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1-Oxa-2,6-Diazaspiro[3.3]heptane as a New Potential Piperazine Bioisostere – Flow-Assisted Preparation and Derivatisation by Strain-Release of Azabicyclo[1.1.0]butanes

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Abstract: The development of novel strained spiro heterocycles (SSHs) as bioisosteres for aromatic or non-strained aliphatic rings is highly sought after for improving drug design. Their high molecular rigidity and predictable vectorization can enhance drug-likeness, target selectivity and clinical success. Towards this goal, 1-oxa-2,6-diazaspiro[3.3]heptane (ODASE) is reported as a novel potential SSH-bioisostere. We demonstrate through theoretical studies the potential of this strained spiro heterocycle to act as a bioisostere for piperazine. We have developed its synthesis from the highly strained azabicyclo[1.1.0]butyl intermediate through a robust and mild flow technology-assisted two-step protocol. Its tolerance and stability towards medicinally relevant *N*-functionalisation protocols are studied, as well as its mild reduction to the C3-aminoalkylazetidinol motif found in the anti-cancer drug cobimetinib.

Keywords: Azabicyclo[1.1.0]butane; Flow chemistry; Bioisostere; Strained spiro heterocycle; Azetidine

Introduction

Despite improvements in technology, developments in synthetic methodology, advancements in computer-aided design and high-throughput screening, the number of new drugs approved per billion US dollars spent on research and development has *halved* approximately every nine years.[1–3] This counterintuitive trend has, at least in part, been attributed to compound libraries tending to be very limited in skeletal and stereochemical diversity due to favoring achiral, aromatic compounds. In fact, a representative screening library contains only 10^3 chemotypes, although up to 10^{62} chemotypes would comply with *Lipinski's Rule of Five*.[1,4,5] A shift towards higher molecular complexity, and hence a higher fraction of sp^3-hybridized carbons, has been shown to correlate with reduced promiscuity, lowered toxicity and reduced candidate failure.[6–9] It is thus unsurprising that fully saturated *N*-heterocycles containing exclusively sp^3-hybridised carbons (e.g., piperidine, pyrrolidine, or piperazine) are one of the most popular building blocks in modern pharmaceuticals, being prevalent in 88% of FDA-approved pharmaceuticals between 2015–2020.[10] Recently, the discovery of bioisosteres for these classical non-strained heterocycles has gained significant traction for the occurrence of new binding events in first-in-class small-molecule drug development. For this

purpose, strained spiro heterocycles (SSHs) have received particular attention, given their improved metabolic stability, decreased lipophilicity and increased solubility, imparted by their high 3D-character and molecular rigidity.[11] Their limited conformational freedom offers predictable vectorization and hence a more selective target interaction.[12,13] Seminal contributions by Carreira,[14–21] followed more recently by Mikhailiuk,[22–24] Grygorenko,[25,26] Morandi[27] and others[28–31] showcased the importance of SSHs such as 2,6-diazaspiro[3.3]heptane (DASE), 1-oxa-6-azaspiro[3.3]heptane (1-OASE), 2-oxa-6-azaspiro[3.3]heptane (2-OASE), 2-azaspiro[3.3]heptane (2-ASE) and 1-azaspiro[3.3]heptane (1-ASE), as potential bioisosteres of piperazines, morpholines and piperidines. The imminent positive impact of the available synthetic strategies for accessing such strained spirocyclic heterocycles as bioisosteres is witnessed by the development of potential drugs such as AZD1979 bearing the 2-ASE motif by Astra Zeneca (Figure 1).[32,33] Notably, an advancement in pharmacokinetics was also demonstrated in the substitution of the piperazine motif in ciprofloxacin with DASE (Figure 1).[15] Evidently, adding further such easily accessible potential bioisosteres to the medicinal chemists' toolbox could positively impact drug development.[34,35] In line with this theme, we hypothesized that the hitherto underexplored strained spiro heterocycle 1-oxa-2,6-diazaspiro[3.3]heptane (ODASE) might serve as a bioisostere for saturated non-strained *N*-heterocycles. Our interest in this scaffold for potential integration into drug discovery programs was sparked by the presence of an additional heteroatom, which introduces possibilities for unforeseen biological properties, stemming from its hydrogen bond acceptor capability.

