Journal of Advanced Bioinformatics Applications and Research
ISSN 0976-2604.Online ISSN 2278–6007
Vol 6, Issue2, 2015, pp33-44
http://www.bipublication.com

Marine Drug Discovery Database (MDDD) – A Database of *In silico* Predicted Physico-Chemical, Drug Likeness and Toxicological Properties of Marine Compounds.

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Received: 24/04/2015 Accepted: 17/05/2015 Published: 28/05/2015

ABSTRACT:
Marine is one of the largest and richest natural resources of bioactive compounds. Constant efforts have been made to screen and develop drug using these vast and chemically diverse marine compounds. Drug likeness and toxicological property screening are basic requirements of any bioactive compounds to move forward from hit to drug. Hence in this study, drug likeness and toxicological properties of set of marine compounds were predicted using *in silico* tools and results were compiled in the form of data base to aid drug development using marine bioactive compounds. Marine compounds were collected from PubChem and subjected to *in silico* analysis using ADMET predictor™, validated commercial software for predicting physico-chemical, drug likeness and toxicity. Total of 252 marine compounds from various marine bioresources including bacteria, actinomyces, cyanobacteria, fungi and sponges were collected. Results of *in silico* analysis were compiled as – Marine Drug Discovery Database (MDDD). MDDD is freely accessible to all the researchers at www.bdu.ac.in/MDDD/. MDDD is expected to improve drug discovery and development from marine bioactive compounds.

Keywords: MDDD, Database, Marine compounds, *in silico*, drug development, physic-chemical, drug likeness, toxicity, actinomyces, cyanobacteria, fungi, sponges, ADMET

[I] INTRODUCTION

Billion years of evolution have provided enormous pool of organisms ranging from large animals to microscopic creatures in marine environment. These organisms produce enormous amount of compounds or secondary metabolites which are of biological importance. These compounds ay be produced by single organism by itself or in association with more than one organisms such as symbionts. Intracellular and extracellular compounds produced by these organisms were found to have implausible biological activity. Such compounds have been exploited in several ways such as food ingredients, dietary supplements and/or novel drugs. Many compounds from marine sources have been well characterized and developed as functional food ingredients. Polyunsaturated fatty acids (PUFAs), sterols, proteins, polysaccharides, antioxidants and pigments are few among those vital food

ingredients to name [1]. These food ingredients are added to food to improve its nutritive value, shelf life and/or organo-leptic properties. Researchers have also identified several marine compounds with potential therapeutic applications. As of 2013, seven of such compounds from marine origin have been approved as pharmaceuticals by US- FDA, 11 compounds are in different stages of clinical trials and 262 are in preclinical development. These compounds possess diverse biological activities including antibacterial, antidiabetic, antifungal, immune-modulatory activity, anti-Inflammatory, antiprotozoal, antituberculosis, antiviral and so on [2]. Compounds such as fatty acids, sterols, vitamins, minerals and peptides have not only identified to have therapeutic potentials but their mechanisms of action are also well established.

Currently out of 22,000 identified marine compounds, seven has been clinically proven to be useful pharmaceutical product. Diademin B, Ara A, Ara C and Cytarabine are few among those. Some like Ecteinascidin 743 (drug for soft tissue sarcoma) and Conus toxin (pain reliever) have been approved for use as pharmaceutical drug [3]. The success rate of drug development from marine compounds (1 drug from 3,140 reported compounds) is 1.7 to 3.3 fold higher than the average success rate of drug discovery from other sources (1 drug from 5000 to 10000 identified/ tested compounds) [4]. These figures are indicative of greater potentials of marine compounds to be developed as drug. At the same time, establishment of mechanism and site of action, development of structure activity relationships, formulation, evaluations of toxicity and efficacy and characterization of pharmacokinetic and pharmacodynamic properties still remain as major challenges in development of drugs from marine resources. An ideal drug is not only expected to have effective targeted biological activity but also should possess favourable drug like properties and ideally non-toxic in nature.

Discovery and development of NCE to pharmaceutically approved drug is a massive task demanding about 10-15 years of preclinical and clinical research at an expense of more than 2 billion USD. In spite of all that, pharmaceutical industry faces high attrition rate in the past few decades [5]. Past decade (2000 - 2009), recorded the lowest percentage of product approval in the past 25 years [6]. Only 16% clinical approval success rate was recorded for the candidate drugs entered clinical phase between 1999 and 2004. This ranges from 27% for systemic anti-infectives to miserable 8 and 7% for neuropharmacologic and cardiovascular agents, respectively [7].

