015b; Tata et al., 2015) or oxylipins (Combès et al., 2012). However, more  
698 importantly, it is interesting to note that some key chemical scaffolds in regards to interspecies  
699 chemical mediation are not reported as induced in co-culture yet. No small terpenes, highly  
700 lipophilic compounds related to plant communication (Ta and Arnason, 2015) was reported as  
701 induced. The quinolones which act in bacterial quorum sensing (Dubern and Diggle, 2008) were  
702 also not observed as induced. Similarly, among reported molecules, only one glucosides,  
703 stromemycin (**84**) (Nonaka et al., 2011), was reported as induced. This observation may raise  
704 questions about the mechanisms of induction. In case of pathways activation, various initiation  
705 mechanisms may be envisaged, such as a response to a chemical signal. In that case, the  
706 chemical signal may not be induced itself. Various cases were tentatively explored that may  
707 provide some understanding in the induction mechanisms. For example, the induction may be

708 reproduced by sterilizing one of the partner (Ancheeva et al., 2017; Liang et al., 2019; Rateb et  
709 al., 2013), but sometime specific interaction with living microorganisms is necessary (Angell et  
710 al., 2006). Unfortunately, only rare examples exist where the authors explore how specific is the  
711 interaction. Such studies should be conducted in depth in the future to provide new insight in the  
712 induction mechanisms.

713         Yet, based on the reported co-culture induced metabolites, as compared with other  
714 strategies traditionally used in microbial NPs research (i.e. OSMAC approach), no prediction can  
715 be done on what kind of scaffold can be induced. One exception is the production of “linear  
716 polyketides, Oxylipins and Fatty acids” and “Cyclic peptides, diketopiperazines and related  
717 compounds” that seems to occurs mostly during liquid fermentation independently of the type of  
718 organisms. In fact, this is highly dependent on both the biosynthetic capabilities of both the co-  
719 cultured organisms, and also to the couple of micro-organisms used. Thus, to the best of our  
720 knowledge, all culture-based induction strategies are unfortunately still based on serendipity. In  
721 addition, the literature survey achieved here also highlights the lack of information provided by  
722 articles studying co-culture. As a general guideline for future co-culture articles, additional  
723 information should be provided such as:

- 724         - a clear comparison with mono-culture chemical profiles,
- 725         - the number of replicates used during the study,
- 726         - the induction levels of all reported compounds (fold change of up-regulation or *de novo*  
727         induction)
- 728         - the presence of other similar compounds produced by the mono-cultures.

729 Such information, should help delineating the mechanism of induction for comparison with other  
730 studies.

731 Most chemical novelty is still discovered from exploring novel microbial sources, even if  
732 all compounds are not produced under standard laboratory conditions. In addition, chemical  
733 novelty is also easily obtained by OSMAC approach, albeit it is not an exhaustive strategy.  
734 While monitoring of induction is nowadays achievable, no clear study comparing chemical  
735 novelty access or coverage from microbial co-culture or OSMAC is available. Therefore,  
736 comparing those strategies remains difficult to achieve, and this provides new directions that  
737 need to be explored in the near future. Furthermore, combining both strategies was also not yet  
738 applied to extend explore microbial chemical space. This may, in addition to highlight novel  
739 compounds, provide information about NPs production regulation mechanisms.

740 In addition, in comparison to the screening of novel microbial sources or OSMAC  
741 approach applied to one microbial strain, co-culture still suffers from difficulties for large scale  
742 production and structural identification of those compounds. The single strain culture approaches  
743 present the great advantage that up-scaling for further purification and structural elucidation is  
744 rather easy to achieve. In the case of microbial co-culture, the up-scaling is still rather  
745 complicated and all induced compounds may not be observed after up-scaling, in particular for  
746 minor induced compounds (Bertrand et al., 2014a). This may also be due to difficulties in  
747 obtaining stable large scale microbial consortium (Stephens et al., 2019). Thus, up-scaling  
748 strategies need to be explored in-depth to provide access to all induced compounds in large scale.  
749 Unfortunately, this step remains highly time-consuming. Such up-scaling problems are  
750 sometimes related to the ignorance of the organisms responsible for co-culture induced  
751 compound production. Therefore, exploring biosynthetic gene cluster activation under co-culture  
752 conditions (Schroeckh et al., 2009; Torres-Monroy and Ullrich, 2018) is very crucial. Thus,  
753 transcriptomic studies should be used as often as possible to be able to link compound induction

754 with gene transcription. Such an approach may provide novel strategies for specific compound  
755 production such as heterologous expression (Gomez-Escribano and Bibb, 2014), homologous  
756 activation (Zhang, B. et al., 2017).

757 In conclusion, to make use of microbial co-culture at the same level as the OSMAC  
758 approach, more studies still need to be engaged to provide solutions to overcome the previously  
759 discussed bottlenecks. Overcoming those aspects of the co-culture strategy will definitely help  
760 future drug discovery programs, as well as studies of microbial community in a chemical  
761 ecology viewpoint.

762

## 763 Acknowledgments

764 DA gratefully acknowledges CEFIPRA for providing Raman Charpak Fellowship. SJ  
765 thank to Department of Science & Technology (DST), Govt. of India for financial assistance  
766 with Grant No. ECR/2017/001381.

## 767 References

- 768 Abe, F., Hiraki, T., 2009. Mechanistic role of ergosterol in membrane rigidity and cycloheximide  
769 resistance in *Saccharomyces cerevisiae*. *Biochim. Biophys. Acta* 1788(3), 743-752.
- 770 Afiyatullo, S.S., Zhuravleva, O.I., Antonov, A.S., Berdyshev, D.V., Pivkin, M.V., Denisenko,  
771 V.A., Popov, R.S., Gerasimenko, A.V., von Amsberg, G., Dyshlovoy, S.A., Leshchenko, E.V.,  
772 Yurchenko, A.N., 2018. Prenylated indole alkaloids from co-culture of marine-derived fungi  
773 *Aspergillus sulphureus* and *Isaria felina*. *J. Antibiot.* 71(10), 846-853.
- 774 Ahmann, G.B., Mathey, A., 1967. Lecanoric Acid and Some Constituents of *Parmelia tinctorum*  
775 and *Pseudevernia intensa*. *Bryologist* 70(1), 93-97.
- 776 Akone, S.H., Mándi, A., Kurtán, T., Hartmann, R., Lin, W., Daletos, G., Proksch, P., 2016.  
777 Inducing secondary metabolite production by the endophytic fungus *Chaetomium* sp. through  
778 fungal-bacterial co-culture and epigenetic modification. *Tetrahedron* 72(41), 6340-6347.
- 779 Allegra T., A., Emily, G., Kerry L., M., Louis Felix, N., Mélissa, N.-E., Amina, B., Daniel, P.,  
780 Julia M., G., Nicole, S., Fernando, V., Justin J., J.v.d.H., Madeleine, E., Kyo Bin, K., Christine  
781 M., A., Andrés Mauricio, C.-R., Irina, K., Kelly C., W., Samuel, B., Catherine, R., Kunyang, S.,  
782 Richard M., T., Cristopher A., B., Christian, M.H., Marcelino, G., Aldo Moreno, U., Javier  
783 Andres Tejada, M., Randy, M.-F., Johant, L.-B., Victor, V.-C., Angela, I.C., Nicole, T., Robert  
784 A., K., Fidele, T., Nombuso, N., Alexander A., A., Alan K., J., Robin, S., Andrew W., T., Nuno,  
785 B., Mingxun, W., Pieter, D., 2019. Reproducible Molecular Networking Of Untargeted Mass  
786 Spectrometry Data Using GNPS. *ChemRxiv*, doi: 10.26434/chemrxiv.9333212.v9333211.
- 787 Ancheeva, E., Küppers, L., Akone, S.H., Ebrahim, W., Liu, Z., Mándi, A., Kurtán, T., Lin, W.,  
788 Orfali, R., Rehberg, N., 2017. Expanding the Metabolic Profile of the Fungus *Chaetomium* sp.  
789 through Co-culture with Autoclaved *Pseudomonas aeruginosa*. *Eur. J. Org. Chem.* 2017(22),  
790 3256-3264.
- 791 Angell, S., Bench, B.J., Williams, H., Watanabe, C.M.H., 2006. Pyocyanin Isolated from a  
792 Marine Microbial Population: Synergistic Production between Two Distinct Bacterial Species  
793 and Mode of Action. *Chem. Biol.* 13(12), 1349-1359.

- 794 Anjum, K., Sadiq, I., Chen, L., Kaleem, S., Li, X.-C., Zhang, Z., Lian, X.-Y., 2018. Novel  
795 antifungal janthinopolyenemycins A and B from a co-culture of marine-associated  
796 *Janthinobacterium* spp. ZZ145 and ZZ148. *Tetrahedron Lett.* 59(38), 3490-3494.
- 797 Arora, D., Chashoo, G., Singamaneni, V., Sharma, N., Gupta, P., Jaglan, S., 2018. *Bacillus*  
798 *amyloliquefaciens* induces production of a novel blennolide k in co-culture of *Setophoma*  
799 *terrestris*. *J. Appl. Microbiol.* 124(3), 730-739.
- 800 Arora, D., Gupta, P., Jaglan, S., Bertrand, S., 2019. Dynamics of fungal co-cultures from  
801 competition to induction of bioactive specialized metabolites: A case study of *Aspergillus*  
802 *sclerotiorum* and *Xylaria psidii*. submitted manuscript.
- 803 Azzollini, A., Boggia, L., Boccard, J., Sgorbini, B., Lecoultre, N., Allard, P.-M., Rubiolo, P.,  
804 Rudaz, S., Gindro, K., Bicchi, C., Wolfender, J.-L., 2018. Dynamics of Metabolite Induction in  
805 Fungal Co-cultures by Metabolomics at Both Volatile and Non-volatile Levels. *Front. Microbiol.*  
806 9, 72.
- 807 Bao, J., Wang, J., Zhang, X.-Y., Nong, X.-H., Qi, S.-H., 2017. New furanone derivatives and  
808 alkaloids from the co-culture of marine-derived fungi *Aspergillus sclerotiorum* and *Penicillium*  
809 *citrinum*. *Chem. Biodiv.* 14(3), e1600327
- 810 Bertrand, S., Azzollini, A., Schumpp, O., Bohni, N., Schrenzel, J., Monod, M., Gindro, K.,  
811 Wolfender, J.-L., 2014a. Multi-well fungal co-culture for *de novo* metabolite-induction in time  
812 series studies based on untargeted metabolomics. *Mol. Biosyst.* 10(9), 2289-2298.
- 813 Bertrand, S., Bohni, N., Schnee, S., Schumpp, O., Gindro, K., Wolfender, J.-L., 2014b.  
814 Metabolite induction via microorganism co-culture: a potential way to enhance chemical  
815 diversity for drug discovery. *Biotechnol. Adv.* 32(6), 1180-1204.
- 816 Bertrand, S., Helesbeux, J.-J., Larcher, G., Duval, O., 2013a. Hydroxamates, a Key  
817 Pharmacophore Exhibiting a Wide Range of Biological Activities. *Mini-Rev. Med. Chem.* 13(9),  
818 1311-1326.
- 819 Bertrand, S., Schumpp, O., Bohni, N., Bujard, A., Azzollini, A., Monod, M., Gindro, K.,  
820 Wolfender, J.-L., 2013b. Detection of metabolite induction in fungal co-cultures on solid media  
821 by high-throughput differential ultra-high pressure liquid chromatography-time-of-flight mass  
822 spectrometry fingerprinting. *J. Chromatogr. A* 1292, 219-228.
- 823 Bertrand, S., Schumpp, O., Bohni, N., Monod, M., Gindro, K., Wolfender, J.-L., 2013c. *De novo*  
824 production of metabolites by fungal co-culture of *Trichophyton rubrum* and *Bionectria*  
825 *ochroleuca*. *J. Nat. Prod.* 76(6), 1157-1165.
- 826 Bode, H.B., Bethe, B., Höfs, R., Zeeck, A., 2002. Big effects from small changes: possible ways  
827 to explore nature's chemical diversity. *ChemBioChem* 3(7), 619-627.
- 828 Bohni, N., Hofstetter, V., Gindro, K., Buyck, B., Schumpp, O., Bertrand, S., Monod, M.,  
829 Wolfender, J.-L., 2016. Production of Fusaric Acid by *Fusarium* spp. in Pure Culture and in  
830 Solid Medium Co-Cultures. *Molecules* 21(3), 370.

