JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00656 • Publication Date (Web): 05 May 2020

A rearrangement of 3-hydroxyazetidines into 2-oxazolines.

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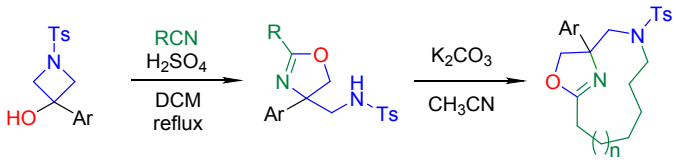
KEYWORDS heterocycles, Ritter Reaction, Cascade, Oxazoline.

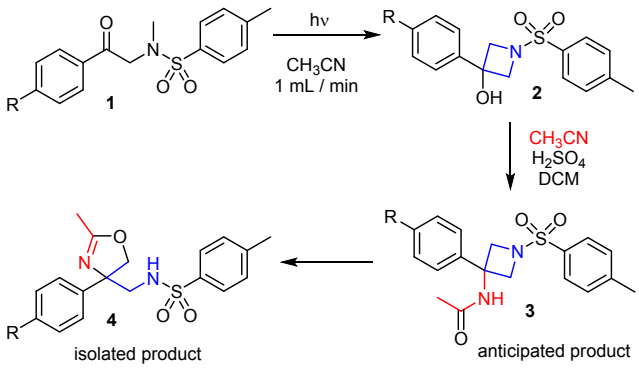


ABSTRACT: A novel rearrangement sequence of 3-hydroxyazetidines via a Ritter initiated cascade provides highly substituted 2-oxazolines in high yields. The reaction conditions and substrate scope of the transformation have been studied demonstrating the generality of the process. The derived products can also be functionalized in order to undergo further intramolecular cyclisation leading to a new class of macrocycle. The final cyclisation step was shown to be a transformation amenable to continuous flow processing allowing for a dramatic reduction in the reaction time and simple scale-up.

INTRODUCTION

In a recent report, we described the preparation of a range of 3-hydroxyazetidines accessed via an efficient photochemical Yang reaction processed under flow conditions (Scheme 1, **1**→**2**).[1] Having successfully demonstrated the scope, versatility and scalability of the reaction, we were particularly interested in expanding the medicinal chemistry value of the compound collection by applying simple secondary transformations to conduct functional group interconversions. As the starting materials **2** all possess a prominent tertiary benzylic alcohol, we contrived to replace this group with an amide through a Ritter reaction.

Scheme 1. Formation of the 3-hydroxyazetidine via the Yang reaction and proposed Ritter reaction.



In a simple procedure, the substrate was refluxed in DCM (30 min) in the presence of 1 equivalent of sulfuric acid and an excess of acetonitrile. Although the reaction proceeded smoothly with full consumption of the starting material, to our initial surprise, the compound formed was a new cyclic, rearranged structure (90% isolated yield) which we determined to be a 2-oxazoline derivative (Scheme 1, Figure 1).

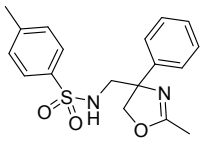
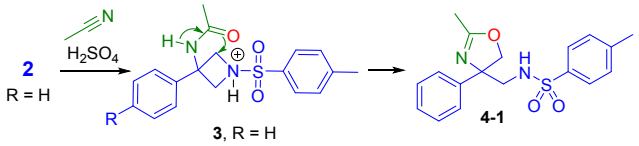


Figure 1. Compound **4-1** isolated from the attempted Ritter reaction of **2** (R = Me, for X-ray structure see SI).

To account for its formation, we propose a direct cascade sequence which initiates through a standard Ritter reaction. The intermediate Ritter amide (hydrolysis re-incorporates the displaced water from the 3-hydroxyazetidine) then rapidly undergoes further rearrangement; in which the amide carbonyl attacks and ring opens the azetidine, driven by the relaxation of the ring strain (Scheme 2).

Scheme 2. Proposed mechanism for the rearrangement of 3-hydroxyazetidines under Ritter type conditions.



Although this was not our intended transformation, this reaction represents a previously unreported and interesting rearrangement sequence leading in high yield to a set of novel oxazoline scaffolds. Oxazolines are an important class of heterocycle being prominent functional units in several biologically active molecules (antimicrobial,[2] anti-inflammatory,[3] anti-malarial,[4] antibacterial,[5] antitumor,[6] anti-viral,[7] antipyretic,[8] antituberculotic,[9] CNS stimulant activity,[10] antioxidant[11]) and several natural products.[12] In addition, they have found other uses as protective coatings (corrosion inhibitors), as additives in gasoline and lube oil, and as antifoaming agents.[13] However, one of the most common uses of oxazolines is in asymmetric catalysis, where chiral oxazolines are widely used as ligands.[14] Based upon our interest in the product structure and the simplicity of the reaction sequence, we elected to investigate the generality of the transformation which we report in full here.

RESULTS AND DISCUSSION

Optimization: Acid Screening

In an attempt to further optimize the reaction, we evaluated a range of acid sources to determine the impact on the transformation. Reactions were run with 1 equivalent of H_2SO_4, HBF_4, CH_3SO_3H and *p*-TSA giving respectively 90%, 85%, 40% and 35% isolated yield (standard 30 min reaction time). It should also be noted that substoichiometric quantities of acid gave comparable results but required the use of much extended reaction times; this was ultimately found to also be detrimental to the quality of the crude product which showed more decomposition over prolonged reaction times, equating to lower isolated yields. Other acids tested, such as acetic acid, CF_3CO_2H, polyphosphoric acid, Eaton's reagent (phosphorus pentoxide - methanesulfonic acid 10:1 wt) and camphorsulfonic acid were all completely ineffective, with no product being detected (>4 h reaction time), and the starting material being fully recovered (Note: we never observed the corresponding Ritter intermediate in any of these experiments). Attempting to employ a solution of $HCl{\cdot}Et_2O$ resulted in the slow formation of the corresponding chloro-substituted product **5** (Figure 2). In independent experiments, this was shown to exist in equilibrium with the parent alcohol. Thus, increasing the proportion of HCl over water in the mixture resulted in higher quantities of the resultant chloro product **5** being detected but never full conversion.

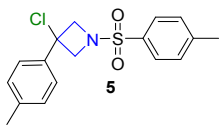


Figure 2. Reaction product obtained through treatment with hydrochloric acid (see SI for X-ray structure).

Catalysis of the transformation was also attempted employing several Lewis acids (1 equiv.), among these $FeCl_3$, $ZnCl_2$, $AlCl_3$ and $Cu(OTf)_2$ all failed to promote any reaction, whereas $BF_3{\cdot}OEt_2$ initially looked promising giving fast early reaction turnover but only giving ~50% conversion (38% isolated) as the reaction quickly stalled. We suspect that the boron trifluoride becomes rapidly deactivated by acting as a dehydrating agent preventing the desired reaction. Adding additional amounts of $BF_3{\cdot}OEt_2$ (> 2 equiv.) continues to progress the reaction, although the reaction mixture become increasingly complex with decomposition products.

While the results obtained with H_2SO_4, CH_3SO_3H and *p*-TSA can be accounted for by their relative *p*Ka and dehydrating effect, the surprising outcome was with HBF_4 (48 wt% aqueous solution) which gave 85% based upon full consumption of the starting material. By contrast, dilution of the other acids i.e. H_2SO_4 with water led to a significant drop in reactivity and incomplete (stalled) reaction. This seems to confirm the interesting property of the HBF_4 aqueous solution as previously noted by Stutz *et al.*[15] who found mixtures of HBF_4 (aq.) in acetonitrile was able to rapidly cleave acetals, BOC groups and *tert*-butyldimethylsilyl ethers within minutes at room temperature, and was more effective than many other acids/solutions of acids.

In summary, H_2SO_4 gave the best conversion and yield, thus, considering factors like safety, price and availability, it remains the best choice of catalyst for the transformation.

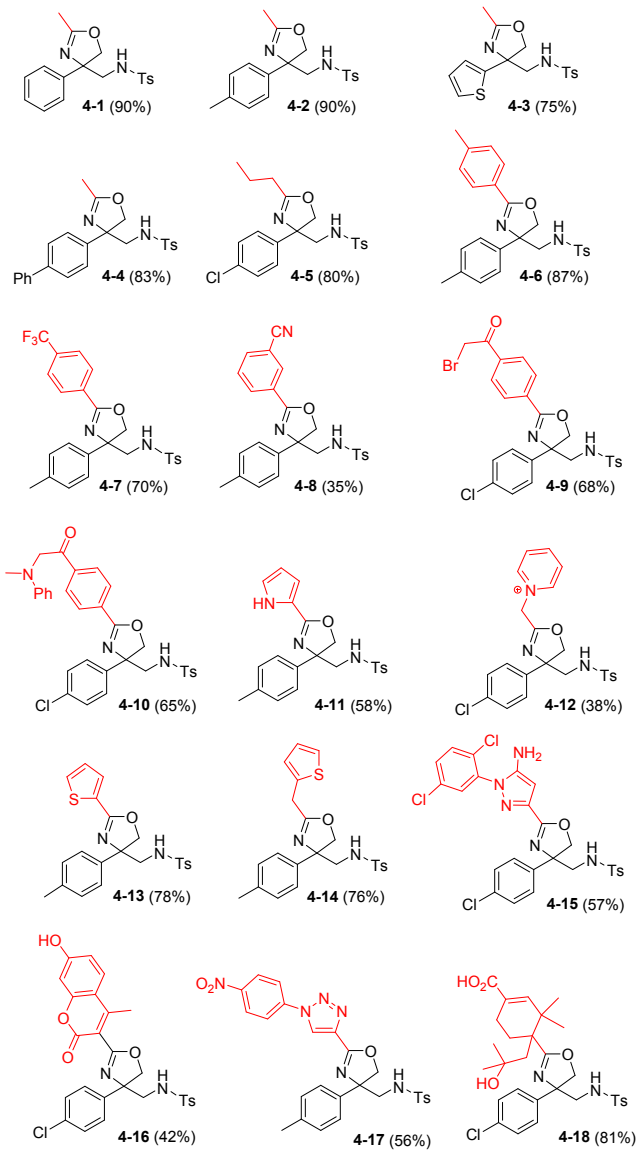


Figure 3. Investigation of substrate scope (Isolated yields).

