ARTICLE

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A phase-switch purification approach for the expedient removal of tagged reagents and scavengers following their application in organic synthesis

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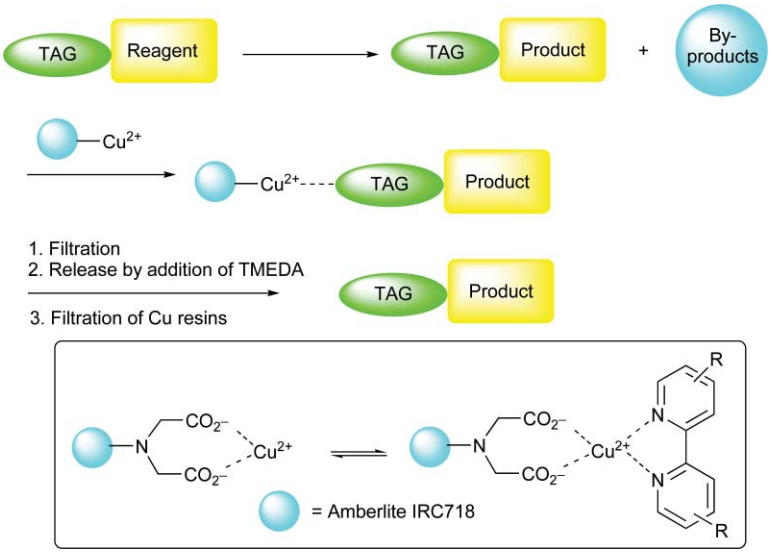
In this paper we wish to report on a variety of expedient chemical transformations and purifications achieved *via* a generic 'catch and release' methodology, based on a synthetically inert bipyridyl chelating tag that can be selectively captured with a resin-bound copper(II) species. Utilising this approach we are able to derive many of the same benefits associated with both solid phase synthesis and supported reagent methods.

Introduction

The most significant productivity-limiting issue continually encountered by modern synthetic chemistry is one of product purification and isolation. This is of particular importance in combinatorial chemistry with the ever-increasing availability of automated high-throughput synthesis techniques which enable the rapid preparation and diversification of key intermediates through powerful parallel processing capabilities. As a result many of the existing methods based on conventional chromatographic separation are simply unable to match the unprecedented synthetic output emanating from current medicinal discovery programmes, thus creating an unacceptable bottleneck. Consequently, the necessity for new purification strategies[1] is of paramount interest not only for the continued development of this area but also as a key commercial driver in future chemical processes.

A technology which has impacted significantly on the viability of preparing both large compound arrays and also more focused target synthesis is the application of supported reagents and scavengers.[1] Encompassed within this method the technique commonly known as the 'catch and release' principle has found extensive utility as a very powerful purification protocol.[2] The process involves the selective binding of a specific component from the reaction mixture onto a solid matrix followed by a washing sequence to elute the impurities. The desired material is then displaced from the resin in a purified state and isolated by simple evaporation of the solvents. We have previously demonstrated[3] an extension to this concept using a phase-switch[4] approach for the purification of key intermediates in multi-step synthetic transformations. Our premise was that a phase-separation could well be achieved by a reversible and selective interaction between a metal ion immobilised on a solid support and an organic metal-chelating "tag" linked to the molecule of interest (Scheme 1).[3]

As well as a versatile handle for the manipulation and temporary immobilisation of a substrate for purification, we felt that the same principle could be developed further for the generation of a novel set of soluble reagents and scavengers that may also find application in flow processes. We believed that due to the selective and tunable nature of the metal–tag interaction we could produce a complementary reagent and scavenger tool box that could offer synthetic opportunities which are not possible with existing immobilised systems. Herein we wish to report in full on the synthesis and application of these systems for the rapid preparation and purification of small molecule arrays.



Scheme 1 'Catch and release' protocol in application to tagged reagent methodology.

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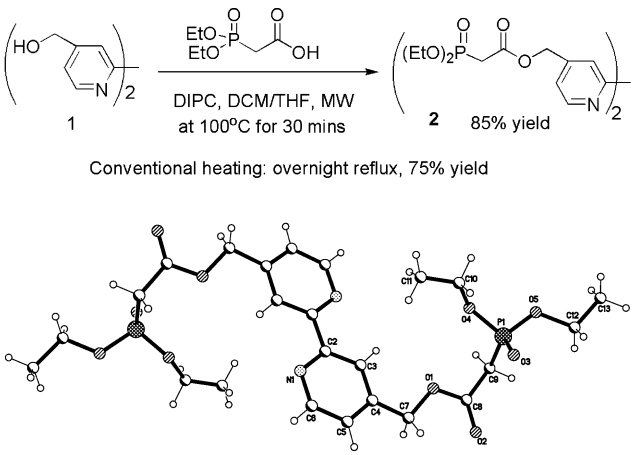
A previous investigation into suitable binding partners[3] determined a preferred system comprising an IRC-718 resin possessing iminodiacetic acid appendages which showed an optimal loading for copper(II) ions. Additionally, a functionalisable tag based on a substituted 2,2′-bipyridine scaffold showed ideal properties due to it being moderately chemically inert coupled with a high affinity for coordination to the bound copper(II) ions.[5] This was therefore the system that was adopted for use throughout the following chemistries.

Our initial target was the preparation of a Horner–Emmons equivalent, specifically chosen because of the extensive precedent of solid-phase syntheses that have been explored.[6] However, unlike the existing solid-phase work, because of the solution-phase nature of our reagent we envisaged a more efficient optimisation process.[7] As in our previous publication,[3] 4,4′-*bis*(hydroxymethyl)-2,2′-bipyridine **1**[8] was used as a suitable starting material: the hydroxyl groups of this molecule constitute a linker component, which can be easily decorated with various reagent or scavenger functionalities (Scheme 2).

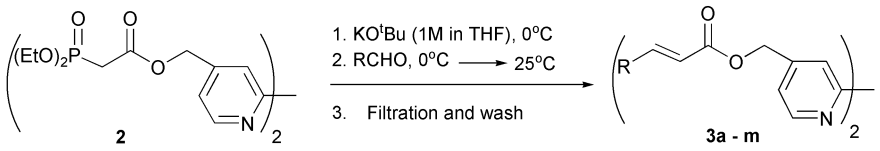
Acylation of the bipyridine diol **1** with diethyl phosphonoacetic acid using 1,3-diisopropylcarbodiimide (DIPC) at 100 °C under microwave irradiation gave the corresponding *bis*-phosphonate reagent **2** (Horner–Emmons Reagent) in 85% isolated yield. The structure was later confirmed by X-ray crystallography (Scheme 2).[9]



Scheme 2 Preparation of the bipyridine-supported reagent **2**.

The Horner–Emmons reaction was screened with a range of 31 different aldehydes using either sodium hydride or potassium *tert*-butoxide as the base to generate the phosphonium anion: in all cases, the resulting "tagged" α,β-unsaturated esters were obtained in quantitative conversion and were exclusively of the *trans* geometry (Table 1 and Table 2). Certain substrates

Table 1 Purification of Horner–Emmons products by precipitation



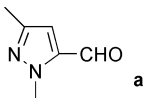
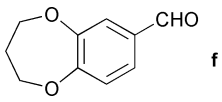
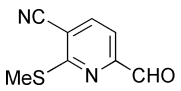
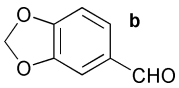
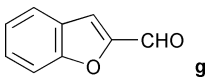
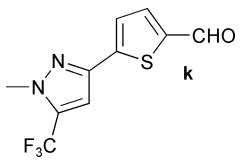
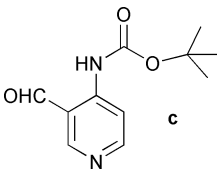
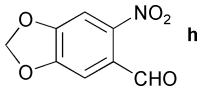
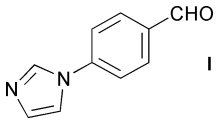
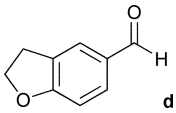
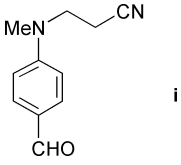
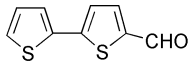
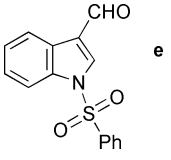
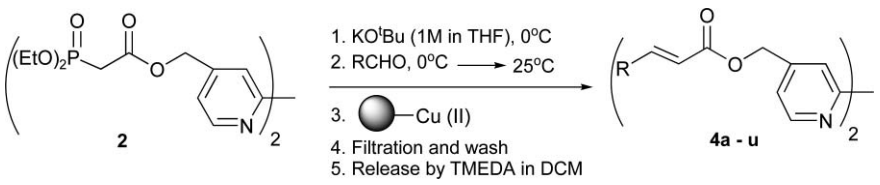
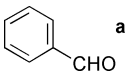
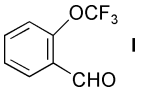
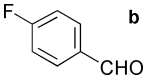
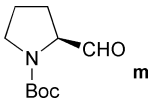
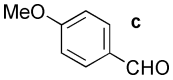
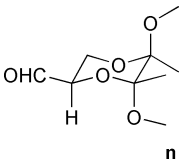
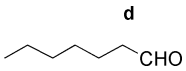
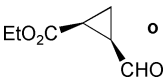
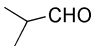
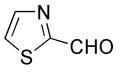
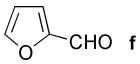
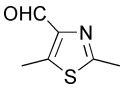
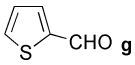
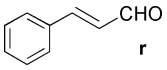
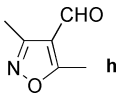
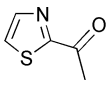
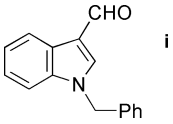
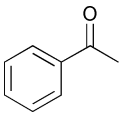
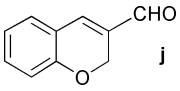
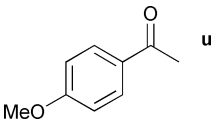
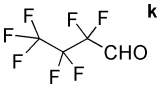
Entry	Substrate	Isolated yield of product **3**	Entry	Substrate	Isolated yield of product **3**	Entry	Substrate	Isolated yield of product **3**
1	 **a**	95%	**6**	 **f**	90%	**10**	 **j**	72%
2	 **b**	92%	**7**	 **g**	85%	**11**	 **k**	74%
3	 **c**	85%	**8**	 **h**	95%	**12**	 **l**	87%
4	 **d**	90%	**9**	 **i**	85%	**13**	 **m**	92%
5	 **e**	80%						

Table 2 "Catch-and-release" Horner–Emmons reaction



Entry	Substrate	Isolated yield of product **4**	Quantity of resin[a]	Entry	Substrate	Isolated yield of product **4**	Quantity of resin[a]
1	 **a**	98%	0.7	**12**	 **l**	83%	1.8
2	 **b**	92%	1.2	**13**	 **m**	75%	0.6
3	 **c**	90%	0.8	**14**	 **n**	95%	1.2
4	 **d**	85%	2.5	**15**	 **o**	82%	0.5
5	 **e**	82%	1.6	**16**	 **p**	85%	0.7
6	 **f**	83%	0.6	**17**	 **q**	70%	0.9
7	 **g**	70%	0.6	**18**	 **r**	74%	1.0
8	 **h**	92%	0.7	**19**	 **s**	95% (mixed isomers = 3 : 2)	0.8
9	 **i**	65%	2.1	**20**	 **t**	75% (mixed isomers = 2 : 1)	1.4
10	 **j**	80%	2.6	**21**	 **u**	73% (mixed isomers = 2 : 1)	1.2
11	 **k**	82%	2.0				

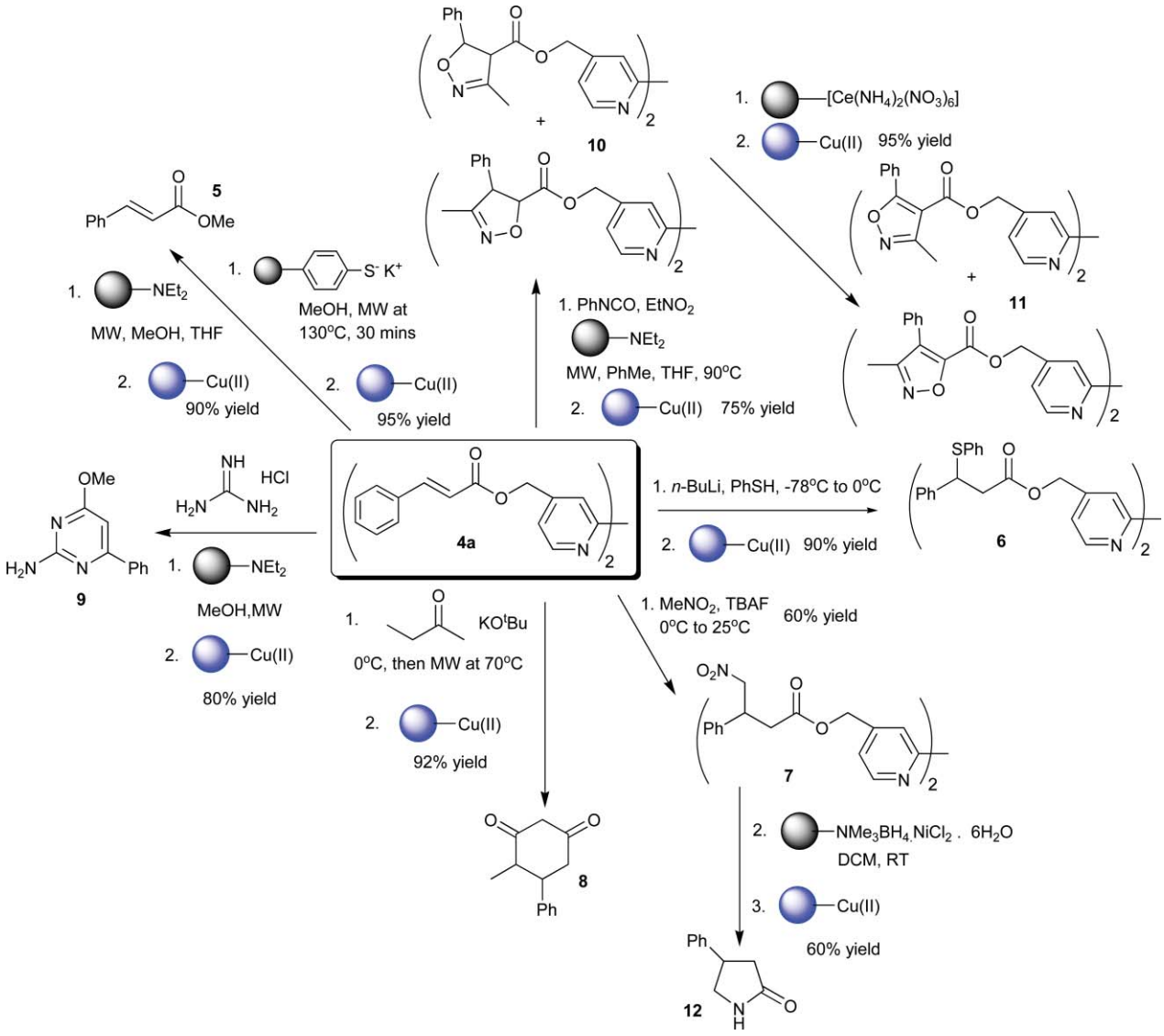
[a] Gram of resin required per mmol of substrate.

gave the corresponding products as precipitates **3a–m** which required only simple filtration to facilitate purification and isolation (Table 1). However, many of the systems produced soluble products which required purification by our sequestration methodology (Scheme 1). For these materials the *bis*-Horner–Emmons adducts **4a–u** (Table 2) were captured by the addition of the copper(II)-impregnated IRC-718 resin, which was washed extensively with DCM to remove any phosphate by-products and unreacted aldehydes. The purified diester was then released from the polymeric beads by the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (bp 120–122 °C) – a competitive ligand with a superior binding affinity – and the suspension shaken overnight. Filtration of the resin and concentration of the filtrate afforded the Horner–Emmons products (Table 2) in high yield and >95% purity, as established by ^{1}H NMR spectroscopy. In addition to the reaction with

aldehydes, a small test was conducted on three ketones (Entries 19–21; Table 2) however these substrates, although again showing quantitative conversion of the tagged phosphonate, gave very low levels of selectivity in the formation of the double bond geometry, so no further effort was made to extend the investigation. It should be noted that in all these examples, both the uptake and release of the bipyridine-tethered Horner–Emmons adducts could be easily monitored by thin-layer chromatography and LC-MS.

In addition to the generation of α,β-unsaturated esters, we wished to explore the potential for the rapid diversification of these intermediates using the 'catch and release' methodology to generate a small compound set (Scheme 3). Compound **4a** was chosen as the starting point because of its simple structure and easy availability. We were thus able to rapidly conduct a number of transformations including transesterification **5**, 1,4-addition of thiophenol **6** and nitromethane **7**, a tandem Michael addition and Claisen condensation **8**; heterocyclic formation with concomitant release **9**; [3 + 2] cycloaddition **10** followed by aromatisation **11** and γ-lactam formation **12**. Although this type of chemical processing was effective and required only minimal optimisation (compared to the analogous solid-phase approach), therefore justifying a short investigation to demonstrate the proof of concept, we felt the true benefits of this tagged phase-switch approach would reside in its use as a sequesterable reagent and scavenging tool.

One of the most commonly encountered chemical transformations involving the application of scavengers is in the clean up of condensation reactions when preparing amide or sulfonamide bonds. Two alternative routes are available: 1) the direct addition of an amine to an acid halide, or 2) through the *in situ* activation of an acid using an activator such as EDC or DCC. We decided to investigate both of these methods by applying the method independently to each process. In the case of the first approach, an acid-functionalised resin such as Amberlyst 15 or a related sulfonic acid is normally used to remove excess amine components.[10] Alternatively, a nucleophilic scavenger such as the polymer-supported trisamine or aminomethylpolystyrene is employed to facilitate removal of acidic impurities or excess acid halide.[11] However, in order to attain pure material it is often necessary to combine both of these routines or subject the reaction mixture to further modification with an additive which alters one of the undesired components by inverting its electronic nature before carrying out a single generic scavenging sequence.[12] Another tactic already alluded to is the "catch-and-release" purification, however, here again problems can be encountered if the molecule of interest does not have functionalities that are distinguishable from the other unwanted components. Many of these difficulties can be overcome with the suitable selection of scavenging agent and careful control of the reaction conditions, but one significant factor remains, which is the heterogeneous nature of



Scheme 3 Compound generation based on bipyridine-supported α,β-unsaturated ester scaffold.

the sequestering reagent. This can often result in extremely slow uptake of the impurities (or intermediate in the case of the "catch-and-release" process) or the incomplete removal of the desired material without resorting to the use of very large excesses of the solid support. Our approach uses a relatively small molecular weight compound (equal to >9 mmol g^{-1} functionality) which is highly soluble, easily monitored and gives excellent reaction kinetics. In this way only a modest excess (1.1 equiv.) of the tagged scavenger is required, and in addition the scavenged components are captured and purified in the process, therefore allowing easy retrieval and recycling, an important consideration when using expensive commercial or late-stage proprietary molecules. Furthermore, a simple LC-MS or TLC quickly identifies the relative proportion of functionality that has been used (or remains available), and so makes subsequent calculations based on the required amount of a scavenger involving reaction mixtures with initial unknown quantities of impurities a trivial process.

Following a simple protocol, we could carry out a standard solution-phase reaction then quench the mixture by the addition of the tagged scavenger, which rapidly reacts with the excess reagent. Subjecting the mixture to gentle shaking in the presence of the copper(II)-loaded resin then facilitates removal of the captured reagent and any residual scavenger, allowing for a direct filtration of the suspension and evaporation of the solvent to yield the purified material (Fig. 1).

To validate this protocol we used the readily available bipyridine diol **1**[8] as a suitable scavenger for a selection of acid chlorides (Table 3). In order to evaluate the selective nature of the copper(II) sequestering process we specifically chose the coupling partners in the array to resemble common medicinal chemistry fragments possessing multiple basic sites that could in principle

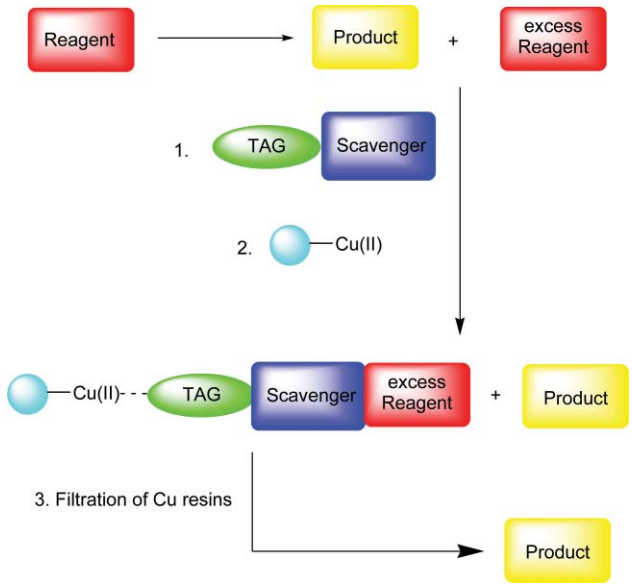
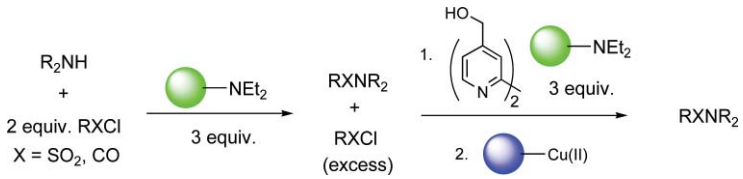


Fig. 1 Phase-transfer scavenger sequence.

Table 3 Results of 'catch and release' scavenging experiments using bipyridyl diol as a scavenger



Isolated yields

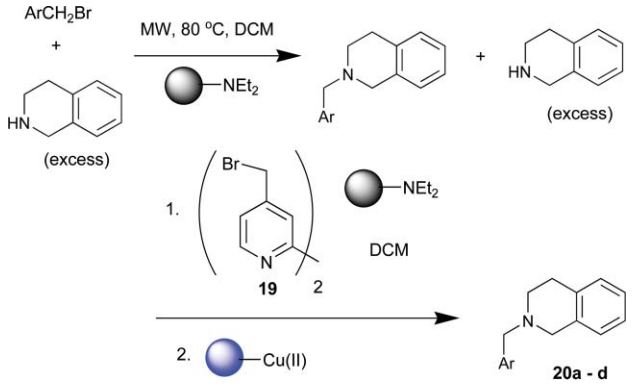
	31a 94%	**31b** 96%	**31c** 98%	**31d** 89%	**31e** 99%	**31f** 90%	**31g** 92%
	14a 98%	**14b** 99%	**14c** 95%	**14d** 95%	**14e** 96%	**14f** 97%	**14g** 96%
	15a 97%	**15b** 91%	**15c** 93%	**15d** 93%	**15e** 95%	**15f** 95%	**15g** 96%
	16a 89%	**16b** 96%	**16c** 99%	**16d** 95%	**16e** 97%	**16f** 96%	**16g** 96%
	17a 92%	**17b** 95%	**17c** 96%	**17d** 93%	**17e** 88%	**17f** 90%	**17g** 97%
	18a 93%	**18b** 97%	**18c** 93%	**18d** 92%	**18e** 93%	**18f** 945	**18g** 95%

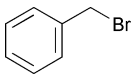
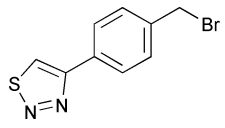
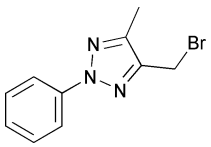
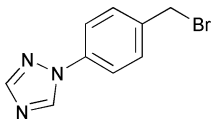
Purities > 95% by LCMS and ^{1}H NMR

act as competitive binders to the immobilised copper(II) species. As can be seen from the isolated yields and purity, the selectivity of the process was extremely good, and no copper contamination of the reaction solutions was observed at either stage of the process (capture or release), even in the presence of an excess of the products, or TMEDA over prolonged reaction times <16 h.[13] In a further extension of this work we also prepared the corresponding dibromo derivative **19**, which also proved a very effective scavenger for the removal of the secondary amine; tetrahydroisoquinoline in various benzylation reactions following the same principles (Table 4).

Returning to our original coupling concept, we decided to pursue the second amide-forming route by designing a bipyridine-based carbodiimide equivalent. The use of reagents such as DCC and DIC in traditional peptide synthesis is now standard practice and well documented in the literature. However, one major drawback is always the removal of the urea by-product generated during the reaction. This has been partially overcome by the development of reagents such as EDCI that have basic sites which can be scavenged by ion exchange resins or acidic aqueous work-up. Although this method works well for simple compounds, it fails when one of the coupling fragments contains additional basic functionality, as in most pharmaceutical substances. However, this problem is easily overcome by using a bipyridine-modified carbodiimide, with the removal of this species being entirely reliant on the binding coefficient of the bipyridine to the immobilised metal.

