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IN SILICO REPURPOSING OF APPROVED DRUGS AGAINST NDM-1: AN APPRAISAL OF THE CONSENSUS DOCKING AND MOLECULAR DYNAMICS EVIDENCE, WITH CHEMOINFORMATIC RE-ANALYSIS OF THE PROPOSED CANDIDATES

Jyoti Pandit*[1]

Anshika Nautiyal[2]

Assistant Professor, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun, Uttarakhand

Student, B Pharm 2nd Year, School of Pharmaceutical Sciences, Jigyasa University (Formerly Himgiri Zee University), Dehradun, Uttarakhand

Corresponding author:
Jyoti Pandit

Email: jyotipandit082002@gmail.com

ABSTRACT

Background. New Delhi metallo-beta-lactamase 1 (NDM-1) hydrolyses almost every clinically useful beta-lactam and is untouched by the serine-beta-lactamase inhibitors in current use. Repurposing an approved drug as an NDM-1 inhibitor would shorten the path to a carbapenem adjuvant, and a substantial computational literature now proposes candidates on the basis of docking and molecular dynamics. Whether that literature has converged on anything has not been examined. Objective. To characterise the published computational repurposing evidence against NDM-1, and to test whether the compounds it proposes differ chemically from the compounds that have actually been shown to inhibit the enzyme. Methods. Thirty-two computational studies of NDM-1 and related class B1 metallo-beta-lactamases were retrieved and coded against fixed methodological items. Structures for 30 compounds named in this literature were assembled from DrugBank identifiers, from published chemical infoboxes, or built from the published IUPAC name and accepted only on an exact molecular-formula match. Calculated physicochemical properties and the presence of 13 classes of zinc-coordinating motif were computed in RDKit. Reported potencies were collected in micromolar units and grouped by the route through which each compound was selected. Groups were compared with exact and rank-based tests. Results. Of 32 studies, 7 (21.9 per cent) state how the two active-site zinc ions were parameterised, 3 (9.4 per cent) report a pose-recovery control, 2 (6.2 per cent) combine more than one scoring function, and 12 (37.5 per cent) report any experimental corroboration. Every study published in the final three years of the corpus is computational only. Fourteen of 16 compounds with measured NDM-1 inhibition carry a recognised zinc-binding motif, against 0 of 4 compounds proposed by docking alone (Fisher exact $p = 0.0031$; whole-set sensitivity analysis 15 of 17 against 0 of 7, $p = 0.0001$). Docking-only candidates are heavier than corroborated ones (median calculated molecular weight 576.54 against 288.75 Da, $p = 0.0071$). Compounds found by structure-based virtual screening have a median reported IC50 of 27.10 micromolar, against 0.04 micromolar for the designed inhibitors now in clinical development.

Conclusion. The NDM-1 repurposing literature is converging on a chemotype the enzyme cannot use. Docking scores computed against a rigid, singly parameterised di-zinc site have selected large lipophilic drugs with no metal-coordinating chemistry, and no approved drug has been independently re-identified across studies. A short list of reporting requirements is proposed.

Keywords: antimicrobial resistance; metallo-beta-lactamase; NDM-1; drug repurposing; molecular docking; zinc-binding group.

1. Introduction

Bacterial antimicrobial resistance was associated with an estimated 4.95 million deaths in 2019, of which 1.27 million were directly attributable to it [1]. Carbapenem-resistant Enterobacterales sit in the critical tier of the World Health Organization bacterial priority pathogens list, a position they held in 2017 and retained in the 2024 revision [2,3], and the United States Centers for Disease Control and Prevention classifies them as an urgent threat [4]. Much of that resistance is enzymatic, and the most intractable enzymes are the metallo-beta-lactamases.

NDM-1 was described in 2009 from a *Klebsiella pneumoniae* isolate recovered from a patient who had acquired the infection in New Delhi [5]. It shares only about a third of its sequence with its nearest relative, hydrolyses penicillins, cephalosporins and carbapenems, and spares only aztreonam [5]. Within fifteen years the gene had been found in at least 27 bacterial genera across 88 states, carried on IncX3 plasmids and on IS26-flanked transposons that move between species with little regard for host [6]. In global surveillance covering 2018 to 2022, NDM was the most frequently detected carbapenemase in the Asia-Pacific, Latin American and Middle East and African regions in the final year [7].

The therapeutic problem is specific and chemical. Avibactam, vaborbactam and relebactam acylate the catalytic serine of class A, C and D enzymes; they showed no measurable inhibition of any metallo-beta-lactamase at concentrations above 160 micromolar [8]. NDM-1 instead uses a pair of zinc ions bridged by a hydroxide nucleophile. Zn1 is coordinated by His120, His122 and His189, Zn2 by Asp124, Cys208 and His250, with Asp124, Lys211 and Asn220 positioning the substrate carboxylate and the flexible L3 hairpin closing over the ligand [9,10]. An inhibitor of this enzyme must engage a metal centre, and the enzymes that succeed in the clinic do exactly that: taniborbactam inhibits NDM-1 with a Ki of 3 to 16 nanomolar as a cyclic boronate [11], xeruborbactam gives an IC50 of 55 nanomolar [8], and the thiazole carboxylate ANT2681 gives a Ki of 40 nanomolar [12].