Lack of efficacy (30%), unacceptable clinical safety and toxicity (30%) and poor pharmacokinetic profile (10%) were found to be major factors for discontinuation of clinical candidates in 2000 [5]. Screening of physicochemical parameters coupled with ADMET testing in the early stage of drug discovery will assist in determining drugability of molecules. Initial screening should include ADME properties such as Solubility (equilibrium, kinetic solubility), rate of dissolution, membrane permeability (PAMPA, cell models, BBB), active transport, ionisation Constant (pKa), lipophilicity (LogP, LogD), chemical stability, metabolic clearance, CYP450 inhibition, CYP450 induction, protein/serum-binding and metabolite identification and toxicological properties such as hERG, other cardiac ion channels, genetic toxicology, target organ/cytotoxicity and mutagenicity and basic *in vitro* and *in vivo* safety profiling [8]. *In vitro* screening of all these properties for vast number of compounds in short time is a daunting task. Alternatively, Computer Aided Drug Design (CADD) and QSAR models are available to computationally predict toxicity by correlating and comparing the structure with available compound libraries and its relavent in vitro and in vivo toxicological data [9] [10]. *In silico* prediction of drug like and ADMET (Absorption, Distribution, Metabolism, Elimination and Toxicity) properties are gaining more importance since past decade to minimize the cost, time and failure rate in drug discovery and development.

Though identification of new bioactive marine compounds increases consistently, information on its drug likeness and toxicity still remain sparse. Evaluation of these properties and construction of database with ADMET information for reported marine compounds will considerably reduce the cost and time required for drug development using compounds from marine sources. There are several databases available online, which deals with compounds reported from marine sources. Marine natural product database is one of the most exclusive and extensive database available for marine compounds. It contains structure, physical, chemical and biological properties of approximately 6000 chemical compounds derived from over 10,000 marine-derived materials [11]. Another exclusive marine compound database with 182 compounds contains clinical trial information inaddition to the above [12].

Seaweed metabolite database (SWMD) is chemo-informatics database contains chemical and biological information of metabolites from marine algae [13]. A data base of mycosporines and mycosporine-like amino acids (MAAs) has various information related to MAAs reported from diverse organism such as fungi, cyanobacteria, macroalgae, phytoplankton and various animals such as arthropods, rotifers, molluscs, fishes, cnidarians, tunicates, eubacteriobionts, poriferans, nemertineans, echinodermates, platythelminthes, polychaetes, bryozoans and protozoans [14]. Dragon Exploration System on Marine Sponge Compounds Interactions - DESMSCI is a web source where in information on marine sponges compounds can be obtained in detail. It has information such as its therapeutic applications, chemical information, gene &/or protein interactions and biological activities [15]. As discussed most of these databases provide information on its therapeutic application and physic-chemical properties but to the best of our knowledge there isn't any database other than MDDD that provides toxicological and drug likeness information of marine compounds.

MDDD is an initiative made to bridge the knowledge gap between the developments of marine compound from hit to lead. Efforts have been made to compile the predicted phycio-chemical, biological, drug likeness and toxicological properties of randomly selected structurally diverse marine compounds.

[II] MATERIALS AND METHODS:

Marine compounds cited in several literatures [16] [3] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] were randomly selected and respective 2D structures were downloaded from PubChem website [30].

2.1 *In Silico* Prediction:

Collected marine compounds were subjected to *in silico* analysis using ADMET predictor™ (V5.0, Simulations Plus, Inc., Lancaster, CA) to predict physico-chemical and toxicological properties. ADMET predictor has different modules. Among which physic-chemical and toxicological modules were used for this study. In both the cases, default parameters were set and predictions were made as per the instructions provided. Table 1 briefs the general, physico-chemical and toxicological information of compounds included in MDDD and its respective description.

Using physic-chemical module, parameters such as molecular weight, number of hydrogen bond donars (H-BOND donars), number of hydrogen bond acceptors (H-BOND Acceptor) and differential/partition co-efficients (DiffCoef, MLogP, S+logP, S+logD) were predicted. These were considered to be indicative of drug likeness of a molecule. Using this module, ADMET risk was also predicted.

Using toxicological module, toxicity and mutagenicity of molecules were assessed. Toxicity screening includes endocrine disruptors (estrogen receptor and androgen receptor toxicity), allergenicity (skin and respiratory sensitization), *in vivo* toxicity (prediction of LD50 against fathead minnow, *Tetrahymena pyriformis*, *Daphnia magna*, rat and mouse), chromosomal aberration, phospholipidosis, reproductive toxicity, cardio

toxicity (hERG toxicity) and liver toxicity (ability to alter alkaline phosphatise, GGT, LDH, SGOT and SGPT enzyme levels). All these parameters were predicted using toxicity module of ADMET predictor™. Mutagenecity of molecules and its possible microsomal rat liver metabolites to 6 different strains of *S. typhimurium* was predicted using toxicity module of ADMET predictor™.

