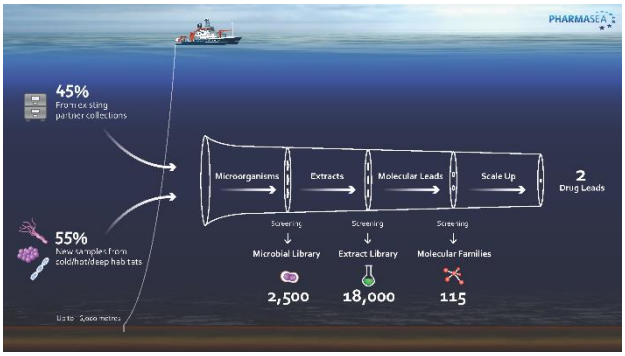
Executive Summary

Objective	Proposed	Achieved
Dereplicated microbial strains	2 500	>13 000
Dereplicated extracts	18 000	>15 000
Biological assays	-	>130 000
Bioactive extracts	540	>600
Molecular families	115	90
Drug leads in animal trials	2	**5**

2.1) The PharmaSea Concept



2.2) Objectives of PharmaSea

As targeted objectives, PharmaSea promised to deliver:

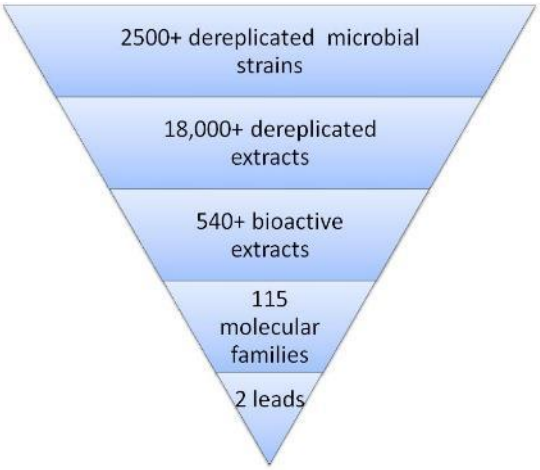


Figure 1 PharmaSea libraries and products.

2.3) Beyond the State of the Art

Table 1 Widening the Bottlenecks in the Marine Biodiscovery Pipeline – the aims of PharmaSea

Bottleneck	**How PharmaSea will solve this**	**Work Package**
Access to bioresources	1) Develop deep sea sampling technology	WP1
	2) Develop legal framework for EU-wide A&BS	WP6
	3) Resolve IP issues inherent in different legal regimes	WP6
	4) Produce best practice guidelines	WP6
Quality of marine resources	1) Habitat selection leading to novel microbial strains	WP1
	2) Selective cultivation leading to novel microbial strains	WP1
	3) Phylogenetic analysis of strains to ensure diversity/quality	WP1
	4) Genome scanning to uncover biosynthetic capacity of strains	WP1
Extract generation	1) Media development to realise biosynthetic capacity of strains	WP2
	2) Stress/elicitation to realise biosynthetic capacity of strains	WP2
	3) Heterologous expression of biosynthetic genes	WP2
	4) Extraction technology/Robotics/Automation	WP2
Extract dereplication	1) Chemometrics for dereplication and prioritisation of extracts	WP2
	2) Innovative high content assays/assay technology	WP3
Isolation & Purification	1) Explorative solid phase extraction to develop isolation protocols	WP4
	2) Targeted chromatography	WP4
Chemical dereplication	1) Liquid chromatography-mass spectrometry	WP4
	2) Novelty screening using NMR techniques	WP4
	3) Datamining using predicted NMR & MS properties	WP4
Structure determination	1) Low volume probes/cryomicroprobes	WP4
	2) Computer aided structure elucidation	WP4
Hit selection	1) Innovative MOA screens (zebrafish) & counterscreens	WP3
	2) Property prediction of compounds for ADMET/PK/PD	WP5
	3) Rapid *in-vivo* evaluation	WP5
Supply issue	1) Use of microbial strains	WP5
	2) Process intensification	WP5
	3) Scale-up in saline media	

	4) Heterologous expression	WP5 WP5
Uptake of technology	1) Data management 2) PatentBox 3) End user panel 4) Inventory of assets/outputs 5) Targeted technology transfer briefs	WP7 WP6/7 WP6/7 WP7 WP7

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3.1.1) A library of marine microorganisms assessed for their ability to produce novel chemistry.

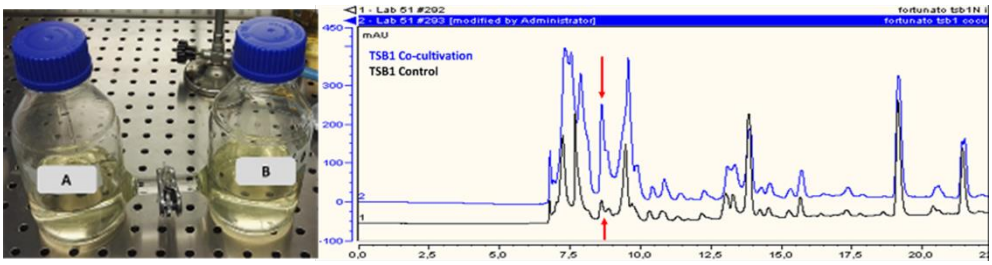

Figure 2. The use of a co-cultivation vessel (left) shows that the LC-MS chromatogram changes from the control culture (right, black trace) and when subjected to challenge by a second strain (right, blue trace) showing the appearance of new, bioactive peaks (red arrow)

3.1.2) Improved methods for extracting, isolating, screening, dereplicating and identifying bioactive molecules.