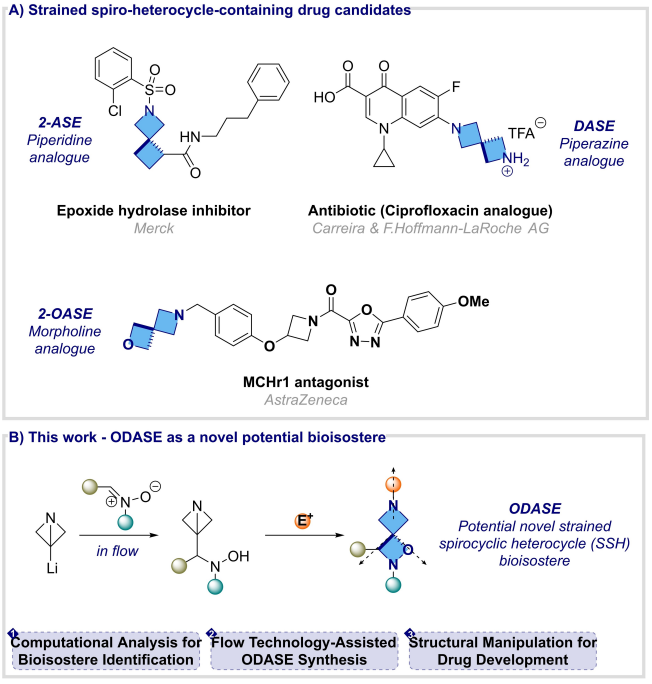


Figure 1. (A) Drug candidates containing strained spiro heterocycles as property-improving bioisosteres. (B) This work – ODASE as a novel bioisostere.

Results and Discussion

We initially set out to test our hypothesis if the proposed strained spiro heterocycle could function as a potential bioisostere for saturated *N*-heterocycles, commonly found in MedChem libraries and drug candidates. The molecular properties of ODASE were therefore compared to 45 chemical cores of spiro, fused, and monocyclic diamine derivatives (i.e. piperazine and oxadiazinane, see Section 6.2 Representative cycle types of Supporting Information). The 3D structures were generated using the RDKit tool and further optimized by employing *ab-initio* DFT calculations.[36,37] Next, a pool of 17 easily explainable molecular descriptors was computed using RDKit, including key physicochemical properties, drug-likeness, and shape-related indexes. In addition, two local descriptors were also considered to model the nitrogen atoms in terms of reciprocal distances (i.e., N–N distance) and spatial orientations (i.e., N–N planar angles) (Figure 2, A).

To better assess the most important properties of this pool of bioisosteric cores, we reduced the hyperdimensional space of the 19 descriptors using principal component analysis (PCA). The new coordinates of this condensed space were subjected to a cluster analysis by employing a k-means algorithm. The ideal number of clusters was determined to be equal to 6 through careful metric evaluation (see Supporting Information). Cluster analysis reveals that piperazine, oxadiazinane, DASE and ODASE belong to the same reference cluster, along with 2 other spiro cores and 2 fused cores (Figure 2, B). To justify this result, we further examined the differences in certain meaningful descriptors. For example, the dipole moment calculated by quantum mechanical optimization is similar for most of the cores. More importantly, the 2D and 3D drug-likeness scores (i.e., QED and PBF) show only minimal variation in the reference cluster (Figure 2, C). Taken together, these preliminary results therefore suggest that ODASE is a viable option for bioisosteric replacement of piperazine in modern drug discovery programs.

Based on this information, we turned our attention to the synthesis and synthetic manipulation of this unusual motif. An emerging strategy to access such 3,3-bis-substituted azetidines is the use of azabicyclo[1.1.0]butane (ABB) as a precursor,[38] and