- 831 Boruta, T., Milczarek, I., Bizukojc, M., 2019. Evaluating the outcomes of submerged co-  
832 cultivation: production of lovastatin and other secondary metabolites by *Aspergillus terreus* in  
833 fungal co-cultures. *Appl. Microbiol. Biotechnol.* 103(14), 5593-5605.
- 834 Buedenbender, L., Carroll, A.R., Kurtböke, D.İ., 2019. Detecting co-cultivation induced  
835 chemical diversity via 2D NMR fingerprints. *Microbiol. Australia*, doi: 10.1071/MA19054.
- 836 Buedenbender, L., Habener, L.J., Grkovic, T., Kurtböke, D.İ., Duffy, S., Avery, V.M., Carroll,  
837 A.R., 2018. HSQC–TOCSY Fingerprinting for Prioritization of Polyketide- and Peptide-  
838 Producing Microbial Isolates. *J. Nat. Prod.* 81(4), 957-965.
- 839 Cai, F., Yu, G., Wang, P., Wei, Z., Fu, L., Shen, Q., Chen, W., 2013. Harzianolide, a novel plant  
840 growth regulator and systemic resistance elicitor from *Trichoderma harzianum*. *Plant Physiol.*  
841 *Biochem.* 73, 106-113.
- 842 Cañedo Hernandez, L.M., de la Fuente Blanco, J.A., Baz, J.P., Fernández Puentes, J.L., Romero  
843 Millán, F., Espliego Vázquez, F., Fernández-Chimeno, R.I., Grávalos, D.G., 2000. 4'-*N*-methyl-  
844 5'-hydroxystaurosporine and 5'-hydroxystaurosporine, new indolocarbazole alkaloids from a  
845 marine *Micromonospora* sp. strain. *J. Antibiot.* 53(9), 895-902.
- 846 Carlson, S., Tanouye, U., Omarsdottir, S., Murphy, B.T., 2014. Phylum-Specific Regulation of  
847 Resistomycin Production in a *Streptomyces* sp. via Microbial Coculture. *J. Nat. Prod.* 78(3), 381-  
848 387.
- 849 Chagas, F.O., Dias, L.G., Pupo, M.T., 2013. A mixed culture of endophytic fungi increases  
850 production of antifungal polyketides. *J. Chem. Ecol.* 39(10), 1335-1342.
- 851 Chen, H., Daletos, G., Abdel-Aziz, M.S., Thomy, D., Dai, H., Brötz-Oesterhelt, H., Lin, W.,  
852 Proksch, P., 2015. Inducing secondary metabolite production by the soil-dwelling fungus  
853 *Aspergillus terreus* through bacterial co-culture. *Phytochem. Lett.* 12, 35-41.
- 854 Chen, T., Zhou, Y., Lu, Y., Zhang, H., 2019. Advances in heterologous biosynthesis of plant and  
855 fungal natural products by modular co-culture engineering. *Biotechnol. Lett.* 41(1), 27-34.
- 856 Chen, Y., Garcia de Lomana, M., Friedrich, N.-O., Kirchmair, J., 2018. Characterization of the  
857 Chemical Space of Known and Readily Obtainable Natural Products. *J. Chem. Inf. Model.* 58(8),  
858 1518-1532.
- 859 Cheng, Y.F., Jin, W., Mao, S.Y., Zhu, W.-Y., 2013. Production of Citrate by Anaerobic Fungi in  
860 the Presence of Co-culture Methanogens as Revealed by H NMR Spectrometry. *Asian Australas.*  
861 *J. Anim. Sci.* 26(10), 1416-1423.
- 862 Cho, J.Y., Kim, M.S., 2012. Induction of antifouling diterpene production by *Streptomyces*  
863 *cinnabarinus* PK209 in co-culture with marine-derived *Alteromonas* sp. KNS-16. *Biosci.*  
864 *Biotechnol. Biochem.* 76(10), 1849-1854.

- 865 Combès, A., Ndoye, I., Bance, C., Bruzard, J., Djediat, C., Dupont, J., Nay, B., Prado, S., 2012.  
866 Chemical Communication between the Endophytic Fungus *Paraconiothyrium Variabile* and the  
867 Phytopathogen *Fusarium oxysporum*. PLoS One 7(10), e47313.
- 868 Cueto, M., Jensen, P.R., Kauffman, C., Fenical, W., Lobkovsky, E., Clardy, J., 2001. Pestalone,  
869 a new antibiotic produced by a marine fungus in response to bacterial challenge. J. Nat. Prod.  
870 64(11), 1444-1446.
- 871 Dashti, Y., Grkovic, T., Abdelmohsen, U., Hentschel, U., Quinn, R., 2014. Production of  
872 Induced Secondary Metabolites by a Co-Culture of Sponge-Associated Actinomycetes,  
873 *Actinokineospora* sp. EG49 and *Nocardiosis* sp. RV163. Mar. Drugs 12(5), 3046-3059.
- 874 Ding, W., Lu, Y., Feng, Z., Luo, S., Li, C., 2017. A New Nonadride Derivative from the Co-  
875 Culture Broth of Two Mangrove Fungi. Chem. Nat. Compd. 53(4), 691-693.
- 876 do Nascimento, J.S., Silva, F.M., Magallanes-Noguera, C.A., Kurina-Sanz, M., Dos Santos,  
877 E.G., Caldas, I.S., Luiz, J.H.H., Silva, E.O., 2019. Natural trypanocidal product produced by  
878 endophytic fungi through co-culturing. Folia Microbiol., doi: 10.1007/s12223-12019-00727-x.
- 879 Do Nascimento, M., Dublan, M.d.l.A., Ortiz-Marquez, J.C.F., Curatti, L., 2013. High lipid  
880 productivity of an *Ankistrodesmus-Rhizobium* artificial consortium. Bioresour. Technol. 146,  
881 400-407.
- 882 Dubern, J.-F., Diggle, S.P., 2008. Quorum sensing by 2-alkyl-4-quinolones in *Pseudomonas*  
883 *aeruginosa* and other bacterial species. Mol. Biosyst. 4(9), 882-888.
- 884 Ebrahim, W., El-Neketi, M., Lewald, L.-I., Orfali, R.S., Lin, W., Rehberg, N., Kalscheuer, R.,  
885 Daletos, G., Proksch, P., 2016. Metabolites from the Fungal Endophyte *Aspergillus*  
886 *austroafricanus* in Axenic Culture and in Fungal–Bacterial Mixed Cultures. J. Nat. Prod. 79(4),  
887 914-922.
- 888 El-Sayed, A.S.A., Mohamed, N.Z., Safan, S., Yassin, M.A., Shaban, L., Shindia, A.A., Shad Ali,  
889 G., Sitohy, M.Z., 2019. Restoring the Taxol biosynthetic machinery of *Aspergillus terreus* by  
890 *Podocarpus gracilior* Pilger microbiome, with retrieving the ribosome biogenesis proteins of  
891 WD40 superfamily. Sci. Rep. 9(1), 11534.
- 892 Feher, M., Schmidt, J.M., 2003. Property Distributions: Differences between Drugs, Natural  
893 Products, and Molecules from Combinatorial Chemistry. J. Chem. Inf. Comput. Sci. 43(1), 218-  
894 227.
- 895 Fu, P., Zhuang, Y., Wang, Y., Liu, P., Qi, X., Gu, K., Zhang, D., Zhu, W., 2012. New  
896 indolocarbazoles from a mutant strain of the marine-derived actinomycete *Streptomyces fradiae*  
897 007M135. Org. Lett. 14(24), 6194-6197.
- 898 Gebreselassie, N.A., Antoniewicz, M.R., 2015. <sup>13</sup>C-metabolic flux analysis of co-cultures: A  
899 novel approach. Metab. Engin. 31, 132-139.



- 900 Geurts, B.P., Neerincx, A.H., Bertrand, S., Leemans, M.A.A.P., Postma, G.J., Wolfender, J.L.,  
901 Cristescu, S.M., Buydens, L.M.C., Jansen, J.J., 2017. Combining ANOVA-PCA with  
902 POCHEMON to analyse micro-organism development in a polymicrobial environment. *Anal.*  
903 *Chim. Acta* 963, 1-16.
- 904 Ghose, A.K., Viswanadhan, V.N., Wendoloski, J.J., 1998. Prediction of Hydrophobic  
905 (Lipophilic) Properties of Small Organic Molecules Using Fragmental Methods: An Analysis of  
906 ALOGP and CLOGP Methods. *J. Phys. Chem. A* 102(21), 3762-3772.
- 907 Glauser, G., Gindro, K., Fringeli, J., De Joffrey, J.-P., Rudaz, S., Wolfender, J.-L., 2009.  
908 Differential analysis of mycoalexins in confrontation zones of grapevine fungal pathogens by  
909 ultrahigh pressure liquid chromatography/time-of-flight mass spectrometry and capillary nuclear  
910 magnetic resonance. *J. Agric. Food Chem.* 57(4), 1127-1134.
- 911 Gomez-Escribano, J.P., Bibb, M.J., 2014. Heterologous expression of natural product  
912 biosynthetic gene clusters in *Streptomyces coelicolor*: From genome mining to manipulation of  
913 biosynthetic pathways. *J. Indus. Microbiol. Biotechnol.* 41(2), 425-431.
- 914 Gonzalez-Sabin, J., 2012. Natural products: back to the future in drug discovery. *Biochem.*  
915 *Pharmacol.* 1, e112.
- 916 Goodwin, Cody R., Covington, Brett C., Derewacz, Dagmara K., McNeese, C.R., Wikswo,  
917 John P., McLean, John A., Bachmann, Brian O., 2015. Structuring Microbial Metabolic  
918 Responses to Multiplexed Stimuli via Self-Organizing Metabolomics Maps. *Chem. Biol.* 22(5),  
919 661-670.
- 920 Guo, H., Kreuzenbeck, N.B., Otani, S., Garcia-Altare, M., Dahse, H.-M., Weigel, C., Aanen,  
921 D.K., Hertweck, C., Poulsen, M., Beemelmans, C., 2016. Pseudoxyllallemycins A–F, Cyclic  
922 Tetrapeptides with Rare Allenyl Modifications Isolated from *Pseudoxyllaria* sp. X802: A  
923 Competitor of Fungus-Growing Termite Cultivars. *Org. Lett.* 18(14), 3338-3341.
- 924 Hara, Y., Arai, M.A., Toume, K., Masu, H., Sato, T., Komatsu, K., Yaguchi, T., Ishibashi, M.,  
925 2018. Coculture of a Pathogenic Actinomycete and Animal Cells To Produce Nocarjamide, a  
926 Cyclic Nonapeptide with Wnt Signal-Activating Effect. *Org. Lett.* 20(18), 5831-5834.
- 927 Harvey, A.L., Edrada-Ebel, R., Quinn, R.J., 2015. The re-emergence of natural products for drug  
928 discovery in the genomics era. *Nat. Rev. Drug Discov.* 14(2), 111-129.
- 929 Harwani, D., Begani, J., Lakhani, J., 2018. Co-cultivation Strategies to Induce De Novo  
930 Synthesis of Novel Chemical Scaffolds from Cryptic Secondary Metabolite Gene Clusters, in:  
931 Gehlot, P., Singh, J. (Eds.), *Fungi and their Role in Sustainable Development: Current*  
932 *Perspectives*. Springer Singapore, Singapore, pp. 617-631.
- 933 Hider, R.C., Kong, X., 2010. Chemistry and biology of siderophores. *Nat. Prod. Rep.* 27(5), 637-  
934 657.

