Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides

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Abstract: Bioisosteres provide valuable design elements for medicinal chemists to adjust the structural and pharmacokinetic characteristics of bioactive compounds towards viable drug candidates. Aryl oxetane amines offer exciting potential as bioisosteres for benzamides, an extremely common pharmacophore, but are rarely examined due to the lack of available synthetic methods. Here, we describe a new class of reactions for sulfonyl fluorides to form aminooxetanes by an alternative pathway to the established SuFEx (sulfonyl-fluoride exchange) click reactivity. An unprecedented defluorosulfonylation forms planar oxetane carbocations simply on warming. This disconnection, comparable to a typical amidation, will allow the application of vast existing amine libraries. The reaction is tolerant to a wide range of polar functionalities and is suitable for array formats. Ten oxetane analogues of bioactive benzamides and marketed drugs are prepared. Kinetic and computational studies support the formation of an oxetane carbocation as the rate determining step, followed by a chemoselective nucleophile coupling step.

New reaction classes have enormous potential to access underexplored chemical space and influence molecular design.[1,2] A limited set of reliable and predictable reactions continue to have a disproportionate influence on the ability to construct medicinal and agrochemical compounds.[3] Such reactions can enable rapid access to derivatives, while also influencing, and limiting, molecular design. Most notably, click reactions have had an enormous impact in the chemical and biological sciences, which proceed on complex substrates without stringent conditions.[4,5,6,7] In drug discovery, amide bond formation continues to be the most common reaction,[3] exploiting vast amine and carboxylic acid libraries available to pharmaceutical companies. Amides are therefore prevalent in marketed pharmaceutical and agrochemical compounds, and display valuable features being more stable than other carbonyl derivatives, powerful H-bond donors and acceptors, and ubiquitous as critical bonding units in natural peptides and proteins.[8] Nonetheless, the amide sub-structure will frequently not provide the subtle balance of properties that is required for a successful active ingredient. Consequently, bioisosteres of amides are also common, providing a mimic of the features of the amide and adjusting the global properties of a compound.[9,10,11] While amidation is extensively investigated, with powerful, mostly stoichiometric coupling reagents,[12] the same cannot be said for amide-isosteres, which often require bespoke synthetic efforts (Fig. 1a).

3,3-Disubstituted oxetanes have garnered considerable interest as carbonyl replacements, due to the similar dipole moments, hydrogen-bonding capacity, and oxygen lone pair orientation.[13,14] Their use as a bioisostere or replacement group also introduces a more 3-dimensional element to a drug compound that can have beneficial binding and solubility effects.[15] The motif is exemplified by antiviral Ziresovir, bearing a primary aminooxetane, which is undergoing clinical trials.[16] However, methods to prepare aminooxetanes are extremely limited, providing few opportunities to investigate this attractive isostere design, whereby the oxetane both mimics the carbonyl group and affects the basicity of the adjacent amine. Carreira and Shipman have pioneered synthetic routes to oxetane-modified peptides, reliant on a conjugate addition to 3-(nitro-methylene)oxetane.[17,18,19,20,21] These oxetane-modified structures have engendered interesting effects on conformation and metabolic stability. A similar approach allowed the preparation of an oxetane derivative of thalidomide (Fig. 1b).[22] Methods for the preparation of aryl aminooxetanes as

mimics for the benzamide motifs prevalent in marketed drugs are yet more limited (Fig. 1c).[23] Previous approaches, which involve organometallic additions to oxetane imines[24,25,26] or photoredox catalysed decarboxylative couplings of oxetane amino acids,[27] cannot leverage the same extensive amine libraries common in amide chemistry. An approach to form aminooxetanes through coupling of an oxetane reagent with amines in an amide bond-like disconnection would facilitate the broad investigation of the aminooxetane functional group for general usage (Fig. 1d and e).

Here, we report an approach to aryl aminooxetanes as benzamide isosteres exploiting an unprecedented reaction of sulfonyl fluorides. Aryl-oxetane sulfonyl fluorides provide stable oxetane carbocation precursors that react under mild and slightly basic conditions, promoted simply by warming. A wide range of substrates are demonstrated in the pseudo-amide bond formation, and 10 oxetane-analogues of benzamide containing drugs are prepared. The involvement of an oxetane carbocation intermediate and the S_N1 nature of the reaction is investigated through kinetic and computational studies.

Results and discussion

Discovery and development of the defluorosulfonylative coupling of oxetane sulfonyl fluorides. Sulfonyl fluoride reagents have been espoused by Sharpless as click reagents for the reaction with nucleophiles to form sulfonates and sulfonamides, in a process referred to as a SuFEx (sulfur-fluoride exchange) reaction.[5,6,7,28] As first demonstrated in seminal works by Steinkopf[29,30] and others,[31,32,33] the stronger and highly polarised S–F bond confers vastly increased stability to sulfonyl fluorides in comparison to sulfonyl chlorides. The fluoride ion is a poor leaving group and consequently sulfonyl fluorides are highly stable towards nucleophilic substitution as well as reductive and aqueous conditions. Nonetheless, the fluoride can be activated with certain Brønsted or Lewis acidic reagents to promote exchange reactions specifically at the sulfur centre.[6,34,35] Sulfonyl fluorides have therefore been exploited as covalent warheads in chemical biology, due to the potential to be activated in precise environments with specific hydrogen-bonding interactions.[36,37,38]

We envisaged that oxetane sulfonyl fluoride (OSF) **1** would provide a rare example of a tertiary benzylic sulfonyl fluoride, noting that alkyl sulfonyl fluorides are anecdotally less stable than aryl

systems (Fig. 2a). Oxetane sulfide **1b** was formed from oxetanol **1a** using a lithium Lewis acid catalyst,[39] and was converted to the sulfonyl fluoride (**1**) in an optimised short and scalable sequence, via oxetane sulfinate **1d** (Supplementary Information pages S9–S23). These reagents readily reacted with amines on gentle warming in the presence of triethylamine. However, to our surprise, the envisaged oxetane-sulfonamide product **3** was not detected. The reaction instead proceeded by an alternative pathway, with loss of fluoride and sulfur dioxide to form aminooxetane **2** in high yield. Comparison with commercial benzyl sulfonyl fluoride (PMSF) was stark, which provided sulfonamide **4** with complete selectivity (Fig. 2b). We identified the potential of this pathway, being comparable to a typical amide-coupling disconnection, to exploit the readily available libraries of amines to directly form complex amide isosteres. Notably, all our attempts to form aminooxetanes directly from oxetanol **1a** by hydroxyl activation were unsuccessful (Supplementary Table S4).

The defluorosulfonylation of **1** was shown to be thermally promoted, with polar solvents being more effective (Supplementary Table S3 and page S62). Performing the reaction in methanol gave the oxetane ether product (**5**, Fig. 2c). Acetonitrile was an effective solvent to form the carbocation at 60 ºC. In the absence of an added nucleophile oxetane fluoride **6** was formed in 78% yield (by ^{1}H NMR), which was seen as a minor product in the presence of the amine. The use of a silylated amine (TMS-morpholine) formed the aminooxetane in high yield without added base, scavenging the liberated fluoride ion to prevent formation of the oxetane fluoride (Fig. 2d). Ultimately, our preferred conditions involved the free amine and the addition of K_2CO_3 to suppress formation of the fluoride side product through sequestration of the fluoride ion as insoluble KF.[40] These conditions gave an excellent yield of aminooxetane **2** (86%, Fig. 2e). It is notable that oxetane sulfonyl fluoride **1** is stable to storage (≥6 months on the bench, ≥1 year at –20 °C, Supplementary Information page S17), but reacts on simple warming and generates no by-products commonly associated with amide-coupling reagents. The optimised conditions involved a facile experimental set-up and the reaction was generally insensitive to moisture and was performed under air (Supplementary Tables S6 and S15).

Evaluation of nucleophiles. A wide range of amines were investigated to broadly assess the viability of the reaction (Table 1). Primary alkyl amines proved to be successful nucleophiles and

showed a high functional group compatibility (**7**–**20**). The reactions proceeded very cleanly and the aminooxetane products were purified through simple chromatographic techniques. Hindered derivatives such as *t*-BuNH$_2$ (**10**), challenging in typical amide bond forming reactions, were successful under the standard conditions, though oxetanol **1a** and oxetane fluoride **6** were observed as side products. Performing the reaction with exclusion of water and with 2 equivalents of amine increased the yield of **10** from 40% to 82% (Supplementary Table S7). Unprotected and polar functionality was well tolerated, including alcohols, amides, tertiary amines, as well as saturated oxygen- and nitrogen-heterocycles. Complete selectivity for the aminooxetane product was observed with aminoalcohols (**11**, **12**, **17**, **28**, Supplementary Information pages S27–S28). Acyclic (**21**–**24**) and cyclic (**25**–**35**) secondary amines also gave good yields. There was no loss of enantiomeric excess when enantiopure amines were employed that might be sensitive to racemisation (**25**–**26**).

A series of piperidine nucleophiles were investigated as the most recurring N-heterocycles in pharmaceutical compounds.[41] Interestingly, oxetanyl piperidines with electron-neutral (**27**) and electron-rich (**28**–**29**) groups were obtained in moderate yields, whereas piperidines carrying electron-withdrawing substituents gave high yields (**30**–**32**), indicating an interesting inverse selectivity (Supplementary Table S11). Often sensitive functional groups such as esters, chlorides and fluorides were compatible with the reaction, and the TBS-protected alcohol was not deprotected under the reaction conditions (Supplementary Table S12). Privileged motifs in medicinal chemistry programs such as 3-piperidino-6-fluoro-benzisoxazole, found in many antimicrobials and antipsychotics (e.g. Risperidone),[42] could be readily introduced (**33**). Other heterocycles such as *N*-Boc-piperazine and oxazaspiro[3.3]heptane, used as a bioisostere of morpholine,[43] were also incorporated (**34**, **35**). Aromatic amines were excellent coupling partners (**36**–**45**). A boronic ester functionality was tolerated (**38**), providing a handle for downstream diversification. Amines containing medicinally important heteroaromatics such as pyridine, and more complex electron-deficient derivatives reacted successfully (**41**–**45**).