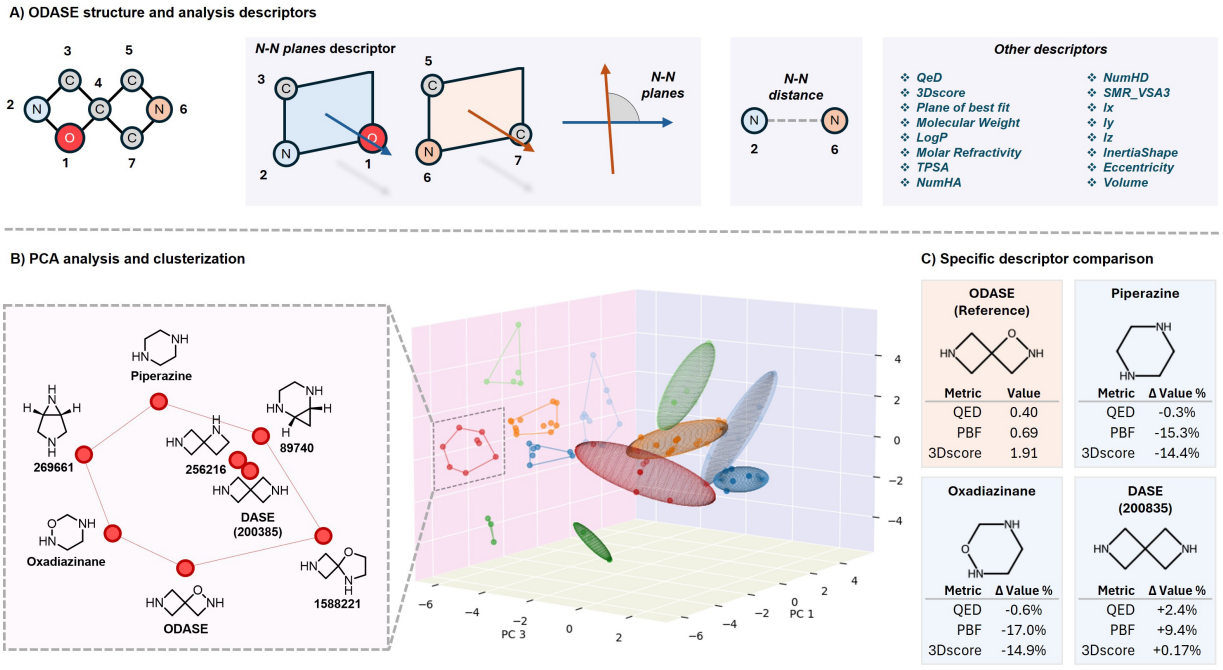
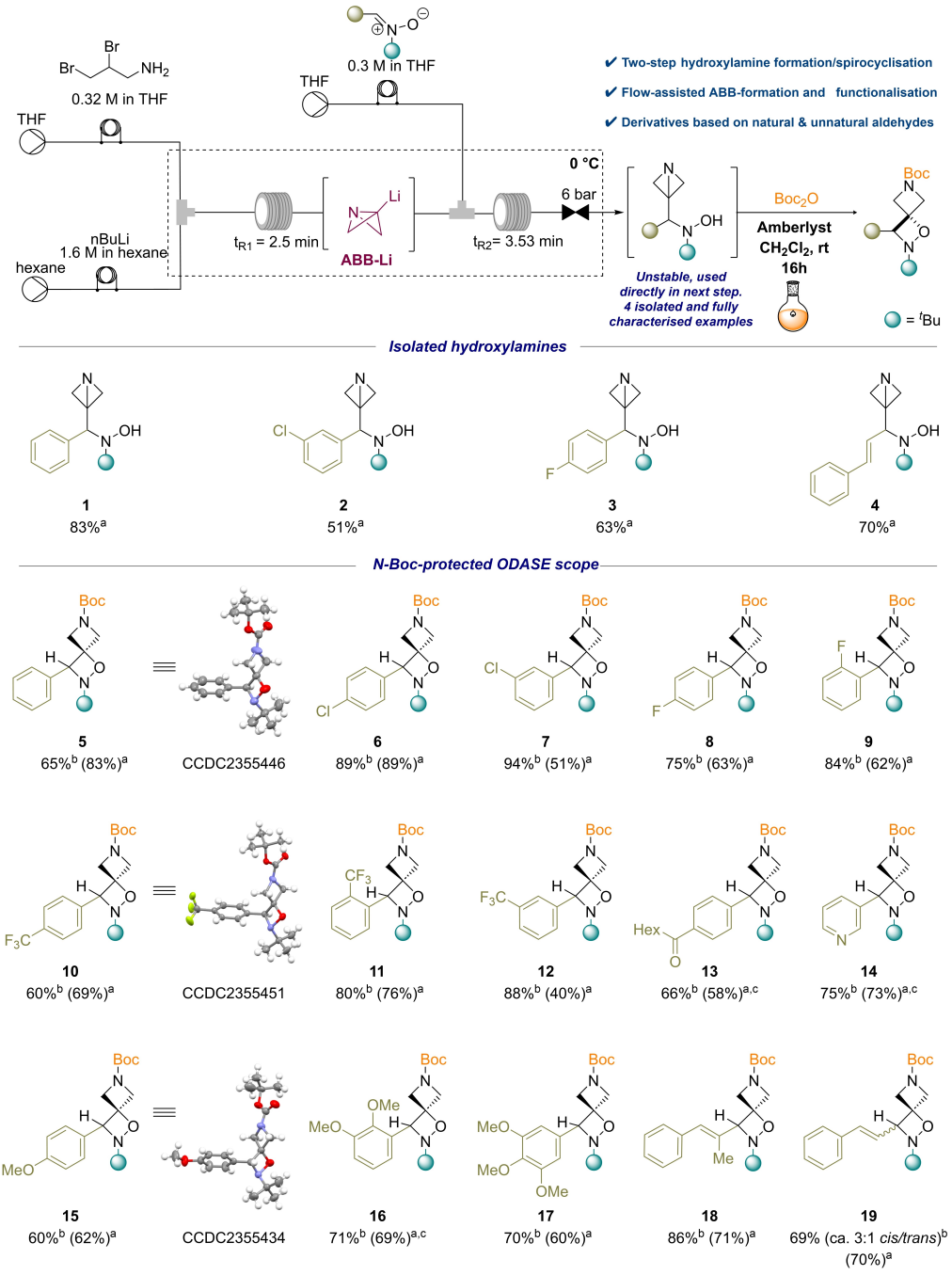