2.2 Database:

All the *in silico* physico-chemical and toxicological predictions were used for the construction of this database. *In silico* predictions of marine compounds were systematically assorted and compiled to form a database. The User Interface had been designed using HTML 5.0 and CSS 3.0 with JQuery. The application had 3 search options namely "Compound name", "Organism" & "Biological activity". The database had been created with MySQL database and PHP had been used to fetch and display the results. The entire application had been built with open source web development tools.

[III] RESULTS:

3.1 Database Features:

Database consists of physico-chemical, biological, drug likeness and toxicological information of 252 randomly selected chemically diverse marine compounds. A link has been provided to pubchem website for each compound to access more information and download its respective 2D & 3D structures.

3.2 Compound Information:

To construct this database, total of 252 marine compounds were randomly collected from the PubChem website. These compounds were isolated and characterized elsewhere, from Bacteria (27 compounds), Sponges (25 compounds), Cyanobacteria (33 compounds), Fungi (72 compounds), Algae (48 compounds), Dinoflagellate (4 compounds), Actinomycete (19 compounds) and other /unidentified sources (where source organisms weren't precisely mentioned such as compounds identified from symbionts) (24 compounds). Figure 1, comprises the percentage distribution of compound in MDDD based on its source. As illustrated majority of the randomly selected compounds in MDDD were from fungi (29%) followed by algae (19%), cyanobacteria (13%), bacteria (11%) and sponges (10%).

3.3 Compound Chemical Diversity:

Structurally these 252 compounds were very diverse and were from different sources. In figure 2, chemical diversity and sources of respective group of compounds were mentioned. Compounds included in MDDD were Macrolide (41 compounds), Alkaloid (29 compounds), Peptide (30 compounds), Polyketide (13 compounds), Quinone (6 compounds), Phenyl derivative (3 compounds), Sesquiterpene (10 compounds), Nucleoside (5 compounds), Pyridine derivative (2 compounds), Cyclic polyether compounds (3 compounds), Phenazine derivative (4 compounds), Sterols (6 compounds), Phthalate derivative (3 compounds), Diketopiperazine (2 compounds), Terpene (5 compounds), Lactone (6 compounds), Phyrone derivatives (3 compounds), Anthracycline derivatives (5 compounds), Aminoglycoside derivative (2 compounds), Fatty acids and lipids (2 compounds), Mycotoxin (2 compounds), Dienoyl tetramic acids (2 compounds), other heterocyclic compounds (5 compounds) and others (63 compounds) (which includes cyclic bipyridine glycosides, gentamicin derivative, oxohexacyclic chromone, xanthone derivative, sorbicilline derivative, brominated phenols, phloroglucinol derivative, Isoflavones, Aldehyde, Phenolic acids, macrolactum antibiotic, polysaccharide, amino acids, macrolactin, naphthalenone, epoxycyclohexanone, monacolins, chloropyrrole, ramulosin, guanidine derivatives, cyclopentanone, tremorgenic metabolite, tetronic acid derivative and other undefined compounds). Macrolides (16.27%), alkaloids (11.51%) and peptide (11.9%) form major part of this randomly selected compound pool.

As illustrated in figure 2, macrolides in MDDD were from algae, dinoflagellates, bacteria,

cyanobacteria, sponges, fungi and actinomycetes origin. Peptides in MDDD were from algae, bacteria, cyanobacteria, sponges, fungi and actinomycetes origin. Majority of polyketides, sesquiterpenes, phenyl derivatives, quinones, mycotoxins, pyrone derivatives and alkaloids in MDDD were found to be fungal metabolites. Dienoyltetramic acids, aminoglycoside derivatives and antracyclin derivatives in MDDD were from *Actinomycetes* sp. More than half of the terpenes, heterocyclic nitrogenous compounds, sterols, lactone and phenazine derivatives in MDDD were algal metabolites.