- 935 Hoshino, S., Okada, M., Wakimoto, T., Zhang, H., Hayashi, F., Onaka, H., Abe, I., 2015a.  
936 Niizalactams A–C, Multicyclic Macrolactams Isolated from Combined Culture of *Streptomyces*  
937 with Mycolic Acid-Containing Bacterium. *J. Nat. Prod.* 78(12), 3011-3017.
- 938 Hoshino, S., Ozeki, M., Awakawa, T., Morita, H., Onaka, H., Abe, I., 2018a. Catenulobactins A  
939 and B, Heterocyclic Peptides from Culturing Catenuloplanes sp. with a Mycolic Acid-Containing  
940 Bacterium. *J. Nat. Prod.* 81(9), 2106-2110.
- 941 Hoshino, S., Wakimoto, T., Onaka, H., Abe, I., 2015b. Chojalactones A–C, Cytotoxic  
942 Butanolides Isolated from *Streptomyces* sp. Cultivated with Mycolic Acid Containing Bacterium.  
943 *Org. Lett.* 17(6), 1501-1504.
- 944 Hoshino, S., Wong, C.P., Ozeki, M., Zhang, H., Hayashi, F., Awakawa, T., Asamizu, S., Onaka,  
945 H., Abe, I., 2018b. Umezawamides, new bioactive polycyclic tetramate macrolactams isolated  
946 from a combined-culture of *Umezawaea* sp. and mycolic acid-containing bacterium. *J. Antibiot.*  
947 71(7), 653-657.
- 948 Hoshino, S., Zhang, L., Awakawa, T., Wakimoto, T., Onaka, H., Abe, I., 2015c. Arcyriaflavin E,  
949 a new cytotoxic indolocarbazole alkaloid isolated by combined-culture of mycolic acid-  
950 containing bacteria and *Streptomyces cinnamoneus* NBRC 13823. *J. Antibiot.* 68(5), 342-344.
- 951 Hu, D.X., Withall, D.M., Challis, G.L., Thomson, R.J., 2016. Structure, Chemical Synthesis, and  
952 Biosynthesis of Prodiginine Natural Products. *Chem. Rev.* 116(14), 7818-7853.
- 953 Huang, S., Ding, W., Li, C., Cox, D.G., 2014. Two new cyclopeptides from the co-culture broth  
954 of two marine mangrove fungi and their antifungal activity. *Pharmacogn. Mag.* 10(40), 410.
- 955 Hueza, I.M., Raspantini, P.C.F., Raspantini, L.E.R., Latorre, A.O., Górnjak, S.L., 2014.  
956 Zearalenone, an estrogenic mycotoxin, is an immunotoxic compound. *Toxins* 6(3), 1080-1095.
- 957 Imhoff, J., 2016. Natural Products from Marine Fungi—Still an Underrepresented Resource.  
958 *Mar. Drugs* 14(1), 19.
- 959 Jansen, J.J., Blanchet, L., Buydens, L.M.C., Bertrand, S., Wolfender, J.-L., 2015. Projected  
960 Orthogonalized CHEmical Encounter MONitoring (POCHEMON) for microbial interactions in  
961 co-culture. *Metabolomics* 11(4), 908-919.
- 962 Jayaseelan, S., Ramaswamy, D., Dharmaraj, S., 2014. Pyocyanin: production, applications,  
963 challenges and new insights. *World J. Microbiol. Biotechnol.* 30(4), 1159-1168.
- 964 Jones, J.A., Vernacchio, V.R., Sinkoe, A.L., Collins, S.M., Ibrahim, M.H.A., Lachance, D.M.,  
965 Hahn, J., Koffas, M.A.G., 2016. Experimental and computational optimization of an *Escherichia*  
966 *coli* co-culture for the efficient production of flavonoids. *Metab. Engin.* 35, 55-63.
- 967 Jones, J.A., Wang, X., 2018. Use of bacterial co-cultures for the efficient production of  
968 chemicals. *Curr. Opin. Biotechnol.* 53, 33-38.

- 969 Kamdem, R.S., Wang, H., Wafo, P., Ebrahim, W., Özkaya, F.C., Makhloufi, G., Janiak, C.,  
970 Sureechatchaiyan, P., Kassack, M.U., Lin, W., 2018. Induction of new metabolites from the  
971 endophytic fungus *Bionectria* sp. through bacterial co-culture. *Fitoterapia* 124, 132-136.
- 972 Keilhofer, N., Nachtigall, J., Kulik, A., Ecke, M., Hampp, R., Sussmuth, R.D., Fiedler, H.P.,  
973 Schrey, S.D., 2018. *Streptomyces* AcH 505 triggers production of a salicylic acid analogue in the  
974 fungal pathogen *Heterobasidion abietinum* that enhances infection of Norway spruce seedlings.  
975 *Antonie Van Leeuwenhoek* 111(5), 691-704.
- 976 Khalil, Z.G., Cruz-Morales, P., Licon-Cassani, C., Marcellin, E., Capon, R.J., 2019. Inter-  
977 Kingdom beach warfare: Microbial chemical communication activates natural chemical  
978 defences. *ISME J.* 13(1), 147-158.
- 979 König, C.C., Scherlach, K., Schroeckh, V., Horn, F., Nietzsche, S., Brakhage, A.A., Hertweck,  
980 C., 2013. Bacterium Induces Cryptic Meroterpenoid Pathway in the Pathogenic Fungus  
981 *Aspergillus fumigatus*. *ChemBioChem* 14(8), 938-942.
- 982 Kosawang, C., Karlsson, M., Véléz, H., Rasmussen, P.H., Collinge, D.B., Jensen, B., Jensen,  
983 D.F., 2014. Zearalenone detoxification by zearalenone hydrolase is important for the antagonistic  
984 ability of *Clonostachys rosea* against mycotoxigenic *Fusarium graminearum*. *Fungal Biol.*  
985 118(4), 364-373.
- 986 Kossuga, M.H., Ferreira, A.G., Sette, L.D., Berlinck, R.G.S., 2013. Two Polyketides from a Co-  
987 culture of Two Marine-derived Fungal Strains. *Nat. Prod. Commun.* 8(6), 721-724.
- 988 Kuhlisch, C., Pohnert, G., 2015. Metabolomics in chemical ecology. *Nat. Prod. Rep.* 32(7), 937-  
989 955.
- 990 Kuiper-Goodman, T., Scott, P.M., Watanabe, H., 1987. Risk assessment of the mycotoxin  
991 zearalenone. *Regul. Toxicol. Pharmacol.* 7(3), 253-306.
- 992 Kurosawa, K., Ghiviriga, I., Sambandan, T.G., Lessard, P.A., Barbara, J.E., Rha, C., Sinskey,  
993 A.J., 2008. Rhodostreptomycins, Antibiotics Biosynthesized Following Horizontal Gene  
994 Transfer from *Streptomyces padanus* to *Rhodococcus fascians*. *J. Am. Chem. Soc.* 130(4), 1126-  
995 1127.
- 996 Laursen, J.B., Nielsen, J., 2004. Phenazine Natural Products: Biosynthesis, Synthetic Analogues,  
997 and Biological Activity. *Chem. Rev.* 104(3), 1663-1686.
- 998 Li, C.-W., Xia, M.-W., Cui, C.-B., Peng, J., Li, D., 2016. A Novel Oxaphenalenone,  
999 Penicimutalidine: Activated Production of Oxaphenalenones by the Diethyl Sulphate  
1000 Mutagenesis of Marine-derived Fungus *Penicillium purpurogenum* G59. *RSC Adv.* 6(85),  
1001 82277-82281.
- 1002 Li, C., Sarotti, A., Yang, B., Turkson, J., Cao, S., 2017. A New *N*-methoxypyridone from the Co-  
1003 Cultivation of Hawaiian Endophytic Fungi *Camporesia sambuci* FT1061 and *Epicoccum*  
1004 *sorghinum* FT1062. *Molecules* 22(7), 1166.

- 1005 Li, C., Wang, J., Luo, C., Ding, W., Cox, D.G., 2014. A new cyclopeptide with antifungal  
1006 activity from the co-culture broth of two marine mangrove fungi. *Nat. Prod. Res.* 28(9), 616-621.
- 1007 Li, C., Zhang, J., Shao, C., Ding, W., She, Z., Lin, Y., 2011. A new xanthone derivative from the  
1008 co-culture broth of two marine fungi (strain No. E33 and K38). *Chem. Nat. Compd.* 47(3), 382-  
1009 384.
- 1010 Li, H.-T., Zhou, H., Duan, R.-T., Li, H.-Y., Tang, L.-H., Yang, X.-Q., Yang, Y.-B., Ding, Z.-T.,  
1011 2019. Inducing Secondary Metabolite Production by Co-culture of the Endophytic Fungus  
1012 *Phoma* sp. and the Symbiotic Fungus *Armillaria* sp. *J. Nat. Prod.* 82(4), 1009-1013.
- 1013 Li, X., Wu, Q., Xie, Y., Ding, Y., Du, W.W., Sdiri, M., Yang, B.B., 2015. Ergosterol purified  
1014 from medicinal mushroom *Amauroderma rude* inhibits cancer growth in vitro and in vivo by up-  
1015 regulating multiple tumor suppressors. *Oncotarget* 6(19), 17832-17846.
- 1016 Liang, L., Sproule, A., Haltli, B., Marchbank, D.H., Berru e, F., Overy, D.P., McQuillan, K.,  
1017 Lanteigne, M., Duncan, N., Correa, H., Kerr, R.G., 2019. Discovery of a New Natural Product  
1018 and a Deactivation of a Quorum Sensing System by Culturing a “Producer” Bacterium With a  
1019 Heat-Killed “Inducer” Culture. *Front. Microbiol.* 9, 3351.
- 1020 Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J., 2012. Experimental and  
1021 computational approaches to estimate solubility and permeability in drug discovery and  
1022 development settings. *Adv. Drug Deliv. Rev.* 64, 4-17.
- 1023 Liu, M., Grkovic, T., Liu, X., Han, J., Zhang, L., Quinn, R.J., 2017. A systems approach using  
1024 OSMAC, Log P and NMR fingerprinting: An approach to novelty. *Synth. Syst. Biotechnol.* 2(4),  
1025 276-286.
- 1026 Lo, Y.C., Senese, S., Damoiseaux, R., Torres, J.Z., 2016. 3D Chemical Similarity Networks for  
1027 Structure-Based Target Prediction and Scaffold Hopping. *ACS Chem. Biol.* 11(8), 2244-2253.
- 1028 Lodhi, A.F., Zhang, Y., Adil, M., Deng, Y., 2018. Antibiotic discovery: combining isolation chip  
1029 (iChip) technology and co-culture technique. *Appl. Microbiol. Biotechnol.* 102(17), 7333-7341.
- 1030 Luo, H., Yamamoto, Y., A Kim, J., Jung, J.S., Koh, Y.J., Hur, J.-S., 2009. Lecanoric acid, a  
1031 secondary lichen substance with antioxidant properties from *Umbilicaria antarctica* in maritime  
1032 Antarctica (King George Island). *Polar Biol.* 32(7), 1033-1040.
- 1033 Ma, Y.J., Zheng, L.P., Wang, J.W., 2019. Inducing perylenequinone production from a  
1034 bambusicolous fungus *Shiraia* sp. S9 through co-culture with a fruiting body-associated  
1035 bacterium *Pseudomonas fulva* SB1. *Microb. Cell. Fact.* 18(1), 121.
- 1036 Maass, W.S.G., 1975. Lichen substances. V. Methylated derivatives of orsellinic acid, lecanoric  
1037 acid, and gyrophoric acid from *Pseudocyphellaria crocata*. *Can. J. Bot.* 53(10), 1031-1039.
- 1038 Mart nez-Buitrago, P.A., Ramos, F.A., Castellanos, L., 2019. Binary Co-Culture Selection from  
1039 Marine-Derived Microorganisms for Differential Production of Specialized Metabolites. *Quim.*  
1040 *Nova* 42, 713-719.