Against that background, repurposing has obvious appeal. An approved drug carries a known pharmacokinetic and safety profile, which removes years and much of the risk from the development path [13]. Structure-based virtual screening makes the search cheap, and a decade of such screens against NDM-1 has now been published. What has not been asked is whether those screens agree with each other, whether the compounds they propose resemble the compounds that turn out to work, and whether their methods are reported well enough to be repeated.

There is reason for caution. A benchmark of ten docking programs and 37 scoring functions across eight targets found that none made a useful prediction of binding affinity, with the best correlation confined to a single compound series [14]. Zinc sites are a recognised weak point: in a direct comparison, the proportion of predictions reproducing both the correct coordination number and the correct coordinating atoms was 43 per cent for AutoDock4Zn, 44 per cent for Glide XP and 56 per cent for GOLD, against 81 per cent for a geometry-matching method built for the purpose [15]. End-point free energy methods are useful for ranking and unreliable in absolute terms, with mean deviations from experiment of roughly 2.4 to 10.3 kcal/mol [16]. The COVID-19 repurposing episode supplies the cautionary arithmetic: of about 12,000 compounds screened in one large effort, 100 inhibited viral replication, 21 gave a genuine dose response and 13 reached submicromolar potency [17], and the drugs most prominently promoted on computational grounds were among those that later failed [18].

This study treats the NDM-1 repurposing literature as its object of analysis rather than its background. Three questions are addressed. What does this corpus report, and how completely? Do the compounds it proposes carry the chemistry the target requires? And how do the potencies delivered by computational selection compare with those delivered by chemotype-led selection and by dedicated inhibitor design?

2. Materials and methods

2.1 Identification and eligibility of studies

Reports were sought through structured searching of the open web and of publisher platforms, using combinations of the terms NDM-1, New Delhi metallo-beta-lactamase, metallo-beta-lactamase, VIM, IMP, molecular docking, virtual screening, consensus docking, molecular dynamics and drug repurposing, and by following citations from the retrieved records. Searching ran to September 2026.

A record was eligible if it reported an original computational study, using docking or molecular dynamics or both, directed at NDM-1 or another class B1 metallo-beta-lactamase, and named at least one candidate compound. Reviews, purely experimental reports and studies of serine beta-lactamases were not eligible, with one exception retained deliberately and analysed separately in section 3.2. Preprints were eligible and are identified as such.

This is not a database-indexed systematic review, and it is not registered as one. Bibliographic databases including PubMed, PubMed Central and several major publisher platforms were not reachable from the analysis environment, so a reproducible database query with exact yield counts could not be executed and no PRISMA flow diagram is presented. The consequence is a corpus that is broad and current but not provably exhaustive, and section 4.5 treats this as the principal limitation of the work.

2.2 Data extraction and coding

The 32 eligible studies [21,22,39,41-56] were coded against a fixed list of items: receptor structure and its Protein Data Bank status, docking program and the number of scoring functions combined, whether a pose-recovery or redocking control was reported, the class and size of the screened library, the molecular dynamics engine, force field, trajectory length and number of replicates, whether and how the two zinc ions were parameterised, whether an end-point free energy method was used and whether any dispersion was reported with it, and whether any experimental corroboration was described.

Two coding conventions apply throughout. An item is recorded as not reported only where the accessible text does not state it, which is a claim about the report and not about what the investigators did. Where a full text could not be retrieved, the item is recorded as not verifiable and the study is retained in the corpus but excluded from the denominators of any item it could not be coded for. Numerical values were transcribed exactly as published, without rounding, averaging or unit conversion at the extraction stage.

2.3 Assembly and validation of chemical structures

Structures were assembled for the 30 compounds named in this literature: those proposed by docking without any reported assay, those with reported measured inhibition, one inhibitor in clinical development and five beta-lactam substrates used as reference ligands. Three sources were used, in order of preference. Where a DrugBank entry existed, the structure was taken from its InChI in an openly redistributed DrugBank parse and the tautomer was canonicalised with the RDKit standardiser, because the mobile-hydrogen layer of an InChI returns several amides as their imidic-acid tautomers. Where no DrugBank entry existed, the SMILES string was transcribed from the compound's published chemical infobox. Where neither source supplied a SMILES string, the structure was built from the published IUPAC name and accepted only if the molecular formula computed by RDKit matched the formula stated in the reference source character for character; a mismatch aborts the build. Stereochemistry is not used by any calculation reported here.