Compounds **30** and **38** were further characterised by X-ray crystallography. Notably, the 3-aryl substituents are twisted almost orthogonal to the plane defined by the oxetane-O, the oxetane-C3

carbon atom, and the aromatic-C (or amino-N) atoms, to minimise steric interactions and hence reduce planarity (Table 1).

The same reaction conditions gave defluorosulfonylative coupling with nucleophiles such as imidazole (reacting through N, **46**), indole (reacting through C, **47**) and cyclohexanol (through O, **48**). Unlike other nucleophiles, phenols also showed SuFEx reactivity in the reaction with **1**. The product was determined by the base, promoting selectively either the SuFEx (**49**) or defluorosulfonylative (**50**) coupling (Supplementary Table S13). TMS-protected phenol gave the defluorosulfonylative product with very high selectivity over SuFEx. The use of 4-aminophenol under the standard conditions gave aminooxetane **51** in excellent yield and chemoselectivity. Changing the base to Cs_2CO_3 led to a remarkable switch in selectivity to yield sulfonate ester **52**.

Synthesis of oxetane analogues of benzamide drugs. We directly targeted a series of oxetane analogues of benzamide drugs to investigate variations in the oxetane sulfonyl fluoride reagents and demonstrate how these reagents may be applicable in a drug discovery setting. Oxetane analogues were targeted by tactically choosing the appropriate oxetane sulfonyl fluoride and amine parts of the benzamide bond; preparation of such analogues would be a Sisyphean task using traditional methods. Oxetane sulfonyl fluorides **53**–**59** were prepared by the process depicted in Fig. 2a and applied directly to the synthesis of oxetane drug analogues (Fig. 3a; **1**, **54** and **56** were characterised by X-ray crystallography). All aminooxetane products were obtained in good yields. The 4-methoxyphenyl-oxetane sulfonyl fluoride was used to generate an analogue of a recently-reported D3 dopamine receptor agonist (**60**).[44] The 3,4-dimethoxy derivative **53** gave analogues of both Vesnarinone[45] (**61**) and Itopride[46] (**62**). The 3,4,5-trimethoxyphenyl pharmacophore, present in a wide variety of bioactive agents,[47] was introduced using oxetane sulfonyl fluoride **54** in the synthesis of 4 drug analogues (**63**–**67**).[48,49,50,51,52]

Phenolic aminooxetanes were identified as strategic intermediates that, after triflation, could be used as coupling partners in cross-coupling reactions, hence expanding the scope of the aryl substitution beyond electron-rich examples (Fig. 3b). OTIPS-sulfonyl fluoride **55** was reacted with morpholine and to our delight, the silyl group was removed under the reaction conditions yielding directly the desired phenolic morpholine-oxetane **68** in 94% yield, with the yield benefiting from the silyl group scavenging the released fluoride ion. On the other hand, the TIPS protecting group was

retained by employing a TMS-protected amine without addition of base, whereby the TMS group trapped the fluoride ions to give TIPS-protected aminooxetane **72** in high yield. From **68**, conversion to the triflate (**69**), Suzuki cross-coupling (**70**) and alkylation steps afforded **71**, an oxetanyl analogue of an H3 receptor antagonist[53] in a high-yielding sequence. Next, an oxetane analogue of a cathepsin K inhibitor was prepared (**74**, Fig. 3c). The published inhibitor contained a chiral trifluoroethylamine moiety as a bioisosteric replacement for an amide group.[54] Here, the oxetane equivalent was formed by preparation of phenolic aminooxetane **73**, followed by cross-coupling of the corresponding triflate. The same OTIPS-sulfonyl fluoride **55** was reacted selectively with an aminopyrazole to give aminooxetane **75** in excellent yield as a substructure of FGFR inhibitor AZD4547.[55,56] The simultaneous TIPS removal under the reaction conditions was also exploited to directly synthesise the oxetane analogue of Ethamivan (**76**, Fig. 3d).[57] To further compare the different oxetane sulfonyl fluoride derivatives (**53**–**59**), these were reacted with morpholine to generate 5 additional amido-morpholine analogues (**77**–**81**), all providing 70–95% yields of the corresponding aminooxetane (Supplementary Scheme S1).

Application of the defluorosulfonylative coupling to array chemistry and late-stage functionalisation. In medicinal chemistry, the rapid preparation of diverse chemical libraries is widely used to accelerate compound discovery. Using parallel synthesis techniques, we conducted a 30-member array using sulfonyl fluoride **1**, where the objective was to prepare sufficient product quantities (>1 mg) to allow direct testing. 25 compounds were prepared using amines with high structural diversity, achieving an 83% success rate after HPLC purification, a high success rate for such an array (Table 2, Supplementary Scheme S6). The direct functionalisation of existing lead molecules and natural products allows rapid investigations of structure activity relationships and access to new chemical space.[58,59,60] We applied oxetane sulfonyl fluorides **1** and **55** in the reaction with complex drug compounds and related structures to demonstrate chemoselectivity (Table 3). All oxetane-functionalised derivatives were obtained in complete selectivity. Of particular note is oxetane **86** which reacted exclusively through the piperidine nitrogen and not the pyrimidine–NH_2. The use of OTIPS sulfonyl fluoride **55** generated a free phenol functionality (**85**–**87**) as an additional synthetic handle for further modifications. Finally, OSF **1** reacted with

protected tyrosine and histidine derivatives through the phenol and imidazole functionality to provide unnatural amino acid derivatives (**89**–**90**).

Assessment of mechanism through kinetic and computational investigations. We propose that the reaction proceeds by formation of an oxetane carbocation intermediate, in an S_N1 mechanism involving loss of SO_2 and F^-. Kinetic experiments were performed using Bures' VTNA method,[61] by monitoring the reaction in situ using ^{1}H NMR with Et_3N as base. The rate for the consumption of the oxetane sulfonyl fluoride (OSF) was dependent only on the concentration of sulfonyl fluoride, with first order dependency. Zero order was seen for the amine and base (Supplementary Figures S15–S19). Consequently, the rate of reaction of oxetane sulfonyl fluoride **1** in the presence of different nucleophiles was the same (Fig. 4a; k_{Obs} = (39.7 ± 0.6) × 10^{-3} min^{-1}; calculated with morpholine). Variable temperature studies in combination with an Arrhenius plot gave an activation energy of 97.2 ± 1.6 kJ mol^{-1}(Supplementary Figures S20–S21). The half-life of OSF **1** was determined to be ~40 days at 25 ºC and 18 min at 60 ºC, highlighting its stability at room temperature but high reactivity at 60 °C (Supplementary Information pages S52–S53). The yield of the coupled product was more variable and dependent on the nucleophile (Fig. 4b). These observations are consistent with a rate-determining formation of an oxetane carbocation and a competitive product-forming step (Fig. 4d). The formation of the carbocation was supported by mass spectrometry studies on the oxetane sulfonyl fluorides, which detected the corresponding carbocation M–SO_2F^+ as the major (base) peak (Supplementary Table S18). Low quantities of fluoride **6** as a minor product, did not account for the full mass balance suggesting a degradative pathway, likely via elimination of a proton from the carbocation. One such degradation product, aldehyde **91**, was identified by ^{1}H NMR in the absence of amine (Supplementary Figure S13). The reactivity of other oxetane sulfonyl fluorides showed the requirement for a conjugated electron-donating group to stabilise the carbocation. The more electron rich dimethoxy derivative **53** displayed a faster rate of reaction (Fig. 4c). On the other hand, the reaction of trimethoxy derivative **54** was markedly slower due to a steric barrier to conjugation of the 4-methoxy substituent. This is highlighted in the crystal structure of **54** where the 4-methoxy group is prevented from being coplanar by the *ortho*-substituents (Supplementary Figures S5–S8). Unsubstituted phenyloxetane sulfonyl fluoride **92** was remarkably stable, and unreactive with

amines by either defluorosulfonylative or SuFEx pathways even under elevated temperatures or in the presence of activators (Fig. 4e; Supplementary Table S14). Interestingly, the more nucleophilic phenolates[62,63] still yielded the corresponding sulfonate ester SuFEx product (**93**, Fig. 4e).

A computational study was undertaken to further investigate the nature of the oxetane carbocation and the mechanism of the reaction. The oxetane carbocation $\mathbf{[O_{PMP}]^+}$ derived from sulfonyl fluoride **1** strongly favours a planar conformation (Fig. 4f) compared to a bicyclic structure that would invoke stabilisation by the oxygen lone pairs, reminiscent of bicyclic strain release reagent 1-azabicyclo[1.1.0]butane.[64] The planar conformation improves the resonance stabilisation ($\Delta E^{(2)}_{\pi,\text{planar} \rightarrow \text{bicyclic}}$ = –302 kJ mol^{-1}) and minimises steric clashes between the oxetane CH_2 and the *ortho*-C–H bonds of the aryl group ($\Delta r_{H\cdots H}$ = –0.537 Å), resulting in a preference for the planar conformation by +59.4 kJ mol^{-1} (Supplementary Information pages S56–S57). Furthermore, we estimate that the methoxy resonance stabilisation effect is worth ~25 kJ mol^{-1}.

The S_N1 ionisation process for compound **1** was found to proceed through cleavage of the C–S bond to form cation $\mathbf{[O_{PMP}]^+}$ and an SO_2F^- anion that subsequently fragments to SO_2 and F^-. The free energy barrier was calculated to be 110.5 kJ mol^{-1} at 60 ºC (Fig. 4g), whereby the stability of the forming carbocation controls the rate of the reaction.