- 1041 Mavituna, F., Luti, K.J.K., Gu, L., 2016. In Search of the *E. coli* Compounds that Change the  
1042 Antibiotic Production Pattern of *Streptomyces coelicolor* During Inter-species Interaction. *Enz.*  
1043 *Microbiol. Technol.* 90, 45-52.
- 1044 Meng, L.-H., Liu, Y., Li, X.-M., Xu, G.-M., Ji, N.-Y., Wang, B.-G., 2015. Citrifelins A and B,  
1045 Citrinin Adducts with a Tetracyclic Framework from Cocultures of Marine-Derived Isolates of  
1046 *Penicillium citrinum* and *Beauveria felina*. *J. Nat. Prod.* 78(9), 2301-2305.
- 1047 Minerdi, D., Bossi, S., Gullino, M.L., Garibaldi, A., 2009. Volatile organic compounds: a  
1048 potential direct long-distance mechanism for antagonistic action of *Fusarium oxysporum* strain  
1049 MSA 35. *Environ. Microbiol.* 11(4), 844-854.
- 1050 Moree, W.J., Phelan, V.V., Wu, C.-H., Bandeira, N., Cornett, D.S., Duggan, B.M., Dorrestein,  
1051 P.C., 2012. Interkingdom metabolic transformations captured by microbial imaging mass  
1052 spectrometry. *Proc. Natl. Acad. Sci. U. S. A.* 109(34), 13811-13816.
- 1053 Moree, W.J., Yang, J.Y., Zhao, X., Liu, W.-T., Aparicio, M., Atencio, L., Ballesteros, J.,  
1054 Sánchez, J., Gavilán, R.G., Gutiérrez, M., Dorrestein, P.C., 2013. Imaging mass spectrometry of  
1055 a coral microbe interaction with fungi. *J. Chem. Ecol.* 39(7), 1045-1054.
- 1056 Moussa, M., Ebrahim, W., Bonus, M., Gohlke, H., Mándi, A., Kurtán, T., Hartmann, R.,  
1057 Kalscheuer, R., Lin, W., Liu, Z., Proksch, P., 2019. Co-culture of the fungus *Fusarium tricinctum*  
1058 with *Streptomyces lividans* induces production of cryptic naphthoquinone dimers. *RSC Adv.*  
1059 9(3), 1491-1500.
- 1060 Nai, C., Meyer, V., 2018. From Axenic to Mixed Cultures: Technological Advances  
1061 Accelerating a Paradigm Shift in Microbiology. *Trends Microbiol.* 26(6), 538-554.
- 1062 Netzker, T., Flak, M., Krespach, M.K.C., Stroe, M.C., Weber, J., Schroeckh, V., Brakhage, A.A.,  
1063 2018. Microbial interactions trigger the production of antibiotics. *Curr. Opin. Microbiol.* 45, 117-  
1064 123.
- 1065 Nguyen, P.-A., Strub, C., Lagrée, M., Bertrand-Michel, J., Schorr-Galindo, S., Fontana, A.,  
1066 2019. Study of in vitro interaction between *Fusarium verticillioides* and *Streptomyces* sp. using  
1067 metabolomics. *Folia Microbiol.*, doi: 10.1007/s12223-12019-00725-z.
- 1068 Niu, G., Chater, K.F., Tian, Y., Zhang, J., Tan, H., 2016. Specialised metabolites regulating  
1069 antibiotic biosynthesis in *Streptomyces* spp. *FEMS Microbiol. Rev.* 40(4), 554-573.
- 1070 Nonaka, K., Abe, T., Iwatsuki, M., Mori, M., Yamamoto, T., Shiomi, K., Omura, S., Masuma,  
1071 R., 2011. Enhancement of metabolites productivity of *Penicillium pinophilum* FKI-5653, by co-  
1072 culture with *Trichoderma harzianum* FKI-5655. *J. Antibiot.* 64(12), 769-774.
- 1073 Nonaka, K., Iwatsuki, M., Horiuchi, S., Shiomi, K., Omura, S., Masuma, R., 2015. Induced  
1074 production of BE-31405 by co-culturing of *Talaromyces siamensis* FKA-61 with a variety of  
1075 fungal strains. *J. Antibiot.* 68(9), 573-578.

- 1076 O'Hagan, S., Swainston, N., Handl, J., Kell, D.B., 2015. A 'rule of 0.5' for the metabolite-  
1077 likeness of approved pharmaceutical drugs. *Metabolomics* 11(2), 323-339.
- 1078 Oh, D.-C., Jensen, P.R., Kauffman, C.A., Fenical, W., 2005. Libertellenones A–D: Induction of  
1079 cytotoxic diterpenoid biosynthesis by marine microbial competition. *Bioorg. Med. Chem.*  
1080 13(17), 5267-5273.
- 1081 Oh, D.-C., Kauffman, C.A., Jensen, P.R., Fenical, W., 2007. Induced production of  
1082 emericellamides A and B from the marine-derived fungus *Emericella* sp. in competing co-  
1083 culture. *J. Nat. Prod.* 70(4), 515-520.
- 1084 Ola, A.R.B., Thomy, D., Lai, D., Brötz-Oesterhelt, H., Proksch, P., 2013. Inducing secondary  
1085 metabolite production by the endophytic fungus *Fusarium tricinctum* through coculture with  
1086 *Bacillus subtilis*. *J. Nat. Prod.* 76(11), 2094-2099.
- 1087 Onaka, H., Mori, Y., Igarashi, Y., Furumai, T., 2011. Mycolic acid-containing bacteria induce  
1088 natural-product biosynthesis in *Streptomyces* species. *Appl. Environ. Microbiol.* 77(2), 400-406.
- 1089 Oppong-Danquah, E., Parrot, D., Blümel, M., Labes, A., Tasdemir, D., 2018. Molecular  
1090 Networking-Based Metabolome and Bioactivity Analyses of Marine-Adapted Fungi Co-  
1091 Cultivated with Phytopathogens. *Front. Microbiol.* 9, 2072.
- 1092 Ory, L., Nazih, E.-H., Daoud, S., Mocquard, J., Bourjot, M., Margueritte, L., Delsuc, M.-A.,  
1093 Bard, J.-M., Pouchus, Y.F., Bertrand, S., Roullier, C., 2019. Targeting bioactive compounds in  
1094 natural extracts - Development of a comprehensive workflow combining chemical and biological  
1095 data. *Anal. Chim. Acta* 1070, 29-42.
- 1096 Park, H.B., Kwon, H.C., Lee, C.-H., Yang, H.O., 2009. Glionitrin A, an Antibiotic-Antitumor  
1097 Metabolite Derived from Competitive Interaction between Abandoned Mine Microbes. *J. Nat.*  
1098 *Prod.* 72(2), 248-252.
- 1099 Park, H.B., Park, J.-S., Lee, S.I., Shin, B., Oh, D.-C., Kwon, H.C., 2017. Gordonic Acid, a  
1100 Polyketide Glycoside Derived from Bacterial Coculture of *Streptomyces* and *Gordonia* Species.  
1101 *J. Nat. Prod.* 80(9), 2542-2546.
- 1102 Pettit, R.K., 2011. Small-molecule elicitation of microbial secondary metabolites. *Microb.*  
1103 *Biotechnol.* 4(4), 471-478.
- 1104 Ponomarova, O., Patil, K.R., 2015. Metabolic interactions in microbial communities: untangling  
1105 the Gordian knot. *Curr. Opin. Microbiol.* 27, 37-44.
- 1106 Rateb, M.E., Hallyburton, I., Houssen, W., Bull, A., Goodfellow, M., Santhanam, R., Jaspars,  
1107 M., Ebel, R., 2013. Induction of diverse secondary metabolites in *Aspergillus fumigatus* by  
1108 microbial co-culture. *RSC Adv.* 3(34), 14444-14450.
- 1109 Roell, G.W., Zha, J., Carr, R.R., Koffas, M.A., Fong, S.S., Tang, Y.J., 2019. Engineering  
1110 microbial consortia by division of labor. *Microb. Cell. Fact.* 18(1), 35.

- 1111 Ross, C., Opel, V., Scherlach, K., Hertweck, C., 2014. Biosynthesis of antifungal and  
1112 antibacterial polyketides by *Burkholderia gladioli* in coculture with *Rhizopus microsporus*.  
1113 *Mycoses* 57(Suppl. 3), 48-55.
- 1114 Roullier, C., Bertrand, S., Blanchet, E., Peigné, M., Robiou du Pont, T., Guitton, Y., Pouchus,  
1115 Y.F., Grovel, O., 2016. Time dependency of biosynthetic pathways and chemodiversity: an LC-  
1116 MS metabolomic study of marine-sourced *Penicillium* *Mar. Drugs* 14(5), 103.
- 1117 Schäberle, T.F., Orland, A., König, G.M., 2013. Enhanced production of undecylprodigiosin in  
1118 *Streptomyces coelicolor* by co-cultivation with the corallopyronin A-producing myxobacterium,  
1119 *Coralloccoccus coralloides*. *Biotechnol. Lett.* 36(3), 641-648.
- 1120 Schroeckh, V., Scherlach, K., Nützmann, H.-W., Shelest, E., Schmidt-Heck, W., Schuemann, J.,  
1121 Martin, K., Hertweck, C., Brakhage, A.A., 2009. Intimate bacterial-fungal interaction triggers  
1122 biosynthesis of archetypal polyketides in *Aspergillus nidulans*. *Proc. Natl. Acad. Sci. U. S. A.*  
1123 106(34), 14558-14563.
- 1124 Shang, Z., Salim, A.A., Capon, R.J., 2017. Chaunopyran A: Co-Cultivation of Marine Mollusk-  
1125 Derived Fungi Activates a Rare Class of 2-Alkenyl-Tetrahydropyran. *J. Nat. Prod.* 80(4), 1167-  
1126 1172.
- 1127 Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., Amin, N.,  
1128 Schwikowski, B., Ideker, T., 2003. Cytoscape: A Software Environment for Integrated Models  
1129 of Biomolecular Interaction Networks. *Genome Res.* 13(11), 2498-2504.
- 1130 Shen, X.-T., Mo, X.-H., Zhu, L.-P., Tan, L.-L., Du, F.-Y., Wang, Q.-W., Zhou, Y.-M., Yuan, X.-  
1131 J., Qiao, B., Yang, S., 2019. Unusual and highly bioactive sesterterpenes synthesized by  
1132 *Pleurotus ostreatus* during the co-culture with *Trametes robiniophila* *Murr.* *Appl. Environ.*  
1133 *Microbiol.* 85(14), AEM.00293-00219.
- 1134 Shin, D., Byun, W.S., Moon, K., Kwon, Y., Bae, M., Um, S., Lee, S.K., Oh, D.-C., 2018.  
1135 Coculture of Marine *Streptomyces* sp. With *Bacillus* sp. Produces a New Piperazic Acid-Bearing  
1136 Cyclic Peptide. *Front. Chem.* 6, 498.
- 1137 Soliman, S.S.M., Raizada, M.N., 2013. Interactions between co-habiting fungi elicit synthesis  
1138 of Taxol from an endophytic fungus in host *Taxus* plants. *Front. Microbiol.* 4, 3.
- 1139 Sonnenbichler, J., Bliestle, I.M., Peipp, H., Holdenrieder, O., 1989. Secondary fungal  
1140 metabolites and their biological activities, I. Isolation of antibiotic compounds from cultures of  
1141 *Heterobasidion annosum* synthesized in the presence of antagonistic fungi or host plant cells.  
1142 *Biol. Chem. Hoppe Seyler* 370(2), 1295-1304.
- 1143 Sonnenbichler, J., Dietrich, J., Peipp, H., 1994. Secondary fungal metabolites and their biological  
1144 activities, V. Investigations concerning the induction of the biosynthesis of toxic secondary  
1145 metabolites in basidiomycetes. *Biol. Chem. Hoppe Seyler* 375(1), 71-79.