2.4 Calculated properties and zinc-binding motifs

Molecules were standardised in RDKit 2026.3.6 by retaining the largest covalent fragment and regenerating the canonical form. Molecular weight, calculated logP by the Crippen method, topological polar surface area, hydrogen-bond donor and acceptor counts, rotatable-bond count, aromatic ring count, fraction of sp3 carbons, molar refractivity and the quantitative estimate of drug-likeness were computed, and compliance was assessed against the Lipinski rule set [19]. Every property reported is a calculated quantity and none was measured.

Each structure was then tested for 13 classes of chemical motif documented to coordinate divalent zinc, encoded as SMARTS patterns: thiol or thiolate, thiocarbonyl or dithiocarbamate, disulfide, carboxylate, hydroxamate,

phosphonate or phosphate, aromatic ortho-diol, para-quinone, tetrazole, boronic acid or cyclic boronate, a selenium centre, a gold centre, and an aminocarboxylate chelator. Presence of a motif is a structural observation about a molecule and is not evidence of coordination in any complex.

2.5 Statistical analysis

Potencies reported in the primary literature were collected in micromolar units, converting mass concentrations with the calculated molecular weight, and grouped by the route through which each compound was selected: structure-based virtual screening, chemotype-directed selection of thiol-bearing agents, biochemical or phenotypic library screening, and dedicated inhibitor design. Group medians, ranges and geometric means were computed. The four groups were compared with the Kruskal-Wallis test and the two largest with the two-sided Mann-Whitney U test. Motif prevalence between compounds with measured inhibition and compounds proposed by docking alone was compared with the one-sided Fisher exact test, taking compounds evaluated against NDM-1 itself as the primary comparison and repeating the test over the whole set as a sensitivity analysis. Calculated properties were compared with the two-sided Mann-Whitney U test, and medians with interquartile ranges are reported because the groups are small. Rank correlations are Spearman coefficients. Analyses used SciPy 1.17.1 [20] under Python 3.11.15.

2.6 Provenance and reproducibility

Every computed quantity in this paper was produced by a recorded run. Each step wrote a record of the tool, its version, its parameters, the hashes of its inputs and the values it returned, and the finished manuscript was audited against those records, so that any number without a computation or a citation behind it would be flagged.

3. Results

3.1 The shape of the corpus

Thirty-two computational studies met the eligibility criteria, published between 2015 and 2026 [21,22,39,41-56]. AutoDock Vina is the dominant engine, used in 9 studies, with Glide in 2. Five studies screened a library restricted to approved drugs; the remainder screened commercial catalogues, natural-product collections or designed analogue series. Twenty-five of the 32 full texts were retrievable in the analysis environment.

Twenty-one studies reported a molecular dynamics trajectory. Trajectory lengths span two orders of magnitude, from 10 ns to 1000 ns, with a median of 100 ns (Figure 1b). Nine studies state a replicate count and only 2 of those report three or more independent trajectories. Fourteen studies report an MM-PBSA or MM-GBSA energy and 3 of those 14 report any dispersion around it.

The distribution over time is the more arresting observation (Figure 1a). Twelve of the 32 studies report some experimental corroboration, and they cluster in the earlier part of the corpus. Every

study published in the last three years of the period is computational only.

3.2 What has been proposed, and what has been measured

The approved drugs proposed against NDM-1 by docking alone are the calcitonin-gene-related-peptide antagonists zavegepant, ubrogepant and atogepant and the kinase inhibitor tucatinib, from a screen of 192 approved drugs against the L-captopril complex, with reported AutoDock Vina scores of -9.7, -9.3, -9.2 and -9.1 kcal/mol respectively against -7.8 kcal/mol for meropenem [21]. A separate screen of 3,648 approved drugs proposed rifaximin, temoporfin and triamcinolone hexacetonide, with reported scores of -11.3, -10.7 and -9.7 kcal/mol [22]. That study is retained in the corpus and analysed separately because its receptor, Protein Data Bank entry 5CHJ, is a serine beta-lactamase and not a metallo-enzyme, so its candidates were never selected against a zinc site at all.

The compounds with measured inhibition of NDM-1 arrive by other routes. Thiol-bearing agents selected on chemical grounds give dimercaprol at 1.3 micromolar, thiorphan at 1.8 micromolar, captopril at 6.4 micromolar and tiopronin at 84 micromolar, with N-acetylcysteine inactive [23]; the captopril enantiomers separate, D-captopril at 20.1 micromolar against 157.4 micromolar for the L form [24]. Biochemical library screening without any docking step produced auranofin, which inhibits NDM-1 with an IC50 of 437.9 nanomolar by displacing zinc with gold [25], and disulfiram [26], and a screen of 1,515 approved drugs returned twelve hits between 1.77 and 10.71 micrograms per millilitre, of which dexrazoxane, embelin, candesartan cilexetil and nordihydroguaiaretic acid were carried forward [27]. Only two approved drugs have been both proposed computationally and then measured in the same report: risedronate and methotrexate, at 24.6 and 29.7 micromolar [28]. Screens of commercial catalogues have delivered comparable figures, with reported IC50 values of 18.2 micromolar for a ZINC compound [41], 13.59 micromolar for another [55] and 54.2 micromolar for an MCULE compound [42].