Figure 2. In silico bioisostere evaluation (A) Atomic positions optimized by DFT (ωB97X–D3BJ/6–31 + + G(d,p)) and local descriptors accounting for planar angles and distances of two shared nitrogen atoms, PBF – Plane of Best Fit, QED – Quantitative Estimate of Drug-Likeness, 3D Score – Sum of the Normalized Principle Moments of Inertia (Ix/Iz + Iy/Iz) (for the comprehensive description of local descriptors see Supporting Information file); (B) 3D space of Principal Component Analysis (PCA) and clustering. (C) The calculated QED, PBF and 3Dscore (Value) of ODASE are compared with those of piperazine, oxadizinane and DASE, reported as differences in percentage (Δ Value %).

several protocols have recently been reported by the Aggarwal group.[39–43] To achieve 1,3 bis-functionalization, *in situ* generated ABB is readily lithiated at the C3-position and reacted with an electrophile to achieve the first functionalization. For the second functionalization, the ABB nitrogen atom is electrophilically activated to favor the nucleophilic addition at the C3-position driven by the cleavage of the highly strained bridge-head bond, thus providing not only 3,3-disubstitution, but also versatility on the nitrogen-functionalisation. Inspired by this, we thus envisioned a flow-assisted sequence consisting of ABB-formation, ABB-lithiation, addition to a nitrone, and electrophile-induced strain-release-assisted spirocyclisation (Scheme 1). Given that the electrophile already contains an oxygen atom which is predisposed for nucleophilic addition, we envisaged that the desired spirocyclic ODASE motif could be readily formed. Given our experience in the use of flow technology, and its well-studied advantages for the generation and taming of highly reactive and unstable intermediates, we wanted to leverage this enabling technology for the synthesis of ODASE.[44,45] Based on our results on the flow-assisted generation of **ABB-Li** and reaction with various electrophiles including ketones, aldehydes and one example of a nitrone,[46] we initiated further investigation into the reaction of **ABB-Li** with various nitrones and their derivatization with the flow set-up reported in Scheme 1. Specifically, 2,3-dibromopropylamine and *n*-butyllithium were mixed at 0 °C under continuous flow conditions to generate **ABB-Li** with a residence time of 2.5 min. Quenching of this unstable intermediate with phenyl-substituted nitrone in a second T-shape mixer, followed by a 3.5 min residence time afforded the desired hydroxylamine **1** in 83% yield. Notably, such protocol avoids the use of cryogenic conditions and significantly shortens the required reaction duration compared to hitherto reported batch procedures. Encouraged by this, this protocol was subsequently applied to a range of nitrones providing a range of different hydroxylamines in moderate to excellent yields. The specific choice of nitrogen protecting group on the nitrone was dictated by the relative ease of synthesis, as well as its stability towards organolithium compounds. Expectedly, aryl nitrones bearing electron-withdrawing substituents on the aromatic ring underwent the desired addition reaction more effectively than those bearing electron-donating substituents. Nitrones that showed truncated reactivity under flow conditions were converted to the desired hydroxylamines in improved yield under batch conditions by allowing extended reaction durations (see Supporting Information). Notably also vinyl nitrones successfully underwent the desired transformation



Scheme 1. Flow-assisted hydroxylamine formation/Boc_2O-induced spirocyclisation. (a) Quantitative ^1H NMR yield of hydroxylamine. (b) Isolated yield of N-Boc protected spirocycle based on hydroxylamine. (c) Yield obtained of hydroxylamine synthesised in batch due to lower productivity in flow. See Supporting Information.