- 1146 Spraker, J.E., Wiemann, P., Baccile, J.A., Venkatesh, N., Schumacher, J., Schroeder, F.C.,  
1147 Sanchez, L.M., Keller, N.P., 2018. Conserved Responses in a War of Small Molecules between a  
1148 Plant-Pathogenic Bacterium and Fungi. *mBio* 9(3), e00820-00818.
- 1149 Stephens, K., Pozo, M., Tsao, C.-Y., Hauk, P., Bentley, W.E., 2019. Bacterial co-culture with  
1150 cell signaling translator and growth controller modules for autonomously regulated culture  
1151 composition. *Nat. Com.* 10(1), 4129.
- 1152 Stierle, A.A., Stierle, D.B., Decato, D., Priestley, N.D., Alverson, J.B., Hoody, J., McGrath, K.,  
1153 Klepacki, D., 2017. The Berkeleylactones, Antibiotic Macrolides from Fungal Coculture. *J. Nat.*  
1154 *Prod.* 80(4), 1150-1160.
- 1155 Sumner, L.W., Mendes, P., Dixon, R.A., 2003. Plant metabolomics: large-scale phytochemistry  
1156 in the functional genomics era. *Phytochemistry* 62(6), 817-836.
- 1157 Ta, C.A., Arnason, J.T., 2015. Mini Review of Phytochemicals and Plant Taxa with Activity as  
1158 Microbial Biofilm and Quorum Sensing Inhibitors. *Molecules* 21(1), E29.
- 1159 Tan, Z.Q., Leow, H.Y., Lee, D.C.W., Karisnan, K., Song, A.A.L., Mai, C.W., Yap, W.S., Lim,  
1160 S.H.E., Lai, K.S., 2019. Co-Culture Systems for the Production of Secondary Metabolites:  
1161 Current and Future Prospects. *Open Biotechnol. J.* 13(1), 18-26.
- 1162 Tasdemir, D., 2017. Marine fungi in the spotlight: opportunities and challenges for marine fungal  
1163 natural product discovery and biotechnology. *Fungal Biol. Biotechnol.* 4(1), 5.
- 1164 Tata, A., Perez, C., Campos, M.L., Bayfield, M.A., Eberlin, M.N., Ifa, D.R., 2015. Imprint  
1165 Desorption Electrospray Ionization Mass Spectrometry Imaging for Monitoring Secondary  
1166 Metabolites Production during Antagonistic Interaction of Fungi. *Anal. Chem.* 87(24), 12298-  
1167 12305.
- 1168 Tokimoto, K., Fujita, T., Takeda, Y., Takaishi, Y., 1987. Increased or Induced Formation of  
1169 Antifungal Substances in Cultures of *Lentinus edodes* by the Attack of *Trichoderma* spp. *Proc.*  
1170 *Japan Acad. Ser. B* 63(7), 277-280.
- 1171 Torres-Monroy, I., Ullrich, M.S., 2018. Identification of bacterial genes expressed during  
1172 diatom-bacteria interactions using an *in vivo* expression technology approach. *Front. Mar. Sci.* 5,  
1173 200.
- 1174 Traxler, M.F., Watrous, J.D., Alexandrov, T., Dorrestein, P.C., Kolter, R., 2013. Interspecies  
1175 Interactions Stimulate Diversification of the *Streptomyces coelicolor* Secreted Metabolome.  
1176 *mBio* 4(4), e00459-00413
- 1177 Tshikantwa, T.S., Ullah, M.W., He, F., Yang, G., 2018. Current Trends and Potential  
1178 Applications of Microbial Interactions for Human Welfare. *Front. Microbiol.* 9, 1156-1156.
- 1179 Vallet, M., Vanbellingen, Q.P., Fu, T., Le Caer, J.-P., Della-Negra, S., Touboul, D., Duncan,  
1180 K.R., Nay, B., Brunelle, A., Prado, S., 2017. An Integrative Approach to Decipher the Chemical



- 1181 Antagonism between the Competing Endophytes *Paraconiothyrium variable* and *Bacillus*  
1182 *subtilis*. J. Nat. Prod. 80(11), 2863-2873.
- 1183 van Herk, K., Aptroot, A., 2007. The Sorediate *Punctelia* Species With lecanoric Acid in Europe.  
1184 The Lichenologist 32(3), 233-246.
- 1185 Wang, B., Tao, Y., Liu, Q., Liu, N., Jin, Z., Xu, X., 2017. Algicidal Activity of Bacillamide  
1186 Alkaloids and Their Analogues against Marine and Freshwater Harmful Algae. Mar. Drugs  
1187 15(8), 247.
- 1188 Wang, J.-p., Lin, W., Wray, V., Lai, D., Proksch, P., 2013. Induced Production of Depsipeptides  
1189 by Co-Culturing *Fusarium tricinctum* and *Fusarium begoniae*. Tetrahedron Lett. 54(20), 2492-  
1190 2496.
- 1191 Wang, J., Bertrand, S., 2019. PocheRmon (Projected Orthogonalized CHEMical Encounter  
1192 MONitoring) for mixed metabolome analysis (R function). [https://gitlab.univ-nantes.fr/bertrand-](https://gitlab.univ-nantes.fr/bertrand-s-1/pochermon)  
1193 [s-1/pochermon](https://gitlab.univ-nantes.fr/bertrand-s-1/pochermon).
- 1194 Wang, J., Ding, W., Li, C., Huang, S., She, Z., Lin, Y., 2013. A New Polysubstituted  
1195 Benzaldehyde from the co-culture broth of Two Marine Fungi (Strains Nos. E33 and K38).  
1196 Chem. Nat. Compd. 49(5), 799-802.
- 1197 Wang, J., Huang, S., Li, C., Ding, W., She, Z., Li, C., 2015. A New Coumarin Produced by  
1198 Mixed Fermentation of Two Marine Fungi. Chem. Nat. Compd. 51(2), 239-241.
- 1199 Wang, M., Carver, J.J., Phelan, V.V., Sanchez, L.M., Garg, N., Peng, Y., Nguyen, D.D.,  
1200 Watrous, J., Kapon, C.A., Luzzatto-Knaan, T., Porto, C., Bouslimani, A., Melnik, A.V.,  
1201 Meehan, M.J., Liu, W.-T., Crusemann, M., Boudreau, P.D., Esquenazi, E., Sandoval-Calderon,  
1202 M., Kersten, R.D., Pace, L.A., Quinn, R.A., Duncan, K.R., Hsu, C.-C., Floros, D.J., Gavilan,  
1203 R.G., Kleigrew, K., Northen, T., Dutton, R.J., Parrot, D., Carlson, E.E., Aigle, B., Michelsen,  
1204 C.F., Jelsbak, L., Sohlenkamp, C., Pevzner, P., Edlund, A., McLean, J., Piel, J., Murphy, B.T.,  
1205 Gerwick, L., Liaw, C.-C., Yang, Y.-L., Humpf, H.-U., Maansson, M., Keyzers, R.A., Sims, A.C.,  
1206 Johnson, A.R., Sidebottom, A.M., Sedio, B.E., Klitgaard, A., Larson, C.B., Boya P, C.A.,  
1207 Torres-Mendoza, D., Gonzalez, D.J., Silva, D.B., Marques, L.M., Demarque, D.P., Pociute, E.,  
1208 O'Neill, E.C., Briand, E., Helfrich, E.J.N., Granatosky, E.A., Glukhov, E., Ryffel, F., Houson,  
1209 H., Mohimani, H., Kharbush, J.J., Zeng, Y., Vorholt, J.A., Kurita, K.L., Charusanti, P., McPhail,  
1210 K.L., Nielsen, K.F., Vuong, L., Elfeki, M., Traxler, M.F., Engene, N., Koyama, N., Vining, O.B.,  
1211 Baric, R., Silva, R.R., Mascuch, S.J., Tomasi, S., Jenkins, S., Macherla, V., Hoffman, T.,  
1212 Agarwal, V., Williams, P.G., Dai, J., Neupane, R., Gurr, J., Rodriguez, A.M.C., Lamsa, A.,  
1213 Zhang, C., Dorrestein, K., Duggan, B.M., Almaliti, J., Allard, P.-M., Phapale, P., Nothias, L.-F.,  
1214 Alexandrov, T., Litaudon, M., Wolfender, J.-L., Kyle, J.E., Metz, T.O., Peryea, T., Nguyen, D.-  
1215 T., VanLeer, D., Shinn, P., Jadhav, A., Muller, R., Waters, K.M., Shi, W., Liu, X., Zhang, L.,  
1216 Knight, R., Jensen, P.R., Palsson, B.O., Pogliano, K., Lington, R.G., Gutierrez, M., Lopes,  
1217 N.P., Gerwick, W.H., Moore, B.S., Dorrestein, P.C., Bandeira, N., 2016. Sharing and community  
1218 curation of mass spectrometry data with Global Natural Products Social Molecular Networking.  
1219 Nat. Biotechnol. 34(8), 828-837, URL: <https://gnps.ucsd.edu/>.

