RESEARCH PAPER

Discovery of Novel NDM-1 Inhibitors from Marine Natural Product Analogues Using an Integrated Ligand-Based Virtual Screening Strategy

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ABSTRACT

The world wide prevalence of New Delhi metallo-β-lactamase 1 (NDM-1) in Gram-negative bacteria has led to increased resistance towards almost all β-lactam antibiotics including carbapenems; yet; there are currently no metallo-β-lactamase inhibitors available for clinical application. Marine natural products provide an abundant yet underutilized source of bioactive agents; recently CMNPD17791 (a compound derived from the Sea of Japan) exhibited NDM-1 inhibitory activity. To identify novel NDM-1 inhibitors using CMNPD17791 as a reference compound and by utilising a multi-step virtual screening pipeline that includes similarity searches, drug-likeness filtering, ADMET profiling and molecular docking. A ligand based virtual similarity search against the ZINC database performed with SwissSimilarity yielded 400 analogues of CMNPD17791, all of which were scored for similarity before the top 100 scores were filtered using drug-likeness criteria (Lipinski's, Veber's, Egan's, Ghose's and Muegge's rules) using Chemaudit. Subsequently, all compounds were further characterised according to ADMET properties (absorption, distribution, metabolism, excretion and toxicity) via ADMET-AI. The top 15 candidates were subjected to molecular docking studies against NDM-1 (PDB ID: 5ZGE) using PyRx and calculating predicted binding affinities. The results revealed relatively high similarity scores (0.293-0.621) for the 15 selected compounds that displayed good likeness, pharmacokinetic properties and low predicted toxicity values. The molecular docking data indicated that the compound CMNPD17791 had the highest affinity for the target protein (−8.9 kcal/mol). In addition, ZINC000022011900 was found to have a very good balance of desirable characteristics, including oral bioavailability (0.967) and penetration through the blood-brain barrier (0.996), an excellent ADMET profile and docking score (−7.9 kcal/mol). Similarly, ZINC000895325934 (−7.8 kcal/mol) and ZINC000095459346 (−7.7 kcal/mol) had high binding affinity values and acceptable pharmacokinetic properties. The integrated pipeline yielded ZINC000022011900, ZINC000895325934, and ZINC000095459346 as potential NDM-1 inhibitors.

Keywords: NDM-1; marine natural products; virtual screening; molecular docking; antimicrobial resistance.

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INTRODUCTION

Antimicrobial resistance (AMR), especially in Gram-negative bacteria, is increasing globally and the increasing occurrence of difficult-to-treat infections is resulting in longer hospital stays, higher medical costs, and increased mortality[1]. Antimicrobial resistance (AMR) is a pressing global issue that requires collaborative efforts from nations and foundations worldwide [2]. Carbapenems are β-lactam antibiotics that are commonly used as last-resort drugs for the treatment of serious multi-drug-resistant gram-negative bacterial infections [3]. However, the massive increase in antibiotic resistance in bacteria is due to the excessive use of β-lactam antibiotics [4].

Among several mechanisms of resistance pathogenic bacteria have developed against antimicrobial therapy, the hydrolysis of β-lactam antibiotics by β-lactamase enzymes is one of the most prevalent in resistant strains [4]. Class B enzymes, also known as metallo-β-lactamases (MBLs), employ zinc as a cofactor at the active site of the β-lactam ring [2]. This class mainly includes New Delhi metallo-beta-lactamase (NDM), Verona Integron-encoded metallo-beta-lactamase (VIM), and imipenemase (IMP) [2]. NDM-1 was first discovered in New Delhi at the end of 2008 and it is now considered as the most clinically relevant target for antibiotic resistance due to its worldwide prevalence [4]. Since the first detection of the NDM-1 gene in Enterobacterales isolated from a patient traveling from India to Sweden in 2008, a total of 41 NDM variants have been identified in clinically significant pathogens such as Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii complex, and Pseudomonas aeruginosa [2]. In clinical Gram-negative pathogens, NDM-1 confers carbapenem resistance through a zinc-dependent catalytic mechanism that involves key residues such as His120, His122, Asp124, His189, Cys208, and His250, which are crucial for substrate binding and β-lactam hydrolysis [4]. NDM-1 hydrolyzes nearly all beta-lactam antibiotics, including last-resort carbapenems [5]. The global spread of metallo-β-lactamases is particularly problematic and has aroused significant concerns due to their ability to inactivate almost all clinically approved β-lactams except for aztreonam [3]. Avibactam, relebactam, and vaborbactam have been developed and introduced to the market as serine-β-lactamase inhibitors [2]. However, no metallo-β-lactamase inhibitors have been approved for clinical use to date [3]. Due to their physicochemical properties, specificity, and safety to the human body, clinical studies have not been approved to market anti-NDM-1 inhibitors [4]. Clinically approved metallo-β-lactamase inhibitors are still unknown [6]. Regrettably, there were no inhibiting agents that seemed readily available for clinical use, and none of these are within the reach of clinicians [2]. Therefore, the need for discovering novel NDM-1 inhibitors arises from the emergence of 'superbug' strains that exhibit resistance to a wide range of antibiotics [4].

Marine natural products contain several bioactive components that might be used in medical treatments, and especially marine algae are vital for providing a rich source of bioactive substances with a wide range of biological activities, including antiviral, antimicrobial, antibacterial, and anti-inflammatory characteristics [4]. Given that NDM-1 activity is dependent on zinc ions at the active site, algal metabolites provide a targeted approach to disrupt this metallo-enzyme structure [4]. The Comprehensive Marine Natural Products Database (CMNPD) contains over 32,000 marine natural products [4]. Marine algal products provide a valuable and underexplored source of structurally diverse bioactive compounds relevant to drug discovery, and the computational analysis of marine algal-derived candidates provides a cost-effective and rapid strategy for the initial step of molecular prioritization prior to experimental validation [4]. Previous work has shown that the marine product CMNPD17791 exhibited high potential for inhibitory activity with the NDM-1 protein of Klebsiella pneumoniae [4].