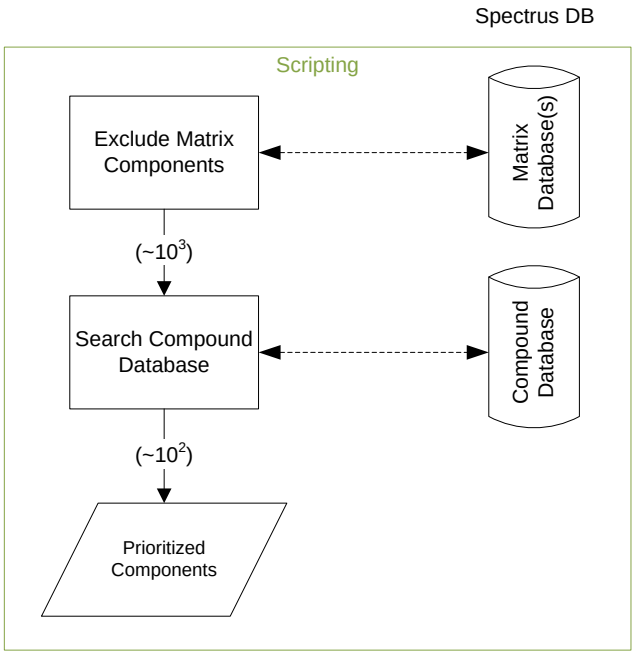

Figure 3. The dereplication workflow developed by ACD/Labs for PharmaSea.

3.1.3) Generate a library of novel chemical entities with high bioactivity in antimicrobial, anti-inflammatory and CNS screens

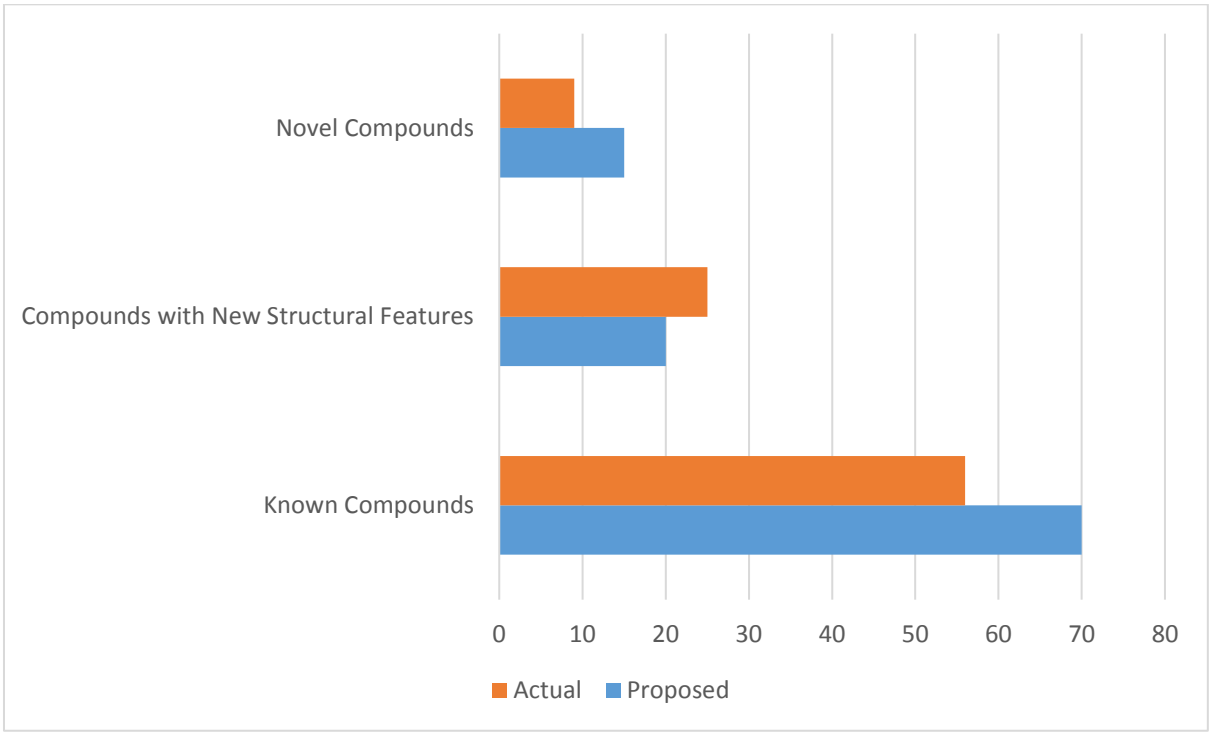

Figure 4. Actual *vs*. proposed numbers of compounds in various categories produced during PharmaSea