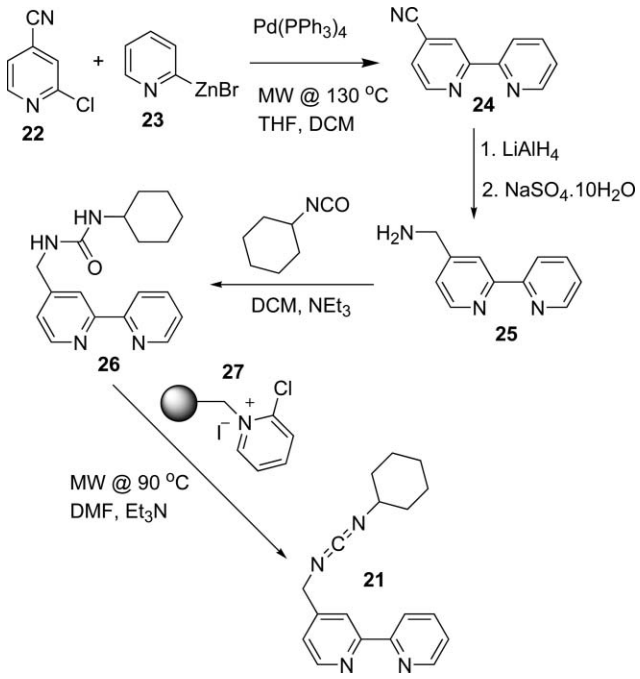
Table 4 Scavenging using bipyridyl dibromide



	Substrate	Yield[a]	Resin quantity[b]
a		92%	1.5
b		92%	2.0
c		93%	2.6
d		90%	2.3

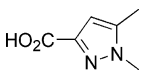
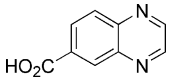
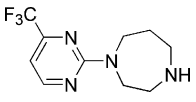
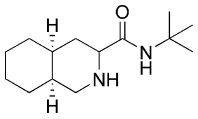
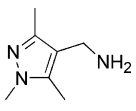
[a] Purities >90% by LC-MS and ^{1}H NMR. [b] Amount of copper(II) resin required for "catching" (g mmol^{-1}).

Because of the perceived insolubility of a symmetrical 4,4′-bifunctionalised carbodiimide reagent (especially the resultant urea) we opted to prepare the monosubstituted system **21** (Scheme 4). Hence a palladium-catalysed coupling of the α-chloropyridine **22** and the organozinc reagent **23** under microwave irradiation gave the functionalised bipyridine **24** in excellent yield. Reduction and addition of the resultant amine **25** to cyclohexylisocyanate furnished the urea **26** which was successfully dehydrated using the polymer-supported Mukaiyama reagent **27**. With the DCC equivalent **21** in hand, we coupled a small demonstration set of heterocyclic acids and amines (Table 5). The results were very encouraging, with conversion to the corresponding amides being almost quantitative, as determined by LC-MS. Likewise, extraction of the urea by-product **26** from the reaction mixture through selective sequestration with the immobilised copper(II) resin proceeded efficiently, enabling high yields of the amide products to be isolated without the need for chromatographic purification. It should be noted that during the course of this research a publication by Tye *et al.* reported



Scheme 4 Preparation of the DCC-supported reagent **21**.

Table 5 Synthesis of amides using DCC-supported reagent **21**

Isolated yields[a]		
	**28a** 87%	**28d** 83%
	**28b** 91%	**28e** 89%
	**28c** 90%	**28f** 85%

[a] Purities >95% by LCMS and ^{1}H NMR.

on a similar reagent system for amide coupling reactions, also displaying a high degree of scavenging selectivity and great utility for high-throughput synthesis.[14]

Conclusion

In conclusion, we have developed a range of chemistries allowing rapid and efficient purification of a diverse set of compounds based on the ability to selectively sequester a chemically benign bipyridyl scaffold tag. This universal tag offers a very versatile handle for the development of many more reagents and scavengers. Many additional ligand templates and metal combinations can be envisaged, as well as additional applications in the areas of synthetic chemistry, chemical recycling and water purification.

Experimental

General

Melting points were determined on a Reichert hot-stage apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded either on a Brüker DRX-600, DRX-500 or on a DPX-400 instrument with $CHCl_3$ (δ = 7.26) and $CDCl_3$ (δ = 77.0) as internal reference signals. Signals were assigned by means of DEPT and 2D spectra (COSY, HMQC, HMBC). IR spectra were recorded on a Perkin–Elmer 'Spectrum-One' spectrometer equipped with an Attenuated Total Reflectance (ATR) sampling accessory. Mass spectra and accurate mass data were recorded on a Micromass Platform LC-MS, Kratos MS890MS, Kratos Concept IH, Micromass Q-TOF or a Bruker BIOAPEX 4.7 FTICR spectrometer using electrospray (ESI) or electron impact (EI) techniques (the matrix was *m*-nitrobenzyl alcohol (NOBA)) at the Department of Chemistry, University of Cambridge: relative abundances and assignments are given in parentheses. LC-MS was performed on a Hewlett Packard HPLC 1100 chromatograph (Mercury hexylphenyl column) attached to a HP LC/MSD platform LC APCI mass spectrometer. Elution was carried out using a reverse phase gradient (flow rate 1 mL min^{-1}, 3 min, 5% MeCN, 3–5 min linear gradient to 95% MeCN, 5–6 min back to 5% MeCN, hold 5% MeCN 2 min) using acetonitrile–water both containing 0.1% TFA. Reactions were monitored by TLC on precoated glass-backed plates (Merck Kieselgel 60 F254) and visualised by UV. Optical rotations were measured on a Perkin–Elmer Model 343 polarimeter, and $[a]_D$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentration (*c*) is in g per 100 cm^3. Microanalyses were determined in the microanalytical laboratories at the Department of Chemistry, University of Cambridge using a CE-440 Elemental Analyser.

Preparation of Amberlite IRC-718 Cu(II) resin

Amberlite IRC-718 resin (iminodiacetic acid resin, as supplied by Aldrich) (50 g) was suspended in H_2O (150 cm^3), and shaken for 30 min. It was filtered and washed with H_2O (500 cm^3). The resin was then resuspended in a saturated solution of copper(II) sulfate (250 cm^3) and shaken for 5 h. The resin was then filtered, resuspended again in a saturated solution of copper(II) (250 cm^3) sulfate and shaken overnight. The resin was filtered, and washed with H_2O (500 cm^3), DCM (500 cm^3) and THF (500 cm^3). The resulting blue resin was dried under high vacuum.

General procedure for Horner–Emmons reactions

Potassium *tert*-butoxide (1 M in THF; 480 μL, 0.48 mmol, 1.2 equiv.) was added to a solution of bipyridine-supported phosphonate **2** (114 mg, 0.2 mmol) in THF (2.5 cm^3) at 0 °C, and allowed to stir for 15 min. The specified aldehyde (0.44 mmol, 2.2 equiv.) in THF (2 cm^3) was added to the reaction mixture, and the solution allowed to warm slowly to ambient temperature and stir overnight.

Work-up procedure A – the "catch-and-release" method for purification of soluble products. The reaction mixture was diluted with DCM (8 cm^3), and then IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}; quantities as specified in Table 2) was added and the reaction mixture was gently shaken using a vortexing shaker. The "catching" process was monitored by both TLC and LC-MS (samples were typically left for 6–12 h). The suspended resin was filtered and washed with DCM (5 cm^3 × 3). The resin was then re-suspended in DCM (10 cm^3) and TMEDA (2.5 equiv. based on the resin), and the release of the product back into solution monitored by TLC and LC-MS. The resin was then filtered, washed (5 cm^3 × 3), and the filtrate evaporated to dryness under high vacuum. The crude mixture was loaded onto a Bond Elut reservoir[15] (22 mm in diameter, 1 g silica) and eluted with Et_2O–NEt_3 (1 : 0.1; 10 cm^3 × 3). The combined filtrates were concentrated under reduced pressure to yield the corresponding Horner–Emmons products.

Work-up procedure B – direct filtration of the precipitated products. The precipitated bipyridine product was filtered and washed with diethyl ether (10 cm^3), and the isolated solid dried under high vacuum.

4-Phenylazobenzoic acid 4′-(4-phenylazobenzoic acid)-[2,2′]-bipyridinyl-4-ylmethyl ester. Deep orange solid, 82% yield, LC retention time = 0.45 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 72.25; H, 4.49; N, 13.29, $C_{38}H_{28}N_6O_4$ requires C, 72.14; H, 4.46; N, 13.28%); ν_{max}(neat)/cm^{-1} 1714, 1656, 1599, 1445, 1364, 1269, 1133, 994, 708, 685; δ_H(400 MHz; acetone-d_6–$CDCl_3$) 8.70 (2H, d, *J* 5 Hz, bipy H-6), 8.38 (2H, s, bipy H-3), 8.22 (4H, dd, *J* 7.8 Hz, Ph AA′BB′), 7.93 (4H, dd, *J* 7.8 Hz, Ph AA′BB′), 7.85 (4H, m, Ph–H), 7.55 (6H, m, Ph–H), 7.33 (2H, d, *J* 5 Hz, bipy H-5), 5.45 (bipy CH_2); δ_C(100 MHz; $CDCl_3$) 167.8 (C=O), 156.8 (Ph C-4′), 156.6 (bipy C-2), 154.7 (Ph C-4), 149.9 (bipy C-6), 147.5 (bipy C-4), 133.2 (Ph C-1′), 131.7 (Ph C-1), 131.5 (Ph C-2′, Ph C-6′), 128.9 (Ph C-2, Ph C-6), 124.2 (bipy C-3), 122.8, 122.6 (Ph C-3, Ph C-5), 120.1 (bipy C-5), 64.8 (bipy CH_2); *m/z* (ESI+) 633.24095 (M + H, $C_{38}H_{29}N_6O_4$ requires 633.22503); 655.2 (28%) (M + Na).

Synthesis of 4-phenylazobenzoic acid 2-nitrobenzyl ester. Deep orange solid, 78% yield, LC retention time = 0.45 (DCM–Et_2O = 1 : 1); (Found: C, 66.54; H, 4.56; N, 11.76, $C_{20}H_{15}N_3O_4$ requires C, 66.48; H, 4.18; N, 11.63%); ν_{max}(neat)/cm^{-1} 1712, 1667, 1526, 1429, 1399, 1165, 994, 839, 728; δ_H(400 MHz; $CDCl_3$) 8.17 (2H, d, *J* 8 Hz, Ph–H), 8.12 (1H, s, Ph–H), 8.07 (2H, d, *J* 8 Hz, Ph–H), 7.99–7.45 (8H, m, Ph–H), 5.54 (benzyl CH_2); δ_C(100 MHz; $CDCl_3$) 168.3 (C=O), 156.9 (Ph C-4′), 153.6 (Ph C-4), 146.3 (benzyl C-2), 136.2 (benzyl C-1), 135.3 (benzyl C-5), 134.5 (Ph C-1′), 131.2 (Ph C-4), 129.7 (Ph C-3, Ph C-5), 128.3 (benzyl C-6), 124.2 (benzyl C-3), 129.5 benzyl (C-4), 122.6 (Ph C-3′, Ph C-5′), 130.2 (Ph C-2′, Ph C-6′), 123.5 (Ph C-2, Ph C-6), 64.9 (Ph CH_2); *m/z* (EI+) 361.10757 (M$^+$, $C_{20}H_{15}N_3O_4$ requires 361.10626); 361.1 (32%) (M$^+$).

Microwave-assisted synthesis of (diethoxyphosphoryl)acetic acid 4′-[(diethoxyphosphoryl)acetoxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (bipyridine-supported phosphonate) 2. To a solution of diethylphosphonoacetic acid (763 mg, 3.89 mmol, 2.8 equiv.) in DCM (2 cm^3) and bipyridine diol (300 mg, 1.989 mmol, 1 equiv.) dissolved in THF (1 cm^3) was added diisopropylcarbodiimide (DIPC) (732 mg, 5.80 mmol, 5 equiv.). The mixture was heated in an Emrys Liberator[16] at 100 °C for 20 min. The reaction mixture was poured into DCM–light petroleum (1 : 1) (30 cm^3), and the insoluble by-product removed by filtration. The crude product was purified by flash column chromatography with DCM, then Et_2O–DCM (1 : 1), and finally Et_2O–DCM–NEt_3 (1 : 1 : 0.1). Recrystallisation from DCM–light petroleum gave the desired phosphonate product as an off-white solid, 85% yield, LC retention time = 0.23 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.1); mp 134 °C (lit. mp 134–137.5 °C); (Found: C, 50.21; H, 5.85; N, 4.77, P, 10.64. $C_{24}H_{34}N_2O_{10}P_2$

requires C, 50.35; H, 5.99; N, 4.89; P, 10.83%); ν_{max}(neat)/cm^{-1} 1734, 1598, 1557, 1232, 1016, 962, 828, 799; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.35 (2H, s, bipy H-3), 7.42 (2H, d, *J* 5Hz, bipy H-5), 5.32 (4H, s, bipy CH_2), 4.13 (8H, q, *J* 5 Hz, OCH_2CH_3), 3.12 (4H, d, *J* 26 Hz, $COCH_2P$), 1.32 (12H, t, *J* 5 Hz, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 165.3 (C=O), 155.8 (bipy C-6), 152.3 (bipy C-2), 145.3 (bipy C-4), 121.9 (bipy C-5), 119.2 (bipy C-3), 65.2 (bipy CH_2), 62.6 (OCH_2CH_3), 33.7 ($COCH_2P$ *J* 138 Hz), 16.2 (OCH_2CH_3); *m/z* (ESI+) 595.1584 (M + Na, $C_{24}H_{34}N_2O_{10}P_2Na$ requires 595.1586); 595.16 (100%) (M + Na), 573.18 (100%) (M + H), 353.1 (50%), 295.2 (70%). X-Ray crystallographic structure determination of **2**: Crystal data: $C_{24}H_{34}N_2O_{10}P_2$ MW = 572.47, colourless prism 0.37 × 0.32 × 0.18 mm, triclinic $P\bar{1}$ (No. 2), a = 6.9456(5), b = 8.5692(5), c = 12.8364(8) Å, α = 95.764(4), β = 92.302(3), γ = 113.556(3)°, V = 694.09(8) Å^3, T = 230(2) K, D_X = 1.370 g cm^{-3}, λ = 0.71073 Å, μ = 0.213 mm^{-1}, Nonius Kappa CCD diffractometer, 3.57 < θ < 27.54°, 6154 measured reflections, 3139 independent, 2671 with $I > 4\sigma(I)$. The structure was solved by direct methods (SHELXS-97)[9a] and refined by least squares (SHELXL-97)[9b] using Chebyshev weights on F_o^2 to R_1 = 0.058, wR_2 = 0.141 [$I > 2\sigma(I)$], 174 parameters: all H atoms in calculated positions. Goodness-of-fit on F^2 1.079, residual electron density 0.71 e Å^{-3}. CCDC reference number 242163. See http://dx.doi.org/10.1039/b503778f for crystallographic data in CIF or other electronic format.

(*E*)-3-(2,5-Dimethyl-1*H*-pyrazol-3-yl)acrylic acid 4′-[(*E*)-3-(2,5-dimethyl-1*H*-pyrazol-3-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3a). Light yellow solid, 95% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 65.73; H, 5.69; N, 16.57, $C_{28}H_{28}N_6O_4$ requires C, 65.61; H, 5.51; N, 16.40%); ν_{max}(neat)/cm^{-1} 1704, 1602, 1446, 1356, 1254, 1239, 1048, 961, 832, 807; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.79 (2H, d, *J* 5 Hz, bipy H-6), 8.43 (2H, s, bipy H-3), 7.69 (2H, d, *J* 5 Hz, bipy H-5), 7.49 (2H, d, *J* 15 Hz, H-3), 6.51 (2H, d, *J* 15 Hz, H-2), 5.40 (4H, s, bipy CH_2), 3.92 (6H, s, NCH_3), 2.22 (6H, s, pyrazole C-5 CH_3); *m/z* (ESI+) 513.26548 (M + H, $C_{28}H_{29}N_6O_4$ requires 513.22502); 531.3 (37%) (M + H).

(*E*)-3-(Benzo[1,3]dioxol-5-yl)acrylic acid 4′-[(*E*)-3-(benzo-[1,3]dioxol-5-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-yl-methyl ester (3b). Light yellow solid, 92% yield, LC retention time = 0.40, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 68.12; H, 4.32; N, 4.97, $C_{32}H_{24}N_2O_8$ requires C, 68.02; H, 4.28; N, 4.96%); ν_{max}(neat)/cm^{-1} 3374, 1703, 1602, 1501, 1454, 1228, 1036, 932, 796; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.73 (2H, d, *J* 5 Hz, bipy H-6), 8.40 (2H, s, bipy H-3), 7.67 (2H, d, *J* 5 Hz, bipy H-5), 7.49 (2H, d, H-3), 6.87 (2H, s, benzodioxane H-4), 6.83 (2H, d, *J* 8 Hz, benzodioxane H-6), 6.60 (2H, d, *J* 8 Hz, benzodioxane H-7), 6.17 (2H, d, *J* 15 Hz, H-2), 5.81 (4H, s, benzodioxane H-2), 5.29 (4H, s, bipy CH_2); *m/z* (ESI+) 565.14684 (M + H, $C_{32}H_{23}N_4O_{12}$ requires 565.16110); 565.2 (45%) (M + H).

(*E*)-3-(4-*tert*-Butoxycarbonylaminopyridin-3-yl)acrylic acid 4′-[(*E*)-3-(4-*tert*-butoxycarbonylaminopyridin-3-yl)acryloyloxy-methyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3c). Off-white solid, 85% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 64.42; H, 5.79; N, 11.98, $C_{38}H_{40}N_6O_8$ requires C, 64.40; H, 5.69; N, 11.86%); ν_{max}($CHCl_3$)/cm^{-1} 1722, 1691, 1575, 1504, 1409, 1312, 1279, 1226, 1175, 1157, 1043, 946, 821, 794, 720, 706; δ_H(400 MHz; $CDCl_3$) 9.06 (2H, d, *J* 5 Hz, py H-2), 8.72 (2H, d, *J* 5 Hz, bipy H-6), 8.71 (2H, d, *J* 7 Hz, py H-6), 8.57 (2H, s, py H-3), 8.49 (2H, d, *J* 6 Hz, bipy H-5), 7.81 (2H, d, *J* 15 Hz, H-3), 7.64 (2H, d, *J* 5 Hz, py H-5), 7.32 (2H, br s, N–H), 6.82 (2H, d, *J* 15 Hz, H-2), 5.42 (4H, s, bipy CH_2), 1.93 (18H, s, O^{t}Bu); *m/z* (ESI+) 731.25093 (M + Na, $C_{38}H_{40}N_6NaO_8$ requires 731.28053); 731.3 (36%) (M + Na).

(*E*)-3-(2,3-Dihydrobenzofuran-5-yl)acrylic acid 4′-((*E*)-3-2,3-dihydrobenzofuran-5-yl-acryloyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (3d). Light yellow solid, 90% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 72.94; H, 5.07; N, 5.02, $C_{34}H_{28}N_2O_6$ requires C, 72.84; H, 5.03; N, 5.00%); ν_{max}(neat)/cm^{-1} 1708, 1603, 1489, 1223, 1049, 948, 797; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.80 (2H, d, *J* 5 Hz, bipy H-6), 8.41 (2H, s, bipy H-3), 7.76 (2H, d, *J* 5 Hz, bipy H-5), 7.61 (2H, d, *J* 15 Hz, H-3), 7.33 (2H, s, benzofuran H-4), 7.20 (4H, d, *J* 8 Hz, bezofuran H-6), 6.63 (4H, d, *J* 8 Hz, benzofuran H-7), 6.26 (2H, d, *J* 15 Hz, H-2), 5.38 (4H, s, bipy CH_2), 4.47 (4H, t, *J* 8 Hz, benzofuran H-2), 3.10 (4H, t, *J* 8Hz, benzofuran H-3); δ_C(125 MHz; $CDCl_3$) 168.1 (C=O), 157.7 (bipy C-2), 157.6 (benzofuran C-7a), 151.9 (C-3), 151.0 (bipy C-6), 147.5 (bipy C-4), 134.6 (benzofuran C-6), 129.8 (bipy C-5), 129.4 (benzofuran C-4), 126.4 (benzofuran C-5), 126.0 (benzofuran C-3a), 125.8 (bipy C-3), 117.1 (benzofuran C-2), 114.3 (benzofuran C-7), 76.5 (benzofuran C-2), 68.0 (bipy CH_2), 33.6 (benzofuran C-3); *m/z* (ESI+) 560.19987 (M$^+$, $C_{34}H_{28}N_2O_6$ requires 560.19474); 560.2 (55%) (M$^+$).

(*E*)-3-(1-Benzenesulfonyl-1*H*-indol-3-yl)acrylic acid 4′-[(*E*)-3-(1-benzenesulfonyl-1*H*-indol-3-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3e). White solid, 80% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 66.20; H, 4.13; N, 6.71, $C_{46}H_{34}N_4O_8S_2$ requires C, 66.17; H, 4.10; N, 6.71%); ν_{max}(neat)/cm^{-1} 1716, 1633, 1598, 1368, 1218, 1040, 945, 795, 740; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.74 (2H, d, *J* 5Hz, bipy H-6), 8.46 (2H, s, bipy H-3), 7.79 (4H, m, Ph H-2, Ph H-6), 7.77 (2H, d, *J* 7 Hz, indole H-4), 7.73 (4H, m, Ph H-3, Ph H-5), 7.57 (4H, d, *J* 5 Hz, bipy H-5), 7.37 (2H, t, *J* 7 Hz, indole H-7), 7.30 (2H, m, Ph H-4), 7.25 (2H, t, *J* 7 Hz, indole H-4, H-6), 7.10 (2H, m, indole H-2, H-5), 6.45 (4H, d, *J* 15 Hz, C-2), 5.32 (4H, s, bipy CH_2); *m/z* (ESI+) 834.18193 (M$^+$, $C_{46}H_{34}N_4O_8S_2$ requires 834.18181); 834.2 (45%) (M$^+$).

(*E*)-3-(3,4-Dihydro-2*H*-benzo[*b*][1,5]dioxepin-7-yl)acrylic acid 4′-((*E*)-3-(3,4-dihydro-2*H*-benzo[*b*][1,5]dioxepin-7-yl-acryloyl-oxymethyl) [2,2′]-bipyridinyl-4-ylmethyl ester (3f). Off-white solid, 90% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 69.95; H, 5.53; N, 4.59, $C_{36}H_{32}N_2O_8$ requires C, 69.67; H, 5.20; N, 4.51%); ν_{max}(neat)/cm^{-1} 1712, 1645, 1625, 1564, 1285, 1125, 1012, 812, 735; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.43 (2H, s, bipy H-3), 7.64 (2H, d, *J* 15 Hz, H-3), 7.33 (2H, d, *J* 5 Hz, bipy H-5), 7.16 (2H, s, Ph H-6), 7.11 (2H, d, *J* 8 Hz, Ph H-8), 6.94 (2H, d, *J* 8 Hz, Ph H-9), 6.38 (2H, d, *J* 15 Hz, H-2), 5.33 (4H, s, bipy CH_2), 4.22 (8H, m, bezodioxepine H-2, H-4), 2.17 (4H, quin, *J* 6 Hz, benzodioxepine H-3); δ_C(100 MHz; $CDCl_3$) 166.6 (C=O), 156.2 (bipy C-2), 153.2 (Ph C-9a), 151.1 (Ph C-5a), 149.5 (bipy C-6), 146.3 (bipy C-4), 145.0 (C-3), 129.5 (bipy C-7), 123.5 (Ph C-8), 122.1 (bipy C-5), 121.9 (Ph C-9), 121.1 (Ph C-6), 119.5 (bipy C-3), 116.0 (C-2), 70.4 (benzodioxepine C-2, C-7), 64.5 (bipy CH_2), 31.3 (benzodioxepine C-3); *m/z* (ESI+) 620.21467 (M$^+$, $C_{36}H_{32}N_2O_8$ requires 620.21587); 620.2 (55%) (M$^+$), 621.2 (M + H) (10%).

(*E*)-3-Benzofuran-2-yl-acrylic acid 4′-((*E*)-3-benzofuran-2-yl-acryloyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (3g). Off-white solid, 85% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 73.54; H, 4.56; N, 5.29, $C_{34}H_{24}N_2O_6$ requires C, 73.37; H, 4.35; N, 5.03%); ν_{max}($CHCl_3$)/cm^{-1} 1720, 1638, 1600, 1252, 1209, 1164, 760; δ_H(400 MHz; $CDCl_3$) 8.70 (2H, d, *J* 5 Hz, bipy H-6), 8.70 (2H, s, bipy H-3), 7.63 (2H, d *J* 15 Hz, H-3), 7.57 (2H, t, *J* 7 Hz, benzofuran H-6), 7.47 (2H, m, benzofuran H-5), 7.37 (4H, m, benzofuran H-4, Py H-5), 7.23 (2H, d, *J* 7 Hz, benzofuran H-7), 6.98 (2H, s, benzofuran H-3), 6.59 (2H, d, *J* 15 Hz, H-2), 5.38 (4H, s, bipy CH_2); δ_C(100 MHz; $CDCl_3$) 166.2 (C=O), 155.7 (benzofuran C-2), 155.6 (benzofuran C-7a), 152.1 (bipy

C-2), 149.4 (bipy C-6), 145.6 (bipy C-4), 131.5 (C-3), 128.3 (benzofuran C-3a), 126.7 (benzofuran C-4), 123.3 (benzofuran C-7), 122.5 (bipy C-5), 121.7 (benzofuran C-6), 119.4 (bipy C-3), 118.7 (C-2), 111.5 (benzofuran C-5), 111.4 (benzofuran C-3), 64.7 (bipy CH_2); *m/z* (ESI+) 556.18254 (M^+, $C_{34}H_{24}N_2O_6$ requires 556.16344); 556.2 (65%) (M^+).

