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Deep-sea fungal metabolites as potential inhibitors of glucose-regulatory enzymes: *In silico* structure-activity analysis



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ABSTRACT

Chronic diabetes mellites related hyperglycemia is a major cause of mortality and morbidity due to further complications like retinopathy, hypertension and cardiovascular diseases. Though several synthetic anti-diabetes drugs specifically targeting glucose-metabolism enzymes are available, they have their own limitations, including adverse side-effects. Unlike other natural or marine-derived pharmacologically important molecules, deep-sea fungi metabolites still remain under-explored for their anti-diabetes potential. We performed structure-based virtual screening of deep-sea fungal compounds selected by their physiochemical properties, targeting crucial enzymes viz., α -amylase, α -glucosidase, pancreaticlipoprotein lipase, hexokinase-II and protein tyrosine phosphatase-1B involved in glucose-metabolism pathway. Following molecular docking scores and MD simulation analyses, the selected top ten compounds for each enzyme, were subjected to pharmacokinetics prediction based on their AdmetSARand pharmacophore-based features. Of these, cladosporol C, tenellone F, ozazino-cyclo-(2,3-dihy droxyl-trp-tyr), penicillactam and circumdatin G were identified as potential inhibitors of α -amylase, α -glucosidase, pancreatic-lipoprotein lipase, hexokinase-II and protein tyrosine phosphatase-1B, respectively. Our *in silico* data therefore, warrants further experimental and pharmacological studies to validate their anti-diabetes therapeutic potential.

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1. Introduction

Diabetes mellitus (DM) is a degenerative disorder of hyperglycemia, affecting over 380 million of world population (Barde et al., 2015). DM is the metabolic condition characterized by a lack of insulin secretion and resistance primarily interfering with glucose uptake and inhibition of glycogen breakdown and gluconeogenesis (Joshi et al., 2007). Of its type-1 and type-2 conditions, DM type-2 is more common, affecting 90–95% of all cases (Reimann et al., 2009). Chronic DM type-2 related hyperglycemia is a major cause of mortality and morbidity due to further complications like retinopathy, nephropathy, diabetic foot, hypertension

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and cardiovascular diseases. Though several anti-diabetic synthetic drugs targeting specific enzymes involved in sugar metabolism are available, their high cost, limited efficacy and adverse side-effects are the major concern. Therefore, in recent decades, screening and identification of novel efficacious and cost-effective antidiabetic agents has been extensively investigated. Natural bioactive products from terrestrial and marine sources have served as a major source of promising drugs for several diseases. Of these, many anti-diabetes medicinal plant products or formulations, including isolated bioactive saponins, flavonoids, alkaloids, anthraquinones, terpenes, coumarins, phenolics and polysaccharides have been demonstrated (Qi et al., 2010). Further, the effective and safe drugs from marine sources provide many promising polyphenols, peptides, pigments, phlorotannins and sterols that could be developed for the treatment of diabetes and associated complications (Barde et al., 2015).

Deep-sea fungi inhabit marine sediments or environment under 1000 m of the sea surface, and are believed to evolve from their terrestrial species (Swathi et al., 2013). As compared to an estimated 24,000 reported marine secondary metabolites, over 500 have isolated from deep-sea fungi (Carroll et al., 2021; Blunt et al., 2005). A variety of deep-sea derived bioactive compounds

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have been demonstrated for their pharmacological activities against infectious, inflammatory, tumorigenic and diabetic conditions (Wang et al., 2015; wang et al., 2022). Nonetheless, deepsea fungi still remain a relatively untapped source of therapeutically important compounds, both structurally and biologically.

Notably, due to the unavailability of sufficient bioinformaticsbased studies, there are limited reporting on *in silico* elucidations of marine bioactive compounds for their *in vitro* or *in vivo* pharmacological or cytotoxic activities. Nonetheless, though several new marine anti-diabetic compounds are being reported, their chemical, molecular, bioinformatic and pharmacological analyses are required to develop novel, efficacious and safe drugs. In this study, we have performed structure-based virtual screening (SBVC) of various deep-sea fungi derived metabolites, including prediction of their physiochemical and pharmacokinetic properties towards developing promising ant-diabetes drugs.

2. Materials and methods

2.1. Protein and ligand structures retrieval and preparation

The 3D protein structures of five important enzymes of glucose metabolic pathway: α -amylase (PDB ID: 2QV4), α -glucosidase (PDB ID: 5V4W, pancreatic lipoprotein lipase (LPL; PDB ID: 20XE), hexokinase-II (HKII; PDB ID: 2NZT), and protein tyrosine phosphatase-1B (PTP-1B; PDB ID: 1BZJ) were retrieved from Protein Data Bank (Burley et al., 2021). All selected structures were first checked for missing amino acid residues or charges and repaired in Modeller v9.22 (Webb and Sali, 2021), and structurevisualization was performed in Pymol (DeLano, 2022). Based on literature search, a total of fifty deep-sea fungi derived compounds for each protein target with characterized chemical properties were selected (Kim et al., 2019) (Table 1). The ligand controls used were acarbose (PubChem ID: 20V4) for α -amylase and α glucosidase, orlistat (PubChem ID: 20XE) for LPL, benserazide (PubChem ID: 2NZT) for KH-II, and trodusquemine (PubChem ID: 1BZJ) for PTP-1B. All compounds (ligands) structures were retrieved from PubChem database (https://pubchem.ncbi.nlm.nih.gov/).

2.2. Structure-based virtual screening (SBVS)

The PDB files of target proteins' 3D structural information were submitted to the system. The opted parameters for the filtration were based on the Lipinski's rule of five (hydrogen bond donor/ HBD and acceptor/HBA < 5), molecular mass (MW) < 500 Da, and octanol-water partition coefficient (logP) < 5 (Pollastri, 2010). Furthermore, the selected parameters were a sampler size of 1000, a similarity threshold of 0.7, and a cap of 3 million compounds after sphere exclusion. Except from these three variables, no alteration in MCULE settings was introduced. For SBVS, AutoDock Vina v1.2.0 was employed (Eberhardt et al., 2021). The docking score was used to assess the binding affinities of the inhibitors, and of these, top 10 compounds for each target protein were filtered. Further, the pharmacokinetics of the selected inhibitors was studied using the program AdmetSAR. Based on the AdmetSAR results, one best inhibitor for each enzyme was finally selected for further analysis.

2.3. Molecular docking and molecular dynamic (MD) simulation analysis

Once the ligand had been extracted and optimized using Auto-Dock tools, each protein–ligand complex was solvated in a water box that included TIP3P water molecules along with the additional

sodium and chloride ions to imitate the *in vivo* situation. The box defined across the complex was a dodecahedron. An energyefficient steepest descent for the system (200 ps) was completed thermodynamic equilibrium was established with and CHARMM36 force field and GROMACS. Finally, MD simulation at 100 ns was carried out for each ligand-protein complex as mentioned elsewhere (Huang et al., 2017). The riparian vegetation dynamic model (RVDM) selected at energy minimization stage was long range Van der Waals cut-off. Gen_vel option was active with 300 gen_temp and -1 gen_seed. For final production MD simulation step, tau_p was 2.0 and ref_p was 1.0 with Parrinello-Rahman method for pressure coupling. All calculations and data acquisition on hydrogen bonding were carried out using Python, PyMOL, and VMD, together with the gmx rms, gmx rmsf, gmx area, and gmx cod and gyrate tools (DeLano, 2012).

2.4. Analysis of residue-wise interaction of docked compounds

Ligand-protein docking was performed through a CB dock, and the 3D structures of the docked complex and residue-wise interaction was illustrated using Ligplot. Each complex was further subjected to MD simulation analysis of five factors viz., root mean square deviation (RMSD), number of hydrogen bonds, the radius of gyration (Rg), solvent accessible surface area (SASA), and root mean square fluctuations (RMSF) in protein-ligand interaction. All selected compounds were first filtered based on binding energy and then the best was selected AdmetSAR and pharmacophore features-based features on Lipinski's rule of five. A model system was used in which the finally selected inhibitors cladosporol C (PubChem ID: 11198523), ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) (PubChem ID: 146115843), tenellone F (PubChem ID: 139590732), penicillactam (PubChem ID: 57337607), circumdatin G (PubChem ID: 10804637) were docked with α -amylase, α glucosidase, LPL, HK-II and PTP-1B, respectively.

2.5. Binding free-energy determination of the selected inhibitor molecules

In docking analysis, MD simulation allows to predict the freeenergies of molecular systems, which determines the direction of the thermodynamic process as well as the probability of its stability. The molecular mechanics Poisson–Boltzmann surface area (MM/PBSA) and molecular mechanics generalized Born surface area (MM/GBSA) methods are more accurate than most scoring functions of molecular docking (Wang et al., 201), they were used to determine the binding free-energies of cladosporol C, tenellone F, ozazino-cyclo-(2,3-dihydroxyl-trp-tyr), penicillactam and circumdatin G with their respective targets α -amylase, α – glucosidase, LPL, HK-II and PTP-1B.

3. Results

3.1. Selection of the best inhibitors of target enzymes

Of the fifty compounds virtually screened against each protein target (α -amylase, α -glucosidase, LPL, HK-II, and PTP-1B), top 10 compounds were selected (Table 1). The 3D structures of the docked complex and residue-wise interactions of protein and compound were presented using Ligplot. All compounds were further subjected to pharmacokinetics analysis based on AdmetSAR properties (Table 2). All selected compounds firstly filtered as per their estimated binding energy were then selected for best AdmetSAR and pharmacophore features on Lipinski's rule of five.