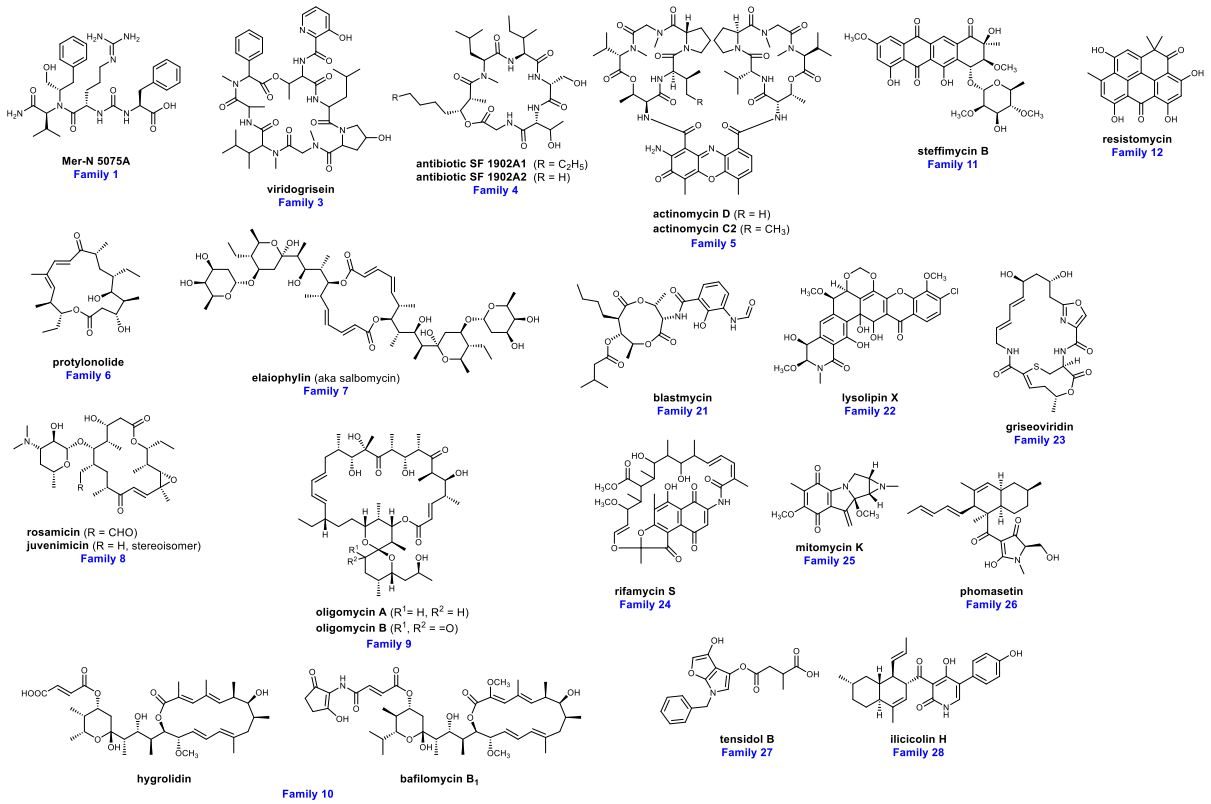

Figure 5. An indication of the chemical diversity of the compounds produced by PharmaSea.

3.1.6) Provide recommendations and solutions to address legal/policy barriers to the access and sustainable use of marine genetic resources.

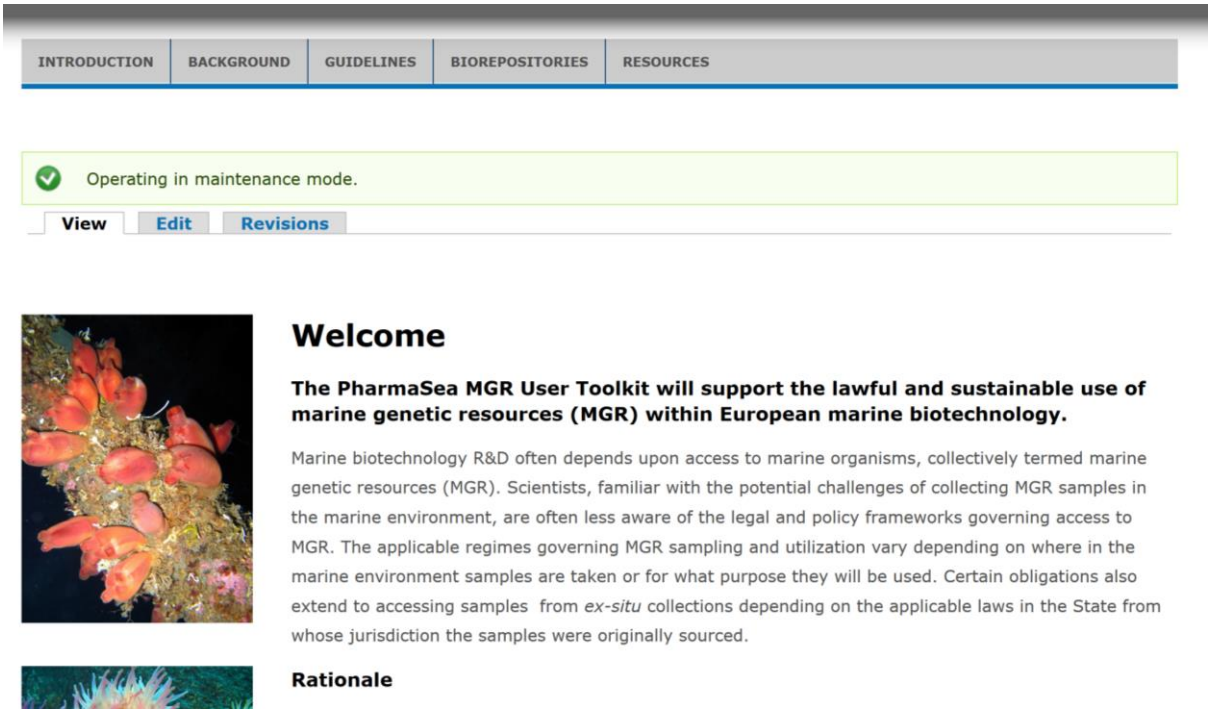

Figure 6. The layout of the PharmaSea web-based toolkit.