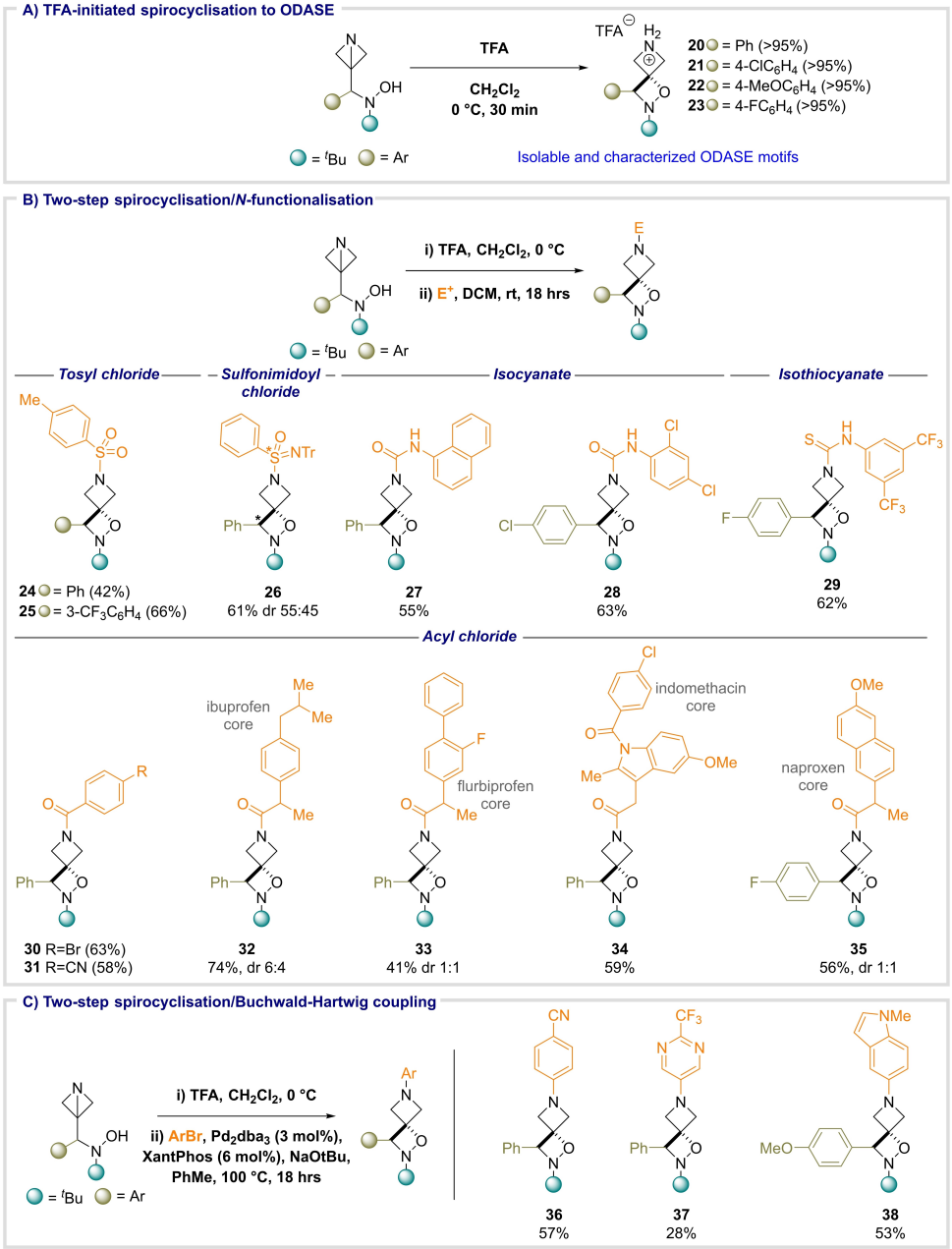
to afford the corresponding hydroxylamines in up to 71% yield. Expectedly, nitrone bearing a nitrile-group in the *para*-position, was transformed *in situ* to the ketone by addition of hexyllithium to the nitrile group and subsequent aqueous work-up. Given the instability of the resulting ABB-bearing hydroxylamines towards flash chromatography, only solid hydroxylamines **1**–**4** were purified by precipitation for unambiguous structural identification, while in all other cases, the crude material was directly subjected to electrophile-induced spirocyclization.

With a range of ABB-tethered hydroxylamines in hand, we turned our attention to affect the spirocyclization towards the ODASE motif (Scheme 1). It became immediately apparent that a careful choice of the electrophile was required to affect *N*-activation. For

example, direct conversion with acid chlorides or chloroformates provided poor results in our hands as chlorination at the C3-position occurred as a competitive side-reaction suppressing the desired spirocyclisation.[40] Pleasingly, hydroxylamines were smoothly transformed into the ODASE motif by treatment with di-*tert*-butyl dicarbonate and Amberlyst 15 at room temperature in up to 94% yield. With these conditions in hand, all the obtained hydroxylamines were converted into the spirocycles **5**–**19** in good to excellent yields regardless of the electronic properties of the aromatic ring (Scheme 1). It is worth pointing out that acid-mediated isomerization of the double bond was observed with spirocycle **19** obtained in 69% yield in approx. 3:1 *cis*/*trans* ratio. In contrast, no alkene isomerization was observed for ODASE **18** containing a tri-substituted alkene.