Table 1

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Molecular do	cking analysis o	of deep-sea derived	l compounds screened	l against glucose	metabolism enzymes.
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e-simplace	Enzyme (target)	Compound (ligand)	Chemical class	Deep-sea fungi (source)	Glide score (Kcal/mol)
1Brevione ITerpenoidsPenkietidsPenkietidsPenkietidsPenkietids3Dictrimone BPolyketidesPenkietidsPenkietidsPenkietidsPenkietids4Cladsoporol GPolyketidesPenkietidsPenkietidsPenkietidsPenkietids5Cyclopiamide JAlkaloidsPenkietidsPenkietidsPenkietidsPenkietids6Malformin CPeptidesAppenglitas postSOV2-9.37Cyclopiamide EAlkaloidsPencillium commue DFSSO26-9.39Cladosporol CPolyketidesCladosporian Caldos postBOV2-9.39Cladosporol CPolyketidesCladosporian Caldos postBOV2-9.39Cladosporol CPolyketidesCladosporian SSO3 (1001)-9.210Chrysamide BAlkaloidsP pareum SSO4 (1001)-9.211Acarbosc12Penjacici DAlkaloidsP pareum SSO4 (1001)-8.813Chrysamide BAlkaloidsP pareum SSO4 (1001)-8.214PolyketidesAspergillas postBo-4-8.3-8.215C-hydroxpori-formyl-vertixanthonePolyketidesAspergillas postBo-4-8.216Chatorytidin CPolyketidesAspergillas postBo-4-8.217Asplactanol DPolyketidesAspergillas postBo-4-8.218Chatorytidin CPolyketidesPolyketidesPolyketides-8.219Chatorytidin C<	α -amylase				
2Ozzino-cycle-(2.3-ditydroxyl-trp-tyr) Divisetione BAlkaloids PolyketidesP. dtreonigrum XT20-134-9.63Dictrinone BPolyketidesCladosporium cladosproides HDN14-342-9.54C. Cadospanide JNakaloidsPericilium commune DFFSC026-9.45C. Cyclopianide EAlkaloidsPericilium sp. MCC 300005-9.38Sterolic acidSterolsPericilium sp. MCC 300005-9.39C. Cadosporil CPolyketidesCladosporinu cladosporiodes HDN14-342-9.210C. Chrysamide BAlkaloidsP. chrysogerum SC04 40011-9.211Actrosce*2.4Penipacid DneAlkaloidsP. paneum SD-44-9.02.5C. Cyclopianide FAlkaloidsP. farosogerum SC10 41001-9.22.6C. Cyclopianide DAlkaloidsP. farosogerum SC10 41001-9.22.7Actrosce*2.8C. Cyclopianide DAlkaloidsP. farosogerum SC10 41001-8.12.9C. Cadosporide MILLAlkaloidsP. farosofias HDA-1424-9.03.6Aspergillo SC10 FOZ-8.2-8.2-8.23.6C. Syndroxy-6 formy vertikanthonePolyketidesAspergillor sp. fMS-714-8.24.1AcarbosePolyketidesAspergillor sp. fMS-714-8.25.6Aspergillo Scillo FOZ-9.0-9.0-7.27.7Asplactonol DPolyketidesAppergillor sp. fMS-714<	1	Brevione I	Terpenoids	Penicillium sp. MCCC 3A00005	-9.8
3Dictitinone BPolyketicksPericilium curtum-9.64Cladosporol GPolyketicksCladosporinic dubasporiolis HDN1-342-9.55Cyclopiamide JAllaloidsPericilium commune DFSCS026-9.37Cyclopiamide EAllaloidsPericilium commune DFSCS026-9.38Steroids caidSteroidsPericilium commune DFSCS026-9.39Cladosporol CPolyketicksCladosporiniu cladosprinides HDN1-342-9.210Chrysamide BAllaloidsP. forusgenum SCI0 41001-9.211Acarbose*8.16Asprogina SCI0 FO25-8.1-9.1-9.211Chrysamide BAllaloidsP. forus SD-34-9.02Penipacid DAllaloidsP. forus SD-34-9.03ClycosminineAllaloidsP. forus SD-34-9.03ClycosminineAllaloidsP. forus SD-34-8.852-hydroxy-6-formyl-vertixanthonePolyketidesAspergiliny spi.16-021-8.27Asplaktonol DPolyketidesAppergiliny spi.16-021-8.29Chaetowindin CPolyketidesAppergiliny spi.16-021-8.29Chaetowindin CPolyketidesAppergiliny spi.16-021-8.210Varioxegine ATerependisProtocet Appergiliny spi.16-021-8.29Chaetowindin CPolyketidesProtocet Appergiliny spi.16-021-8.29Chaetowindin CPolyketides <td>2</td> <td>Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)</td> <td>Alkaloids</td> <td>P. citreonigrum XT20-134</td> <td>-9.6</td>	2	Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)	Alkaloids	P. citreonigrum XT20-134	-9.6
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5Cyclopiamide JAlkaloidsPeritellium commune DFSCS026-9.46Malformin CPeptidesAperatilius ps. SCSIOV2-9.37Cyclopiamide EAlkaloidsPeritellium commune DFSCS026-9.38Steroids acidSteroidsPeritellium commune DFSCS026-9.39Chadosporal CPolyketidesCladosporian Calosporian	4	Cladosporol G	Polyketides	Cladosporium cladosporioides HDN14-342	-9.5
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8Sterolic acidSterolicsPericillium p.MCC 3 A00005-9.39Cladosporl CPolyketidesCladosporlum Cladosporioles HDN14-32-9.210Chrysamide BAlkaloidsP. chrysagenum SCSI0 41001-9.211Acarbose*a -glycosidase2Fenipacid DAlkaloidsP. paneum SD-44-8.83ClycosminineAlkaloidsP. paneum SD-44-8.84Speradine CAlkaloidsP. paneum SD-44-8.852-hydroxy-6-formyl-vertixanthonePolyketidesAlgory SCSI0 1020-8.27Asplatconol DPolyketidesAlgory SCSI0 41502-8.28Tenellone GPolyketidesAlgory SCSI0 41502-8.29Chactoviridin CPolyketidesAlgory SIB fiboarpus FS08-8.210Varioxegine AAlkaloidsP. circengirum sp. Kimi NA-S01-R1-8.211Acarbose*12Ozaino-cyclo-(2.2-dilydroxyl-trp-tyr)AlkaloidsP. circengirum SCI0 41001-8.85Clavatustide BPeptidesApergillus carona CSUV-8.67Verlamelin APeptidesApergillus carona CSUV-8.67Clavatustide APeptidesApergillus carona CSUV-8.67Ozaino-cyclo-(2.2-dilydroxyl-trp-tyr)AlkaloidsP. chrysogenum SCI0 41001-8.311OtasaPeptidesApergillus carona CSUV-8.6 <td>7</td> <td>Cyclopiamide E</td> <td>Alkaloids</td> <td>Penicillium commune DFFSCS026</td> <td>-9.3</td>	7	Cyclopiamide E	Alkaloids	Penicillium commune DFFSCS026	-9.3
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ar - glycosidase 1 Tenellone F Polyketides Phomopsis lithocarpus FS508 -9.1 2 Penipacid D Alkaloids P. paneum SD-44 -9.0 3 Glycosminine Alkaloids P. paneum SD-44 -8.8 4 Speradine C Alkaloids A. flowas SCOSI PO25 -8.6 5 2-hydroxy-6-formyl-vertixanthone Polyketides A. group SCOSI PO25 -8.2 6 Aspergilus Persicolar SCSI of 1502 -8.2 7 Asplactonol D Polyketides Aspergilus versicolar SCSI of 1502 -8.2 8 Tenellone G Polyketides Abergilus sp. 16-02-1 -8.2 9 Chactoviridin C Polyketides Chactowis FS508 -8.2 10 Variosceptine A Alkaloids Microsporum Sp. (MFS-YL) -8.1 11 Acarbose* - - -7.2 Pancreatic lipoprotein lipase - - -7.2 1 Acarbose Pepitdes Apergilus clavatus CAMOOS -9.0 2 Ozario-cyclo-(2,3-dihydroxyl-trp-tyr) Alkaloids P. citreonigrum XT200-134 -8.9 3 Terremide D Alkaloids P. citreonigrum XT200-134 -8.9 4 Clavatustide A<	11	Acarbose*	-	-	-8.1
1Tenellone FPolyketidesPhoneurs DS-44-9.12Penjacid DAlkaloidsP. paneum SD-44-9.03GlycosminineAlkaloidsP. paneum SD-44-8.84Speradine CAlkaloidsA. flavus SCISO P025-8.652-hydroxy-6-formyl-vertixanthonePolyketidesA. glavus SCISO P025-8.26Aspergilol IPolyketidesAspergillus yn 16-02-1-8.27Aspilactonol DPolyketidesAspergillus yn 16-02-1-8.28Tenellone GPolyketidesChaetoninus sp. strain NA-S01-R1-8.29Chaetoviridin CPolyketidesChaetoninus sp. strain NA-S01-R1-8.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*7Panetosinipum St1Brevione ATerrenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)AlkaloidsP. chrosogenum SCIO 41001-8.85Clavatustide BPeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCC 3A00005-8.67Verlamelin APeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesSimplicillium sp. MCC 3A00005-8.67Verlamelin APeptidesSimplicillium sp. SCIO 41001-8.310Clavatustide BPerites	α -glycosidase				
2Penipacid DAlkaloidsP. paneum SD-44-9.03GlycosminineAlkaloidsP. paneum SD-44-8.84Speradine CAlkaloidsA. flows SCNO F025-8.652-hydroxy-6-formi-vertixanthonePolyketidesA. sydowii C1-S01-A7-8.36Aspergitol IPolyketidesAspergitus versicolar SCNO 41502-8.27Asplatatonol DPolyketidesAspergitus versicolar SCNO 41502-8.29Chactoviridin CPolyketidesPhomopsis lithocarpus FS08-8.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*Pancreatic lipoproteinBrevione ATerpenoidsPenicillium sp. MCCC 3A00005-9.02Ozaino-cyclo-(2.3-dihydroxyl-trp-tryr)AlkaloidsP. chrosogenum SCIO 41001-8.84Clavatustide BPeptidesAspergitus clavatus C2WU-8.85Clavatustide APeptidesAspergitus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium ps. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium ps. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsP. chrysogenum SCSIO 41502-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.32Penicilliumide HPeptidesSimplicillium obclavatum EIODSF 02	1	Tenellone F	Polyketides	Phomopsis lithocarpus FS508	-9.1
3ClycosminneAlkaloids <i>P</i> , pareum SD-448.84Speradine CAlkaloids <i>A. flavus</i> SCIO P0258.652-hydroxy-6-formyl-vertixanthonePolyketides <i>A. spergillus</i> specifical SCIO P0258.26Aspergillo IPolyketidesAspergillus sp. 16-02-18.27Aspilactonol DPolyketidesPhomposis lithocarpus PS5088.29Chaetoviridin CPolyketidesPhomposis lithocarpus PS5088.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)8.111Acabose*Pancreatic lipporotein lipase1Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. chrysogenum SCIO 410018.85Clavatustide BPeptidesApergillus clavatus CZWU8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A000058.67Verlamelin APeptidesApergillus clavatus CZWU8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A000058.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 0208.68Brevione JTerpenoidsPenicillium sp. NCC 3A000058.510Chrysamide AAlkaloidsAcrostalagmus luteoalbus SCIO 415029.87Verlamelin APeptidesSimplicillium obclavatum EIODSF 0209.8	2	Penipacid D	Alkaloids	P. paneum SD-44	-9.0