However, no previous study has systematically integrated similarity searching, comprehensive drug-likeness filtering, ADMET profiling, and molecular docking in a single multi-step virtual screening pipeline specifically targeting NDM-1, nor has CMNPD17791 been evaluated as a reference compound in such a workflow. Therefore, the objective of this study was to identify novel NDM-1 inhibitors using a multi-step virtual screening approach integrating similarity search, drug-likeness filtering, ADMET profiling, and molecular docking, with CMNPD17791 as a reference compound. We hypothesized that this integrated pipeline would identify hit compounds with binding affinities and pharmacokinetic profiles comparable to or better than CMNPD17791.

MATERIALS AND METHODS

Similarity Search

The structure of CMNPD17791 was downloaded from Comprehensive Marine Natural Products Database (https://www.cmnpd.org/)[7]. And using Swisssimilarity's website, similar molecules were found[8].

Drug likeliness and ADMET Studies

For drug likeliness studies, Chemaudit (https://chemaudit.naturalproducts.net/) was used[9]. For these 5 different rules were used, these are, Lipinski, Veber, Egan, Ghose, Muegge.

After drug likeliness studies were performed, for the next step was ADMET studies, for this purpose ADMET-AI (https://admet.ai.greenstonebio.com/) was used[10]. This tool helps to study various parameters as follows:

Physiochemical properties: molecular weight, logP, hydrogen bond acceptor, hydrogen bond donor, Lipinski rule of 5, quantitative estimation of drug

likeliness (QED), stereo centres, Topological polar surface area (TPSA).

Absorption properties: human intestinal absorption, oral bioavailability, aqueous solubility, lipophilicity, hydration free energy, cell effective permeability, PAMPA permeability, p-glycoprotein inhibition

Distribution properties: Blood brain barrier penetration, plasma protein binding rate, volume of distribution at steady rate

Metabolism properties: CYP1A2 inhibition, CYP2C19 inhibition, CYP2C9 inhibition, CYP2D6 inhibition, CYP3A4 inhibition, CYP2C9 substrate, CYP2D6 substrate, CYP3A4 substrate

Excretion properties: half life, drug clearance (hepatocyte), drug clearance (microsome)

Toxicity Properties: hERG blocking, clinical toxicity, mutagenicity, drug induced liver injury, carcinogenicity, acute toxicity LD50, skin reaction, androgen receptor (full length), Androgen receptor (ligand binding domain), aryl hydrocarbon receptor, aromatase, estrogen receptor (full length), estrogen receptor (ligand binding domain), Peroxisome proliferator-activated receptor gamma, nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element, ATPase Family AAA Domain -containing protein 5 (ATAD5), heat shock factor response element, mitochondrial membrane potential, tumor protein p53

Molecular Docking

The protein structure was downloaded from RCSB PDB (https://www.rcsb.org/). The NDM-1 (PDB ID: 5ZGE) was downloaded in PDB format[11].

The protein structure file (PDB format) was prepared using BIOVIA Discovery Studio. Water molecules and hetero atoms were removed from the protein structure, and polar hydrogen atoms were added to optimize the receptor for molecular docking studies[12]. The prepared protein structure was subsequently saved in PDB format.

Molecular docking studies were performed using PyRx[13]. The prepared protein structure was imported into the software, followed by the sequential loading of ligand molecules. Energy minimization was carried out for all ligands prior to docking. The minimized ligands were then converted into AutoDock-compatible ligand formats. Appropriate grid box dimensions were defined to encompass the active binding site of the target protein. Docking simulations were subsequently performed, and the docking results were exported and saved in CSV format for further analysis.

RESULT AND DISCUSSION

Similarity Search

A compound identified as CMNPD17791 which has shown activity as a potential inhibitor to the bacterial enzyme NDM-1, was screened using the SwissSimilarity platform to perform ligand-based virtual screening against a number of different compounds. The SwissSimilarity platform utilizes a combination of molecular fingerprints and shape-based algorithms to determine which compounds have similar structures to the input compound queried. CMNPD17791 was used as the input compound and produced a total of 400 compounds that are structurally similar to CMNPD17791 from the ZINC database.

In order to prioritize the compounds for further analysis, similarity scores were employed as a means of ranking the retrieved molecules. Compounds had similarity scores that ranged from 0.293 – 0.621 with an average of 0.35093. The maximum similarity score of 0.621 was found to pertain to ZINC000096442879 and ZINC000096442880 indicating these two had the most similar structures when compared to the reference compound. The top 100 compounds with the highest similarity scores were selected for drug-likeness and ADMET evaluations.

Numerous compounds exhibited similarity scores greater than 0.40, such as ZINC000014947575 (0.520), ZINC000006186074 (0.488), ZINC000005495227 (0.486), and ZINC000000110756 (0.446). The compounds' high degree of structural similarity with CMNPD17791 combined with their chemical variation gives them strong potential as candidate agents.

Table 1. Similarity Search Results table with ZINC ID, Similarity score and SMILES

S. No.	ZINC ID	Similarity Score	SMILES
1.	ZINC000096442879	0.621	CO[C@@H](C)CCOC(=O)C1=CC2=CC=CC=C2OC1
2.	ZINC000096442880	0.621	CO[C@H](C)CCOC(=O)C1=CC2=CC=CC=C2OC1

