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Reaction-manifold diversion enables general access to oxa-β-lactam chemical space

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Oxa-β-lactams (1,2-oxazetidin-3-ones) constitute the formal oxygen analogues of β-lactams yet remain largely absent from chemical and biological studies because general synthetic access has been lacking, historically limited to specialized cycloaddition and precursor-encoded ring-contraction strategies. We report that incorporation of aminooxyacetic acid into the Ugi multicomponent reaction diverts the canonical reaction manifold and selectively furnishes oxa-β-lactams under mild, room-temperature conditions from simple carbonyl compounds and isocyanides. Automated nanoscale high-throughput experimentation enabled mapping of the accessible reaction space and identification of productive substrate classes, which translated to preparative synthesis of structurally diverse, fully characterized derivatives, including single-crystal X-ray structures. Structural analysis revealed pronounced pyramidalization and reduced coplanarity within the amide substructure, suggesting an electronically perturbed, strain-activated amide motif with potential relevance for covalent ligand design. This possibility was supported by preliminary high-throughput mass spectrometric screening, which identified covalent engagement of a mutant NPM1 W288C target by selected members of the scaffold class. *In situ* NMR kinetics support a pathway involving oxime formation, isocyanide insertion, and intramolecular *O*-acyl capture leading to four-membered ring closure, consistent with interception of the Ugi intermediate rather than formation of classical products. Together, this transformation establishes a general entry into oxa-β-lactam chemical space and suggests that these underexplored heterocycles may constitute a new class of covalent modifier scaffolds.

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Introduction

Four-membered heterocycles occupy a distinctive region of chemical space in which pronounced angle and torsional strain, combined with heteroatom substitution, give rise to unusual electronic structures, conformational distortion, and enhanced reactivity.[1–3] While β-lactams, owing to their central role in clinically important antibiotics, represent one of the most extensively studied scaffold classes in medicinal chemistry and arguably one of its greatest success stories, heteroatom-modified analogues remain comparatively underexplored.[4] In particular, oxa-β-lactams (1,2-oxazetidin-3-ones), the formal oxygen analogues of β-lactams, remain a conspicuously underrepresented scaffold, with only limited synthetic studies and essentially no broader chemical or biological exploration.[5] The scarcity of this scaffold does not arise from a lack of conceptual interest but from the absence of general synthetic access. A PubChem search (April 2026) reveals that only 166 oxa-β-lactam derivatives have been reported, with the scaffold space largely confined to compounds accessible *via* the classical Staudinger [2 + 2] cycloaddition highlighting the severe synthetic bias that has limited exploration of this scaffold class.[6] Historically, access to oxa-β-lactams has been restricted to cycloadditions and precursor-encoded ring contractions, strategies that impose strict structural constraints and have prevented systematic diversification of this scaffold (Fig. 1).[7–9] For example, [2 + 2] cycloaddition leads exclusively to bis aromatic substituted ring systems due to the availability of the ketene and the nitroso building blocks. We questioned whether this limitation could be overcome not by optimizing existing strategies but by redirecting a fundamentally different reaction manifold. Multicomponent reactions offer a particu-

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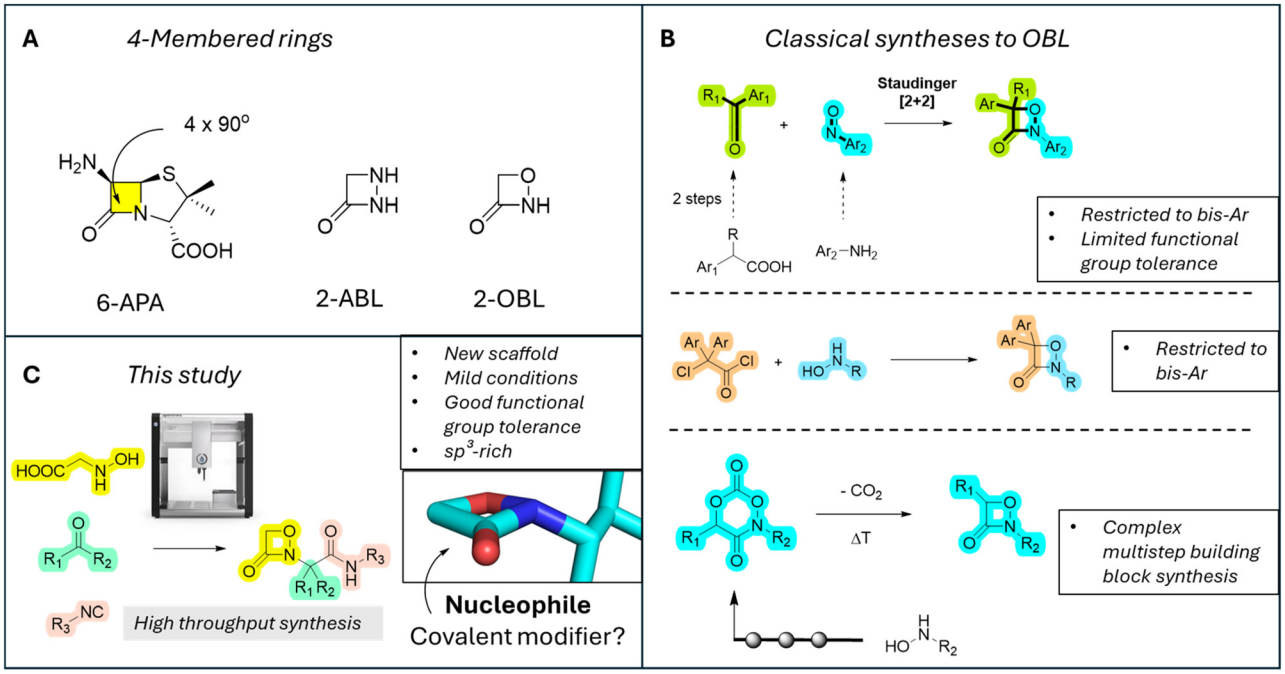