It is apparent that the oxetane sulfonyl fluorides occupy a specific thermal stability/reactivity window. For example, the oxetane cation formed from **1** is considerably more stable than the corresponding benzyl cation (ΔG = +24.8 kJ mol^{-1}, Fig. 4h and Supplementary Figure S24), in line with the finding that while **1** readily undergoes S_N1 ionisation, benzyl sulfonyl fluorides such as PMSF instead favour direct substitution at sulfur to form sulfonamides, benefitting from lower steric hindrance around the sulfur centre. On the other hand, the inductive destabilisation of the oxetane carbocation by the oxygen atom was found to be essential for stability of the sulfonyl fluoride. The equivalent cyclobutyl cation is 10.4 kJ mol^{-1} more stable than the oxetane cation, meaning that 4-methoxyphenylcyclobutyl sulfonyl fluoride readily undergoes defluorosulfonylation, and is thus unstable under the fluorination conditions (Supplementary Scheme S11). This fine balance permits oxetane sulfonyl fluorides to undergo defluorosulfonylative transformations under mild conditions, whilst allowing for convenient storage and handling. The defluorosulfonylative pathway may provide a general explanation for the relative instability of electron-rich alkyl sulfonyl fluorides.

Conclusions

Oxetane sulfonyl fluorides do not show the SuFEx reactivity expected for sulfonyl fluorides on reaction with amines, but instead undergo an unprecedented defluorosulfonylation reaction. The activation occurs on gentle warming to form an intermediate planar oxetane carbocation, that can be trapped with nucleophiles. Neutral amines readily couple with aryloxetane carbocations to form aminooxetanes as bioisosteres or replacement groups for benzamides. The disconnection mimics the ubiquitous amide-bond formation, allowing the direct use of vast amine libraries. The reaction is high-yielding, chemoselective and functional group tolerant even with challenging amines, as demonstrated in a wide reaction scope, late-stage functionalisation reactions and array chemistry. Furthermore, 10 oxetane analogues of bioactive benzamides were prepared to demonstrate the potential for utility in medicinal chemistry. Kinetic and computational data support an S_N1 reaction pathway via the rate-determining formation of an oxetane carbocation and a subsequent chemoselective nucleophilic addition. The unique nature of the oxetane structure presents a reactivity window whereby upon mild thermal activation (60 °C) S_N1 reactions are viable while offering convenient storage and handling of reagents. We envisage this disconnection will significantly facilitate the preparation of under-investigated aminooxetanes as amide analogues in drug discovery campaigns.

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Author contributions

R.A.C., J.A.B., C.C. and J.J.M. initiated the project. R.A.C., J.J.R., E.L.B., D.A., L.B. and C.C. planned and performed the synthetic experiments and analysed the data. D.C.S. designed, performed and analysed the array screen. J.J.R. and P.H. designed, performed and analysed the kinetic experiments. A.J.P.W. collected, processed and refined single-crystal X-ray diffraction data.

A.S. and F.D. designed and conducted the computational studies. J.A.B. managed the project. J.J.R., A.S., F.D. and J.A.B. wrote the manuscript. All authors discussed the results, contributed to editing the manuscript and preparing supplementary information.

Competing interests

The authors declare no competing interests.

Figure Legends/Captions

Fig 1. Defluorosulfonylative coupling of oxetane sulfonyl fluorides with amines. a, Common bioisosteres of amides. **b**, Oxetanothalidomide, an oxetane amine analogue of thalidomide. **c**, Examples of benzamide containing drugs. **d**, Most common reaction in medicinal chemistry: amide coupling. This couples carboxylic acids with amines to form amides, often using powerful coupling reagents. **e**, This work: oxetane amine coupling as an alternative reaction pathway of sulfonyl fluorides. This mimics the typical amide disconnection and so can make use of the vast available amine libraries.

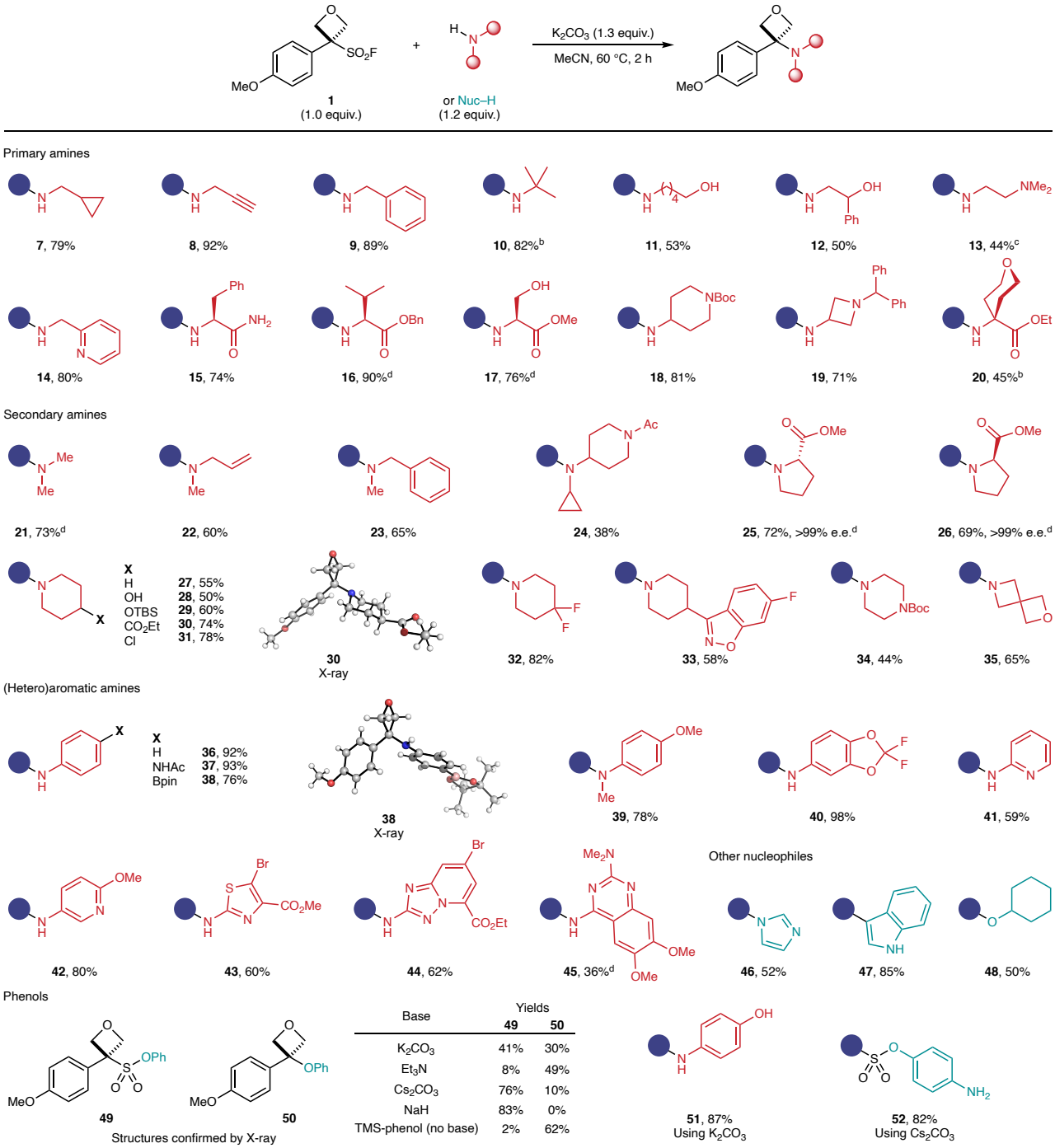
Fig 2. Synthesis and reactivity of oxetane sulfonyl fluorides. a, Practical synthetic route to oxetane sulfonyl fluoride **1** and reactivity with amines. Oxetanol **1a** is transformed to sulfide **1b** using Li-catalysis,[39] then oxidised to sulfone **1c** (not shown), eliminated to sulfinate **1d** (not isolated) and finally fluorinated using Selectfluor to give oxetane sulfonyl fluoride **1**. **1** did not show the typical SuFEx reactivity to form sulfonamide **3**, but underwent defluorosulfonylation to yield aminooxetane **2**. **b**, Contrasting behaviour of benzyl sulfonyl fluoride (PMSF) which reacted with morpholine to form sulfonamide **4** in 93% yield. **c**, A carbocation is generated from **1** thermally in polar solvents such as methanol and acetonitrile. In methanol, solvolysis product **5** is obtained while in acetonitrile oxetane fluoride **6** is formed. **d**, Formation of aminooxetane **2** occurs with TMS-morpholine without the need of an external base, the TMS group scavenging the fluoride ion to minimise formation of **6**. **e**, Optimised reaction conditions performed in presence of K_2CO_3 which serves as base and scavenger of fluoride ions to minimise formation of **6**. [a]Isolated and characterised for the *p*-methoxyphenyl derivative, but the telescoped protocol proved to be beneficial for most of the oxetane sulfonyl fluoride examples. [b]Yield calculated by analysis of the ^{1}H NMR spectrum of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

Fig 3. Reaction scope varying the oxetane sulfonyl fluoride and their application towards the synthesis of analogues of benzamide-containing drugs. **a**, Facile access to oxetanyl drug analogues by coupling the corresponding aryl-oxetane sulfonyl fluoride and amine parts. **b**, Divergent reactivity of OSF **55** with different amine nucleophiles. TMS-morpholine led to TIPS containing oxetane amine **72**, whilst with morpholine the TIPS group was removed in situ to yield phenol oxetane amine **68**. Triflation gave **69**, which was used as coupling partner for a Suzuki coupling to yield oxetane **70**. Two further alkylation steps of intermediate **70** led to the oxetane analogue of an H3 receptor antagonist (**71**). **c**, Further reactions of **55** towards other drug analogues. Reaction with an aminopyrazole gave phenol oxetane amine **75**, which corresponds to the core of FGFR inhibitor AZD4547 (Fig. 1c). Reaction of **55** with a leucine amide derivative yielded **73**, which after triflation, Suzuki coupling and Boc deprotection was transformed into oxetane **74**, an analogue of a cathepsin K inhibitor. **d**, Application of in situ TIPS-group deprotection for the synthesis of Ethamivan analogue **76**. Reagents and conditions: (a) Tf_2O (1.08 equiv.), pyridine (2.0 equiv.), CH_2Cl_2, 25 °C. (b) Boronic ester (1.4 equiv.), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4 (2.0 equiv.), dioxane:water (4:1), 65 °C. (c) 1-Bromo-3-chloropropane (2.0 equiv.), K_2CO_3 (3.0 equiv.), 2-butanone, 80 °C. (d) 2,5-Dimethylpyrrolidine hydrochloride (2.0 equiv.), K_2CO_3 (3.0 equiv.), potassium iodide (2.0 equiv.), 2-butanone, 80 °C. (e) NTf_2Ph (1.5 equiv.), DMAP (10 mol%), NEt_3 (3.0 equiv.), CH_2Cl_2, 0–25 °C. (f) Boronic ester (1.3 equiv.), $PdCl_2(dppf)$ (5 mol%), Na_2CO_3 (3.0 equiv.), DMF:water (2:1), 90 °C. (g) MsOH (10 equiv.), THF, ~500 mbar, 0 °C. [a]Reaction run for 13 h. [b]Isolated as the TFA salt.