3.2.2) Quality of marine resources

Figure 7. A selection of strains isolated during the PharmaSea project

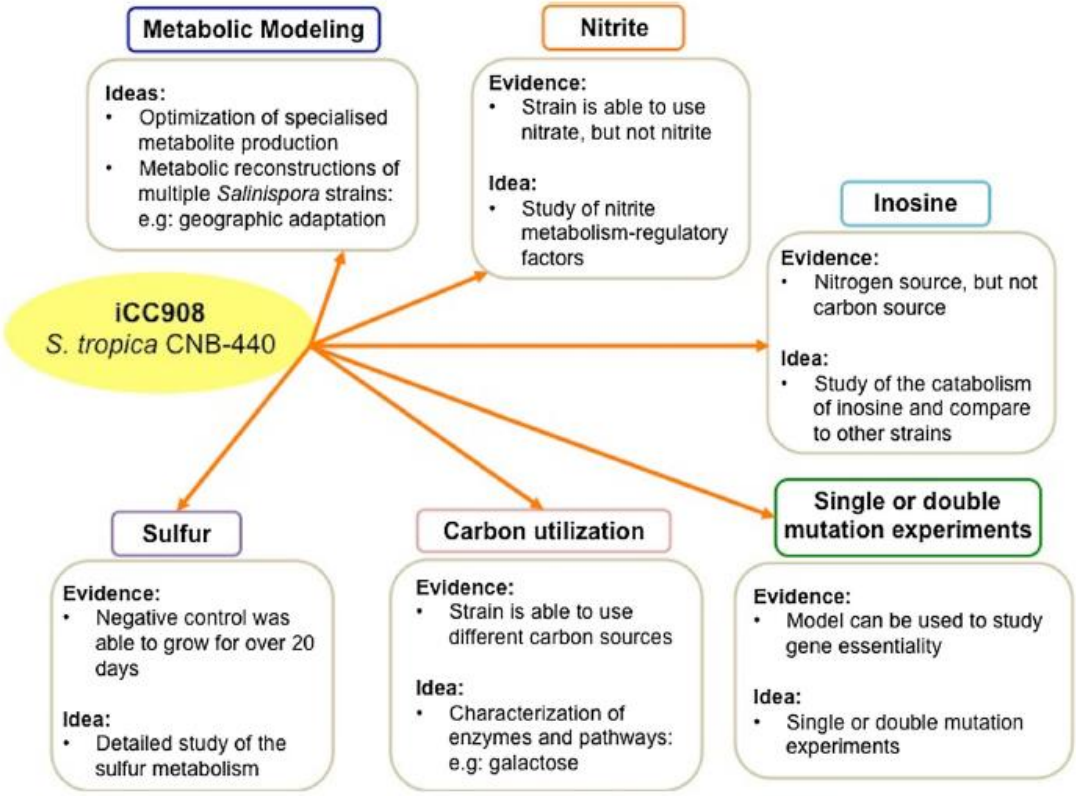

Figure 8. The development of the full genome-scale metabolic model for *Salinispora tropica.*

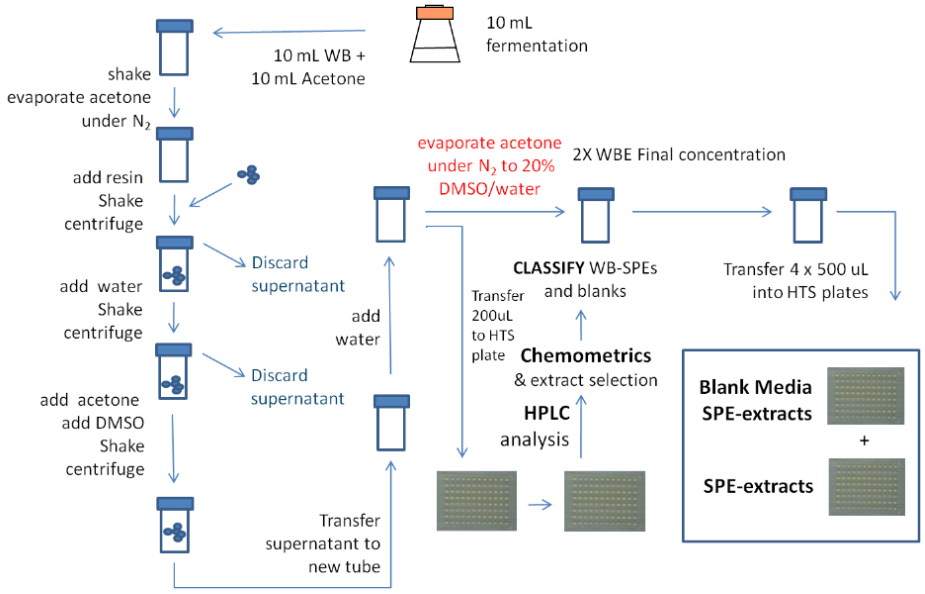

Figure 9. The PharmaSea extraction and sample preparation protocol.