3.4 Drug Like Property Study (Lipinski's Rule of 5):

Using ADMET tool all MDDD compounds (252 marine compounds) were tested for its drug likeness (Lipinski's rule of five) [31], an important criterion for lead selection in modern drug discovery. Similations Plus Inc has developed its modified set of Lipinski's rule of five, which includes lipophilicity (S+logP < -0.891), permeability (S+Peff < 0.120), acidity at saturation point (S+pH < 3.396), hydrogen bond donors (HBDch > 1.135), polar surface area (T_PSA > 139.86), polarity-atomic charges (ABSQ > 5.111) and permanent charge (Formal Q ≠ 0). These were reported to be well correlated with real time values. A score of 0 to 4 was given to each compound screened. The number indicates the number of parameters failed in the above mentioned Lipinski's rule of five. Compounds with a score of "0" were considered to have high drug like properties, as the score increases drug likeness decreases. A score of 4 indicates that the molecule has failed in all parameters of Lipinski's rule of five.

MDDD's 252 compounds when tested, ~51% of compounds showed high drug likeness and hence can be considered for lead or drug development. All heterocyclic nitrogenous compounds(5), phenyl derivatives(3), diketopiperazines (2), dienoyl tetramic acids (2), pyrones (3), lactones (6) and phenazine derivatives (4) tested showed very high drug likeness. Apart from these, ~92% of polyketide, 80% terpene, 83% Quinone and 72% alkaloids, present in MDDD, also passed drug likeness criteria. Steroids, peptides, phthalates and aminoglycoside compounds with several proven biological activities resulted in poor drug like property (Figure 3). The compounds that have high drug likeness were mainly from fungal, bacterial and algal origin. Among all the compounds screened, compounds from cyanobacteria have least drug likeness.

3.5 Reported Biological Activity of MDDD Compounds:

Specific and effective biological activity is the primary criterion for selection of any compound to enter in to the drug development pathway. Hence effort has been made to compile all reported biological activity of MDDD compounds. This will aid drug discovery scientist to be better informed about the molecule. Figure 4 briefs the diversity of biological activity of MDDD compounds. Compounds like macrolides, peptides and alkaloids reported to have diverse biological activity ranging from antimicrobial, anticancer, cytotoxicity etc. Surprisingly ~28% of MDDD compound's biological activity is yet to be identified. Diverse biological activity of MDDD compounds were antimicrobial (21.03%), cytotoxicity (18.65%), anticancer (11.9%), anticoagulant (0.4%), antioxidant (0.4%), antimalarial (3.57%), antiviral (2.78%), protein/kinase/enzyme inhibitory activity (3.57%) and anti-inflammatory activity (2.38%). 11.51% of MDDD compounds were reported to have other biological activity, including antineoplastic, antinematoidal, antimitotic/antitubulin, cholesterol biosynthesis inhibitor, antiplasmodial, Ca channel modulator, phospholipase inhibitor and antihelminthic activity.

3.6 Toxicity:

Predicted *In silico* data of MDDD compounds for various toxicity parameters were consolidated in Figure 5 & 6. All 252 compounds were tested for its hERG K+ ion channel toxicity, reproductive toxicity, alkaline phosphatase toxicity, gamma glutamyl peptidase toxicity, lactate dehydrogenase toxicity, serum glutamic oxaloacetic transaminase toxicity, serum glutamic

pyruvic transaminase toxicity, mutagenicity, ability to induce phospholipidosis and ability to cause chromosomal aberration. For certain compounds toxicity couldn't be predicted, as those weren't structurally very different from the software's structural database and such compound's data were mentioned as "information not available".

Percentage of MDDD compounds predicted to be toxic for each toxicity parameter tested were compiled in Figure 6. Out of 252 compounds present in MDDD only 4.76% and 3.17% compounds, respectively, were predicted to exhibit hERG K+ ion channel toxicity and phospholipidosis induction. Percentage of MDDD compounds toxic for each toxicity parameter tested were predicted to be 24.6% reproductive toxicity, 43.65% ALP (Alkaline Phosphatase) toxicity, 45.63% GGP (Gamma glutamyl peptidase) toxicity, 32.54% lactate dehydrogenase toxicity, 28.57% SGOT (Serum glutamic oxaloacetic transaminase) toxicity, 43.65% SGPT (Serum glutamic pyruvic transaminase) toxicity, 29.76% mutagenicity and 35.71% chromosomal aberration. Based on the *in silico* prediction it is clear that majority of compounds in the MDDD doesn't have hERG K+ ion toxicity and doesn't induce phospholipidosis. Conversely most compounds in MDDD showed effect on enzymes such as serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), gamma glutamyl peptidases and alkaline phosphatase.

[IV] DISCUSSION:

The database is the compilation of physic-chemical, drug likeness, biological and toxicological properties of 252 compounds of marine origin belonging to diverse chemical groups. There are very few databases which are exclusively designed for marine compounds such as marine natural product database, MarineLit, seaweed metabolite database and Marine compound database (Lei and Zhou., 2002; Babu et al., 2008; Davis and Vasanthi, 2011).