Fig. 1 Motivation and conceptual framework of this work. (A) β-Lactams represent one of the most important classes of antibiotics, with profound clinical impact, whereas heteroatom-modified analogues such as amino- (ABL) and oxa-β-lactams (OBL) remain comparatively underexplored. (B) Classical synthetic approaches for oxa-β-lactams are limited by restricted building-block diversity, a bias toward highly aromatic substitution patterns, and reliance on specialized multistep strategies. (C) The present high-throughput experimentation-enabled approach provides modular multicomponent access to a previously underexplored oxa-β-lactam scaffold under mild conditions, enabling broad structural diversification and entry into new chemical space. The resulting strain-activated, electronically perturbed *O*-amide motif exhibits enhanced nucleophilic ring-opening reactivity, suggesting potential as a covalent modifier scaffold.

larly attractive platform for such an approach because subtle changes in component functionality can redirect the fate of key intermediates and thereby alter product topology.[10,11] Introduction of an aminooxy acid reprograms the Ugi reaction manifold: the nitrilium intermediate is preferentially trapped intramolecularly by the oxygen nucleophile, leading to selective formation of a four-membered heterocycle instead of the conventional acyclic adducts. While such cyclization is chemically plausible, the successful engagement of aminooxy substrates in the Ugi reaction is not. Hydroxylamine derivatives represent challenging substrates in the Ugi reaction, due to the electron-withdrawing effect of the adjacent oxygen, which diminishes nucleophilicity and disfavors imine formation as they preferentially form oximes or nitrones rather than imines, thereby disrupting the canonical reaction pathway. Accordingly, productive examples are largely limited to *O*-protected variants and require activation strategies.[12,13] Consequently, it was not evident that replacing a β-amino acid with aminooxyacetic acid would result in a productive multicomponent reaction at all.

Here, we show that aminooxyacetic acid, carbonyl compounds, and isocyanides undergo a mild room-temperature multicomponent reaction that selectively furnishes oxa-β-lactams and provides the first general synthetic entry into this previously underdeveloped scaffold class. Automated nanoscale high-throughput experimentation enabled mapping of the accessible reaction space and identification of productive substrate classes, followed by preparative synthesis of structurally diverse examples. Single-crystal structural analysis revealed a pronounced deviation of the *O*-amide substructure from coplanarity, including nitrogen pyramidalization consistent with attenuated amide resonance and suggesting an electronically perturbed, strain-activated amide motif. This unusual structural feature points to oxa-β-lactams as a potentially distinct class of electrophilic scaffolds for covalent modifier design, a possibility supported by preliminary high-throughput mass spectrometry screening against mutant NPM1. Together, these findings provide the first general and diversity-oriented access to oxa-β-lactams while positioning this scaffold as an unexplored region of electrophilic chemical space.

Results and discussion

Idea and synthesis, singleton, and optimization

To identify productive conditions for oxa-β-lactam formation, the reaction of aminooxyacetic acid hemihydrochloride, isobutyraldehyde, and cyclohexyl isocyanide was selected as a model system. Because the aminooxy component is commercially available as its hemihydrochloride salt, base-mediated liberation of the free aminooxy species was expected to be critical

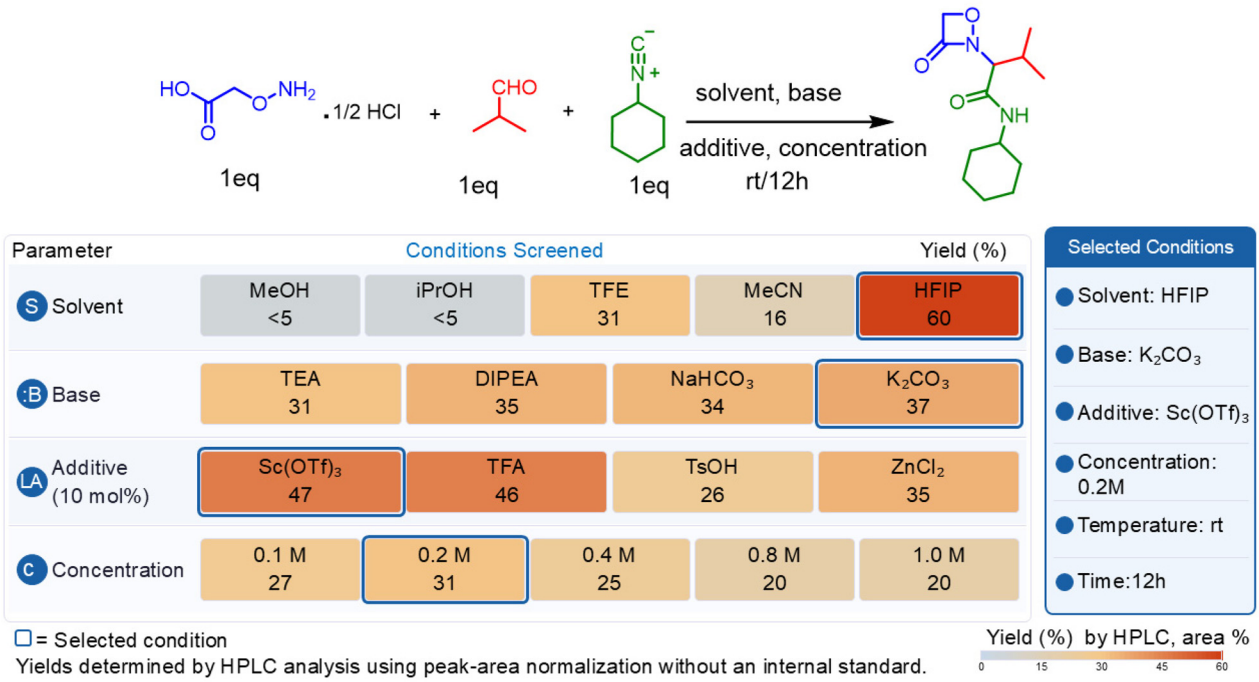


Fig. 2 Optimization matrix for multicomponent oxa-β-lactam formation. Heat-map representation summarizes the effects of solvent, base, catalyst, and concentration on product formation in the model reaction. Conditions selected for subsequent reaction-space exploration are boxed.