(*E*)-3-(6-Nitrobenzo[1,3]dioxol-5-yl)acrylic acid 4′-[(*E*)-3-(6-nitrobenzo[1,3]dioxol-5-yl)acryloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3h). Light yellow solid, 95% yield, LC retention time = 0.42, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 58.76; H, 3.41; N, 8.75, $C_{32}H_{22}N_4O_{12}$ requires C, 58.72; H, 3.39; N, 8.56%); ν_{max}(neat)/cm^{-1} 3364, 1710, 1520, 1504, 1330, 1221, 1032, 945, 817, 794; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.87 (2H, d, *J* 5 Hz, bipy H-6), 8.58 (2H, s, bipy H-3), 8.21 (2H, d, *J* 15 Hz, H-3), 7.82 (2H, d, *J* 5 Hz, bipy H-5), 7.17 (2H, s, benzodioxane H-7), 6.99 (2H, s, benzodioxane H-4), 6.31 (2H, d, *J* 15 Hz, H-2), 6.13 (4H, s, benzodioxane H-2), 5.52 (4H, s, bipy CH_2); *m/z* (ESI) 655.13279 (M + H, $C_{32}H_{23}N_4O_{12}$ requires 655.13126); 655.1 (45%) (M + H), 677.1 (18%) (M + Na).

(*E*)-3-(5-Cyano-6-(methylsulfanyl)pyridin-2-yl)acrylic acid 4′-[(*E*)-3-(5-cyano-6-(methylsulfanyl)pyridin-2-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3i). Off-white solid, 72% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 62.19; H, 4.12; N, 13.58, $C_{32}H_{24}N_6O_4S_2$ requires C, 61.92; H, 3.90; N, 13.54%); ν_{max}(neat)/cm^{-1} 3380, 2925, 1713, 1567, 1547, 1363, 1299, 1211, 1162, 1040, 947, 818, 796; δ_H(400 MHz; $CDCl_3$) 8.80 (2H, d, *J* 5 Hz, bipy H-6), 8.41 (2H, s, bipy H-3), 7.75 (4H, d *J* 7 Hz, py H-3, py H-4), 7.57 (2H, d, *J* 15 Hz, H-3), 7.10 (2H, d, *J* 5 Hz, bipy H-5), 7.02 (2H, d, *J* 15 Hz, H-2), 5.40 (4H, s, bipy CH_2), 2.54 (6H, s, SCH_3); *m/z* (ESI+) 490.07865 (M^+, $C_{24}H_{18}N_4O_4S_2$ requires 490.07695); 490.1 (65%) (M^+).

(*E*)-3-[4-(Cyanomethyl(methyl)amino)phenyl]acrylic acid 4′-{(*E*)-3-[4-(cyanomethyl(methyl)amino)phenyl]acryloyloxymethyl}-[2,2′]bipyridinyl-4-ylmethyl ester (3j). Light yellow solid, 85% yield, LC retention time = 0.41, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 71.28; H, 5.64; N, 13.24, $C_{38}H_{36}N_6O_4$ requires C, 71.23; H, 5.66; N, 13.12%); ν_{max}(neat)/cm^{-1} 1707, 1591, 1521, 1145, 1107, 1036, 957, 814, 765; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.86 (2H, d, *J* 5 Hz, bipy H-6), 8.46 (2H, s, bipy H-3), 7.71 (2H, d, *J* 5 Hz, bipy H-5), 7.64 (2H, d, *J* 15 Hz, H-3), 7.40 (4H, d, *J* 8 Hz, Ph AA′BB′ H-2, H-6), 6.61 (4H, d, *J* 8 Hz, Ph AA′BB′ H-3, H-5), 6.27 (2H, d, *J* 15 Hz, H-2), 5.22 (4H, s, bipy CH_2), 3.68 (4H, t, *J* 5 Hz, NCH_2CH_2CN), 3.04 (6H, s, NCH_3), 2.53 (4H, t, *J* 5 Hz, NCH_2CH_2CN); *m/z* (ESI+) 641.29261 (M + H, $C_{38}H_{37}N_6O_4$ requires 641.28763); 641.3 (25%) (M + H).

(*E*)-3-[5-(1-Methyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)thiophen-2-yl]acrylic acid 4′-{(*E*)-3-[5-(1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)thiophen-2-yl]acryloyloxymethyl}-[2,2′]bipyridinyl-4-ylmethyl ester (3k). Light yellow solid, 74% yield, LC retention time = 0.42, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 55.35; H, 3.28; N, 10.75, $C_{36}H_{26}F_6N_6O_4S_2$ requires C, 55.10; H, 3.34; N, 10.71%); ν_{max}(neat)/cm^{-1} 1710, 1624, 1599, 1302, 1224, 1205, 1165, 1120, 1085, 1038, 977, 944, 791; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.80 (2H, d, *J* 5 Hz, bipy H-6), 8.41 (2H, s, bipy H-3), 7.78 (2H, d, *J* 15 Hz, H-3), 7.26 (2H, d, *J* 5 Hz, bipy H-5), 7.13 (2H, d, *J* 4 Hz, thiophene H-3), 6.59 (2H, s, thiophene H-4), 6.27 (2H, d, *J* 15 Hz, H-2), 5.37 (2H, s, pyrazole H-4), 5.19 (4H, Py CH_2), 3.93 (6H, s, pyrazole CH_3); *m/z* (ESI+) 784.14264 (M^+, $C_{36}H_{26}F_6N_6O_4S_2$ requires 784.13611); 784.1 (36%) (M^+).

(*E*)-3-(4-Imidazol-1-ylphenyl)acrylic acid 4′-[(*E*)-3-(4-imidazol-1-ylphenyl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (3l). Off-white solid, 87% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 71.02; H, 4.67; N, 13.83, $C_{36}H_{28}N_6O_4$ requires C, 71.04; H, 4.64; N, 13.81%); ν_{max}($CHCl_3$)/cm^{-1} 3357, 1709, 1604, 1523, 1306, 1220, 1172, 1044, 948, 822, 743; δ_H(400 MHz; $CDCl_3$–DTFA–acetone-d_6) 9.31 (2H, s, imidazole H-2), 9.20 (2H, d, *J* 7 Hz, imidazole H-5), 8.75 (2H, d, *J* 5 Hz, py H-6), 8.49 (2H, s, py H-3), 8.00 (4H, d, *J* 7.8 Hz, Ph H-2, H-6), 7.78 (4H, d, *J* 7.8 Hz, Ph H-3, H-5), 7.70 (2H, d, *J* 8.9 Hz, H-3), 7.59 (2H, d, *J* 10 Hz, imidazole H-4), 6.55 (2H, d, *J* 15 Hz, H-2), 5.40 (2H, s, bipy CH_2); *m/z* (ESI+) 631.20756 (M + Na, $C_{36}H_{28}N_6NaO_4$ requires 631.20697); 631.2 (24%) (M + Na).

(*E*)-3-[2,2′]Bithiophenyl-5-ylacrylic acid 4′-((*E*)-3-[2,2′]bithiophenyl-5-yl-acryloyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (3m). Light yellow solid, 92% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 62.67; H, 3.89; N, 4.31, $C_{34}H_{24}N_2O_4S_4$ requires C, 62.55; H, 3.71; N, 4.29%); ν_{max}(neat)/cm^{-1} 3388, 1714, 1614, 1598, 1453, 1210, 1166, 1041, 946, 798, 697; δ_H(500 MHz; $CDCl_3$–DTFA–acetone-d_6) 8.67 (2H, d, *J* 5 Hz, bipy H-6), 8.29 (2H, s, bipy H-3), 7.63 (2H, d, *J* 5 Hz, bipy H-5), 7.59 (2H, d, *J* 15 Hz, H-3), 7.05 (2H, m, thiophene H-4), 6.88 (6H, m, thiophene H-2′, H-3′, H-4′), 6.77 (2H, m, thiophene H-3), 6.00 (2H, d, *J* 15 Hz, H-2), 5.26 (4H, s, bipy CH_2); *m/z* (ESI+) 653.07891 (M^+, $C_{32}H_{25}N_2O_4S_4$ requires 653.06972); 653.1 (48%) (M + H), 675.1 (M + Na) (16%).

(*E*)-3-Phenylacrylic acid 4′-[(*E*)-(3-phenylacryloyl)oxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4a)[17,18]. White solid, 98% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.47; H, 4.99; N, 5.79, $C_{30}H_{24}N_2O_4$ requires C, 75.63; H, 5.04; N, 5.88%); ν_{max}(neat)/cm^{-1} 1712, 1637, 1599, 1449, 1309, 1169, 978, 819, 765, 709; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.35 (2H, s, bipy H-3), 7.78 (2H, d, *J* 15 Hz), 7.53 (4H, m, Ph H-2, H-6), 7.40 (6H, m, Ph H-3, H-4, H-5), 7.38 (2H, d, *J* 5 Hz, bipy H-5), 6.55 (2H, d, *J* 15 Hz, H-2), 5.35 (4H, s, bipy CH_2); δ_C(100 MHz; $CDCl_3$) 166.5 (C=O), 157.2 (bipy C-2), 149.5 (bipy C-6), 146.3 (bipy C-4), 145.8 (C-3), 134.2 (Ph C-1), 130.5 (Ph C-3, Ph C-5), 128.9 (Ph C-4), 128.2 (Ph C-2, Ph C-6), 122.2 (bipy C-3), 119.6 (bipy C-5), 117.3 (C-2), 64.5 (bipy CH_2); *m/z* (EI) 476.17452 (M^+, $C_{30}H_{24}N_2O_4$ requires 476.52264); 476.2 (25%) (M^+).

(*E*)-3-(4-Fluorophenyl)acrylic acid 4′-[(*E*)-3-(4-fluorophenyl-acryloyl)oxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4b). White solid, 92% yield, LC retention time = 0.46, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 70.32; H, 4.45; N, 5.56, $C_{30}H_{22}F_2N_2O_4$ requires C, 70.31; H, 4.33; N, 5.47%); ν_{max}(neat)/cm^{-1} 2927, 1714, 1636, 1598, 1508, 1308, 1219, 1161, 1104, 980, 828, 819, 792, 777; δ_H(400 MHz; $CDCl_3$) 8.67 (2H, d, *J* 5 Hz, bipy H-6), 8.46 (2H, s, bipy H-3), 7.72 (2H, d, *J* 15 Hz, H-3), 7.52 (4H, dd, *J* 14 Hz, 7 Hz, Ph AA′BB′ H-2, H-6), 7.35 (2H, d, *J* 5 Hz, bipy H-5), 7.09 (4H, dd, *J* 17 Hz, 8 Hz, Ph H-3, Ph H-5), 6.42 (2H, d, *J* 15 Hz, H-2), 5.35 (4H, s, bipyCH_2); δ_C(100 MHz; $CDCl_3$) 166.4 (C=O), 164.5 (J_{C-F} 240 Hz, Ph C-4), 156.2 (bipy C-2), 149.5 (bipy C-6), 146.2 (bipy C-4), 144.5 (C-3), 130.4 (Ph C-1), 130.1 (J_{C-F} 8.5 Hz, Ph C-2, Ph C-6), 122.2 (bipy C-3), 119.6 (C-2), 117.0 (bipy C-5), 116.0 (J_{C-F} 210 Hz, Ph C-3, Ph C-5), 64.6 (bipy CH_2); *m/z* (ESI+) 512.15458 (M^+, $C_{30}H_{22}F_2N_2O_4$ requires 512.15476); 512.2 (20%) (M^+).

(*E*)-3-(4-Methoxyphenyl)acrylic acid 4′-[(*E*)-3-(4-methoxyphenyl)-acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4c). White solid, 90% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.47; H, 4.99; N, 5.79, $C_{32}H_{28}N_2O_6$ requires C, 71.63; H, 5.26; N, 5.22%); ν_{max}(neat)/cm^{-1} 1709, 1634, 1602, 1514, 1292, 1253, 1157, 1025, 825, 816, 779; δ_H(400 MHz; $CDCl_3$) 8.66 (2H, d, *J* 5 Hz, bipy H-6), 8.44 (2H, s, bipy H-3), 7.73 (2H, d, *J* 15 Hz, H-3), 7.50 (4H, d, *J* 8 Hz, Ph H-2, Ph H-6), 7.35 (2H, d, *J* 5 Hz, bipy H-5), 6.90 (4H, d, *J* 8 Hz, Ph H-3, Ph H-5), 6.43 (2H, d, *J* 15 Hz, H-2), 5.35 (4H, s, bipy CH_2), 3.85 (6H, s, OCH_3); δ_C(100 MHz; $CDCl_3$) 166.8 (C=O), 161.6 (Ph C-4), 156.9 (bipy C-2), 149.4 (bipy C-6), 147.2 (bipy C-4), 145.6 (C-3), 129.9 (Ph C-2, Ph C-6), 127.0 (Ph C-1), 122.2 (bipy C-5), 119.6 (bipy C-3), 114.7 (bipy

C-5), 114.4 (Ph C-3, C-5), 64.4 (bipy CH_2), 55.4 (OCH_3); *m/z* (ESI+) 536.19863 (M^+, $C_{32}H_{28}N_2O_6$ requires 536.19474); 537.2 (35%) (M + H), 536.2 (45%) (M^+).

(*E*)-Non-2-enoic acid 4′-((*E*)-non-2-enoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4d). White solid, 85% yield, LC retention time = 0.53, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 73.25; H, 8.34; N, 5.89, $C_{30}H_{40}N_2O_4$ requires C, 73.14; H, 8.18; N, 5.69%); ν_{max}(neat)/cm^{-1} 2928, 1719, 1651, 1598, 1459, 1296, 1169, 1029, 977, 839, 824; δ_H(400 MHz; $CDCl_3$) 8.63 (2H, d, *J* 5 Hz, bipy H-6), 8.37 (2H, s, bipy H-3), 7.37 (4H, d, *J* 5 Hz, bipy H-5), 7.13 (2H, dd, *J* 15 Hz, 5 Hz, H-3), 5.93 (2H, d, *J* 15 Hz, H-2), 5.35 (4H, s, bipy CH_2), 2.34 (4H, m, H-4), 1.45 (4H, m, H-8), 1.23 (12H, br d, H-5, H-6, H-7), 0.87 (6H, m, H-9); δ_C(100 MHz; $CDCl_3$) 166.2 (C=O), 156.1 (bipy C-2), 151.1 (bipy C-6), 149.4 (C-3), 146.3 (bipy C-4), 122.1 (bipy C-3), 120.4 (C-2), 119.5 (bipy C-5), 64.2 (bipy CH_2), 35.7 (C-4), 32.3 (C-7), 28.8 (C-6), 27.9 (C-8), 14.1 (C-9); *m/z* (ESI+) 492.29924 (M^+, $C_{30}H_{40}N_2O_4$ requires 492.29881); 492.3 (45%) (M^+), 515.3 (M + Na) (20%).

(*E*)-4-Methylpent-2-enoic acid 4′-((*E*)-4-methylpent-2-enoyloxymethyl)-[2,2′]bipyidinyl-4-ylmethyl ester (4e). White solid, 82% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.47; H, 4.99; N, 5.79, $C_{30}H_{24}N_2O_4$ requires C, 75.63; H, 5.04; N, 5.88%); ν_{max}(neat)/cm^{-1} 1710, 1638, 1600, 1568, 1292, 1251, 996, 723; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.35 (2H, s, bipy H-3), 7.34 (2H, d, *J* 5 Hz, bipy H-5), 7.05 (2H, dd, *J* 15 Hz, 5 Hz, H-3), 5.85 (2H, d, *J* 15 Hz, H-2), 5.28 (4H, s, bipy CH_2), 2.55 (2H, m, H-4), 1.05 (12H, d, *J* 6 Hz, $(CH_3)_2CH$); δ_C(100 MHz; $CDCl_3$) 166.5 (C=O), 156.9 (C-3), 156.2 (bipy C-2), 149.4 (bipy C-6), 146.3 (bipy C-4), 122.1 (bipy C-3), 199.6 (bipy C-5), 116.5 (C-2), 64.3 (bipy CH_2), 31.1 ($(CH_3)_2CH$), 21.1 ($(CH_3)_2CH$); *m/z* (ESI+) 409.21260 (M + 1, $C_{30}H_{24}N_2O_4$ requires 409.21284); 409.2 (25%) (M + 1), 431.2 (80%) (M + Na), 345.2 (10%).

(*E*)-3-Furan-2-ylacrylic acid 4′-((*E*)-3-furan-2-ylacryloyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4f). Off-white solid, 83% yield, LC retention time = 0.34 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); mp 134 °C (Found: C, 68.64; H, 4.67; N, 6.19, $C_{26}H_{20}N_2O_6$ requires C, 68.42; H, 4.42; N, 6.14%); ν_{max}(neat)/cm^{-1} 1709, 1633, 1598, 1552, 1475, 1423, 1386, 1304, 1286, 1265, 1154, 990, 866, 821, 757, 732, 697; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.35 (2H, s, bipy H-3), 7.57 (2H, d, *J* 15 Hz, H-3), 7.52 (2H, br d, furan H-5), 7.35 (2H, d, *J* 5 Hz, Py H-5), 6.67 (2H, br d, furan H-3), 6.53 (2H, br t, furan H-4), 6.48 (2H, d, *J* 15 Hz, H-2) 5.37 (4H, s, bipy CH_2); δ_C(100 MHz; $CDCl_3$) 166.6 (C=O), 156.2 (bipy C-2), 150.7 (furan C-2), 149.5 (bipy C-6), 146.3 (bipy C-4), 145.0 (furan C-5), 132.0 (C-3), 122.1 (C-2), 119.5 (bipy C-3), 115.4 (bipy C-5), 114.8 (furan C-4), 112.4 (furan C-3), 64.5 (bipy CH_2); *m/z* (+EI) 456.13171 (M^+, $C_{26}H_{20}N_2O_6$ requires 456.13213); 456.1 (20%) (M^+).

(*E*)-3-Thiophen-2-ylacrylic acid 4′-((*E*)-3-thiophen-2-ylacryloylmethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4g). White solid, 70% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.47; H, 4.99; N, 5.79, $C_{26}H_{20}N_2O_4S_2$ requires C, 63.92; H, 4.13; N, 5.73%); ν_{max}(neat)/cm^{-1} 1715, 1636, 1598, 1508, 1307, 1219, 1162, 980, 829, 792; δ_H(400 MHz; $CDCl_3$) 8.69 (2H, d, *J* 5 Hz, bipy H-6), 8.45 (2H, s, bipy H-3), 7.87 (2H, d, *J* 15 Hz, H-3), 7.42 (2H, d, *J* 6 Hz, thiophene H-3), 7.35 (2H, d, *J* 5 Hz, bipy H-5), 7.30 (2H, d, *J* 6 Hz, thiophene H-5), 7.08 (2H, t, *J* 6Hz, thiophene H-4), 6.35 (2H, d, *J* 15 Hz, H-2), 5.32 (4H, s, bipy CH_2); δ_C(100 MHz; $CDCl_3$) 166.3 (C=O), 156.2 (bipy C-2), 149.5 (bipy C-6), 146.2 (bipy C-4), 139.4 (thiophene C-2), 138.2 (C-3), 131.3 (thiophene C-5), 128.9 (thiophene C-4), 128.1 (thiophene C-3), 122. (C-2), 119.5 (bipy C-3), 116.0 (bipy C-5), 64.5 (bipyCH_2); *m/z* (ESI+) 511.07590 (M + Na, $C_{26}H_{20}N_2O_4S_2Na$ requires 511.07622); 489.1 (65%) (M + 1), 511.1 (100%) (M + Na).

(*E*)-3-(3,5-Dimethylisoxazol-4-yl)acrylic acid 4′-[(*E*)-3-(3,5-dimethylisoxazol-4-yl)acryloyloxymethyl)-[2,2′]bipyridin-yl-4-ylmethyl ester (4h). White solid, 92% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 65.53; H, 5.21; N, 10.79, $C_{28}H_{26}N_4O_6$ requires C, 65.36; H, 5.09; N, 10.89%); ν_{max}(neat)/cm^{-1} 1712, 1654, 1608, 1586, 1524, 1302, 1157, 834, 820; δ_H(400 MHz; $CDCl_3$) 8.46 (2H, d, *J* 5 Hz, bipy H-6), 8.45 (2H, s, bipy H-3), 7.57 (2H, d, *J* 15 Hz, H-3), 7.44 (2H, d, *J* 5 Hz, bipy H-5), 6.24 (2H, d, *J* 15 Hz, H-2), 5.36 (4H, s, bipy CH_2), 2.52 (6H, s, C-5 CH_3), 2.42 (6H, s C-3 CH_3); δ_C(100 MHz; $CDCl_3$) 170.1 (C-5), 166.3 (C=O), 158.4 (C-3), 156.2 (bipy C-2), 149.5 (bipy C-6), 146.1 (bipy C-4), 133.9 (H-3), 122.3 (bipy H-5), 119.6 (bipy H-3), 117.0 (C-2), 111.4 (C-4), 64.7 (bipy CH_2), 12.0 (C-5 CH_3), 11.7 (C-3 CH_3); *m/z* (ESI+) 514.18789 (M^+, $C_{28}H_{26}N_4O_6$ requires 514.185524); 514.2 (35%) (M^+), 515.2 (M + H) (20%).

(*E*)-3-(1-Benzyl-1*H*-indol-3-yl)acrylic acid 4′-[(*E*)-3-(1-benzyl-1*H*-indol-3-yl)acryloyloxymethyl)-[2,2′]bipyridin-yl-4-ylmethyl ester (4i). Off-white solid, 65% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 78.24; H, 5.50; N, 7.45, $C_{48}H_{38}N_4O_4$ requires C, 78.45; H, 5.21; N, 7.62%); ν_{max}(neat)/cm^{-1} 1710, 1634, 1602, 1575, 1456, 1256, 1097, 825, 760, 734; δ_H(400 MHz; $CDCl_3$) 8.75 (2H, d, *J* 5 Hz, Py H-6), 8.45 (2H, s, Py H-3), 8.02 (2H, d, *J* 15 Hz, H-3), 7.95 (2H, m, indole H-2), 7.33–7.29 (18H, m, Ph–H), 6.52 (2H, d, *J* 15 Hz, H-2), 5.37 (4H, s, bipy CH_2), 5.33 (4H, s, benzyl CH_2); δ_C(100 MHz; $CDCl_3$) 166.9 (C=O), 155.3 (C-3), 156.2 (bipy C-2), 150.1 (bipy C-6), 146.6 (bipy C-4), 139.2 (benzyl Ph C-1), 136.1 (indole C-7a), 129.9 (benzyl Ph C-2, C-6), 128.5 (benzyl Ph C-3, C-5), 128.0 (indole C-3a), 126.2 (benzyl Ph C-4), 124.4 (indole C-2), 122.7 (bipy C-5), 122.4 (indole C-5), 121.1 (indole C-4), 119.9 (indole C-6), 119.6 (bipy C-3), 117.0 (C-2), 111.9 (indole C-7), 102.8 (indole C-3), 64.7 (bipy CH_2), 60.3 (benzyl Ph CH_2); *m/z* (ESI+) 735.93464 (M + H, $C_{48}H_{39}N_4O_4$ requires 735.29714); 735.9 (35%) (M + H).

(*E*)-3-(2*H*-Chromen-3-yl)acrylic acid 4′-((*E*)-3-(2*H*-chromen-3-ylacryloyloxymethyl)-[2,2′]bipyridin-yl-4-yl methyl ester (4j). Light yellow solid, 80% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 74.06; H, 4.98; N, 4.89, $C_{48}H_{38}N_4O_4$ requires C, 73.96; H, 4.83; N, 4.79%); ν_{max}(neat)/cm^{-1} 1719, 1599, 1488, 1459, 1241, 1161, 1041, 758, 732; δ_H(400 MHz; $CDCl_3$) 8.69 (2H, d, *J* 5 Hz, bipy H-6), 8.49 (2H, s, bipy H-3), 7.44 (2H, d, *J* 15 Hz, H-3), 7.33 (2H, d, *J* 4 Hz, bipy H-5), 7.17 (2H, *J* 7 Hz, chromene H-5), 7.07 (2H, d, *J* 7 Hz, chromene H-7), 6.89 (2H, t, *J* 7 Hz, chromene H-6), 6.83 (2H, d, *J* 8 Hz, chromene H-8), 6.77 (2H, s, chromene H-4), 5.85 (2H, *J* 15 Hz, H-2), 5.33 (4H, s, bipy CH_2), 4.99 (4H, s, chromene H-2); δ_C(100 MHz; $CDCl_3$) 166.3 (C=O), 157.5 (bipy C-2), 154.5 (chromene C-8a), 149.7 (bipy C-6), 145.3 (bipy C-4), 142.7 (C-3), 131.5 (chromene C-4), 131.0 (chromene C-5), 128.3 (chromene C-3), 128.1 (chromene C-7), 122.2 (chromene C-4a), 121.8 (bipy C-5), 121.6 (chromene C-6), 120.1 (bipy C-3), 116.0 (chromene C-8), 115.8 (C-2), 65.0 (chromene C-2), 64.6 (bipy CH_2); *m/z* (ESI+) 584.18908 (M^+, $C_{36}H_{28}N_2O_6$ requires 584.19474); 584.2 (55%) (M^+).