3.	ZINC000014947575	0.52	O[C@@H](C\\C=C\\[C@H]1CC=CC(=O)O1)C[C@@H](O)\\C=C\\C1=CC=CC=C1
4.	ZINC000006186074	0.488	COCCOC(=O)C(=C/C1=CC=C(OC(C)=O)C=C1)\\C(C)=O
5.	ZINC000005495227	0.486	COCCOC(=O)C(=C\\C1=CC=C(OC(C)=O)C=C1)\\C(C)=O
6.	ZINC000000110756	0.446	COC1=CC=C(\\C=C\\C(=O)C2(O)CCCCC2)C=C1OC
7.	ZINC000824751014	0.445	COC1=CC=C2OCC(CN(C)CCC[C@H]3CCCO3)=CC2=C1
8.	ZINC000824751015	0.443	COC1=CC=C2OCC(CN(C)CCC[C@@H]3CCCO3)=CC2=C1
9.	ZINC001772820456	0.433	C\\C=C(/C)C(=O)O[C@@H]1CC(C)=C[C@@H](O)CC(C)=C[C@H]2OC(=O)C(=C)[C@H]12
10.	ZINC001772820343	0.428	C\\C=C(\\CO)C(=O)O[C@@H]1CC(C)=CCCC(C)=C[C@H]2OC(=O)C(=C)[C@H]12
11.	ZINC000257332405	0.424	O[C@@H]1CCCOC11CCN(CC2=CC3=CC=CC=C3OC2)CC1
12.	ZINC000003129362	0.416	COC1=CC=C(\\C=C\\C(=O)[C@@]23CCCC[C@@H]2O3)C=C1OC
13.	ZINC000000163750	0.416	COC1=CC=C(\\C=C\\C(=O)[C@]23CCCC[C@H]2O3)C=C1OC
14.	ZINC000001424389	0.41	COC1=CC(\\C=C\\C(=O)C2(O)CCCCC2)=CC(OC)=C1OC
15.	ZINC001772820457	0.406	C\\C=C(\\C)C(=O)O[C@@H]1CC(C)=C[C@@H](O)CC(C)=C[C@H]2OC(=O)C(=C)[C@H]12
16.	ZINC001772820305	0.405	CC[C@@H](C)C(=O)O[C@@H]1CC(C)=C[C@@H](O)CC(C)=C[C@H]2OC(=O)C(=C)[C@H]12
17.	ZINC000035459194	0.393	C\\C=C(/C)C(=O)O[C@@H]1CCC(=O)O[C@@H]1\\C=C\\[C@H](O)[C@@H](C)O
18.	ZINC000035459203	0.382	C\\C=C(/C)C(=O)O[C@H]1CCC(=O)O[C@H]1\\C=C\\[C@H](O)[C@@H](C)O
19.	ZINC000031165618	0.373	C\\C=C(/C)C(=O)O[C@@H]1CCC(=O)O[C@@H]1\\C=C\\[C@@H](O)[C@@H](C)O
20.	ZINC000253389681	0.371	C\\C=C(/C)C(=O)O[C@@H]1CCC(=O)O[C@@H]1\\C=C\\[C@@H](O)[C@H](C)O
21.	ZINC000022011900	0.369	O[C@@H]1C[C@@H]2OC(=O)C[C@@H]2[C@H]1\\C=C\\C(F)(F)COC1=CC=CC=C1

22.	ZINC000095459346	0.367	COC1=CC=CC2=C1OCC(=C2)C(=O)NCC(C)(C)CCCO
23.	ZINC000253369777	0.362	C\\C=C(\\C)C(=O)O[C@@H]1CC[C@@]2(C)[C@@H]([C@H](O)CC3=C2C(=O)OC3)C1(C)C
24.	ZINC000035457764	0.36	CC[C@@H](C)CC(=O)O[C@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
25.	ZINC000230148845	0.36	C\\C=C(\\C)C(=O)O[C@@H]1CC[C@@]2(C)[C@@H]([C@@H](O)CC3=C2C(=O)OC3)C1(C)C
26.	ZINC000019375136	0.359	O[C@@]12CCCC[C@H]1CN(CC1=CC3=CC=CC=C3OC1)CC2
27.	ZINC000097575135	0.357	CCN(CC1=CC2=CC=CC(OC)=C2OC1)C1CCOCC1
28.	ZINC000252483850	0.357	CCOC1=CC=CC2=C1OCC(=C2)C(=O)NC[C@@]1(O)CCO[C@H]1C
29.	ZINC000004982326	0.356	COCCNC(=O)[C@@H](OC(=O)C1=CC2=CC=CC=C2OC1)C(C)C
30.	ZINC000019375134	0.355	O[C@]12CCCC[C@@H]1CN(CC1=CC3=CC=CC=C3OC1)CC2
31.	ZINC000253369776	0.355	C\\C=C(\\C)C(=O)O[C@@H]1CC[C@@]2(C)[C@H]([C@H](O)CC3=C2C(=O)OC3)C1(C)C
32.	ZINC000053102467	0.352	COCCOC1=CC=CC(\\C=C2/COC3=CC=CC=C3C2=O)=C1
33.	ZINC000035457742	0.35	CC(C)CC(=O)O[C@@H]1[C@@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
34.	ZINC000035457759	0.35	CC[C@@H](C)CC(=O)O[C@@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
35.	ZINC000035457767	0.35	CC[C@H](C)CC(=O)O[C@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
36.	ZINC000048239307	0.349	CCOC1=CC=C2OCC(=CC2=C1)C(=O)NCCCCOC
37.	ZINC000193670409	0.347	C\\C(=C/C(=O)OC[C@H]1CCCCO1)C1=CC=CC=C1
38.	ZINC000193670395	0.347	C\\C(=C/C(=O)OC[C@@H]1CCCCO1)C1=CC=CC=C1
39.	ZINC000229763974	0.346	CC[C@H](C)CC(=O)O[C@H]1[C@@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
40.	ZINC000044123156	0.341	COC(=O)C1=CC=CC(\\C=C2/COC3=CC=C(O)C=C3C2=O)=C1
41.	ZINC000230162020	0.34	CC(CC\\C=C(/C)[C@H]1CC=C(C)C(=O)O1)C=C1[C@@H](O)C