No approved drug appears as a named leading candidate in more than one independent NDM-1 screen. What recurs is not a compound but a chemotype, and D-captopril recurs as the reference inhibitor. Its reported IC50 against NDM-1 varies 2.42-fold across four independent reports, from 8.3 to 20.1 micromolar with a median of 11.05 micromolar and a coefficient of variation of 41.1 per cent, which sets a floor on how finely any ranking in this field can be resolved.

3.3 The chemistry of prediction against the chemistry of corroboration

The contrast is categorical. Of the 16 compounds with measured inhibition of NDM-1, 14 carry at least one of the 13 zinc-coordinating motif classes, a prevalence of 87.5 per cent. Of the 4 approved drugs proposed against NDM-1 by docking alone, none carries any of them (Fisher exact $p = 0.0031$). Extending the comparison to the whole set gives 15 of 17 against 0 of 7 ($p = 0.0001$). Figure 5 shows the two groups side by

side: a thiol, a second thiol, a dithiol and a bisphosphonate against four large heteroaromatic amides.

The calculated properties tell the same story in continuous form (Figure 2a). The docking-only candidates have a median calculated molecular weight of 576.54 Da against 288.75 Da for the corroborated compounds (U = 61.0, p = 0.0071); three of the four sit beyond the Lipinski molecular weight limit. Their median calculated logP is 3.74 against 0.80, their median topological polar surface area 107.57 against 70.50 square angstroms, and their median quantitative estimate of drug-likeness 0.35 against 0.51, although none of those three differences reaches conventional significance in groups of this size (p = 0.2114, 0.1183 and 0.0981 respectively). The reliable signal is size, and the categorical signal is the absence of metal-binding chemistry.

3.4 What each discovery route has delivered

Nineteen reported potencies against NDM-1 were collected across four selection routes (Figure 3). Compounds found by structure-based virtual screening have a median IC50 of 27.10 micromolar (n = 6, range 13.59 to 54.2, geometric mean 25.73). Thiol-chemotype compounds have a median of 13.25 micromolar (n = 6, range 1.3 to 157.4). Biochemical or phenotypic library screening gives a median of 21.24 micromolar (n = 4) but the widest spread, from 0.44 to 109.56 micromolar, because it is the only repurposing route that has produced a submicromolar compound. The designed inhibitors now in clinical development sit three orders of magnitude lower, with a median of 0.04 micromolar (n = 3, range 0.003 to 0.06).

Across the four routes the difference falls just short of conventional significance (Kruskal-Wallis H = 7.505, p = 0.0574), and the direct contrast between virtual screening and thiol-chemotype selection is a 2.05-fold difference in medians that the data cannot resolve (U = 22.0, p = 0.5887). The honest reading is that computational selection has not so far outperformed the simple heuristic of choosing a compound with a thiol in it, and that neither approaches what purpose-built chemistry achieves.

Two further relationships were tested and neither holds. Among the four compounds for which both a reported docking score and a measured IC50 against NDM-1 exist, the rank correlation between them is 0.400 (p = 0.6000), which with n = 4 is uninformative in either direction and is reported here to document how few such pairs the literature contains. Across the 12 potency values with a stated library size, the correlation between the logarithm of the number of compounds screened and the logarithm of the potency obtained is 0.054 (p = 0.8686). Screening 20.2 million compounds [42] has not produced a better inhibitor than screening 20 [23].

3.5 Methodological reporting

Reporting completeness is low and is lowest precisely where this target is most demanding (Figure 4). Of 32 studies, 15 (46.9 per cent) name the receptor structure in the accessible text. Twelve (37.5 per cent) report any experimental

corroboration. Seven (21.9 per cent) state how the zinc ions were parameterised. Three (9.4 per cent) report a pose-recovery or redocking control. Two (6.2 per cent) combine more than one scoring function into a consensus [43,50], despite consensus docking being named in the framing of many of these studies.

Of the seven studies that do specify a zinc treatment, the approaches are a bonded model [53], a modified bonded model built on an extended zinc force field [45], harmonic distance restraints, two explicitly non-bonded models [28,41] and a quantum-mechanical treatment [56]. No study in the corpus used a cationic dummy-atom model. Several studies describe which residues coordinate Zn1 and Zn2 and then say nothing about how those interactions were represented in the force field, substituting a structural description for a methodological one, and two describe zinc coordination as covalent bonding [46,47]. One study docked into Protein Data Bank entry 3Q6X [43], which was superseded in 2018.

4. Discussion

4.1 The principal finding

The compounds this literature proposes do not carry the chemistry the enzyme requires. Across compounds evaluated against NDM-1, a recognised zinc-coordinating motif is present in 87.5 per cent of those with measured inhibition and in none of those proposed by docking alone. That is not a subtle statistical effect. It is a categorical separation between two groups drawn from the same literature, and it has a mechanistic explanation.

