Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Bifunctional building blocks in the Ugi-azide condensation reaction: a general strategy toward exploration of new molecular diversity†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 6036

Steven Gunawan and Christopher Hulme*

Received 30th April 2013,
Accepted 25th June 2013

DOI: 10.1039/c3ob40900g

www.rsc.org/obc

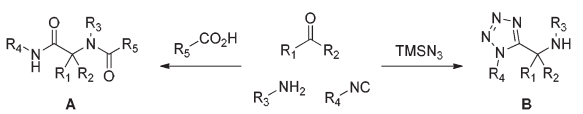
1,5-Disubstituted tetrazoles are an important drug-like scaffold known for their ability to mimic the *cis*-amide bond conformation. The scaffold is readily accessible *via* substitution of the carboxylic acid component of the Ugi multi-component reaction (MCR) with $TMSN_3$ in what is herein denoted the Ugi-azide reaction. This full paper presents a concise, novel, general strategy to access a plethora of new heterocyclic scaffolds utilizing tethered aldo/keto-acids/esters in the Ugi-azide reaction followed by a ring closing event that generates novel highly complex bis-heterocyclic lactam-tetrazoles.

Introduction

The design of peptidomimetics to circumvent small molecule biological stability issues, thus delivering improved pharmacokinetic profiles, has gained massive interest over the last twenty years.[1] In particular, *cis*-amide bonds have been shown to play key roles in protein secondary structures involved in several important biological systems.[2] In studies to determine effective mimics of the *cis*-amide bond, the tetrazole ring and more specifically the 1,5-disubstituted tetrazole, has proven to be a valuable bioisostere, extensively reported on by Marshall *et al*.[3] The biological significance of related ring systems has grown in recent years with a number of tetrazole analogs reported to exhibit biological activity toward the cannabinoid-1 receptor (CB1),[4] fatty acid amide hydrolase,[5] melanin-concentrating hormone receptor 1,[6] polo-like kinase 1,[7] and to act as orally effective human growth hormone secretagogues.[8] Clearly, development of concise routes to novel 1,5-disubstituted tetrazole chemical space has the potential to deliver small molecule partners or probes for new or established protein receptors, enabling studies on protein function or even initiation of translational campaigns.

The classical Ugi MCR is comprised of four components, an aldehyde, amine, isocyanide and carboxylic acid, which on mixing generate the peptidic-like structure A containing 4 points of diversification (Scheme 1). As such, it is probably the premiere isocyanide based MCR, and subsequent chemical manipulation of the flexible product has received immense interest in the medicinal chemistry community providing access to arrays of highly diverse small molecules.[9] Moreover, an offspring of the Ugi reaction, denoted the Ugi-azide reaction, offers a concise chemical route to 1,5-disubstituted tetrazoles which is initiated with simple replacement of the carboxylic acid with $TMSN_3$, delivering 1,5-disubstituted tetrazoles B (Scheme 1).[10] Through use of a variety of assorted reagents and systematically exploring different ring closing possibilities of the Ugi-azide product B, unique scaffolds such as ketopiperazine-tetrazoles,[11] azepine-tetrazoles,[12] benzodiazepine-tetrazoles[13] and quinoxaline-tetrazoles[14] have been successfully generated.

Recently, we reported on the use of methyl levulinate **1**, a tethered keto-ester, in the Ugi-azide MCR followed by subsequent rigidification.[15] This full paper details the versatility and generality of the methodology with greatly enhanced scope in tether diversity between the aldehyde and electrophilic acid or ester appendage (Scheme 2), enabling access to multiple collections of bis-heterocyclic lactam-tetrazoles



Scheme 1 Ugi and Ugi-azide MCR.

Scheme 2 General strategy to lactam-tetrazoles.

BIO5 Oro Valley, The University of Arizona, 1580 E. Hanley Blvd., Oro Valley, AZ 85737, USA. E-mail: hulme@pharmacy.arizona.edu; Tel: +1 (520) 626-5322

†Electronic supplementary information (ESI) available: General procedure, ^1H and ^{13}C NMR spectra for aldo/keto-esters (**8b**, **19b**, **19** and **30**). ^1H and ^{13}C NMR spectra for all new synthesized compounds (**10**, **10b–j**, **20a–e**, **22a–f**, **24a–e**, **29a–e** and **31a–f**). CCDC 936637. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40900g

recently submitted to the United States Molecular Libraries Small Molecule Repository (MLSMR).