for productive condensation and subsequent cyclization. Systematic variation of solvent, base, additive, and concentration (Fig. 2) revealed several notable trends. Among solvents, fluorinated alcohols were strongly favored, with hexafluoroisopropanol (HFIP) markedly outperforming MeOH, iPrOH, TFE, and MeCN (SI S2). The exceptional performance of HFIP likely reflects more than simple solubility effects and may arise from its strong hydrogen-bond donor ability, low nucleophilicity, and high ionizing power, which can stabilize polarized nitrilium-type intermediates, facilitate intramolecular *O*-acyl capture, and suppress competing side pathways,[14] thereby biasing the reaction manifold toward productive oxa-β-lactam formation. Such effects are consistent with the increasingly recognized role of HFIP as a promoter of unusual reaction pathways, particularly in isocyanide-based multicomponent reactions.[15,16] Among bases, K_2CO_3 provided the highest conversion, consistent with efficient *in situ* generation of the free aminooxy species. Lewis acid additives further enhanced product formation, with $Sc(OTf)_3$ delivering optimal yields. The beneficial role of $Sc(OTf)_3$ is attributed to its oxophilic character, serving as a dual Lewis acid catalyst that accelerates the initial condensation/oxime formation and activates the intermediate nitrilium species toward intramolecular nucleophilic capture by the carboxylate moiety.

Product formation was also sensitive to concentration, with dilute conditions proving advantageous and 0.2 M affording optimal performance. Collectively, these studies identified HFIP, K_2CO_3 (1 equiv.), and $Sc(OTf)_3$ (10 mol%) at room temperature as the optimal conditions for subsequent reaction-space exploration.

HTE scope and limitation study

With optimized conditions in hand, we next sought to define the accessible reaction space and delineate the scope and limitations of the transformation through automated high-throughput experimentation in a 384-well format (Fig. 3). To this end, a chemically diverse substrate collection comprising 96 carbonyl compounds and 16 representative isocyanides was assembled to probe broad steric, electronic, and functional-group diversity. The library was intentionally enriched in sp^3-rich and medicinal-chemistry-relevant motifs to evaluate both reactivity and scaffold diversification potential.

The carbonyl collection included small and sterically demanding aliphatic ketones, cyclic ketones spanning cyclobutyl to cyclooctyl systems, spirocyclic and heterocyclic ketones, and substrates containing esters, amines, sulfones, thioethers, acetals, halides, difluoromethyl groups, and embedded stereochemical complexity. The aldehyde subset encompassed linear and branched aliphatic aldehydes, dialdehydes, bulky aldehydes, aromatic and heteroaromatic aldehydes, as well as structurally complex natural-product-derived substrates, including tylosin derivatives (SI S4). Rather than exhaustively evaluating the full 96 × 16 matrix (1536 possible combinations), a statistically representative randomized subset of 384 unique reactions was selected to maximize chemical-space coverage while maintaining practical throughput. Experimentally, the library was assembled using an OT-2 dispenser (SI S3, SI video).

Reaction outcomes of all 384 wells were analyzed by LC-MS and UV detection, and product formation was assigned

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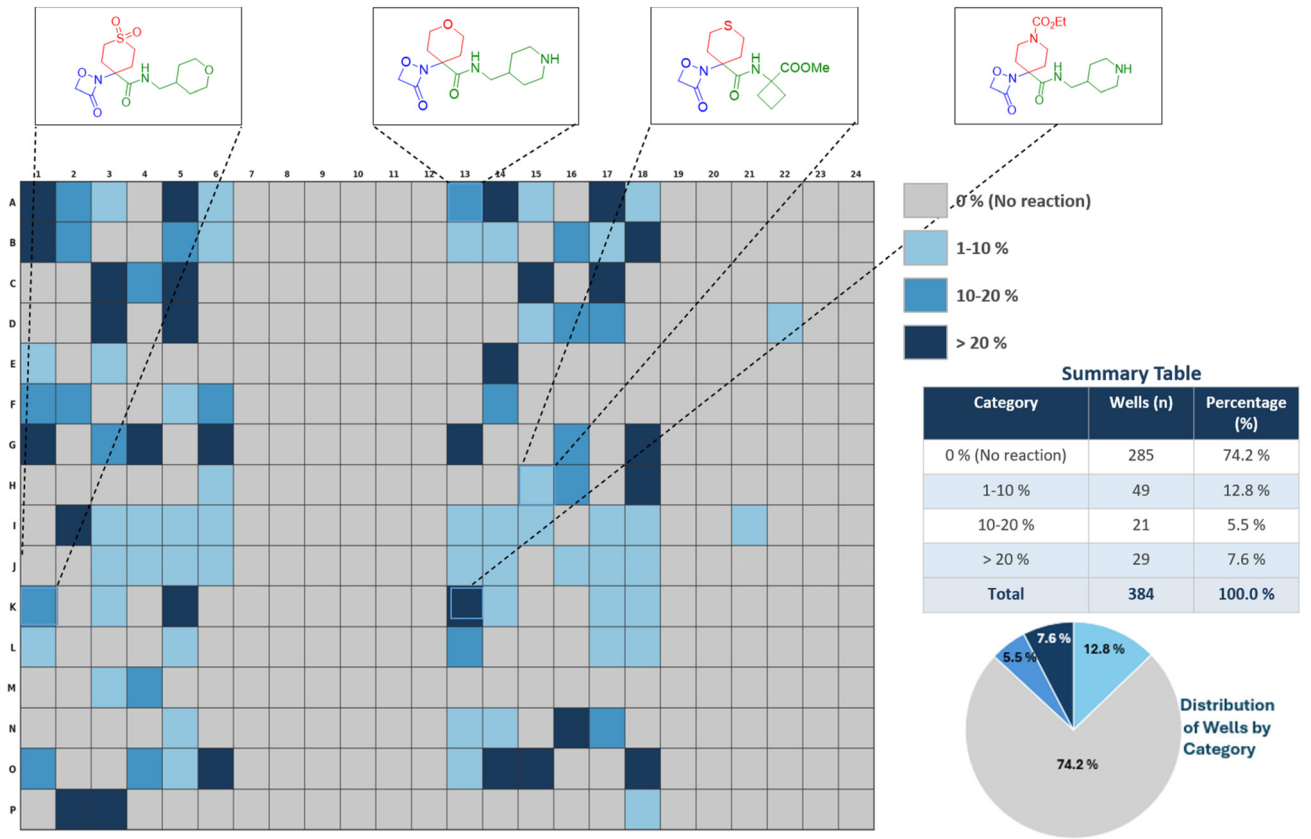