3.2.5) Extract dereplication

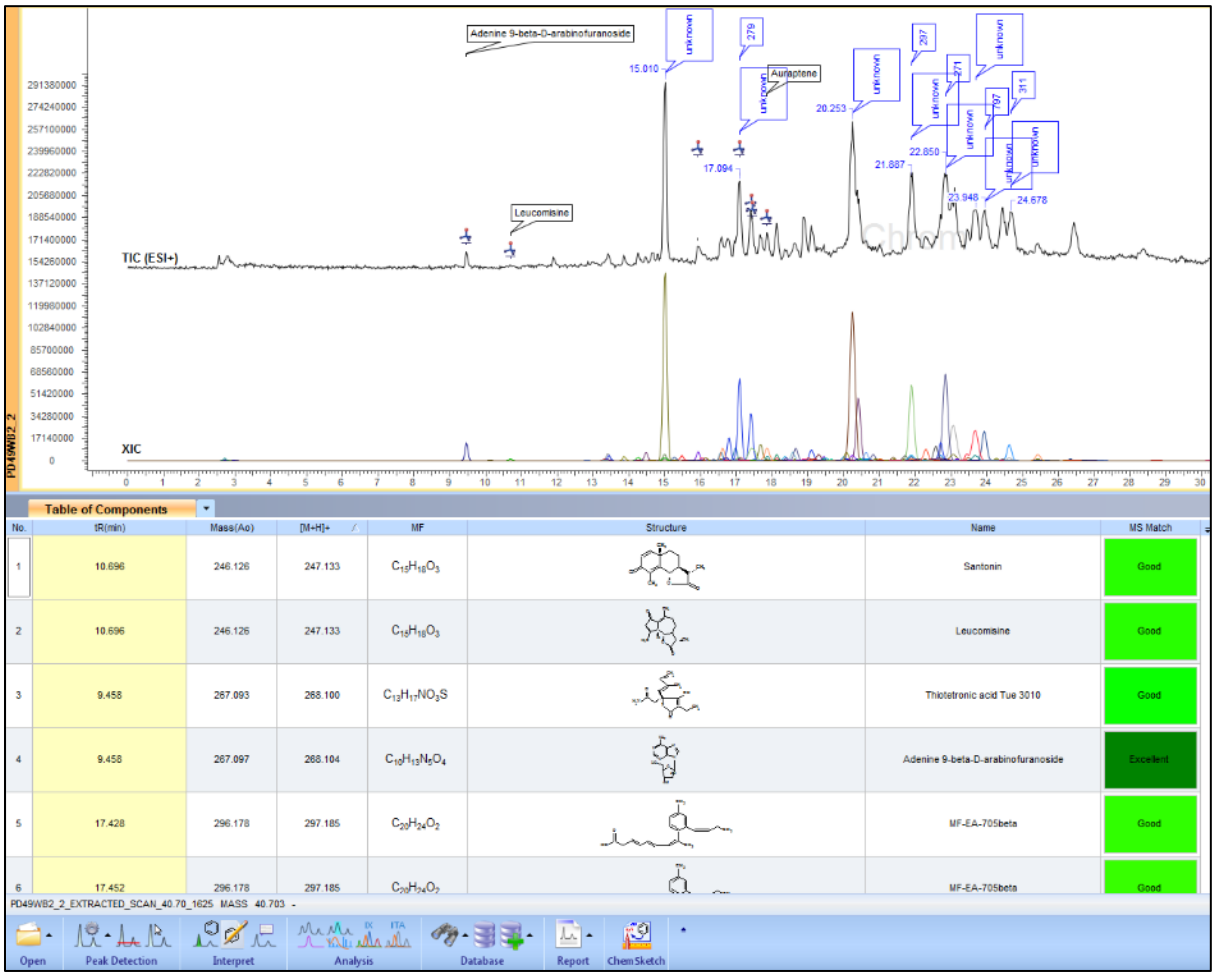

Figure 10. The PharmaSea StrepDB used to identify known and unknown peaks in an LC-MS trace.

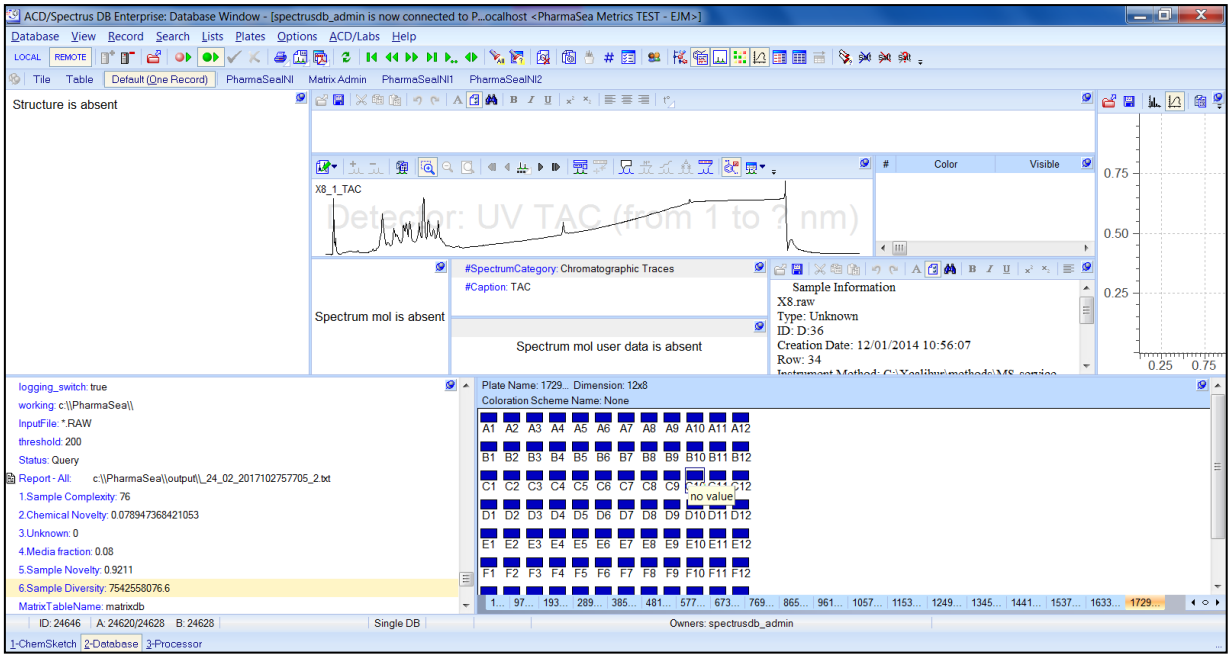

Figure 11. Chemical novelty and chemical diversity analysis on an extract LC-MS dataset.