Optimization: Solvent choice

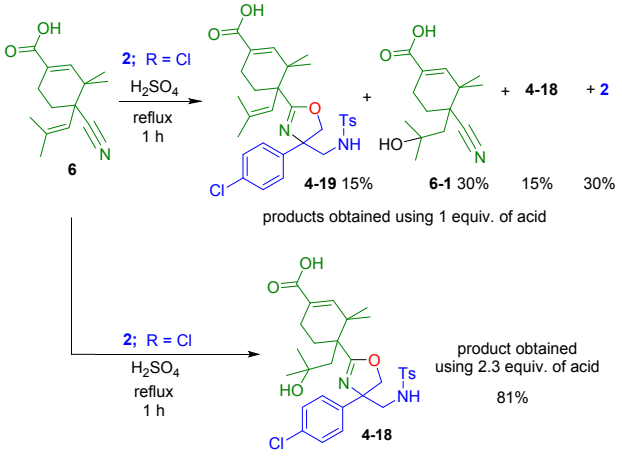
Our solvent selection for the process was rather restricted due to reactivity and the solubility of the substrate and product. Chloroform was found to work equally well as DCM; ethyl acetate and THF could also be used, but the yields were reduced (~5-15%) and accompanied by unidentified minor impurities. Other potential solvents, such as toluene, xylenes, chlorobenzene and trifluorobenzene, were insufficiently solubilizing. Interestingly, the effect of reflux temperature between DCM and chloroform seemed to offer little advantage with both reactions being complete in ~10-12 minutes and yielding essentially identical product outcomes.

Substrate scope

Having determined the general reaction conditions, we next embarked upon an evaluation of the reaction scope in terms of both the azetidine and nitrile components. We were pleased to find the reaction proved general allowing a range of products to be assembled in good to high yield (Figure 3). The rapid rate of reaction (~10 min) and relatively mild conditions enabled several different functional groups to be tolerated. In each case, the progression of the reaction was easily followed by LC-MS.

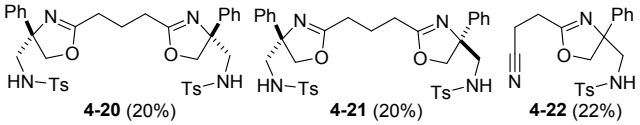
In general, simple alkyl and aryl nitriles worked well (**4-1** – **4-6**). Even basic and acidic containing functionalities proved amenable, although isolation involving neutralisation of the product mixture was more difficult and thus, resulted in lower recoveries (**4-10** – **4-12**, **4-15** – **4-18**). We also experienced issues with the isolation of compound **4-12**, which was produced as a mixed salt; additional optimisation beyond the proof of concept on this substrate was not performed. Finally, compound **4-18** could be isolated but required the use of excess acid as the hydration of the alkene competes with the protonation of the azetidine alcohol required for the carbocation formation (Scheme 3). As such, when only 1 equivalent of acid was used, a complex mixture of the alkene **6**, alcohol starting material **2** and the corresponding mixed hydrated products (**4-18**, **4-19**) was obtained. Whereas with an excess of acid (2.3 equiv.) selective conversion of the starting material to compound **4-18** in a respectable 81% isolated yield was achieved.

Scheme 3. Cascade sequence forming hydrated compound **4-18** (Product conversions were determined using an internal standard on the crude reaction mixtures).



Considering the positive results obtained, we considered the possibility of preparing dyad molecules through double addition to *bis*-nitrile precursors. These compounds were of general interest as potential ligands; as indicated in the introduction oxazoline are excellent metal binders and chelating systems possessing chirality would be of additional significance. Starting with 1,3-dicyanobenzene and using 2 equivalents of the azetidine (**2**, R= Me), we were initially surprised that no product from the double addition was detected. Instead, only a low yield (35%) of the mono oxazolidine **4-8** was produced. However, when observing a repeat reaction more closely, we attributed this to the poor solubility of the starting nitrile and its resulting single addition adduct **4-8**, which seemed to immediately precipitate upon formation. Overall, the limited dissolution resulted in poor mixing and ineffective reaction. Unfortunately, the use of DMF added to help solubilize the starting materials completely shut down the reaction, presumably by attenuating the pH. Other solvents or additives also failed to improve the situation.

We therefore selected a more soluble *bis*-nitrile starting material, glutaronitrile, which was subjected to the same reaction conditions. In this case, we successfully isolated from the reaction, 3 compounds; the meso **4-20** and racemic **4-21** diastereoisomers, confirmed by X-ray analysis along with the corresponding mono substituted oxazolidine **4-22** (Figure 4). These were formed in a ratio of 1:1:1.1, respectively, as determined by ^{1}H NMR analysis of the crude reaction mixture.



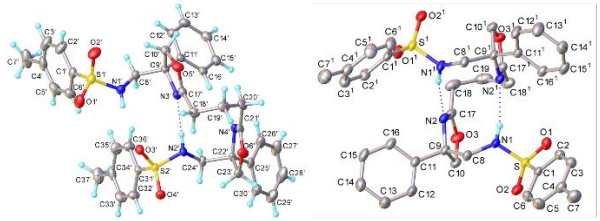


Figure 4 Reaction products of 1,3-dicyanopropane (glutaronitrile) with 3-hydroxazetidine **2** (R = Me) forming dyad molecules. X-ray images of **4-20** (left) and **4-21** (right)(Atomic displacement ellipsoids are drawn at the 50% probability level, for further X-ray data see SI).

The two dyads possess very different and interesting solid state and solution interactions, which due to their interesting structures and potential uses in supramolecular and materials chemistry we decided to explore them further. As can be seen from the single crystal X-ray representations (Figure 4), the racemic structure **4-21**, forms a set of complementary hydrogen bonds creating a tight dimeric pairing (oxazole to sulfonamide NH linkage). This interaction seems to also be observed in solution as evidenced by the ^{1}H NMR, where the NH signals appear at a high chemical shift of 9.17 ppm (2H, $CDCl_3$). This same synergistic interaction is absent in the meso compound **4-20**, instead only a single intramolecular hydrogen bond occurs, a bridging H-bonding methanol molecule helps form a secondary interaction in the solid-state structure (Figure 5, For full X-ray data see SI).

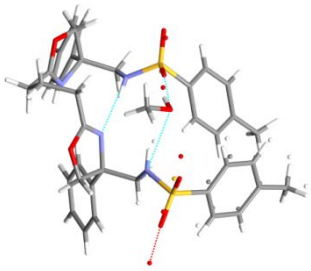


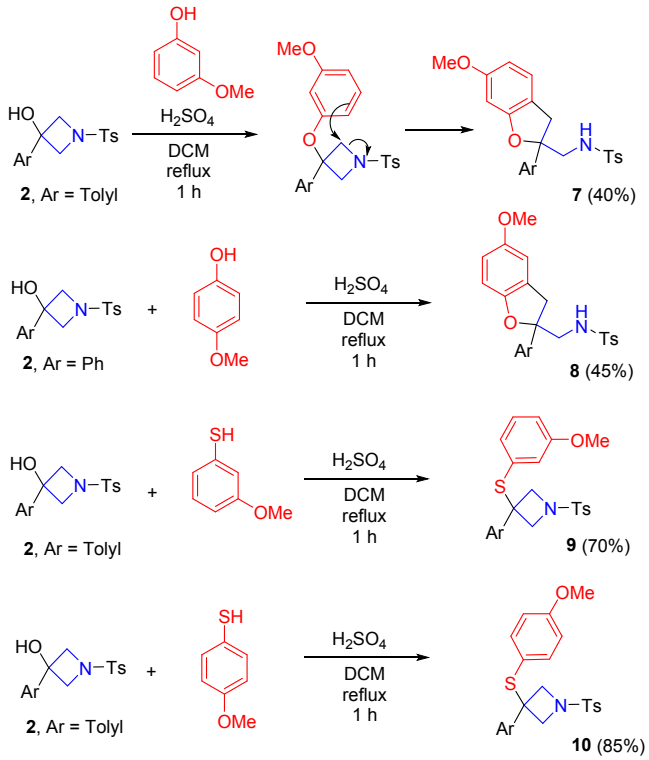
Figure 5. X-ray image of meso compound **4-20** showing the additional solvent (MeOH) H-bonding interaction, atomic displacement ellipsoids are drawn at the 50% probability level.

The corresponding ^{1}H NMR solution state NH signals of **4-20** gives rise to a much lower resonance at 7.06 ppm (2H, $CDCl_3$). This data is consistent with compound **4-20** adopting a weaker set of hydrogen bond interactions. Indeed, this trend is completed when it is compared to the monomer **4-22** which shows a NH signal at 5.21 ppm (indicative of no H-bonding), this is also fully consistent with the other mono-oxaxole structures (Figure 3), NH signal range 5-6.5 ppm). We therefore hypothesis that structure **4-20** is unable to hydrogen bond as tightly as **4-21** due to its mismatching stereochemistry (easily seen by comparing the X-ray forms, Figure 4) and as such adopts in solution a more dynamic structure allowing rapid exchange between the two sets of H-bonding sulfonamide and oxazole (equating to an average NH signal). This exchange process is potentially assisted by the presence of small H-bonding solvent molecules. This is exemplified when using extensively dried NMR solvent ($CDCl_3$). The recorded spectra of **4-20** gives broad and poorly resolved signals, yet with the addition of a H-donor/acceptor molecule i.e. H_2O or MeOH the signals immediately sharpen giving well defined patterns and coupling. We take this as an indication of a faster exchange process in the presence of the H-bonding capable molecule. In comparison, no effect is seen in the ^{1}H NMR for structures **4-21** or **4-22**.

Investigating Alternative Nucleophiles

Having established that the azetidine ring can be readily opened in an intramolecular process, we considered the possibility of creating other related cascades involving for example, an aromatic ring acting as the nucleophile (Scheme 4, compound **7** – **10**). We note that after this work had been performed, we became aware of an intramolecular by-product reported by Denis *et al.* which gives precedent to this type of ring opening in a similar context.[16]

Scheme 4. Products **7** – **10** obtained from using the use of aromatic nucleophiles.