Azetidine *N*-substitution adds additional 3D-character to drug candidates, which has been shown to improve chances for clinical success without requiring the addition of a further stereogenic center.[8,47,48] We thus turned to investigating the possibility of additional derivatization on the azetidine nitrogen – other than the Boc-protecting group – to showcase the versatility and promote introduction of this novel bioisostere into drug-like scaffolds (Scheme 2). To provide a more general functionalization platform, ABB-hydroxylamines were converted into the corresponding NH-free amine by trifluoroacetic acid within 30 min (Scheme 2, A). The obtained salts **20**–**23** were easily purified by precipitation, and further derivatized. Reaction with tosyl chloride under basic conditions provided the tosyl-protected ODASE motifs **24** and **25** in 42% and 66% yield, respectively. To further expand the novel chemical space explored in this project, the ODASE core was also converted to sulfonimidamide **26**, an increasingly important motif in agrochemical and medicinal development, in 61% yield from TrNSO according to a one-pot two-step approach recently developed by Willis.[49] This not only allows the combination of ODASE with a medicinally relevant bioisostere providing new chemical space but also introduces additional points for functional derivatization for structure-activity relationship studies. Addition of ODASE to isocyanates and isothiocyanates provides urea-containing compounds **27** and **28**, and thiourea **29** in up to 63% yield. Next, given that 3-chlorinated azetidines were observed as the major by-products when hydroxylamine **1** was treated with acyl chlorides, we then tested if this side-reaction could be suppressed when the TFA-salts of ODASE were treated with acyl chlorides. To our delight, reaction with acyl chlorides in the presence of triethylamine provided amides **30** and **31** in up to 63% yield over two steps, thus allowing access to this motif without the formation of C3-chlorinated by-products. To showcase the utility of such process, marketed drugs ibuprofen, naproxen, indomethacin and flurbiprofen were converted into the corresponding ODASE-containing amides **32**–**35** *via* their respective acyl chlorides. It is worth noting that these larger and more complex amides were shown to be exceptionally rigid, resulting in a mixture of highly stable rotamers even at high temperatures. Next, given the importance of palladium-catalyzed couplings in pharmaceutical development, we tested if ODASE was a competent reagent for palladium-catalyzed cross-coupling reactions (Scheme 2, C).[39] To our delight, arylated amines **36**–**38** were obtained in up to 57% yield over two steps through Buchwald-Hartwig couplings, demonstrating the chemical stability of this novel bioisostere under those reaction conditions. The tolerance to such versatile *N*-functionalization protocols renders this motif suitable to incorporation in pharmaceutical research campaigns.