			=C(C)C1=O
42.	ZINC000230162026	0.34	CC(CC\\C=C(/C)[C@H]1CC=C(C)C(=O)O1)C=C1[C@@H](O)C=C(C)C1=O
43.	ZINC000895325934	0.339	CO[C@@H]1COC[C@@H]1NC(=O)N1CCC[C@@]2(C1)OC1=CC=CC=C1C=C2
44.	ZINC000019375138	0.339	O[C@]12CCCC[C@H]1CN(CC1=CC3=CC=CC=C3OC1)CC2
45.	ZINC000019375133	0.339	O[C@@]12CCCC[C@@H]1CN(CC1=CC3=CC=CC=C3OC1)CC2
46.	ZINC000035458793	0.339	C\\C=C\\C(=O)O[C@@H]1\\C=C\\[C@H](O)[C@@H](CCC(=O)O[C@@H]1C)OC(C)=O
47.	ZINC000035458798	0.339	C\\C=C\\C(=O)O[C@@H]1\\C=C\\[C@@H](O)[C@@H](CCC(=O)O[C@@H]1C)OC(C)=O
48.	ZINC000031164409	0.339	C\\C=C\\C(=O)O[C@@H]1\\C=C\\[C@H](O)[C@H](CCC(=O)O[C@@H]1C)OC(C)=O
49.	ZINC000895325935	0.337	CO[C@@H]1COC[C@@H]1NC(=O)N1CCC[C@]2(C1)OC1=CC=CC=C1C=C2
50.	ZINC000252483848	0.336	CCOC1=CC=CC2=C1OCC(=C2)C(=O)NC[C@]1(O)CCO[C@H]1C
51.	ZINC000253388332	0.336	CC[C@H](C)CC(=O)O[C@H]1[C@H](C(C)C)[C@@H](OC(C)=O)C=C(CO)C1=O
52.	ZINC000046777408	0.335	CCOC1=CC=CC2=C1OCC(=C2)C(=O)N[C@@H](C)[C@H]1CCCO1
53.	ZINC000035457734	0.335	CC(C)CC(=O)O[C@@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
54.	ZINC000046777412	0.334	CCOC1=CC=CC2=C1OCC(=C2)C(=O)N[C@H](C)[C@H]1CCCO1
55.	ZINC000067805910	0.334	CC[C@H]1CN(CC2=CC3=CC(OC)=CC=C3OC2)CC[C@@]1(C)O
56.	ZINC000067982264	0.333	CC1=C(C(=O)N2CCC[C@]3(CC2)OC2=CC=CC=C2C=C3)C(C)=NN1
57.	ZINC000253389297	0.332	C\\C=C\\C(=O)O[C@@H]1\\C=C\\[C@H](O)[C@H](CCC(=O)O[C@H]1C)OC(C)=O
58.	ZINC000000506215	0.332	COC1=CC=C(\\C=C\\C(=O)C2(O)CCCCC2)C=C1

59.	ZINC000046777404	0.332	CCOC1=CC=CC2=C1OCC(=C2)C(=O)N[C@H](C)[C@@H]1CCCO1
60.	ZINC000035457737	0.331	CC(C)CC(=O)O[C@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
61.	ZINC000035457746	0.33	CC(C)CC(=O)O[C@H]1[C@@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
62.	ZINC000091848977	0.33	COC[C@]1(O)CCN(CC2=CC3=CC=CC(OC)=C3OC2)CC1(C)C
63.	ZINC000253389298	0.329	C\\C=C\\C(=O)O[C@@H]1\\C=C\\[C@H](O)[C@@H](CCC(=O)O[C@H]1C)OC(C)=O
64.	ZINC000035457762	0.328	CC[C@H](C)CC(=O)O[C@@H]1[C@H](C(C)C)[C@H](OC(C)=O)C=C(CO)C1=O
65.	ZINC000091663685	0.327	COCC[C@]1(CO)CCCN(CC2=CC3=CC=CC(OC)=C3OC2)C1
66.	ZINC000021095560	0.324	CC(C)OCCCNC(=O)C1=CC2=CC=CC=C2OC1
67.	ZINC000031162394	0.322	CC[C@H](C)CC(=O)O[C@H]1[C@@H](C(C)C)[C@@H](OC(C)=O)C=C(CO)C1=O
68.	ZINC000046777399	0.321	CCOC1=CC=CC2=C1OCC(=C2)C(=O)N[C@@H](C)[C@@H]1CCCO1
69.	ZINC000014813558	0.319	C\\C=C(/C)C(=O)O[C@@H]1[C@@H](C(C)C)[C@@H](OC(C)=O)C=C(CO)C1=O
70.	ZINC000205972582	0.319	C\\C(CCC[C@](C)(O)C1=CC(=O)C(C)(C)O1)=C/[C@@H]1CC(C)=CC(=O)O1
71.	ZINC000044939947	0.318	CCOC1=CC=CC2=C1OCC(=C2)C(=O)NC[C@@H]1CCOC1
72.	ZINC000101403118	0.316	CC(O)=C(CCCCOC1=CC=C(C)C=C1)C(C)=O
73.	ZINC000031165921	0.316	C\\C=C(/C)C(=O)O[C@H]1C=C(CO)C(=O)[C@H](OC(C)=O)[C@H]1C(C)C
74.	ZINC000021095555	0.315	CCOCCCNC(=O)C1=CC2=CC=CC=C2OC1
75.	ZINC000004982282	0.314	COCCNC(=O)[C@@H](C)OC(=O)C1=CC2=CC=CC=C2OC1
76.	ZINC000105364742	0.314	C\\C1=C/[C@@H](O)[C@H]2[C@H](C\\C(C)=C/CC1)OC(=O)[C@H]2CN1CCCCC1
77.	ZINC000001345071	0.314	C[C@@H](OC(=O)C1=CC2=CC=CC=C2OC1)C(=O)NC[C@H]1CCCO1