(*E*)-4,4,5,5,6,6,6-Heptafluorohex-2-enoic acid 4′-((*E*)-4,4,5,5,6,6,6-heptafluorohex-2-enoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4k). White solid, 82% yield, LC retention time = 0.48, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 43.78; H, 2.35; N, 4.44; $C_{24}H_{14}F_{14}N_2O_4$ requires C, 43.65; H, 2.14; N, 4.24%); ν_{max}(neat)/cm^{-1} 1712, 1623, 1598, 1525, 1286, 1224, 1145, 1025, 826; δ_H(500 MHz; $CDCl_3$) 8.62 (2H, d, *J* 5 Hz, bipy H-6), 8.35 (2H, s, bipy H-3), 7.25 (2H, d, *J* 5 Hz, bipy H-5), 6.82 (2H, dd, *J* 15 Hz, 5 Hz, H-3), 5.58 (2H, d, *J* 15 Hz, H-2), 5.29 (4H, s, bipy CH_2); δ_C(100 MHz; $CDCl_3$) 165.1 (C=O), 156.1 (bipy C-2), 149.6 (bipy C-6), 145.0 (bipy C-4), 144.9 (C-3), 131.6 (C-5), 131,4 (bipy C-5), 130.0 (bipy C-3), 122.2 (C-2), 111.7 (C-6), 108.6 (C-4), 65.6 (bipy CH_2); *m/z* (ESI+) 683.06458 (M + Na,

$C_{24}H_{14}F_{14}N_2NaO_4$ requires 683.06277); 683.1 (45%) (M + Na), 661.1 (80%) (M + H).

(*E*)-3-(2-Trifluoromethoxyphenyl)acrylic acid 4′-[(*E*)-3-(2-trifluoromethoxyphenyl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4l). White solid, 83% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 59.84; H, 3.47; N, 4.54, $C_{32}H_{22}F_6N_2O_6$ requires C, 59.63; H, 3.44; N, 4.35%); ν_{max}($CHCl_3$)/cm^{-1} 1720, 1638, 1600, 1252, 1209, 1164, 760; δ_H(400 MHz; $CDCl_3$) 8.63 (2H, d, *J* 5 Hz, bipy H-6), 8.40 (2H, s, bipy H-3), 7.95 (2H, d, *J* 15 Hz, H-3), 7.62 (2H, dd, *J* 8 Hz, 1.5 Hz, Ph H-6), 7.36 (2H, dd, *J* 8 Hz, 1.5 Hz, Ph H-4), 7.29 (2H, d, *J* 5 Hz, bipy H-5), 7.24 (4H, m, Ph H-5, H-3), 6.52 (2H, d, *J* 15 Hz, H-2), 5.31 (4H, s, bipy CH_2); δ_C(125 MHz; $CDCl_3$) 165.9 (C=O), 156.2 (bipy C-2), 149.5 (bipy C-2), 146.1 (bipy C-4), 138.5 (C-3), 131.6 (Ph C-4), 128.1 (Ph C-6), 127.6 (Ph C-1), 127.1 (Ph C-5), 122.1 (bipy C-5), 121.4 (Ph C-3), 120.3 (C-2), 119.6 (bipy C-3), 119.5 ($J_{C\text{-}F}$ 206 Hz, OCF_3), 64.7 (bipy CH_2); *m*/*z* (ESI+) 644.13984 (M^+, $C_{32}H_{22}F_6N_2O_6$ requires 644.13821); 644.1 (42%) (M^+), 131 (73%).

(*S*)-2-[(*E*)-2-(4′-{(*E*)-3-[1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]acryloyloxymethyl}-[2,2′]bipyridinyl-4-ylmethoxycarbonyl)-vinyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (4m). Colourless oil, 75% yield, LC retention time = 0.46, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 65.54; H, 7.23; N, 8.56, $C_{36}H_{46}N_4O_8$ requires C, 65.24; H, 7.00; N, 8.45%); ν_{max}(neat)/cm^{-1} 2976, 1702, 1790, 1164, 876, 765; δ_H(500 MHz; $CDCl_3$) 8.67 (2H, d, *J* 5 Hz, bipy H-6), 8.38 (2H, s, bipy H-3), 7.29 (2H, d, *J* 5 Hz, bipy H-5), 6.51 (2H, br d, H-3), 5.92 (2H, d, *J* 15 Hz, H-2), 5.28 (4H, s, bipy CH_2), 4.32 (4H, br t, pyrrolidine H-2), 3.38 (2H, br t, pyrrolidine H-5), 1.84 (8H, br t, pyrrolidine H-3, H-4), 1.41 (6H, s, OMe_3); δ_C(100 MHz; $CDCl_3$) 166.5 (bipy C=O), 157.6 (bipy C-2), 150.2 (C-3), 149.7 (bipy C-6), 146.9 (bipy C-4), 138.4 (pyrrolidine C=O), 122.4 (bipy C-5), 120.3 (C-2), 119.9 (bipy C-3), 80.3 ($OC(CH_3)_3$), 65.2 (bipy CH_2), 58.5 (pyrrolidine C-2), 46.7 (pyrrolidine C-5), 31.3 (pyrrolidine C-3), 29.2 ($OC(CH_3)_3$), 23.5 (pyrrolidine C-4); *m*/*z* (ESI+) 663.3589 (M + H, $C_{36}H_{47}N_4O_8$ requires 663.3394); 663.4 (52%) (M + H).

***E*-3-((5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-[1,4]dioxan-2-yl)acrylic acid 4′-[(*E*)-3-((5*S*,6*S*)-5,6-dimethoxy-5,6-dimethyl-[1,4]dioxan-2-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4n).** Colourless oil, 95% yield, LC retention time = 0.35 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); ν_{max}(neat)/cm^{-1} 2953, 1725, 1600, 1141, 1116, 1036, 878, 732; δ_H(400 MHz; $CDCl_3$) 8.68 (2H, d, *J* 5 Hz, bipy H-6), 8.37 (2H, s, Py H-3), 7.30 (2H, d, *J* 5 Hz, bipy H-5), 6.87 (2H, dd, *J* 15, 4 Hz, bipy $O_2CCHCHR$), 6.27 (2H, d, *J* 15 Hz, bipy $O_2CCHCHR$), 5.27 (4H, m, bipy CH_2), 4.62 (2H, d, *J* 5 Hz, C-3), 3.52 (2H, m, C-2), 3.26 (6H, s, OMe); 1.27 (6H, m, CH_3); δ_C(100 MHz; $CDCl_3$) 165.6 (C=O), 156.1 (bipy C-2), 149.5 (C-6), 145.9 (bipy C-4), 143.6 ($ArO_2CCHCHR$), 122.1 (bipy C-5), 121.5 ($ArO_2CCHCHR$), 119.5 (bipy C-3), 99.4 (C-6), 98.0 (C-5), 66.8 (C-3), 64.6 (bipy CH_2), 62.0 (C-2), 48.1 (OMe), 17.7 (CH_3); *m*/*z* (ESI+) 672.29673 (M^+, $C_{34}H_{44}N_2O_{12}$ requires 672.28943); 672.3 (53%) (M^+).

(*S*)-2-[(*E*)-2-(4′-{(*E*)-3-[(*S*)-2-(ethoxycarbonyl)cyclopropyl]-acryloyloxymethyl}-[2,2′]bipyridinyl-4-ylmethoxycarbonyl)vinyl]-cyclopropanecarboxylic acid ethyl ester (4o). Colourless oil, 82% yield, LC retention time = 0.47, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 65.79; H, 6.01; N, 5.16, $C_{30}H_{32}N_2O_8$ requires C, 65.68; H, 5.88; N, 5.11%); ν_{max}(neat)/cm^{-1} 2982, 1708, 1701, 1381, 1454, 1305, 1187, 1023; δ_H(500 MHz; $CDCl_3$) 8.70 (2H, d, *J* 5 Hz, bipy H-6), 7.28 (2H, s, bipy H-3), 7.27 (2H, d, *J* 5 Hz, bipy H-5), 6.51 (2H, dd, *J* 9.9 Hz, 9.9 Hz, H-3), 6.08 (2H, d, *J* 15 Hz, H-2), 5.26 (4H, s, bipy CH_2), 4.14 (4H, q, *J* 7 Hz, OCH_2CH_3), 2.16 (2H, m, cyclopropane H-3), 1.86 (2H, ddd, *J* 10.0 Hz, 4.8 Hz, 3.3 Hz, cyclopropane H-2), 1.56 (2H, ddd, *J* 10.0 Hz, 4.8 Hz, 4.8 Hz, cyclopropane H-1), 1.16 (2H, ddd, *J* 15.0 Hz, 4.8 Hz, 3.8 Hz, cyclopropane H-1), 1.15 (6H, t, *J* 7 Hz, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 172.2 (cyclopropane ester C=O), 165.6 (C=O), 156.2 (bipy C-2), 150.1 (C-3), 149.4 (bipy C-6), 146.1 (bipy C-4), 122.1 (bipy C-5), 120.1 (C-2), 119.5 (bipy C-3), 64.3 (bipy CH_2), 61.0 (OCH_2CH_3), 24.3 (cyclopropane C-3), 23.1 (cyclopropane C-2), 16.5 (cyclopropane C-1), 14.2 (OCH_2CH_3); *m*/*z* (ESI+) 548.21453 (M^+, $C_{30}H_{32}N_2O_8$ requires 548.21587); 549.2 (36%) (M + 1), 256.7 (25%).

(*E*)-3-Thiazol-2-ylacrylic acid 4′-((*E*)-3-thiazol-2-ylacryloyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4p). Off-white solid, 85% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 58.84; H, 3.82; N, 11.65, $C_{24}H_{18}N_4O_4S_2$ requires C, 58.76; H, 3.70; N, 11.42%); ν_{max}(neat)/cm^{-1} 1716, 1600, 1299, 1168, 907, 829, 726; δ_H(400 MHz; $CDCl_3$) 8.69 (2H, d, *J* 5 Hz, bipy H-6), 8.48 (2H, s, bipy H-3), 7.97 (2H, d *J* 4 Hz, thiazole H-4), 7.85 (2H, d, *J* 15 Hz, H-3), 7.48 (2H, d, *J* 4 Hz, thiazole H-5), 7.37 (2H, d, *J* 5 Hz, bipy H-5), 6.82 (2H, d, *J* 15 Hz, H-2); δ_C(100 MHz; $CDCl_3$) 166.3 (C=O), 163.2 (thiazole C-2), 156.2 (bipy C-2), 149.6 (bipy C-6), 145.8 (bipy C-4), 144.9 (thiazole C-4), 136.8 (C-3), 122.1 (bipy C-5), 122.0 (C-2), 121.7 (thiazole C-5), 119.5 (bipy C-3), 77.0 (bipy CH_2); *m*/*z* (ESI+) 491.09725 (M + H, $C_{24}H_{19}N_4O_4S_2$ requires 491.08478); 491.1 (65%) (M + H).

(*E*)-3-(2,5-Dimethylthiazol-4-yl)acrylic acid 4′-[(*E*)-3-(2,5-dimethylthiazol-4-yl)acryloyloxymethyl]-[2,2′]bipyridinyl-4-ylmethyl ester (4q). Off-white solid, 70% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 61.62; H, 4.91; N, 11.72, $C_{28}H_{26}N_4O_4S_2$ requires C, 61.52; H, 4.79; N, 11.71%); ν_{max}($CHCl_3$)/cm^{-1} 3391, 1715, 1615, 1224, 1056, 956, 796; δ_H(400 MHz; $CDCl_3$) 8.71 (2H, d, *J* 5 Hz, bipy H-6), 8.44 (2H, s, bipy H-3), 7.67 (2H, d *J* 5 Hz, bipy H-5), 7.61 (2H, d, *J* 15 Hz, H-3), 6.09 (2H, d, *J* 15 Hz, H-2), 5.30 (4H, s, bipy CH_2), 2.64 (6H, s, thiazole C-4 CH_3), 2.35 (6H, s, thiazole C-2 CH_3); *m*/*z* (ESI+) 546.17635 (M^+, $C_{28}H_{26}N_4O_4S_6$ requires 546.13955); 546.2 (36%) (M^+), 169 (62%).

(2*E*,4*E*)-5-Phenylpenta-2,4-dienoic acid 4′-((2*E*,4*E*)-5-phenylpenta-2,4-dienoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4r). White solid, 74% yield, LC retention time = 0.43, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 77.26; H, 5.35; N, 5.34, $C_{34}H_{28}N_2O_4$ requires C, 77.25; H, 5.34; N, 5.30%); ν_{max}(neat)/cm^{-1} 1710, 1624, 1598, 1444, 1353, 1267, 1132, 994, 832, 819, 708, 684; δ_H(400 MHz; $CDCl_3$) 8.70 (2H, d, *J* 5 Hz, bipy H-6), 8.38 (2H, s, bipy H-3), 7.55 (2H, dd, *J* 15 Hz, 15 Hz, H-3), 7.53–7.32 (8H, m, Ph H-2, H-3, H-4, H-5. H-6), 6.95 (4H, m, H-4, H-5), 6.12 (2H, d, *J* 15 Hz, H-2) 5.30 (bipy CH_2), 2.80 (2H, d, *J* 15 Hz, H-2); δ_C(100 MHz; $CDCl_3$) 166.5 (C=O), 156.2 (bipy C-2), 149.5 (bipy C-6), 146.3 (bipy C-4), 145.8 (C-4), 145.8 (C-3), 141.2 (C-5), 135.9 (Ph C-1), 129.2 (Ph C-4), 128.8 (Ph C-3, Ph C-5), 127.3 (C-4), 126.0 (Ph C-2, Ph C-6), 122.1 (C-2), 120.2 (bipy C-3), 119.6 (bipy C-5), 64.1 (bipy CH_2); *m*/*z* (EI) 528.20187 (M^+, $C_{34}H_{28}N_2O_4$ requires 528.20491); 528.2 (43%) (M^+).

(*E*)-3-Thiazol-2-ylbut-2-enoic acid 4′-((*E*)-3-thiazol-2-yl-but-2-enoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4s). Light yellow solid, 95% yield, mixed isomers, 3 : 2; LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 58.76; H, 3.26; N, 8.59, $C_{26}H_{22}N_4O_4S_2$ requires C, 60.21; H, 4.28; N, 10.80%); ν_{max}($CHCl_3$)/cm^{-1} 1717, 1622, 1599, 1464, 1355, 1248, 1168, 1026, 826, 728; δ_H(400 MHz; $CDCl_3$) 8.75, 8.69 (2H, d, *J* 5 Hz, bipy H-6), 8.40, 8.35 (2H, s, bipy H-3), 7.90, 7.85 (2H, d, *J* 4.8 Hz, thiazole H-4), 7.42, 7.25 (4H, d, *J* 4.8 Hz, thiazole H-5, bipy H-5), 6.88, 6.21 (2H, s, H-2), 5.30, 5.26 (4H, bipy CH_2), 2.70, 2.42 (6H, s, C-3 CH_3); δ_C(150 MHz; $CDCl_3$) 168.9 (C-3), 165.7, 165.4 (C=O), 163.9 (C-3), 156.2, 156.1 (bipy C-2), 149.5, 149.4 (bipy C-6), 147.9 (thiazole C-2), 145.8 (bipy C-4), 144.3 (thiazole C-2), 144.2, 142.8 (thiazole C-4), 121.6 (bipy C-3), 121.5 (bipy C-5), 120.9 (thiazole C-5), 119.5 (bipy C-3), 119.4, 117.8 (C-2), 64.6, 64.4 (bipy CH_2), 25.3, 16.9 (C-3

CH_3); *m/z* (ESI+) 519.115523 (M + H, $C_{26}H_{22}N_4O_4S_2$ requires 519.116075); 519.1 (M + H), 541.1 (50%) (M + Na).

(*E*)-3-Phenylbut-2-enoic acid 4′-((*E*)-3-phenylbut-2-enoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4t). Light yellow solid, 98% yield, mixed isomers, 3 : 2; LC retention time = 0.32, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 76.24; H, 5.62; N, 5.61, $C_{32}H_{28}N_2O_4$ requires C, 76.17; H, 5.59; N, 5.50%); ν_{max}(neat)/cm^{-1} 1722, 1626, 1624, 1357, 1266, 1056, 826, 739; δ_H(400 MHz; $CDCl_3$) 8.72, 8.66 (2H, d, *J* 5 Hz, bipy H-6), 8.66, 8.64 (2H, s, bipy H-3), 7.39–7.15 (10H, m, Ph-H), 7.32, 7.28 (2H, d, *J* 5 Hz, bipy H-5), 6.21, 6.17 (H-2), 5.55, 5.42 (4H, bipy CH_2), 1.77, 1.72 (6H, s, C-3 CH_3); δ_C(150 MHz; $CDCl_3$) 165.7, 165.4 (C=O), 163.9 (C-3), 158.2, 157.3 (bipy C-2), 149.9, 149.3 (bipy C-6), 148.8 (bipy C-4), 132.2, 131.5 (Ph C-3, C-5), 128.9, 127.5 (Ph C-2, C-6), 126.9 (Ph C-4), 125.1 (Ph C-1), 124.3 (bipy C-3), 121.9 (bipy C-5), 118.4, 116.5 (C-2), 65.2, 64.1 (bipy CH_2), 25.3, 16.9 (C-3 CH_3); *m/z* (ESI+) 504.20635 (M^+, $C_{32}H_{28}N_2O_4$ requires 504.20491); 504.2 (M^+).

(*E*)-3-(4-Methoxyphenyl)but-2-enoic acid 4′-((*E*)-3-(4-methoxyphenyl)but-2-enoyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (4u). White solid, 98% yield, mixed isomers, 3 : 2; LC retention time = 0.32, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 72.45; H, 4.99; N, 5.73, $C_{34}H_{32}N_2O_6$ requires C, 72.32; H, 4.96; N, 5.71%); ν_{max}(neat)/cm^{-1} 1765, 1678, 1645, 1276, 1067, 829, 749; δ_H(400 MHz; $CDCl_3$) 8.72, 8.66 (2H, d, *J* 5 Hz, bipy H-6), 8.66, 8.64 (2H, s, bipy H-3), 7.45–7.23 (4H, m, Ph AA′BB′), 7.32, 7.28 (2H, d, *J* 5 Hz, bipy H-5), 6.85–6.75 (4H, m, Ph AA′BB′), 6.21, 6.17 (H-2), 5.55, 5.42 (4H, bipy CH_2), 1.77, 1.72 (6H, s, C-3 CH_3), 3.89 (6H, s, OMe); δ_C(150 MHz; $CDCl_3$) 165.8, 165.2 (C=O), 162.9 (C-4), 158.2, 157.9 (bipy C-2), 151.2, 150.2 (bipy C-6), 149.2 (bipy C-4), 148.3 (Ph C-4), 115.3, 115.1 (Ph C-3, C-5), 129.0, 127.5 (Ph C-2, C-6), 128.2 (Ph C-1), 122.1 (bipy C-5), 125.3 (bipy C-3), 114.4, 113.5 (C-2), 67.3, 65.2 (bipy CH_2), 56.2 (OMe), 20.4, 17.4 (C-3 CH_3); *m/z* (ESI+) 564.23467 (M^+, $C_{34}H_{32}N_2O_6$ requires 564.22604); 564.3 (M^+).

***Trans*-3-phenylprop-2-enoic acid methyl ester (5).**

Preparation A. Following the general procedure outlined by MacCoss *et al.*,[19] **4a** (238 mg, 0.5 mmol) and immobilised potassium thiophenol (10 mg, catalyst) in MeOH (3.5 cm^3) were heated under microwave irradiation at 130 °C for 30 min. The suspended resin was removed by filtration and washed with DCM (2 cm^3). The cleaved bipyridine diol was scavenged by the addition of IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 577 mg, 1.5 equiv.). Filtration of the resin followed by washing with DCM (3 × 5 cm^3), and removal of solvent under reduced pressure yielded the desired ester **5** in 95% yield.

Preparation B. **4a** (238 mg, 0.5 mmol) and triethylamine (51 mg, 0.5 mmol) in a mixture of MeOH (2 cm^3) and THF (2 cm^3) were heated under microwave irradiation at 120 °C for 120 min. The cleaved bipyridine diol was scavenged by the addition of IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 577 mg, 1.5 equiv.). Filtration of the resin followed by washing with DCM (3 × 5 cm^3), and removal of solvent under reduced pressure yielded the desired ester **5** in 95% yield.

3-Phenyl-3-phenylsulfanylpropionic acid 4′-(3-phenyl-3-(phenylsulfanyl)propionyloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (6). A solution of *n*-BuLi (0.144 cm^3, 1.6 M, 0.231 mmol, 2 equiv.) in THF was added to a stirred solution of thiophenol (228 mg, 2.07 mmol, 18 equiv.) in THF at −78 °C over 10 min; the stirring was continued for an hour while the reaction was allowed to slowly warm up to −10 °C. A solution of the bipyridine supported Horner–Emmons ester **4a** (55 mg, 0.116 mmol, 1 equiv.) in THF was added to this mixture over 15 min at −78 °C, and the reaction allowed to warm up to room temperature overnight. The progress of this reaction was followed by LC-MS and TLC. The solution was diluted with DCM (25 cm^3), and IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 200 mg, 2.2 equiv.) suspended in the reaction mixture, which was allowed to stir overnight. Uptake of the bipyridine product was followed by LC-MS. The copper(II) resin was then filtered through a Bond Elut reservoir, and washed with DCM (25 cm^3) and ether (10 cm^3). The "release" was carried out by suspending this resin in TMEDA (0.013 g, 0.116 mmol) in DCM (25 cm^3) for 3 h. The resin was then filtered, washed with DCM (30 cm^3), and the combined filtrate evaporated to give the desired product in 92% yield: White solid, LC retention time = 0.54, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 72.60; H, 5.25; N, 4.13, $C_{42}H_{36}N_2O_4S_2$ requires C, 72.39; H, 5.21; N, 4.02%); ν_{max}(neat)/cm^{-1} 1726, 1597, 1438, 1231, 1148, 1024, 824, 747, 696; δ_H(400 MHz; $CDCl_3$) 8.55 (2H, d, *J* 5 Hz, bipy H-6), 8.28 (2H, s, bipy H-3), 7.30 (10H, m, Ph–H), 7.02 (2H, d, *J* 5 Hz, bipy H-5), 5.12 (4H, s, bipy CH_2), 4.68 (2H, t, *J* 6 Hz, PhC*H*CH_2CO_2), 3.05 (4H, d, *J* 6 Hz, PhCHC*H*$_2CO_2$); δ_C(100 MHz; $CDCl_3$) 170.3 (C=O), 156.0 (bipy C-2), 149.3 (bipy C-6), 148.4 (bipy C-4), 145.6 (Ph C-1), 140.2 (Ph C-1′), 133.4 (Ph C-3, Ph C-5), 128.9 (Ph C-2, Ph C-6), 128.5 (Ph C-2′, Ph C-6′, Ph C-4′), 127.7 (Ph C-4′), 121.3 (bipy C-5), 119.4 (bipy C-3), 64.7 (bipy CH_2), 49.2 (PhC*H*CH_2CO_2), 40.9 (PhCH*C*H_2CO_2); *m/z* (ESI+) 697.21810 (M + H, $C_{42}H_{37}N_2O_4S_2$ requires 697.21947); 697.2 (14%) (M + H), 576.4 (100%), 571.1 (50%), 335.1 (100%).

Synthesis of (±)-4-nitro-3-phenylbutyric acid 4′-(4-nitro-3-phenylbutyryloxymethyl)-[2,2′]bipyridinyl-4-ylmethyl ester (7) by nitromethane addition. A solution of TBAF (1 M in THF) (0.74 cm^3, 0.735 mmol, 7.35 equiv.) was added to a stirred solution of nitromethane (38 mg, 0.63 mmol, 6 equiv.) and bipyridine-supported Horner–Emmons product **4a** (47.6 mg, 0.1 mmol, 1 equiv.) in THF at −10 °C in a 25 cm^3 round-bottomed flask. The solution was allowed to warm up to room temperature overnight. The progress of the reaction was followed by LC-MS and TLC. The solution was then diluted in turn with methanol (5 cm^3), and DCM (10 cm^3). IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 323 mg, 4 equiv.) was then suspended to the reaction mixture, and the uptake of the bipyridine product was followed by LC-MS. The resin was then filtered through a Bond Elut reservoir, and washed with DCM (5 cm^3) and THF (5 cm^3). The release of the product from the resin was performed by re-suspending the resin in a solution of TMEDA (31 µl, 0.263 mmol, 2.5 equiv.) in DCM (10 cm^3), and was stirred over 2 h. The resin was then filtered, and the filtrate was then evaporated to dryness under high vacuum to give our desired addition product in 78% yield: Colourless oil, LC retention time = 0.41, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); ν_{max}(neat)/cm^{-1} 2922, 1738, 1599, 1548, 1455, 1377, 1107, 823, 765, 699; δ_H(400 MHz; $CDCl_3$) 8.61 (2H, d, *J* 5 Hz, bipy H-6), 8.28 (2H, s, bipy H-3), 7.25 (5H, m, Ph–H), 7.08 (2H, d, *J* 5 Hz, bipy H-5), 5.18 (4H, s, bipy CH_2), 4.67 (4H, m, CH_2NO_2), 4.02 (2H, quin, *J* 6 Hz, PhC*H*), 2.92 (4H, d, *J* 6 Hz, CHCH_2CO_2); δ_C(100 MHz; $CDCl_3$) 170.3 (C=O), 156.0 (bipy C-2), 149.5 (bipy C-6), 145.4 (Ph C-1), 137.9 (bipy C-4), 129.2 (Ph C-3, Ph C-5), 128.2 (Ph C-4), 127.4 (Ph C-2, Ph C-6), 122.1 (bipy C-3), 119.4 (bipy C-5), 79.4 (*C*H_2NO_2), 64.9 (bipy CH_2), 40.2 (PhCH*C*H_2CO_2), 21.1 (PhCHCH_2CO_2); *m/z* (ESI+) 621.19570 (M + Na, $C_{32}H_{30}NaN_4O_8$ requires 621.19613); 621.2 (75%) (M + Na), 600.2 (35%) (M + 2), 599.2 (100%) (M + 1).