Fig. 3 Heat map of 384 randomized substrate combinations screened under optimized conditions. Product formation was quantified by LC-MS/UV analysis and categorized according to relative UV product area as no reaction (0%), low conversion (1–10%), moderate conversion (10–20%), and high conversion (>20%). Distinct privileged islands of productive chemistry emerge rather than uniform reactivity across substrate space, with productive reactions clustering predominantly within saturated, aliphatic substrate regions. Distribution of wells by product-formation category and summary statistics of reaction outcomes across the 384-well screen show that 25.8% of screened reactions gave detectable oxa-β-lactam formation, including 7.6% high-confidence productive reactions (>20% relative UV area).

through correlation of mass and chromatographic signatures (SI S16). The resulting reaction-space map (Fig. 3) revealed pronounced structure–reactivity relationships, with productive transformations concentrated in discrete regions of chemical space rather than uniformly distributed across the dataset. In particular, saturated sp^3-rich carbonyl partners and aliphatic isocyanides consistently afforded the highest-confidence product formation, whereas aromatic and conjugated substrates proved largely unproductive (SI S5).

Chemical space analysis

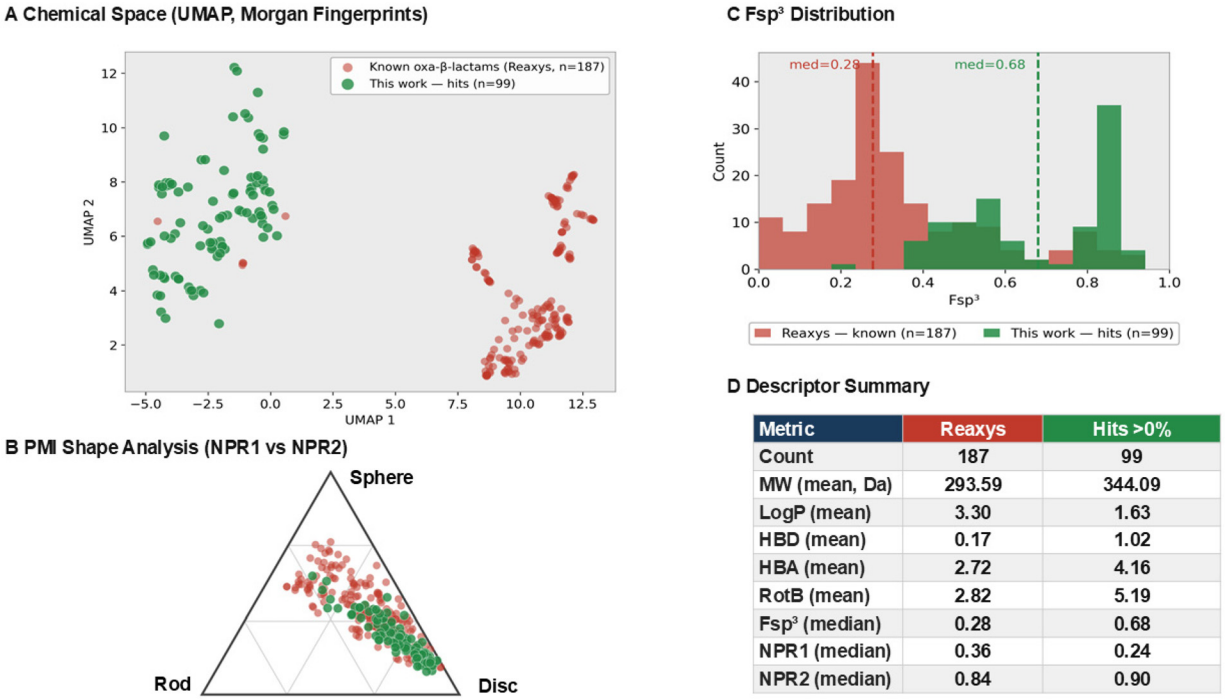
To assess the structural novelty of the HTE hits, a comparative chemical-space analysis was performed against 187 known oxa-β-lactams retrieved from Reaxys (Table S4). UMAP projection of Morgan fingerprints revealed that the 99 HTE hits occupy a region of chemical space largely non-overlapping with the Reaxys reference set (Fig. 4A), which clusters predominantly around aryl- and fluoroalkyl-substituted scaffolds. PMI analysis further confirmed that the HTE hits favor elongated, non-planar 3D shapes underrepresented in the prior art (Fig. 4B).

Descriptor analysis reinforced this differentiation: the HTE hits exhibit a median Fsp^3 of 0.68 *versus* 0.28 for the Reaxys set (Fig. 4C), alongside markedly lower lipophilicity (mean log *P* 1.63 *vs.* 3.30) and higher molecular weight (mean MW 344.1 *vs.* 293.6 Da) (Fig. 4D). These data collectively confirm that this multicomponent reaction accesses a region of oxa-β-lactam chemical space that is structurally complementary to all previously reported compounds (SI S6).