Fig 4. Kinetic and computational analysis of the defluorosulfonylative oxetane amination. a, Reaction profiles for the consumption of OSF **1** in the presence of different nucleophiles (also see Supplementary Figure S12 and S19). **b**, Reaction profiles for the formation of different oxetane products from OSF **1** (also see Supplementary Figure S12). The profile for the formation of morpholine product **2** is the average of three runs. **c**, Reaction profile for the consumption of OSF **1**, **53** and **54** in the reaction with morpholine (also see Supplementary Figure S11 and pages S32–S33). **d**, Proposed S_N1 mechanism via an oxetane carbocation. The carbocation either reacts with the amine to give the desired aminooxetane, the fluoride ion to give oxetane fluoride **6**, or it loses a proton to lead to degradation to, amongst others, aldehyde **91**. **91** was identified by means of the diagnostic chemical shifts of the alkene and aldehyde signals in the ^{1}H NMR spectrum of the reaction mixture and comparison to literature values.[65] **e**, Reactivity of electron-neutral Ph-OSF **92** (also see the Supplementary Information page S34). **f**, Comparison of planar and bicyclic geometries for PMP-oxetane cation $\mathbf{[O_{PMP}]^+}$. Van der Waal's spheres highlight steric interactions. Energy differences (ΔE, kJ mol^{-1}) calculated at the [SMD[66](MeCN)-DLPNO-CCSD(T)[67]/def2-TZVPP[68]//SMD(MeCN)-SCS-MP2[69]/def2-TZVP] level of theory. $\Delta E^{(2)}_{\pi}$ denotes the difference in π-delocalisation energy calculated using second order perturbation theory analysis of the NBO Fock matrix. The C–O distance in the bicyclic structure was constrained to 1.673 Å, as this structure is not a minimum on the PES (also see the Supplementary Information pages S56–S57). **g**, S_N1 ionisation process for OSF **1** with its TS geometry (also see the Supplementary Information page S58). **h**, Comparison of stability of **1**, PMP-benzyl and PMP-cyclobutyl cations with respect to each corresponding sulfonyl fluoride; free energies calculated at 25 ºC and 1 M concentration (also see the Supplementary Information page S59). The free energies of **g** and **h** were evaluated at the [SMD(MeCN)-DLPNO-CCSD(T)/def2-TZVPP, ma-def2-TZVPP on F)//SMD(MeCN)-ωB97X-D3[70]/def2-SVP (ma-def2-SVP)] level of theory. All calculations were carried out using the ORCA 4.1.1 Software package.[71]

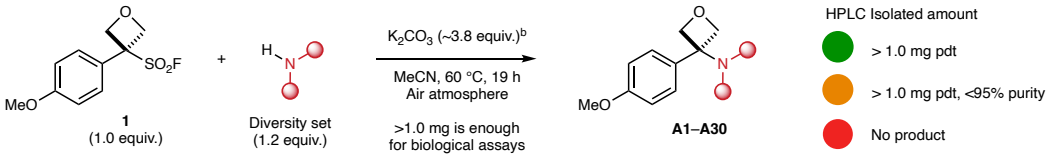
Tables

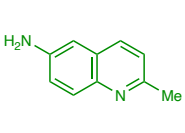
Table 1 Reaction scope of the defluorosulfonylation of oxetane sulfonyl fluorides with amines and other nucleophiles[a]

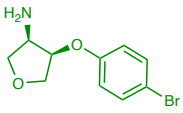


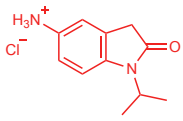
[a]Reactions performed on a 0.2 mmol scale. [b]Under argon and using 2.0 equiv. of amine. [c]On 2.0 mmol scale. [d]The hydrochloride salt of the amine and 2.6 equiv. K_2CO_3 were used.

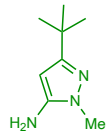
Table 2 30-Compound array with OSF 1 and a diversity set of amines[a]

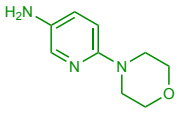


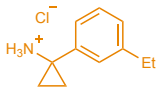

A1, 17.4 mg, 100% purity

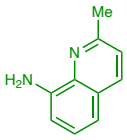

A2, 11.3 mg, 100% purity

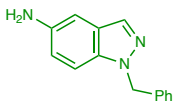

A3

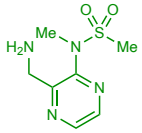

A4, 3.5 mg, 100% purity

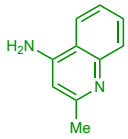

A5, 8.9 mg, 100% purity

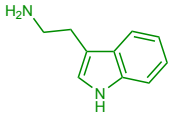

A6, 4.7 mg, 87% purity

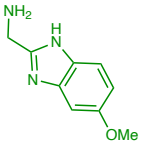

A7, 9.7 mg, 100% purity

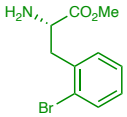

A8, 19.4 mg, 100% purity

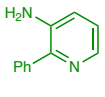

A9, 10.7 mg, 100% purity

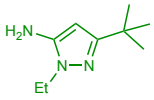

A10, 12.6 mg, 100% purity

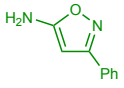

A11, 14.6 mg, 100% purity

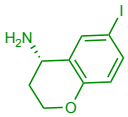

A12, 7.7 mg, 100% purity

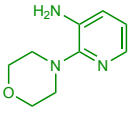

A13, 15.4 mg, 100% purity

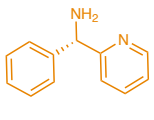

A14, 7.3 mg, 100% purity

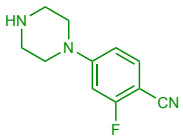

A15, 16.2 mg, 100% purity

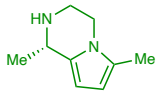

A16, 3.8 mg, 100% purity[c]