78.	ZINC000044939951	0.314	CCOC1=CC=CC2=C1OCC(=C2)C(=O)NC[C@H]1CCOC1
79.	ZINC000004982280	0.31	COCCNC(=O)[C@H](C)OC(=O)C1=CC2=CC=CC=C2OC1
80.	ZINC000001345073	0.307	C[C@H](OC(=O)C1=CC2=CC=CC=C2OC1)C(=O)NC[C@@H]1CCCO1
81.	ZINC000067975414	0.306	CCC(=O)NCC1CCN(CC2=CC3=CC(OC)=CC=C3OC2)CC1
82.	ZINC000069352225	0.306	CCOC1CCN(CC1)C(=O)C1=CC2=CC=CC(OC)=C2OC1
83.	ZINC000252694738	0.305	C\\C1=C/[C@@H](O)[C@H]2[C@H](CC(C)=CCC1)OC(=O)[C@H]2CN1CCCCC1
84.	ZINC000001345070	0.305	C[C@H](OC(=O)C1=CC2=CC=CC=C2OC1)C(=O)NC[C@H]1CCCO1
85.	ZINC000012656690	0.304	C\\C1=C/[C@@H](O)[C@H]2[C@H](C\\C(C)=C\\CC1)OC(=O)[C@@H]2CN1CCCCC1
86.	ZINC000257344313	0.302	CCOC1=CC(=CC=C1O)C(=O)N1CCC2(CC1)COCC=CC2
87.	ZINC000057562498	0.301	O=C(NCCCCN1CCOCC1)C1=CC2=CC=CC=C2OC1
88.	ZINC000012656692	0.3	C\\C1=C/[C@@H](O)[C@H]2[C@H](C\\C(C)=C\\CC1)OC(=O)[C@H]2CN1CCCCC1
89.	ZINC000065527012	0.3	COC1=CC=C2OCC(CN3CCC4(CNC(=O)C4)CC3)=CC2=C1
90.	ZINC000095441531	0.297	CCOC1=CC=C2OCC(=CC2=C1)C(=O)N[C@@H](C)C1=CNN=C1
91.	ZINC000021095352	0.296	COCCCNC(=O)C1=CC2=CC(OC)=CC=C2OC1
92.	ZINC000021095296	0.295	CCN(CC)CCCNC(=O)C1=CC2=CC(OC)=CC=C2OC1
93.	ZINC000078612268	0.295	O=C(O[C@H]1CCOC1)\\C=C\\C1=CC=C2OCOC2=C1
94.	ZINC000044939203	0.295	CCOC1=CC=CC2=C1OCC(=C2)C(=O)NC[C@H]1CCCO1
95.	ZINC000031430198	0.294	COC1=CC(C=CC(=O)CC(=O)C=CC2=CC=C(O)C=C2)=CC=C1O
96.	ZINC000005115722	0.294	COC1=CC(C=CC(=O)CC(=O)C=CC2=CC=C(O)C=C2)=CC=C1O
97.	ZINC000031430204	0.294	COC1=CC(C=CC(=O)CC(=O)C=CC2=CC=C(O)C=C2)=CC=C1O
98.	ZINC000031430201	0.294	COC1=CC(C=CC(=O)CC(=O)C=CC2=CC=C(O)C=C2)=CC=C1O

99.	ZINC000105364737	0.293	C\\C1=C/[C@@H](O)[C@H]2[C@H](C\\C(C)=C/CC1)OC(=O)[C@@H]2CN1CCCCC1
100.	ZINC000014503461	0.293	COC1=CC(\\C=C\\C(=O)OC[C@@H](O)C2=CC=C(O)C=C2)=CC=C1O

At its core, similarity searching is a form of ligand-based drug discovery that assumes that two molecules have the same potential to exhibit biological activity if they share a similar chemical structure. The tools available through the SwissSimilarity service allowed for the rapid identification of chemical compounds that shared common molecular features with CMNPD17791, a newly identified marine natural product that shows promise for its ability to inhibit NDM-1.

The top score of similarity across all 425 compounds in this analysis was 0.621, which indicates moderate structural similarity between the two sets of analyzed compounds and the `reference` compound. While there were no compounds that showed a high level of structural similarity to the reference compound, this is beneficial to drug development as structurally related analogues could potentially possess enhanced pharmacokinetic behaviour, lower toxicity or improved target-binding interactions while still displaying biological activity.

The chemical structures of the compounds retrieved from the SwissSimilarity database had great variety in structure but shared many of the same pharmacophoric features as CMNPD17791. This structural diversity is advantageous because it expands the range of potential chemical space that can be investigated during pharmacological screening and increases the likelihood of discovering new inhibitory compounds with preferable pharmacokinetic characteristics as a result of screening for drug-like characteristics. Therefore, the top 100 compounds retrieved from the SwissSimilarity database are useful and will be subjected to additional pharmacological testing based on their drug-like characteristics along with an analysis of their ADMET properties.

Drug likeliness studies and ADMET Studies

Assessing Drug-Likeness of Compounds from SwissSimilarity Screening using ADMET-AI Chemaudit Platform to Determine Oral Drug Development Candidates by Applying the Lipinski, Veber. Egan, Ghose, and Mugeg Rules to the 100 Best Performing Compounds Based on SwissSimilarity Screening Data Were Structured and Tested. All 100 Compounds That Met Most of The Criteria of Drug-Likeness Are Considered Acceptable Candidates For Development of Orally Administered Drugs and The ADMET Analyses Via ADMER AI Chemaudit were performed on The 100 Compounds That Met the Drug-Likeness Criteria.

After a comprehensive assessment of the 15 candidate compounds to find how they behave in the human body (pharmacokinetics) and how they might be toxic (toxicity), it was determined that the candidate compounds would be good drug candidates with favourable pharmacological and safety characteristics.

On a general level, candidates for selection displayed acceptable physicochemical properties and acceptable absorption, distribution and a manageable metabolic profile along with low predicted levels of toxicity. Therefore these candidate compounds will be the basis of molecular docking studies.