Aromatic *vs.* aliphatic carbonyl reactivity

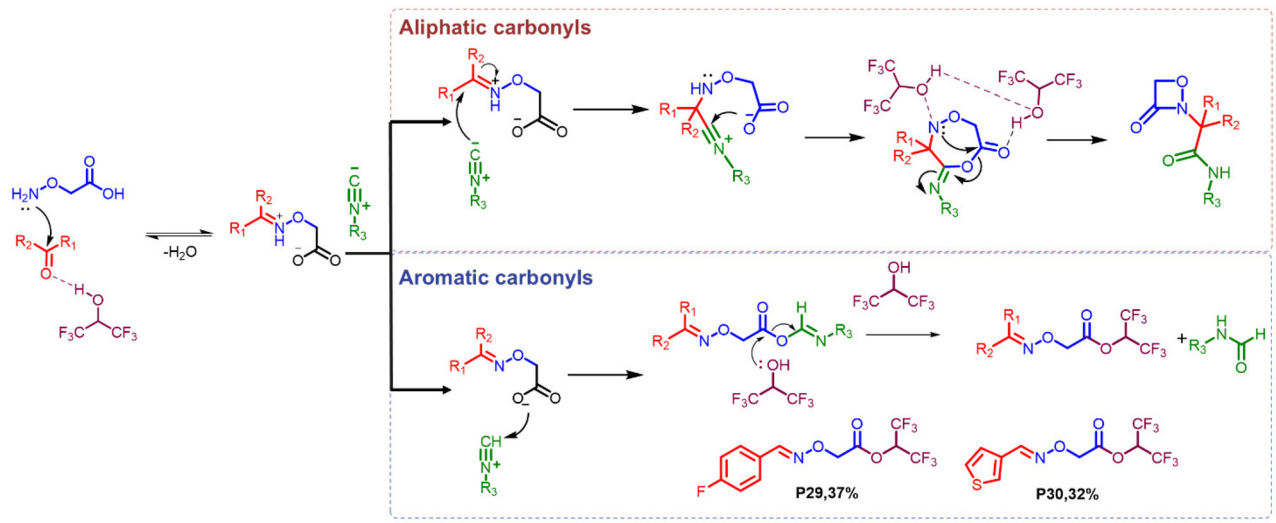
A particularly striking outcome of the HTE study was the sharp divergence between aliphatic and aromatic carbonyl substrates. Whereas aliphatic aldehydes and ketones frequently furnished the expected oxa-β-lactams, aromatic and heteroaromatic carbonyl compounds were largely unproductive. Instead, these substrates consistently generated an alternative product displaying the mass corresponding to an $x + y$ condensation product, which was isolated in representative cases and characterized by NMR as a distinct oxime-derived side-product manifold.

A proposed mechanism for the divergent reactivity of aromatic carbonyl substrates is depicted in Scheme 1. Initial condensation of aminooxyacetic acid with the carbonyl compound, facilitated by $Sc(OTf)_3$ acting as an oxophilic Lewis acid, generates an oxime-derived carboxylate intermediate. For



Metric	Reaxys	Hits >0%
Count	187	99
MW (mean, Da)	293.59	344.09
LogP (mean)	3.30	1.63
HBD (mean)	0.17	1.02
HBA (mean)	2.72	4.16
RotB (mean)	2.82	5.19
Fsp³ (median)	0.28	0.68
NPR1 (median)	0.36	0.24
NPR2 (median)	0.84	0.90

Fig. 4 Comparative chemical space analysis of 99 HTE oxa-β-lactam hits *versus* 187 known oxa-β-lactam structures retrieved from Reaxys. (A) UMAP projection of Morgan fingerprints (Jaccard metric) showing the positions of Reaxys prior-art compounds (red) and productive HTE hits (green). (B) PMI ternary plot (NPR1 *vs.* NPR2) illustrating 3D shape space coverage. (C) Fsp^3 distribution comparing Reaxys compounds (red, median 0.28) and productive hits (green, median 0.68). (D) Descriptor summary table comparing key physicochemical properties.



Scheme 1 Proposed mechanistic divergence between productive oxa-β-lactam formation from aliphatic carbonyl substrates and competing off-pathway reactivity observed for aromatic aldehydes.

aliphatic substrates, subsequent addition of the isocyanide yields an activated nitrilium-type intermediate analogue that undergoes efficient intramolecular *O*-acyl capture, leading to productive oxa-β-lactam formation. In contrast, aromatic substrates appear to favor a competing pathway in which the oxime-derived intermediate exists as stabilized, potentially *E*/*Z*-persistent species that are less prone to productive cyclization and instead undergo alternative transformation,[17,18] including interception by the nucleophilic solvent (HFIP) to yield the observed hexafluoroisopropyl esters with elimination of a formamide byproduct (R_3NHCHO). Conjugative stabilization associated with aryl substitution may further favor the

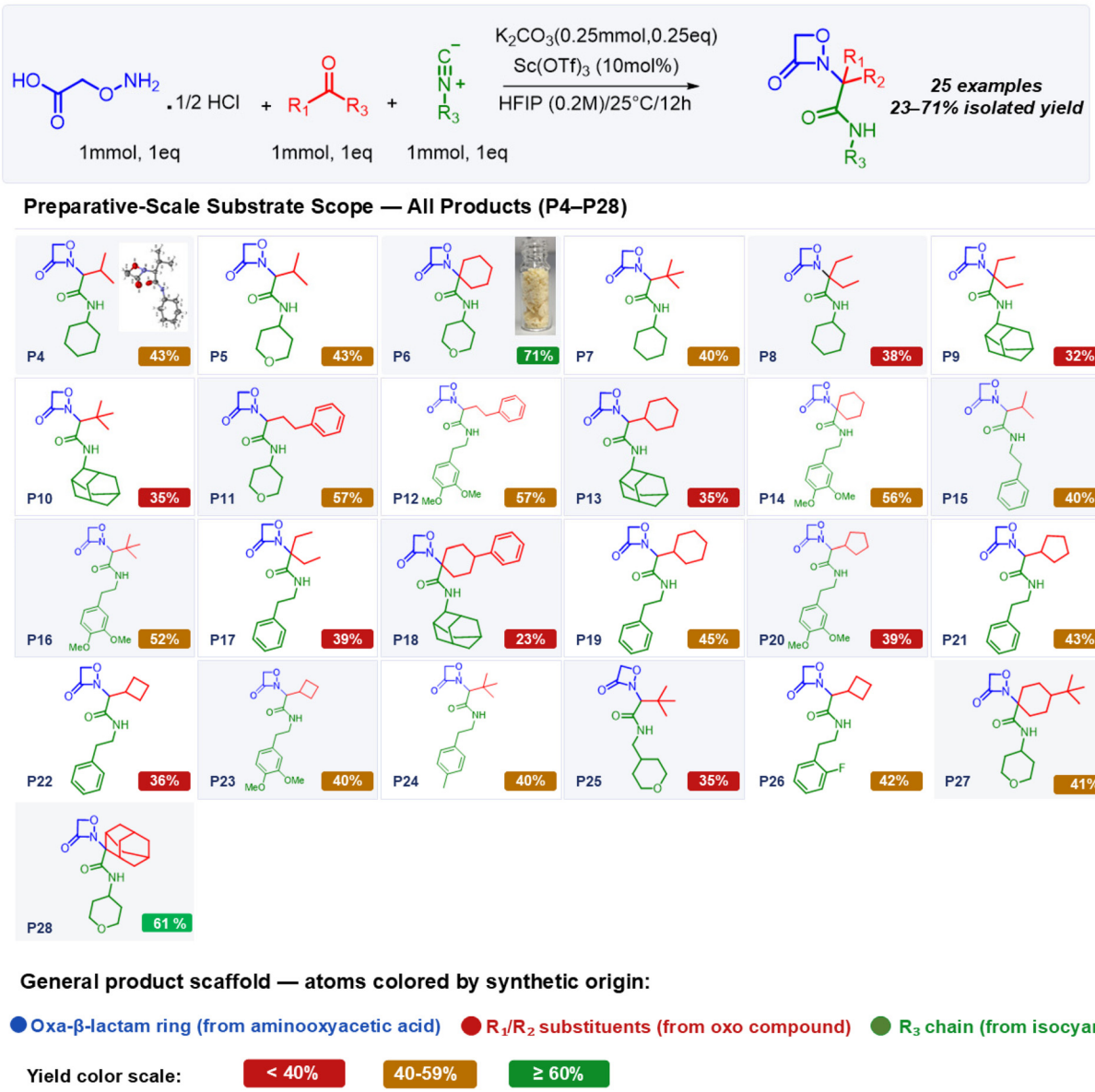
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persistence of stabilized precursors over progression to the higher-energy oxa-β-lactam product. Isolation and NMR characterization of representative aromatic-substrate side products support operation of this competing manifold and suggest that aromatic substrate failure reflects mechanistic divergence rather than simple lack of reactivity. Notably, HFIP-mediated trapping of the diverted intermediate may itself represent an unusual secondary reaction manifold uncovered by this study. Together, this mechanistic bifurcation is fully consistent with the sharp aliphatic–aromatic divergence observed in the HTE reaction-space map (Fig. 3).