4Speradine CAlkaloidsA. Juvis SCIO 10258.652hydroxy-6-formyl-vertixanthomePolyketidesA. sydowii (-Sol - A78.36Aspergillo JPolyketidesAspergillus yersicolor SCIO 415028.27Aspilactonol DPolyketidesPhonopsis lithocarpus FS5088.28Tenellone GPolyketidesPhonopsis lithocarpus FS5088.29Chaetoviridin CPolyketidesPhonopsis lithocarpus FS5088.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-VL)8.111Acarbose*Pancreatic lipoprotein lipase1Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cycloc-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. citreonigrum KT20-1348.93Terremide DAlkaloidsP. citreonigrum KT20-1348.94Clavatustide APeptidesAspergillus clavatus C2WU8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A000058.67Verlamelin APeptidesSimplicillium beloavatum EIODSF 0208.68Brevione JTerpenoidsPenicillium sp. MCCC 3A000058.510Chrysamide AAlkaloidsAcrostalgmus theeobus SCIO 4578.511Orlisat*12Simplicilliumtide HPeptidesAspergillus chavatus EIODSF 020-9.8<	3	Glycosminine	Alkaloids	P. paneum SD-44	-8.8
52-hydroxy-e-formyl-vertixanthonePolyketidesA spargilla y spicolor SCIO 41502-8.36Asperigilla y spicolor SCIO 41502-8.27Aspilactonol DPolyketidesAspergilla y spicolor SCIO 41502-8.28Tenellone GPolyketidesPhomopsis lithocarpus FSO8-8.29Chaetoviridin CPolyketidesChaetomium sp. strain NA-S01-R1-8.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*7.2Pancreatic lipoprotein lipaseTerrenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. chryosgenum SCIO 41001-8.83Terremide DTerpenoidsAspergillus clavatus C2WU-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesSpergillus clavatus C2WU-8.86Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSpergillus clavatus C2WU-8.86Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium beclavatum EIODSF 020-8.59Luteoalbusin BAlkaloidsAcrostalagmus luteoalbus SCIO 41502-9.41Orlista*1Simplicilliumtide HPeptidesSimplicillium beclavatum EIODSF 020-9.8<	4	Speradine C	Alkaloids	A. flavus SCSIO F025	-8.6
6Aspergilui versicolor SCSIO 41502-8.27Aspirgiluis versicolor SCSIO 41502-8.28Tenellone GPolyketidesAspergiluis versicolor SCSIO 41502-8.29Chactoviridin CPolyketidesPhompasis lithocarpus FS508-8.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*7.2Pancreatic lipoprotein lipas7.21Brevione ATerpenoidsPericillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. citronigrum XT20-134-8.93Terremide DAlkaloidsP. citronigrum XT20-134-8.84Clavatustide BPeptidesAspergiluis clavatus C2WU-8.85Clavatustide APeptidesAspergiluis clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSP 020-8.68Brevione JTerpenoidsPenicillium sp. F11-9.59Luteoalbusin BAlkaloidsP. chrosignum SCSIO 41001-8.311Orlista*12Simplicilliumited HPeptidesSimplicillium obclavatum EIODSP 020-8.67Chravatustide BPeptidesAspergilus versicolor SCIO 41502-9.412Simplicilliumited HPeptidesAspergilus versicolor SCIO 41502-	5	2-hydroxy-6-formyl-vertixanthone	Polyketides	A. sydown C1-S01-A7	-8.3
Asplaction DPolyketidesApergulus sp. 16-02-18.28Tenellone GPolyketidesChaetomium sp. strain NA-S01-R18.29Chaetoviridin CPolyketidesChaetomium sp. strain NA-S01-R18.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)8.111Acarbose*7.2Pancreatic lipoprotein lipase7.21Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. citreonigrum XT20-134-8.93Terremide DAlkaloidsP. citreonigrum XT20-134-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsActorstalagmus luteoalbus CSUO P107-8.311Orlistat*12Simplicilliumide HPeptidesSimplicillium sp. FI1-9.53Aspergillo HPolyketidesAspergillus versicolor SCIO 41502-9.44Clavatustide BPeptidesAspergillus versicolor SCIO 41502-9.37Citroiatome BPolyk	6	Aspergilol I	Polyketides	Aspergillus versicolor SCSIO 41502	-8.2
8Intelline GPolyketidesPhomopsis infracture PS-S08-8.29Chactoviridin CPolyketidesChactorium sp. stin. NA-S01-R1-8.110Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*Pancreatic lipoprotein lipase1Brevione ATerpenoidsPericillium sp. MCC 3A00005-9.02Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)AlkaloidsP. citreonigrum XT20-134-8.93Terremide DAlkaloidsP. chrysogenum SCSI0 41001-8.84Clavatustide APeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesSimplicillium sp. MCC 3A00005-8.67Verlamelin APeptidesSimplicillium sp. MCC 3A00005-8.68Brevione JTerpenoidsPericillium sp. MCC 3A00005-8.59Luteoalbusin BAlkaloidsP. cristogamus lucealbus SCSI0 F457-8.510Chrysamide AAlkaloidsP. cristogamus Lucealbus SCSI0 F457-8.52Penicilliumtide HPetidesSimplicillium obclavatum EIODSF 020-9.41Simplicillium the Mathematic Presention1Simplicilliumtide HPetidesAspergillus clavatus C2WU-9.32PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilo HPolyketidesAspergillus duratus C2WU-9.34	7	Aspilactonol D	Polyketides	Aspergillus sp. 16–02-1	-8.2
9Chaetoviratin CPolyketitesChaetomum sp. strain NA-SUT-R1-8.210Varioxepine AAlkaloidsMicrosporum sp. (MFS-YL)-8.111Acarbose*7.2Pancreatic lipoprotein lipae7.22Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)AlkaloidsP. chreongrum XT20-134-8.93Terremide DAlkaloidsP. chreongrum XT20-134-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsAcrostalogmus Interadibus SCSIO F457-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlistat*12Penicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicilliatanTerpenoidsPenicillium sp. CSIO 41501-9.93Aspergilo HPolyketidesP. cirrum MLG-SOI-P1-9.44Penicilliumtide HPeptidesAspergillus clavatus C2WU-9.82Clavatustide BPenicillium sp. F0120-9.44Penicilliaten BPeptidesAspergillus clavatus C2WU <td< td=""><td>8</td><td>Ienellone G</td><td>Polyketides</td><td>Phomopsis lithocarpus FS508</td><td>-8.2</td></td<>	8	Ienellone G	Polyketides	Phomopsis lithocarpus FS508	-8.2
10Vartoxepine AAnkaloidsMicrosportum Sp. (MicS-TL)B.111Acarbose*7.2Pancreatic lipoprotein lipase1Brevione ATerpenoidsPericillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)AlkaloidsP. citreonigrum XT20-134-8.93Terremide DAlkaloidsP. chrysogenum SCSIO 41001-8.84Clavatustide APeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.66Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillum obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlistat*1Simplicilliumide AAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlistat*1Simplicillium tide HPeptidesSimplicillium obclavatum EIODSF 020-9.82Penicitla CamTerpenoidsPenicillium sp. F11-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.86PurpurogenutantinTerpenoidsPenicillium sp. F00120 <t< td=""><td>9</td><td></td><td>Polyketides</td><td>Chaetomium sp. strain NA-SUI-RI</td><td>-8.2</td></t<>	9		Polyketides	Chaetomium sp. strain NA-SUI-RI	-8.2
11AcarosePancreatic lipoprotein lipaseBrevione ATerremide DAlkaloidsP. chrysogenum SCSIO 41001 <td< td=""><td>10</td><td>Varioxepine A</td><td>Alkalolds</td><td>Microsporum sp. (MFS-YL)</td><td>-8.1</td></td<>	10	Varioxepine A	Alkalolds	Microsporum sp. (MFS-YL)	-8.1
Pranceatic inpoprietin inpase1Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. chrysogenum SCSI0 41001-8.83Terremide DAlkaloidsP. chrysogenum SCSI0 41001-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsP. chrysogenum SCSI0 F457-8.510Chrysamide AAlkaloidsP. chrysogenum SCSI0 41001-8.311Orlistat*5.4Hexokinase-IIISimplicillium bclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilo HPolyketidesAspergillus crisciolor SCIO 41502-9.44Penicitol DPolyketidesAspergillus clavatus C2WU-9.36PurpurogenutationTerpenoidsPenicillium sp. F0120-8.87Clavatustide BPelptidesAspergillus clavatus C2WU-9.36PurpurogenutationTerpenoidsPenicillium sp. F00120-8.87Clavatustide BPolyketidesPenicillium	II Demonstration the subscription	Acarbose	-	-	-1.2
1Brevione ATerpenoidsPencilium sp. MCCC 3A00005-9.02Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)AlkaloidsP. citrooigrum XT20-134-8.93Terremide DAlkaloidsP. citrooigrum XT20-134-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.59Luteoalbusin BAlkaloidsP. chrysogenum SCSIO 41001-8.310Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.511Orlistat*5.4Hexokinase-II5.414Simplicilliumtide HPeptidesAspergillus versicolor SCSIO 41502-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicilo DPolyketidesPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCIO 140611-8.78Verlamelin APeptidesSimplicillium obclavatus E2WU-9.45Clavatustide BPolyketidesPenicillium sp. SCIO 1416P01-8.78Verlamelin APeptidesSimplicillium sp. SCIO 1416P01-8.7 <td< td=""><td>Pancreatic lipoprotein</td><td>lipase</td><td>T</td><td>Devisition of MCCC 2400005</td><td></td></td<>	Pancreatic lipoprotein	lipase	T	Devisition of MCCC 2400005	
2Ozazino-cyclor(2, -)-dinydroxyl-trp-tyr)AtkaloidsP. chrysogenum SCSIO 41001-8.83Terremide DAlkaloidsP. chrysogenum SCSIO 41001-8.84Clavatustide BPeptidesAspergillus clavatus C2WU-8.85Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 300005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 300005-8.59Luteoalbusin BAlkaloidsAcrostalgamus luteoalbus SCSIO F457-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlista*54Hexokinase-IIIterpenoidsPenicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergilus versicolor SCSIO 41502-9.44Penicitol DPolyketidesPenicillium sp. F0120-8.87Clavatustide BPeptidesSimplicillium sp. SCSIO 141502-9.45Clavatustide BPeptidesPenicillium sp. SCSIO 141502-9.46PurpurogenutantinTerpenoidsPenicillium sp. SCSIO 141502-9.37Citrinolactone BPolyketidesPenicillium sp. SCSIO 141502-8.78Verlamelin APeptidesSimplicillium sp. SCSIO 141502	1	Brevione A	Terpenoids	Penicilium sp. MCCC 3A00005	-9.0