Results and discussion

Syntheses of tetrazolyl-pyrrolidinones and -indolinones

Initial studies concentrated on exploring the suitability of commercially available methyl levulinate **1** to provide the tetrazolyl-lactam **5a** with supporting reagents thiophen-2-ylamine **2** and 2-isocyano-1,3-dimethylbenzene **3** (Scheme 3).[15] After formation of the Ugi product **4**, direct addition of a solution of 10% TFA in DCE [Note: without removal of MeOH] facilitated lactam formation to give **5a** in 56% yield over two steps (Scheme 3). Interestingly, when methanol was removed prior to addition and dissolution of **4** in 10% TFA/DCE, **5a** was only observed in negligible amounts. The Ugi product was thus isolated and subjected to basic conditions (Scheme 3, 2. KOH, MeOH, THF, H_2O). Gratifyingly, **2a** was attained in comparable yields (59% over 2 steps), presumably through cyclization of the secondary amine directly onto a newly formed carboxylic acid from the methyl ester moiety. With two complementary routes in hand the more operationally friendly acid mediated protocol was employed to establish the reactivity domain through preparation of a further eight tetrazolyl-pyrrolidinones **2** (Table 1). Furthermore, the methodology was importantly shown to be compatible with plate based production, delivering 96 congeners in rapid fashion.[16]

Encouraged by this operationally friendly protocol, we embarked upon additional studies of new tether diversity exploring the production of tetrazolyl-indolinones **10**. Preliminary attempts focused on the use of methyl 2-acetylbenzoate **8a**, *n*-pentyl isocyanide **7a** and furfurylamine **6a** in the Ugi-azide MCR (Scheme 4). Unexpectedly, the condensation performed poorly for the acetophenone **8a**, whereas the aldehyde congener, methyl 2-formylbenzoate **8b**, performed in exemplary fashion and **10b** was formed directly without the need for addition of acid (85% isolated yield, 2 steps).

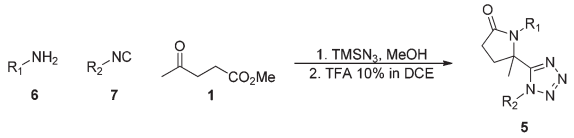
Eight analogs were thus prepared using an assortment of primary amines and isocyanides (Table 2) and the chemistry was progressed to plate based production delivering 96 additional analogs of indolinone-tetrazoles **8**.[17,18]

Syntheses of tetrazolyl-piperidinones, -ketopiperazines, and -thiomorpholinones

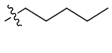
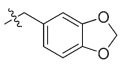
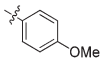
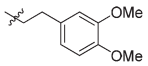
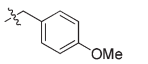
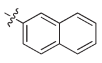
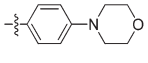
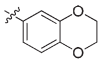
Using the same diversity reagents **6a** and **7a**, the feasibility of expanding the generality of this methodology to afford 6 membered rings was subsequently investigated with bifunctional reagents methyl ester **11a** and free carboxylic acid **11b**. Thus, after Ugi-azide reaction of **6a**, **7a** and **11a**, TFA was added to the methanolic reaction medium of **12a** and contrary to observations with its 5-membered ring congener no cyclization to desired product **13a** was observed.

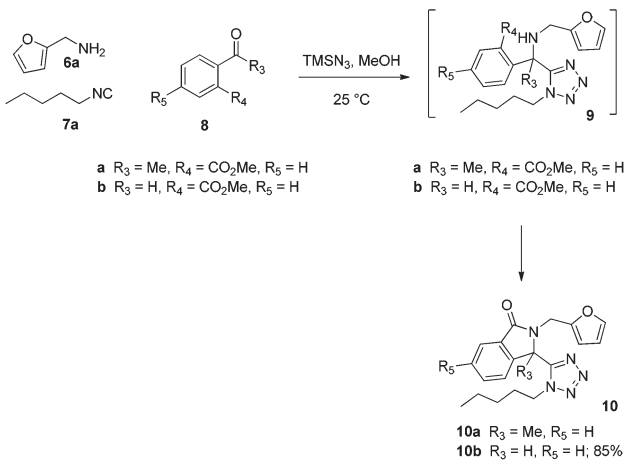
From prior experience with **4** (Scheme 3) possessing both ester and amine functionalities akin to **12a**, lactamization was attempted *via* two additional steps *i.e.* ester cleavage to the free acid and amide bond formation to afford the lactam. Thus, reaction of methyl 5-oxohexanoate **11a** in the azide modified