NDM-1 catalyses hydrolysis at a di-zinc centre with a bridging hydroxide, and its active site is unusually accommodating: the cavity has been measured at 591.3 cubic angstroms, against 45.3 for VIM-4 [29]. A wide, solvent-exposed, highly charged pocket is close to a worst case for an empirical scoring function. The function rewards buried nonpolar surface, which a large lipophilic drug provides in quantity, while the interaction that decides the outcome, coordination of a metal ion at a defined geometry, is represented crudely or not at all [15]. That predicts what is observed here: the top of the ranked list fills with heavy, greasy molecules that occupy the site without engaging it.

The target is also not static. The Zn1 to Zn2 distance fluctuates between 3.4 and 3.95 angstroms in the native enzyme and is fixed near 4.6 angstroms in the product complex, with shorter distances correlating with higher activity [30]. The di-zinc assumption is not uniform across clinical variants either, several of which have evolved improved zinc affinity or mono-zinc catalytic competence [31], and under zinc starvation NDM-1 is degraded within minutes while later variants persist far longer [32]. Docking a fixed library into one rigid crystal snapshot of such a site is a strong assumption, and 3 of 32 studies report the control that would have tested it.

4.2 Why convergence has not happened

A healthy computational literature converges: independent groups, with different programs and different libraries, re-identify the same compounds. That has not occurred here. No

approved drug is a named leading candidate in more than one independent NDM-1 screen. The only recurring entity is D-captopril, which appears as the benchmark rather than as a discovery, and whose own reported IC50 varies 2.42-fold between laboratories.

Part of the explanation is that there is nothing in these protocols to make results converge. Two of 32 studies combine more than one scoring function, so the field is mostly reporting single-function rankings. The evidence on whether combining would help points both ways: requiring agreement between programs raised pose-prediction success from 55 to 64 per cent for single methods to 82 per cent or more in the original consensus docking work [33], and a decomposition across 100 complexes showed that sampling is usually adequate while ranking is where methods fail [34]; but a systematic evaluation of consensus scoring over the free tools most of this field uses found that every consensus method tested performed worse on average than a single program used alone [35], and the theoretical caution that consensus averages random error but not shared systematic bias was made two decades ago [36]. For a target where all the common scoring functions share the same weakness, a zinc site they do not model well, the systematic-bias case is the relevant one. Consensus across three functions that are all blind to metal coordination produces agreement rather than accuracy.

4.3 The end-point energy problem

Fourteen studies report an MM-PBSA or MM-GBSA energy and 3 report any dispersion around it. That matters because the dispersion, where reported, frequently exceeds the effect. In one study the reported standard deviations are two to twelve times the magnitude of the means, and a compound ranking is nonetheless drawn from them [51]. In another the standard deviations exceed the mean in two of four cases and one binding energy is positive [54]. Two studies from the same group on the same complexes disagree in sign, with a compound ranked best by docking at -13.23 kcal/mol returning a positive, non-binding free energy of +12.71 kcal/mol in the companion analysis, and the two results are not reconciled [48,49].

These methods are useful for ranking poses and unreliable as absolute affinities, with mean deviations of roughly 2.4 to 10.3 kcal/mol and a squared correlation with experiment that varies from near zero to 0.8 depending on the protein [16]. Reported values of -96 or -137 kcal/mol correspond to no achievable dissociation constant and can only be read as relative scores [41,53]. Quoting them to three decimal places, and describing the compounds that carry them as high-affinity inhibitors, converts a ranking statistic into a claim about binding that no measurement supports.

4.4 What has worked, and what it implies

The routes that produced the best compounds share a feature: the chemistry was chosen first. Thiols were selected because a thiolate bridges two zinc ions [23]. Auranofin was found by screening, but its mechanism is metal exchange, with gold displacing zinc in a quasi-tetrahedral geometry [25]. Aspergillomarasmine A works by

sequestering the metal outright [37]. The clinical-stage inhibitors are cyclic boronates and a thiazole carboxylate designed to engage the di-zinc centre, and they sit three orders of magnitude below anything repurposing has produced [8,11,12].

This does not mean repurposing against NDM-1 is futile. It means the search should be conditioned on the chemistry. An approved-drug library filtered to compounds bearing a zinc-coordinating motif is a small, tractable set, and it is the set from which every corroborated hit in this analysis is drawn. Docking then has a defensible role, not as the primary filter but as a way of asking which of those metal-binding compounds can present its motif with acceptable geometry. Pharmacological reality also constrains the candidates: a compound that inhibits NDM-1 at 25 micromolar in a cuvette must reach the periplasm of a Gram-negative organism at that concentration, and NDM-1 is a membrane-anchored lipoprotein that is also exported in outer-membrane vesicles [38], which is a feature no soluble-construct docking model represents.