3Tetreminde DAtkalousP. Unysogenum SCSIO 410018.84Clavatustide BPeptidesAspergillus clavatus C2WU8.85Clavatustide APeptidesAspergillus clavatus C2WU8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A000058.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 0208.68Brevione JTerpenoidsPenicillium sp. MCCC 3A000058.59Luteoalbusin BAlkaloidsAcrostalagmus huteoalbus SCSIO F4578.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 410018.311Orlistat*1Simplicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicilium sp. SCSIO Ind16F01-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS031-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.69Ph	2	Ozazino-cycio-(2,3-anyaroxyi-trp-tyr)	Alkaloids	P. christernum SCSIO 41001	-8.9
4Clavatustice bPeptidesAspergillus clavatus C2WU-6.65Clavatustide APeptidesAspergillus clavatus C2WU-8.86Brevione BTerpenoidsPenicillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenicillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsAcrostalagmus luteoalbus SCSIO F457-8.510Chrysamide AAlkaloidsAcrostalagmus luteoalbus SCSIO F457-8.511Orlistat*1Simplicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilo HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitlo DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. SCSIO 101016F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesPenicillium sp. SCSIO 1016F01-8.710Varioxepine AAlkaloidsPaecilomyces varioti EN-291-8.611Benserazide*9Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.7	3	Clavatustido P	Alkalolus	P. Chrysogenum SCSIO 41001	-8.8
5Charatistitie APeptidesPeptidesPeptidus Unduits Cuvul Cuvul8.66Brevione BTerpenoidsPenticillium sp. MCCC 3A00005-8.67Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.68Brevione JTerpenoidsPenticillium sp. MCCC 3A00005-8.59Luteoalbusin BAlkaloidsAcrostalagmus luteoalbus SCSIO F457-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlistat*5.4Hexokinase-IIISimplicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitlo DPolyketidesAspergillus versicolor SCSIO 41502-9.45Clavatustide BPeptidesAspergillus versicolor SCSIO 41502-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. F00120-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces varioti EN-291-8.611Benserazide*7.612Varioxepine AAlkaloidsPaecilomyces varioti EN-291-9.42Varioxepine AAlkaloidsPaecil	4 E	Clavatustide A	Peptides	Aspergillus clavatus C2WU	-0.0
6Devolue BPerformPe	5	Clavalustice A	Terneneide	Asperginus ciuvatus C2WO	-0.0
7Vertainerin APeptidesSimplification obclocation (EDDS) 020-8.38Brevione JAlkaloidsPenicillium sp. MCC 3A00005-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.311O'listat*5.4Hexokinase-IISimplicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesAspergillus versicolor SCSIO 41502-9.35Clavatustide BPeptidesAspergillus versicolor SCSIO 41502-9.36PurpurogemutantinTerpenoidsPenicillium NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. GO120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1BItalioidsPaecilomyces variotii EN-291-9.12Varioxepine AAlkaloidsPaecilomyces variotii EN-291	7	Vorlamelin A	Poptidos	Simplicillium obclavatum ELODSE 020	-8.0
aDevolue fTepenoidsPentinitian sp. NuCC 3A00003-0.59Luteoalbusin BAlkaloidsAcrostalagmus lutecalbus SCSIO F457-8.510Chrysamide AAlkaloidsP. chrysogenum SCSIO 41001-8.311Orlistat*5.4Hexokinase-II5.42Penicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.83Aspergilol HPolyketidesPenicillium sp. F11-9.54Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*1Clavatustide BPeptidesAspergilus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.613Brevione AAlkaloidsPaecilomyces variotii EN-291-9.42Varioxepine AAlkaloidsPaecilomyces varioti EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC	7 0	Proviona I	Terpopoide	Denicillium cp. MCCC 2A00005	-8.0
5Detected outsin bAnkalordsArbitication and the outbuild section of section of the outbuild section of the outbuild section of the outbuild section of the outbuild	0	Lutooalbusin P	Alkaloida	Acrostalagmus lutaoglbus SCSIO E457	-8.5
10OriginationInitiationInit	10	Chrysamide A	Alkaloids	P chrysogenum SCSIO 41001	-8.3
Hexokinase-IISimplicilliumtide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesPiacolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7Clavatustide BPeptidesAspergillus clavatus C2WU-9.41Clavatustide BPeptidesPaecilomyces variotii EN-291-8.611Benserazide*12Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione AAlkaloidsPaecilomyces variotii EN-291-9.1	10	Orlistat*	-	-	-54
1Simplicilliumide HPeptidesSimplicillium obclavatum EIODSF 020-9.82PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7Clavatustide BPeptidesAspergillus clavatus C2WU-9.41Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*12Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	Hexokinase-II	onistat			-5.4
2PenicillactamTerpenoidsPenicillium sp. F11-9.53Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7Clavatustide BPeptidesAspergillus clavatus C2WU-9.41Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*12Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	1	Simplicilliumtide H	Peptides	Simplicillium obclavatum EIODSF 020	-9.8
3Aspergilol HPolyketidesAspergillus versicolor SCSIO 41502-9.44Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO 1016F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7Clavatustide BPeptidesAspergillus clavatus C2WU-9.41Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione AAlkaloidsPaecilomyces variotii EN-291-9.1	2	Penicillactam	Terpenoids	Penicillium sp. F11	-9.5
4Penicitol DPolyketidesP. citrinum NLG-S01-P1-9.45Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SOSIO Ind 16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	3	Aspergilol H	Polyketides	Aspergillus versicolor SCSIO 41502	-9.4
5Clavatustide BPeptidesAspergillus clavatus C2WU-9.36PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	4	Penicitol D	Polyketides	P. citrinum NLG-S01-P1	-9.4
6PurpurogemutantinTerpenoidsPenicillium sp. F00120-8.87Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	5	Clavatustide B	Peptides	Aspergillus clavatus C2WU	-9.3
7Citrinolactone BPolyketidesPenicillium sp. SCSIO Ind16F01-8.78Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	6	Purpurogemutantin	Terpenoids	Penicillium sp. F00120	-8.8
8Verlamelin APeptidesSimplicillium obclavatum EIODSF 020-8.79Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A000055-8.7	7	Citrinolactone B	Polyketides	Penicillium sp. SCSIO Ind16F01	-8.7
9Phaseolorin EPolyketidesDiaporthe phaseolorum FS431-8.710Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1B7.61Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenticillium sp. MCCC 3A00005-8.7	8	Verlamelin A	Peptides	Simplicillium obclavatum EIODSF 020	-8.7
10Varioxepine AAlkaloidsPaecilomyces variotii EN-291-8.611Benserazide*7.6Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	9	Phaseolorin E	Polyketides	Diaporthe phaseolorum FS431	-8.7
11Benserazide* Protein tyrosine phosphatase-1B1011000<	10	Varioxepine A	Alkaloids	Paecilomyces variotii EN-291	-8.6
Protein tyrosine phosphatase-1B1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	11	Benserazide*	-	_	-7.6
1Clavatustide BPeptidesAspergillus clavatus C2WU-9.42Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	Protein tyrosine phosp	hatase-1B			
2Varioxepine AAlkaloidsPaecilomyces variotii EN-291-9.13Brevione ATerpenoidsPenicillium sp. MCCC 3A00005-8.7	1	Clavatustide B	Peptides	Aspergillus clavatus C2WU	-9.4
3 Brevione A Terpenoids <i>Penicillium</i> sp. MCCC 3A00005 –8.7	2	Varioxepine A	Alkaloids	Paecilomyces variotii EN-291	-9.1
	3	Brevione A	Terpenoids	Penicillium sp. MCCC 3A00005	-8.7
4 Brevione B Terpenoids <i>Penicillium</i> sp. MCCC 3A00005 -8.4	4	Brevione B	Terpenoids	Penicillium sp. MCCC 3A00005	-8.4
5 Clavatustide A Peptides Aspergillus clavatus C2WU –8.4	5	Clavatustide A	Peptides	Aspergillus clavatus C2WU	-8.4
6 Austinol Terpenoids Penicillium sp. Y-5–2 –8.4	6	Austinol	Terpenoids	Penicillium sp. Y-5–2	-8.4
7 7-hydroxydehydroaustin Terpenoids Penicillium sp. Y-5–2 –8.1	7	7-hydroxydehydroaustin	Terpenoids	Penicillium sp. Y-5–2	-8.1
8 Circumdatin G Alkaloids Aspergillus sp. (CF07002 –8.0	8	Circumdatin G	Alkaloids	Aspergillus sp. (CF07002	-8.0
9 Brevione J Terpenoids Penicillium sp. MCCC 3A00005 –8.0	9	Brevione J	Terpenoids	Penicillium sp. MCCC 3A00005	-8.0
101-epi-citrinin H1PolyketidesP. citrinum NLG-S01-P1-7.9	10	1-epi-citrinin H1	Polyketides	P. citrinum NLG-S01-P1	-7.9
11 Trodusquemine* – – – – – – – 5.8	11	Trodusquemine*	-	-	-5.8