Table 1 Tetrazolyl-pyrrolidinones series

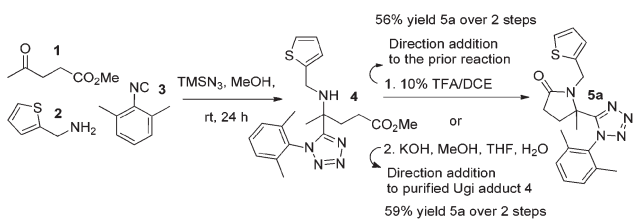


6 7 1 5

R_1	R_2	Product	Yield (%)
		**5b**	78
		**5c**	54
		**5d**	69
		**5e**	59
		**5f**	52
		**5g**	64
		**5h**	40
		**5i**	48

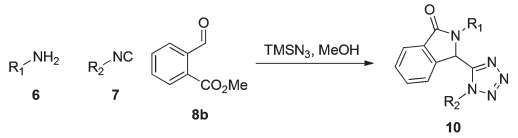


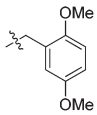
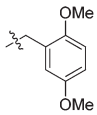
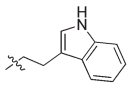
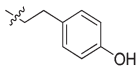
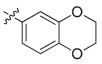
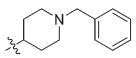
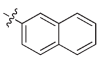
Scheme 4 Synthesis of 2-(furan-2-ylmethyl)-isoindolin-1-one **10b**.

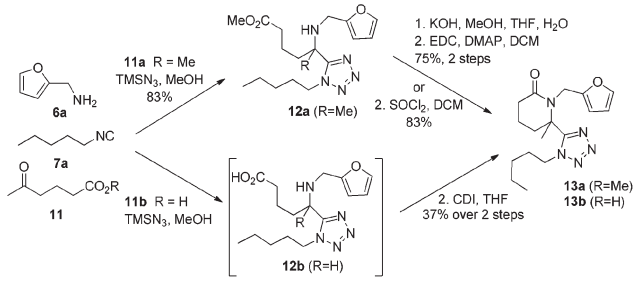


Scheme 3 Access to tetrazolyl-pyrrolidinone **5a**.

Table 2 Indolinone tetrazole series

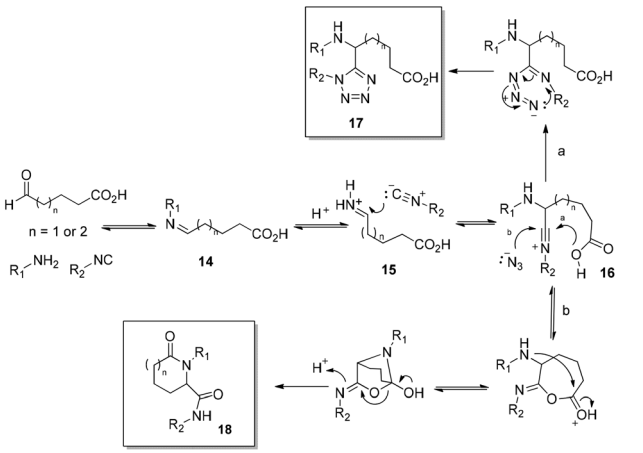


R_1	R_2	Product	Yield (%)
		**10c**	51
		**10d**	58
		**10e**	66
		**10f**	43
		**10g**	51
		**10h**	58
		**10i**	29
		**10j**	36



Scheme 5 Optimization of the preparation of piperidine-tetrazole **13**.