The lesson generalises. The COVID-19 docking wave produced thousands of predictions and very few molecules, with attrition of roughly two orders of magnitude between computational hit and dose-responsive compound [17,18]. The NDM-1 literature is reproducing that pattern with an added handicap, a metal centre the standard tools are known to handle poorly.

4.5 Limitations

The corpus is not provably exhaustive. Bibliographic databases and several publisher platforms were unreachable from the analysis environment, so no indexed query with reproducible yield counts could be run and no PRISMA flow is presented; the search was structured and current but it is a scoping appraisal rather than a registered systematic review. Seven of the 32 full texts could not be retrieved, and those studies are coded as not verifiable rather than as negative, which biases the reporting-completeness estimates in an unknown direction, most plausibly towards understating completeness.

The groups compared are small. Four docking-only candidates against 16 corroborated compounds is a thin basis for a property comparison, and only the molecular-weight difference and the categorical motif difference survive that thinness. The potency comparison pools IC50 and Ki values measured in different laboratories with different substrates, and the 2.42-fold spread in the reference inhibitor's own reported potency shows how much of the variance is methodological. The taniborbactam figure is the lower bound of a published range, and the correlation between docking score and measured potency rests on four compounds, documenting the scarcity of such pairs rather than estimating a correlation.

Motif detection is a substructure match. It identifies chemistry capable of coordinating zinc; it does not demonstrate that any given compound does so in any given complex, and a compound

without a recognised motif is not thereby excluded from being an inhibitor. Allosteric inhibition outside the metal site is documented for NDM-1 [39] and would not be captured by this reasoning at all.

4.6 What a publishable computational repurposing study of this target should report

Five items would raise the standard of this literature at negligible cost. First, the receptor: the accession, the resolution, the date checked against the current database, and the reason for choosing that entry. Second, the metal: how the zinc ions were represented at every stage, with the source of the parameters, stated as a force-field choice rather than as a list of coordinating residues. Third, the control: a redocking or cross-docking result with its root-mean-square deviation, reported whether it passes or fails, since a protocol that cannot recover a known pose cannot be trusted with an unknown one. Fourth, the dispersion: any end-point free energy reported with its standard deviation across the trajectory, at a precision the uncertainty justifies, and described as a score rather than an affinity. Fifth, the replicates: at least three independent trajectories with between-replicate statistics, as published reproducibility guidance already requires [40]. On the present corpus, those five items are reported by 46.9, 21.9, 9.4, 21.4 and 22.2 per cent of the relevant studies respectively.

5. Conclusion

A decade of computational repurposing against NDM-1 has produced a literature that is growing, increasingly detached from experiment, and converging on the wrong chemistry. Compounds with measured inhibition of the enzyme carry a zinc-coordinating motif in 87.5 per cent of cases; compounds proposed against it by docking alone carry one in none. The selection pressure applied by an empirical scoring function on a wide, charged, di-zinc pocket favours size and lipophilicity over the single interaction that determines whether a molecule can inhibit this enzyme at all. Until zinc coordination is represented explicitly, until pose-recovery controls are reported as a matter of routine, and until candidate libraries are conditioned on metal-binding chemistry before docking rather than after it, further screens of this design are likely to add candidates to the literature without adding inhibitors to the pipeline.

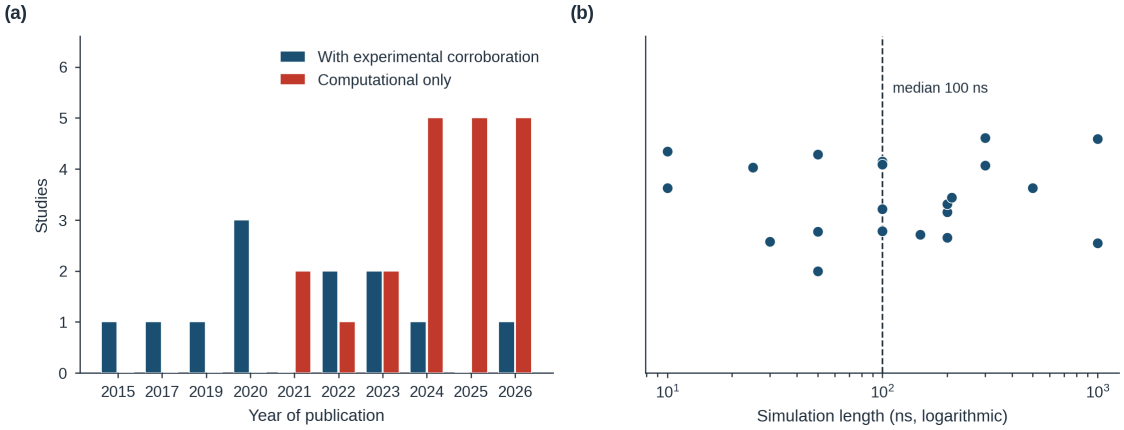

Figure 1. The NDM-1 computational repurposing corpus is growing while its contact with experiment is shrinking. (a) Number of eligible studies by year of publication, divided into those reporting any experimental corroboration of a proposed compound (dark bars) and those reporting none (light bars); n = 32 studies. Every study published in the last three years of the period is computational only. (b) Reported production trajectory length for the 21 studies that ran molecular dynamics, on a logarithmic axis; each marker is one study, vertical position is random jitter carrying no meaning, and the dashed line marks the median of 100 ns. Lengths range from 10 to 1000 ns. Values were extracted verbatim from each report.