4-Methyl-5-phenylcyclohexane-1,3-dione (8)[20]. A solution of potassium *tert*-butoxide (83.1 mg, 0.741 mmol, 1.2 equiv.) was added to a solution of butan-2-one (53.3 mg, 0.741 mmol) in THF (2 cm^3) at 0 °C in a 5 cm^3 microwave sample vial, and was allowed to stir for 20 min at this temperature. Then a solution of bipyridine supported Horner–Emmons ester **4a** (295 mg, 0.62 mmol) in THF (2 cm^3) was added and allowed to warm up to room temperature. The sample vial was then heated under microwave irradiation at 70 °C for 45 min. The by-product bipyridine diol was then scavenged by the addition of IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 713 mg, 1.5 equiv.). Filtration of resin, washing with DCM, and removal of solvents of the filtrate gave the desired cyclohexane-1,3-dione

in 92% yield: Off-white crystals, mp 106 °C (lit. mp 103–105 °C);[20] δ_H(400 MHz; $CDCl_3$) 7.38 (3H, t, *J* 8.5 Hz, Ph H-3, H-5), 7.28 (2H, t, *J* 8.5 Hz, Ph H-2, Ph H-6), 7.19 (1H, m, Ph H-4), 3.58 (1H, m, H-2), 3.48 (1H, m, H-5), 2.92 (1H, m, H-4), 2.89 (2H, m, H-6), 1.04 (d, 3H, *J* 7 Hz, CH_3); ^{1}H NMR was in agreement with the literature assignments.[20]

4-Methoxy-6-phenylpyrimidin-2-ylamine (9)[21,22]. A solution of guanidine hydrochloride (21 mg, 0.221 mmol, 3 equiv.) in methanol (2.5 cm^3) was added to a solution of bipyridine-supported Horner–Emmons ester **4a** (35 mg, 0.074 mmol) in THF in a microwave sample vial, then polymer-supported triethylamine equivalent (280 mg, 0.384 mmol, 4 equiv., diethylaminomethylpolystyrene, ~3.2 mmol g^{-1}; Fluka Cat. No. 31866) was added, and the mixture heated at 150 °C for 7 h. The bipyridine by-product was then scavenged by the shaking with copper(II) resin (loading 1.3 mmol g^{-1}, 142 mg, 2.5 equiv.) at room temperature. After filtration of resin, and washing with DCM, the filtrate was evaporated to dryness. Recrystallisation gave the desired pyrimidine in 80% yield: Off-white solid, mp 153 °C (lit. mp[21,22] 152 °C); LC retention time = 0.24 (DCM–NEt_3 = 2 : 1); (Found: C, 65.84; H, 5.62; N, 21.01, $C_{11}H_{11}N_3O$ requires C, 65.66; H, 5.51; N, 20.88%); ν_{max}(neat)/cm^{-1} 3472, 3367, 1578, 1485, 1298, 1189, 1054, 823, 739, 723; δ_H(400 MHz; $CDCl_3$) 7.56 (2H, d, *J* 7.2 Hz, Ph H-2, H-6), 7.43 (2H, t, *J* 7.2 Hz, Ph H-3, Ph H-5), 7.29 (1H, t, *J* 7.2 Hz, Ph H-4), 6.32 (1H, s, pyrimidine H-5), 5.54 (2H, br s, NH_2), 4.08 (3H, s, OCH_3); δ_C(100 MHz; $CDCl_3$) 173.2 (pyrimidine C-4), 170.1 (pyrimidine C-6), 168.2 (pyrimidine C-2), 142.8 (Ph C-1), 130.9 (Ph C-4), 130.6 (Ph C-3, C-5), 128.2 (Ph C-2, Ph C-6), 105.5 (pyrimidine C-5), 59.4 (OCH_3); *m/z* (EI+) 202.09765 (M + H, $C_{11}H_{12}N_3O$ requires 202.09094); 202.1 (55%) (M + H), 124.1 (36%), 77 (21%).

Microwave-assisted [3 + 2] cycloaddition of nitrile oxide and bipyridine-supported Horner–Emmons ester

A solution of phenyl isocyanate (79.3 mg, 0.672 mmol, 8 equiv.) and nitroethane (25.2 mg, 0.336 mmol) with a catalytic amount of polymer-supported triethylamine equivalent (80 mg, 0.256 mmol, diethylaminomethylpolystyrene, ~3.2 mmol g^{-1}; Fluka Cat. No. 31866) in THF (3 cm^3) were heated under microwave irradiation at 90 °C for 40 min. To the reaction mixture was added bipyridine-supported Horner–Emmons ester **4a** (47.6 mg, 0.1 mmol) in THF (1 cm^3) and the reaction heated under microwave irradiation for 10 cycles of 30 min. The reaction progress was followed by LC-MS and TLC. Upon complete reaction the mixture was filtered, the resin washed with DCM (2 × 2 cm^3) and the combined filtrates collected. It was then diluted with DCM (25 cm^3), IRC-718 copper(II) resin (loading 1.3 mmol g^{-1}, 100 mg, 1.3 equiv.) added and allowed to shake for 5 h. The uptake of the bipyridine product to the resin was monitored by LC-MS. The resin was then filtered through a Bond Elut reservoir, and washed with DCM (2 × 10 cm^3) and Et_2O (10 cm^3). The resin was then re-suspended in a solution of TMEDA (24 mg, 0.21 mmol, 1.6 equiv. based on the resin) in DCM (20 cm^3), and gently shaken for 5 h. The resin was filtered, washed DCM (2 × 5 cm^3), and the combined filtrates evaporated to yield compound **10** as a pale yellow oil comprising of a mixture of regioisomers. ^{1}H NMR was in agreement with the literature assignments.

Oxidation of the [3 + 2] cycloadduct with silica-supported ceric ammonium nitrate. To a cooled suspension of ceric ammonium nitrate on silica (1.871 g, 0.468 mmol, ammonium cerium(IV) nitrate on silica gel, ~0.25 mmol g^{-1}; Fluka Cat. No. 22254) in acetone (25 cm^3) was added a solution of cycloadduct (75 mg, 0.117 mmol) in acetone (5 cm^3). The solution was stirred for 2 h then filtered through a pad of Celite (4 g) and the solvent removed under reduced pressure to yield compound **11** as a mixture of regioisomers (**11a** and **11b**). ^{1}H NMR was in agreement with the literature assignments.

(3-Methyl-4-phenylisoxazol-5-yl)acetic acid 4′-[(3-methyl-4-phenylisoxazol-5-yl)acetoxymethyl]-[2,2′]bipyridinyl-4-yl methyl ester (11a). Off-white solid, ν_{max}(neat)/cm^{-1} 2974, 1757, 1743, 1599, 1557, 1456, 1233, 1204, 1028, 866, 744, 698; δ_H(400 MHz; $CDCl_3$) 8.63 (2H, d, *J* 5 Hz, bipy H-6), 8.40 (2H, s, bipy H-3), 7.65 (4H, m, Ph H-2, H-6), 7.58 (4H, m, Ph H-3, Ph H-5), 7.52 (2H, m, Ph H-4), 7.32 (2H, d, *J* 5 Hz, bipy H-5), 5.34 (4H, s, bipy CH_2), 2.45 (6H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 169.5 (C=O), 160.2 (isoxazole C-5), 158.3 (bipy C-2), 153.2 (bipy C-6), 151.6 (isoxazole C-3), 147.2 (bipy C-4), 139.5 (Ph C-1), 131.4 (Ph C-3, Ph C-5), 129.7 (Ph C-4), 129.3 (Ph C-2, Ph C-6), 125.3 (bipy C-3), 122.4 (bipy C-5), 104.2 (isoxazole C-4), 67.5 (bipy CH_2), 8.5 (isoxazole CH_3); *m/z* (ESI+) 609.17823 (M + Na, $C_{34}H_{26}N_4NaO_6$ requires 609.17500); 609.2 (35%) (M + Na).

(3-Methyl-5-phenylisoxazol-4-yl)acetic acid 4′-[(3-methyl-5-phenylisoxazol-4-yl)acetoxymethyl]-[2,2′]bipyridinyl-4-yl methyl ester (11b). ν_{max}(neat)/cm^{-1} 1757, 1746, 1634, 1537, 1459, 1236, 1209, 1034, 866, 747; δ_H(400 MHz; $CDCl_3$) 8.63 (2H, d, *J* 5 Hz, bipy H-6), 8.40 (2H, s, bipy H-3), 7.65 (4H, m, Ph H-2, H-6), 7.58 (4H, m, Ph H-3, Ph H-5), 7.52 (2H, m, Ph H-4), 7.32 (2H, d, *J* 5 Hz, bipy H-5), 5.34 (4H, s, bipy CH_2), 2.45 (6H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 169.5 (C=O), 160.2 (isoxazole C-5), 158.3 (bipy C-2), 153.2 (bipy C-6), 151.6 (isoxazole C-3), 147.2 (bipy C-4), 139.5 (Ph C-1), 131.4 (Ph C-3, Ph C-5), 129.7 (Ph C-4), 129.3 (Ph C-2, Ph C-6), 125.3 (bipy C-3), 122.4 (bipy C-5), 104.2 (isoxazole C-4), 67.5 (bipy CH_2), 8.5 (isoxazole CH_3); *m/z* (+EI) 609.17690 (M + Na, $C_{34}H_{26}N_4NaO_6$ requires 609.17500); 609.2 (75%) (M^+).

4-Phenylpyrrolidin-2-one (12)[23,24]. Polymer-supported borohyride resin (Amberlite IRA-400 as supplied by Aldrich; loading 2.5 mmol, 252 mg, 0.63 mmol, 6 equiv.) was suspended in a solution of nickel(II) chloride hexahydrate (150 mg, 0.63 mmol) in MeOH (25 cm^3) and was shaken for 2 h. The resin was isolated by filtration and re-suspended in a solution of bipyridine-supported Horner–Emmons adduct **7** (50 mg, 0.105 mmol, 1 equiv.) in DCM (30 cm^3). The progress of the reductive cyclisation was followed by LC-MS and TLC. Upon completion of the reaction, the nickel(II) borohydride resin was removed by filtration. IRC-718 copper(II) resin (loading 1.3 mmol, 323 mg, 4 equiv.) was added to the solution in order to scavenge any bipyridine diol by-products. The suspension was gently shaken for 2 h, and the copper(II) resin then filtered and washed with DCM (2 × 10 cm^3). Concentration of the filtrate under reduced pressure yielded the desired γ-lactam in 60% yield: Colourless crystals, mp 95 °C (lit. mp 96–97 °C);[23,24] LC retention time = 2.49 (*m/z* 162, M + H); ν_{max}(neat)/cm^{-1} 2419, 1609, 1498, 1298, 1178, 1127, 982, 721; δ_H(400 MHz; $CDCl_3$) 7.23 (2H, t, *J* 8.3 Hz, Ph H-3, H-5), 7.19 (2H, t, *J* 8.3 Hz, Ph H-2, Ph H-6), 7.12 (1H, t, *J* 8.3 Hz, Ph H-4), 3.73 (2H, d, *J* 5.3 Hz, pyrrolidine H-5), 3.45 (1H, m, pyrrolidine H-4), 2.58 (2H, d, *J* 5.3 Hz, pyrrolidine H-3); ^{1}H NMR was in agreement with the literature assignments.

General scavenging procedure using bipyridyl diol (1) as a substrate scavenger for the synthesis of heterocyclic sulfonamides and amides. Polymer-supported triethylamine equivalent (260 mg, 0.831 mmol, 3.0 equiv., diethylaminomethyl polystyrene, ~3.2 mmol g^{-1}; Fluka Cat. No. 31866) was suspended in a solution of the specified secondary amine (0.3 mmol, 1 equiv.) in DCM (5 cm^3). To the reaction mixture was added a solution of the corresponding sulfonyl chloride (0.6 mmol, 2.0 equiv.) in DCM (5 cm^3). The mixture was then shaken overnight. A solution of bipyridine diol (0.216 g, 0.594 mmol, 2.0 equiv.) in DCM (5 cm^3) was added and the reaction monitored by LC-MS. Upon complete reaction of the excess sulfonyl chloride, Amberlite IRC-718 copper(II) resin (520 mg, 0.743 mmol, loading 1.34 mmol g^{-1}, 2.5 equiv.) was added to the mixture; the "catching" of the bipyridine tag was monitored by LC-MS. The resin was removed by filtration, and washed in turn with ether (5 cm^3) and DCM (5 cm^3). The filtrates were combined

and the solvent removed under reduced pressure. The purity of the corresponding sulfonamide was determined by LC-MS and ^{1}H NMR (see Table 3).

2-[4-(6-Morpholin-4-ylpyridine-3-sulfonyl)-[1,4]diazepam-1-yl]nicotinonitrile (13a). Off-white solid, mp 168 °C, LC retention time = 2.94 (*m/z* 428.2, M$^+$); ν_{max}(neat)/cm^{-1} 2859, 1585, 1551, 1504, 1308, 1143, 1104, 1042, 997, 941, 837, 758, 702; δ_H(500 MHz; $CDCl_3$) 8.45 (1H, d, *J* 5 Hz, py H-6′), 8.19 (1H, d, *J* 5 Hz, py H-5), 7.68 (2H, d, *J* 8 Hz, py H-4), 7.63 (2H, d, *J* 8 Hz, py H-3′), 6.57 (1H, t, *J* 5 Hz, py H-5), 6.48 (1H, d, py H-5′), 3.94 (4H, t, *J* 6.5 Hz, diazepine H-3, H-5), 3.72 (4H, t, *J* 6.5 Hz, morpholine H-2, H-6), 3.56 (4H, t, *J* 6.5 Hz, morpholine H-3, H-5), 3.43 (2H, t, *J* 6.5 Hz, diazepine H-2), 3.19 (2H, t, *J* 6.5 Hz, diazepine H-7), 2.02 (2H, t, *J* 6.5 Hz, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 160.2 (C), 157.6 (C), 152.2 (CH), 147.9 (CH), 144.8 (CH), 136.2 (CH), 123.7 (C), 119.0 (CN), 112.5 (CH), 105.3 (CH), 90.4 (C), 66.5 (CH_2), 51.3 (CH_2), 49.3 (CH_2), 48.6 (CH_2), 47.6 (CH_2), 44.9 (CH_2), 28.5 (CH_2); *m/z* (EI+) 428.16426 (M$^+$, $C_{20}H_{24}N_6O_3S$ requires 428.16306); 428.2 (100%) (M$^+$).

2-[4-(4-Methyl-3,4-dihydro-2*H*-benzo[1,4]oxazine-7-sulfonyl)-[1,4]diazepan-1-yl]nicotinonitrile (13b). LC retention time = 3.42 (*m/z* 413.2); ν_{max}(neat)/cm^{-1} 1649, 1598, 1336, 1209, 1182, 1089, 1039, 928, 751; δ_H(500 MHz; $CDCl_3$) 8.30 (1H, d, *J* 6 Hz, py H-6), 7.45 (2H, d, *J* 6 Hz, py H-4), 6.95 (1H, m, benzooxazine H-8), 6.75 (1H, d, *J* 7.2 Hz, benzooxazine H-5), 6.63 (2H, t, *J* 6 Hz, py H-5), 4.24 (2H, t, *J* 7 Hz, benzooxazine H-2), 4.08 (2H, br t, diazepine H-3), 4.02 (2H, br t, diazepine H-2), 3.74 (2H, br t, diazepine H-7), 3.65 (2H, br t, diazepine H-5), 3.28 (2H, t, *J* 6 Hz, benzooxazine H-3), 2.85 (3H, s, benzooxazine N-4 CH_3), 2.17 (2H, br t, diazepine H-6); δ_C(100 MHz; $CDCl_3$) 157.2 (sat. carbon), 152.4 (CH), 148.2 (sat. carbon), 144.9 (CH), 133.5 (sat. carbon), 128.6 (sat. carbon), 118.9 (CN), 118.1 (CH), 116.1 (CH), 112.9 (CH), 111.0 (CH), 91.3 (sat. carbon), 65.1 (CH_2), 51.4 (CH_2), 50.1 (CH_2), 48.1 (CH_2), 47.6 (CH_2), 45.2 (CH_2), 38.8 (CH_3), 26.4 (CH_2); *m/z* (EI+) 413.15425 (M$^+$, $C_{20}H_{23}N_5O_3S$ requires 413.15216); 413.2 (43%) (M$^+$).

2-[4-(Quinoxaline-6-carbonyl)-[1,4]diazepan-1-yl]-nicotinonitrile (13c). Yellow oil, LC retention time = 2.74 (*m/z* 359.10); ν_{max}(neat)/cm^{-1} 2208, 1627, 1587, 1549, 1445, 1424, 1363, 1234, 1174, 1021, 906, 757, 743, 731; δ_H(500 MHz; $CDCl_3$) 8.86 (2H, s, quinoxaline H-2, H-3), 8.30 (1H, d, *J* 6 Hz, py H-6), 8.12 (1H, s, quinoxaline H-5), 8.02 (4H, d, *J* 5.5 Hz, quinoxaline H-8), 7.45 (2H, d, *J* 6 Hz, py H-4), 6.63 (2H, t, *J* 6 Hz, py H-5), 4.08 (2H, br t, diazepine H-3), 4.02 (2H, br t, diazepine H-2), 3.74 (2H, br t, diazepine H-7), 3.65 (2H, br t, diazepine H-5), 2.17 (2H, br t, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 168.2 (C=O), 157.3 (C), 152.2 (CH), 145.9 (CH × 2), 144.8 (CH), 143.1 (C), 142.4 (C), 129.9 (CH), 128.2 (CH), 127.4 (CH), 118.8 (CN), 112.8 (CH), 91.1 (C), 51.2 (CH_2), 50.4 (CH_2), 49.6 (CH_2), 48.4 (CH_2), 47.0 (CH_2), 45.1 (CH_2), 26.3 (CH_2); *m/z* (EI+) 358.15410 (M$^+$, $C_{20}H_{18}N_6O$ requires 358.15421); 358.2 (35%) (M$^+$).

2-[4-(3,5-Dimethylisoxazole-4-carbonyl)-[1,4]diazepan-1-yl]nicotinonitrile (13d). Off-white solid, mp 103 °C, LC retention time = 3.22 (*m/z* 326.0); ν_{max}(neat)/cm^{-1} 2920, 1587, 1503, 1439, 1333, 1171, 1120, 977, 902, 839, 755, 690; δ_H(500 MHz; $CDCl_3$) 8.22 (1H, d, *J* 5 Hz, py H-6), 7.65 (1H, d, *J* 5 Hz, py H-4), 6.65 (1H, s, py H-5), 3.95 (4H, t, *J* 6 Hz, diazepine H-2, H-3), 3.48 (2H, t, *J* 6 Hz, diazepine H-5), 3.29 (2H, t, *J* 6 Hz, diazepine H-7), 2.61 (3H, s, isoxazole C-5 CH_3), 2.28 (3H, s, isoxazole C-3 CH_3), 2.08 (2H, t, *J* 6 Hz, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 173.2 (C=O), 166.4 (C), 157.4, 157.4 (C), 152.2 (CH), 144.8 (CH), 118.0 (CN), 116.0 (C), 112.8 (CH), 90.5 (C), 51.4 (CH_2), 48.9 (CH_2), 48.8 (CH_2), 47.1 (CH_2), 28.6 (CH_2), 12.8 (CH_3), 11.1 (CH_3); *m/z* (EI+) 325.15745 (M$^+$, $C_{17}H_{19}N_5O_2$ requires 325.15387); 202.1 (55%) (M + H), 124.1 (36%).

2-[4-(1,5-Dimethyl-1*H*-pyrazole-3-carbonyl)-[1,4]diazepan-1-yl]nicotinonitrile (13e). Yellow oil, LC retention time = 2.75 (*m/z* 325.1, M + H); ν_{max}(neat)/cm^{-1} 2924, 1613, 1587, 1549, 1496, 1427, 1220, 1160, 1113, 939, 759, 730; δ_H(500 MHz; $CDCl_3$) 8.18 (1H, d, *J* 5 Hz, py H-6), 7.62 (1H, d, *J* 5 Hz, py H-4), 6.53 (1H, t, *J* 5 Hz, py H-5), 6.32 (1H, s, pyrazole H-4), 3.94, 3.92 (4H, t, *J* 6 Hz, diazepine H-2, H-3), 3.89, 3.83 (4H, t, *J* 6 Hz, diazepine H-5, H-7), 3.75 (3H, s, pyrazole N-1 CH_3), 2.22 (3H, s, pyrazole C-5 CH_3), 2.05 (2H, quintet, *J* 6 Hz, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 164.0 (C=O), 157.6 (C), 152.2 (C), 144.8 (CH), 141.8 (C), 138.9 (C), 119.2 (CN), 112.16 (CH), 108.0 (CH), 90.2 (C), 52.5 (CH_2), 50.1 (CH_2), 48.8 (CH_2), 46.2 (CH_2), 36.5 (CH_3), 25.7 (CH_2), 11.0 (CH_3); *m/z* (EI+) 324.16858 (M$^+$, $C_{17}H_{20}N_6O$ requires 324.16986); 324.2 (45%) (M$^+$).

2-[4-(1-Methyl-1*H*-imidazole-4-sulfonyl)-[1,4]diazepan-1-yl]nicotinonitrile (13f). Yellow crystals, mp 151–152 °C, LC retention time = 2.73 (*m/z* 347.1); ν_{max}(neat)/cm^{-1} 2211, 1585, 1552, 1486, 1454, 1443, 1327, 1218, 1156, 1117, 1039, 958, 868, 857, 759, 691; δ_H(500 MHz; $CDCl_3$) 8.19 (1H, d, *J* 6 Hz, py H-6), 7.34 (1H, d, *J* 6 Hz, py H-4), 7.33 (2H, m, imidazole H-2, py H-5), 6.55 (1H, t, *J* 6 Hz, py H-5), 3.94 (4H, m, diazepine H-2, H-3), 3.66 (3H, imidazole N-1 CH_3), 3.54, 3.34 (4H, t, *J* 6 Hz, diazepine H-5, H-7), 2.03 (2H, m, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 157.7 (C), 152.2 (CH), 144.8 (CH), 140.3 (C), 138.9 (CH), 123.7 (CH), 119.1 (CN), 112.3 (CH), 90.3 (C), 51.6 (CH_2), 49.6 (CH_2), 48.5 (CH_2), 48.1 (CH_2), 33.9 (CH_3), 28.5 (CH_2); *m/z* (EI+) 346.12050 (M$^+$, $C_{15}H_{18}N_6O_2S$ requires 346.12119); 346.1 (45%) (M$^+$), 264.1 (45%).

2-[4-(1,2-Dimethyl-1*H*-imidazole-4-sulfonyl)-[1,4]diazepan-1-yl]nicotinonitrile (13g). Colourless crystals, mp 105 °C, LC retention time = 2.54 (*m/z* 361.0); ν_{max}(neat)/cm^{-1} 1586, 1547, 1460, 1329, 1148, 1123, 1034, 903, 759, 707, 672; δ_H(500 MHz; $CDCl_3$) 8.20 (1H, d, *J* 5 Hz, py H-6), 7.62 (1H, d, *J* 5 Hz, py H-4), 7.21 (1H, s, imidazole H-5), 6.57 (1H, t, *J* 5 Hz, py H-5), 3.93 (4H, t, *J* 6 Hz, diazepine H-2, H-3), 3.55 (2H, t, *J* 6 Hz, diazepine H-7), 3.50 (3H, s, imidazole N-1 CH_3), 3.35 (2H, t, *J* 6 Hz, diazepine H-5), 2.27 (3H, s, imidazole C-2 CH_3), 2.07 (2H, t, *J* 6 Hz, diazepine H-6); δ_C(125 MHz; $CDCl_3$) 157.6 (C), 152.2 (CH), 146.9 (C), 144.7 (CH), 137.5 (CH), 124.2 (CH), 119.1 (CN), 112.3 (CH), 90.2 (C), 51.5 (CH_2), 49.5 (CH_2), 49.5 (CH_2), 48.0 (CH_2), 33.3 (CH_3), 28.5 (CH_2), 13.0 (CH_3); *m/z* (EI+) 360.13838 (M$^+$, $C_{16}H_{20}N_6O_2S$ requires 360.13684); 360.1 (25%) (M$^+$), 201.1 (36%).

4-{5-[4-(2-Nitro-4-(trifluoromethyl)phenyl)piperazine-1-sulfonyl]-pyridin-2-yl}morpholine (14a). Yellow solid, mp 202–203 °C, LC retention time = 2.78 (*m/z* 502.1, M + H); ν_{max}(neat)/cm^{-1} 1621, 1512, 1317, 1225, 1178, 1128, 935, 856, 767; δ_H(500 MHz; $CDCl_3$) 8.52 (1H, s, py H-6), 7.92 (1H, s, Ph H-3), 7.78 (1H, m, *J* 7 Hz, py H-4), 7.71 (1H, m, py H-3), 7.05 (1H, d, *J* 8.2 Hz, Ph H-5), 6.48 (1H, d, *J* 8.2 Hz, Ph H-6), 3.65 (4H, br t, morpholine H-3, H-5), 3.57 (4H, br t, piperazine H-2, H-6), 3.07 (4H, br t, morpholine H-2, H-6), 2.98 (4H, br t piperazine H-3, H-5); δ_C(125 MHz; $CDCl_3$) 160.3 (C), 148.6 (CH), 147.6 (C), 141.5 (CH), 139.4 (C), 136.7 (CH), 130.3 (CH), 125.1 (C), 123.7 (CH), 121.6 (CH), 120.3 (J_{C-F} 48 Hz, CF_3), 119.0 (C), 105.4 (CH), 66.3 (CH_2), 50.6 (CH_2), 45.6 (CH_2), 44.7 (CH_2); *m/z* (EI+) 501.12867 (M$^+$, $C_{20}H_{22}F_3N_5O_5S$ requires 501.12937); 501.1 (48%) (M$^+$).