- 1220 Wang, R., Zhao, S., Wang, Z., Koffas, M.A.G., 2020. Recent advances in modular co-culture  
1221 engineering for synthesis of natural products. *Curr. Opin. Biotechnol.* 62, 65-71.
- 1222 Wang, Y., Wang, L., Zhuang, Y., Kong, F., Zhang, C., Zhu, W., 2014. Phenolic Polyketides  
1223 from the Co-Cultivation of Marine-Derived *Penicillium* sp. WC-29-5 and *Streptomyces fradiae*  
1224 007. *Mar. Drugs* 12(4), 2079-2088.
- 1225 Wasternack, C., Feussner, I., 2018. The Oxylin Pathways: Biochemistry and Function. *Annu.*  
1226 *Rev. Plant Biol.* 69(1), 363-386.
- 1227 Whitt, J., Shipley, S.M., Newman, D.J., Zuck, K.M., 2014. Tetramic Acid Analogues Produced  
1228 by Coculture of *Saccharopolyspora erythraea* with *Fusarium pallidoroseum*. *J. Nat. Prod.* 77(1),  
1229 173-177.
- 1230 Williams, R.B., Henrikson, J.C., Hoover, A.R., Lee, A.E., Cichewicz, R.H., 2008. Epigenetic  
1231 remodeling of the fungal secondary metabolome. *Org. Biomol. Chem.* 6(11), 1895-1897.
- 1232 Williamson, N.R., Fineran, P.C., Leeper, F.J., Salmond, G.P.C., 2006. The biosynthesis and  
1233 regulation of bacterial prodiginines. *Nat. Rev. Microbiol.* 4(12), 887-899.
- 1234 Wolfender, J.-L., Marti, G., Thomas, A., Bertrand, S., 2015. Current approaches and challenges  
1235 for the metabolite profiling of complex natural extracts. *J. Chromatogr. A* 1382, 136–164.
- 1236 Wolfender, J.-L., Nuzillard, J.-M., van der Hooft, J.J.J., Renault, J.-H., Bertrand, S., 2019.  
1237 Accelerating metabolite identification in natural product research: toward an ideal combination  
1238 of LC-HRMS/MS and NMR profiling, *in silico* databases and chemometrics. *Anal. Chem.* 91(1),  
1239 704-742.
- 1240 Wrede, D., Taha, M., Miranda, A.F., Kadali, K., Stevenson, T., Ball, A.S., Mouradov, A., 2014.  
1241 Co-Cultivation of Fungal and Microalgal Cells as an Efficient System for Harvesting Microalgal  
1242 Cells, Lipid Production and Wastewater Treatment. *PLoS One* 9(11), e113497.
- 1243 Wu, C., Zacchetti, B., Ram, A.F.J., van Wezel, G.P., Claessen, D., Hae Choi, Y., 2015.  
1244 Expanding the chemical space for natural products by *Aspergillus-Streptomyces* co-cultivation  
1245 and biotransformation. *Sci. Rep.* 5, 10868.
- 1246 Xu, X.-Y., Shen, X.-T., Yuan, X.-J., Zhou, Y.-M., Fan, H., Zhu, L.-P., Du, F.-Y., Sadilek, M.,  
1247 Yang, J., Qiao, B., Yang, S., 2018. Metabolomics Investigation of an Association of Induced  
1248 Features and Corresponding Fungus during the Co-culture of *Trametes versicolor* and  
1249 *Ganoderma applanatum*. *Front. Microbiol.* 8, 2647.
- 1250 Yang, S.-Q., Li, X.-M., Li, X., Li, H.-L., Meng, L.-H., Wang, B.-G., 2018. New citrinin  
1251 analogues produced by coculture of the marine algal-derived endophytic fungal strains  
1252 *Aspergillus sydowii* EN-534 and *Penicillium citrinum* EN-535. *Phytochem. Lett.* 25, 191-195.
- 1253 Yu, G., Sun, Z., Peng, J., Zhu, M., Che, Q., Zhang, G., Zhu, T., Gu, Q., Li, D., 2019. Secondary  
1254 Metabolites Produced by Combined Culture of *Penicillium crustosum* and a *Xylaria* sp. *J. Nat.*  
1255 *Prod.* 82(7), 2013-2017.

- 1256 Yu, L., Ding, W., Ma, Z., 2016. Induced production of cytochalasans in co-culture of marine  
1257 fungus *Aspergillus flavipes* and actinomycete *Streptomyces* sp. Nat. Prod. Res. 30(15), 1718-  
1258 1723.
- 1259 Yu, L., Hu, Z., Ma, Z., 2015. Production of bioactive tryptamine derivatives by co-culture of  
1260 marine *Streptomyces* with *Bacillus mycoides*. Nat. Prod. Res. 29(22), 2087-2091.
- 1261 Yu, M., Li, Y., Banakar, S.P., Liu, L., Shao, C., Li, Z., Wang, C., 2019. New Metabolites From  
1262 the Co-culture of Marine-Derived Actinomycete *Streptomyces rochei* MB037 and Fungus  
1263 *Rhinocladiella similis* 35. Front. Microbiol. 10, 915.
- 1264 Zarei, M., Ghahfarokhi, M.E., Fazlara, A., Bahrami, S., 2019. Effect of bacterial growth phase  
1265 and co-culture conditions on the interaction of *Acanthamoeba castellanii* with *Shigella*  
1266 *dysenteriae*, *Shigella flexneri* and *Shigella sonnei*. J. Basic Microbiol. 59(7), 735-743.
- 1267 Zhang, B., Tian, W., Wang, S., Yan, X., Jia, X., Pierens, G.K., Chen, W., Ma, H., Deng, Z., Qu,  
1268 X., 2017. Activation of Natural Products Biosynthetic Pathways via a Protein Modification Level  
1269 Regulation. ACS Chem. Biol. 12(7), 1732-1736.
- 1270 Zhang, C., Straight, P.D., 2019. Antibiotic discovery through microbial interactions. Curr. Opin.  
1271 Microbiol. 51, 64-71.
- 1272 Zhang, L., Niaz, S., Khan, D., Wang, Z., Zhu, Y., Zhou, H., Lin, Y., Li, J., Liu, L., 2017.  
1273 Induction of Diverse Bioactive Secondary Metabolites from the Mangrove Endophytic Fungus  
1274 *Trichoderma* sp. (Strain 307) by Co-Cultivation with *Acinetobacter johnsonii* (Strain B2). Mar.  
1275 Drugs 15(2), 35.
- 1276 Zhang, W., Liu, Z., Li, S., Yang, T., Zhang, Q., Ma, L., Tian, X., Zhang, H., Huang, C., Zhang,  
1277 S., 2012. Spiroindimicins A–D: New bisindole alkaloids from a deep-sea-derived actinomycete.  
1278 Org. Lett. 14(13), 3364-3367.
- 1279 Zhang, Z.-X., Yang, X.-Q., Zhou, Q.-Y., Wang, B.-Y., Hu, M., Yang, Y.-B., Zhou, H., Ding, Z.-  
1280 T., 2018. New Azaphilones from *Nigrospora oryzae* Co-Cultured with *Beauveria bassiana*.  
1281 Molecules 23(7), 1816.
- 1282 Zhang, Z., He, X., Zhang, G., Che, Q., Zhu, T., Gu, Q., Li, D., 2017. Inducing Secondary  
1283 Metabolite Production by Combined Culture of *Talaromyces aculeatus* and *Penicillium*  
1284 *variabile*. J. Nat. Prod. 80(12), 3167-3171.
- 1285 Zhou, Q.-Y., Yang, X.-Q., Zhang, Z.-X., Wang, B.-Y., Hu, M., Yang, Y.-B., Zhou, H., Ding, Z.-  
1286 T., 2018. New azaphilones and tremulane sesquiterpene from endophytic *Nigrospora oryzae*  
1287 cocultured with *Irpex lacteus*. Fitoterapia 130, 26-30.
- 1288 Zhu, F., Chen, G., Chen, X., Huang, M., Wan, X., 2011. Aspergicin, a new antibacterial alkaloid  
1289 produced by mixed fermentation of two marine-derived mangrove epiphytic fungi. Chem. Nat.  
1290 Compd. 47(5), 767-769.

1291 Zhu, F., Lin, Y., 2006. Marinamide, a novel alkaloid and its methyl ester produced by the  
1292 application of mixed fermentation technique to two mangrove endophytic fungi from the South  
1293 China Sea. Chinese Sci. Bull. 51(12), 1426-1430.

1294

1295

## 1296 **Figure Legends**

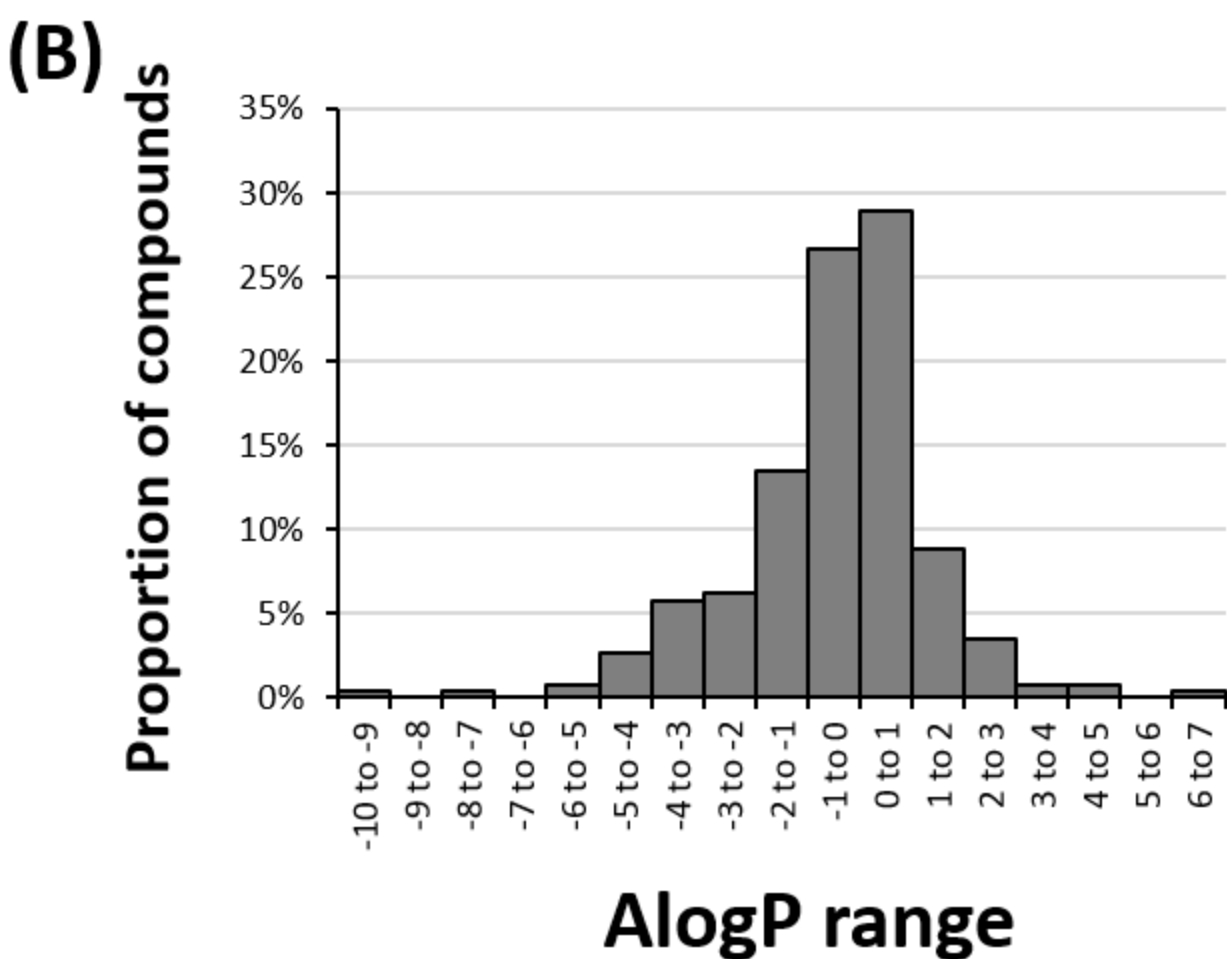
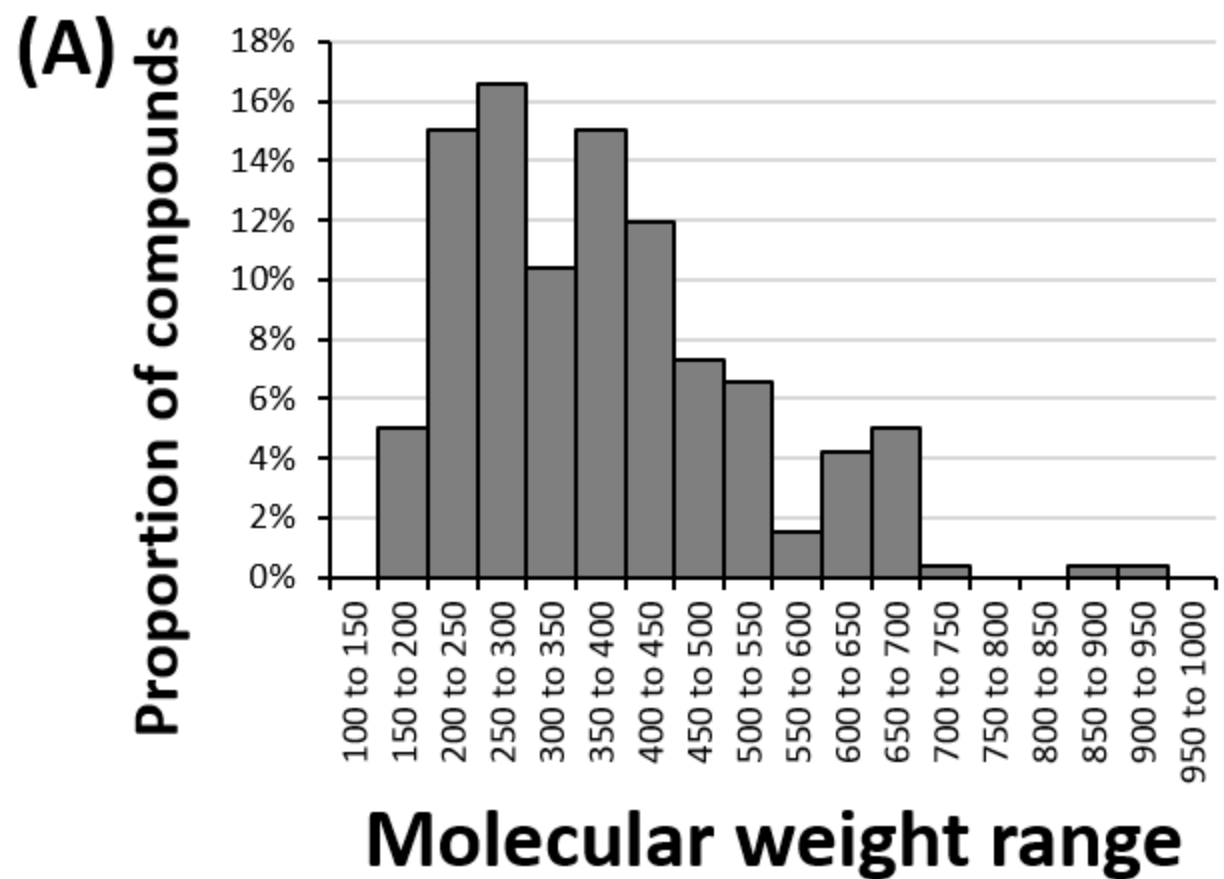
1297 **Figure 1.** Distribution of molecular weight (**A**) and lipophilicity (AlogP) (**B**) calculated  
1298 using Cytoscape (Shannon et al., 2003) and the ChemViz2 plugin  
1299 (<http://www.rbvi.ucsf.edu/cytoscape/chemViz2/>).