The reaction pathway was further investigated by *in situ* benchtop flow NMR spectroscopy. Continuous monitoring of aldehyde consumption and product formation provided direct kinetic evidence for sequential oxime formation followed by isocyanide-mediated cyclization, supporting the mechanistic proposal (SI S7).

Preparative-scale substrate scope

Based on the structure–reactivity insights obtained from the high-throughput screening campaign, representative high-confidence substrate combinations were selected for preparative-scale synthesis to validate the robustness and scalability of the transformation (SI S12). As shown in Scheme 2, a diverse set of aliphatic aldehydes and ketones was successfully converted into the corresponding oxa-β-lactam products under the opti-



Scheme 2 Preparative-scale substrate scope of the multicomponent oxa-β-lactam synthesis. Representative productive combinations identified in the HTE campaign were translated to a preparative scale under optimized conditions (HFIP (0.2 M), K_2CO_3 (0.25 eq.), $Sc(OTf)_3$ (10 mol%), and rt (25 °C)), providing 25 structurally diverse oxa-β-lactam derivatives in moderate to good isolated yields.

mized reaction conditions, affording the desired compounds in moderate to good isolated yields. The reaction tolerated a variety of linear, branched, and cyclic carbonyl substrates, demonstrating broad compatibility within the productive aliphatic substrate space identified during the screening studies. Variation of the isocyanide component was also well accommodated, enabling access to structurally diverse oxa-β-lactam derivatives. To further assess the synthetic practicality of the methodology, compound **P6** was prepared on a gram scale, furnishing the desired oxa-β-lactam in comparable yield and purity to those obtained on the smaller scale (SI S13). These results confirm that the high-throughput screening outcomes translate reliably to preparative-scale synthesis and establish the developed multicomponent strategy as a practical platform for the rapid generation of oxa-β-lactam libraries.

Structural and electronic features of oxa-β-lactams

Single-crystal X-ray analysis of *N*-cyclohexyl-3-methyl-2-(3-oxo-1,2-oxazetidin-2-yl) butanamide (**P4**)[19] (SI S15) revealed an unexpected structural feature: in contrast to classical monocyclic β-lactams, whose amide nitrogens are typically close to planar as a consequence of n → π* amide conjugation, the nitrogen atom in the oxa-β-lactam ring displays pronounced pyramidalization and deviation from coplanarity with the carbonyl group (Fig. 5A). Comparison with the only other structurally characterized oxa-β-lactam reported to date revealed that this is not an isolated observation but may represent an intrinsic feature of the scaffold (Fig. 5B).[20]

The present oxa-β-lactam exhibits pronounced pyramidalization and an elongated C–N amide bond relative to planar *O*-amides, placing it among the most strongly distorted members of this structural class. These data support substantial attenuation of amide resonance and indicate that oxa-β-lactams constitute an electronically perturbed, strain-activated class of *O*-amides rather than simple oxygen analogues of classical β-lactams. Such reduced resonance stabilization suggested altered electrophilic reactivity. To probe this directly, ring opening of the oxa-β-lactam and its matched β-lactam analogue was monitored by time-resolved benchtop ^{1}H NMR spectroscopy in the presence of a strongly nucleophilic cysteine derivative (SI S8). NMR spectra recorded over 24 h enabled quantitative monitoring of substrate consumption, while integration of characteristic resonances provided kinetic profiles for both scaffolds. Remarkably, the oxa-β-lactam