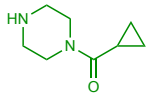

A17, 2.5 mg, 100% purity

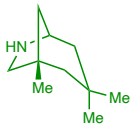

A18, 14.4 mg, 100% purity

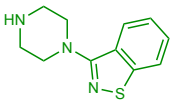

A19, 12.1 mg, 89% purity

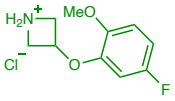

A20, 13.9 mg, 100% purity

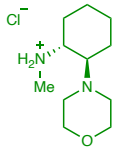

A21, 2.5 mg, 100% purity

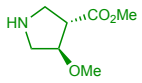

A22, 8.5 mg, 100% purity

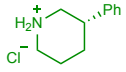

A23, 1.5 mg, 100% purity

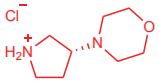

A24, 11.6 mg, 100% purity

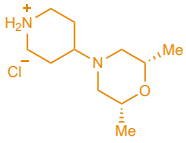

A25, 10.9 mg, 100% purity


A26, 7.1 mg, 100% purity


A27, 12.7 mg, 100% purity

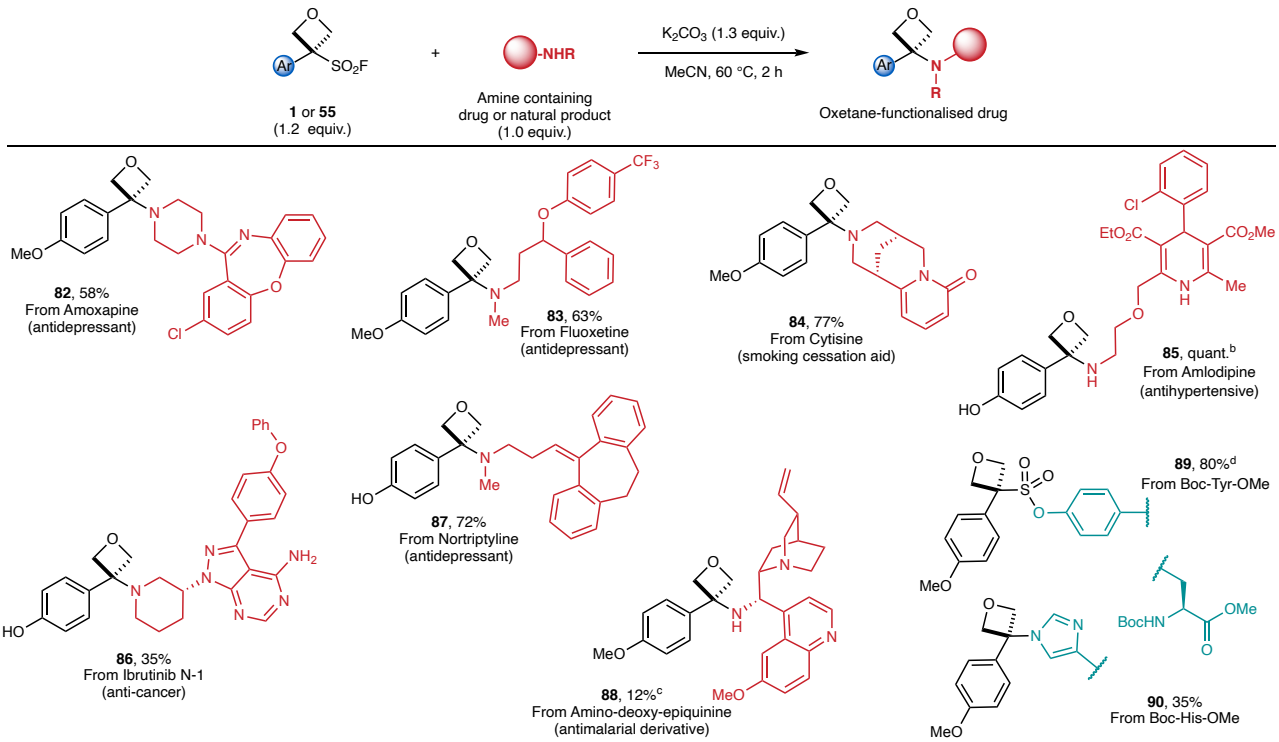

A28, 8.9 mg, 100% purity


A29


A30, 1.8 mg, 92% purity

[a]Reactions performed on a 0.1 mmol scale in 1-dram vials under air and using a stock solution of OSF **1** in acetonitrile. The products were purified by high-throughput purification using a C18 Waters Sunfire column and purities were determined by ELSD detector on LCMS (see Supplementary Information pages S35–S36 for further details). [b]Not individually measured (a spatula tip ≈ 52 mg ≙ 3.8 equiv.). For the convenient use of amines available as their hydrochloride salt, an excess of K_2CO_3 was added. [c]The purity of this compound is considered as 100% but consisted of two compounds (79.7% and 20.3%) with the same mass. This most likely resulted from the amino-isoxazole being a mixture of regioisomers which led to regioisomeric products.

Table 3 Late-stage functionalisation of amine-containing drugs and amino acids[a]



[a]Reactions performed on a 0.1 mmol scale with the nucleophile as limiting reagent and OSF **1** or **55** in slight excess. [b]Benzene sulfonate salt of Amlodipine used with 2.6 equiv. of K_2CO_3. [c]3.0 equiv. of K_2CO_3 used, reaction run for 16 h and yield after purification by HPLC. [d]Cs_2CO_3 used as a base with 1.0 equiv. of **1** and 1.2 equiv of Boc-Tyr-OMe on a 0.2 mmol scale (OSF **1**).

References

1 Campos, K. R. *et al.* The importance of synthetic chemistry in the pharmaceutical industry. *Science* **363**, eaat0805 (2019).

2 Blakemore, D. C. *et al.* Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **10**, 383–394 (2018).

3 Brown, D. G. & Boström, J. Analysis of Past and Present Synthetic Methodologies on Medicinal Chemistry: Where Have All the New Reactions Gone? *J. Med. Chem.* **59**, 4443–4458 (2016).

4 Kolb, H. C., Finn, M. G. & Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* **40**, 2004–2021 (2001).

5 Thirumurugan, P., Matosiuk, D. & Jozwiak, K. Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. *Chem. Rev.* **113**, 4905–4979 (2013).

6 Dong, J., Krasnova, L., Finn, M. G. & Sharpless, K. B. Sulfur(VI) Fluoride Exchange (SuFEx): Another Good Reaction for Click Chemistry. *Angew. Chem. Int. Ed.* **53**, 9430–9448 (2014).

7 Barrow, A. S. *et al.* The growing applications of SuFEx click chemistry. *Chem. Soc. Rev.* **48**, 4731–4758 (2019).

8 Ertl, P., Altmann, E. & McKenna, J. M. The Most Common Functional Groups in Bioactive Molecules and How Their Popularity Has Evolved over Time. *J. Med. Chem.* **63**, 8408–8418 (2020).

9 Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **54**, 2529–2591 (2011).

10 Sun, S., Jia, Q. & Zhang, Z. Applications of amide isosteres in medicinal chemistry. *Bioorg. Med. Chem. Lett.* **29**, 2535–2550 (2019).

11 Kumari, S., Carmona, A. V., Tiwari, A. K. & Trippier, P. C. Amide Bond Bioisosteres: Strategies, Synthesis, and Successes. *J. Med. Chem.* **63**, 12290–12358 (2020).

12 Sabatini, M. T., Boulton, L. T., Sneddon, H. F. & Sheppard, T. D. A green chemistry perspective on catalytic amide bond formation. *Nat. Catalysis* **2**, 10–17 (2019).

13 Burkhard, J. A., Wuitschik, G., Rogers-Evans, M., Müller, K. & Carreira, E. M. Oxetanes as Versatile Elements in Drug Discovery and Synthesis. *Angew. Chem. Int. Ed.* **49**, 9052–9067 (2010).

14 Bull, J. A., Croft, R. A., Davis, O. A., Doran, R. & Morgan, K. F. Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **116**, 12150–12233 (2016).

15 Wuitschik, G. *et al.* Oxetanes in drug discovery: structural and synthetic insights. *J. Med. Chem.* **53**, 3227–3246 (2010).

16 Zheng, X. *et al.* Discovery of Ziresovir as a Potent, Selective, and Orally Bioavailable Respiratory Syncytial Virus Fusion Protein Inhibitor. *J. Med. Chem.* **62**, 6003–6014 (2019).
17 McLaughlin, M., Yazaki, R., Fessard, T. C. & Carreira, E. M. Oxetanyl Peptides: Novel Peptidomimetic Modules for Medicinal Chemistry. *Org. Lett.* **16**, 4070–4073 (2014).
18 Powell, N. H. *et al.* Synthesis and structure of oxetane containing tripeptide motifs. *Chem. Commun.* **50**, 8797–8800 (2014).
19 Beadle, J. D. *et al.* Solid-Phase Synthesis of Oxetane Modified Peptides. *Org. Lett.* **19**, 3303–3306 (2017).
20 Möller, G. P. *et al.* Oxetanyl Amino Acids for Peptidomimetics. *Org. Lett.* **19**, 2510–2513 (2017).
21 Roesner, S. *et al.* Macrocyclisation of small peptides enabled by oxetane incorporation. *Chem. Sci.* **10**, 2465–2472 (2019).
22 Burkhard, J. A., Wuitschik, G., Plancher, J.-M., Rogers-Evans, M. & Carreira, E. M. Synthesis and Stability of Oxetane Analogs of Thalidomide and Lenalidomide. *Org. Lett.* **15**, 4312–4315 (2013).
23 Present in around 110 approved drugs according to the DrugBank database. Wishart, D. S. *et al.* DrugBank: a comprehensive resource for in silico drug discovery and exploration. *Nucleic Acids Res.* **34**, D668–D672 (2006).
24 Jung, H. H., Buesking, A. W. & Ellman, J. A. Highly Functional Group Compatible Rh-Catalyzed Addition of Arylboroxines to Activated N-tert-Butanesulfinyl Ketimines. *Org. Lett.* **13**, 3912–3915 (2011).
25 Hamzik, P. J. & Brubaker, J. D. Reactions of Oxetan-3-tert-butylsulfinimine for the Preparation of Substituted 3-Aminooxetanes. *Org. Lett.* **12**, 1116–1119 (2010).
26 For N-Ar coupling of amino-oxetane, see: Bollenbach, M. *et al.* On water *N*-arylation of oxetanylamines for the preparation of *N*-aryl-oxetanylamines; potentially useful aryl-amide isosteres. *Chem. Commun.* **55**, 1623–1626 (2019).
27 Kolahdouzan, K. *et al.* Dual Photoredox/Nickel-Catalyzed Conversion of Aryl Halides to Aryl Aminooxetanes: Computational Evidence for a Substrate-Dependent Switch in Mechanism. *ACS Catal.* **10**, 405–411 (2020).
28 Smedley, C. J. *et al.* Diversity Oriented Clicking (DOC): Divergent Synthesis of SuFExable Pharmacophores from 2-Substituted-Alkynyl-1-Sulfonyl Fluoride (SASF) Hubs. *Angew. Chem. Int. Ed.* **59**, 12460–12469 (2020).
29 Steinkopf, W. Über Aromatische Sulfofluoride. *J. für Prakt. Chemie* **117**, 1–82 (1927).
30 Steinkopf, W. & Jaeger, P. Über Aromatische Sulfofluoride. II. Mitteilung. *J. für Prakt. Chemie* **128**, 63–88 (1930).
31 Lange, W. & Müller, E. Über Aryl-fluorsulfonate, Ar. O. SO_2F. *Berichte der Dtsch. Chem. Gesellschaft (A B Ser.)* **63**, 2653–2657 (1930).
32 Davies, W. & Dick, J. H. 57. Aliphatic sulphonyl fluorides. *J. Chem. Soc.*, 483–486 (1932).
33 Davies, W. & Dick, J. H. 285. Benzenesulphonyl fluoride derivatives. *J. Chem. Soc.* 2042–2046 (1932).
34 Other activators have also been recently developed, for example Ca(NTf_2): Mukherjee, P. *et al.* Sulfonamide Synthesis via Calcium Triflimide Activation of Sulfonyl Fluorides. *Org. Lett.* **20**, 3943–3947 (2018).
35 Lee, C. *et al.* The Emerging Applications of Sulfur(VI) Fluorides in Catalysis. *ACS Catal.* 6578–6589 (2021).
36 Baker, B. R. Irreversible enzyme inhibitors. CXLIX. Tissue-specific irreversible inhibitors of dihydrofolic reductase. *Acc. Chem. Res.* **2**, 129–136 (1969).
37 Narayanan, A. & Jones, L. H. Sulfonyl fluorides as privileged warheads in chemical biology. *Chem. Sci.* **6**, 2650–2659 (2015).
38 Jones, L. H. & Kelly, J. W. Structure-based design and analysis of SuFEx chemical probes. *RSC Med. Chem.* **11**, 10–17 (2020).
39 Croft, R. A., Mousseau, J. J., Choi, C. & Bull, J. A. Lithium-Catalyzed Thiol Alkylation with Tertiary and Secondary Alcohols: Synthesis of 3-Sulfanyl-Oxetanes as Bioisosteres. *Chem. Eur. J.* **24**, 818–821 (2018).
40 Xin, N., Sun, Y., He, M., Radke, C. J. & Prausnitz, J. M. Solubilities of six lithium salts in five non-aqueous solvents and in a few of their binary mixtures. *Fluid Phase Equilib.* **461**, 1–7 (2018).
41 Vitaku, E., Smith, D. T. & Njardarson, J. T. Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals. *J. Med. Chem.* **57**, 10257–10274 (2014).
42 Rakesh, K. P., Shantharam, C. S., Sridhara, M. B., Manukumar, H. M. & Qin, H.-L. Benzisoxazole: A privileged scaffold for medicinal chemistry. *Medchemcomm* **8**, 2023–2039 (2017).
43 Carreira, E. M. & Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **114**, 8257–8322 (2014).
44 Moritz, A. E. *et al.* Discovery, Optimization, and Characterization of ML417: A Novel and Highly Selective D_3 Dopamine Receptor Agonist. *J. Med. Chem.* **63**, 5526–5567 (2020).
45 Cavusoglu, E., Frishman, W. H. & Klapholz, M. Vesnarinone: A new inotropic agent for treating congestive heart failure. *J. Card. Fail.* **1**, 249–257 (1995).
46 Iwanaga, Y. *et al.* A novel water-soluble dopamine-2 antagonist with anticholinesterase activity in gastrointestinal motor activity. Comparison with domperidone and neostigmine. *Gastroenterology* **99**, 401–408 (1990).
47 Skinner, W. A., Kennedy, J., DeGraw, J. I. & Johnson, H. Structure-Activity Studies of 3,4,5-Trimethoxybenzamides. I. Variation of the Amine Function. *J. Med. Chem.* **12**, 715–717 (1969).