1300 **Figure 2.** Structural similarity network of structures reported to be induced during  
1301 microbial co-culture based on Tanimoto Index. Solid line edges correspond to Tanimoto Index  
1302 higher or equal to 0.7 (the line width indicates how similar the structures are – larger width  
1303 indicates more structural similarity); dash line edges indicated a forced link in the case of lonely  
1304 structures. The network is available in Cytoscape file format as supplementary information for in  
1305 depth exploration ([https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-culture-](https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-culture-induced-compounds)  
1306 [induced-compounds](https://gitlab.univ-nantes.fr/bertrand-s-1/structural-network-of-co-culture-induced-compounds)).

1307 **Figure 3.** Structural similarity network of Cluster 1 using a Tanimoto Index higher or  
1308 equal to 0.8 (the line width indicates how similar the structures are – larger width indicates more  
1309 structural similarity). The network is available in Cytoscape file format as supplementary  
1310 information for in depth exploration.

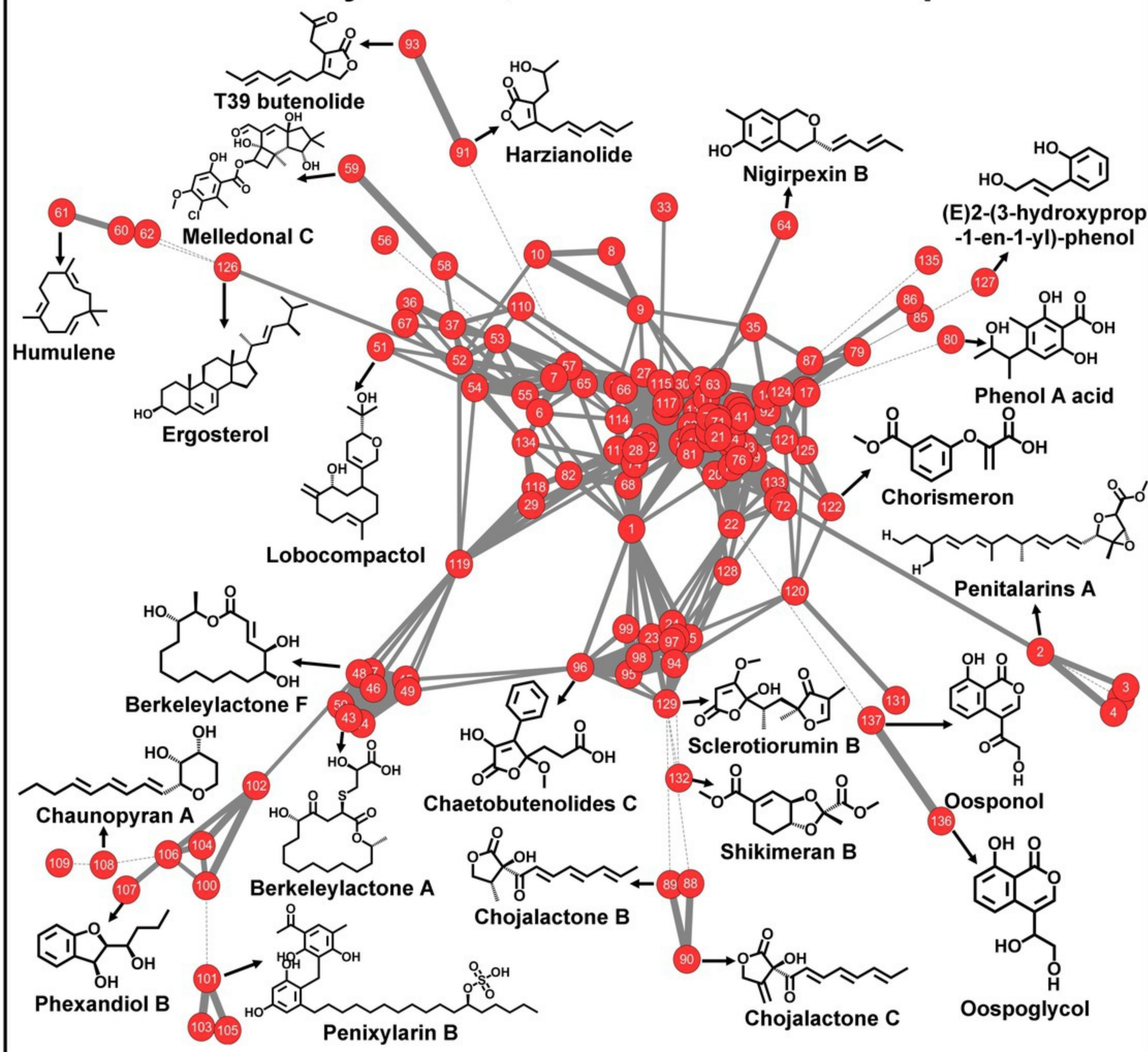
1311 **Figure 4.** Distribution of co-culture microbial couples used in reported experiments.

1312 **Figure 5.** Distribution of relevant biological activity (< 10  $\mu$ M) reported for all co-culture  
1313 induced compounds (complementary information about distribution taking into consideration  
1314 moderate activity are presented in Figure S3).