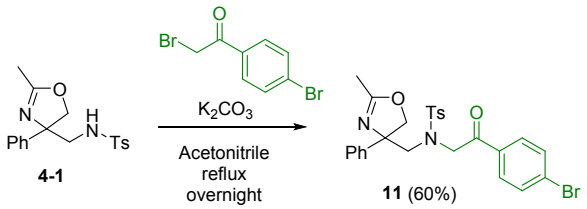


Initial success was immediately achieved using 3- and 4-methoxyphenol, which each gave the rearrangement product as determined by NMR and later confirmed by single crystal X-ray analysis for compound **7**. However, when the alternative 3- and 4-methoxythiophenol was used, the azetidine was converted to the intermediate substitution product, but the secondary cyclisation was not observed, even after prolonged reaction times. We eventually managed to obtain an X-ray crystal structure of compound **9** (see SI for X-ray data) which clearly shows the long C-S bonds (C2/S2 1.825 & S2/C18 1.779 Å), this makes it impossible to adopt the correct alignment with sufficient orbital overlap between C23 – C1/C3 for the ring opening to occur. Considering the different aspects of the reaction we also speculatively attempted the reaction with the equivalent 3-/4-methoxy anilines but unfortunately no reaction was observed using either 0.5, 1 or 2 equivalents of acid catalyst.

Further Intramolecular Reactions

In our initial substrate scope experiments, we had shown it was feasible to carry a bromide appendage on the nitrile component, compound **4-9**. In addition, we explored the tosylamide nucleophilicity, which we expected to be good due to the high degree of sp^3 character suggested both by looking at the x-ray structure (Figure 1) and at the ^{1}H-NMR NH shift and *J* values (NH coupling with the vicinal CH_2). To experimentally confirm the nucleophilic reactivity, we performed a displacement reaction on 2-bromo-1-(4-bromophenyl) ethanone (Scheme 5).

Scheme 5. Identification of *N*-nucleophilicity in the formation of compound **11**. The reaction yield was not optimised.



These observations and preliminary results led us to explore the use of nitrile precursors which would result in products containing residual alkyl halide chains generated from the Ritter cascade (Figure 6). Our proposal was that these could then enable an intramolecular substitution reaction furnishing very interesting bicyclic products.

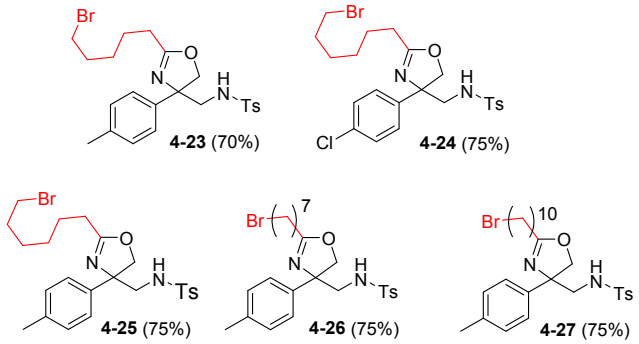


Figure 6. Products of the azetidine rearrangement prepared with pendant alkyl bromide side chains.

We successfully prepared a series of suitable starting materials (**4-23** – **4-27**, Figure 6) using the previously described methodology with good isolated yields. These were then treated with K_2CO_3 under reflux in acetonitrile (36 h) to generate new cyclised compounds **14-1** – **14-5** (Figure 7). The structure of **14-2, 14-3, 14-5** was confirmed by X-ray analysis (see SI for X-ray data). To our knowledge, this type of oxazoline bridge head system has never been reported to date.

The isolated yields of these macrocyclic compounds can be rationalised by considering both the change in ring size (ring strain) and the increasing length of the linking tether in terms of the statistical likelihood of the cyclisation. Hence, due to the smaller ring size, **14-1**, a 10 membered ring, is a more strained structure (leads to a lower yield); whereas formation of the 15 membered ring, **14-5,** is kinetically less favoured, again resulting in a lower yield. Overall, this series of products represents a further intriguing structural diversification of the parent oxazolines **4** via very simple chemical manipulations.

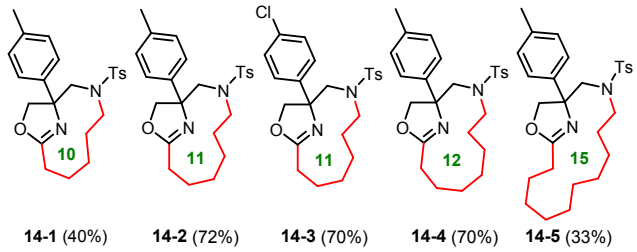


Figure 7. Intramolecular cyclization products **14-1** – **14-5**.

Development of a Continuous Process

As these macrocyclic compounds were of particular interest as novel molecular entities, we wished to scale up their synthesis in order to access greater quantities of material for biological investigation. Therefore, the same intramolecular cyclizations were also attempted in flow where the enclosed reactor would allow higher reaction temperatures to be achieved to promote potentially faster reactions.[17]

The reactions were performed using a Vapourtec-E series flow reactor system[18] fitted with a packed column reactor containing K_2CO_3 (Figure 8). The use of a back-pressure regulator (100 psi) allowed the reaction temperature to be increased to 130 °C without changing the solvent (acetonitrile). The reaction was carried out by directing a flow stream of the starting alkyl halide (**4-23** – **4-27**) stock solution at a concentration of 0.1 M through the packed column at rate of 400 µL min^{-1}. Notably under these conditions, equitable yields were obtained whilst reducing the reaction time from 36 h to 1.5 h. This enables easy access to gram quantities of the products with a productivity of 772 mg h^{-1} (**14-3**, 72% yield), and the ability to produce 5 g in a standard 8 h working day even taking into account reactor set-up, priming, washing and shutdown.

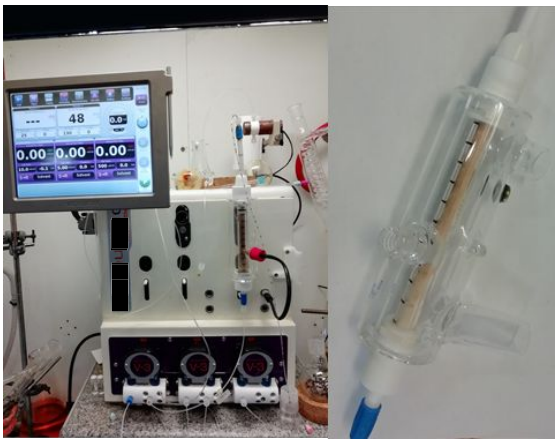


Figure 8. Flow reactor set up used for scale up of products **14-1**– **14-5**.

CONCLUSION

We have shown a novel and general Ritter based cascade involving the condensation of a nitrile and a 3-hydroxyazetidine leading to the formation of new 2-oxazoline scaffolds. The cascade can also be exploited using other nucleophilic components such as phenols, which indicates additional bifunctional nucleophiles may also be viable. In addition, we have shown that specific alkyl bromide substituted 2-oxazolines prepared using this methodology can be further cyclised in an intramolecular process to create unique bicyclic heterocycles.

EXPERIMENTAL SECTION

General procedure for the rearrangement: To a solution of 3-hydroxyazetidine (3.15 mmol) in DCM (10 mL), was added 1 equiv. of H_2SO_4 dropwise, followed by 1 equiv. of nitrile (6 equiv. when the nitrile was acetonitrile) dissolved in DCM (3 mL). The reaction was refluxed and monitored by GC/LC-mass spectra. Upon complete disappearance of the starting material, the mixture was neutralised with an excess of sat. aq. Na_2CO_3, and the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The resulting material was purified by chromatography column (typically with a mixture of hexane: EtOAc).

General flow procedure: A stock solution was prepared from the appropriate alkyl halide (2 mmol, **4-23** – **4-27**) are dissolved in acetonitrile (0.1 M). The solution was pumped at a flow rate of 400 µL min^{-1} through a 100 x 6.6 mm packed column reactor (4.10 mL) filled with K_2CO_3 and equipped with adjustable end pieces. A 100 psi back pressure regulator was added to the outlet line and the column reactor heated in the Vapourtec E2 column heater at 130 °C. The acetonitrile was removed by evaporation, the residue was dissolved in EtOAc, washed with water, brine and dried over Na_2SO_4. After evaporation the resulting material was purified by chromatography column (hexane EtOAc).

X-Ray crystals: The sample for X-ray analysis have been obtained by crystallization in EtOAc/Hexane

Starting materials for compounds **4-15**, **4-17** and **4-18** were available to this project having previously been synthetized in our group.[19-21]

3-chloro-1-[(4-methylphenyl)sulfonyl]-3-4phenyl-azetidine

Methanesulfonyl chloride (1.5 mL). was added, dropwise, to a solution of 3 3-(4-methyl)-1-tosylazetidin-3-ol (4.0 g) and N,N-diisopropylethylamine (3.5 mL) in DCM (100 mL) at 0 °C The mixture was stirred at 0 °C for 7 hrs and then to room temperature overnight. The resulting mixture was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo.

IR ν= 1493 (m), 1330 (s), 1312 (s), 1185 (m), 1150 (s), 1049 (s), 1147 (s), 1090 (s), 813 (s), 829 (s), 675 (s); Melting point: 100-102 °C (crystallised from EtOAc: hexane); HR-MS: calculated for $C_{17}H_{19}ClNO_2S$ 336.0825, found 338.0831 (Δ = 0.6 mDa).

4-methyl-*N*-((2-methyl-4-phenyl-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**4-1**).

Product obtained as Yellow oil (0.976 g, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz,): δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.18 (m, 9H), 5.53 (dd, J = 9.1, 4.6 Hz, 1H), 4.78 (d, 1H, *J* = 8.5 Hz), 4.31 (d, 1H, *J* = 8.5 Hz), 3.27 (dd, 1H, *J* = 12.8, 9.1 Hz,), 3.02 (dd, 1H, *J* = 12.8, 4.6 Hz,), 2.38 (s, 3H), 2.10 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 167.3 (C), 143.8 (C), 143.5 (C), 137.0 (C), 129.8 (CH), 128.8 (CH), 127.7 (CH), 127.02 (CH), 125.5 (CH), 75.9 (C), 75.8 (CH_2), 51.7 (CH_2), 21.5 (CH_3), 14.1 (CH_3). IR: (neat) ν = 3282 (w), 1737 (m), 1696 (m), 1648 (m), 1359 (m), 1219 (m), 1211 (s), 1024 (m), 914 (m), 721 (m), 701 (m), 651 (m), 590 (s), 542 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{18}H_{21}N_2O_3S$, 345.1273; found, 345.1281.

4-methyl-*N*-((2-methyl-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**4-2**).