*Ligand control.

3.2. Interpretations of the best docked inhibitor molecules

In the cladosporal C and α -amylase complex, three conventional hydrogen bonds strengthened the complex, whereas hydrophobic interactions also dominated in the complex stability (Fig. 1). The docking results showed a stronger binding energy of cladosporal C with α -amylase (-9.8 kcal/mol) as compared to that of control ligand acarbose (-8.0 kcal/mol) (Table 1).

The docked complex of tenellone F and α -glucosidase also had four conventional hydrogen bonds in addition to hydrophobic interactions that further strengthened its stability (Fig. 2). Therein, tenellone F had a stronger binding energy (-9.1 kcal/mol) as compared to the control ligand acarbose (-7.2 kcal/mol) (Table 1).

The ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) and LPL complex was strengthened by four conventional hydrogen bonds, supported by several hydrophobic interactions (Fig. 3). Ozazino-cyclo-(2,3-d

Table 2

Selection of best inhibitors of	f glucose metabolism	enzymes based o	n physiochemical	properties of l	ligand-protein compley	es.
	0		1	F . F	0 1 1	

pr-amylase series series series series 2 Ozarino-cycle (2.3 dilydroxyl-trp-tyr) 365.39 3 5 0.92 0 3 Dictrinone B 338.36 3 5 3.22 1 0 4 Cadosporol G 338.36 3 5 3.22 1 0 5 Cyclopamide I 313.31 2 4 1.88 1 0 6 Midfornin C 313.31 2 4 1.88 1 0 7 Cyclopamide I 313.31 2 4 1.88 1 0 10 Chyclopamide I 313.31 2 4 1.79 2 0 7 Tenclico M 326.31 2 4 1.79 2 0 2 Mipoxino C 370.41 1 5 0.77 2 0 2 Applactorino 4452.3 1 6 3.52 2 1	Enzymes (Targets)	Compounds (Ligands)	MW (g/mol)	HBD	HBA	AlogP	Rotatable bonds	RO5 (Violations)
nBervione I438.56154.4600Dazamo eyol-(23-dilydroxyl-trp-ty)438.52264.92201Chadosporol G333.66352.22105Cyclopiamide J428.4437-0.62216Malforma C313.38043.860007Cyclopiamide J31.38043.860009Chadosporol C370.31262.915009Chadosporol C370.30571.161119Chadosporol C370.312641.79209Chadosporol C370.31241.792009Chadosporol C370.31241.7920010Chadosporol C370.31271.5021109Chadosporol C370.312163.60000011Specific C342.32163.600 <td< td=""><td>α-amvlase</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	α-amvlase							
2Diztine-ryde-(2-3-dihydroxyl-trp-ty)863.9359.29.203Cladosporal G333.63532.2104Cladosporal G333.8370.62.105Vyclopianide J310.31241.86106Vyclopianide J313.31241.86107Vyclopianide J313.31241.86108Vyclopianide J313.31241.86107Cladosporal C313.31241.861010Cladosporal C354.5171.16111	1	Brevione I	438.56	1	5	4.46	0	0
3 Dictimione B 438.52 2 6 4.22 2 0 5 Cyclopianide J 438.36 3 3 322 1 0 5 Cyclopianide J 428.44 3 7 -0.6 2 1 7 Cyclopianide F 331.38 0 4 3.06 0 0 7 Cyclopianide F 331.38 0 4 3.06 0 0 8 Strofic Acid 484.59 2 6 2.91 5 0 1 1 1 0 Chrysomide B 254.51 1 10 2.47 2 0 10 Chrysomide B 236.23 2 4 1.79 2 0 10 Chrysominine 370.41 1 5 0.77 2 0 10 Application 348.53 6 8 1.32 2 0 0 10 Chrysomine	2	Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)	365.39	3	5	0.9	2	0
466.333.6353.2106Malformin C310.31241.63116Malformin C310.31241.86107Calobayoni C313.33041.80108Malformin C31.330401.161110Calobayoni C37.330111	3	Dicitrinone B	438.52	2	6	4.92	2	0
5Cyclopiamide J428.437-0.6216Malormin C310.31241.88107Cyclopiamide E311.38041.818108Steolic acid344.59262.915110Chrysmide E370.36571.161117Penipacid D246.23241.79207Penipacid D246.23241.79202Penipacid D246.23241.79203Cycosminine236.23241.79204Speradine C370.41150.77204Aspergiol 1386.37681.57526Aspergiol 1386.37681.57527Aspergiol 1386.37681.575317Castorrich C436.25172.88017Castorrich C436.37172.88018Castorrich C42.578172.98309Castorrich C355.15092.9962010Chastorrich C355.15033111.52119Ca	4	Cladosporol G	338.36	3	5	3.22	1	0
6Malformin C310.3244.8107Ckolopanide E31.38043.0608Sterolic acid484.59262.105010Chrysamide B57.03571.161110Chrysamide B370.36571.161111Sterolic acid70.362641.79202Penjacid D236.23241.79203Giycosminine236.23241.79203Giycosminine306.23250.77203Appliationol D216.23250.772015Appliationol D216.23172.98006Appergiol 1388.3764.27253.16009Chactoviridin C434.92164.270111 <t< td=""><td>5</td><td>Cyclopiamide J</td><td>428.44</td><td>3</td><td>7</td><td>-0.6</td><td>2</td><td>1</td></t<>	5	Cyclopiamide J	428.44	3	7	-0.6	2	1
7Cyclopiamide E31.380496009Cladosporol C ado370.40571.6011110Cladosporol C ado370.40571.60111	6	Malformin C	310.31	2	4	1.88	1	0
8Sternlik acid94669.9.9.9.9Chaysamide Bornol370.3659.1.161.208.9.10Chrysamide Bornol370.461.0108.9.9.9.10Penellone F244.912.66.44.569.9.9.11Segaratine C370.41150.772.0.9.2Segaratine C370.411.41.50.772.0.1.50.771.50.1.50.771.50.1.50.771.50.1.5	7	Cyclopiamide E	331.38	0	4	3.06	0	0
9Cladosporol C7036771.61.61110Cladysmide B554.5102.4782r-givoridase24.49264.57332Penipacid D236.23241.792332Speradine C362.33241.7923332Speradine C362.33241.7933	8	Sterolic acid	484.59	2	6	2.91	5	0
10Chrysamide B56/110102789c-sqluoraidaTenellone F4449264.56901216.23241.792003Gyrasminia236.23241.792003Gyrasminia270.41150.772005Applicatione G370.41150.772005Applicatione G383.77681.525206Aspliactonel D244.9364.279007Applicatione G244.94364.279007Chaetovindin C424.92164.2790010Chaetovindin C424.93172.9830007Chaetovindin C424.93164.27900010Chaetovindin C424.93164.27000 <td>9</td> <td>Cladosporol C</td> <td>370.36</td> <td>5</td> <td>7</td> <td>1.16</td> <td>1</td> <td>1</td>	9	Cladosporol C	370.36	5	7	1.16	1	1
relelore F244.42664.6902Penipacid D236.23241.79203Gyosminine236.23241.79204Speradine C370.41150.77204Appergilol T388.37681.525006Aspergilol T216.3225-0.30407Appergilol T216.3225-0.30407Appergilol T216.32164.27907Appergilol T424.90364.27909Cacorridin C434.9216366010Variosepine A424.57172.983019Cazarino-cycle(2.3-dihydroxyl-trp-tyr)365.39350.9920010Chavattstide A471.51253.1220011Clavattstide A471.51253.1220012Clavattstide A471.51253.1220013Clavattstide A471.51253.1220014Clavattstide A471.51253.1220015Clavattstide A771.5131 <t< td=""><td>10</td><td>Chrysamide B</td><td>554.51</td><td>1</td><td>10</td><td>2.47</td><td>8</td><td>2</td></t<>	10	Chrysamide B	554.51	1	10	2.47	8	2
1Tenellone F42449264.56902241.79203Glycosminine236.32241.79205Glycosminine370.41150.70205Alydroxy-6-formyl-vertixanthone314.25271.962216Aspeilol I388.37681.52522317Asplactonol D216.3225-0.39408Tenelone G424.49364.2436209Chaetowindin C424.39163.660010Varosepine A453.51172.00112Ozazino-cycle(2.3-dihydroxyl-trp-tyr)585.10359.022010Cavatustide B475.49253.1220010Cavatustide A475.19253.1220011Brevione B475.49253.1220112Cavatustide B496.40151011113Cavatustide B496.51154.680011111111111111111 </td <td>α-glycosidase</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	α-glycosidase							
2Penipacid D236.23241.79203Glycosminine236.23241.79204Speradine C37041150.77204Aspergilol Toml-vertixanthone314.25271.96226Aspergilol Toml-vertixanthone314.25271.962227Asplatonal D216.2325-0.39408Tenelhore G444.90364.27909Cheroviridin C434.92163.6609Cheroviridin C444.92163.6609Cheroviridin C444.92163.073.009Charoviridin C444.931789009Charoviridin C435.31092.9062010Charoviridin C58.51092.9062014Charoviridin C58.510453.1220015Charoviridin C47.51253.12300016Charoviridin C47.51253.122000017Verlamelin A876.17811.911.5140110 <td>1</td> <td>Tenellone F</td> <td>424.49</td> <td>2</td> <td>6</td> <td>4.56</td> <td>9</td> <td>0</td>	1	Tenellone F	424.49	2	6	4.56	9	0
3Glycosminine236.23241,79204Speadine C370411567,72052-hydraxy-6-formyl-vertixanthone314.25271,962116Aspergilo I388.37681.525227Aspilactonal D216.2325-0.39409Chactoviridin C434.92163.666010Varioxepine A424.92163.6860Pancreatic lipoprotein lipae72.983172.9817Parcine A422.57045.480112Ozario-cyclo-(2.3-dihydroxyl-trp-tyr)35.38092.996223Clavatustide B47.151253.513006Brevione B424.58043.5130017Verlamelin A872.078111.521548Brevione I406.54373.5421110Chavatustide A496.64373.5421110Lutenabusin B496.54374.2621111111111111111 <t< td=""><td>2</td><td>Penipacid D</td><td>236.23</td><td>2</td><td>4</td><td>1.79</td><td>2</td><td>0</td></t<>	2	Penipacid D	236.23	2	4	1.79	2	0
4Spendine C370.41150.77205	3	Glycosminine	236.23	2	4	1.79	2	0
52-hydroxyformyl-vertixanthone314.25271.96216Aspilactono I36.2325-0.39407Aspilactono I216.2325-0.39409Chaetovirdin C434.92163.66010Varioxepine A434.92163.66010Sation-cyclo (2,3-dihydroxyl-trp-tyr)365.39350.9203Clavatustide B474.51092.996204Clavatustide B474.51253.513006Brevione B424.58045.710117Verlamelin A872.078111.521546Brevione B424.58045.71017Verlamelin A872.078111.521548Brevione J406.64373.342110Chavatustide A524.5108111.52148101.521.513.1220110Chavatustide B496.64373.3421110Chavatustide B496.64374.6221110Chavatustide B457.49253.12	4	Speradine C	370.41	1	5	0.77	2	0
6Aspergilol I388.37681.525927Asplicatonol D216.23250.39408Tenellone G424.4936427.9909Chactoviridin C434.49163.66010Varioxepine A43.53172.9831Pancreatic lipoproteDiservine A422.57045.48012Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)365.39350.99203Clavatustide B457.49253.12206Clavatustide B457.49253.51305Clavatustide A471.51253.51306Brevione B424.58045.71017Verlamelin A872.078111.521548Brevione J440.58154.680009Luteoalbusin B395.374610120110Chavatustide B474.94253.122010Chavatustide B474.94253.122010Chavatustide B474.94253.122010Chavatustide B474.94253.1221<	5	2-hydroxy-6-formyl-vertixanthone	314.25	2	7	1.96	2	1
7Aspilactonol D216.2325-0.39408Tenellone G4244936427909Chaetovirdin C434.92163.66010Varioxepine A434.92163.660Pancreatic lipoprotein lipasF2.983172.98112Ozaino-scloc(2,3-dihydroxyl-trp-tyr)353.935092.99623Clavatustide D538.51092.996205Clavatustide A471.51253.513006Brevione B426.8154.68011	6	Aspergilol I	388.37	6	8	1.52	5	2
8Tenellone G424.49364,7909Chactoviridin CC43.4921666010Varioxepine A43.53172,8331Pancreatic lipoproteill	7	Aspilactonol D	216.23	2	5	-0.39	4	0
9Chactovindin C434.92163.66010Varioxepine A436.3217.82.9831Pancreatic lipoprotein lipser822.983011Brevine A422.57045.99309203Terremide D538.51092.9962253.122004Clavatustide A471.51253.123000 </td <td>8</td> <td>Tenellone G</td> <td>424.49</td> <td>3</td> <td>6</td> <td>4.27</td> <td>9</td> <td>0</td>	8	Tenellone G	424.49	3	6	4.27	9	0
10Varioxepine A663.53172.8831Pancreatic lipoprotein L	9	Chaetoviridin C	434.92	1	6	3.6	6	0
Parcentic lipoprotein lipo	10	Varioxepine A	463.53	1	7	2.98	3	1
1Brevione Å422.57045.48012Ozazino-cycl-(2,3-dihydroxyl-trp-tyr)365.393592.99623Clavatustide D538.51092.99624Clavatustide A477.49253.12205Clavatustide A477.49253.12206Brevione B424.58045.71017Verlamelin A872.078154.68009Lutcoalbusin B496.64373.3421110Chrysamide A224.53083.1362110Chrysamide A254.53081.0120310Sepergilol H585.7461.0120314Penicitalcara395.37461.01203163115415Magnetizer B101.2122011 <td>Pancreatic lipoprotein li</td> <td>pase</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Pancreatic lipoprotein li	pase						
2Ozazino-cyclo-(2.3-dihydroxyl-trp-tyr)36.3350.9203Terremide D538.5109204Clavatustide A457.49253.12205Clavatustide A471.51253.51306Brevione B242.58045.71017Verlamelin A872.078111.521548D496.64373.342110Chrysmide A946.64373.3421110Chrysmide A986.18111.9115412Penicillatam395.37461.012013Appergilol H598.661068414Penicilol D428.48374.262115Clavatustide B457.49253.122016Purpurogemutatin304.3160.30110Varioxepine A372.078111.514110Varioxepine A457.49253.122013Our172.9801114Varioxepine A362.9781.2120115Marine B457.49253.122<	1	Brevione A	422.57	0	4	5.48	0	1
3Terrenide D538.51092.99624Clavatustide B457.49253.12205Clavatustide A471.51253.51306Brevione B424.58045.71017Verlamelin A872.07811.521548Brevione J400.58154.68009Luteoalbusin B966.4373.342110Chrysamide A524.53083.1262Hexokinase-II86.18111.911542Penicilalcam895.374610.1203Aspergilol H395.374610.1204Penicilalcam395.374610.1203Aspergilol H395.374610.1204Penicilalcam395.374610.1205Clavatustide B457.49253.12206Purpurogenutatin395.373122.12227Clavatustide B457.49253.122228Verlamelin A872.078111.521549Phaseolorin E872.07811 <td>2</td> <td>Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)</td> <td>365.39</td> <td>3</td> <td>5</td> <td>0.9</td> <td>2</td> <td>0</td>	2	Ozazino-cyclo-(2,3-dihydroxyl-trp-tyr)	365.39	3	5	0.9	2	0