48 Trocimine: Luts, H. A., Zucarello, W. A., Nobles, W. L. & Grattan, J. F. Amides Derived From Hepta- and Octamethyleneimine. *J. Pharm. Sci.* **55**, 1459–1461 (1966).
49 Troxipide: Irikura, T. & Kasuga, K. New Antiulcer Agents. 1. Synthesis and Biological Activities of 1-Acyl-2-, -3-, and -4-substituted Benzamidopiperidines. *J. Med. Chem.* **14**, 357–361 (1971).
50 Trimetozine: Schweizer Apotheker-Verein. *Index Nominum 2000: International Drug Directory*. (Medpharm Scientific Publishers, 2000).
51 Trithiozine: Pellegrini, R. Clinical Effects of Trithiozine, a Newer Gastric Anti-Secretory Agent. *J. Int. Med. Res.* **7**, 452–458 (1979).
52 Trimethobenzamide: Hurley, J. D. & Eshelman, F. N. Trimethobenzamide HCl in the Treatment of Nausea and Vomiting Associated with Antineoplastic Chemotherapy. *J. Clin. Pharmacol.* **20**, 352–356 (1980).
53 Faghih, R. *et al.* Synthesis and SAR of Aminoalkoxy-biaryl-4-carboxamides: Novel and Selective Histamine H_3 Receptor Antagonists. *Bioorganic Med. Chem. Lett.* **13**, 1325–1328 (2003).
54 Black, W. C. *et al.* Trifluoroethylamines as amide isosteres in inhibitors of cathepsin K. *Bioorg. Med. Chem. Lett.* **15**, 4741–4744 (2005).
55 Gavine, P. R. *et al.* AZD4547: An Orally Bioavailable, Potent, and Selective Inhibitor of the Fibroblast Growth Factor Receptor Tyrosine Kinase Family. *Cancer Res.* **72**, 2045–2056 (2012).
56 Kang, J. *et al.* A Selective FGFR inhibitor AZD4547 suppresses RANKL/M-CSF/OPG-dependent ostoclastogenesis and breast cancer growth in the metastatic bone microenvironment. *Sci. Rep.* **9**, 8726 (2019).
57 Hirsh, K. & Wang, S. C. Respiratory Stimulant Effects of Ethamivan and Picrotoxin. *J. Pharmacol. Exp. Ther.* **193**, 657–663 (1975).
58 Gesmundo, N. J. *et al.* Nanoscale synthesis and affinity ranking. *Nature* **557**, 228–232 (2018).
59 Moir, M., Danon, J. J., Reekie, T. A. & Kassiou, M. An overview of late-stage functionalization in today's drug discovery. *Expert Opin. Drug Discov.* **14**, 1137–1149 (2019).
60 Börgel, J. & Ritter, T. Late-Stage Functionalization. *Chem* **6**, 1877–1887 (2020).
61 Burés, J. Variable Time Normalization Analysis: General Graphical Elucidation of Reaction Orders from Concentration Profiles. *Angew. Chem. Int. Ed.* **55**, 16084–16087 (2016).
62 Kanzian, T., Nigst, T. A., Maier, A., Pichl, S. & Mayr, H. Nucleophilic Reactivities of Primary and Secondary Amines in Acetonitrile. *Eur. J. Org. Chem.* **2009**, 6379–6385 (2009).
63 Mayer, R. J., Breugst, M., Hampel, N., Ofial, A. R. & Mayr, H. Ambident Reactivity of Phenolate Anions Revisited: A Quantitative Approach to Phenolate Reactivities. *J. Org. Chem.* **84**, 8837–8858 (2019).
64 Gianatassio, R. *et al.* Strain-release amination. *Science.* **351**, 241–246 (2016).
65 Davies, H. M. L. & Dai, X. Lewis Acid-Catalyzed Tandem Diels−Alder Reaction/Retro-Claisen Rearrangement as an Equivalent of the Inverse Electron Demand Hetero Diels−Alder Reaction. *J. Org. Chem.* **70**, 6680–6684 (2005).
66 Marenich, A. V., Cramer, C. J. & Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **113**, 6378–6396 (2009).
67 Riplinger, C. & Neese, F. An efficient and near linear scaling pair natural orbital based local coupled cluster method. *J. Chem. Phys.* **138**, 034106 (2013).
68 Weigend, F. & Ahlrichs, R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: Design and assessment of accuracy. *Phys. Chem. Chem. Phys.* **7**, 3297–3305 (2005).
69 Grimme, S. Improved second-order Møller–Plesset perturbation theory by separate scaling of parallel- and antiparallel-spin pair correlation energies. *J. Chem. Phys.* **118**, 9095–9102 (2003).
70 Chai, J.-D. & Head-Gordon, M. Long-range corrected hybrid density functionals with damped atom–atom dispersion corrections. *Phys. Chem. Chem. Phys.* **10**, 6615–6620 (2008).
71 Neese, F. Software update: the ORCA program system, version 4.0. *WIREs Comput. Mol. Sci.* 8:e1327 (2018). doi:10.1002/wcms.1327.
72 Rojas, J. J. & Croft, R. A. *et al*. Amino-oxetanes as amide isosteres by an alternative defluorosulfonylative coupling of sulfonyl fluorides. Imperial College London Research Data Repository. https://doi.org/10.14469/hpc/8380 (2021).

Methods

Caution statement when working with pure *m*CPBA

Special attention should be paid when handling pure *m*CPBA since it is shock-sensitive and potentially explosive. Do not heat on rotatory evaporators above 25 °C, do not scratch with a metal spatula when removing from round bottom flask (use for example a plastic spatula) and store at <4 °C. The washing of *m*CPBA is not a requirement, but removes the need for a purification step after the reaction work-up.

Temperature sensitivity of oxetane sulfonyl fluorides

In general, oxetane sulfonyl fluorides are sensitive to temperature. Do not heat above 25 °C when concentrating *in vacuo* on rotatory evaporators. The oxetane sulfonyl fluoride examples reported herein were in general bench stable (25 °C under air), but storage at –20 °C is recommended for long-term purposes.

Instability of oxetane sulfinate salts in solution

In general, oxetane sulfinate salts were found to be stable as pure solids and could be stored indefinitely at –20 °C and handled on the bench. However, some of the more lipophilic (i.e. better soluble in organic solvents) oxetane sulfinate salts (for example **55d**) were unstable in solution. It is hence recommended to take these intermediates directly to the fluorination step without analysis or characterisation.

General procedure for the defluorosulfonylative coupling of oxetane sulfonyl fluorides with nucleophiles

Anhydrous K_2CO_3 (36 mg, 0.26 mmol, 1.3 equiv.), nucleophile (0.24 mmol, 1.2 equiv.) and oxetane sulfonyl fluoride (0.20 mmol, 1.0 equiv.) were added sequentially to a flame-dried reaction tube under air. The reaction vessel was sealed and anhydrous acetonitrile (0.66 mL, 0.3 M) was added by syringe. After stirring the reaction mixture at 60 ºC for 2 h, it was left to cool to 25 °C, EtOAc (5 mL) was added and the mixture was filtered through a plug of Celite, eluting with further EtOAc (3 × 10 mL). The solvent was then removed *in vacuo* using a rotatory evaporator and purification by flash column chromatography afforded the desired functionalised oxetane.

Further remarks: when an ammonium salt was used instead of the free amine, 2.6 equiv. K_2CO_3 (72 mg, 0.52 mmol) were added.

For very hindered amines (e.g. *t*-butylamine) it is beneficial to run the reaction under anhydrous conditions (inert atmosphere) and with 2.0 equivalents of amine.