All these databases contains information only on structural and physico-chemical properties of marine compounds with an exemption to seaweed metabolite dataset where inaddition to these rule of 5 or drug likeness of these molecules were discussed. Thus to the best of our knowledge, none of the available databases, other than MDDD, exclusively provides physico-chemical, drug likeness, biological and toxicological properties of marine compounds.

MDDD is an initiative to aid drug discovery from marine bioresources, which is indeed a rich source of chemically diverse and biologically active compounds. Interestingly, about ~52% of compounds included in MDDD possess drug like properties and most of the compounds have diverse biological properties.

MDDD as described has 252 compounds with physico-chemical, drug likeness, biological and toxicological properties.

Though these need to be evaluated *in vitro* for confirmation of predicted values, these primary information will be useful in screening of compounds for preclinical studies and development of lead compounds in early stage of drug discovery and development.

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Figures

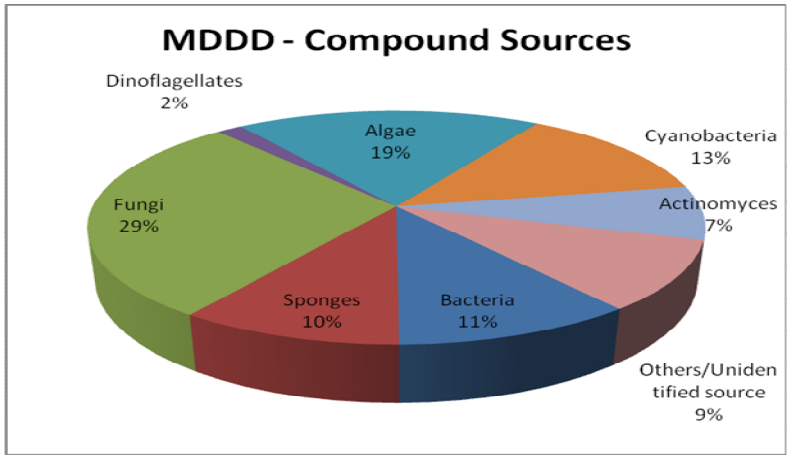

Fig. 1 Percentage distribution of compounds in MDDD based on its source.