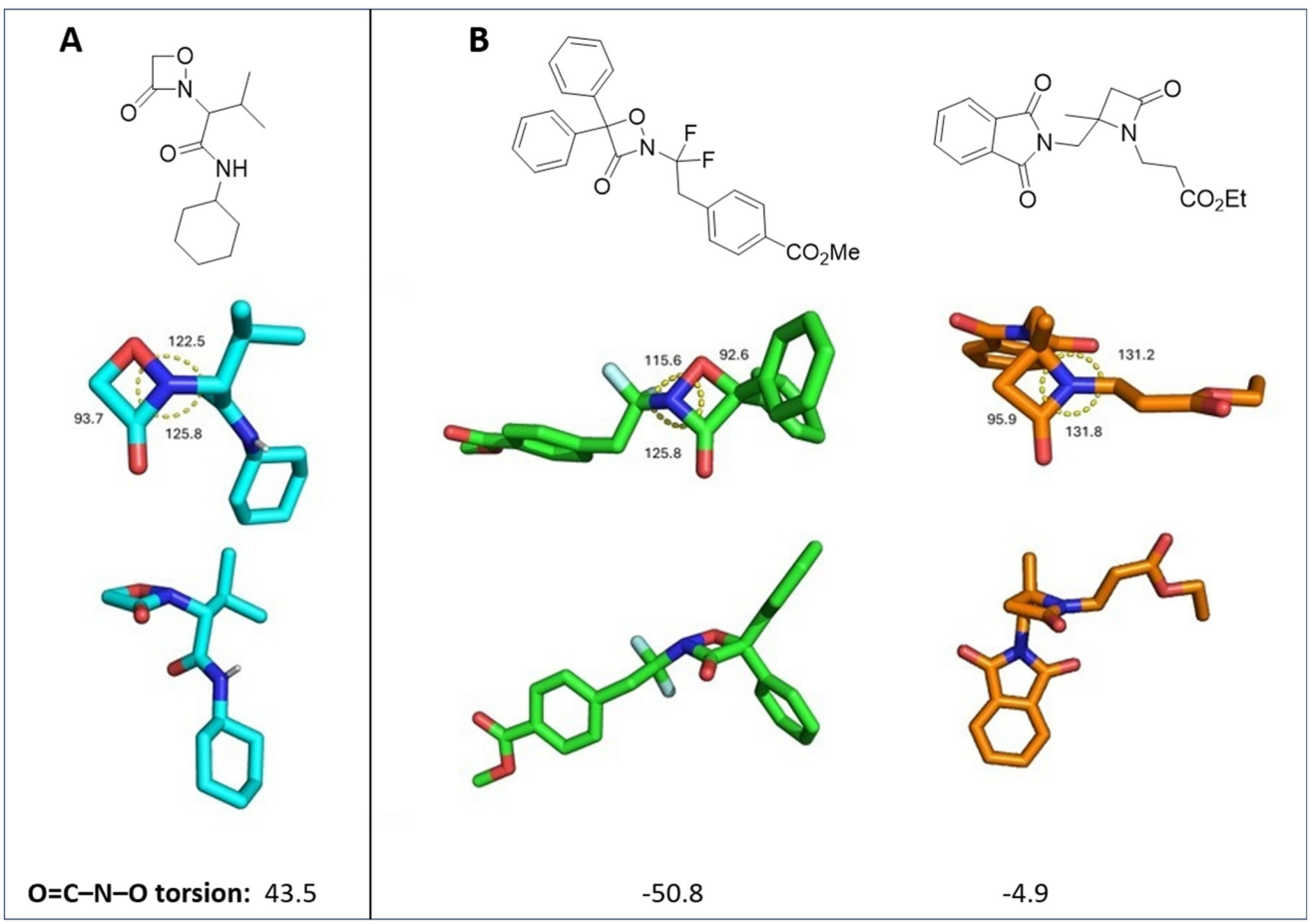


Fig. 5 Structural and electronic analysis of oxa-β-lactam distortion. (A) X-ray structure of **P4** showing nitrogen pyramidalization. (B) X-ray structures of the only other crystallized oxa-β-lactam (CCDC 1054500)[20] and a typical monocyclic β-lactam (CCDC 1508631).[21]

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underwent nucleophilic ring opening faster than the corresponding β-lactam, consistent with increased carbonyl electrophilicity arising from diminished amide conjugation. Together, the structural and reactivity data identify oxa-β-lactams as a previously unrecognized class of activated amide electrophiles and provide a conceptual basis for their exploration as covalent modifier scaffolds.

Preliminary evaluation as covalent modifier scaffolds

The enhanced nucleophilic ring-opening reactivity, combined with the apparent solution stability of the oxa-β-lactam scaffold, suggested that these compounds may constitute a previously unexplored class of covalent modifiers. To probe this possibility, all members of the oxa-β-lactam library were evaluated in an ongoing covalent ligand discovery campaign against the W288C NPM1 C-terminal peptide. The W288C mutation introduces a reactive cysteine residue within the nuclear localization sequence of nucleophosmin, providing a tractable site for covalent ligand targeting in oncogenic acute myeloid leukemia.[22,23] The covalent screening was performed using high-throughput acoustic droplet ejection mass spectrometry (ECHO-MS) (Fig. 6). ECHO-MS technology combines acoustic droplet ejection (ADE) with mass spectrometric analysis, enabling rapid, label-free, and miniaturized screening. In this technique, nanoliter-sized droplets containing reaction mixtures are transferred directly into the mass spectrometer (SI S9).[24] This approach allows analysis times of only a few seconds per sample which is much more high-throughput in comparison with conventional LC-MS workflows. Additional advantages like low sample consumption, reduced reagent costs, and minimal carryover due to contactless liquid handling make ECHO-MS a well-suited approach for high-throughput covalent screening.[25] Notably, several members of the scaffold class showed detectable covalent modification of the