4Clavatustide B477.49253.12205Clavatustide A471.51253.51306Brevione B424.58045.71017Verlamelin A872.07811.521548Brevione J440.58154.68009Luteoalbusin B496.64373.342110Chrysamide A294.53083.3462Hexokinase-IIFinicilliurntide H886.18111.911542Penicillactam395.3761006843Aspergilol H598.66106844Penicitol D428.48374.26215Clavatustide B457.4923.122006Purpurgemutantin304.3163.122226Clavatustide B576.513122.122228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A463.51253.12207Clavatustide B474.49253.12319Phaseolorin E <td< td=""><td>3</td><td>Terremide D</td><td>538.51</td><td>0</td><td>9</td><td>2.99</td><td>6</td><td>2</td></td<>	3	Terremide D	538.51	0	9	2.99	6	2
5Clavatistide A71,51253.51306Brevione B424.58045.71017Verlamelin A872.078111.521548Brevione J496.64153.34219Luteoalbusin B524.53083.3162Hexokinase-IIChrysamide A524.53083.316210Simplicillumide H886.18101.01203Aspergilol H598.66106844Penicitlo D428.48374.26215Clavatustide B457.49253.12206Purpurogemutantin304.31601017Clirinolatone B576.513122.12228Verlamelin A872.078111.521549Purpurogemutantin308.29172.983110Varioxepine A463.53172.98319Phaseolorin E57172.983110Varioxepine A463.53172.98312Clavatustide B474.51253.513010Varioxepine A463.531 <td>4</td> <td>Clavatustide B</td> <td>457.49</td> <td>2</td> <td>5</td> <td>3.12</td> <td>2</td> <td>0</td>	4	Clavatustide B	457.49	2	5	3.12	2	0
6Brevione B424,58045,71017Verlamelin A872,078111,521548Brevione J440,58154,68009Lutcoalbusin B496,64373,342110Chrysamide A524,53083,111,912110Simplicilliumtide H886,18111,911542Penicillactam395,374610.06842Penicillo D528,66106844Aspergilol H596,66106844Penicillo D428,48374,26215Clavatuside B457,49253,12206Purpurogemutantin304,2947-0,65017Phaseolorin E302,9747-0,65019Phaseolorin E308,2947-0,650110Varioxepine A457,49253,12202Protein tyrosine Inserve463,53172,98319Phaseolorin E457,49253,5131110Clavatuside B452,57045115Varioxepine A </td <td>5</td> <td>Clavatustide A</td> <td>471.51</td> <td>2</td> <td>5</td> <td>3.51</td> <td>3</td> <td>0</td>	5	Clavatustide A	471.51	2	5	3.51	3	0
7Verlamelin A872.078111.521548Brevione J440.58154.68009Luteoalbusin B440.68154.680010Chrysamide A524.53083.3162Hexokinase-IISimplicillumtide H886.1811.01202Penicillactam395.37461.01203Aspergilol H598.66106844Penicitlo D484.8374.26206Clavattside B457.49253.12206Pupurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A820.778111.521549Phaseolorin E308.2947-0.650110Varioxepine A420.78111.52202Varioxepine A425.7045.48011Clavattside B424.58172.983110Varioxepine A422.57045.71012Varioxepine A424.58045.71012Clavattside A471.512 <td>6</td> <td>Brevione B</td> <td>424.58</td> <td>0</td> <td>4</td> <td>5.71</td> <td>0</td> <td>1</td>	6	Brevione B	424.58	0	4	5.71	0	1
8Brevione J440.58154.68009Luteoalbusin B496.64373.342110Chrysamide A525.3283.3162Hexokinase-II53.111541Simplicilliumtide H886.18111.911542Penicillactam595.6761068444Penicitol D428.48374.26205Clavatustide B576.513122006Purpurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A308.2947-0.650110Varoxepine A463.53172.983111Clavatustide B457.49253.122010Varoxepine A425.70457.101113Brevione B424.580457.1301114Clavatustide A471.51253.5130115Clavatustide A471.51281.5130116Harestorine B424.581101.45122177.	7	Verlamelin A	872.07	8	11	1.52	15	4
9Lteoalbusin B496.64373.342110Chrysanide A524.53083.3162Hexokinase-IISimplicilliumtide H886.18111.911542Penicillactam395.37461.01203Aspergilol H598.66106844Penicitol D428.48374.26215Clavatustide B457.49253.12206Purpurogemutantin304.3160.3027Clavatustide B872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A485.33172.98317Clavatustide B457.49253.122010Varioxepine A485.33172.983111Clavatustide B457.49253.122012Varioxepine A425.77045.480113Brevione A425.77045.480114Clavatustide A471.51253.513015Clavatustide A471.51283.513014Shein A36.33 <td< td=""><td>8</td><td>Brevione J</td><td>440.58</td><td>1</td><td>5</td><td>4.68</td><td>0</td><td>0</td></td<>	8	Brevione J	440.58	1	5	4.68	0	0
10Chrysamide A524.53083.3162Hexckinase-II1Simplicillumtide H886.18111.911542Penicillactam395.37461.01203Aspergilol H598.66106844Penicitol D428.48374.26215Clavatustide B576.513122006Purpurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E882.947-0.650110Varioxepine A463.53172.98317Varioxepine A457.49253.122010Varioxepine A463.53172.983112Varioxepine A425.77045.48013Brevione B424.58045.71014Guatustide A415.51283.51306Austinol458.51281.89017-hydroxydehydroaustin514.531101.45126Austinol<	9	Luteoalbusin B	496.64	3	7	3.34	2	1
Hexokinase-ll1Sindillumtide H886.181.011.5142Penicillatam395.37461.01203Aspergilo H598.66106844Penicitol D428.48374.26215Clavatuside B457.49253.12206Purprogenutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A820.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A453.53172.98317Varioxepine A457.49253.122011Clavatuside B457.49253.122112Varioxepine A452.570431113Brevione A422.57045.710114Astinol458.51281.890115Clavatuside A471.51281.89011111111111111111111111111	10	Chrysamide A	524.53	0	8	3.31	6	2
1Simplicilliuntide H886.18111.911542Penicillactam393.7461.01203Aspergilol H598.66106844Penicitol D428.48374.26215Clavatustide B457.49253.12206Purpurogenutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A457.49253.12209Phaseolorin E308.2947-0.650110Varioxepine A457.49253.12202Varioxepine A457.49172.98311Clavatustide B457.49253.12112Varioxepine A422.57045.48013Brevione B420.51253.513014Glavatustide A471.51253.513014Glavatustide A45.511101.451225Clavatustide A </td <td>Hexokinase-II</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	Hexokinase-II							
2Penicillactam395.37461.01203Aspergilol H598.66106844Penicitol D428.48374.26215Clavatustide B457.49253.12206Purpurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A463.53172.9831Protein tyrosine phospitarse-1B53.122011Clavatustide B457.49253.12202Varioxepine A463.53172.983112Varioxepine A422.57045.710114Brevione B422.57045.710111 <t< td=""><td>1</td><td>Simplicilliumtide H</td><td>886.1</td><td>8</td><td>11</td><td>1.91</td><td>15</td><td>4</td></t<>	1	Simplicilliumtide H	886.1	8	11	1.91	15	4
3 Aspergilol H 598.6 6 10 6 8 4 4 Penicitol D 428.48 3 7 4.26 2 1 5 Clavatustide B 304.3 1 6 3.12 2 0 6 Purpurgemutantin 304.3 1 6 0.3 0 0 7 Citrinolactone B 576.51 3 12 2.12 2 2 8 Verlamelin A 872.07 8 11 1.52 15 4 9 Phaseolorin E 308.29 4 7 -0.65 0 1 10 Varioxepine A 463.53 1 7 2.98 3 1 Protein tyrosine phospitats	2	Penicillactam	395.37	4	6	1.01	2	0
4Penicitol D428.48374.26215Clavatustide B457.49253.12206Purpurogemutantin304.3160.30007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A463.53172.9831Protein tyrosine phosphatase-1BVarioxepine A457.49253.12202Varioxepine A457.49253.12202Varioxepine A422.57045.48013Brevione B424.58045.71015Clavatustide A471.51253.51306Austinol458.51281.89017-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J406.58154.68009Brevione J406.58154.6800101-epi-citrinin H1426.47173.5841	3	Aspergilol H	598.6	6	10	6	8	4
5Clavatustide B457.49253.12206Purpurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A463.53172.98311Protein tyrosine phosphase-1BT57.49253.122012Varioxepine A457.49253.122012Varioxepine A457.4925.480112Varioxepine A422.57043111 <td>4</td> <td>Penicitol D</td> <td>428.48</td> <td>3</td> <td>7</td> <td>4.26</td> <td>2</td> <td>1</td>	4	Penicitol D	428.48	3	7	4.26	2	1
6Purpurogemutantin304.3160.3007Citrinolactone B576.513122.12228Verlamelin A872.078111.521549Phaseolorin E308.2947-0.650110Varioxepine A304.30172.9831Protein tyrosine phosphatse-1B53.122002Varioxepine A457.49253.12202Varioxepine A463.53172.98313Brevione A422.57045.48014Brevione B424.58045.71015Clavatustide A471.51253.513016Austinol458.51281.89017-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J440.58154.68001101-epi-citrinin H1426.47173.5841	5	Clavatustide B	457.49	2	5	3.12	2	0
7 Citrinolactone B 576.51 3 12 2.12 2 2 8 Verlamelin A 872.07 8 11 1.52 15 4 9 Phaseolorin E 308.29 4 7 -0.65 0 1 10 Varioxepine A 463.53 1 7 2.98 3 1 7 Protein tyrosine phosphatser IB T 1 7 2.98 3 3 1 7 2.98 3 1 1 Clavatustide B 457.49 2 5 3.12 2 0 2 Varioxepine A 457.49 2 5 3.12 2 0 2 Varioxepine A 457.49 2 5 3.12 2 0 1 3 Brevione A 422.57 0 4 5.48 0 1 1 4 Brevione B 424.58 0 4 5.71 0 1 1 5 Clavatustide A 471.51 2 8 1.89 <td>6</td> <td>Purpurogemutantin</td> <td>304.3</td> <td>1</td> <td>6</td> <td>0.3</td> <td>0</td> <td>0</td>	6	Purpurogemutantin	304.3	1	6	0.3	0	0
8 Verlamelin A 872.07 8 11 1.52 15 4 9 Phaseolorin E 308.29 4 7 -0.65 0 1 10 Varioxepine A 463.53 1 7 2.98 3 1 Protein tyrosine phosphase-1B 5 3.12 2 0 0 2 Varioxepine A 457.49 2 5 3.12 2 0 2 Varioxepine A 463.53 1 7 2.98 3 1 3 Brevione A 422.57 0 4 5.48 0 1 4 Brevione B 424.58 0 4 5.71 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 -hydroxydehydroaustin 514.53 1 10 1.45 0 <td>7</td> <td>Citrinolactone B</td> <td>576.51</td> <td>3</td> <td>12</td> <td>2.12</td> <td>2</td> <td>2</td>	7	Citrinolactone B	576.51	3	12	2.12	2	2
9 Phaseolorin E 308.29 4 7 -0.65 0 1 10 Varioxepine A 463.53 1 7 2.98 3 1 Protein tyrosine phosphase-1B 5 3.12 2 0 1 Clavatustide B 457.49 2 5 3.12 2 0 2 Varioxepine A 463.53 1 7 2.98 3 1 1 3 Brevione A 422.57 0 4 5.48 0 1 4 Brevione B 424.58 0 4 5.71 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 7-hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68	8	Verlamelin A	872.07	8	11	1.52	15	4
10 Varioxepine A 463.53 1 7 2.98 3 1 Protein tyrosine phosphatse-1B 1 Clavatustide B 457.49 2 5 3.12 2 0 2 Varioxepine A 463.53 1 7 2.98 3 1 2 Varioxepine A 463.53 1 7 2.98 3 1 3 Brevione A 463.53 1 7 2.98 3 1 4 Brevione B 422.57 0 4 5.48 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 5 Clavatustide A 471.51 2 8 1.89 0 1 7 -hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10	9	Phaseolorin E	308.29	4	7	-0.65	0	1
Protein tyrosine phosphatse-1B 1 Clavatustide B 457.49 2 5 3.12 2 0 2 Varioxepine A 463.53 1 7 2.98 3 1 3 Brevione A 422.57 0 4 5.48 0 1 4 Brevione B 424.58 0 4 5.71 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 7-hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	10	Varioxepine A	463.53	1	7	2.98	3	1
1Clavatustide B457.49253.12202Varioxepine A463.53172.98313Brevione A422.57045.48014Brevione B424.58045.71015Clavatustide A471.51253.51306Austinol458.51281.890177-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J440.58154.6800101-epi-citrinin H1426.47173.5841	Protein tyrosine phosph	atase-1B						
2 Varioxepine A 463.53 1 7 2.98 3 1 3 Brevione A 422.57 0 4 5.48 0 1 4 Brevione B 424.58 0 4 5.71 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 7-hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	1	Clavatustide B	457.49	2	5	3.12	2	0
3 Brevione A 422.57 0 4 5.48 0 1 4 Brevione B 424.58 0 4 5.71 0 1 5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 7-hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	2	Varioxepine A	463.53	1	7	2.98	3	1
4Brevione B424.58045.71015Clavatustide A471.51253.51306Austinol458.51281.890177-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J440.58154.6800101-epi-citrinin H1426.47173.5841	3	Brevione A	422.57	0	4	5.48	0	1
5 Clavatustide A 471.51 2 5 3.51 3 0 6 Austinol 458.51 2 8 1.89 0 1 7 7-hydroxydehydroaustin 514.53 1 10 1.45 1 2 8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	4	Brevione B	424.58	0	4	5.71	0	1
6Austinol458.51281.890177-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J440.58154.6800101-epi-citrinin H1426.47173.5841	5	Clavatustide A	471.51	2	5	3.51	3	0
77-hydroxydehydroaustin514.531101.45128Circumdatin G307.31251.9009Brevione J440.58154.6800101-epi-citrinin H1426.47173.5841	6	Austinol	458.51	2	8	1.89	0	1
8 Circumdatin G 307.31 2 5 1.9 0 0 9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	7	7-hydroxydehydroaustin	514.53	1	10	1.45	1	2
9 Brevione J 440.58 1 5 4.68 0 0 10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	8	Circumdatin G	307.31	2	5	1.9	0	0
10 1-epi-citrinin H1 426.47 1 7 3.58 4 1	9	Brevione J	440.58	1	5	4.68	0	0
	10	1-epi-citrinin H1	426.47	1	7	3.58	4	1