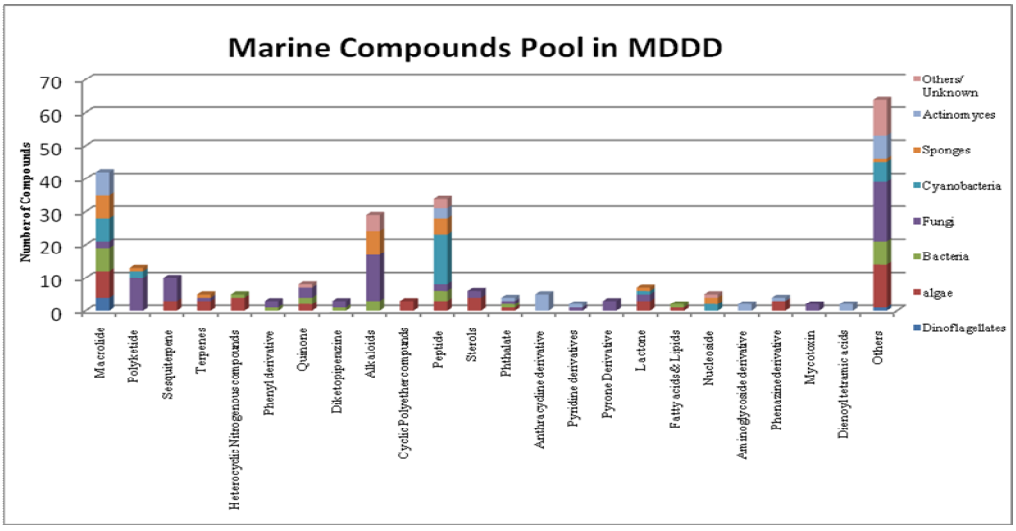

Fig. 2 Chemical Diversity of MDDD compounds and its source

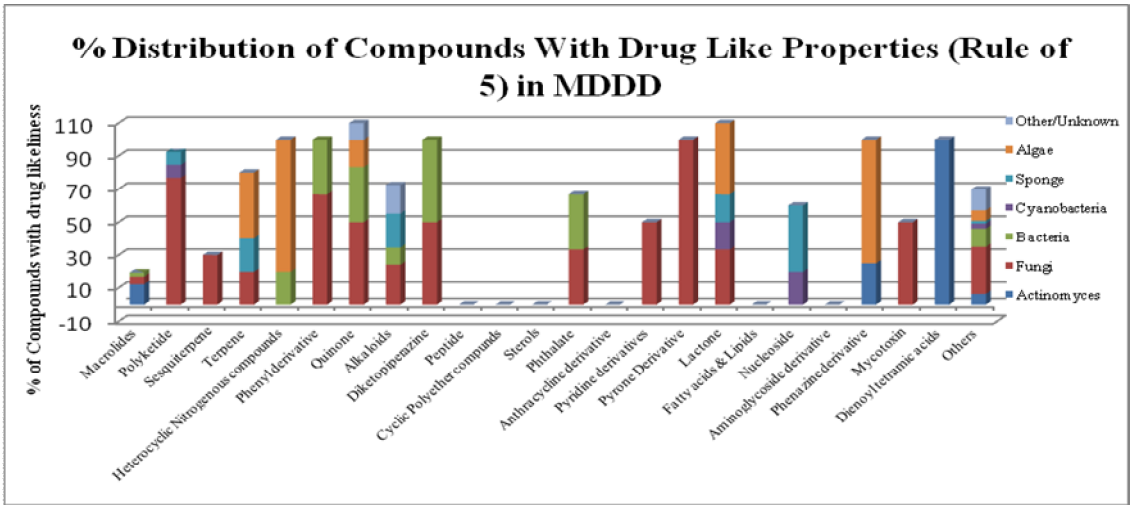

Fig. 3 Percentage distribution of MDDD compounds with fairly good predicted drug like properties and its source

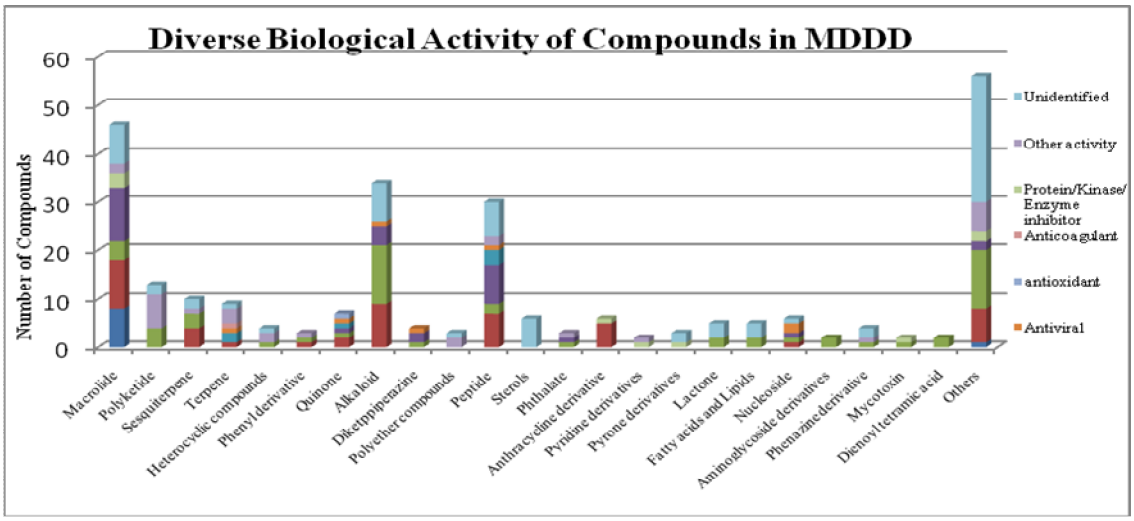

Fig. 4 Graphical representation of different biological activity of compounds in MDDD