Ugi reaction with **6a** and **7a** (Scheme 5) gave the Ugi amino-ester **12a** (83% yield). Basic hydrolysis of **12a** and subsequent 1-ethyl-3-(3-dimethyllaminopropyl)-carbodiimide (EDC) or $SOCl_2$ mediated intramolecular amide coupling provided **13a** in 75% and 83% yield respectively over the final two steps. Looking to improve the route to **13**, we investigated utilizing the tethered keto-acid **11b** in the Ugi-Azide MCR and, to our delight, the Ugi product **12b** as opposed to **18** was formed, Scheme 6. Without purification of **12b**, coupling agent 1,1′-carbonyldiimidazole (CDI) was able to catalyze lactam formation to provide tetrazolyl-piperidinone **13b** in 37% overall yield for the combined two steps (Scheme 5). With a general one-pot, two-step optimized procedure in hand, five other examples

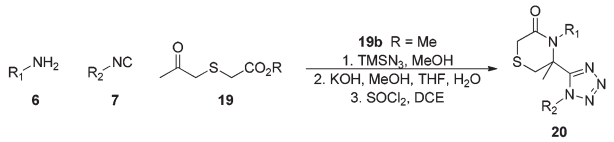


Scheme 6 Ugi-azide condensation to afford **17**.

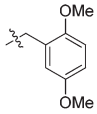
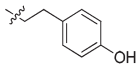
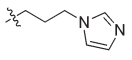
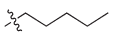
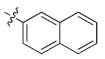
were prepared using an assortment of primary amines and isocyanides reported previously.[16] Mechanistically, this was intriguing and a postulated sequence of events is depicted in Scheme 6.[19] Thus, condensation of an aldo-acid and a primary amine forms imine **15**. Upon imine protonation, isocyanide addition forms the intermediate nitrilium ion **16**. The classical intramolecular Ugi MCR (Path a) would typically afford lactam **18** after Mumm rearrangement. However, the small and highly nucleophilic azide ion intercepts **16** (Path b) in preference to intramolecular ring closure with the free carboxylic acid, affording **17** which is ready for CDI mediated ring closure. Further efforts were devoted to enrich molecular diversity through the assembly of more elaborated heterocyclic cores and three additional libraries incorporating unique molecular features and six membered rings found in medicinally valuable compounds were thus evaluated for route feasibility. Thus, integration of a sulphur atom into the 6-membered ring to generate thiomorpholinone derivatives **20** was attempted. This peculiar moiety has been the subject of intense study due to its pharmacological properties depicted as a 1,4-benzothiazine framework in the calcium antagonist Semotiadil.[20] When keto-acid **19a** (R = H) was mixed with 2,5-dimethoxybenzylamine and cyclopentyl isocyanide, competition between path a and b, illustrated in Scheme 6 gave two products, *i.e.* **17** and **18** derivatives. Subsequently, the crude mixture was treated with CDI to give **20a** in only 21% yield. Due to this low yield, we turned our attention to methyl 2-((2-oxopropyl)thio)-acetate **19b** (R = Me), prepared from methyl thioglycolate and chloroacetone, which delivered **20a** in 69% yield in two steps. Accordingly, a variety of primary amines, isocyanides and **19b** were evaluated to establish a preliminary reactivity domain and furnish an array of five unique thiomorpholinones **20a–e** (Table 3).

Another enticing moiety that drew our attention was the 4-sulfonyl-2-piperazinone skeleton embedded in **22**. This conformationally restricted motif represents an essential structural feature of human factor Xa and gene transcription inhibitors.[21,22] Indeed, sulfonamide keto-acids have previously

Table 3 Array of thiomorpholinone-tetrazole derivatives **20**

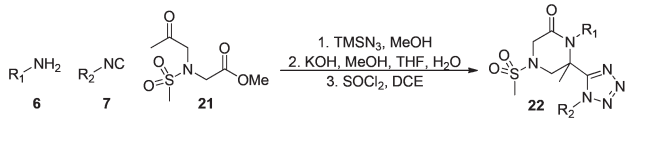


6 7 19 20

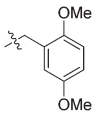
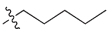
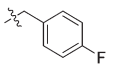
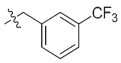
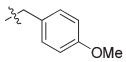
R_1	R_2	Product	Ugi (%)	Final steps[a] (%)
		**20a**	78	88
		**20b**	61	66
		**20c**	42	22
		**20d**	86	73
		**20e**	61	96

[a] Basic hydrolysis and $SOCl_2$ activation.

Table 4 Array of 4-sulfonyl-2-piperazinone-tetrazole derivatives **22**



6 7 21 22

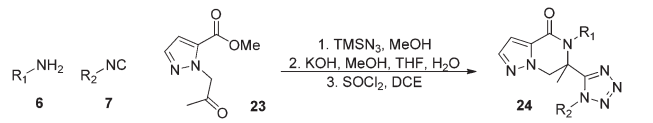
R_1	R_2	Product	Ugi (%)	Final steps[a] (%)
		**22a**	16	78
		**22b**	27	93
		**22c**	59	82
		**22d**	55	86
		**22e**	74	58
		**22f**	64	64

[a] Basic hydrolysis and $SOCl_2$ activation.