Table 2. Top 15 Lead Compounds Selected After ADMET Profiling and Pharmacokinetic Evaluation

1	ZINC000000110756	High QED (0.847), excellent HIA (0.999), best oral bioavailability (0.939), low hERG risk (0.214), good BBB penetration (0.920)
2	ZINC000003129362	High QED (0.617), excellent HIA (0.999), high oral bioavailability (0.957), low toxicity, good PAMPA (0.990)
3	ZINC000000163750	High QED (0.617), excellent HIA (0.999), high oral bioavailability (0.949), low toxicity, good PAMPA (0.989)
4	ZINC000001424389	High QED (0.816), excellent HIA (0.999), high oral bioavailability (0.941), moderate metabolism, good BBB (0.905)
5	ZINC000022011900	Highest oral bioavailability (0.967), excellent HIA (0.999), highest BBB penetration (0.996), good solubility
6	ZINC000095459346	High QED (0.810), good half-life (35.51 h), good HIA (0.999), moderate oral

		bioavailability (0.862)
7	ZINC000252483850	Good QED (0.854), good half-life (25.86 h), high oral bioavailability (0.936), low clearance, good BBB (0.942)
8	ZINC000252483848	Good QED (0.854), good half-life (26.60 h), high oral bioavailability (0.926), low clearance, good BBB (0.932)
9	ZINC000048239307	Good QED (0.749), good half-life (15.36 h), good HIA (0.999), oral bioavailability (0.886), good BBB (0.970)
10	ZINC000895325934	High QED (0.892), good half-life (15.94 h), high oral bioavailability (0.899), low CYP inhibition, good BBB (0.987)
11	ZINC000895325935	High QED (0.892), good half-life (16.68 h), high oral bioavailability (0.886), low CYP inhibition, good BBB (0.985)
12	ZINC000046777408	High QED (0.907), long half-life (39.21 h), high oral bioavailability (0.918), good BBB (0.967), good HIA (0.999)
13	ZINC000046777412	High QED (0.907), long half-life (39.60 h), high oral bioavailability (0.913), good BBB (0.964), good HIA (0.999)
14	ZINC000035459194	Very low hERG risk (0.026), low CYP inhibition, good aqueous solubility, moderate absorption, low toxicity
15	ZINC000035457764	Good QED (0.713), good BBB (0.928), good distribution (Vd: 9.43), moderate toxicity, good for peripheral targets

Drug-likeness assessments and ADMET evaluations are essential phases of computational drug discovery because many compounds that exhibit good biological activity at the discovery phase fail in later phases of development due to their negative impact on pharmacokinetics or their high level of toxicity.

All the chosen chemical compounds conform strongly to the established standards of drug-likeness, verifying their appropriateness as candidate drugs for administration to patients by oral route. Many of the compounds also demonstrated high values that predict good gastrointestinal (GI) absorption into the circulation and therefore good systemic exposure after administration.

Many of the compounds had a high degree of blood-brain barrier permeability. Central nervous system penetration is not a requirement for treating bacterial infections due to the NDM-1 enzyme, nonetheless, the amounts of blood-brain barrier permeability indicated good trans-Membrane permeation and possible transport characteristics. Low predictive hERG inhibition probabilities and minimal CYP450 inhibition liabilities indicate lower risk of drug(s)-causing cardiac toxicity (i.e. cardiotoxic drug) and lower risk of Inter-Drug interactivity, respectively.

ZINC 000000110756, ZINC 000022011900, ZINC 000046777408, and ZINC 000895325934 all had very well balanced pharmacokinetics (bioavailability, volume of distribution, half-life, & so on) and had associated drug-likeness scores with additional desirable pharmacokinetics (such as absorption / distribution / metabolism / toxicity). Therefore, these four compounds were selected to be the best candidates for future molecular docking studies via NDM-1.

Molecular docking

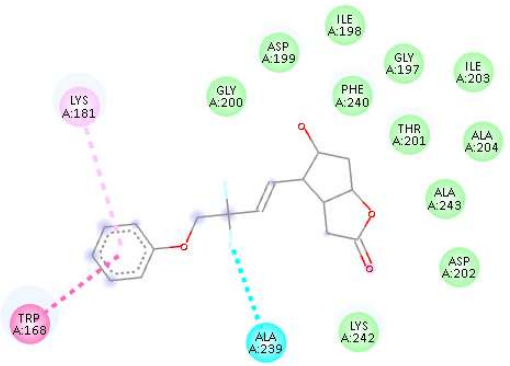
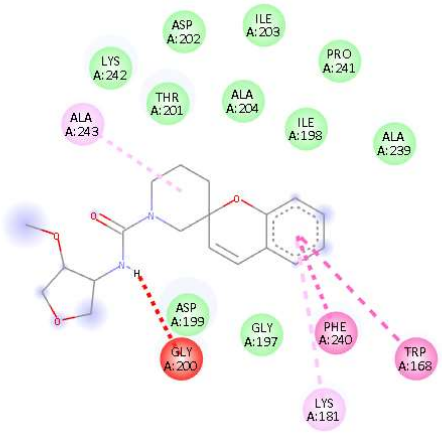
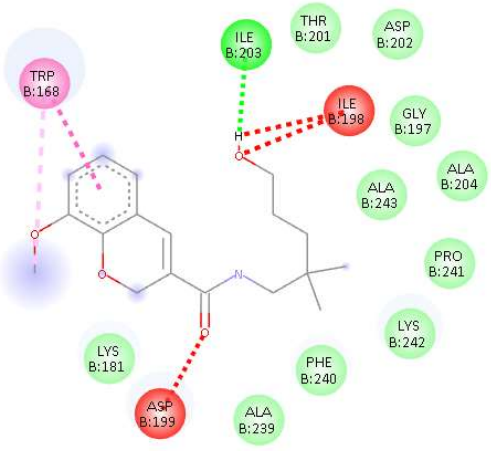
The fifteen lead compounds that were selected based upon an ADMET filtering process underwent molecular docking utilizing PyRx. The molecular docking simulations that were run provided an estimated measure of the degree of binding affinity that each of these compounds had to the active site of NDM-1 (PDB ID: 5ZGE).