Product obtained as White solid (1.016 g, 90%). m.p. = 120-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H, *J* = 8.0 Hz), 7.19 (d, 2H, *J* = 8.0 Hz), 7.10 – 7.01 (m, 4H), 6.57 (dd, 1H, *J* = 9.0, 4.8 Hz), 4.84 (d, 1H, *J* = 8.5 Hz), 4.28 (d, 1H, *J* = 8.5 Hz), 3.28 (dd, 1H, *J* = 13.2, 9.0 Hz), 2.98 (dd, 1H, *J* = 13.2, 4.8 Hz), 2.38 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 167.3 (C), 143.1 (C), 140.8 (C), 137.3 (C), 137.2 (C), 129.7 (CH), 129.3 (CH), 126.8 (CH), 125.3 (CH), 75.7 (CH_2), 75.8 (C), 51.1 (CH_2), 21.5 (CH_3), 20.7 (CH_3), 13.8 (CH_3). IR: (neat) ν = 3468 (w), 2961 (w), 1330 (s), 1180 (m), 1147 (s), 1088 (m), 814 (s), 677 (s), 516 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3S$, 359.1429; found, 359.1424.

4-methyl-*N*-((2-methyl-4-(thiophen-2-yl)-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**4-3**).

Product isolated via column chromatography (Hexane:EtOAc = 8:2 v/v) as Yellow oil (0.827 g , 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, *J* = 8.4 Hz), 7.23 (d, 2H, *J* = 8.4 Hz), 7.17 (dd, 1H, *J* = 5.1, 1.2 Hz), 6.93 (dd, 1H, *J* = 5.1, 3.6 Hz), 6.83 (dd, 1H, *J* = 3.6, 1.2 Hz), 5.86 (dd, 1H, *J* = 9.0, 4.9 Hz), 4.79 (d, 1H, *J* = 8.6 Hz), 4.37 (d, 1H, *J* = 8.6 Hz), 3.30 (dd, 1H, *J* = 13.0, 9.0 Hz), 3.15 (dd, 1H, *J* = 13.0, 4.9 Hz), 2.39 (s, 3H), 2.09 (s, 3H).^{13}C{^{1}H} NMR ($CDCl_3$, 101

MHz): δ 168.2 (C), 147.6 (C), 143.5 (C), 137.0 (C), 129.8 (CH), 127.2 (CH), 127.0 (CH), 124.7 (CH), 122.8 (CH), 76.2 (CH_2), 74.0 (C), 51.1 (CH_2), 21.5 (CH_3), 13.9 (CH_3). IR: (neat) ν = 2923 (w), 1656 (m), 1327 (s), 1156 (s), 1089 (s), 813 (m), 752 (m), 659 (s), 549 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_3S_2$, 351.0837; found, 351.0825.

N-((4-([1,1'-biphenyl]-4-yl)-2-methyl-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-4**).

Product isolated via column chromatography (Hexane:EtOAc = 7:3 v/v) as Pale Yellow oil (1.099 g, 83%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.68 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.52 (m, 4H), 7.44 (t, 2H, *J* = 7.5 Hz), 7.38 – 7.34 (m, 3H), 7.24 (d, 2H, *J* = 8.2 Hz), 5.41 (s, 1H), 4.96 (d, 2H, *J* = 8.7 Hz), 4.49 (d, 2H, *J* = 8.7 Hz), 3.31 (dd, 1H, *J* = 13.1, 9.0 Hz), 3.17 (dd, 1H, *J* = 13.1, 4.9 Hz) 2.37 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (CDCl3, 101 MHz): δ 143.7 (C), 141.1 (C), 140.3 (C), 136.8 (C), 129.9 (CH), 129.8 (C), 128.9 (CH), 128.4 (C), 127.7 (CH), 127.1 (CH), 127.0 (CH), 127.0 (CH), 125.9 (CH), 77.0 (CH_2), 75.1 (C), 51.5 (CH_2), 21.6 (CH_3), 14.2 (CH_3). IR: (neat) ν = 2981 (w), 1744 (m), 1233 m), 1158 (s), 1050 (m), 908 (m), 730 (s), 697 (m), 549 (m). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_3S$, 421.1586; found, 421.1581.

N-((4-(4-chlorophenyl)-2-propyl-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-5**).

Product isolated via column chromatography (Hexane:EtOAc = 7:3 v/v) as Colourless oil (1.025 g, 80%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.12 (m, 6H), 5.58 (dd, 1H, *J* = 8.5, 5.1 Hz), 4.69 (d, 1H, *J* = 8.6 Hz), 4.19 (d, 1H, *J* = 8.6 Hz), 3.22 (dd, 1H, *J* = 12.8, 8.5 Hz), 3.02 (dd, 1H, *J* = 12.8, 5.1 Hz), 2.37 (s, 3H), 2.40 – 2.22 (m, 2H), 1.66 (h, 2H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 170.3 (C), 143.4 (C), 142.3 (C), 136.9 (C), 133.3 (C), 129.7 (CH), 128.7 (CH), 126.9 (CH), 126.8 (CH), 75.5 (CH_2), 75.3 (C), 51.5 (CH_2), 29.9 (CH_2), 21.5 (CH_3), 19.6 (CH_2), 13.7 (CH_3). IR: (neat) ν = 2930 (w), 1630 (m), 1337 (m), 1170 (s), 1097 (s), 811 (s), 648 (s), 553 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{24}ClN_2O_3S$, 407.1184; found, 407.1196.

N-((2,4-di-*p*-tolyl-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-6**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as white solid (1.190 g, 87%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (d, 2H, *J* = 8.2 Hz), 7.66 (d, 2H, *J* = 8.2 Hz), 7.31 – 7.21 (m, 6H), 7.15 (d, 2H, *J* = 7.9 Hz), 4.96 (dd, 1H, *J* = 9.1, 4.5 Hz), 4.88 (d, 1H, *J* = 8.4 Hz), 4.46 (d, 1H, *J* = 8.4 Hz), 3.39 (dd, 1H, *J* = 12.6, 9.1 Hz), 3.22 (dd, 1H, *J* = 12.6, 4.5 Hz), 2.43 (s, 3H), 2.39 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 163.7 (C), 143.4 (C), 142.5 (C), 140.2 (C), 138.5 (C), 136.7 (C), 129.7 (CH), 129.46 (CH), 129.1 (CH), 128.7 (CH), 127.0 (CH), 125.5 (CH), 124.2 (C), 76.0 (CH_2), 75.7 (C), 51.7 (CH_2), 21.7 (CH_3), 21.5 (CH_3), 21.1 (CH_3). IR: (neat) ν = 2981 (w), 1639 (s), 1328 (s), 1158 (s), 1088 (s), 1075 (s), 891 (s), 658 (s), 547 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{26}N_2O_3S$, 435.1742l; found, 435.1737.

N-((4-(4-chlorophenyl)-2-(4-(trifluoromethyl)phenyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-7**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (1.077 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, 2H, *J* = 8.1 Hz), 7.62 (m, 4H), 7.24 (d, 2H, *J* = 8.1 Hz), 7.16 (m, 4H), 5.30 (dd, 1H, *J* = 9.4, 4.6 Hz), 4.95 (d, 1H, *J* = 8.5 Hz), 4.50 (d, 1H, *J* = 8.5 Hz), 3.37 (dd, 1H, *J* = 12.8, 9.4 Hz), 3.17 (dd, 1H, *J* = 12.8, 4.6 Hz), 2.37 (s, 3H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 164.0 (C), 143.6 (C), 140.5 (C), 137.7 (C), 136.7 (C), 133.5 (q, *J* = 32.5 Hz, C), 130.5 (C), 129.8 (CH), 129.62 (CH), 129.1 (CH), 127.0 (q, *J* = 207.1 Hz, C),127.0 (CH), 125.4 (q, *J* = 3.81 Hz, CH), 76.3 (CH), 76.2 (C), 51.9 (CH_2), 21.6 (CH_3), 21.16 (CH_3). IR (neat) ν = 3267 (w), 2982 (w), 1649 (m), 1321 (s), 1160 (s), 1073 (s), 1090 (s), 853 (m), 730 (s), 510 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}F_3N_2O_3S$, 489.1503; found, 489.1505.

N-((2-(3-cyanophenyl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-8**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as white solid (0.491 g, 35%). m.p. = 217-220 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.15 (d, 1H, J = 8.3 Hz), 7.84 (t, 1H, *J* = 6.9 Hz), 7.67 (d, 3H, *J* = 7.7 Hz), 7.30 (d, 5H, *J* = 7.7 Hz), 7.15 (d, 2H, *J* = 7.7 Hz), 4.97 (d, 1H, *J* = 8.4 Hz), 4.44 (d, 1H, *J* = 8.4 Hz), 3.13 (dd, 1H, *J* = 13.4, 7.9 Hz), 2.98 (dd, 1H, *J* = 13.4, 5.9 Hz), 2.30 (s, 3H), 2.25 (s, 3H). ^{13}C{^{1}H} NMR (DMSO-d_6, 101 MHz): δ 162.2 (C), 142.6 (C), 141.0 (C), 137.7 (C), 136.8 (CH), 136.5 (C), 136.1 (CH), 131.3 (CH), 130.7 (CH), 129.5 (CH), 129.1 (CH), 127.6 (C), 126.5 (CH), 125.7 (CH), 117.2 (C), 112.8 (C), 76.4(C), 75.1 (CH_2), 52.1 (CH_2), 20.9 (CH_3), 20.6 (CH_3). IR (neat) ν = 2979 (w), 1633 (m), 1591 (s), 1328 (m), 1156 (s), 1088 (s), 1071 (m), 810 (s), 703 (m), 659 (s), 562 (m), 548 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{24}N_3O_3S$, 446.1538; found, 446.1530.

N-((2-(4-(2-bromoacetyl)phenyl)-4-(4-chlorophenyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-9**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as pale yellow crystals (1.203 g, 68%). m.p. = 120-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.04 (d, 2H, *J* = 8.0 Hz), 7.95 (d, 2H, *J* = 8.0 Hz), 7.58 (d, 2H, *J* = 7.9 Hz), 7.19 (d, 2H, *J* = 7.9 Hz), 5.18 (dd, 2H, *J* = 8.7, 5.0 Hz), 4.90 (d, 2H, *J* = 8.7 Hz), 4.43 (m, 3H), 3.31 (dd, 1H, *J* = 12.8, 8.7 Hz), 3.17 (dd, 1H, *J* = 12.8, 5.0 Hz), 2.37 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 191.6 (C), 164.2 (C), 143.7 (C), 141.9 (C), 136.6 (C), 136.3 (C), 133.8 (C), 131.6 (C), 129.8 (CH), 129.1 (CH), 128.9 (CH), 128.9 (CH), 127.1 (CH), 126.9 (CH), 76.2 (CH_2), 76.1 (C), 49.8 (CH_2), 30.8 (CH_2), 22.7 (CH_3). IR (neat) ν = 3302 (w), 1694 (m), 1642 (m), 1312 (m), 1151 (s), 1088 (s), 834 (s), 814 (s), 654 (s), 546 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_4{}^{79}BrS^{35}Cl$, 561.0250; found, 561.0236.