Data availability

The data supporting the findings of this work can be found in the Supplementary Information (SI) files. Metrical parameters for the structure of aminooxetanes **30** and **38**, oxetane sulfonate esters **49**, **89** and **93**, oxetane ether **50** and sulfonyl fluorides **1**, **54**, **56** and **92** are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/data_request/cif) under reference numbers CCDC 2094791 (**1**), CCDC 2049639 (**30**), CCDC 2049640 (**38**), CCDC 2094792 (**49**), CCDC 2094793 (**50**), CCDC 2049754 (**54**), CCDC 2094794 (**56**), CCDC 2094795 (**89**), CCDC 2094871 (**92**) and CCDC 2094796 (**93**). Raw and processed characterisation data for all novel compounds as well as compiled computational data can be found at the Imperial College London Research Data Repository.[72]

Figure 1

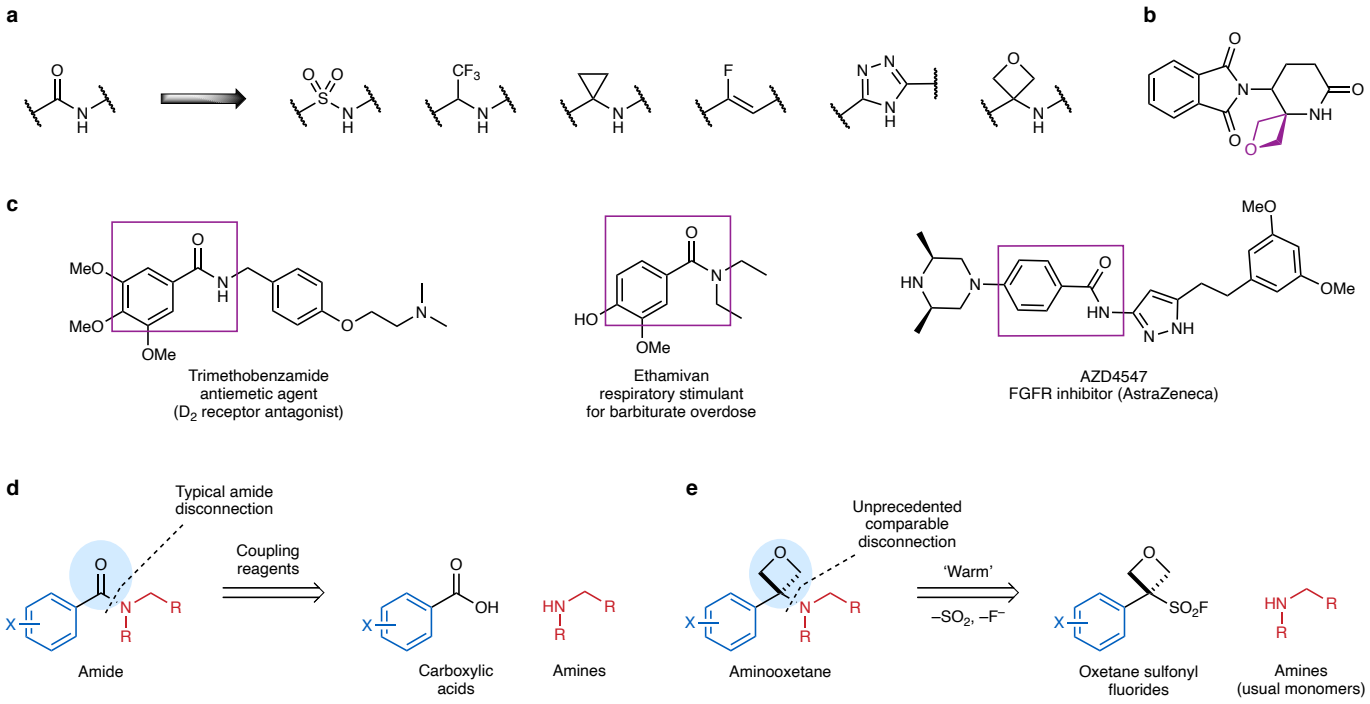

a
b
c
Trimethobenzamide
antiemetic agent
(D2 receptor antagonist)
Ethamivan
respiratory stimulant
for barbiturate overdose
AZD4547
FGFR inhibitor (AstraZeneca)
d
Typical amide
disconnection
Coupling
reagents
Amide
Carboxylic
acids
Amines
e
Unprecedented
comparable
disconnection
'Warm'
–SO2, –F–
Aminooxetane
Oxetane sulfonyl
fluorides
Amines
(usual monomers)

Figure 2

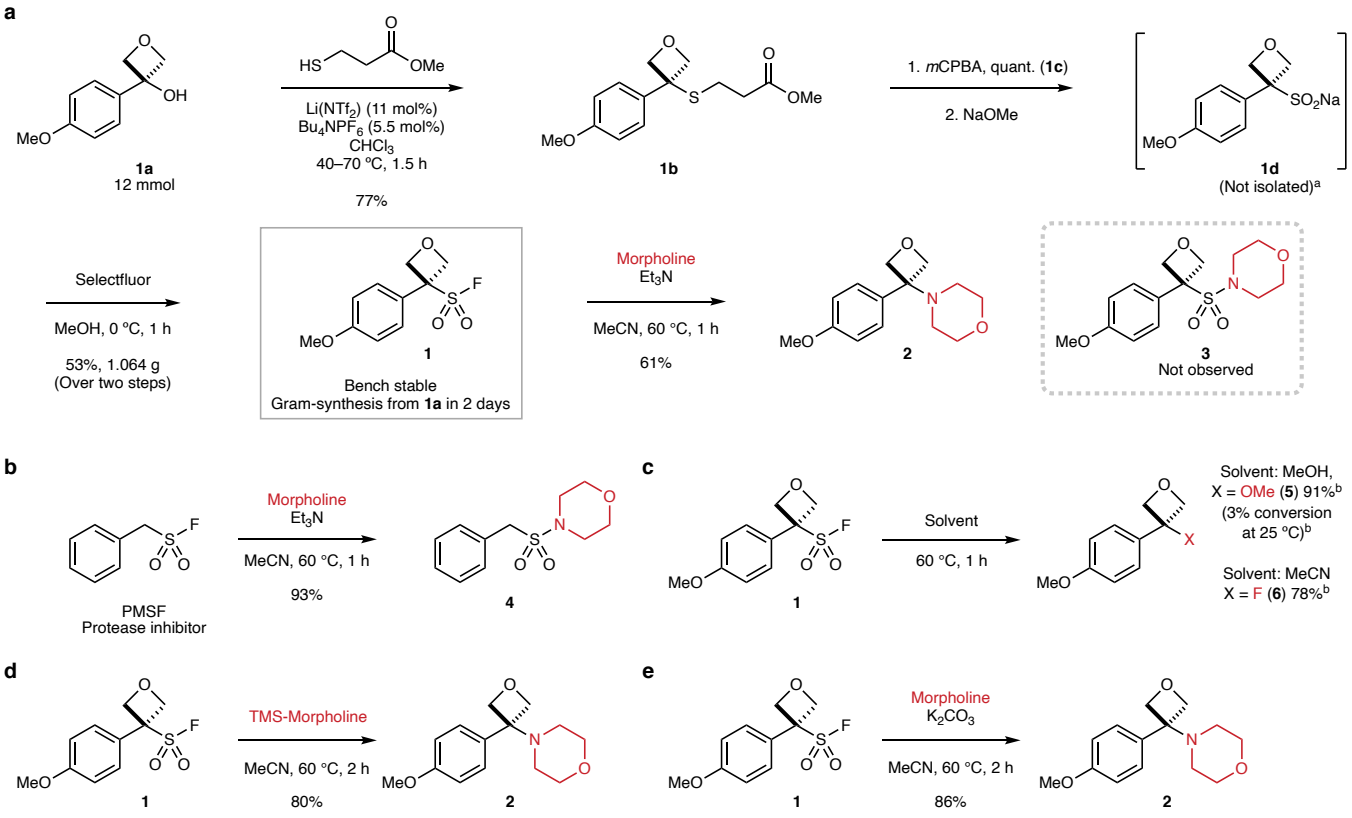

a
1a
12 mmol
HS
OMe
Li(NTf2) (11 mol%)
Bu4NPF6 (5.5 mol%)
CHCl3
40–70 °C, 1.5 h
77%
1b
1. mCPBA, quant. (1c)
2. NaOMe
SO2Na
1d
(Not isolated)a
Selectfluor
MeOH, 0 °C, 1 h
53%, 1.064 g
(Over two steps)
1
Bench stable
Gram-synthesis from 1a in 2 days
Morpholine
Et3N
MeCN, 60 °C, 1 h
61%
2
3
Not observed
b
PMSF
Protease inhibitor
Morpholine
Et3N
MeCN, 60 °C, 1 h
93%
4
c
1
Solvent
60 °C, 1 h
Solvent: MeOH,
X = OMe (5) 91%b
(3% conversion
at 25 °C)b
Solvent: MeCN
X = F (6) 78%b
d
1
TMS-Morpholine
MeCN, 60 °C, 2 h
80%
2
e
1
Morpholine
K2CO3
MeCN, 60 °C, 2 h
86%
2