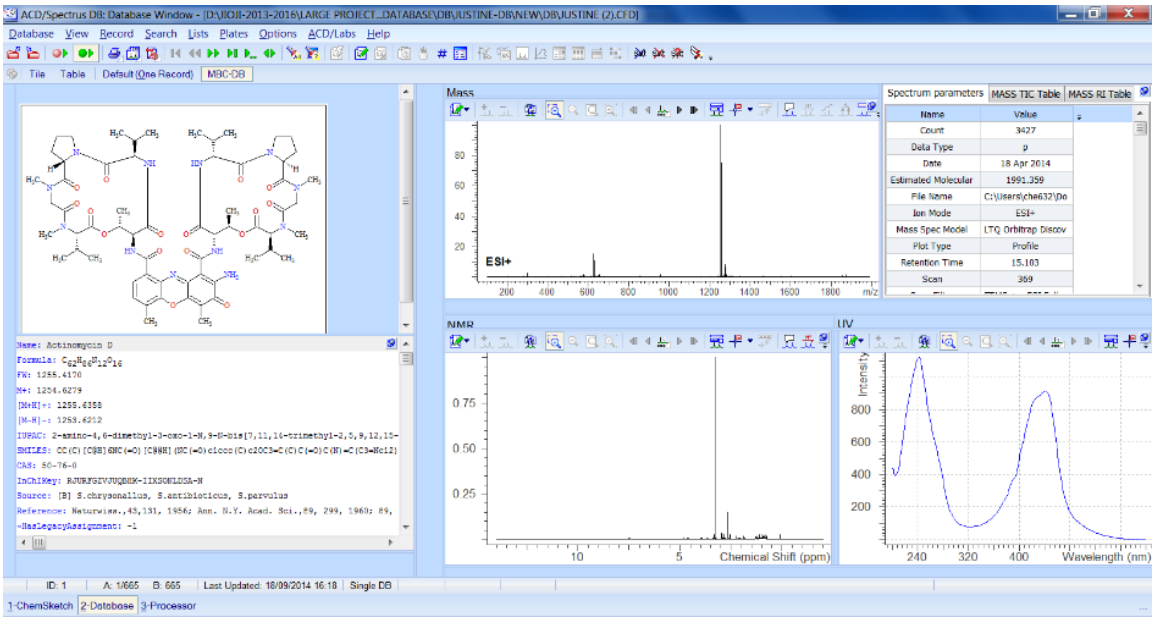

Figure 12. The PharmaSea spectroscopic database showing the searchable data available.

3.2.6) Structure determination

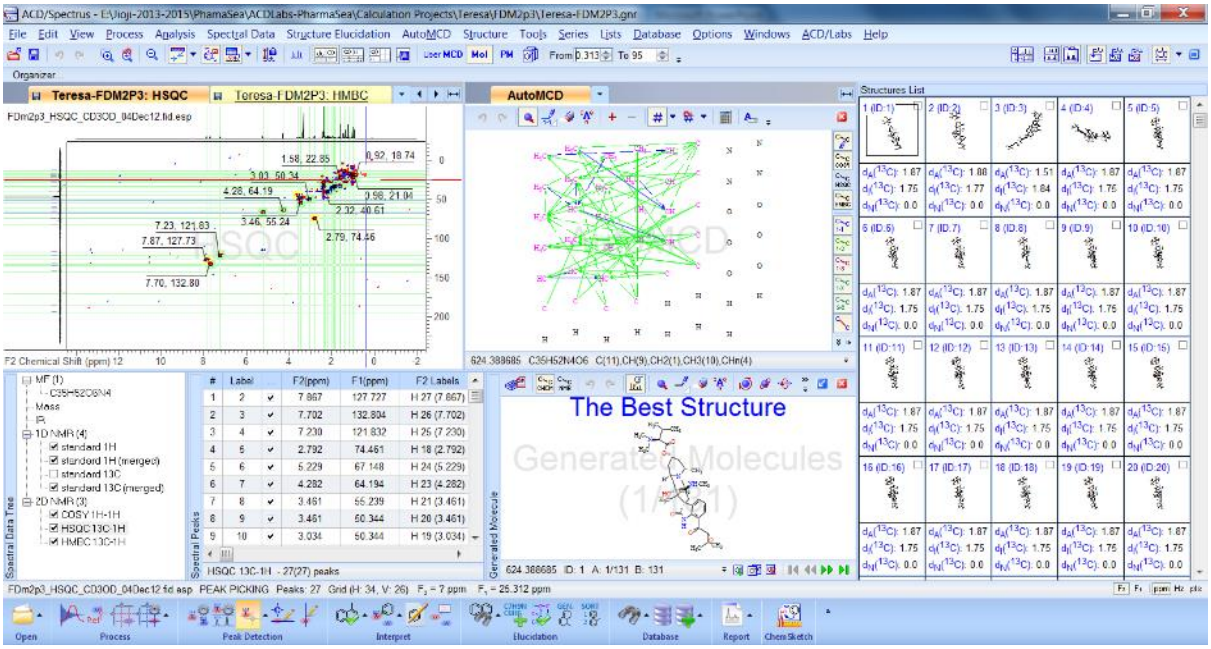

Figure 13. ACDLabs StrucEluc software demonstrated on a compound from a marine derived fungus.

3.2.7) Hit selection

CHEMISTRY_ID	ASSAY_CATEGORY	ASSAY_NAME	DEREPLICATIO	SCALE_UP	ISOLATION	BIOACTIVITY PROFILE
SK0107	NEUROACTIVE	PMR-ASSAY				
BMR_1a, BMR_1E and MBR_1J	ANTICONVULSANT	PTZ-assay				
MDNBC-04359218F	ANTI-INFECTIVE	Abs_MB5393 (MRSA)				
MDNBC-04349594C	ANTI-INFECTIVE	Abs_MB5393 (MRSA)				
MDNBC-04330831T	ANTI-INFECTIVE	Abs_MB5393 (MRSA)				
MDNBC-04366071T	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
MDNBC-04451741N	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
MDNBC-04496513D	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
MDNBC-04349590K	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
01STGROWTH37-1	ANTI-INFECTIVE					
MDNBC-04849719P	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
MDNBC-05165354J	ANTI-INFECTIVE	TUBERCULOSIS/ MRSA				
KB13-8-ZBA-F04	ANTI-INFLAMMATORY	TNF_THPAIF				
KB12-38-ZBA-C06	ANTI-INFLAMMATORY	TNF_THPAIF				
PE08-15-ZBA-H7	ANTI-FUNGAL					
UCC_E128_B_03	ANTI-INFLAMMATORY	TNF_THPAIF				
CHEMFE2/1	ANTI-INFLAMMATORY	TNF_THPAIF				
X0127A-1-04	NEUROACTIVE	PMR-ASSAY				
UCC_E104	ANTI-INFECTIVE	ABS_MB2884 (E.COLI)				
UCC_E360	ANTI-INFECTIVE	ABS_MB2884 (E.COLI)				
USCF025B	ANTI-INFLAMMATORY	TNF_THPAIF				
X0613A-1-05	ANTI-INFLAMMATORY	TNF				
MDNBC-04346468C	ANTI-INFLAMMATORY	TNF_THPAIF				

DONE
ONGOING

Figure 14. Current prioritization list

4. The potential impact (including the socio-economic impact and the wider societal implications of the project so far) and the main dissemination activities and exploitation of results.