4-Methyl-7-[4-(2-nitro-4-(trifluoromethyl)phenyl)piperazine-1-sulfonyl]-3,4-dihydro-2*H*-benzo[1,4]oxazine (14b). Pale yellow gum, LC retention time = 3.34 (*m/z* 486.1); ν_{max}(neat)/cm^{-1} 1638, 1581, 1310, 1292, 1192, 1122, 1074, 1045, 928, 756, 769; δ_H(400 MHz; $CDCl_3$) 8.12 (1H, s, Ph H-3), 7.72 (1H, d, *J* 7.1 Hz, Ph H-5), 7.18 (1H, d, *J* 7.5 Hz, benzooxazine H-6), 7.07 (1H, d, *J* 7.1 Hz, Ph H-6), 6.95 (1H, s, benzooxazine H-8), 6.85 (1H, d, *J* 7.5 Hz, benzooxazine H-5), 4.38 (4H, br d, benzooxazine H-2, H-3), 3.35 (4H, br d, piperazine H-3, H-5), 3.25 (3H, s, N-1 CH_3), 2.95 (4H, br d,

piperazine H-2, H-6); δ_C(100 MHz; $CDCl_3$) 147.8 (sat. carbon), 141.7 (sat. carbon), 136.9 (sat. carbon), 130.4 (CH), 127.5 (sat. carbon), 123.9 (J_{C-F} 278.2 Hz, CF_3), 121.4 (CH), 118.0 (CH), 116.0 (CH), 110.9 (CH), 65.0 (CH_2), 50.6 (CH_2), 48.2 (CH_2), 46.0 (CH_2), 29.7 (N-CH_3); *m/z* (EI+) 486.11925 (M^+, $C_{20}H_{21}F_3N_4O_5S$ requires 486.11847); 486.1 (43%) (M^+).

[4-(2-Nitro-4-(trifluoromethyl)phenyl)piperazin-1-yl]quinoxalin-6-ylmethanone (14c). Yellow crystals, mp 142 °C, LC retention time = 3.45 (*m/z* 432.1, M + H); ν_{max}(neat)/cm^{-1} 1621, 1533, 1323, 1234, 1119, 1013, 905, 727; δ_H(500 MHz; $CDCl_3$) 8.85 (2H, s, quinoxaline H-2, H-3), 8.11 (2H, m, quinoxaline H-7, H-8), 8.04 (1H, s, quinoxaline H-5), 7.68 (1H, d, *J* 8 Hz, Ph H-3), 7.66 (1H, d, *J* 8Hz, Ph H-5), 7.14 (1H, d, Ph H-6), 3.64 (4H, br d, piperazine H-3, H-5), 3.07 (4H, br d, piperazine H-2, H-6); δ_C(125 MHz; $CDCl_3$) 169.1 (C=O), 147.7 (C), 146.1 (CH), 146.0 (CH), 143.3 (C), 142.4 (C), 141.7 (C), 136.7 (C), 130.5 (CH), 130.4 (CH), 128.7 (CH), 128.2 (CH), 124.1 (CH), 122.0 (CF_3), 121.2 (CH), 51.0 (CH_2), 49.8 (CH_2); *m/z* (EI+) 431.11906 (M^+, $C_{20}H_{16}F_3N_5O_3$ requires 431.12052); 431.1 (25%) (M + H).

3,5-Dimethylisoxazol-4-yl-[4-(2-nitro-4-(trifluoromethyl)phenyl)-piperazin-1-yl]methanone (14d). Yellow crystals, mp 151 °C, LC retention time = 3.67 (*m/z* 437.0, M + K); ν_{max}(neat)/cm^{-1} 1626, 1537, 1328, 1182, 1152, 1126, 1089, 944, 731; δ_H(500 MHz; $CDCl_3$) 8.02 (2H, s, Ph H-3), 7.67 (1H, d, *J* 8 Hz, Ph H-5), 7.14 (1H, d, *J* 8 Hz, Ph H-6), 3.26 (4H, t, *J* 5 Hz, piperazine H-2, H-6), 3.16 (4H, t, *J* 5 Hz, piperazine H-3, H-5), 2.60 (3H, s, isoxazole C-5 CH_3), 2.36 (3H, s, isoxazole C-3 CH_3); δ_C(125 MHz; $CDCl_3$) 168.2 (C=O), 174.0 (C=O), 157.9 (C), 147.6 (C), 142.1 (C), 130.5 (CH), 124.8 (q, *J* 34.4 Hz, CF_3), 124.1 (CH), 121.9 (C), 121.6 (CH), 113.2 (C), 50.9 (CH_2), 45.3 (CH_2), 13.0 (CH_3), 11.4 (CH_3); *m/z* (EI+) 398.12145 (M^+, $C_{17}H_{17}F_3N_4O_4$ requires 398.12019); 398.1 (25%) (M^+).

1,5-Dimethyl-1*H*-pyrazol-3-yl-[4-(2-nitro-4-(trifluoromethyl)-phenyl)piperazin-1-yl]methanone (14e). Yellow solid, mp 115–116 °C, LC retention time = 3.40 (*m/z* 398.1, M^+); ν_{max}(neat)/cm^{-1} 1622, 1537, 1322, 1279, 1263, 1120, 1088, 998, 826, 811, 764; δ_H(500 MHz; $CDCl_3$) 8.02 (1H, d, *J* 2 Hz, Ph H-3), 7.62 (1H, d, *J* 8.7 Hz, Ph H-5), 7.11 (1H, d, *J* 8.7 Hz, Ph H-6), 6.40 (1H, s, pyrazole H-4), 3.87 (4H, br d, piperazine H-3, H-5), 3.73 (3H, s, pyrazole N-1 C*H*$_3$), 3.12 (4H, br d, piperazine H-2, H-6), 2.21 (3H, s, pyrazole C-5 C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 163.1 (C=O), 147.9 (C), 145.1 (C), 140.9 (C), 139.2 (C), 130.2 (CH), 124.2 (CH), 123.0 (CF_3), 122.1 (C), 120.7 (CH), 108.4 (CH), 51.7 (CH_2), 50.6 (CH_2), 46.5 (CH_2), 42.2 (CH_2), 36.5 (CH_3), 11.0 (CH_3); *m/z* (EI+) 397.13467 (M^+, $C_{17}H_{18}F_3N_5O_3$ requires 397.13617); 397.1 (45%) (M^+).

1-(1-Methyl-1*H*-imidazole-4-sulfonyl)-4-(2-nitro-4-(trifluoro-methyl)phenyl)piperazine (14f). Yellow crystals, mp 156 °C, LC retention time = 3.26 (*m/z* 420.0, M + H); ν_{max}(neat)/cm^{-1} 2211, 1586, 1553, 1486, 1454, 1327, 1156, 1118, 1040, 715; δ_H(500 MHz; $CDCl_3$) 7.99 (1H, s, Ph H-3), 7.63 (1H, d, *J* 8.7 Hz, Ph H-6), 7.46 (1H, s, imidazole H-2), 7.20 (1H, s, imidazole H-5), 7.13 (1H, d, *J* 8.7 Hz, Ph H-6), 3.72 (3H, imidazole N-1 CH_3), 3.32 (4H, t, *J* 4.8 Hz, piperazine H-2, H-6), 3.16 (4H, t, *J* 4.8 Hz, piperazine H-3, H-5); δ_C(125 MHz; $CDCl_3$) 147.9 (C), 141.8 (CH), 137.6 (C), 130.3 (CH), 124.7 (CH), 124.1 (J_{C-F} 47 Hz, CF_3), 124.0 (CH), 122.0 (C), 121.4 (CH), 50.9 (CH_2), 46.0 (CH_2), 34.1 (CH_3); *m/z* (EI+) 419.08824 (M^+, $C_{15}H_{16}F_3N_5O_4S$ requires 419.08751); 419.1 (35%) (M^+).

1-(1,2-Dimethyl-1*H*-imidazole-4-sulfonyl)-4-(2-nitro-4-(trifluoro-methyl)phenyl)piperazine (14g). Yellow crystals, mp 205 °C, LC retention time = 2.89 (*m/z* 203.1, M + H); ν_{max}(neat)/cm^{-1} 1623, 1533, 1324, 1122, 1086, 944, 917, 815, 766, 727; δ_H(500 MHz; $CDCl_3$) 8.05 (1H, s, Ph H-3), 7.70 (1H, d, *J* 6.7 Hz, Ph H-5), 7.26 (1H, s, imidazole H-5), 7.26 (1H, d, *J* 6.7 Hz, Ph H-6), 3.65 (3H, s, N-1 CH_3), 3.36 (4H, t, *J* 5.2 Hz, piperazine H-2, H-6), 3.21 (3H, t, *J* 5.2 Hz, piperazine H-3, H-5), 2.42 (3H, s, imidazole C-2 CH_3); δ_C(125 MHz; $CDCl_3$) 163.2 (C=O), 148.2 (C), 143.2 (C), 135.6 (C), 131.6 (CH), 125.7 (CH), 124.1 (C), 121.5 (CH), 116.7 (CH), 50.9 (CH_2), 45.9 (CH_2), 33.5 (CH_3), 13.0 (CH_3); *m/z* (EI+) 202.09765 (M + H, $C_{16}H_{18}N_5O_4F_3$ requires 202.09094); 202.1 (55%) (M + H), 124.1 (36%), 77 (21%).

2-(6-Morpholin-4-yl-pyridine-3-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (15a). White solid, mp 148 °C, LC retention time = 3.23 (*m/z* 360.1, M^+); ν_{max}(neat)/cm^{-1} 2833, 1593, 1542, 1508, 1426, 1330, 1264, 1176, 1108, 953, 819, 776, 729; δ_H(500 MHz; $CDCl_3$) 8.53 (1H, d, *J* 3 Hz, pyridine H-2), 7.74 (1H, d, *J* 8.5 Hz, pyridine H-4), 7.07–7.01 (3H, m, isoquinoline H-6, H-8, H-5), 6.95 (1H, m, pyridine H-5), 6.53 (1H, d, *J* 8 Hz, isoquinoline H-7), 4.19 (2H, s, isoquinoline H-1), 3.72 (4H, t, *J* 5 Hz, morpholine H-2), 3.57 (4H, t, *J* 5 Hz, morpholine H-3), 3.29 (2H, t, *J* 6 Hz, isoquinoline H-2), 2.86 (2H, t, *J* 6 Hz, isoquinoline H-4); δ_C(125 MHz; $CDCl_3$) 160.4 (C), 148.7 (CH), 136.9 (CH), 133.1 (C), 131.6 (C), 128.8 (CH), 126.8 (CH), 126.4 (CH), 120.6 (C), 105.3 (CH), 66.5 (CH_2), 47.5 (CH_2), 44.9 (CH_2), 43.6 (CH_2), 28.8 (CH_2); *m/z* (EI+) 359.13134 (M^+, $C_{18}H_{21}N_3O_3S$ requires 359.13036); 359.1 (65%) (M^+).

7-(3,4-Dihydro-1*H*-isoquinoline-2-sulfonyl)-4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazine (15b). LC retention time = 2.56 (*m/z* 345.1, M + H); ν_{max}(neat)/cm^{-1} 2208, 1587, 1574, 1486, 1468, 1325, 1167, 1119, 976, 725; δ_H(500 MHz; $CDCl_3$) 7.04 (4H, m, isoquinoline H-5, H-6, H-7, H-8), 6.95 (2H, m, benzooxazine H-8, benzooxazine H-6), 6.75 (1H, d, *J* 7.2 Hz, benzooxazine H-5), 4.24 (2H, t, *J* 7 Hz, benzooxazine H-2), 4.19 (2H, s, isoquinoline H-1), 3.28 (3H, t, *J* 6 Hz, benzooxazine H-3), 3.22 (2H, t, *J* 5.2 Hz, isoquinoline H-4), 2.85 (3H, s, benzooxazine N-4 CH_3); δ_C(125 MHz; $CDCl_3$) 147.9 (sat. carbon), 136.7 (sat. carbon), 133.2 (sat. carbon), 131.9 (sat. carbon), 128.9 (CH), 128.5 (sat. carbon), 126.7 (CH), 126.7 (CH), 126.4 (CH), 126.3 (CH), 118.2 (CH), 115.9 (CH), 111.1 (CH), 65.0 (CH_2), 48.3 (CH_2), 47.6 (CH_2), 43.8 (CH_2), 38.7 (CH_3), 28.9 (CH_2); *m/z* (EI+) 344.11954 (M^+, $C_{18}H_{20}N_2O_3S$ requires 344.11946); 344.1 (35%) (M^+).

(3,4-Dihydro-1*H*-isoquinolin-2-yl)quinoxalin-6-ylmethanone (15c). Yellow oil, LC retention time = 2.92 (*m/z* 290.1); ν_{max}(neat)/cm^{-1} 2924, 1627, 1445, 1429, 1368, 1302, 1263, 1244, 1176, 1021, 905, 869, 818, 743; δ_H(500 MHz; $CDCl_3$) 8.85 (2H, s, quinoxaline H-2, H-3), 7.18 (2H, d, *J* 3 Hz, quinoxaline H-7, H-8), 7.80 (1H, s, quinoxaline H-5), 7.15–7.06 (4H, m, isoquinoline H-5, H-6, H-7, H-8), 4.59 (2H, br t, isoquinoline H-1), 3.64 (2H, br t, isoquinoline H-3), 2.84 (2H, br t, isoquinoline H-4); δ_C(125 MHz; $CDCl_3$) 167.8 (C=O), 145.9 (CH × 2), 143.3 (C), 142.5 (C), 138.6 (C), 137.6 (C), 132.6 (C), 130.3 (CH), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 125.9 (CH), 45.0 (CH_2), 28.3 (CH_2 × 2); *m/z* (EI+) 289.12161 (M + H, $C_{18}H_{15}N_3O$ requires 289.12151); 289.1 (100%) (M^+), 157.0 (86%), 129.0 (67%).

3,4-Dihydro-1*H*-isoquinolin-2-yl-(3,5-dimethylisoxazol-4-yl)methanone (15d). Colourless crystals, mp 88 °C, LC retention time = 3.37 (*m/z* 257.1, M + H); ν_{max}(neat)/cm^{-1} 2933, 1587, 1406, 1369, 1337, 1179, 1129, 956, 922, 770, 737; δ_H(500 MHz; $CDCl_3$) 7.11 (2H, m, isoquinoline H-8, H-6), 7.06 (1H, m, isoquinoline H-5), 6.99 (1H, m, isoquinoline H-7), 4.32 (2H, s, isoquinoline H-1), 3.43 (2H, t, *J* 6 Hz, isoquinoline H-3), 2.86 (2H, t, *J* 6 Hz, isoquinoline H-4), 2.62 (3H, s, isoxazole C-5 CH_3), 2.34 (3H, s, isoxazole C-3 CH_3); δ_C(125 MHz; $CDCl_3$) 173.7 (C), 166.3 (C=O), 157.9 (C), 132.8 (C), 131.1 (C), 129.0 (CH), 127.1 (CH), 126.6 (CH), 126.3 (CH), 114.4 (C), 46.8 (CH_2), 43.1 (CH_2), 28.6 (CH_2), 13.0 (CH_2), 11.2 (CH_2); *m/z* (EI+) 256.12123 (M^+, $C_{15}H_{16}N_2O_2$ requires 256.12118); 256.1 (100%) (M^+).

3,4-Dihydro-1*H*-isoquinolin-2-yl-(1,5-dimethyl-1*H*-pyrazol-3-yl)methanone (15e). Off-white solid, mp 81–82 °C, LC retention time = 2.91 (*m/z* 256.1, M^+); ν_{max}(neat)/cm^{-1} 2921, 2852, 1589, 1459, 1376, 1312, 1179, 963, 902, 802, 749, 720, 701; δ_H(500 MHz; $CDCl_3$) 7.05 (3H, m, isoquinoline H-5, H-8, H-6), 6.36 (1H, s, pyrazole H-4), 4.80 (1H, s, isoquinoline H-1), 3.93 (2H, t, *J* 6 Hz, isoquinoline H-3), 3.74 (3H, s, pyrazole N-1 CH_3), 2.86 (2H, t, *J* 6 Hz, isoquinoline H-4), 2.20 (3H, s, pyrazole C-5 CH_3); δ_C(125 MHz; $CDCl_3$) 163.5 (C=O), 145.6 (C), 139.0 (C), 134.6 (C), 133.4 (C), 128.9 (CH), 126.1 (CH × 3), 107.7 (CH), 49.0 (CH_2), 44.7 (CH_2), 36.6 (CH_3), 29.7 (CH_2), 14.1 (CH_3); *m/z* (EI+) 255.13819 (M^+, $C_{15}H_{17}N_3O$ requires 255.13716); 255.1 (75%) (M^+).

2-(1-Methyl-1*H*-imidazole-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline (15f). LC retention time = 2.86 (*m/z* 278.1, M + H); ν_{max}(neat)/cm^{-1} 2231, 1612, 1575, 1499, 1467, 1328, 1176, 1129, 976, 754; δ_H(500 MHz; $CDCl_3$) 7.39 (2H, m, imidazole H-2, isoquinoline H-6), 7.06 (1H, m, isoquinoline H-8), 7.02 (2H, m, isoquinoline H-5, H-7), 6.96 (1H, m, imidazole H-5), 4.37 (2H, s, isoquinoline H-1), 3.68 (3H, s, imidazole N-1 CH_3), 3.45 (2H, t, *J* 6 Hz, isoquinoline H-3), 3.14 (2H, t, *J* 6 Hz, isoquinoline H-4), 2.88 (3H, s, benzooxazine N-1 CH_3); δ_C(125 MHz; $CDCl_3$) 138.16 (CH), 137.6 (C), 132.4 (C), 131.0 (C), 127.8 (CH), 125.4 (CH), 125.2 (CH), 123.6 (CH), 46.6 (CH_2), 43.0 (CH_2), 33.0 (CH_3), 28.0 (CH_2); *m/z* (EI+) 277.08963 (M^+, $C_{13}H_{15}N_3O_2S$ requires 277.08850); 277.1 (95%) (M^+).

2-(1,2-Dimethyl-1*H*-imidazole-4-sulfonyl)-1,2,3,4-tetrahydroisoquinoline (15g). Colourless crystals, mp 195 °C, LC retention time = 3.34 (*m/z* 292.1, M + H); ν_{max}(neat)/cm^{-1} 1519, 1455, 1403, 1329, 1153, 1130, 1073, 1024, 979, 957, 926, 767, 757, 734; δ_H(500 MHz; $CDCl_3$) 7.32 (1H, d, *J* 6 Hz, isoquinoline H-6), 7.18 (1H, s, imidazole H-5), 7.06 (1H, m, isoquinoline H-8), 6.99 (1H, m, isoquinoline H-5), 6.97 (1H, m, isoquinoline H-7), 4.37 (2H, s, isoquinoline H-1), 3.51 (3H, s, imidazole N-1 CH_3), 3.44 (2H, t, *J* 6 Hz, isoquinoline H-3), 2.89 (2H, t, *J* 6 Hz, isoquinoline H-4), 2.33 (3H, s, imidazole C-2 CH_3); δ_C(125 MHz; $CDCl_3$) 147.1 (C), 135.5 (C), 133.5 (C), 132.2 (C), 128.8 (CH), 126.4 (CH), 126.2 (CH), 124.2 (CH), 47.6 (CH_2), 43.9 (CH_2), 33.4 (CH_3), 29.7 (CH_2), 13.0 (CH_3); *m/z* (EI+) 291.10526 (M^+, $C_{14}H_{17}N_3O_2S$ requires 291.10415); 291.1 (87%) (M^+).

4-{5-[4-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)piperazine-1-sulfonyl]pyridin-2-yl}morpholine (16a). Off-white solid, mp 199–200 °C, LC retention time = 2.56 (*m/z* 492.1, M + H); ν_{max}(neat)/cm^{-1} 2221, 1598, 1563, 1493, 1454, 1327, 1156, 1121, 998, 720; δ_H(500 MHz; $CDCl_3$) 8.46 (1H, d, *J* 2.5 Hz, py H-2), 8.30 (1H, d, *J* 6.7 Hz, py H-4), 7.70 (1H, d, *J* 9 Hz, py H-4′), 7.68 (1H, d, *J* 2.5 Hz, py H-5), 6.56 (1H, d, *J* 9 Hz, py H-5′), 3.73 (2H, t, *J* 5 Hz, morpholine H-2, H-6), 3.59 (2H, t, *J* 5 Hz, morpholine H-3, H-5), 3.51, 3.11 (4H, t, *J* 5 Hz, piperazine H-2, H-3, H-5, H-6); δ_C(125 MHz; $CDCl_3$) 160.4 (C), 159.3 (C), 148.9 (CH), 143.0 (CH), 137.0 (CH), 136.1 (CH), 122.1 (J_{C-F} 270 Hz, Py C-6′), 120.9 (C), 120.8 (q, *J* $_{C-F}$ 12.6 Hz, CF_3), 119.7 (C), 105.3 (CH), 66.5 (CH_2), 48.6 (CH_2), 45.7 (CH_2), 44.9 (CH_2); *m/z* (EI+) 491.10237 (M^+, $C_{19}H_{21}ClF_3N_5O_3S$ requires 491.10057); 491.1 (35%) (M^+).

7-[4-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)piperazine-1-sulfonyl]-4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazine (16b). Off-white solid, mp 167 °C, LC retention time = 3.24 (*m/z* 477.1, M + H); ν_{max}(neat)/cm^{-1} 2225, 1599, 1578, 1486, 1355, 1125, 1078, 989, 745; δ_H(500 MHz; $CDCl_3$) 7.63 (1H, d, *J* 8Hz, py H-4), 7.12 (1H, d, *J* 8.5 Hz, benzooxazine H-6), 6.96 (1H, d, *J* 8.5 Hz, benzooxazine H-8), 6.79 (1H, br d, py H-5), 6.76 (1H, d, *J* 8.5 Hz, benzooxazine H-5), 4.28 (4H, t, *J* 4.7 Hz, piperazine H-2, H-6), 2.62 (4H, t, *J* 4.7 Hz, piperazine H-3, H-5), 3.14 (4H, br t, benzooxazine H-2, H-3), 2.88 (3H, s, benzooxazine N-1 CH_3); δ_C(125 MHz; $CDCl_3$) 162.5 (C), 147.8 (J_{C-F} 34.4 Hz, Py C-6), 141.7 (C), 136.9 (C), 130.4 (CH), 127.5 (C), 126.3 (J_{C-F} 18 Hz, CF_3), 122.0 (C), 121.4 (CH), 118.1 (CH), 116.0 (CH), 110.9 (CH), 65.0 (CH_2), 50.9 (CH_2), 48.3 (CH_2), 45.8 (CH_2), 38.6 (CH_2); *m/z* (EI+) 476.09102 (M^+, $C_{19}H_{20}ClF_3N_4O_3S$ requires 476.08967); 476.1 (100%) (M^+).

[4-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl]quinoxalin-6-ylmethanone (16c). White solid, mp 136 °C, LC retention time = 2.45 (*m/z* 422.1, M + H); ν_{max}(neat)/cm^{-1} 1625, 1526, 1367, 1252, 1165, 1112, 945, 867; δ_H(500 MHz; $CDCl_3$) 8.85 (2H, s, quinoxaline H-2, H-3), 8.35 (1H, s, quinoxaline H-5), 8.13 (2H, d, *J* 7 Hz, quinoxaline H-7, H-8), 4.28 (1H, d, *J* 5 Hz, pyridine H-4), 7.74 (1H, d, *J* 5 Hz, pyridine H-5), 3.95 (4H, br t, piperazine H-3, H-5), 3.59 (4H, br t, piperazine H-2, H-6); δ_C(125 MHz; $CDCl_3$) 169.1 (C=O), 159.5 (C), 146.0 (CH × 2), 143.3 (C), 142.4 (CH), 137.0 (CH), 136.2 (C), 130.4 (CH), 128.8 (CH), 128.2 (CH), 124.2 (C), 121.3 (C), 121.0 (J_{C-F} 50 Hz, CF_3); *m/z* (EI+) 421.09256 (M^+, $C_{19}H_{15}ClF_3N_5O$ requires 421.09172); 421.1 (51%) (M^+).

[4-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl]-(3,5-dimethylisoxazol-4-yl)methanone (16d). White solid, mp 126 °C, LC retention time = 3.76 (*m/z* 427.0, M + K); ν_{max}(neat)/cm^{-1} 1585, 1489, 1405, 1345, 1318, 1282, 1252, 1180, 1120, 1058, 956, 922, 733; δ_H(500 MHz; $CDCl_3$) 8.33 (1H, d, *J* 5 Hz, py H-4), 7.72 (1H, d, *J* 5 Hz, py H-5), 3.53 (2H, t, *J* 6 Hz, piperazine H-2, H-6), 3.21 (1H, t, *J* 6 Hz, piperazine H-3, H-5), 2.60 (3H, s, isoxazole C-3 C*H*$_3$), 2.37 (3H, s, isoxazole C-5 C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 173.9 (C=O), 159.2 (py C-2), 158.0 (py C-6), 143.1 (CH), 136.2 (CH), 126.3, 124.2 (isoxazole C-3, C-5), 121.5 (isoxazole C-4), 120.7 (q, J_{C-F} 27.2 Hz, CF_3), 113.2 (Py C-3), 48.0 (CH_2), 45.2 (CH_2), 13.0 (CH_3), 11.4 (CH_3); *m/z* (EI+) 388.09156 (M^+, $C_{16}H_{16}N_4O_2ClF_3$ requires 388.09139); 388.1 (55%) (M^+), 264.3 (35%).