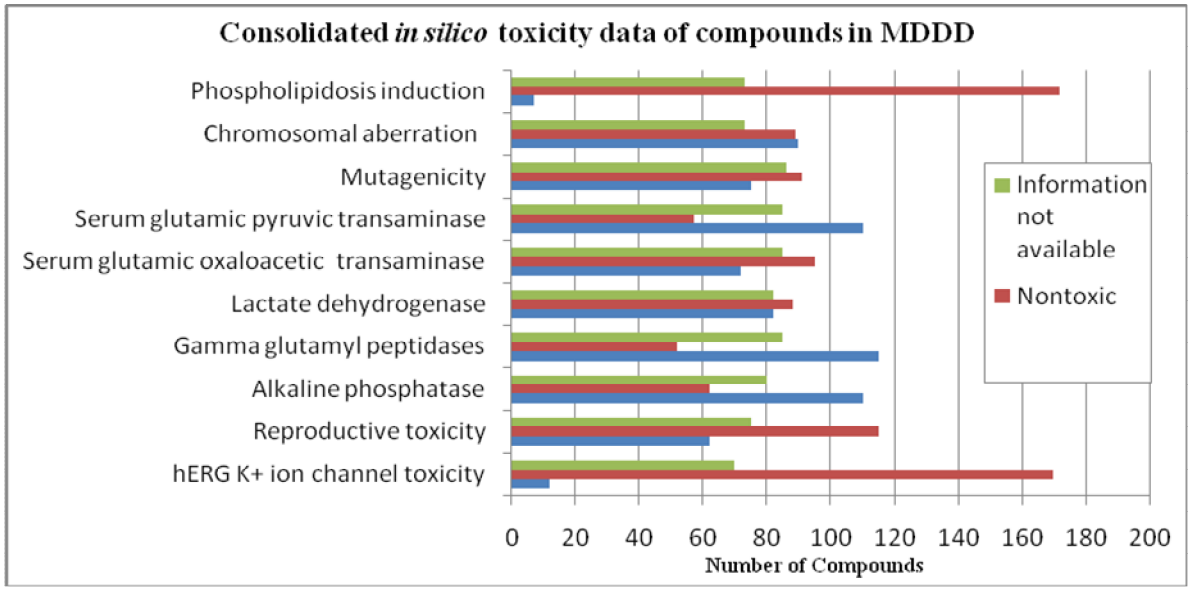

Fig. 5 Consolidated *in silico* toxicity data of compounds in MDDD

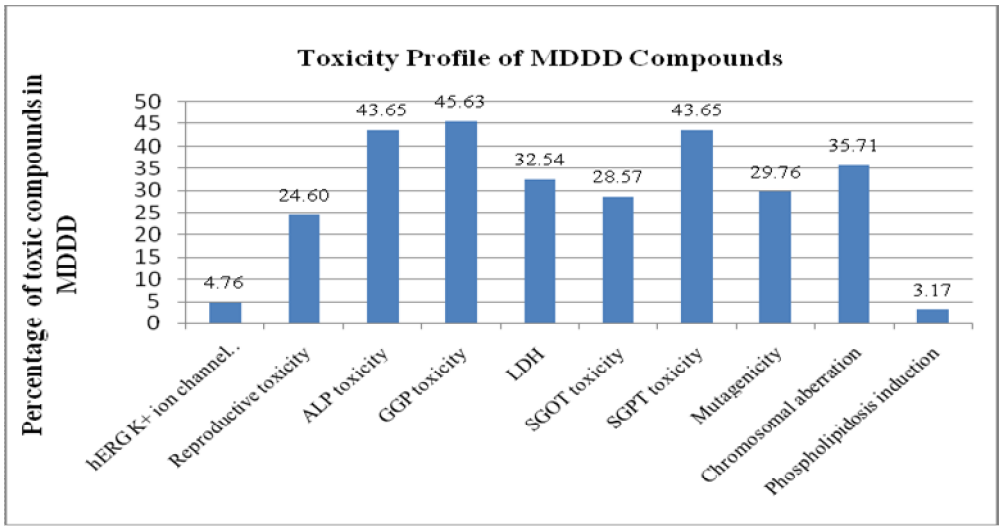

Fig. 6 Percentage of MDDD compounds predicted to be toxic for various toxicity parameters tested using ADMET predictor™

Tables

Table 1 List of general, physico-chemical and toxicological information of MDDD compounds and its description.

Sl. No.	Compound Information	Description
1.	Organism	Marine organism from which compound identified
2.	Genus	Genus of marine organism from which compound identified
3.	Biological activity	Reported biological activity of the compound
4.	Chemical class	Chemical group based on the structure of compound
5.	IUPAC traditional name	IUPAC name
6.	MWt	Molecular weight of compound
7.	PUBCHEM_Compound_CID	PubChem compound ID
8.	H-BOND Acceptor	Number of hydrogen bond acceptors
9.	H-BOND Donor	Number of hydrogen bond donors
10.	ROTATABLE_BOND	Number of rotatable bonds
11.	DiffCoef	Differential Coefficient [$cm^2/s \times 10^5$] molecular diffusion coefficient in water (Hayduk-Laudie formula)
12.	MlogP	Moriguchi model of octanol-water partition coefficient, log P;
13.	S+logP	Octanol-water partition coefficient, log P; Simulations Plus model
14.	S+logD	Octanol-water distribution coefficient, log D; calculated from pKa and S+logP
15.	RuleOf5	Rule of Five takes on numeric values from 0 to 4 depending on how many “potential problems” a compound might have with its absorption or permeation properties.
16.	TOX_MRTD	[mg/kg/day] Qualitative assessment of the Maximum Recommended Therapeutic Dose administered as an oral dose; Simulations Plus model