N-((4-(4-chlorophenyl)-2-(4-(2-(methyl(phenyl)amino)ethyl)phenyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-10**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 8:2 v/v) as Yellow oil (1.204 g, 65%). ^{1}H

NMR ($CDCl_3$, 700 MHz): δ 8.09 (d, 2H, *J* = 8.4 Hz), 8.01 (d, 2H, *J* = 8.4 Hz), 7.62 (d, 2H, *J* = 8.3 Hz), 7.29 (s, 4H), 7.25 – 7.20 (m, 4H), 6.75 (tt, 1H, *J* = 7.6, 1.0 Hz), 6.69 (d, 2H, *J* = 7.6 Hz), 4.91 (d, 1H, *J* = 8.4 Hz), 4.81 – 4.78 (m, 3H), 4.47 (d, 1H, *J* = 8.4 Hz), 3.34 (dd, 1H, *J* = 12.8, 8.6 Hz), 3.21 (dd, 1H, *J* = 12.8, 5.1 Hz), 3.11 (s, 3H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 176 MHz): δ 196.4 (C), 164.4 (C), 149.1 (C), 143.8 (C), 141.9 (C), 138.0 (C), 136.8 (C), 133.9 (C), 131.3 (C), 129.9 (CH), 129.4 (CH), 129.2 (CH), 129.0 (CH), 127.9 (CH), 127.2 (CH), 127.0 (CH), 117.5 (CH), 112.5 (CH), 76.2 (C), 76.2 (CH_2), 59.4 (CH_2), 51.9 (CH_2), 39.7 (CH_3), 21.6 (CH_3). IR: (neat) ν = 1697 (s), 1647 (m), 1331 (m), 1159 (s), 1089 (s), 812 (m), 744 (m), 660 (m), 546 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{32}H_{31}N_3O_4S^{35}Cl$, 588.1724; found, 588.1714.

N-((2-(1H-pyrrol-2-yl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-11**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 8:2 v/v as Yellow oil (0.748 g, 58%). ^1H NMR ($CDCl_3$, 400 MHz): δ 10.02 (s, 1H), 7.53 (d, 2H, *J* = 8.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.08 (d, 2H, *J* = 8.0 Hz), 7.05 – 6.95 (m, 3H), 6.50 (s, 1H), 6.16 (s, 1H), 4.91 (d, 1H, *J* = 8.4 Hz), 4.28 (d, 1H, *J* = 8.4 Hz), 3.54 (dd, 1H, *J* = 13.4, 9.6 Hz), 3.03 (dd, 1H, *J* = 13.4, 4.0 Hz), 2.32 (ap. s, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 160.8 (C), 143.2 (C), 141.0 (C), 137.5 (C), 136.9 (C), 129.7 (CH), 129.5 (CH), 126.8 (CH), 125.5 (CH), 123.0 (CH), 118.6 (C), 114.7 (CH), 110.1 (CH), 75.9 (CH_2), 75.3 (C), 52.6 (CH_2), 21.5 (CH_3), 21.1 (CH_3). IR: (neat) ν = 3333 (w), 1640 (s), 1429 (m), 1307 (m), 1155 (s), 1087 (m), 985 (m), 813 (s), 738 (s), 660 (s), 547(s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{24}N_3O_3S$, 410.1538; found 410.1542.

1-((4-(4-chlorophenyl)-4-((4-methylphenylsulfonamido)methyl)-4,5-dihydrooxazol-2-yl)methyl)pyridin-1-ium salt (**4-12**).

Product isolated by crystallization from Hexane:EtOAc as white solid (0.547 g, 38%). m.p. = 227-230 °C. ^1H NMR (CD_3OD , 400 MHz): δ 8.92 (d, 2H, *J* = 6.0 Hz), 8.64 (t, 1H, *J* = 7.9 Hz), 8.14 (t, 2H, *J* = 7.0 Hz), 7.70 (d, 2H, *J* = 7.9 Hz), 7.35 (m, 6H), 5.62 (s, 2H), 3.98 (d, 1H, *J* = 11.1 Hz), 3.88 (d, 1H, *J* = 11.1 Hz), 3.55 (q, 1H, *J* = 13.8 Hz), 2.44 (s, 3H). $^{13}C\{^1H\}$ NMR (CD_3OD, 101 MHz): δ 156.2 (C), 138.1 (CH), 138.0 (CH), 135.4 (C), 130.5 (C), 129.1(C), 124.5(C), 121.3 (CH), 119.8 (CH), 119.5 (CH), 119.3 (CH), 118.5 (CH), 56.6 (CH_2), 54.7 (C), 53.9 (CH_2), 36.3 (CH_2), 11.9 (CH_3). IR: (neat) ν = 2982 (w), 1700 (m), 1493 (m), 1154 (s), 1010 (s), 548 (s). HRMS (ESI) m/z: [M + H2O] calcd for $C_{23}H_{25}N_3O_4S^{35}Cl$, 474.1254; found, 474.1247.

4-methyl-*N*-((2-(thiophen-2-yl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**4-13**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as yellow oil (1,048 g, 78%). m.p. = 130-133 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (m, 3H), 7.50 (d, *J* = 5.0 Hz, 1H), 7.29 – 7.19 (m, 4H), 7.19 – 7.07 (m, 3H), 4.87 (d, 2H, *J* = 8.3 Hz), 4.46 (d, 1H, *J* = 8.3 Hz), 3.37 (dd, 1H, *J* = 12.6, 9.3 Hz), 3.17 (dd, 1H, *J* = 12.6, 4.4 Hz), 2.38 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.0 (C), 143.5 (C), 140.7 (C), 137.5 (C), 136.7 (C), 131.5 (CH), 130.7 (CH), 129.8 (CH), 129.5 (C), 129.5 (CH), 127.8 (CH), 127.0 (CH), 125.5 (CH), 76.4 (CH_2), 76.1 (C), 51.6 (CH_2), 21.6 (CH_3), 21.1 (CH_3). IR: (neat) ν = 3056 (w), 1635 (s), 1326 (s), 1159 (s), 1084 (s), 813 (s), 727 (s), 714 (s), 659 (s), 548 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_3S_2$, 427.1107; found, 427.1112.

4-methyl-*N*-((2-(thiophen-2-ylmethyl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**4-14**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as yellow oil (1.054 g, 76%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (d, 2H, J = 8.4 Hz), 7.29 (dd, 1H, *J* = 5.0, 3.0 Hz), 7.24 – 7.19 (m, 3H), 7.13 – 7.05 (m, 5H), 5.34 (dd, 1H, *J* = 9.1, 4.7 Hz), 4.80 (d, 1H, *J* = 8.5 Hz), 4.31 (d, 1H, *J* = 8.5 Hz), 3.84 – 3.66 (m, 2H), 3.27 (dd, 1H, *J* = 12.8, 9.1 Hz), 3.04 (dd, 1H, *J* = 12.8, 4.7 Hz), 2.39 (s, 3H), 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 168.1 (C), 143.4 (C), 140. (C), 137.4 (C), 137.0 (C), 134.4 (C), 129.8 (CH), 129.4 (CH), 128.3 (CH), 126.9 (CH), 126.1 (CH), 125.38 (CH), 122.8 (CH), 76.2 (CH_2), 75.6 (C), 51.7 (CH_2), 29.4 (CH_2), 21.5 (CH_3), 21.0 (CH_3). IR: (neat) ν = 1649 (s), 1418 (m), 1326 (s), 1161 (s), 1088 (s), 811 (s), 751 (s), 662 (s), 559 (s), 550 (s), 540 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_3S_2$, 441.1307; found, 441.1321.

N-((2-(5-amino-1-(2,5-dichlorophenyl)-1H-pyrazol-3-yl)-4-(4-chlorophenyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-15**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as white solid (1.060 g, 57%). m.p. = 91-93 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (s, 1H), 7.61 (d, 2H, *J* = 8.3 Hz), 7.53 – 7.46 (m, 2H), 7.42 (dd, 2H, *J* = 8.6, 2.5 Hz), 7.27 – 7.18 (m, 6H), 5.36 (s, 2H), 5.28 (m, 1H), 4.63 (d, 1H, *J* = 8.4 Hz), 4.27 (d, 1H, *J* = 8.4 Hz), 3.26 (dd, 1H, *J* = 12.3, 7.7 Hz), 3.16 (dd, 1H, *J* = 12.3, 5.4 Hz), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 161.5 (C), 149.1 (C), 143.6 (C), 143.6 (C), 142.4 (C), 140.2 (CH), 136.5 (C), 135.8 (C), 133.72 (C), 133.4 (C), 131.6 (CH), 131.1 (CH), 130.4 (C), 130.1 (CH), 129.8 (CH), 128.8 (CH), 127.2 (CH), 127.0 (CH), 75.2 (C), 75.1 (CH_2), 52.1 (CH_2), 21.6 (CH_3). IR: (neat) ν = 3278 (w), 1643 (s), 1616 (s), 1157 (s), 1090 (s), 811 (s), 661 (s), 552 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}N_5O_3S^{35}Cl_3$, 590.0587; found, 590.0595.

N-((4-(4-chlorophenyl)-2-(7-hydroxy-4-methyl-2-oxo-2*H*-chromen-3-yl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-16**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as yellow oil (0.713 g, 42%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, 2H, *J* = 7.9 Hz), 7.43 (d, 1H, *J* = 8.8 Hz), 7.33 – 7.27 (m, 6H), 6.88 (dd, 1H, *J* = 8.8, 2.2 Hz), 6.75 – 6.63 (m, 2H), 5.13 (d, 1H, *J* = 8.7 Hz), 4.45 (d, 1H, *J* = 8.7 Hz), 3.50 – 3.38 (m, 1H), 3.08 (d, 1H, *J* = 12.3 Hz), 2.40 (d, 6H, *J* = 7.2 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 162.9 (C), 160.5 (C), 154.7 (C), 143.7 (C), 143.6 (C), 138.83 (C), 136.2 (C), 133.7 (C), 130.0 (CH), 129.7 (CH), 129.3 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.4 (CH), 114.9 (C), 111.8 (C), 102.1 (C), 76.3 (C), 76.2 (CH_2), 52.0 (CH_2), 21.2 (CH_3), 17.8 (CH_3). IR: (neat) ν = 3453 (m, OH), 1595 (w), 1330 (s), 1182 (s), 1147 (s), 1088 (s), 909 (m), 815 (s), 675 (s), 603 (s), 562 (s), 515 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{24}N_2O_6S^{35}Cl$, 539.1044; found, 539.1036.