[4-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl]-(1,5-dimethyl-1*H*-pyrazol-3-yl)methanone (16e). White solid, mp 72 °C, LC retention time = 3.21 (*m/z* 388.1, M + H); ν_{max}(neat)/cm^{-1} 2221, 1598, 1563, 1493, 1454, 1327, 1156, 1121, 998, 720; δ_H(500 MHz; $CDCl_3$) 8.33 (1H, d, *J* 4.5 Hz, py H-4), 7.70 (1H, d, *J* 4.5 Hz, py H-5), 6.38 (1H, s, pyrazole H-4), 4.13 (4H, br t, piperazine H-3, H-5), 3.73 (3H, s, N-1 CH_3), 3.53 (4H, br t, piperazine H-2, H-6), 2.22 (3H, s, pyrazole C-5 CH_3); δ_C(125 MHz; $CDCl_3$) 163.2 (C=O), 159.7 (C), 145.3 (C), 143.0 (CH), 139.1 (C), 136.1 (CH), 122.2 (C), 120.9 (C), 120.4 (q, J_{C-F} 38 Hz, CF_3), 108.2 (CH), 48.5 (CH_2), 44.8 (CH_2), 36.5 (CH_3); *m/z* (EI+) 387.10865 (M^+, $C_{16}H_{17}ClF_3N_5O$ requires 387.10737); 387.1 (35%) (M^+).

1-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)-4-(1-methyl-1*H*-imidazole-4-sulfonyl)piperazine (16f). Off-white crystals, mp 193 °C, LC retention time = 3.26 (*m/z* 410.0, M + 2), ν_{max}(neat)/cm^{-1} 1601, 1483, 1445, 1341, 1317, 1243, 1169, 1117, 1097, 946, 927, 734; δ_H(500 MHz; $CDCl_3$) 8.30 (1H, d, *J* 5 Hz, py H-4), 7.68 (1H, s, imidazole H-2), 7.40 (1H, d, *J* 5 Hz, py H-5), 7.20 (1H, s, imidazole H-5), 3.70 (3H, s, imidazole N-1 CH_3), 3.51 (4H, t, *J* 6 Hz, piperazine H-2, H-6), 3.30 (4H, t, *J* 6 Hz, piperazine H-3, H-5); δ_C(125 MHz; $CDCl_3$) 147.1 (C), 135.5 (C), 133.5 (C), 132.2 (C), 128.8 (CH), 126.4 (CH), 126.2 (CH), 124.2 (CH), 47.6 (CH_2), 43.9 (CH_2), 33.4 (CH_3), 29.7 (CH_2), 13.0 (CH_3); *m/z* (EI+) 409.05871 (M^+, $C_{14}H_{15}F_3N_5O_2SCl$ requires 409.05884); 409.1 (100%) (M + H).

1-(3-Chloro-6-(trifluoromethyl)pyridin-2-yl)-4-(1,2-dimethyl-1*H*-imidazole-4-sulfonyl)piperazine (16g). White crystals, mp 236 °C, LC retention time = 2.78 (*m/z* 502.1, M + H); ν_{max}(neat)/cm^{-1} 1635, 1516, 1317, 1239, 1159, 1110, 948, 842, 722; δ_H(500 MHz; $CDCl_3$) 8.14 (1H, d, *J* 5 Hz, py H-4), 7.52 (1H, d, *J* 5 Hz, py H-5), 7.23 (1H, s, imidazole H-5), 3.45 (3H, s, imidazole N-1 CH_3), 3.32 (2H, br t, piperazine CH_2), 3.06 (2H, br t, piperazine CH_2), 2.78 (3H, s, imidazole N-1 CH_3);

δ_C(125 MHz; $CDCl_3$) 167.8 (C), 163.2 (C), 161.2 (C), 147.6 (C), 141.5 (CH), 139.4 (C), 127.1 (CH), 123.7 (CH), 121.6 (CH), 120.3 (J_{C-F} 48 Hz, CF_3), 115.0 (C), 114.1 (CH), 57.6 (CH_2), 47.2 (CH_2), 33.2 (CH_3), 10.2 (CH_3); *m/z* (EI+) 423.07532 (M^+, $C_{15}H_{17}ClF_3N_5O_2S$ requires 423.07436); 423.1 (32%) (M^+).

1-(6-Morpholin-4-yl-pyridine-3-sulfonyl)morpholine (17a)[25]. Off-white solid, mp 190 °C (lit[25] mp 189–191 °C), LC retention time = 2.89 (*m/z* 313.1, M + H); ν_{max}(neat)/cm^{-1} 2863, 1586, 1494, 1310, 1260, 1165, 1107, 941, 723; δ_H(500 MHz; $CDCl_3$) 8.52 (1H, s, py H-2), 7.66 (2H, d, *J* 6.2 Hz, py H-4), 6.55 (2H, d, *J* 6.2 Hz, py H-5), 3.74 (3H, t, *J* 6 Hz, morpholine H-2, H-6), 3.67 (3H, t, *J* 6 Hz, morpholine H-2′, H-6′), 2.58 (4H, t, *J* 6 Hz, morpholine H-3, H-5), 2.92 (4H, t, *J* 6 Hz, morpholine H-3′, H-5′); δ_C(125 MHz; $CDCl_3$) 160.4 (py C-6), 148.9 (py C-2), 137.0 (py C-4), 119.3 (py C-3), 105.2 (py C-5), 66.5 (morpholine C-2, C-6), 66.1 (morpholine C-2′, C-6′), 45.9 (morpholine C-3, C-5), 44.9 (morpholine C-3′, C-5′); *m/z* (EI+) 313.11245 (M^+, $C_{13}H_{19}N_3O_4S$ requires 313.10963); 313.1 (45%) (M^+).

4-Methyl-7-(morpholine-4-sulfonyl)-3,4-dihydro-2*H*-benzo-[1,4]oxazine (17b). Off-white crystals, mp 111 °C, LC retention time = 2.91 (*m/z* 299.0, M + H); ν_{max}(neat)/cm^{-1} 1600, 1506, 1317, 1239, 1156, 1106, 945, 842, 719; δ_H(500 MHz; $CDCl_3$) 6.97 (1H, d, *J* 5.4 Hz, benzooxazine H-6), 6.89 (1H, d, *J* 5.4 Hz, benzooxazine H-7), 6.78 (1H, d, *J* 9 Hz, benzooxazine H-5), 4.28 (2H, t, *J* 5.1 Hz, benzooxazine H-2), 3.68 (4H, t, *J* 4.8 Hz, morpholine H-2, H-6), 3.26 (2H, t, *J* 5.1 Hz, benzooxazine H-3), 2.92 (4H, t, *J* 4.8 Hz, morpholine H-3, H-5), 2.86 (3H, s, benzooxazine N-4 CH_3); δ_C(125 MHz; $CDCl_3$) 148.0 (C), 136.8 (C), 127.2 (C), 118.3 (CH), 115.9 (CH), 111.2 (CH), 66.2 (CH_2), 65.0 (CH_2), 48.3 (CH_2), 46.1 (CH_2), 38.6 (CH_3); *m/z* (EI+) 298.09873 (M^+, $C_{13}H_{18}N_2O_4S$ requires 298.09873); 298.1 (45%) (M^+).

Morpholin-4-ylquinoxalin-6-ylmethanone (17c)[26]. Off-white crystals, mp 124 °C, LC retention time = 2.12 (*m/z* 244.1, M + H); ν_{max}(neat)/cm^{-1} 2964, 1725, 1620, 1449, 1428, 1304, 1270, 1244, 1178, 1020, 898, 754, 744; δ_H(500 MHz; $CDCl_3$) 7.66 (2H, d, *J* 3 Hz, quinoxaline H-2, H-3), 8.09 (1H, d, *J* 5.5 Hz, quinoxaline H-7), 8.07 (1H, s, quinoxaline H-5), 7.75 (3H, d, *J* 5.5 Hz, quinoxaline H-8), 3.63 (4H, br t, morpholine H-3, H-5), 3.58 (4H, br t, morpholine H-2, H-6); δ_C(125 MHz; $CDCl_3$) 168.9 (C=O), 145.9 (CH × 2), 143.3 (C), 142.4 (C), 136.8 (C), 130.4 (CH), 128.8 (CH), 128.1 (CH), 66.9 (CH_2 × 2); *m/z* (EI+) 243.10147 (M^+, $C_{13}H_{13}N_3O_2$ requires 243.10078); 243.1 (65%) (M^+).

(3,5-Dimethylisoxazol-4-yl)morpholin-4-ylmethanone (17d). White crystals, mp 130 °C, LC retention time = 2.54 (*m/z* 210.1); ν_{max}(neat)/cm^{-1} 1584, 1343, 1262, 1181, 1114, 946, 733; δ_H(500 MHz; $CDCl_3$) 3.71 (2H, t, *J* 5.5 Hz, morpholine H-2, H-6), 3.03 (1H, d, *J* 5.5 Hz, morpholine H-3, H-5), 2.57 (3H, s, isoxazole C-5 CH_3), 2.34 (3H, s, isoxazole C-3 CH_3); δ_C(125 MHz; $CDCl_3$) 174.0 (C=O), 158.0 (C-5), 151.4 (C-3), 112.9 (isoxazole C-4), 60.0 (morpholine C-2, C-6), 45.4 (morpholine C-3, C-5), 13.0 (isoxazole C-5 CH_3), 11.4 (isoxazole C-3 CH_3); *m/z* (EI+) 210.10371 (M^+, $C_{10}H_{14}N_2O_3$ requires 210.10044); 210.1 (35%) (M^+).

(1,5-Dimethyl-1*H*-pyrazol-3-yl)morpholin-4-ylmethanone (17e). White solid, mp 87 °C, LC retention time = 1.76 (*m/z* 210.0); ν_{max}(neat)/cm^{-1} 2921, 1718, 1607, 1491, 1371, 1272, 1231, 1220, 1111, 982, 834, 770, 756; δ_H(500 MHz; $CDCl_3$) 6.35 (1H, s, pyrazole H-4), 3.99 (4H, br d, morpholine H-2, H-5), 3.70 (3H, s, pyrazole N-1 CH_3), 3.61 (4H, br d, morpholine H-3, H-6), 2.19 (3H, s, pyrazole C-5 CH_3); δ_C(125 MHz; $CDCl_3$) 163.1 (C=O), 145.2, 139.1 (pyrazole C-5, pyrazole C-3), 108.2 (pyrazole C-4), 47.6 (pyrazole C-2, C-5), 42.8 (pyrazole C-3, C-6), 36.5 (pyrazole N-1 CH_3), 11.0 (pyrazole C-5 CH_3); *m/z* (EI+) 209.11756 (M^+, $C_{10}H_{15}N_3O_2$ requires 209.11643); 209.1 (100%) (M^+).

4-(1-Methyl-1*H*-imidazole-4-sulfonyl)morpholine (17f). Off-white crystals, mp 122–123 °C, LC retention time = 1.31 (*m/z* 232.0, M + H); ν_{max}(neat)/cm^{-1} 1530, 1339, 1255, 1163, 1112, 1069, 938, 732; δ_H(500 MHz; $CDCl_3$) 7.43 (1H, s, imidazole H-2), 7.37 (1H, s, imidazole H-5), 3.70 (3H, s, imidazole N-1 CH_3), 3.67 (4H, t, *J* 5.2 Hz, morpholine H-2, H-6), 3.12 (4H, t, *J* 5.2 Hz, morpholine H-3, H-5); δ_C(125 MHz; $CDCl_3$) 139.3 (imidazole C-2), 137.4 (imidazole C-4), 124.8 (imidazole C-5), 66.2 (morpholine C-2, C-6), 46.2 (morpholine C-3, C-5), 34.0 (imidazole N-1 CH_3); *m/z* (EI+) 231.06729 (M^+, $C_8H_{13}N_3O_3S$ requires 231.06776); 231.1 (25%) (M^+).

4-(1,2-Dimethyl-1*H*-imidazole-4-sulfonyl)morpholine (17g)[27]. White solid, mp 198 °C, LC retention time = 2.80 (*m/z* 246.1, M + H); ν_{max}(neat)/cm^{-1} 1530, 1336, 1324, 1159, 1112, 939, 771, 729; δ_H(500 MHz; $CDCl_3$) 7.20 (1H, s, imidazole H-5), 3.67 (4H, t, *J* 6 Hz, morpholine H-3, H-5), 3.55 (3H, s, imidazole N-1, CH_3), 3.11 (4H, t, *J* 6 Hz, morpholine H-2, H-6), 2.34 (3H, s, imidazole C-2 CH_3); δ_C(125 MHz; $CDCl_3$) 147.2 (imidazole C-2), 134.7 (imidazole C 4), 125.4 (imidazole C-5), 66.2 (morpholine C-3, C-5), 46.2 (morpholine C-2, C-6), 33.4 (imidazole N-1 CH_3), 13.0 (imidazole C-2 CH_3); *m/z* (EI+) 245.09387 (M^+, $C_9H_{15}N_3O_3S$ requires 245.08341); 245.1 (100%) (M^+).

1-(6-Morpholin-4-ylpyridine-3-sulfonyl)-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine (18a). Off-white solid, mp 114–115 °C, LC retention time = 2.76 (*m/z* 390, M H); ν_{max}(neat)/cm^{-1} 2966, 1587, 1546, 1346, 1312, 1178, 1106, 1057, 1003, 963, 855, 828, 773, 701; δ_H(500 MHz; $CDCl_3$) 8.43 (1H, s, py H-2), 7.61 (1H, d, *J* 7 Hz, py H-4), 7.30 (1H, d, *J* 7 Hz, py H-5), 6.53 (1H, d, *J* 9Hz, diazepine H-7), 5.33 (1H, d, *J* 9Hz, diazepine H-6), 3.83 (2H, br s, diazepine H-3), 3.62 (4H, br t, morpholine H-2, H-6), 3.58 (4H, br t, morpholine H-3, H-5), 3.26 (2H, t, *J* 5 Hz, diazepine H-2); δ_C(125 MHz; $CDCl_3$) 161.2 (C), 155.7 (q J_{C-F} 27.5 Hz, diazepine C-5), 148.8 (CH), 145.1 (CH), 138.0 (CH), 137.3 (CH), 136.2 (CH), 121.2 (C), 120.2 (J_{C-F} 277.5 Hz, CF_3), 106.4 (CH), 95.2 (CH), 81.3 (CH), 66.8 (CH_2), 54.3 (CH_2), 49.1 (CH_2), 45.4 (CH_2); *m/z* (EI+) 390.09823 (M^+, $C_{16}H_{17}F_3N_4O_3S$ requires 390.09734); 390.1 (75%) (M^+).

4-Methyl-7-(5-trifluoromethyl-2,3-dihydro-[1,4]diazepine-1-sulfonyl)-3,4-dihydro-2*H*-benzo[1,4]oxazine (18b). LC retention time = 3.22 (*m/z* 376.0); ν_{max}(neat)/cm^{-1} 1644, 1591, 1326, 1238, 1189, 1120, 1087, 1039, 926, 772, 758; δ_H(400 MHz; $CDCl_3$) 7.32 (1H, d, *J* 7 Hz, benzooxazine H-6), 6.97 (1H, d, *J* 7 Hz, benzooxazine H-8), 6.84 (1H, s, benzooxazine H-5), 6.78 (1H, d, *J* 9Hz, H-7), 5.33 (1H, d, *J* 9Hz, diazepine H-6), 4.27 (2H, t, *J* 5 Hz, benzooxazine H-3), 3.75 (2H, br s, diazepine H-2), 3.55 (2H, br s, diazepine H-3), 3.26 (2H, t, *J* 5 Hz, benzooxazine H-2), 2.87 (3H, s, NC*H*$_3$); δ_C(100 MHz; $CDCl_3$) 155.7 (q, J_{C-F} 27.5 Hz, diazepine C-5), 148.8 (diazepine C-7), 138.0 (CH), 137.3 (C), 128.7 (C), 121.3 (J_{C-F} 277.5 Hz, CF_3), 119.1 (CH), 116.4 (CH), 109.9 (CH), 94.8 (CH), 65.0 (CH_2), 54.1 (CH_2), 48.6 (CH_2), 49.0 (CH_2), 38.5 (CH_3); *m/z* (EI+) 375.08801 (M^+, $C_{15}H_{16}F_3N_3O_3S$ requires 375.08645); 375.1 (35%) (M^+).

Quinoxalin-6-yl-(5-trifluoromethyl-2,3-dihydro-[1,4]diazepin-1-yl)methanone (18c). Yellow oil, LC retention time = 3.36 (*m/z* 321.1, M + H); ν_{max}(neat)/cm^{-1} 2215, 1587, 1489, 1418, 1223, 1156, 1119, 1103, 978, 869, 863, 789, 699; δ_H(500 MHz; $CDCl_3$) 8.90 (2H, d, *J* 4 Hz, quinoxaline H-2, H-3), 8.20 (1H, d, *J* 4 Hz, quinoxaline H-7), 8.18 (1H, s, quinoxaline H-5), 7.82 (1H, d, *J* 4 Hz, quinoxaline H-8), 7.20 (1H, br d, diazepine H-7), 5.33 (1H, diazepine H-6), 4.19, 4.02 (4H, br d, diazepine H-2, H-3); δ_C(125 MHz; $CDCl_3$) 168.0 (C=O), 155.5 (J_{C-F} 32.3Hz, diazepine C-5), 146.8 (CH), 146.4 (CH), 143.9 (C), 142.2 (C), 138.8 (CH), 134.4 (C), 130.9 (CH), 130.3 (CH), 128.9 (CH), 119.0 (CF_3), 96.5 (CH), 54.6 (CH_2 × 2);

m/z (EI+) 320.08956 (M^+, $C_{15}H_{11}F_3N_4O$ requires 320.08849); 320.1 (83%) (M^+).

3,5-Dimethylisoxazol-4-yl-(5-trifluoromethyl-2,3-dihydro-[1,4]diazepin-1-yl)methanone (18d). Off-white solid, mp 61 °C, LC retention time = 3.08 (*m/z* 287.1, M^+); ν_{max}(neat)/cm^{-1} 1646, 1583, 1322, 1188, 1094, 1122, 1036, 956, 903, 850, 784, 716; δ_H(500 MHz; $CDCl_3$) 7.28 (1H, d, *J* 8 Hz, diazepine H-7), 5.40 (1H, d, *J* 8 Hz, diazepine H-6), 3.95 (2H, br s, diazepine H-3), 3.54 (2H, br s, diazepine H-2), 2.63 (3H, s, isoxazole C-3 C*H*$_3$), 2.30 (3H, s, isoxazole C-5 C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 175.1 (C=O), 157.1 (C), 155.7 (q, J_{C-F} 27.2 Hz, CF_3), 136.6 (CH), 123.3 (C), 118.9 (d J_{C-F} 222 Hz, diazepine C-5), 114.0 (C), 95.6 (diazapine C-6), 54.0 (diazepine C-3), 48.2 (diazapine C-2), 13.0 (isoxazole C-3 CH_3), 11.0 (isoxazole C-5 CH_3); *m/z* (EI+) 287.08764 (M^+, $C_{12}H_{12}F_3N_3O_2$ requires 287.08816); 287.1 (45%) (M + H).

1,5-Dimethyl-1*H*-pyrazol-3-yl-(5-trifluoromethyl-2,3-dihydro-[1,4]diazepin-1-yl)methanone (18e). Yellow crystals, mp 115 °C, LC retention time = 2.48 (*m/z* 287.0, M + H); ν_{max}(neat)/cm^{-1} 1642, 1591, 1439, 1325, 1236, 1190, 1118, 1085, 925, 778, 757; δ_H(500 MHz; $CDCl_3$) 8.15 (1H, d, *J* 10 Hz, diazepine H-7), 6.51 (1H, s, pyrazole H-4), 5.33 (1H, d, *J* 10 Hz, diazepine H-6), 4.06 (4H, br t, diazepine H-2, H-3), 3.76 (3H, s, pyrazole N-1 CH_3), 2.21 (3H, s, pyrazole C-5 CH_3); δ_C(125 MHz; $CDCl_3$) 161.6 (C=O), 155.6 (C), 143.6 (C), 140.7 (CH), 140.0 (C), 117.0 (CF_3), 108.2 (CH), 95.3 (CH), 54.8 (CH_2), 36.9 (CH_3), 11.0 (CH_3); *m/z* (EI+) 286.10440 (M^+, $C_{12}H_{13}F_4N_4O$ requires 286.10414); 286.1 (35%) (M^+), 123.1 (36%).

1-(1-Methyl-1*H*-imidazole-4-sulfonyl)-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine (18f). LC retention time = 3.22 (*m/z* 308.1); ν_{max}(neat)/cm^{-1} 1648, 1593, 1329, 1234, 1193, 1123, 928, 779, 768; δ_H(400 MHz; $CDCl_3$) 7.48 (1H, s, imidazole H-2), 7.45 (1H, s, imidazole H-5), 7.30 (1H, d, *J* 7.6 Hz, diazepine H-7), 5.34 (1H, d, *J* 7.6 Hz, diazepine H-6), 3.90 (4H, bs, diazepine H-2, H-3), 3.71 (3H, s, N-1 CH_3); δ_C(100 MHz; $CDCl_3$) 155.6 (sat. carbon), 139.9 (CH), 138.3 (CH), 138.0 (sat. carbon), 125.1 (CH), 119.0 (J_{C-F} 278.2 Hz, CF_3), 95.2 (CH), 54.4 (CH_2), 49.0 (CH_2), 34.2 (CH_3); *m/z* (EI+) 308.05623 (M^+, $C_{10}H_{11}F_3N_4O_2S$ requires 308.05548); 308.1 (39%) (M^+).

1-(1,2-Dimethyl-1*H*-imidazole-4-sulfonyl)-5-trifluoromethyl-2,3-dihydro-1*H*-[1,4]diazepine (18g). Colourless crystals, mp 159 °C, LC retention time = 2.26 (*m/z* 323.0, M + H); ν_{max}(neat)/cm^{-1} 1644, 1591, 1366, 1320, 1166, 1114, 960, 843, 765, 682; δ_H(500 MHz; $CDCl_3$) 7.30 (1H, d, *J* 10 Hz, diazepine H-7), 7.20 (1H, s, imidazole H-5), 5.33 (1H, d, *J* 10 Hz, diazepine H-6), 3.93 (4H, br t, diazepine H-2, H-3), 3.55 (3H, s, imidazole N-1 CH_3), 2.31 (3H, s, imidazole C-2 CH_3); δ_C(125 MHz; $CDCl_3$) 156.0 (C=O), 148.2 (C), 138.4 (CH), 135.3 (C), 125.8 (CH), 117.0 (CF_3), 95.0 (CH), 54.5 (CH_2), 48.9 (CH_2), 33.7 (CH_3), 13.0 (CH_3); *m/z* (EI+) 322.07113 (M^+, $C_{11}H_{13}F_3N_4O_2$ requires 322.07113); 322.1 (56%) (M^+).

4,4′-Dibromomethylbipyridine (19). Light pink solid, (Found: C, 42.18; H, 2.99; N, 8.23, $C_{12}H_{10}Br_2N_2$ requires C, 42.14; H, 2.95; N, 8.19%); ν_{max}(neat)/cm^{-1} 1537, 1326, 1212, 1029, 832, 723; δ_H(400 MHz; CD_3OD) 8.82 (2H, d, *J* 5 Hz, bipy H-6), 8.65 (2H, s, bipy H-3), 7.82 (2H, d, *J* 5 Hz, bipy H-5), 4.95 (4H, s, bipy C*H*$_2$); ^{1}H NMR was in agreement with the literature assignment.[28]

General scavenging procedure using bipyridyl dibromide as a reaction scavenger in the synthesis of tertiary amines (20a–d) from 1,2,3,4-tetrahydroisoquinoline. To a solution of benzyl bromide (60 mg, 0.35 mmol, 1 equiv.) in DCM (1.5 cm^3) was added a solution of 1,2,3,4-tetrahydroisoquinoline (117 mg, 0.88 mmol, 2.5 equiv.) in DCM (1.5 cm^3) and polymer-supported triethylamine equivalent (167 mg, 0.525 mmol, 1.5 equiv., diethylaminomethyl polystyrene, ~3.2 mmol g^{-1}; Fluka Cat. No. 31866). The mixture was then heated by microwave irradiation at 80 °C for 30 min. Bipyridyl dibromide **19** (257 mg, 0.75 mmol, 0.85 equiv.) was then added to react with the excess isoquinoline. The bipyridine adduct was then scavenged by the addition of IRC 718 copper(II) resin (1.0 g, loading 1.3 mmol g^{-1}, 1.7 equiv.); the uptake was followed by LC-MS. The resin was then removed by filtration, washed with DCM (2 × 10 cm^3), and the combined washings and filtrate evaporated to dryness yielding the corresponding benzyl-protected amine.

2-Benzyl-1,2,3,4-tetrahydroisoquinoline (20a).[20,21] White solid, 92% yield, mp 35–36 °C (lit.[20] mp 37 °C); LC retention time = 0.52 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 86.12; H, 7.65; N, 6.28, $C_{16}H_{17}N$ requires C, 86.05; H, 7.67; N, 6.27%); ν_{max}(neat)/cm^{-1} 2210, 1599, 1565, 1487, 1435, 1336, 1167, 956, 770; δ_H(600 MHz; $CDCl_3$) 7.35–7.23 (4H, m, Ph–H), 7.10 (3H, m, quinoline H-5, H-6, H-8), 7.09 (1H, m, Ph–H), 6.96 (1H, t, *J* 8 Hz, quinoline H-7), 3.74 (2H, s, N-benzyl CH_2), 3.68 (2H, s, quinoline H-1), 2.95 (2H, t, *J* 6 Hz, quinoline H-3), 2.83 (2H, t, *J* 6Hz, quinoline H-4). ^{1}H NMR was in agreement with the literature assignment.