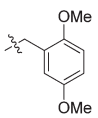
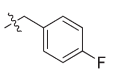
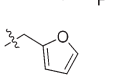
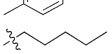
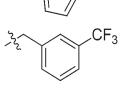
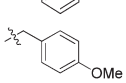
been reported as highly compatible bifunctional reagents in intramolecular Ugi three component condensations affording 5-carbamoyl-5-methyl-4-sulfonyl-2-piperazinones in a single step.[23] The sulfonamide keto-ester **21** was thus synthesized from glycine methyl ester in two steps consisting of sequential sulfonylation and alkylation using 18-crown-6 as a phase-transfer catalyst and a relatively mild base (K_2CO_3). A series of six 4-sulfonyl-2-piperazinones **22** were generated to confirm the utility of **21** in producing novel tetrazolo-fused analogs, thereby further expanding the generality of the lactam-tetrazole forming methodology depicted in Scheme 2 (Table 4).

Additional attempts to further diversify the portfolio of scaffolds derived from this methodology were carried out by fusing heteroaromatic rings onto the bifunctional input. In particular, derivatives of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one represent an uncultivated set of pharmaceutically relevant compounds where the scaffold is currently found in both fibrinogen and vitronectin receptor antagonists.[24,25] Intrigued by the potential new biological applications of this rare bifunctional substituted-pyrazole methyl ester,[26] it was thus employed with supporting reagents **6** and **7** in the development of new synthetic route to scaffold **24**. Alkylation of methyl 1*H*-pyrazole-3-carboxylate with chloroacetone under phase transfer conditions in the presence of K_2CO_3 and 18-crown-6 provided 23 in a single step. In analogous fashion to prior methods reported herein, 23 was mixed with a variety of primary amines and isocyanides in the Ugi-Azide MCR. Subsequent basic hydrolysis and $SOCl_2$-mediated ring closure furnished a compilation of five 4,5,6,7-tetrahydropyrazolo-[1,5-*a*]-pyrazine-4-one derivatives **24a–e** depicted in Table 5 with moderate to good isolated yields.

Table 5 Array of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one tetrazole derivatives **24**



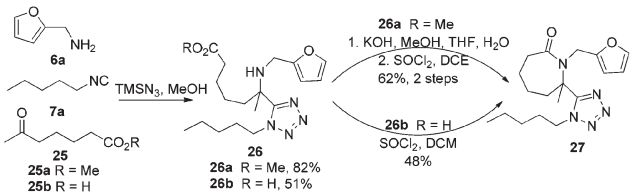
6 7 23 24

R_1	R_2	Product	Ugi (%)	Final steps[a] (%)
		**24a**	74	51
		**24b**	73	57
		**24c**	67	78
		**24d**	51	72
		**24e**	42	55

[a] Basic hydrolysis and $SOCl_2$ activation.

Syntheses of tetrazolyl-azepanones, -thiazepanones, and -benzoxazepinones

With five diverse scaffolds in hand, we subsequently expanded the generality to variations of seven-membered ring lactams. Initial efforts were devoted to preparations of 1-(furan-2-



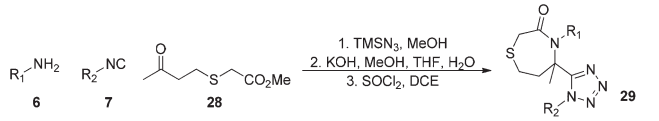
Scheme 7 Optimization of azepinone-tetrazoles **27**.