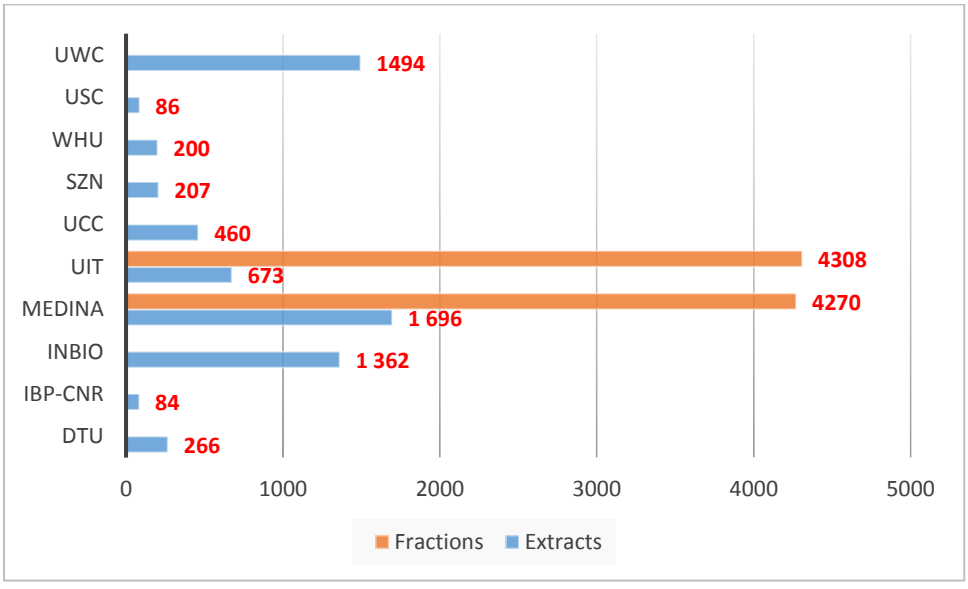

Figure 15. Extracts and fractions generated by the different PharmaSea partners.

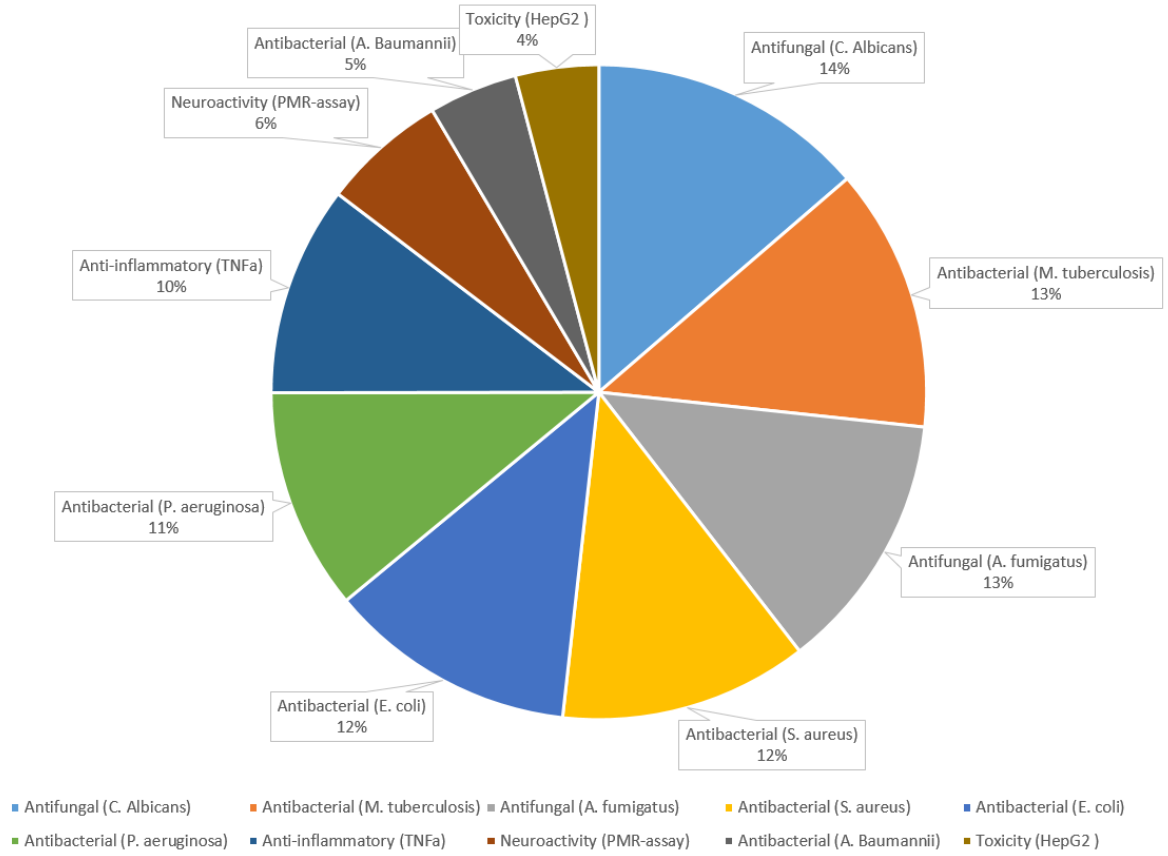

Figure 16. Primary screening events against different targets (N=130369)