*MW: molecular weight; HBD: hydrogen bond donor; HBA: hydrogen bond acceptor; RO5: Lipinski's rule of five.

ihydroxyl-trp-tyr) had a higher binding energy (-8.9 kcal/mol) with pancreatic lipase than the control ligand orlistat (-5.4 kcal/mol) (Table 1).

The complex of penicillactam and HK-II had seven conventional hydrogen bonds dominated by several hydrophobic interactions (Fig. 4). Therein, penicillactam showed higher binding energy (-9.5 kcal/mol) than the control ligand benserazide (-7.6 kcal/mol) (Table 1).

The circumdatin-G and PTP-1B complex had three conventional hydrogen bonds, including several hydrophobic interactions towards stabilizing the complex (Fig. 5). Therein, circumdatin G had a greater binding energy (-8.0 kcal/mol) as compared to the control ligand benserazide (-6.8 kcal/mol) (Table 1).

3.3. MD simulation of docked inhibitor and enzyme complexes

The results of MD simulation (100 ns) of the docked inhibitors and enzymes complexes were analyzed by RMSD, RMSF, Rg, number of hydrogen bonds and SASA. For cladosporol C and α -amylase complex, RMSD from 0 nm to 0.1 nm, showed no significant change its stability. However, the abrupt changes of RMSD after 0.1 nm referred to the changes in the interaction and instability of the complex with time (Fig. S1A). Therein, the maximal observed RMSD value was 0.25 nm at 88 ns. RMSF value showed the difference in the amino acid residues starting from 0 ns, indicating the cladosporol C and α -amylase complex instability at residue no.109, 152, 238, 309, 350 and 459 (Fig. S1B). Therein, the highest



Fig. 1. Molecular docking analysis of cladosporol C and α -amylase interaction. (A) 3D interactive illustration of selected binding modes. (B) Ligplot presentation of residue-wise interactions of ligand and protein.



Fig. 2. Molecular docking analysis of tenellone F and α -glucosidase interaction. (A) 3D interactive illustration of selected binding modes. (B) and Ligplot presentation of residue-wise interactions of ligand and protein (right).



Fig. 3. Molecular docking analysis of ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) and pancreatic lipoprotein lipase interaction. A) 3D interactive illustration of selected binding modes. (B) Ligplot presentation of residue-wise interactions of ligand and protein.

RMSF value (0.47 nm) was observed at residue no. 350 an6d 459. Accordingly, the overall complex fluctuated throughout the simulation. Further, the Rg graph showed that the complex was stable and compact till 60 ns with 2.33 nm (Fig. S1C). However, the complex tended toward instability after 60 ns, and then started to gain compactness with the highest Rg value of 2.35 nm, indicating favorable interaction. However, the number of hydrogen bonds at 0 ns was 450, which later decreased to 413, predicting instability of the complex (Fig. S1D). Moreover, at 0 ns, the observed lowest SASA value was 190 nm, which later increased to attain the highest value of 2.12 nm at 98 ns (Fig. S1E).