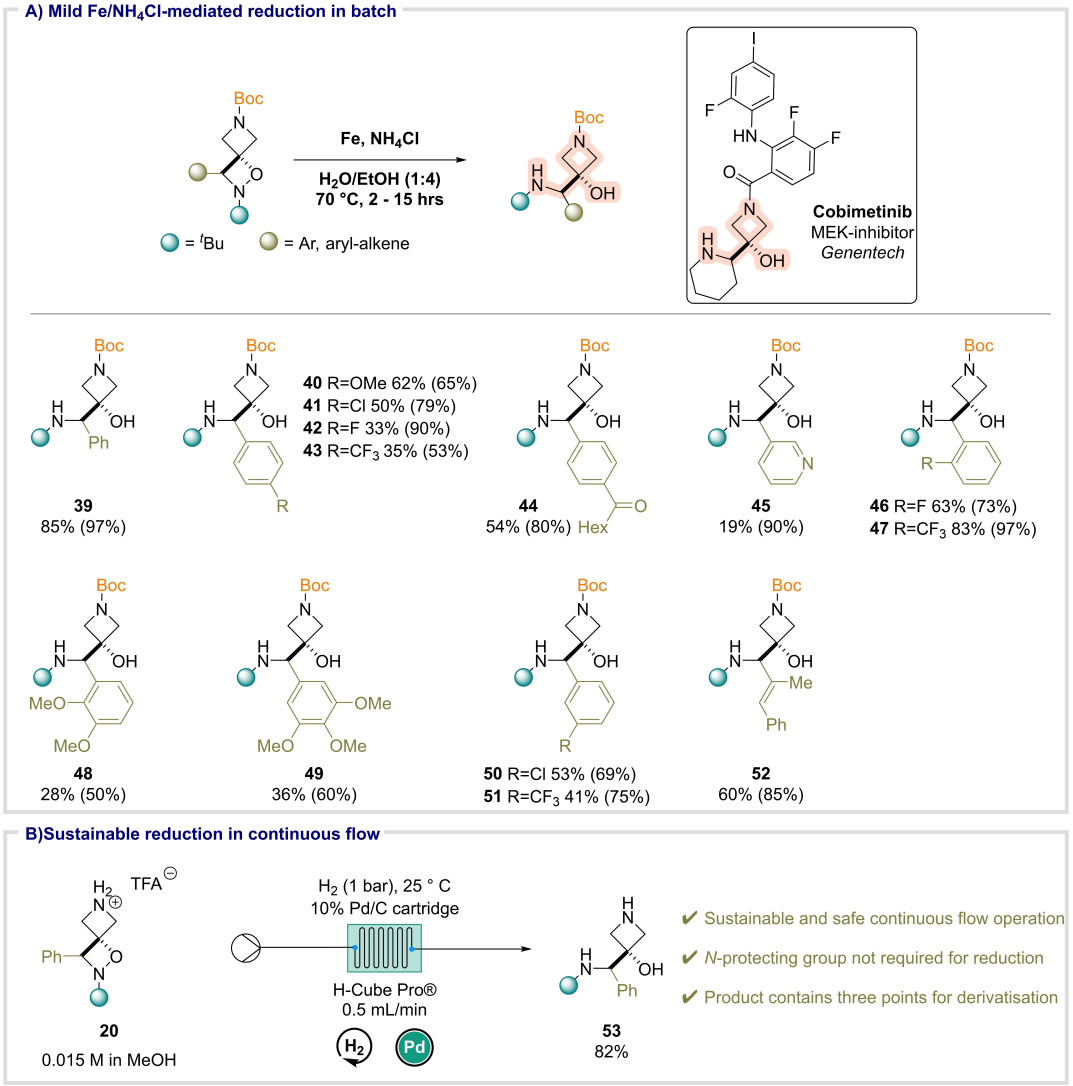
Next, we questioned if ODASE could be transformed into the unusual, but biologically relevant C3-aminoalkylazetidinol motif which is present in the anticancer drug cobimetinib (Scheme 3, A). Aggarwal recently reported an elegant method for accessing this motif based on a sequence of ABB lithiation/borylation/migration, electrophilic nitrogen functionalization and oxidative deborylation.[39] Our method would offer an alternative to this approach. Interestingly, a relatively mild iron-mediated reduction protocol provided the desired amino alcohols **39**–**52** in moderate to good yields.[50] Importantly, the protocol proved to be sufficiently mild and selective to leave acid-sensitive functional groups or those susceptible to reduction, including the *N*-Boc group, carbonyl groups (**44**), alkenes (**52**), or halogens (**50**) untouched. Last, we wondered if isolable ODASE TFA-salt **20** could also be reduced to the corresponding amino alcohols bearing an unprotected azetidine (Scheme 3, B). We hypothesized that the resulting product containing two free amines and one free hydroxy group would be highly polar, and rather challenging to isolate from the water/ethanol solvent mixture used in the iron-mediated protocol. Leveraging our experience with hydrogenation in continuous flow,[51] we thus selected to perform the desired reduction using an H-Cube Pro® operating at room temperature with a flow rate of 0.5 mL/min over a 10% Pd/C cartridge, and 1 bar of hydrogen pressure generated *in situ* from methanol. Satisfactorily, under these conditions ODASE **53** was obtained in 82% yield, after simple evaporation of the solvent, offering a mild and sustainable alternative for the desired reduction. Notably, the obtained product offers three points for further functionalization, and would be laborious to access using traditional synthetic pathways.



Scheme 2. (A) TFA-mediated spirocyclisation to ODASE. (B) Two-step spirocyclisation/N-functionalisation. (C) Two-step spirocyclisation/Buchwald-Hartwig coupling.