Figure 3

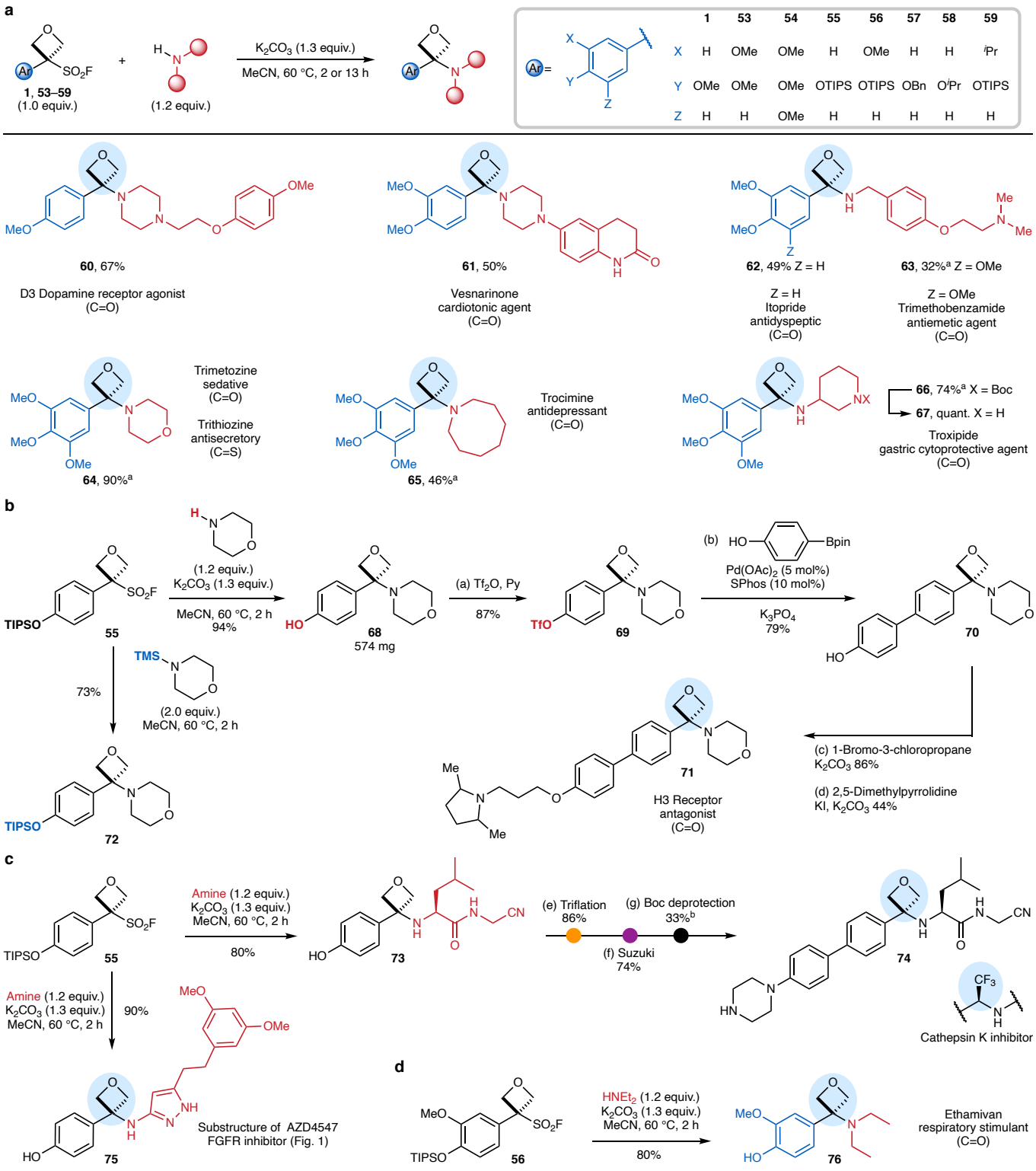
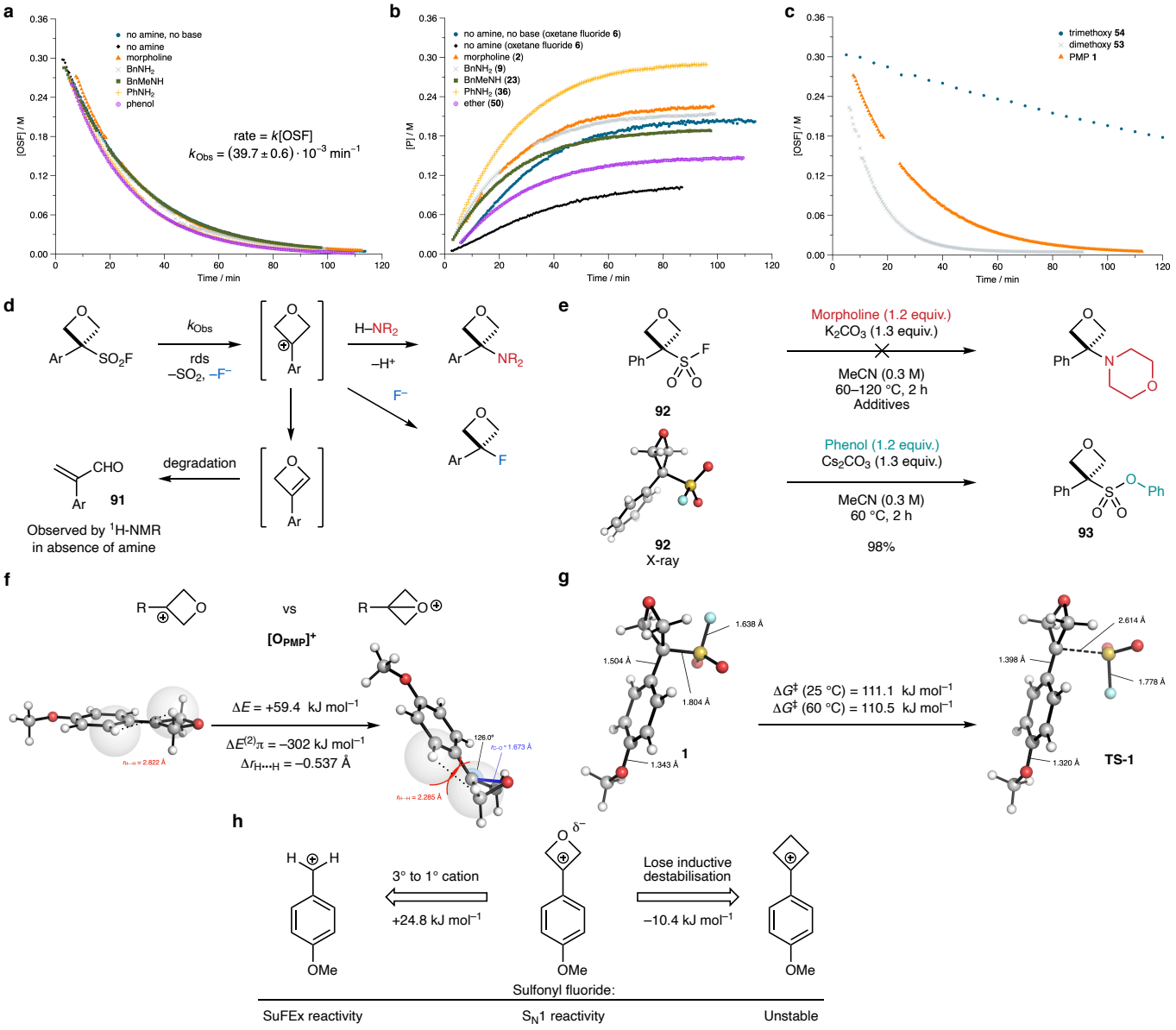

a
1, 53–59
(1.0 equiv.)
(1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN, 60 °C, 2 or 13 h
Ar=
1 53 54 55 56 57 58 59
X H OMe OMe H OMe H H iPr
Y OMe OMe OMe OTIPS OTIPS OBn OiPr OTIPS
Z H H OMe H H H H H
60, 67%
D3 Dopamine receptor agonist
(C=O)
61, 50%
Vesnarinone
cardiotonic agent
(C=O)
62, 49% Z = H
Z = H
Itopride
antidyspeptic
(C=O)
63, 32%a Z = OMe
Z = OMe
Trimethobenzamide
antiemetic agent
(C=O)
64, 90%a
Trimetozine
sedative
(C=O)
Trithiozine
antisecretory
(C=S)
65, 46%a
Trocimine
antidepressant
(C=O)
66, 74%a X = Boc
67, quant. X = H
Troxipide
gastric cytoprotective agent
(C=O)
b
(1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN, 60 °C, 2 h
94%
68
574 mg
(a) Tf2O, Py
87%
69
(b)
Pd(OAc)2 (5 mol%)
SPhos (10 mol%)
K3PO4
79%
70
73%
(2.0 equiv.)
MeCN, 60 °C, 2 h
72
71
H3 Receptor
antagonist
(C=O)
(c) 1-Bromo-3-chloropropane
K2CO3 86%
(d) 2,5-Dimethylpyrrolidine
KI, K2CO3 44%
c
Amine (1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN, 60 °C, 2 h
80%
73
(e) Triflation
86%
(g) Boc deprotection
33%b
(f) Suzuki
74%
74
Cathepsin K inhibitor
Amine (1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN, 60 °C, 2 h
90%
75
Substructure of AZD4547
FGFR inhibitor (Fig. 1)
d
56
HNEt2 (1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN, 60 °C, 2 h
80%
76
Ethamivan
respiratory stimulant
(C=O)

Figure 4


a
no amine, no base
no amine
morpholine
BnNH2
BnMeNH
PhNH2
phenol
rate = k[OSF]
kObs = (39.7 ± 0.6) · 10−3 min−1
[OSF] / M
Time / min
b
no amine, no base (oxetane fluoride 6)
no amine (oxetane fluoride 6)
morpholine (2)
BnNH2 (9)
BnMeNH (23)
PhNH2 (36)
ether (50)
[P] / M
Time / min
c
trimethoxy 54
dimethoxy 53
PMP 1
[OSF] / M
Time / min
d
kObs
rds
–SO2, –F−
H–NR2
–H+
F−
degradation
91
Observed by 1H-NMR
in absence of amine
e
92
92
X-ray
Morpholine (1.2 equiv.)
K2CO3 (1.3 equiv.)
MeCN (0.3 M)
60–120 °C, 2 h
Additives
Phenol (1.2 equiv.)
Cs2CO3 (1.3 equiv.)
MeCN (0.3 M)
60 °C, 2 h
98%
93
f
vs
[OPMP]+
ΔE = +59.4 kJ mol−1
ΔE(2)π = –302 kJ mol−1
ΔrH···H = –0.537 Å
126.0°
g
1.638 Å
1.504 Å
1.804 Å
1.343 Å
1
ΔG‡ (25 °C) = 111.1 kJ mol−1
ΔG‡ (60 °C) = 110.5 kJ mol−1
2.614 Å
1.398 Å
1.778 Å
1.320 Å
TS-1
h
3° to 1° cation
+24.8 kJ mol−1
Lose inductive
destabilisation
–10.4 kJ mol−1
OMe
Sulfonyl fluoride:
SuFEx reactivity
SN1 reactivity
Unstable