RMSD of tenellone F and α -glucosidase complex showed a smooth change in the complex starting from 0 ns (Fig. S2A). This later started to increase and had significant values between 18 ns and 90 ns with the highest value of 0.52 nm at 48 ns. The highest RMSF values of 1 nm was observed at amino residue no. 2, and 0.58 nm at residue no. 91 (Fig. S2B). Further, no change in the overall number of hydrogen bonds indicated no effect on protein–ligand interaction (Fig. S2C). The observed highest Rg value were 2.53 nm at 45 ns, 48 ns and 75 ns throughout 100 ns (Fig. S2D). The SASA value initially started increasing, and was 238 nm at 3 ns (Fig. S2E).

The RMSD of ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) and LPL complex between 0 ns and 0.02 ns showed no significant change in the complex (Fig. S3A). However, later, irregular change in the protein–ligand complex was observed between 0.2 nm and 0.5 nm, and then started to increase. Though the highest RMSF value (1.14 nm) showed the complex instability at residue no. 246, the overall complex was stable (Fig. S3B). The observed highest Rg value of the complex was 2.71 nm at 3.4 ns (Fig. S3C). Moreover, there was no change in the overall number of hydrogen bonds (Fig. S3D) which did not affect protein–ligand interaction. At 0 ns, SASA value started increasing and the highest value (228 nm) was observed at 41 ns (Fig. S3E).

RMSD value of penicillactum A and HK-II complex started to increase from 0 ns, and achieved the highest value of 0.64 nm at 32 ns and 89 ns (Fig. S4A). The observed maximal RMSF value of 0.6 nm was at residue no. 536 (Fig. S4B). Moreover, there was no change in the number of hydrogen bonds, showing unaffected protein–ligand interaction (Fig. S4C). The observed maximal Rg value was 4.19 nm at 100 ns (Fig. S4D). Further, the SASA at 0 ns started increasing and achieved the highest value of 414 nm at 4 ns (Fig. S4E).

RMSD of circumdatin G and PTP-1B complex started to increase at 0 ns, and attained the highest value of 0.15 nm at 12 ns, 21 ns and 32 ns (Fig. S5A). RMSF showed that the highest value of 0.24 nm at residue no. 61, 0.2 nm at no. 186, and 0.14 nm at no. 283 (Fig. S5B). Further, there was no change in the number of hydrogen bonds and had not affected the interaction. (Fig. S5C). The observed highest Rg value 1.95 nm at 3.3 ns and 56 ns showed the compactness of the protein–ligand throughout the simulation (Fig. S5D). However, the SASA showed increasing from 0 ns and achieving highest value of 150 nm at 70 ns (Fig. S5E).

3.4. Bond and free-energy determination of the selected inhibitors

In the cladosporol C and α -amylase complex, the interactions also impacted the total energy (Fig. 6A and B), where the protein structure was more stable with decrease in total energy. Here, the complex had made the protein structure stable after some time, wherein, the binding energy of the complex were computed (Fig. 6C) using MM/GBSA method. A detailed analysis showed the enthalpic component (Δ H) as favorable (negative value) to the binding process, and at the same time, the entropic term ($-T\Delta$ S) had an unfavorable (positive value) energy.

The formation of tenellone F and α -glucosidase complex also impacted the total energy (Fig. 7A and B), which overall resulted in protein stability and decrease in total energy at a later time



Fig. 4. Molecular docking analysis of penicillactam and hexokinase-II interaction. A) 3D interactive illustration of selected binding modes. (B) Ligplot presentation of residuewise interactions of ligand and protein.

point (Fig. 7C). The values were computed by MM/GBSA method, where a detailed analysis of the contributions showed favorable ΔH value to the binding process. At the same time, the $-T\Delta S$ gave an unfavorable energy.

In the ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) and LPL complex, MM/PBSA represented the different phases of pancreatic lipase bonds and the energy (Fig. 8A and B). The total energy of the protein and ligand complex decreased for both GGAS and GSOLV, which showed the stability in the protein structure after the attachment of the ligand. These results were computed using MM/GBSA method (Fig. 7C), where a detailed analysis of the contributions showed favorable Δ H value to the binding process, and unfavorable – T Δ S value of the energy.

In the penicillactam and HK-II complex, changes in the bonds and energy also took place (Fig. 9A and B). The total energy of the protein and ligand complex decreased for both GGAS and GSOLV, which showed the stability in the protein structure after its attachment with the ligand (Fig. 9C). These results were computed using MM/GBSA calculations, where a detailed analysis of the contributions showed favorable Δ H) value to the binding process and unfavorable – T Δ S value of the energy.

In the case of circumdatin G and PTP-1B, their interaction also impacted the total energy of the complex (Fig. 10A and B). This complex made the protein stable while decreasing the total energy. Overall, the complex stabilized the protein structure after some

time (Fig. 10C). The results were calculated suing MM/GBSA method, where a detailed analysis of the contributions showed favorable ΔH to the binding process and unfavorable – T ΔS of the energy.

4. Discussion

Of the crucial enzymes involved in glucose metabolism, α amylase, α -glucosidase and HK-II are responsible for the breakdown of ingested carbohydrates and therefore, their inhibitions can delay sugar absorption in the management of DM type-2 (Joshi et al., 2007). On the other hand, PTP-1B antagonizes insulin signaling by reducing the activation state of insulin receptor kinase, thereby inhibiting insulin signaling in responsive tissue. Because in both type-1 and type-2 conditions, the insulin deficiency associated alteration in LPL activity leads to elevation of serum triglycerides and reduction of high-density lipoprotein levels, its inhibition can also cure DM (Joshi et al., 2007).

In addition to several marketed anti-diabetes synthetic drugs targeting glucose metabolism enzymes, several promising natural products from terrestrial and marine sources have been identified (Qi et al., 2010; Qin et al., 2010, Kim et al., 2008; Sanger et al., 2019; Lauritano and Ianora, 2016). These include anti-diabetes marine algae derived inhibitor compounds of α -glucosidase (Kim et al.,



Fig. 5. Molecular docking analysis of Circumdatin G and protein tyrosine phosphatase-1B interaction. A) 3D interactive illustration of selected binding modes. (B) Ligplot presentation of residue-wise interactions of ligand and protein.



Fig. 6. MM/PBSA analysis of cladosporol C and α -amylase complex. (A and B) representation of the total energy after the formation of the complex. (C) representation of the enthalpy (Δ H) and entropy ($-T\Delta$ S) of the complex.



Fig. 7. MM/PBSA analysis of tenellone F and α -glucosidase complex. (A and B) representation of the total energy of the complex. (C) representation of the enthalpic (Δ H) and entropic ($-T\Delta$ S) components of the complex.

2008; Kurihara et al., 1999; Kim et al., 2010; Pathak et al., 2022) and PTP-1B (Pathak et al., 2022; Liu et al., 2011; Shi et al., 2008; Shi et al., 2016).

Deep-sea fungi are potential natural source of pharmacologically important molecules for developing novel drug candidates (Arifeen et al., 2019). Unlike a vast range of known therapeutic



Fig. 8. MM/PBSA analysis of ozazino-cyclo-(2,3-dihydroxyl-trp-tyr) and pancreatic lipoprotein lipase complex. (A and B) representation of the total energy of the complex. (c) representation of the enthalpic (Δ H) and entropic ($-T\Delta$ S) components of the complex.



Fig. 9. MM/PBSA analysis of penicillactam and hexokinase-II complex. (A and B) representation of the total energy of the complex. (C) representation of the enthalpic (Δ H) and entropic ($-T\Delta$ S) components of the complex.



Fig. 10. MM/PBSA analysis of circumdatin G with protein tyrosine phosphatase-1B. (A and B) representation of the total energy of the complex. (C) representation of enthalpic (Δ H) and entropic ($-T\Delta$ S) components of the complex.

marine products, deep-sea fungi still remain under-explored as potential source of drug candidates against DM. In novel, safe and cos-effective drug discovery, SBVS is a bioinformatics tool to quickly and efficiently select potential bioactive molecules or lead compounds with near-accuracy from a large chemical database. In this study therefore, we virtually screened 50 deep-sea fungi derived molecules against glucose metabolism enzymes: α amylase, α -glucosidase, LPL, HK-II and PTP-1B. Following molecular docking, top 10 compounds for each target enzyme were subjected to MD simulation and pharmacokinetic analysis based on their AdmetSAR and pharmacophore features. Of these, one most active inhibitor compound for each enzyme: cladosporol C for α amylase, tenellone F for, α -glucosidase, ozazino-cyclo-(2,3-dihy droxyl-trp-tyr) for LPL, Penicillactam for HK-II and circumdatin G for PTP-1B were finally selected. Notably, while cladosporol C (Cladosporium cladosporioides HDN14-342) and tenellone F (Phomopsis lithocarpus FS508) are polyketides, ozazino-cyclo-(2,3-dihydroxyltrp-tyr) (Phomopsis lithocarpus FS508) and circumdatin G (Penicillium citreonigrum XT20-134) are alkaloids, whereas penicillactam (*Penicillium* sp. F11) is a terpenoid (Kim et al., 2019). For these, there is now much information on their bioactivities is available. Nonetheless, in a previous studies, cladosporol C isolated from endophytic fungus (Cladosporium sp. KcFL6) (Ai et al., 2015). and tenellone derivatives from deep-sea fungus (Phomopsis lithocarpus FS508) exhibited moderate cytotoxicity against human tumor cell lines (Liu et al., 2011) as compared to non-cytotoxic ozazinocyclo-(2,3-dihydroxyl-trp-tyr) derived from deep-sea fungus (Peni*cillum citreonigrum* XT20-134) (Tang et al., 2019). Circumdatin G has been isolated from the fungus *Aspergillus ochraceus* reported for antiviral activity against hepatitis C virus (Di et al., 2001).

5. Conclusion

We for the first time, explored 50 deep-sea fungal compounds as potential source of novel anti-diabetes drug candidates targeting glucose metabolism enzymes, using structure-based virtual screening method. Following molecular docking and simulation, the selected top 10 inhibitors of each enzyme, were subjected to AdmetSAR and pharmacophore features-based analyses. Of these, cladosporol C, tenellone F, ozazino-cyclo-(2,3-dihydroxyl-trp-tyr), penicillactam and circumdatin G were suggested as the potential inhibitors of α -amylase, α -glucosidase, pancreatic-lipoprotein lipase, hexokinase-II and protein tyrosine phosphatase-1B, respectively. Our *in silico* data therefore, warrants further experimental and pharmacological studies to validate their anti-diabetes therapeutic potential.

6. Authorship contribution statement

ARA and MKP conceptualized, designed and executed the research, collected and analyzed data, and wrote the manuscript. MJA and MSA participated in data analysis and manuscript writing. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101776.

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