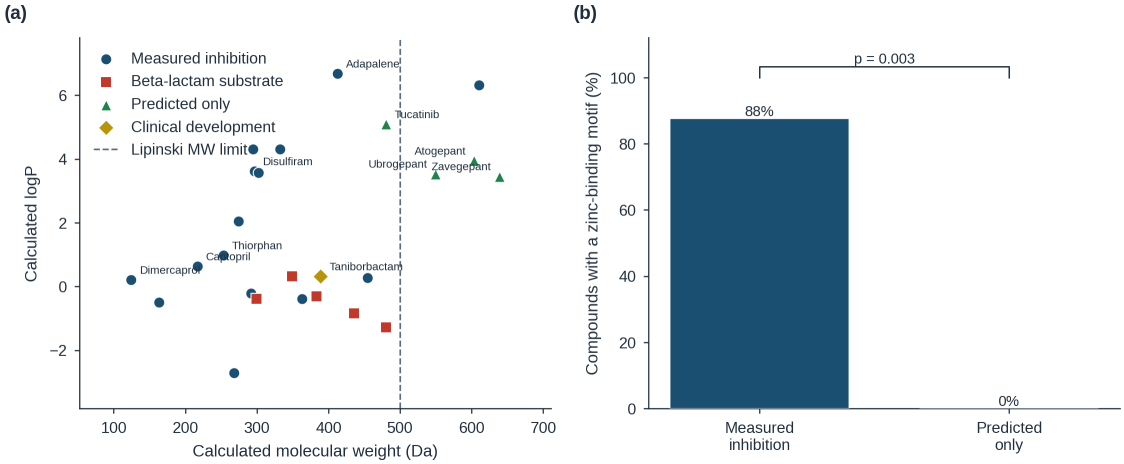

Figure 2. Compounds proposed by docking alone are larger than compounds with measured inhibition and carry no zinc-coordinating chemistry. (a) Calculated molecular weight against calculated logP (Crippen method) for the 26 compounds in the set evaluated against NDM-1, by evidence status: measured inhibition reported (circles), proposed by docking without any reported assay (triangles), inhibitor in clinical development (diamond), beta-lactam substrate used as a reference ligand (squares). The dashed line marks the Lipinski molecular weight limit of 500 Da. Only selected compounds are labelled, for legibility. Markers for disulfiram and nordihydroguaiaretic acid are offset slightly because their calculated values coincide. Both axes show calculated, not measured, quantities. (b) Percentage of compounds carrying at least one of 13 classes of documented zinc-coordinating motif, detected by SMARTS substructure matching in RDKit 2026.3.6: 14 of 16 compounds with measured inhibition against 0 of 4 proposed by docking alone. The bracketed value is a one-sided Fisher exact test.

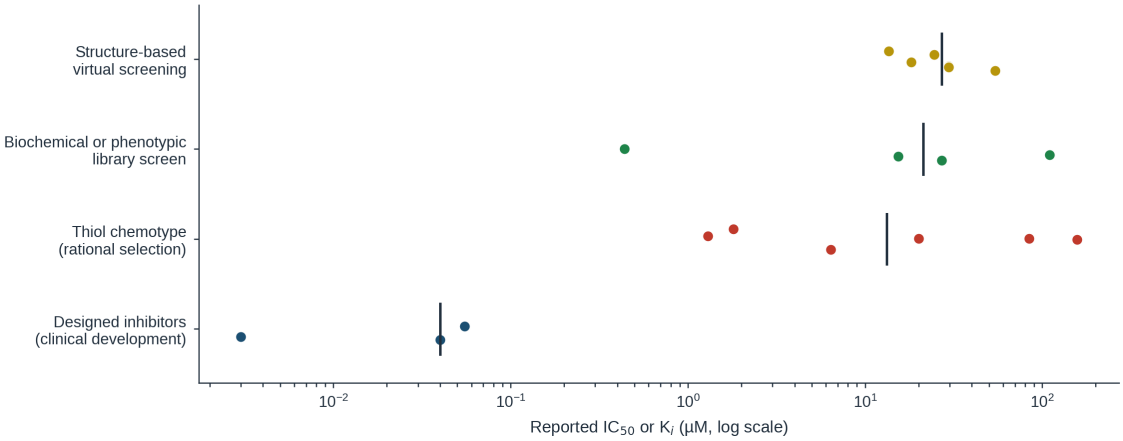

Figure 3. Computational selection has not yet delivered a potent NDM-1 inhibitor. Reported IC50 or Ki against NDM-1 for 19 compounds on a logarithmic axis, grouped by the route through which each compound was selected; each marker is one reported value extracted verbatim from the primary literature, vertical position within a row is random jitter, and the vertical rule is the group median. Mass-concentration values were converted to micromolar with the calculated molecular weight. Medians: designed inhibitors in clinical development 0.04 micromolar (n = 3), thiol chemotype 13.25 micromolar (n = 6), biochemical or phenotypic library screening 21.24 micromolar (n = 4), structure-based virtual screening 27.10 micromolar (n = 6). Kruskal-Wallis across the four groups H = 7.505, p = 0.0574. Values come from different laboratories using different assay conditions and are not directly comparable beyond order of magnitude.