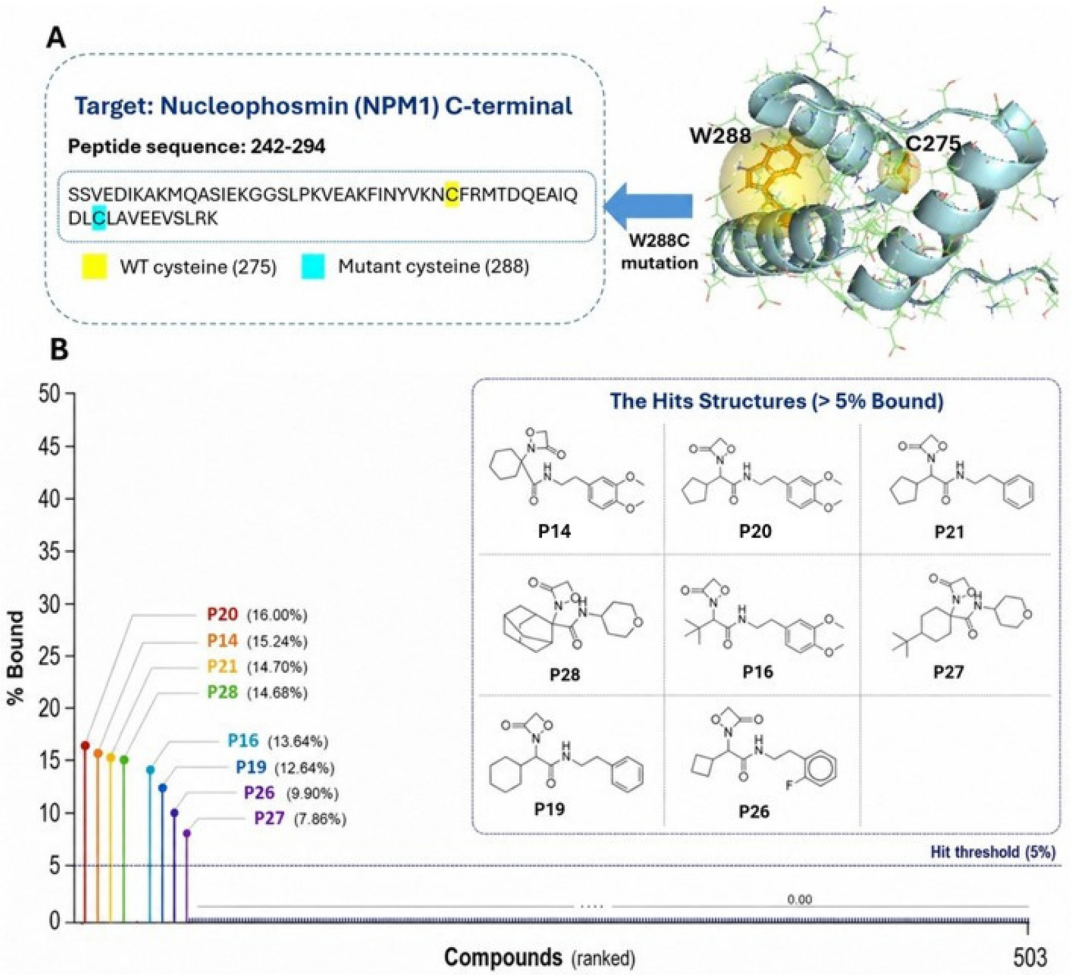


Fig. 6 Preliminary evaluation of oxa-β-lactams as covalent modifier scaffolds. (A) Solution NMR structure of the C-terminal three-helix bundle of nucleophosmin containing the nucleolar localization sequence (NoLS) (PDB ID: 2LLH).[26] The oncogenic W288C mutation introduces a solvent-accessible cysteine residue within the hydrophobic tryptophan-rich region responsible for nucleolar localization, providing a tractable site for covalent ligand targeting in acute myeloid leukemia. Structure adapted from Gallo *et al.*[26] (B) High-throughput ECHO-MS screening of the oxa-β-lactam library against the NPM1 W288C mutant. Eight oxa-β-lactam derivatives showed detectable covalent engagement, with up to 16% target labelling.

peptide target (8 hits out of 503 screened; up to 16% labelling) (SI S10). To gain insight into the site of modification, representative peptide–ligand adducts were subjected to LC-MS/MS fragmentation analysis (SI S11). Comparison of c- and z-type fragment ion series between modified and unmodified peptides localized the modification to Cys34 of the peptide sequence. These findings are consistent with preferential cysteine-directed covalent engagement and provide preliminary evidence that oxa-β-lactams can function as tuneable cysteine-reactive electrophiles. Although exploratory in scope, these results extend the significance of the scaffold beyond synthetic novelty and support its potential as an emerging covalent modifier chemotype.

Conclusion

In summary, we have discovered a diverted Ugi multicomponent reaction that provides the first general and diversity-oriented synthetic entry into the underexplored oxa-β-lactam scaffold class. High-throughput reaction-space mapping revealed distinct privileged regions of productive chemistry and uncovered a sharp mechanistic bifurcation between aliphatic and aromatic carbonyl substrates. *In situ* NMR studies support interception of the canonical Ugi manifold through oxime formation, isocyanide insertion, and intramolecular *O*-acyl capture, providing mechanistic insight into the formation of this unusual four-membered heterocycle. Beyond synthetic access, structural analysis revealed pronounced nitrogen pyramidalization and attenuated amide resonance, placing oxa-β-lactams among a highly distorted class of strain-activated amides.[27] The enhanced nucleophilic ring-opening reactivity observed relative to matched β-lactams, together with preliminary covalent screening and MS/MS localization studies against NPM1 W288C, suggests that these compounds may represent an unexplored class of covalent modifier scaffolds. More broadly, this work demonstrates how reaction-manifold diversion in multicomponent chemistry can open previously inaccessible regions of chemical space while uncovering functional properties not apparent from structure alone.

Author contributions

Alexander Dömling: conceptualization, methodology, data curation, supervision, formal analysis, validation, investigation, funding acquisition, visualization, project administration, resources, writing – review and editing, and writing – original draft. Kaoud Salama: methodology, data curation, investigation, validation, formal analysis, visualization, and writing – review and editing. Zeinab Saedi: investigation, validation, and writing – review and editing. Martina Kintlova: investigation and validation. Tomas Ozdian: investigation and validation. Fiorella Meneghetti: investigation and validation. Matteo Mori: investigation and validation. Marian Hajduch: supervision. Petr Dzubak: supervision and validation.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting the findings of this study are available within the article, the supplementary information (SI), and the Zenodo repository at **https://doi.org/10.5281/zenodo.20737590**. The deposited dataset includes the raw and processed high-throughput experimentation (HTE) data, ECHO-MS and LC-MS data, mechanistic NMR spectra and FIDs, HRMS data, and other primary experimental data supporting the conclusions of this work.

Supplementary information is available. See DOI: **https://doi.org/10.1039/d6qo01185c**.

CCDC 2539381 (**P4**) contains the supplementary crystallographic data for this paper.[19]

Acknowledgements

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