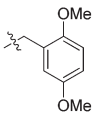
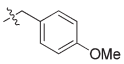
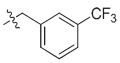
ylmethyl)-7-methyl-7-(1-pentyl-1*H*-tetrazol-5-yl)azepan-2-one **27** analogs (Scheme 7). In similar fashion with attempts to prepare tetrazolyl-piperidines **13**, TFA failed to deliver **27** after direct addition of TFA/DCE to a methanolic solution of the ongoing Ugi-azide reaction with **25a** (R = Me) and supporting reagents **6a** and **7a**. However, unlike **13** which was accessible *via* CDI or EDC-mediated amide coupling, **27** was not obtained after similar coupling methods were employed with crude **26b** (R = H). Azepine-tetrazole **27** was ultimately generated in 48% yield through $SOCl_2$ triggered *in situ* acyl chloride formation on partially purified **26b** (Scheme 7). Due to its high polarity, complete isolation of **26b** did prove difficult and hence attention was turned to the Ugi amino-ester **26a**, synthesized from methyl 6-oxoheptanoate **25a** (82% yield). Yield improvement to 62% was observed when **27** was produced from **26a** (R = H) in two steps comprising consecutive basic hydrolysis and *in situ* acyl chloride formation (Scheme 7). This method was exemplified by the assembly of four analogs and has been previously reported.[16]

Thiazepanone derivatives **29** were successfully prepared in similar fashion to the thiomorpholinones **20**. The key reagent in production of this derivative, namely methyl 2-((3-oxobutyl)-thio)acetate **28**, was prepared from methyl thioglycolate and 4-chlorobutan-2-one in one step. Upon completion of the Ugi-azide condensation, MCR intermediates were subjected to the optimized two-step protocol to ultimately afford five examples **29a–e** in good overall yields for the 3 step process (Table 6).

A final example highlighting the generality of this methodology enabled access to the tetrazolo-benzoxazepinones **31**. Akin to the [1,4]thiazepanone **29**, the benzo[1,4]oxazepinone fragment may also be viewed as a relatively under-developed scaffold in the pharmaceutical sector, although, a handful of articles do describe some utility with the chemotype observed embedded in ACE/neutral endopeptidase (NEP)[27] and HIV-1[28] inhibitors. Methyl esterification of 2-(2-formylphenoxy)acetic acid generated methyl 2-(2-formylphenoxy)acetate **30**, that was used as the tethered bifunctional component (Table 7). Six analogs **31a–31f** were synthesized and the structure of **31c** was confirmed by X-ray crystallography (Fig. 1).[29]

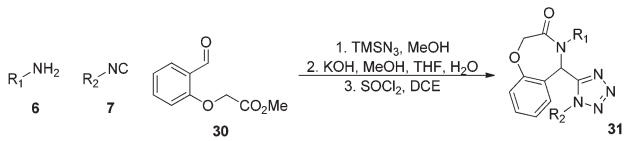
Table 6 Array of [1,4]thiazepanone derivatives **29**

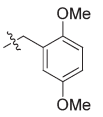
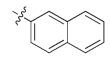
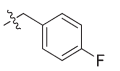
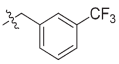
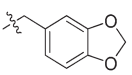


R_1	R_2	Product	Ugi (%)	Final steps[a] (%)
		**29a**	68	57
		**29b**	70	66
		**29c**	70	54
		**29d**	61	45
		**29e**	75	51

[a] Basic hydrolysis and $SOCl_2$ activation.

Table 7 Array of benzo[1,4]oxazepinone derivatives **31**



R_1	R_2	Product	Ugi (%)	Final steps[a] (%)
		**31a**	80	29
		**31b**	63	31
		**31c**	74	84
		**31d**	78	70
		**31e**	77	35
		**31f**	66	62

[a] Basic hydrolysis and $SOCl_2$ activation.

Conclusions

A straightforward, robust and extremely versatile strategy coupling the Ugi-Azide MCR with amidative post-condensation modifications enabling ring-closure to a variety of pharmacologically relevant scaffolds has been established. In this context, tethered aldo-esters/keto-acids/keto-esters were key bifunctional precursors that in combination with supporting isonitrile and amine reagents typically afforded the Ugi-azide adduct in good yield. Not surprisingly during the optimization of the post-condensation ring closing methodology, it was apparent that stronger activating reagents were required as the

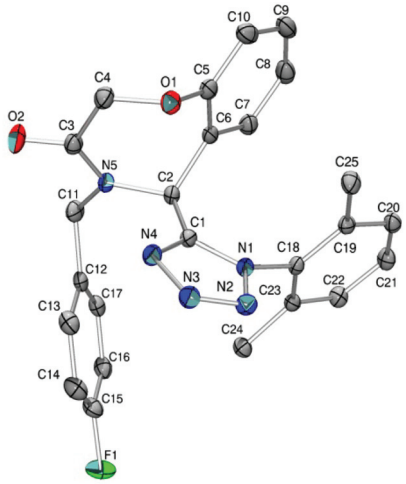


Fig. 1 X-Ray crystal structure of **31c**.