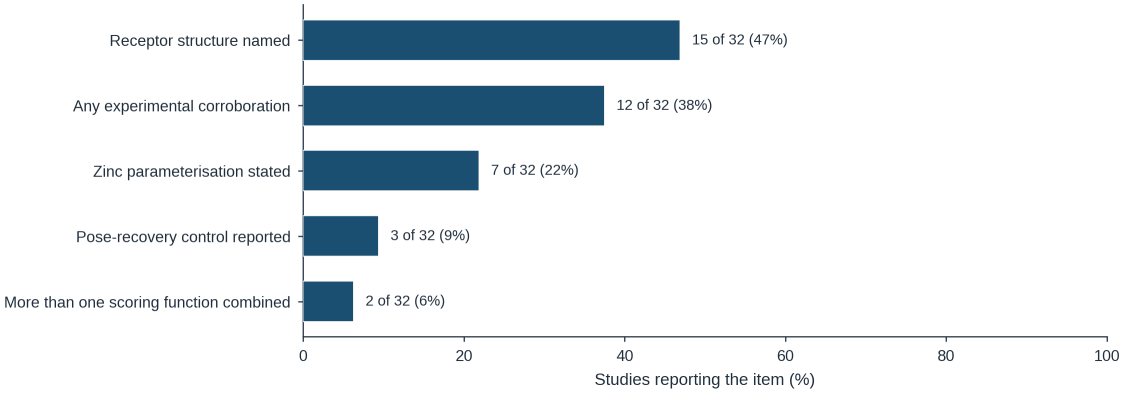

Figure 4. Methodological reporting is weakest where this target is most demanding. Percentage of the 32 eligible studies reporting each methodological item, with counts shown beside each bar. An item is counted as reported only where the accessible text states it, so these values describe the reports rather than the work behind them. Seven of the 32 full texts could not be retrieved and are included in the denominator.

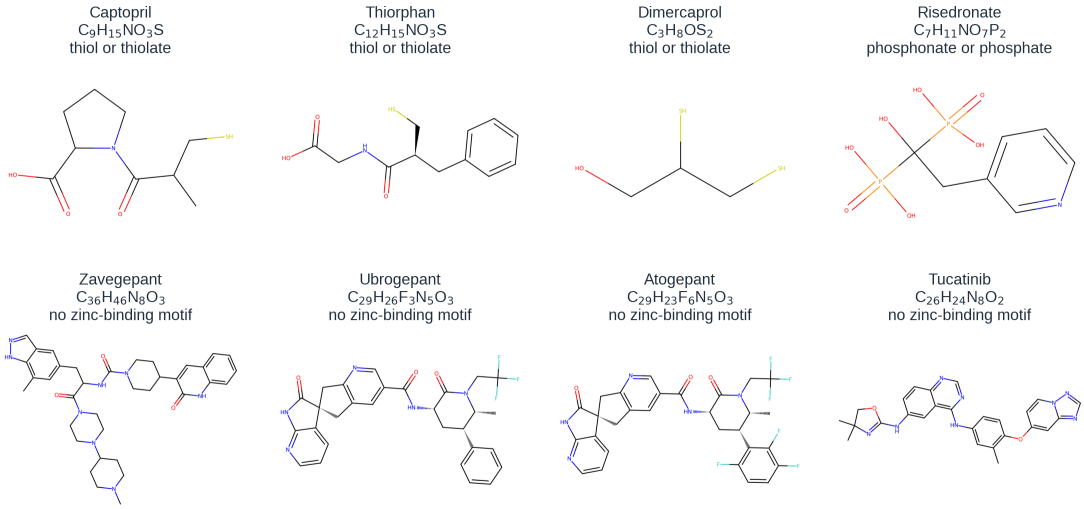

Figure 5. The structural contrast, drawn. Structures of four compounds with measured inhibition of NDM-1 (upper row) and the four approved drugs proposed against NDM-1 by docking alone (lower row), rendered in RDKit 2026.3.6 from the SMILES strings used throughout this analysis, with the molecular formula computed from the same structure. The zinc-coordinating motif detected in each upper-row compound is named beneath it; no motif of any of the 13 classes is present in any lower-row compound. Structures are drawn without stereochemistry, which no calculation reported here uses.

Declaration of competing interest

The authors declare no competing interests.

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