N-((4-(4-chlorophenyl)-2-(1-(4-nitrophenyl)-1*H*-1,2,3-triazol-4-yl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-17**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as yellow oil (0.939 g, 56%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.01 (s, 1H), δ 8.48 (d, 2H, *J* = 9.0 Hz), 8.10 (d, 2H, *J* = 9.0 Hz), 7.59 (d, 2H, *J* = 8.3 Hz), 7.19 – 7.13 (m, 4H), 7.08 (d, 2H, *J* = 8.0 Hz), 6.39 (s, 1H), 5.14 (d, 2H, *J* = 8.6 Hz), 4.49 (d, 2H, *J* = 8.6 Hz), 3.49 (dd, 1H, *J* = 13.4, 9.4 Hz), 3.15 (dd, 1H, *J* = 13.4, 4.6 Hz), 2.32 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): *δ* 158.7 (C), 147.8 (C), 143.6 (C), 140.7 (C), 140.0 (C), 137.9 (C), 137.7 (C), 137.1 (C), 129.9 (CH), 129.7 (CH), 126.8 (CH), 125.8 (CH), 125.4 (CH), 124.6 (CH), 121.2 (CH), 42.1 (CH_2), 27.1 (CH_2), 25.1 (C), 21.6 (CH_3), 21.1 (CH_3). IR: (neat) ν = 1487 (m), 1202 (m), 1157 (m), 904 (s), 728 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{25}N_6O_5S$, 533.1607; found, 533.1590.

4-(4-(4-chlorophenyl)-4-((4-methylphenylsulfonamido)methyl)-4,5-dihydrooxazol-2-yl)-4-(2-hydroxy-2-methylpropyl)-3,3-dimethylcyclohex-1-enecarboxylic acid (**4-18**).

Product obtained by crystallization from Hexane EtOAc) as white solid (1.503 g, 81%). m.p. = 88-90 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.61 (d, 2H, *J* = 8.3 Hz), 7.32 – 7.29 (m, 2H), 7.24 – 7.19 (m, 4H), 6.62 (dt, 1H, *J* = 14.4, 1.8 Hz), 5.59 (m, 1H), 4.35 – 4.26 (m, 2H), 3.37 (dd, 1H, *J* = 13.4, 7.1 Hz), 3.17 (dd, 1H, *J* = 13.4, 4.7 Hz), 2.39 (s, 3H), 2.37 – 2.33 (m, 1H), 2.33 – 2.24 (m, 1H), 2.20 (d, 1H, *J* = 13.5 Hz), 2.06 – 1.99 (m, 1H), 1.88 (dddd, 1H, *J* = 13.9, 10.1, 6.2, 3.3 Hz), 1.75 (d, 1H, *J* = 13.5 Hz), 1.42 (s, 3H), 1.38 (s, 3H), 1.10 (s, 3H), 0.98 (d, 3H, J = 2.5 Hz).^{13}C{^{1}H} NMR ($CDCl_3$, 151 MHz): δ 166.7 (C), 148.0 (CH), 143.5 (C), 139.7 (C), 136.6 (C), 133.7 (C), 129.7 (CH), 128.4 (CH), 127.3 (C), 127.2 (CH), 127.1 (CH), 81.5 (C), 74.6 (C), 69.2 (CH_2), 50.4 (C), 50.1 (CH_2), 45.7 (CH_2), 37.2 (C), 30.5 (CH_3), 30.0 (CH2), 29.90 (CH_3), 29.36 (C), 26.26 (CH_3), 23.06 (CH_3), 21.7 (CH_2), 21.61 (CH_3). IR: (neat) ν = 2986 (w), 1711 (m), 1654 (m), 1248 (s), 1156 (s), 1090 (s), 1046 (m), 814 (m), 660 (s), 549 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{30}H_{38}N_2O_6S^{35}Cl$, 589.2139; found, 589.2136.

N,*N*'-(((meso)-2,2'-(propane-1,3-diyl)*bis*(4-phenyl-4,5-dihydrooxazole-4,2-diyl))*bis*(methylene))bis(4-methylbenzenesulfonamide) (**4-20**)

Product isolated via column chromatography (eluent Hexane:EtOAc = 8:2 v/v) as white solid (0.441 g, 20%). ^{1}H NMR (C_2D_6OS, 400 MHz): δ 7.66 (d, 6H, *J* = 7.9 Hz), 7.35 – 7.28 (m, 12H), 7.25 (m, 2H), 4.69 (d, 2H, *J* = 8.6 Hz), 4.19 (d, 2H, *J* = 8.6 Hz), 3.38 (s, 6H), 2.99 (dd, 2H, *J* = 13.1, 7.9 Hz), 2.82 (dd, 2H, *J* = 13.1, 5.8 Hz), 2.46 – 2.38 (m, 4H), 2.04 – 1.90 (m, 2H). ^{13}C{^{1}H} NMR (C_2D_6OS , 101 MHz): δ 167.0 (C), 144.2 (C), 142.6 (C), 137.7 (C), 129.6 (CH), 128.4 (CH), 127.2 (CH), 126.5 (CH), 125.8 (CH), 75.9 (C), 74.4 (CH_2), 52.0 (CH_2), 26.7 (CH_2), 21.9 (CH_2), 20.9 (CH_3). IR: (neat) ν = 3338 (w), 2971 (w), 1742 (w), 1663 (w), 1333 (m), 1157 (s), 1131 (m), 1092 (m), 818 (m), 700 (s), 664 (s), 543 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{41}N_4O_6S_2$, 701.2468; found, 701.2480.

N,*N*'-(((Rac)-2,2'-(propane-1,3-diyl)*bis*(4-phenyl-4,5-dihydrooxazole-4,2-diyl))bis(methylene))*bis*(4-methylbenzenesulfonamide) (**4-21**)

Product isolated via column chromatography (eluent Hexane:EtOAc = 8:2 v/v) as white solid (0.441 g, 20%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.17 (dd, 2H, *J* = 10.2, 3.7 Hz), 7.56 (d, 4H, *J* = 8.0 Hz), 7.29 (s, 10H), 7.01 (d, 4H, *J* = 8.0 Hz), 5.10 (d, 2H, *J* = 8.6 Hz), 4.29 (d, 2H, *J* = 8.6 Hz), 3.47 (dd, 1H, *J* = 13.7, 10.2 Hz), 3.11 (ddd, 2H, *J* = 15.0, 10.0, 8.7 Hz), 2.82 (dd, 1H, *J* = 13.7, 3.7 Hz), 2.59 (dt, 2H, *J* = 15.0, 4.5 Hz), 2.30 (s, 6H), 2.08 (td, 2H, *J* = 10.0, 8.6, 4.5 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 170.4 (C), 143.6 (C), 142.8 (C), 138.6 (C), 129.6 (CH), 128.9 (CH), 127.8 (CH), 126.2 (CH), 124.6 (CH), 76.3 (CH_2), 76.0 (C), 50.8 (CH_2), 24.6 (CH_2), 20.9 (CH_3), 19.3 (CH_2). IR (neat) ν = 3062 (w), 2870 (w), 1164 (s), 1147 (w), 1130 (s), 1158 (s), 1091 (s), 1010 (s), 912 (m), 723 (m), 764 (s), 554 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{37}H_{41}N_4O_6S_2$, 701.2468; found, 701.2474.

N-((2-(3-cyanopropyl)-4-phenyl-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-22**)

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (0.265 g, 22%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, *J* = 8.1 Hz), 7.36 – 7.30 (m, 2H), 7.30 – 7.18 (m, 5H), 5.21 (dd, 1H, *J* = 8.9, 5.0 Hz), 4.86 (d, 1H, *J* = 8.6 Hz), 4.39 (d, 1H, *J* = 8.6 Hz), 3.24 (dd, 1H, *J* = 13.0, 8.9 Hz), 3.10 (dd, 1H, *J* = 13.0, 5.0 Hz), 2.60 (t, 2H, *J* = 7.1 Hz), 2.53 (t, 2H, *J* = 7.1 Hz), 2.39 (s, 3H), 2.09 (p, 2H, *J* = 7.1 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 167.5 (C), 143.7 (C), 142.5 (C), 136.4 (C), 129.9 (CH), 129.0 (CH), 128.0 (CH), 127.0 (CH), 125.5 (CH), 119.2 (C), 76.3 (CH_2), 75.7 (C), 49.4 (CH_2), 27.2 (CH_2), 21.7 (CH_2), 21.6 (CH_3), 16.7 (CH_2). IR: (neat) ν = 3263 (w), 2177 (w), 1663 (w), 1327 (w), 1160 (s), 1091 (m), 906 (s), 727 (s), 702 (s), 551 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{22}N_3O_3S$, 384.1338; found, 384.1335.

N-((4-methoxy-2-(*p*-tolyl)-2,3-dihydrobenzofuran-2-yl)methyl)-4-methylbenzenesulfonamide (**7**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as white solid (0.533 g, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, *J* = 8.2 Hz), 7.28 (d, 2H, *J* = 8.2 Hz), 7.11 (d, 2H, *J* = 8.2 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.89 (d, 1H, *J* = 8.7 Hz), 6.44 (d, 1H, *J* = 6.5 Hz), 4.71 (d, 1H, *J* = 9.0 Hz), 4.51 (d, 1H, *J* = 9.0 Hz), 4.26 (dd, 1H, *J* = 8.5, 4.5 Hz), 3.79 (s, 3H), 3.55 (dd, 1H, *J* = 12.2, 8.5 Hz), 3.35 (dd, 1H, *J* = 12.2, 4.5 Hz), 2.43 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 162.1 (C), 161.5 (C), 143.7 (C), 139.5 (C), 137.2 (C), 136.5 (C), 129.9 (CH), 129.7 (CH), 127.1 (CH), 126.4 (CH), 125.0 (CH), 120.9 (C), 107.2 (CH), 96.7 (CH), 82.3 (CH_2), 55.6 (CH_3), 53.3 (C), 49.9 (CH_2), 21.6 (CH_3), 21.0 (CH_3). IR: (neat) ν = 3263 (w), 1621 (w), 1326 (m), 1156 (s), 1091 (m), 804 (m), 661 (m), 549 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{26}NO_4S$, 424.1583; found, 424.1583.