17.	TOX_ER_Filter	Qualitative assessment of estrogen receptor toxicity in rats; Simulations Plus model
18.	TOX_ER	IC50(estrogen)/IC50(compound) as a quantitative measure of estrogen receptor toxicity in rats. Simulations Plus model
19.	TOX_AR_Filter	Qualitative assessment of androgen receptor toxicity in rats; Simulations Plus model
20.	TOX_AR	IC50(androgen)/IC50(compound) as a quantitative measure of androgen receptor toxicity in rats. Simulations Plus model
21.	TOX_SKIN	Qualitative assessment of allergenic skin sensitization in mice; Simulations Plus model
22.	TOX_RESP	Qualitative assessment of allergenic respiratory sensitization in mice; Simulations Plus model
23.	TOX_FHM	[mg/L] LC50 for fathead minnow lethal toxicity after 96 hours of exposure; Simulations Plus model
24.	TOX_ATTP	[mmol/L] (pIGC50 for *Tetrahymena pyriformis* growth inhibition toxicity; Simulations Plus model
25.	TOX_DM	[mol/L] Lethal concentration that results in the death of 50% of Daphnia magna (water fleas) after 48 hours
26.	TOX_BCF	bioconcentration factor - a partition coefficient between fish tissues and environmental water at steady state as concentration ratio Cfish/Cwater; Simulations Plus
27.	TOX_hERG_Filter	Qualitative assessment of affinity towards hERG K+ channel and potential for cardiac toxicity; Simulations Plus model
28.	TOX_hERG	IC50 as a measure of affinity towards hERG K+ channel and potential for cardiac toxicity; Simulations Plus model
29.	TOX_RAT	[mg/kg] LD50 for lethal rat acute toxicity, all mechanisms; Simulations Plus model
30.	TOX_BRM_Rat	[mg/kg/day] (TD50, oral dose of a compound required to induce tumors in 50 percent of a rat population after exposure over a standard lifetime; Simulations Plus model)
31.	TOX_BRM_Mouse	[mg/kg/day] (TD50, as above, but for mouse; Simulations Plus model)
32.	TOX_CABR	Ability to cause chromosomal abberation
33.	TOX_PHOS	Ability to induce phospholipidosis
34.	TOX_REPR	Ability to cause reproductive toxicity
35.	TOX_AlkPhos	Human liver adverse effect as the likelihood of causing elevation in the levels of Alkaline Phosphatase enzyme; Simulations Plus model

36.	TOX_GGT	Human liver adverse effect as the likelihood of causing elevation in the levels of GGT enzyme; Simulations Plus model
37.	TOX_LDH	Human liver adverse effect as the likelihood of causing elevation in the levels of LDH enzyme; Simulations Plus model
38.	TOX_SGOT	Human liver adverse effect as the likelihood of causing elevation in the levels of SGOT enzyme; Simulations Plus model
39.	TOX_SGPT	Human liver adverse effect as the likelihood of causing elevation in the levels of SGPT enzyme; Simulations Plus model
40.	TOX_MUT_97+1537	Qualitative assessment of mutagenicity of the pure compound in TA97 and/or TA1537 strains of S. Typhimurium; Simulations Plus model
41.	TOX_MUT_m97+1537	Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA97 and/or TA1537 strains of S. Typhimurium; Simulations Plus model
42.	TOX_MUT_98	Qualitative assessment of mutagenicity of the pure compound in TA98 strain of S. Typhimurium; Simulations Plus model
43.	TOX_MUT_m98	Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA98 strain of S. Typhimurium; Simulations Plus model
44.	TOX_MUT_100	Qualitative assessment of mutagenicity of the pure compound in TA100 strain of S. Typhimurium; Simulations Plus model
45.	TOX_MUT_m100	Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA100 strain of S. Typhimurium; Simulations Plus model
46.	TOX_MUT_102+wp2	Qualitative assessment of mutagenicity of the pure compound in TA102 strain of S. Typhimurium and/or WP2 uvrA strain of E. coli; Simulations Plus model
47.	TOX_MUT_m102+wp2	Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA102 strain of S. Typhimurium and/or WP2 uvrA strain of E. coli; Simulations Plus model
48.	TOX_MUT_1535	Qualitative assessment of mutagenicity of the pure compound in TA1535 strain of S. Typhimurium; Simulations Plus
49.	TOX_MUT_m1535	Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA1535 strain of S. Typhimurium; Simulations Plus