2-(4-[1,2,3]Thiadiazol-5-ylbenzyl)-1,2,3,4-tetrahydroisoquinoline (20b). Light yellow solid, 92% yield, LC retention time = 0.39, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.12; H, 6.85; N, 18.65, $C_{19}H_{20}N_4$ requires C, 74.97; H, 6.62; N, 18.41%); ν_{max}(neat)/cm^{-1} 1612, 1575, 1512, 1198, 1028, 865, 765; δ_H(600 MHz; $CDCl_3$) 8.65 (1H, s, thiadiazole H-4), 8.05 (2H, d, *J* 8 Hz, Ph AA′BB′ H-3, H-5), 7.55 (2H, d, *J* 8 Hz, Ph AA′BB′ H-2, H-6), 7.10 (3H, s, quinoline H-8, H-6, H-5), 6.95 (1H, br t, quinoline H-7), 3.78 (2H, s, N-benzyl CH_2), 3.68 (2H, s, quinoline C-1), 2.92 (2H, t, *J* 6 Hz, quinoline H-3), 2.76 (2H, t, *J* 6 Hz, quinoline H-4); δ_C(150 MHz; $CDCl_3$) 160.4 (Ph C-4), 142.8 (thiadiazole C-5), 134.7 (quinoline C-4a), 134.3 (quinoline C-8a), 129.9 (Ph C-1), 129.8 (thiadiazole C-4, Ph C-2, C-6), 128.7 (quinoline C-5, C-6, C-8), 127.4 (Ph C-3, C-5), 126.2 (quinoline C-7), 125.6, 123.1 (quinoline C-5, C-6, C-8), 62.4 (*N*-benzyl CH_2), 56.1 (quinoline C-1), 50.7 (quinoline C-3), 25.0 (quinoline C-4); *m/z* (ESI) 307.11756 (M^+, $C_{18}H_{17}N_3S$ requires 307.11432); 307.1 (45%) (M^+).

2-(5-Methyl-2-phenyl-2*H*-[1,2,3]triazol-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (20c). Light tan solid, 95% yield, LC retention time = 0.41, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 75.12; H, 6.85; N, 18.65, $C_{19}H_{20}N_4$ requires C, 74.97; H, 6.62; N, 18.41%); ν_{max}(neat)/cm^{-1} 1723, 1665, 1543, 1575, 1514, 1292, 1256, 1159, 1089, 824, 816, 789; δ_H(600 MHz; $CDCl_3$) 8.02 (2H, d, *J* 8 Hz, Ph H-2, H-6), 7.43 (2H, t, *J* 8 Hz, Ph H-3, H-5), 7.27 (1H, t, *J* 8 Hz, Ph H-4), 3.83 (2H, s, *N*-benzyl CH_2), 3.66 (2H, s, *J* 6 Hz, quinoline H-1), 2.91 (2H, t, *J* 6 Hz, quinoline H-3), 2.81 (2H, t, *J* 6 Hz, quinoline H-4), 2.42 (3H, s, triazole C-5 CH_3); δ_C(150 MHz; $CDCl_3$) 144.9 (triazole C-4), 144.1 (triazole C-5), 134.5 (quinoline C-4a), 134.2 (quinoline C-8a), 129.5 (Ph C-1), 129.1 (Ph C-3, C-5), 128.62 (quinoline C-5, C-6, C-8), 126.8 (Ph C-4), 126.5 (quinoline C-5, C-6, C-8), 125.6 (quinoline C-7), 118.4 (Ph H-2, H-6), 55.8 (quinoline C-1), 52.2 (*N*-Benzyl CH_2), 50.5 (quinoline C-4), 29.1 (quinoline C-3), 10.3 (triazole C-5 CH_3); *m/z* (ESI) 304.167896 (M^+, $C_{19}H_{20}N_4$ requires 304.16880); 305.2 (25%) (M^+).

2-(4-[1,2,4]Triazol-1-ylbenzyl)-1,2,3,4-tetrahydroisoquinoline (20d). Light tan solid, 95% yield, LC retention time = 0.46, (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 74.68; H, 6.13; N, 19.47, $C_{18}H_{18}N_4$ requires C, 74.46; H, 6.25; N, 19.30%); ν_{max}(neat)/cm^{-1} 1712, 1656, 1635, 1589, 1512, 1299, 1162, 1028, 829, 772; δ_H(600 MHz; $CDCl_3$) 8.57 (1H, s, triazole H-5), 8.08 (1H, s, triazole H-3), 7.63 (4H, d, *J* 8 Hz, Ph AA′BB′ H-3, H-5), 7.55 (4H, d, *J* 8 Hz, Ph AA′BB′ H-2, H-6), 7.10 (3H, m, quinoline H-5, H-6, H 8), 6.96 (1H, t, *J* 8 Hz, quinoline H-7),

3.77 (2H, s, *N*-benzyl CH_2), 3.69 (2H, s, quinoline H-1), 2.93 (2H, t, *J* 6 Hz, quinoline H-3), 2.82 (2H, t, *J* 6 Hz, quinoline H-4); δ_C(150 MHz; $CDCl_3$) 152.7 (triazole C-3), 140.8 (triazole C-5), 137.6 (Ph C-1), 136.1 (Ph C 4), 133.9 (quinoline C-4a), 131.4 (Ph C-2, C-6), 128.8 (quinoline C-1a), 128.7 (quinoline C-8), 126.6 (quinoline C-7), 126.4 (quinoline C 5), 125.8 (quinoline C-6), 120.0 (Ph C-3, C-5), 61.5 (*N*-Benzyl CH_2), 55.6 (quinoline C-1), 50.4 (quinoline C-4), 28.3 (quinoline C-3); *m/z* (ESI) 290.153234 (M^+, $C_{18}H_{18}N_4$ requires 290.15315); 290.1 (25%) (M^+).

Synthesis of [2,2′]bipyridinyl-4-ylmethylcyclohexylcarbodiimide (21). To a solution of urea **26** (0.7 g, 2.26 mmol) in anhydrous DMF (10 cm^3) weas added the polymer-supported Mukaiyama reagent **27** (loading 2.43 mmol g^{-1}, 2.24 g, 5.4 mmol, 2.4 equiv.), and triethylamine (45.7 mg, 0.452 mmol, 2 equiv.). The reaction was heated by microwave irradiation at 90 °C for 3 cycles of 10 min. The resin was then removed by filtration and washed successively with DMF (10 cm^3) and MeOH (2 × 10 cm^3). The solvent was removed by evaporation to yield the corresponding carbodiimide (561 mg, 85% yield): White solid, Retention time = 0.35 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 74.10; H, 6.93; N, 19.19, $C_{18}H_{20}N_4$ requires C, 73.94; H, 6.89; N, 19.16%); ν_{max}(neat)/cm^{-1} 2122, 1645, 1526, 1324, 1209, 1024, 866, 747; δ_H(400 MHz; $CDCl_3$) 8.85 (2H, d, *J* 5 Hz, bipy H-6), 8.70 (2H, s, bipy H-3, H-3′), 8.45 (2H, d, *J* 5 Hz, bipy H-6′), 7.87 (1H, t, *J* 5 Hz, bipy H-4′), 7.53 (2H, d, *J* 5 Hz, bipy H-5), 7.40 (2H, m, bipy H-5′), 2.89 (2H, s, bipy CH_2), 1.44 (10H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 164.2 (N=C=N), 158.9, 158.4 (bipy C-2, C-2′), 151.3, 151.0 (bipy C-6, C-6′), 143.2 (bipy C-4), 138.3 (bipy C-4′), 123.4 (bipy C-3), 123.2 (bipy C-3′), 121.2 (bipy C-5′), 60.2 (bipy *C*H_2), 52.5 (cyclohexyl CH), 34.2 (cyclohexyl CH), 28.2 (cyclohexyl CH), 23.2 (cyclohexyl CH); *m/z* (EI+) 292.16924 (M^+, $C_{18}H_{20}N_4$ requires 292.16880); 292.2 (35%) (M^+).

Synthesis of [2,2′]bipyridinyl-4-ylmethylcyanide (24). To a solution of 2-chloro-4-cyanopyridine (100 mg, 0.722 mmol, 1 equiv.) in anhydrous DCM (10 cm^3) was added $Pd(PPh_3)_4$ (16.1 mg, 0.014 mmol, 2 mol%) followed by 2-pyridylzinc bromide (0.5 M in THF, 2.88 cm^3, 1.44 mmol, 2 equiv.). The mixture was heated by microwave irradiation for 2 cycles of 30 min at 130 °C. The reaction mixture was then concentrated under reduced pressure and the crude material purified by column chromatography on silica (DCM–Et_2O, 1 : 1; then DCM–Et_2O–NEt_3, 1 : 1 : 0.1, 1 : 0.5: 0.5). The purified product was concentrated, and recrystallisation from DCM–light petroleum (1 : 3) gave the corresponding bipyridine (111 mg, 85%): White solid, 85% yield, LC retention time = 0.21 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 73.02; H, 3.97; N, 23.24, $C_{11}H_7N_3$ requires C, 72.92; H, 3.89; N, 23.19%); ν_{max}(neat)/cm^{-1} 1526, 1324, 1209, 1024, 838, 725; δ_H(400 MHz; $CDCl_3$) 8.85 (2H, d, *J* 5 Hz, bipy H-6), 8.76 (2H, s, bipy H-3, H-3′), 8.46 (2H, d, *J* 5 Hz, bipy H-6′), 7.85 (1H, t, *J* 5 Hz, bipy H-4′), 7.58 (2H, d, *J* 5 Hz, bipy H-5), 7.41 (2H, m, bipy H-5′); δ_C(125 MHz; $CDCl_3$) 159.2, 158.9 (bipy C-2, C-2′), 151.8, 151.2 (bipy C-6, C-6′), 143.8 (bipy C-4), 138.3 (bipy C-4′), 124.2 (bipy C-3), 123.2 (bipy C-3′), 121.2 (bipy C-5′), 120.4 (CN); *m/z* (EI+) 181.06564 (M^+, $C_{11}H_7N_3$ requires 181.06400); 181.1 (75%) (M^+).

Synthesis of [2,2′]bipyridinyl-4-ylmethylamine (25). To a solution of [2,2′]bipyridinyl-4-ylmethylcyanide (50 mg, 0.276 mmol, 1 equiv.) in anhydrous THF (10 cm^3) at 0 °C was added a solution of $LiAlH_4$ (1 M in THF, 0.552 cm^3, 0.552 mmol, 2 equiv.). The mixture was allowed to warm to ambient temperature and stirred overnight. The solution was then quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ (177.7 mg, 0.552 mmol). The crude mixture was filtered and the filtrate concentrated under reduced pressure. The material was used for the next step in the synthesis without further purification. White solid, 82% yield, LC retention time = 0.21 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 71.45; H, 6.07; N, 22.78, $C_{11}H_{11}N_3$ requires C, 71.33; H, 5.99; N, 22.69%); ν_{max}(neat)/cm^{-1} 2935, 1526, 1324, 1209, 1024, 838, 725; δ_H(400 MHz; $CDCl_3$) 8.85 (2H, d, *J* 5 Hz, bipy H-6), 8.75 (2H, s, bipy H-3, H-3′), 8.46 (2H, d, *J* 5 Hz, bipy H-6′), 7.85 (1H, t, *J* 5 Hz, bipy H-4′), 7.53 (2H, d, *J* 5 Hz, bipy H-5), 7.40 (2H, m, bipy H-5′), 4.04 (2H, s, bipy CH_2); δ_C(125 MHz; $CDCl_3$) 158.9, 158.4 (bipy C-2, C-2′), 151.3, 151.0 (bipy C-6, C-6′), 143.5 (bipy C-4), 138.3 (bipy C-4′), 124.2 (bipy C-3), 123.2 (bipy C-3′), 121.2 (bipy C-5′), 50.2 (bipy *C*H_2); *m/z* (EI+) 185.09634 (M^+, $C_{11}H_{11}N_3$ requires 185.09530); 185.1 (65%) (M^+).

Synthesis of 1-[2,2″]bipyridinyl-4-methyl-3-cyclohexyl urea (26). To a solution of [2,2″]bipyridinyl-4-ylmethylamine (100 mg, 0.540 mmol, 1 equiv.) in anhydrous DCM (15 cm^3), was added a solution of cyclohexyl isocyanate (94.5 mg, 0.756 mmol, 1.4 equiv.) in THF (4 cm^3) and polymer-supported triethylamine equivalent (0.338 g, 1.08 mmol, 2 equiv., diethylaminomethyl polystyrene, ~3.2 mmol g^{-1}; Fluka Cat. No. 31866). The mixture was allowed to stir overnight at room temperature. The solution was then filtered, and the filtrate was taken to dryness; recrystallisation from DCM–light petroleum (1 : 2) gave the corresponding bipyridine (142.4 mg, 85%): White solid, 82% yield, LC retention time = 0.65 (DCM–Et_2O–NEt_3 = 1 : 1 : 0.05); (Found: C, 69.73; H, 7.18; N, 18.06, $C_{18}H_{22}N_4O$ requires C, 69.65; H, 7.14; N, 18.05%); ν_{max}(neat)/cm^{-1} 2939, 1634, 1589, 1218, 1029, 869, 756; δ_H(400 MHz; $CDCl_3$) 8.86 (2H, d, *J* 5 Hz, bipy H-6), 8.70 (2H, s, bipy H-3, H-3′), 8.47 (2H, d, *J* 5 Hz, bipy H-6′), 7.87 (1H, t, *J* 5 Hz, bipy H-4′), 7.53 (2H, d, *J* 5 Hz, bipy H-5), 7.44 (2H, m, bipy H-5′), 4.78 (2H, s, bipy CH_2), 3.56 (1H, m, CH), 1.73 (2H, m, CH_2), 1.64 (2H, m, CH_2), 1.44 (6H, m, CH_2); δ_C(125 MHz; $CDCl_3$) 165.2 (C=O), 158.9, 158.1 (bipy C-2, C-2′), 151.3, 151.0 (bipy C-6, C-6′), 142.5 (bipy C-4), 135.3 (bipy C-4′), 123.4 (bipy C-3), 123.8 (bipy C-3′), 122.2 (bipy C-5′), 56.2 (bipy *C*H_2), 52.5 (cyclohexyl CH), 34.2 (cyclohexyl CH), 28.2 (cyclohexyl CH), 23.2 (cyclohexyl CH); *m/z* (EI+) 310.17978 (M^+, $C_{18}H_{22}N_4O$ requires 310.17936); 310.2 (75%) (M^+).

General procedure for amide coupling using the monosubstituted carbodiimide reagent (21). To a solution of the carboxylic acid (0.35 mmol) in anhydrous DCM (3 cm^3) was added bipyridyl-supported carbodiimide **17** (146 mg, 0.5 mmol, 1.4 equiv.). After stirring at ambient temperature for 30 min, the amine (0.35 mmol, 1 equiv.) and diisopropylethylamine (62.8 mg, 0.486 mmol, 1.4 equiv.) were added. The mixture was stirred at ambient temperature overnight. To the reaction mixture was added Amberlite IRC-718 copper(II) resin (784 mg, 1.05 mmol, loading ~1.34 mmol g^{-1}, 3 equiv.) the "catching" process was monitored by LC-MS. Upon completion the reaction mixture was filtered and washed in turn with ether (5 cm^3) and DCM (10 cm^3). The filtrate was evaporated to dryness under reduced pressure, and the purity of the corresponding amide was determined by LC-MS and ^{1}H NMR.

1,5-Dimethyl-1*H*-pyrazol-3-yl)-[4-(4-trifluoromethylpyrimidin-2-yl)-[1,4]diazepam-1-yl]methanone (28a). Yellow oil, LC retention time = 2.89 (*m/z* 368.2, M^+); (Found: C, 52.21; H, 5.15; N, 22.79, $C_{16}H_{19}F_3N_6O$ requires C, 52.17; H, 5.20; N, 22.81%); ν_{max}(neat)/cm^{-1} 1628, 1523, 1325, 1282, 1187, 1112, 1025, 925, 772, 721; δ_H(400 MHz; $CDCl_3$) 8.53 (1H, d, *J* 6.5 Hz, pyrimidine H-2), 6.46 (1H, d, *J* 6.5 Hz, pyrimidine H-3), 6.10 (1H, s, pyrazole H-4), 3.85 (3H, s, N–CH_3), 2.89 (2H, t, *J* 5.5 Hz, diazepam H-2), 2.75 (2H, t, *J* 5.5 Hz, diazepam H-3), 2.72 (2H, quintet, *J* 5.5 Hz, diazepam H-7), 2.63 (pyrazole C-5 CH_3), 2.53 (2H, t, *J* 5.5 Hz, diazepam H-5), 1.90 (2H, quintet, *J* 5.5 Hz, diazepam H-6); δ_C(100 MHz; $CDCl_3$) 171.2 (C), 165.3 (C), 160.2 (CH), 160.1 (C=O), 143.2 (C), 141.2 (C), 119.5 (CF_3), 111.2 (CH), 107.2 (CH), 56.2 (CH_2), 54.2 (CH_2), 47.3 (CH_2), 46.1 (CH_2), 34.2 (CH_3), 29.2 (CH_2), 5.4 (CH_3); $C_{16}H_{19}F_3N_6O$ requires 368.15724; *m/z* (ESI+) 368.16235 (M^+, $C_{16}H_{19}F_3N_6O$ requires 368.15724); 368.2 (56%) (M^+).

(4a*S*, 8a*S*)-2-(1,5-Dimethyl-1*H*-pyrazole-3-carbonyl)decahydroisoquinoline-3-carboxylic acid *tert*-butylamide (28b). Yellow oil, LC retention time = 2.89 (*m*/*z* 368.2, M^+); (Found: C, 66.52; H, 8.72; N, 15.50, $C_{20}H_{32}N_4O_2$ requires C, 66.63; H, 8.95; N, 15.54%); ν_{max}(neat)/cm^{-1} 1641, 1584, 1372, 1229, 1165, 1112, 935, 798, 745; δ_H(400 MHz; $CDCl_3$) 6.52 (1H, s, pyrazole H-4), 4.49 (1H, t, *J* 7.3 Hz, isoquinoline H-3), 3.89 (3H, s, pyrazole N–CH_3), 3.15 (2H, m, isoquinoline C-1 CH_2), 2.32 (3H, s, pyrazole C-5 CH_3), 1.86 (2H, m, isoquinoline H-4), 1.68 (4H, m, isoquinoline H-4a, H-8a), 1.45 (4H, m, isoquinoline H-6, H-7), 1.35 (9H, s, *t*-Bu CH_3), 1.35 (4H, m, isoquinoline H-5, H-8); δ_C(100 MHz; $CDCl_3$) 174.6 (C=O), 170.8 (C=O), 142.1 (C), 106.3 (CH), 141.3 (C), 33.9 (CH_3), 142.3 (C), 54.5 (CH), 45.4 (CH_2), 41.9 (C), 35.2 (CH), 33.1 (CH), 28.9 (CH_2), 28.7 (CH_3), 27.9 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 24.4 (CH_2), 6.6 (CH_3); *m*/*z* (ESI+) 360.25432 (M^+, $C_{20}H_{32}N_4O_2$ requires 360.25253); 360.3 (48%) (M^+).

1,5-Dimethyl-1*H*-pyrazole-3-carboxylic acid (1,3,5-trimethyl-1*H*-pyrazol-4-yl methyl)amide (28c). White crystals, mp 236 °C, LC retention time = 2.78 (*m*/*z* 502.1, M + H); (Found: C, 59.72; H, 7.32; N, 26.82, $C_{13}H_{19}N_5O$ requires C, 59.75; H, 7.33; N, 26.80%); ν_{max}(neat)/cm^{-1} 1625, 1593, 1354, 1287, 1198, 1114, 925, 855; δ_H(400 MHz; $CDCl_3$) 6.52 (1H, s, pyrazole H-4′), 4.37 (2H, d, *J* 6.5 Hz, benzylic CH_2), 3.75 (6H, s, 2 × N–CH_3), 2.32 (9H, s, pyrazole C-3, C-5, C-5′ CH_3); δ_C(100 MHz; $CDCl_3$) 161.9 (C), 146.0 (C), 144.9 (C), 139.9 (C), 112.8 (C), 108.1 (CH), 36.7 (N–CH_3), 35.7 (N–CH_3), 32.6 (CH_2), 11.6 (CH_3), 11.1 (CH_3), 9.5 (CH_3); *m*/*z* (EI+) 261.15978 (M^+, $C_{13}H_{19}N_5O$ requires 261.15896); 501.1 (52%) (M^+).

Quinoxalin-6-yl-[4-(4-trifluoromethylpyrimidin-2-yl)-[1,4]-diazepam-1-yl]methanone (28d). White solid, mp 236 °C, LC retention time = 2.63 (*m*/*z* 402.1, M + H); (Found: C, 56.72; H, 4.29; N, 20.92, $C_{19}H_{17}F_3N_6O$ requires C, 56.71; H, 4.26; N, 20.89%); ν_{max}(neat)/cm^{-1} 1623, 1592, 1425, 1315, 1205, 1123, 915, 745, 721; δ_H(500 MHz; $CDCl_3$) 8.86 (2H, d, *J* 7.2 Hz, quinoxaline H-2, H-3), 8.84 (1H, s, quinoxaline H-5), 7.52 (2H, d, *J* 7.2 Hz, quinoxaline H-7, H-8), 7.23 (1H, d, *J* 6.8 Hz, pyrimidine H-6), 3.45 (1H, d, *J* 6.8 Hz, pyrimidine H-5), 3.89 (4H, br t, diazepam CH_2 H-2, H-7), 3.15 (2H, br t, diazepam CH_2 H-3), 3.10 (2H, br t, diazepam CH_2 H-5), 2.08 (2H, quintet, diazepam CH_2 H-6); δ_C(125 MHz; $CDCl_3$) 172.2 (C), 170.2 (C), 164.5 (C), 159.3 (CH), 148.2 (CH), 147.8 (CH), 1441. (C), 142.6 (C), 139.1 (C), 130.2 (CH), 128.2 (CH), 119.5 (CF_3), 118.3 (CH); *m*/*z* (EI+) 402.14235 (M^+, $C_{19}H_{17}F_3N_6O$ requires 402.14159); 402.2 (35%) (M^+).

(4a*S*, 8a*S*)-2-(Quinoxaline-6-carbonyl)decahydroisoquinoline-3-carboxylic acid *tert*-butylamide (28e). Yellow oil, LC retention time = 2.74 (*m*/*z* 394.2, M^+); (Found: C, 70.03; H, 7.54; N, 14.15, $C_{23}H_{30}N_4O_2$ requires C, 70.02; H, 7.66; N, 14.20%); ν_{max}(neat)/cm^{-1} 1641, 1545, 1423, 1325, 1297, 1184, 1112, 1021, 926, 776, 715; δ_H(400 MHz; $CDCl_3$) 8.91 (2H, d, *J* 7.5 Hz, quinoxaline H-2, H-3), 8.45 (1H, d, *J* 7 Hz, quinoxaline H-7), 8.29 (2H, m, quinoxaline H-5, H-8), 4.31 (1H, t, *J* 7.3 Hz, isoquinoline C-1 CH_2), 1.85 (2H, m, isoquinoline H-4), 1.67 (1H, m, isoquinoline H-4a, H-8a), 1.47 (4H, m, isoquinoline H-6, H-7), 1.35 (9H, s, *t*-Bu CH_3), 1.35 (4H, m, isoquinoline H-5, H-8); δ_C(100 MHz; $CDCl_3$) 175.6 (C=O), 170.8 (C=O), 148.2 (CH), 146.4 (CH), 141.8 (C), 144.9 (C), 130.1 (CH), 128.2 (CH), 138.1 (C), 132.1 (CH), 144.9 (C), 57.1 (CH), 46.2 (CH_2), 35.1 (CH), 33.2 (CH), 28.7 (CH_2), 28.2 (CH_2), 27.2 (CH_2), 25.4 (CH_2), 25.1 (CH_2); *m*/*z* (ESI+) 394.23735 (M^+, $C_{23}H_{30}N_4O_2$ requires 394.23688); 394.2 (48%) (M^+).

Quinoxaline-6-carboxylic acid (1,3,5-trimethyl-1*H*-pyrazol-4-ylmethyl)amide (28f). Yellow oil, LC retention time = 2.78 (*m*/*z* 502.1, M + H); (Found: C, 65.12; H, 5.75; N, 23.72, $C_{16}H_{17}N_5O$ requires C, 65.07; H, 5.80; N, 23.71%); ν_{max}(neat)/cm^{-1} 1634, 1489, 1345, 1265, 1192, 1115, 1097, 1076, 915, 767, 723; δ_H(400 MHz; $CDCl_3$) 8.74 (2H, d, *J* 5 Hz, quinoxaline H-2, H-3), 8.78 (1H, s, quinoxaline H-5), 8.39 (1H, d, *J* 5 Hz, quinoxaline H-7), 8.23 (1H, d, *J* 5 Hz, quinoxaline H-8), 4.56 (2H, s, pyrazole CH_2), 3.84 (2H, s, N-1 CH_3), 2.82 (6H, s, N-3, N-5 CH_3); δ_C(100 MHz; $CDCl_3$) 159.2 (C=O), 151.9 (C), 148.2 (CH), 145.6 (CH), 144.9 (C), 144.2 (C), 141.6 (C), 137.3 (C), 131.3 (CH), 130.2 (CH), 127.8 (CH), 117.3 (C), 29.2 (CH_2), 34.9 (CH_3), 8.2 (CH_3), 1.2 (CH_3); *m*/*z* (EI+) 295.14531 (M^+, $C_{16}H_{17}N_5O$ requires 295.14331); 295.1 (32%) (M^+).

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