N-((5-methoxy-2-phenyl-2,3-dihydrobenzofuran-2-yl)methyl)-4-methylbenzenesulfonamide (**8**)

Product obtained by crystallization (Hexane:EtOAc) as white crystals (0.580 g, 45%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (d, 2H, *J* = 8.2 Hz), 7.33 – 7.18 (m, 7H), 6.77 – 6.70 (m, 2H), 6.59 (dd, 1H, *J* = 2.3, 0.8 Hz), 4.70 (d, 1H, *J* = 9.1 Hz), 4.64 (dd, 1H, *J* = 8.6, 5.4 Hz), 4.52 (d, 1H, *J* = 9.1 Hz), 3.69 (s, 3H), 3.61 (dd, 1H, *J* = 12.5, 8.6 Hz), 3.43 (dd, 1H, *J* = 12.5, 5.4 Hz), 2.41 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 154.6 (C), 154.3 (C), 143.6 (C), 141.5 (C), 136.0 (C), 130.0

(C), 129.8 (CH), 128.9 (CH), 127.4 (CH), 127.0 (CH), 126.5 (CH), 114.5 (CH), 110.8 (CH), 110.5 (CH), 80.9 (CH_2), 55.9 (CH_3), 54.4 (C), 49.3 (CH_2), 20.5 (CH_3). IR (neat) ν = 3270 (w), 2254 (w), 1489 (m), 1160 (m), 904 (s), 723 (s), 648 (s), 661 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}NO_4S$, 410.1426; found, 410.1445.

3-((4-methoxyphenyl)thio)-3-(*p*-tolyl)-1-tosylazetidine (**9**).

Product obtained by crystallization (Hex: EtOAc = 1:1 v/v) as brown solid (0.969 g, 70%). m.p. = 124-126 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.63 (d, 2H, *J* = 8.3 Hz), 7.28 – 7.22 (m, 2H), 7.06 – 6.99 (m, 4H), 6.76 (d, 2H, *J* = 8.2 Hz), 6.71 (d, 2H, *J* = 8.8 Hz), 4.24 (d, 2H, *J* = 8.3 Hz), 4.13 (d, 2H, *J* = 8.3 Hz), 3.78 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): *δ* 160.8 (C), 144.1 (C), 139.1 (C), 138.0 (CH), 137.0 (C), 132.2 (C), 129.7 (CH), 128.9 (CH), 128.2 (CH), 126.1 (CH), 121.9 (C), 114.3 (CH), 61.7 (CH_2), 55.3 (CH_3), 49.3 (C), 21.6 (CH_3), 21.1 (CH3). IR: (neat) ν = 2980 (w), 1588 (m), 1465 (m), 1344 (m), 1158 (s), 1037 (m), 813 (m), 725 (s), 673 (s), 548 (s). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{26}NO_3S_2$, 440.1354; found, 440.1342.

3-((3-methoxyphenyl)thio)-3-(*p*-tolyl)-1-tosylazetidine (**10**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as orange oil (1.177 g, 85%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H, *J* = 8.3 Hz), 7.27 (d, 2H, *J* = 7.7 Hz), 7.09 (dd, 1H, *J* = 8.4, 7.6 Hz), 7.02 (d, 2H, *J* = 7.7 Hz), 6.87 – 6.79 (m, 3H), 6.72 (ddd, 1H, *J* = 7.6, 1.6, 1.0 Hz), 6.48 (dd, 1H, *J* = 1.6, 1.0 Hz), 4.26 (d, 2H, *J* = 8.4 Hz), 4.15 (d, 2H, *J* = 8.4 Hz), 3.60 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 159.3 (C), 144.2 (C), 138.9 (C), 137.1 (C), 132.3 (C), 131.8 (C), 129.7 (CH), 129.5 (CH), 128.9 (CH), 128.2 (CH), 127.6 (CH), 126.2 (CH), 119.8 (CH), 115.6 (CH), 62.1 (CH_2), 55.1 (CH_3), 49.1 (C), 21.6 (CH_3), 21.0 (CH_3). IR: (neat) ν = 2980 (w), 1587 (m), 1346 (m), 1157 (s), 908 (m), 813 (m), 725 (s), 672 (s), 548 (s). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{24}H_{26}NO_3S_2$, 440.1357; found, 440.1346.

N-(2-(4-bromophenyl)-2-oxoethyl)-4-methyl-*N*-((2-methyl-4-(p-tolyl)-4,5-dihydrooxazol-4-yl)methyl)benzenesulfonamide (**11**).

Product isolated as Yellow oil (0.649 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, 2H, *J* = 8.6 Hz), 7.61 (d, 2H, *J* = 8.3 Hz), 7.57 (d, 2H, *J* = 8.4 Hz), 7.33 – 7.31 (m, 4H), 7.24 (d, 2H, *J* = 8.4 Hz), 4.98 (d, 1H, *J* = 8.7 Hz), 4.88 – 4.70 (m, 2H), 4.33 (d, 1H, *J* = 8.7 Hz), 3.83 (d, 1H, *J* = 14.8 Hz), 3.61 (d, 1H, *J* = 14.8 Hz), 2.40 (s, 3H), 1.86 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 192.7 (C), 166.3 (C), 144.1 (C), 143.6 (C), 136.5 (C), 134.0 (C), 132.1 (CH), 129.7 (CH), 129.34 (CH), 128.7 (CH), 128.7 (C), 127.6 (CH), 127.6 (CH), 125.8 (CH), 77.0 (C), 76.1 (CH_2), 56.5 (CH_2), 54.5 (CH_2), 21.6 (CH_3), 14.1 (CH_3). IR: (neat) ν = 2924 (w), 1672 (m), 1585 (m), 1334 (m), 1156 (s), 982 (s), 908 (s), 729 (s), 547 (s). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{26}N_2O_4S^{79}Br$, 541.0797; found, 541.0780.

N-((2-(5-bromopentyl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-23**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (1.088 g, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.23 (d, 2H, *J* = 8.0 Hz), 7.16 – 7.06 (m, 4H), 5.02 (dd, 1H, *J* = 9.3, 4.6 Hz), 4.72 (d, 1H, *J* = 8.5 Hz), 4.28 (d, 1H, *J* = 8.5 Hz), 3.41 (t, 2H, *J* = 6.7 Hz), 3.24 (dd, 1H, *J* = 12.6, 9.3 Hz),), 3.04 (dd, 1H, *J* = 12.6, 4.6 Hz), 2.39 (s, 3H), 2.31 (s, 3H), 1.94 – 1.83 (m, 2H), 1.78 – 1.62 (m, 2H), 1.52 (ddd, 2H, *J* = 10.2, 8.4, 4.8 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 169.8 (C), 143.5 (C), 140.8 (C), 137.4 (C), 136.8 C), 129.9 (CH), 129.4 (CH), 127.0 (CH), 125.4 (CH), 75.8 (CH_2), 75.0 (C), 51.7 (CH_2), 33.7 (CH_2), 32.3 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 25.3 (CH_2), 22.3 (CH_3), 21.0 (CH_3).); IR (neat) ν = 3089 (w), 2868 (w), 1651 (m), 1333 (s), 1160 (s), 1089 (s), 811 (s), 659 (m), 554 (s), 545 (s). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{30}{}^{79}BrN_2O_3S$, 493.1161; found, 493.1146.

N-((2-(6-bromohexyl)-4-(4-chlorophenyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-24**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (1.247 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, 2H, *J* = 8.2 Hz), 7.20 (m, 4H), 7.15 (d, 2H, *J* = 8.7 Hz), 5.44 (dd, 1H, *J* = 8.7, 5.0 Hz), 4.68 (d, 1H, *J* = 8.6 Hz), 4.20 (d, 1H, *J* = 8.6 Hz), 3.37 (t, 2H, *J* = 7.0 Hz), 3.21 (dd, 1H, *J* = 12.8, 8.7 Hz), 3.01 (dd, 1H, *J* = 12.8, 5.0 Hz), 2.37 (s, 3H), 2.35 – 2.24 (m, 2H), 1.83 (p, 2H, *J* = 7.0 Hz), 1.64 (p, 2H, *J* = 7.0 Hz), 1.52 – 1.28 (m, 4H).^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 170.2 (C), 143.5 (C), 142.3 (C), 137.2 (C), 133.4 (C), 130.0 (CH), 129.7 (CH), 126.9 (CH), 126.8 (CH), 75.5 (CH_2), 75.3 (C), 51.5 (CH_2), 33.9 (CH_2), 32.4 (CH_2), 28.2 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 25.8 (CH_2), 21.5 (CH_3). IR: (neat) ν = 2932 (w), 1658 (m), 1328 (m), 1157 (s), 1090 (s), 813 (s), 661 (s), 548 (s). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{29}{}^{79}Br^{35}ClN_2O_3S$, 527.0736; found, 527.0743.

N-((2-(7-bromoheptyl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-26**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (1.232 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, *J* = 8.1 Hz), 7.22 (d, 2H, *J* = 8.1 Hz), 7.15 – 7.05 (m, 4H), 5.26 (dd, 1H, *J* = 9.2, 4.6 Hz), 4.72 (d, 1H, *J* = 8.4 Hz), 4.27 (d, 1H, *J* = 8.4 Hz), 3.39 (t, 2H, *J* = 6.8 Hz), 3.25 (dd, 1H, *J* = 12.7, 9.2 Hz), 3.01 (dd, 1H, *J* = 12.7, 4.6 Hz), 2.43- 2.30 (m, 2H), 2.38 (s, 3H), 2.30 (s, 3H), 1.84 (p, *J* = 6.9 Hz, 2H), 1.71 – 1.62 (m, 2H), 1.49 – 1.28 (m, 6H).^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz): δ 170.1 (C), 143.4 (C), 140.9 (C), 137.3 (C), 136.8 (C), 129.7 (CH), 129.4 (CH), 126.9 (CH), 125.3 (CH), 75.7 (CH_2), 75.3 (C), 51.6 (CH_2), 34.0 (CH_2), 32.7 (CH_2), 29.0 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 28.0 (CH_2), 26.0 (CH_2), 21.5 (CH_3), 21.0 (CH_3). IR: (neat) ν = 1652 (m), 906 (s), 726 (s), 661 (m), 551 (m). HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{25}H_{34}{}^{79}BrN_2O_3S$, 521.1474; found, 521.1475.