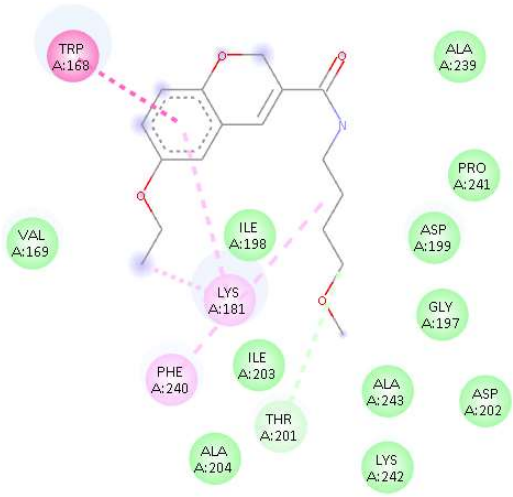
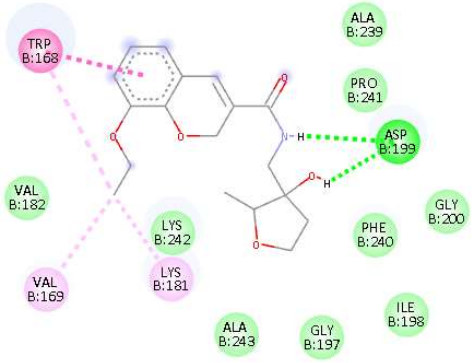
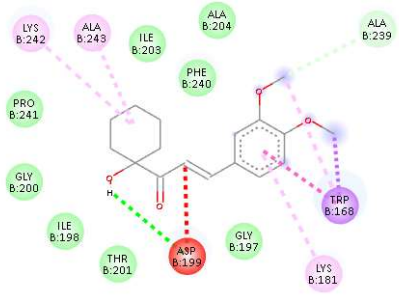
CMNPD17791 as the reference compound has the most robust docked binding interaction at -8.9 Kcal/mol followed by the top three hit compounds of ZINC000022011900 (-7.9 Kcal/mol), ZINC000895325934 (-7.8 Kcal/mol) and ZINC000095459346 (-7.7 Kcal/mol).

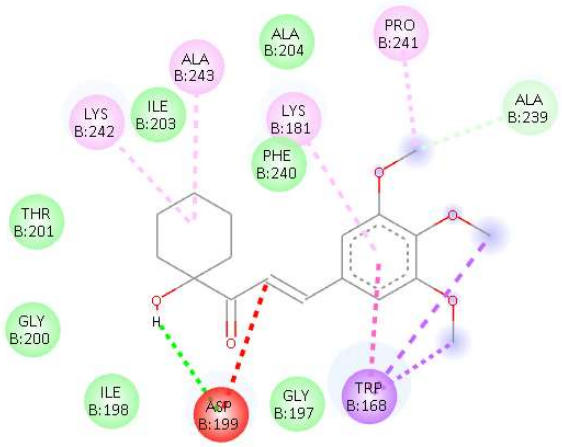
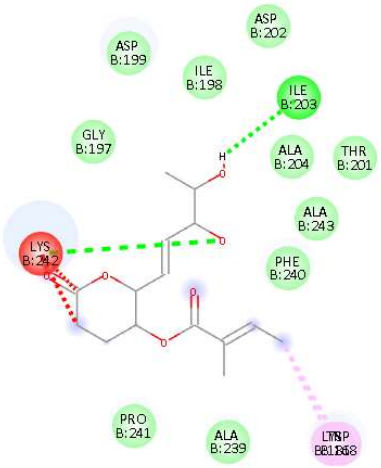
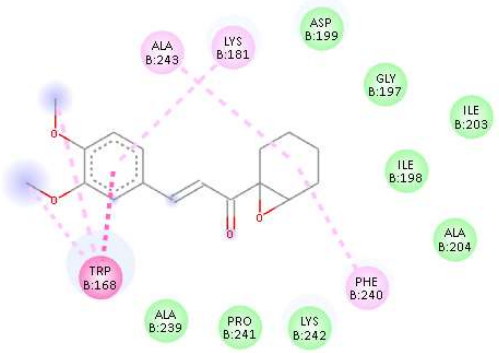
Among the other compounds that had a favorable docking score were ZINC000048239307 (−7.4 kcal/mol), ZINC000252483850 (−7.4 kcal/mol), ZINC000000110756 (−7.3 kcal/mol), ZINC000001424389 (−7.1 kcal/mol), and ZINC000035459194 (−7.1 kcal/mol). The weakest interaction of the compounds in the screening was ZINC000895325935 that exhibited a binding energy of -5.8 kcal/mol.

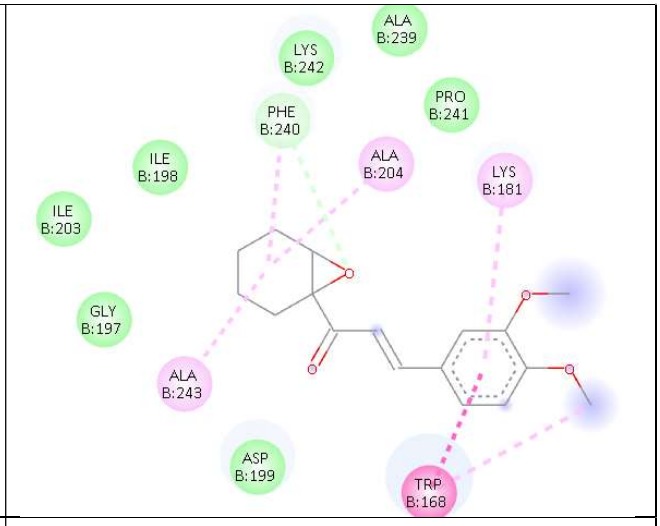
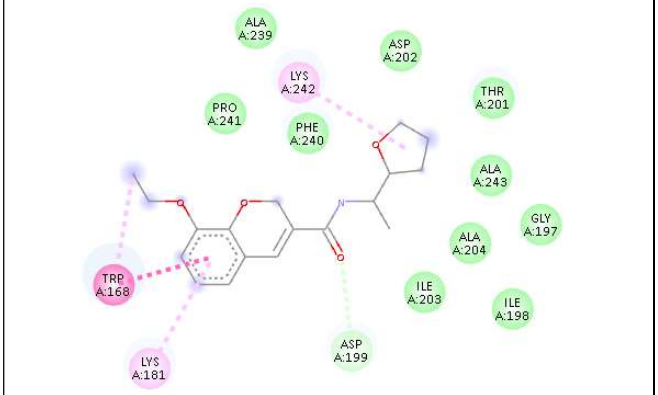
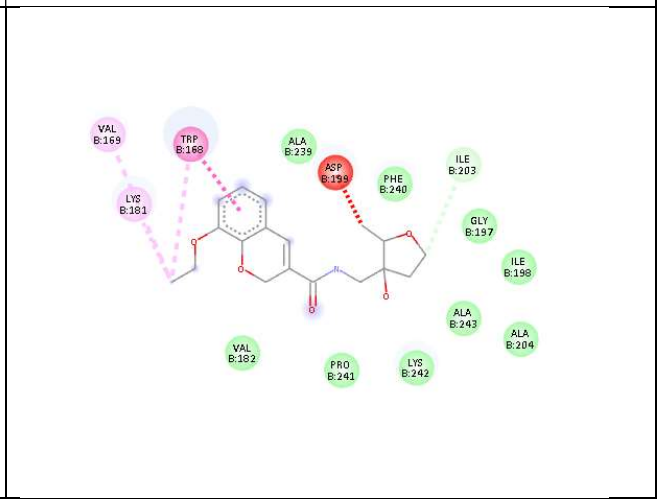
Table 3. Molecular Docking Results of Selected Compounds Against NDM-1