Conclusion

In summary, we report here the synthesis and derivatization of ODASE as a novel potential piperazine bioisostere. Based on theoretical studies, we proved that ODASE can be an effective bioisostere for piperazine, with great potential in terms of drug-likeness, target selectivity and clinical success. By combination of flow-assisted ABB-functionalization and spirocyclization, we report a robust and reliable protocol for accessing this motif. We have further demonstrated its tolerance and stability towards a range of *N*-functionalization protocols, including amidation, tosylation, (thio−)urea formation and Buchwald-Hartwig couplings, as well as the introduction to pharmaceutically relevant cores. Last, ODASE was shown to constitute a rapidly accessible starting material for the synthesis of the C3-aminoalkylazetidinol motif. We thus envisage the incorporation of this motif and its derivatives into modern drug discovery programs in the near future.



Scheme 3. (A) Iron-mediated reduction of ODASE to C3-aminoalkylazetidinols. Isolated yields (Quantitative ^{1}H NMR yield shown in brackets). (B) Sustainable reduction in continuous flow. Quantitative ^{1}H NMR yield.

Experimental Section

Flow Synthesis of C3-Functionalized ABBs

The process was performed using a Vapourtec R2+ series reactor with two PTFE reactors (Øint = 1.0 mm) of 2 mL (R1) and 5 mL (R2) with a passive back pressure regulator. The system and operative conditions can be displayed as follows: The solutions were prepared and loaded in PTFE loops as follows: Loop A, 5 mL, n-BuLi 1.6 M in dry hexane (8.0 mmol) [Solution A]; Loop B, 5 mL, dibromopropylamine 0.32 M in dry THF (1.6 mmol, 347 mg) [Solution B]; Loop C, 5 mL, electrophile 0.3 M in dry THF (1.5 mmol) [Solution C]. Solvent bottles containing freshly distilled THF were employed for pushing solutions B, and C in the system. Solvent bottle containing freshly distilled hexane was employed for pushing solution A in the system. The three solutions were pumped into the system using the following flow rates: Solution A [n-BuLi]: 0.30 mL/min; Solution B [dibromopropylamine]: 0.50 mL/min; Solution C [electrophile]: 0.60 mL/min. The T-mixers and reactors were kept at 0 °C using a thermostated water bath under constant sonication for the reaction duration to prevent clogging. Solutions A and B were mixed using a PEEK T-shape micromixer (Øint = 1.00 mm). The resulting solution was passed through R1 (2 mL, t_{R1} = 2.5 min), and was mixed with solution C using a PEEK T-shape micromixer (Øint = 1.00 mm) and introduced in R2 (5 mL, t_{R2} = 3.5 min). The resulting solution was collected directly in a stirred flask with water (5 mL), after reaching the steady state (1.4 min) for 6 min & 13 s. The mixture was extracted with DCM (3×15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. In most cases, the obtained crude was used directly for further steps. The reported yields are calculated by quantitative ^{1}H-NMR analysis. For unambiguous structural identification, some hydroxylamines were purified by washes with hexane/diethyl ether and fully characterised spectroscopically.

Boc-Induced Spirocyclisation for the Synthesis of 1-Oxa-2,6 diazaspiro[3.3]heptane

To a stirred solution of crude hydroxylamine (1.0 equiv.) and Boc_2O (1.5 equiv.) in DCM (0.1 M), was added Amberlyst 15 (160 mg per mmol of hydroxylamine). After stirring for 16 h at room temperature, the mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

TFA-Induced Spirocyclisation to 1-Oxa-2,6 diazaspiro[3.3]heptane

To a solution of hydroxylamine (1.0 equiv.) in dichloromethane (0.1 M) at 0 °C was added trifluoroacetic acid (TFA) (1.1 equiv.) dropwise. After addition, the mixture was allowed to warm to room temperature and stirred for 30 min, before being concentrated under reduced pressure. In most cases, the crude material was sufficiently pure to be used directly in subsequent steps. If required, the crude material can be washed with ice-cold hexane/diethyl ether (2×10 mL, 9:1 v/v) to obtain the pure title compound. Note: The salts are slightly soluble in ice-cold hexane/diethyl ether, leading to drops in isolated yields by ca. 10%).

Reduction of ODASE to C3-Aminoalkylazetidinols

To a glass vial containing a solution of corresponding 1-oxa-2,6 diazaspiro[3.3]heptane (1.0 equiv.) in EtOH/H_2O (4:1, 0.68 M) was added iron powder (10 equiv.) and ammonium chloride (10 equiv.) consecutively. The resulting suspension was stirred at 70 °C (oil bath) for 2 h. The reaction mixture was then allowed to cool to room temperature, filtered through a short pad of celite and concentrated under reduced pressure. The crude product was purified by flash column chromatography.

Information for Crystallographic Data

CCDC-2355446, CCDC-2355451, CCDC-2355434 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Supporting Information Summary

The authors have cited additional references within the Supporting Information.[52–61]

Acknowledgements

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