N-((2-(10-bromodecyl)-4-(*p*-tolyl)-4,5-dihydrooxazol-4-yl)methyl)-4-methylbenzenesulfonamide (**4-27**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (1.331 g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, *J* = 8.0 Hz), 7.22 (d, 2H, *J* = 8.0 Hz), 7.13 (d, 2H, *J* = 8.3 Hz), 7.08 (d, *J* = 8.3 Hz, 2H), 5.34 (dd, 1H, *J* = 9.1, 4.6 Hz), 4.73 (d, 1H, *J* = 8.4 Hz), 4.27 (d, 1H, *J* = 8.4 Hz), 3.39 (t, 2H, *J* = 6.9 Hz), 3.25 (dd, 1H, *J* = 12.7, 9.1 Hz), 3.03 (dd, 1H, *J* = 12.7, 4.6 Hz), 2.38 (s, 3H),

2.30 (s, 3H), 1.84 (p, 2H, *J* = 6.9 Hz), 1.66 (t, 2H, *J* = 7.4 Hz), 1.47 – 1.21 (m, 14H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): *δ* 170.4 (C), 143.3 (C), 140.8 (C), 137.2 (C), 136.8 (C), 129.7 (CH), 129.3 (CH), 126.9 (CH), 125.3 (CH), 75.7 (CH_2), 75.2 (C), 51.5 (CH_2), 34.0 (CH_2), 32.7 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 28.1 (CH_2), 28.1 (CH_2), 26.1 (CH_2), 21.4 (CH_3), 21.0 (CH_3). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{40}{}^{79}BrN_2O_3S$, 563.1965; found, 563.1970.

1-(*p*-tolyl)-3-tosyl-10-oxa-3,12-diazabicyclo[7.2.1]dodec-9(12)-ene (**14-1**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as colourless oil (0.330 g, 40%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (d, 2H, *J* = 8.3 Hz), 7.29 – 7.22 (m, 4H), 7.18 – 7.14 (m, 2H), 5.20 (d, 1H, *J* = 8.5 Hz), 4.20 (d, 1H, *J* = 8.5 Hz), 3.81 (d, 1H, *J* = 14.0 Hz), 3.17 – 2.96 (m, 2H), 2.77 (d, 1H, *J* = 13.9 Hz), 2.57 – 2.48 (m, 1H), 2.38 (s, 3H), 2.33 (s, 3H), 2.15 (ddd, 1H, *J* = 14.6, 11.3, 3.8 Hz), 1.99 – 1.82 (m, 4H), 1.59 (ddq, 2H, *J* = 10.9, 8.0, 5.2 Hz). $^{13}C\{^1H\}$NMR ($CDCl_3$, 101 MHz): δ 170.1 (C), 143.4 (C), 140.9 (C), 137.1 (C), 134.6 (C), 129.7 (CH), 129.3 (CH), 127.4 (CH), 125.7 (CH), 76.8 (C), 74.5 (CH_2), 61.5 (CH_2), 49.8 (CH_2), 29.5 (CH_2), 27.2 (CH_2), 24.5 (CH2), 23.6 (CH_2), 21.4 (CH_3), 21.0 (CH3). IR: (neat) ν = 2923 (w), 1664 (m), 1334 (m), 1159 (s), 1014 (m), 908 (m), 815 (m), 728 (s), 712 (s), 646 (m), 547 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}N_2O_3S$, 413.1899; found, 413.1895.

1-(*p*-tolyl)-3-tosyl-11-oxa-3,13-diazabicyclo[8.2.1]tridec-10(13)-ene (**14-2**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as white solid (0.614 g, 72%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (d, 2H, *J* = 8.6 Hz), 7.33 (d, 2H, *J* = 8.2 Hz), 7.27 (d, 1H, *J* = 8.6 Hz), 7.17 (d, 2H, *J* = 8.2 Hz), 5.52 (d, 1H, *J* = 8.9 Hz), 4.28 (d, 1H, *J* = 8.9 Hz), 3.96 (d, 1H, *J* = 15.0 Hz), 3.32 – 3.21 (m, 1H), 2.84 (d, 1H, *J* = 15.0 Hz), 2.59 (dt, 1H, *J* = 13.2, 4.1 Hz), 2.51 – 2.42 (m, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.30 – 2.03 (m, 3H), 1.73 – 1.54 (m, 3H), 1.54 – 1.30 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 168.7 (C), 143.5 (C), 142.9 (C), 136.9 (C), 134.7 (C), 129.6 (CH), 129.2 (CH), 127.6 (CH), 125.7 (CH), 76.5 (C), 74.9 (CH_2), 61.7 (CH_2), 52.5 (CH_2), 27.7 (CH_2), 27.3 (CH_2), 26.4 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 21.4 (CH_3), 20.9 (CH_3). IR: (neat) ν = 2930 (w), 1661 (m), 1335 (m), 1160 (s), 984 (m), 816 (m), 697 (m), 548 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{31}N_2O_3S$, 427.2055; found, 427.2042.

1-(4-chlorophenyl)-3-tosyl-11-oxa-3,13-diazabicyclo[8.2.1]tridec-10(13)-ene (**14-3**).

Product isolated by cryatallization (DCM) as white solid (0.625 g, 70%). m.p. = 143-145 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, 1H, *J* = 8.0 Hz), 7.27 (d, 1H, *J* = 8.6 Hz), 7.23 – 7.16 (m, 4H), 5.42 (d, 1H, *J* = 9.0 Hz), 4.13 (d, 1H, *J* = 9.0 Hz), 3.81 (d, 1H, *J* = 15.0 Hz), 3.16 (ddd, 1H, *J* = 13.2, 11.0, 3.5 Hz), 2.71 (d, 1H, *J* = 15.0 Hz), 2.46 (dt, 1H, *J* = 13.2, 4.0 Hz), 2.42 – 2.33 (m, 1H), 2.30 (s, 3H), 2.17 – 1.94 (m, 3H), 1.68 – 1.16 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): δ 169.3 (C), 144.4 (C), 143.7 (C), 134.7 (C), 133.1 (C), 129.8 (CH), 128.7 (CH), 127.7 (CH), 127.5 (CH), 76.5 (C), 74.8 (CH_2), 61.5 (CH_2), 52.6 (CH2), 27.8 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 22.6 (CH_2), 22.2 (CH_2), 21.5 (CH_3). IR: (neat) ν = 2937 (w), 1661 (m), 1332 (m), 1155 (s), 1086 (m), 999 (m), 952 (m), 816 (s), 700 (m), 648 (m), 579 (s), 563 (s), 545 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{28}N_2O_3S^{35}Cl$, 447.1509; found, 447.1508.

1-(*p*-tolyl)-3-tosyl-15-oxa-3,17-diazabicyclo[12.2.1]heptadec-14(17)-ene (**14-4**).

Product isolated via column chromatography (eluent Hexane : EtOAc = 7:3 v/v) as white solid (0.616 g, 70%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, 2H, *J* = 8.3 Hz), 7.27 (d, 2H, *J* = 8.3 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 5.07 (d, 1H, *J* = 8.8 Hz), 4.38 (d, 1H, *J* = 8.8 Hz), 3.81 (d, 1H, *J* = 14.8 Hz), 3.13 (ddd, 1H, *J* = 13.7, 8.3, 5.3 Hz), 3.01 – 2.86 (m, 2H), 2.39 (m, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.10 (dtt, 1H, *J* = 15.9, 7.7, 3.3 Hz), 1.83 (ddt, 2H, *J* = 16.7, 8.7, 4.4 Hz), 1.70 (ddt, 1H, *J* = 10.6, 8.7, 3.3 Hz), 1.66 – 1.45 (m, 4H), 1.20 (dtd, 2H, *J* = 16.7, 7.7, 4.4 Hz). $^{13}C\{^1H\}$ NMR (CD_3OD , 101 MHz): δ 171.4 (C), 145.2 (C), 143.3 (C), 138.3 (C), 135.2 (C), 130.8 (CH), 130.3 (CH), 128.7 (CH), 126.5 (CH), 77.7 (C), 76.9 (CH_2), 60.6 (CH_2), 51.4 (CH_2), 28.6 (CH2), 28.3 (CH_2), 28.2 (CH_2), 25.4 (CH_2), 23.4 (CH2), 22.4 (CH2), 21.5 (CH3), 21.1 (CH_3). IR: (neat) ν = 2931 (w), 1662 (m), 1334 (m), 1159 (s), 1088 (m), 815 (m), 730 (s), 696 (s), 547 (s). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_3S$, 441.2212; found, 441.2208.

1-(*p*-tolyl)-3-tosyl-15-oxa-3,17-diazabicyclo[12.2.1]heptadec-14(17)-ene (**14-5**).

Product isolated via column chromatography (eluent Hexane:EtOAc = 7:3 v/v) as Pale yellow oil (0.318 g, 33%). ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.59 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 4.99 (d, *J* = 8.3 Hz, 1H), 4.34 (d, *J* = 8.3 Hz, 1H), 3.78 (d, *J* = 14.7 Hz, 1H), 3.21 (dd, *J* = 14.7, 10.2 Hz, 1H), 3.10 (m, 2H), 2.39 (s, 3H), 2.33 (s, 3H), 1.77 – 1.63 (m, 3H), 1.43 – 1.11 (m, 15H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 101 MHz): *δ* 143.4 (C), 142.3 (C), 137.1 (C), 136.1 (C), 136.0 (C), 129.7 (CH), 129.2 (CH), 127.3 (CH), 125.8 (CH), 77.0 (C), 75.4 (CH_2), 58.1 (CH_2), 51.3 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.2 (CH2), 28.7 (CH_2), 28.4 (CH_2), 27.4 (CH_2), 25.8 (CH_2), 21.5 (CH_3), 21.0 (CH_3). IR: (neat) ν = 2924 (w), 1662 (w), 1334 (m), 1160 (m), 907 (s), 729 (s), 649 (m), 549 (m). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{39}N_2O_3S$, 483.2681; found, 483.2684.

ASOCIATED CONTENT

Supporting information

Supporting information is available free of charge at ….

Supporting information contains: ^1H, ^{13}C, correlation spectroscopy (COSY) NMR spectra and Crystallographic data for compounds **4-1, 4-9, 4-13, 4-20, 4-21, 4-23, 5, 7, 9, 14-2, 14-3 and 14-4.**.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

Funding Sources

We would like to thank AbbVie Inc. for funding (MR).

ACKNOWLEDGMENT

We also thank Dr Andrej Batsanov and Dr Dmitry S. Yufit of Durham University for solving the X-ray structures of compounds: **4-1**, **4-9**, **4-13**, **4-20**, **4-21**, **4-23**, **5**, **7**, **9**, **14-2**, **14-3** and **14-4**.

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