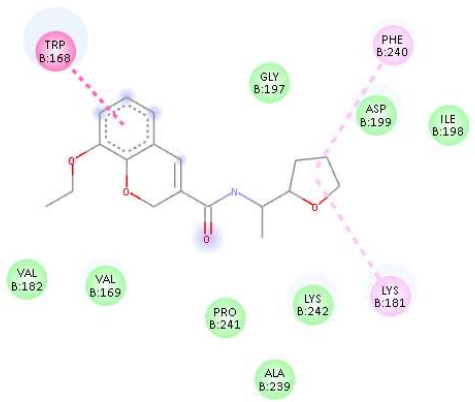
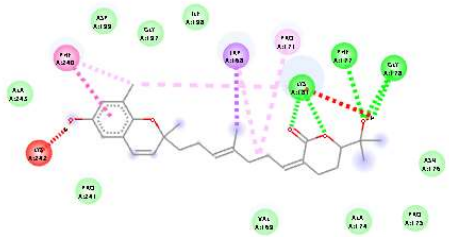
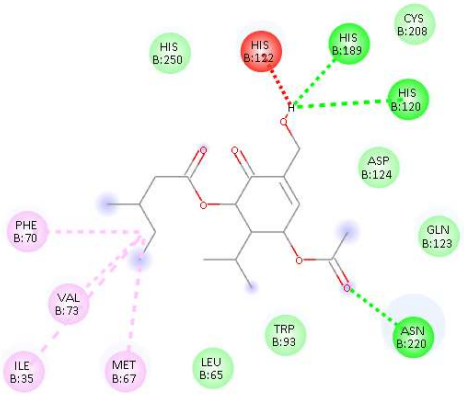
S. No.	**Ligand (ZINC ID)**	**Best Binding Affinity (kcal/mol)**	**2D Pose Diagram**

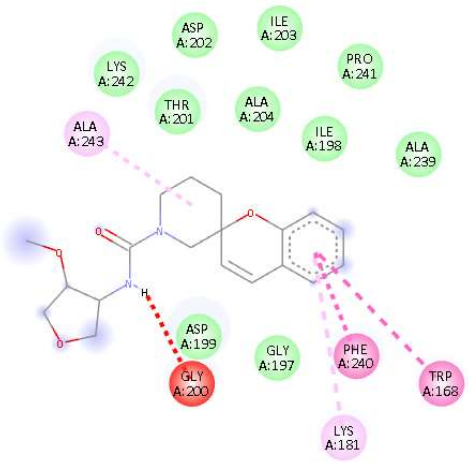
1	ZINC000022011900	-7.9	
2	ZINC000895325934	-7.8	
3	ZINC000095459346	-7.7	

4	ZINC000048239307	-7.4	
5	ZINC000252483850	-7.4	
6	ZINC000000110756	-7.3	

7	ZINC000001424389	-7.1	
8	ZINC000035459194	-7.1	
9	ZINC000003129362	-6.9	

10	ZINC000000163750	-6.9	
11	ZINC000046777408	-7.0	
12	ZINC000252483848	-6.8	

13	ZINC000046777412	~ -6.7	
14	CMNPND17791	-8.9	
15	ZINC000035457764	-6.1	

16	ZINC000895325935	-5.8	

The binding interactions and stability of the compounds selected for molecular docking to NDM-1 were analyzed using molecular docking methods. The results obtained from the docking runs (docking scores) are representative of the binding strength of the compound to NDM-1. A higher docking score would indicate a stronger predicted interaction between NDM-1 and the compound and possibly an increased level of inhibition by the compound compared to a compound with a lower score.

Among candidates that underwent screening and evaluation, ZINC000022011900 was the most attractive compound since it had the highest docked score (-7.9 kcal/mol) compared to the remaining compounds, along with other factors: the compound exhibited very good oral bioavailability via the ADMET analysis and demonstrated strong protein binding (high pharmacokinetic characteristics). All these factors create a very compelling lead compound.

While ZINC000895325934 and ZINC000095459346 had lower docking scores than the reference compound, their ability to show good binding affinities and good

ADMET profiles indicates that they could potentially be used as alternative NDM-1 inhibitors; therefore, their predicted advantages in the area of PK will potentially offset any disadvantage created by their lesser binding energy relative to the reference compound.

Overall, the results from the docking study indicate the many compounds generated from SwissSimilarity have significant affinity toward the active site of NDM-1, meaning they could be considered promising lead candidates.

CONCLUSION

The SwissSimilarity ligand-based virtual screening method identified compounds that were similar to the reference compound CMNPD17791. The screening process retrieved 400 structurally similar compounds and the top 100 candidates were tested for drug-like properties and ADMET. Out of these candidates, 15 lead compounds had favorable pharmacokinetic and safety properties. When molecular docking studies were done with the NDM-1 enzyme, ZINC000022011900, ZINC000895325934 and ZINC000095459346 were revealed to have the strongest binding affinities of all of the compounds screened. Based on docking results and ADMET properties, ZINC000022011900 was the most promising lead candidate.

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