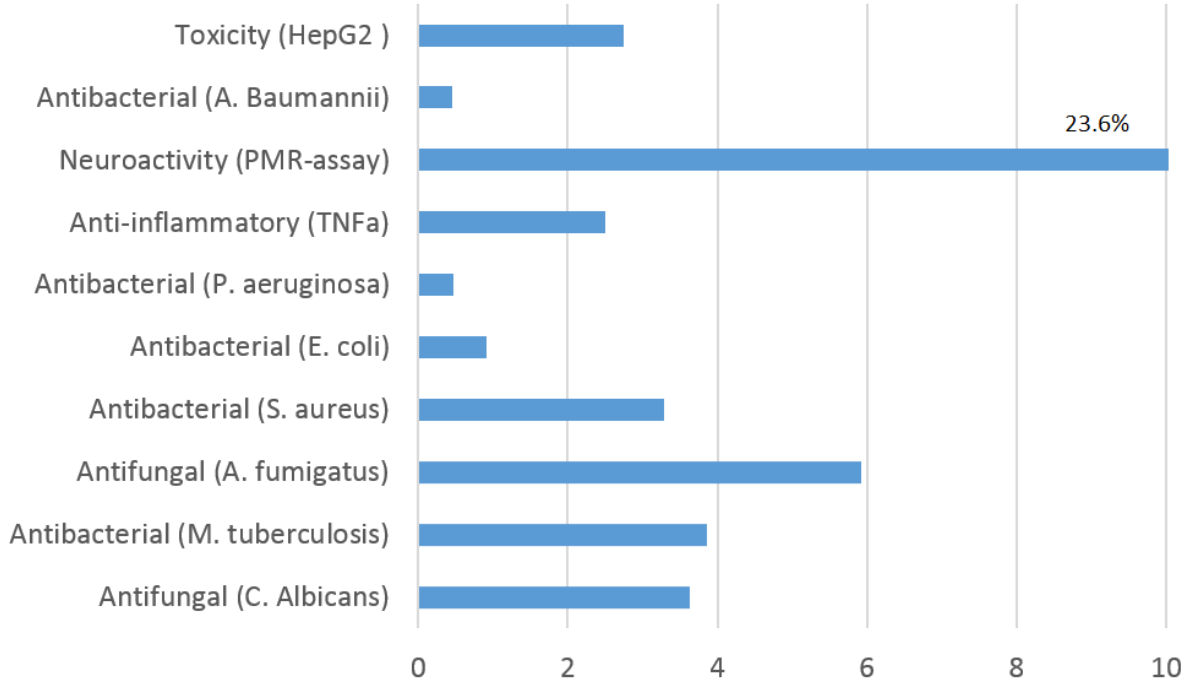

Figure 17. PharmaSea primary screening hit rates. In total 130369 assays were carried out with 5372 actives, giving an overall 4.12% hit rate.

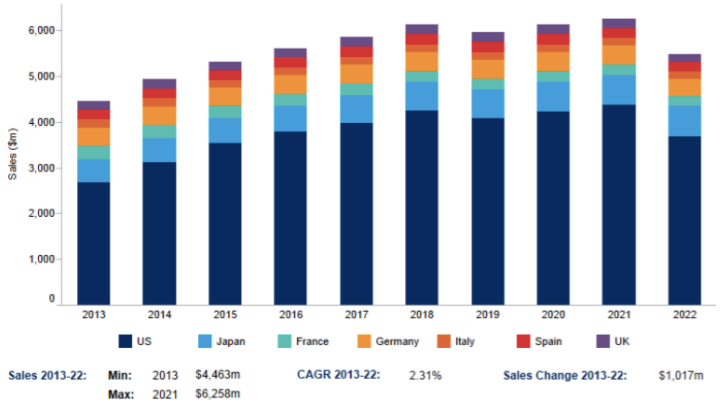

Figure 18. Anti-seizure drug sales value in US, Japan and 5 major EU markets ($m) 2013-2022.

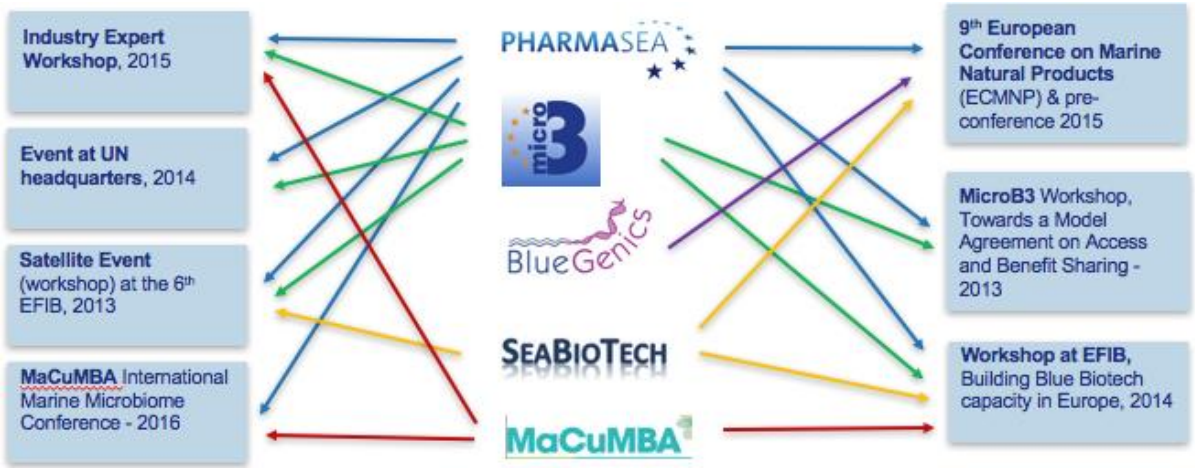

Figure 19. Common dissemination and communication activities