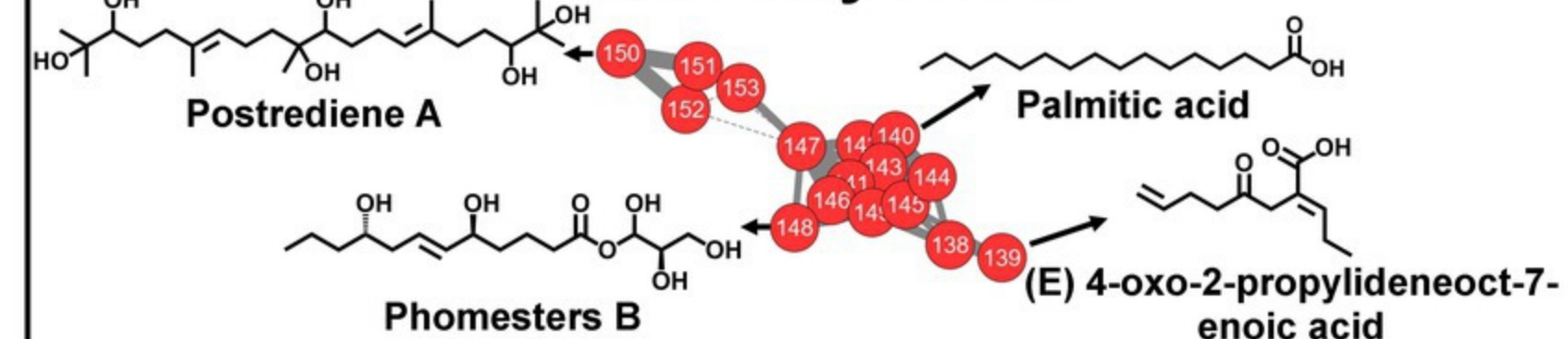




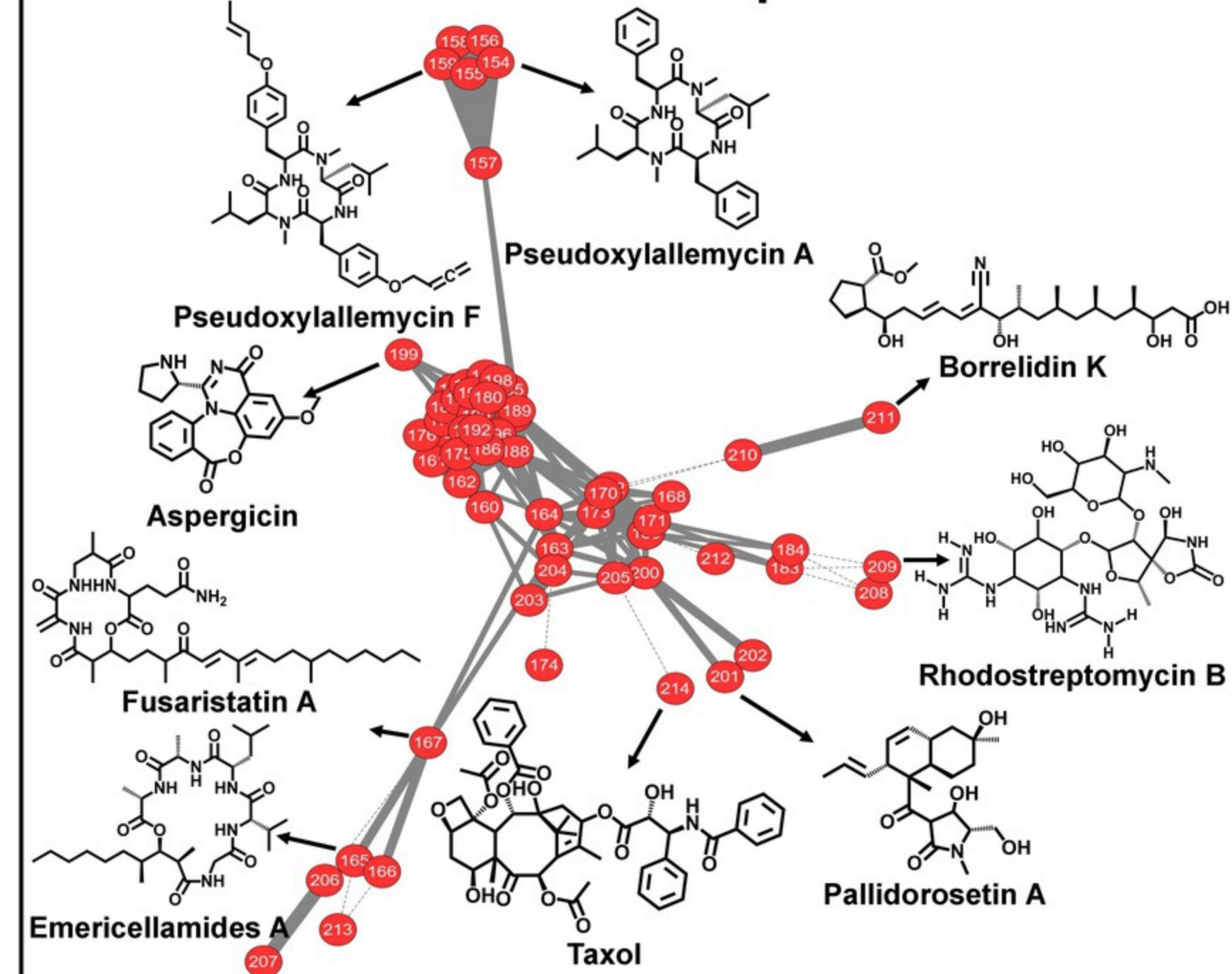
### Cluster 1: Polyketides, Macrolides and Diterpenoids



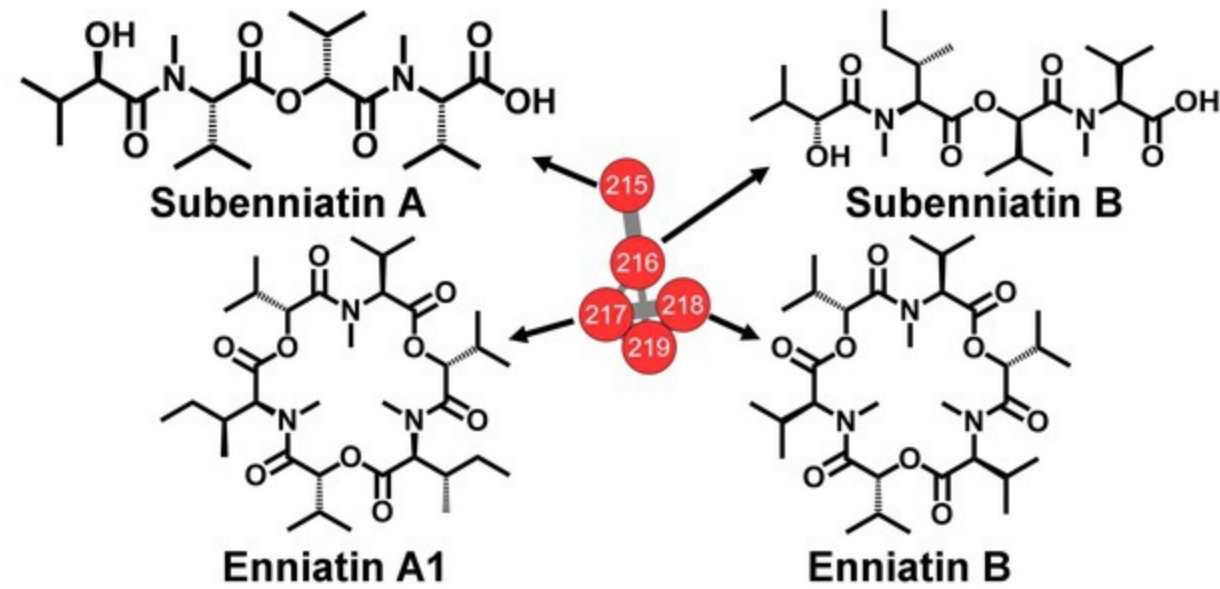
### Cluster 2: Linear Polyketides, Oxylinins and Fatty acids



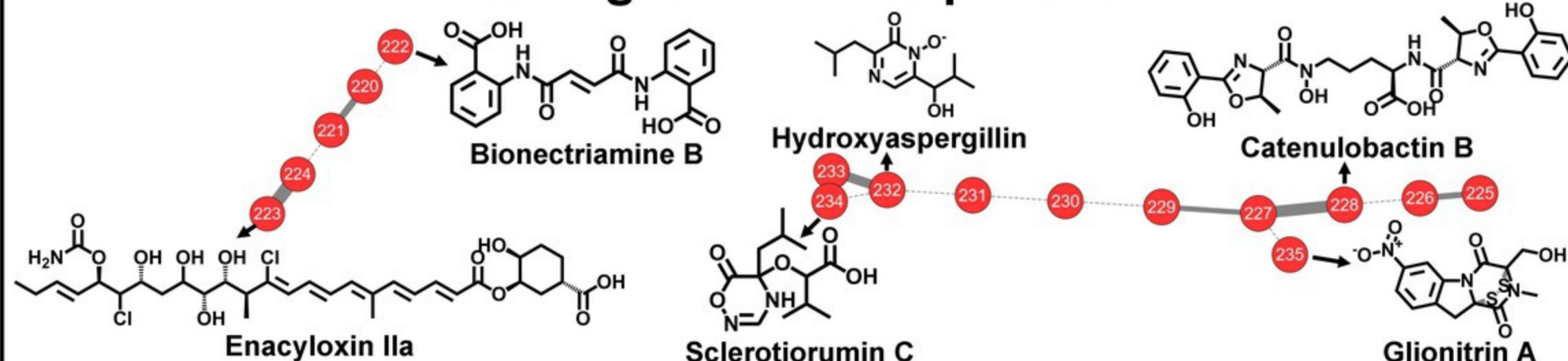
### Cluster 3: Cyclic Peptides, Diketopiperazines and Related Compounds



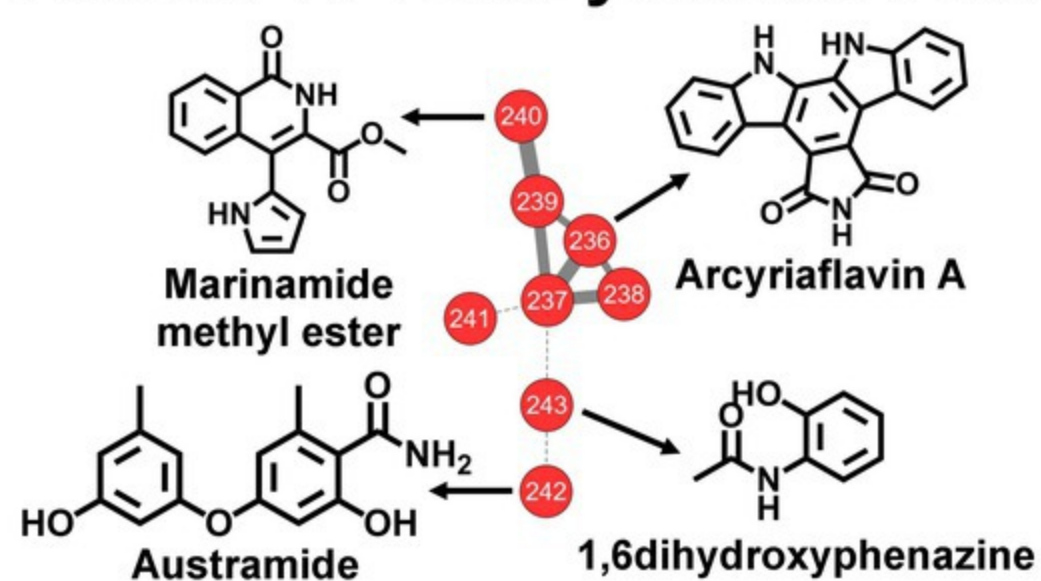
### Cluster 4: Other Non-Ribosomal Peptides



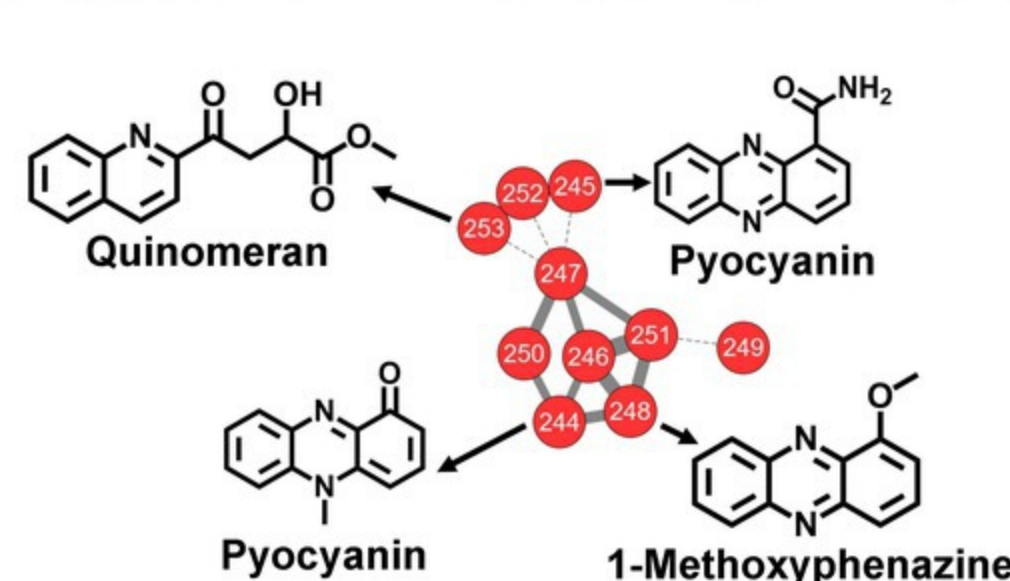
### Cluster 5 and 6: Miscellaneous Non-Alkaloidic Nitrogenated Compounds



### Cluster 7: Benzylamine Alkaloids



### Cluster 8: Phenazine Alkaloids



### Cluster 9: Tryptamine and Pyrrole Alkaloids