desired lactam ring size increased, yet all of the 5 to 7-*exo-trig* processes remained, as expected, ultimately feasible.[30] By means of this general route, nine bis-heterocyclic tetrazolo-scaffolds and related congener sets were prepared incorporating a wide array of bifunctional input linker diversity (Scheme 2, x = linker) and additional diversity elements from supporting reagents **6** and **7**. Coupled with the *cis*-amide bond surrogacy possessed by the 1,5-disubstituted tetrazole nucleus, these new bis-heterocylic scaffolds represent potential innovative new molecular probes to interrogate peptidergic biological systems.

Experimental

General remarks

All reagents were purchased from Acros Organics, Alfa Aesar, Sigma Aldrich and TCI America. Microwave assisted reactions were conducted in a 10-ml vial on a CEM microwave initiator. The flash column chromatography was carried out on Teledyne Isco Combi*Flash* Rf 200. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or $DMSO_{d6}$ on a Varian 400 MHz spectrometer. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm, *d*) downfield from the internal standard Me_4Si (TMS). Chemical shifts in ^{13}C NMR spectra are reported relative to the central line of the chloroform signal (*d* = 77.70 ppm) or the DMSO signal (*d* = 40.0 ppm). Low-resolution mass spectra were obtained with a Shimadzu Prominence UFLCXR/LCMS-2020/ELSD-LTII instrument. High-resolution mass spectra were obtained with 9.4 Tesla Bruker FT/ICR-MS instrument.

General procedure for aldo/keto-esters (8b, 19b, 28 and 30)

All can be found in the ESI.†

General experimental procedure for synthesis of indolinone tetrazoles (10b–10j)

Methyl 2-formylbenzoate **8b** (0.250 mmol), R_1NH_2 **6** (0.250 mmol), $TMSN_3$ (0.250 mmol) and R_2NC **7** (0.250 mmol) were dissolved in MeOH (1.0 ml) in a 10 ml vial. The reaction was allowed to run at room temperature for 24 h. The crude mixture was concentrated *in vacuo* and purified by flash chromatography (hexane–EtOAc) to afford the indolinone tetrazoles.

2-(Furan-2-ylmethyl)-3-(1-pentyl-1*H*-tetrazol-5-yl)isoindo-lin-1-one (10b). White solid (m.p. 95–97 °C); 85% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 8.02–7.97 (m, 1H), 7.65–7.56 (m, 2H), 7.28–7.22 (m, 2H), 6.26–6.21 (m, 2H), 6.19–6.15 (m, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.57 (d, *J* = 15.6 Hz, 1H), 3.57 (ddd, *J* = 14.8, 8.8, 6.3 Hz, 1H), 3.43 (ddd, *J* = 14.8, 8.8, 6.3 Hz, 1H), 1.38–1.24 (m, 1H), 1.19–1.08 (m, 1H), 1.08–0.95 (m, 2H), 0.89–0.78 (m, 2H), 0.71 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 167.7, 150.2, 148.6, 142.9, 140.3, 133.0, 131.2, 130.1, 124.7, 123.1, 110.7, 109.6, 55.1, 55.0, 47.6, 38.1, 28.4, 28.2, 21.7, 13.6; $[M + H]^+$ = 352.4; HRMS (ESI): *m*/*z* calcd for ($C_{19}H_{22}N_5O_2$): 352.1768; found: 352.1772.

3-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-2-(2,5-dimethoxybenzyl) iso-indolin-1-one (10c). Yellow solid (m.p. 118–119 °C); 51% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 8.01–7.94 (m, 1H), 7.62–7.50 (m, 2H), 7.21–7.15 (m, 1H), 6.96–6.91 (m, 1H), 6.77 (ddd, *J* = 8.9, 3.0, 1.6 Hz, 2H), 6.71 (dd, *J* = 8.9, 1.3 Hz, 2H), 6.20 (s, 1H), 4.96 (d, *J* = 14.5 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 3.99–3.88 (m, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 2.01–1.75 (m, 3H), 1.74–1.59 (m, 1H), 1.59–1.47 (m, 1H), 1.41–1.28 (m, 1H), 1.19–1.07 (m, 1H), 1.06–0.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 168.4, 153.5, 151.4, 150.3, 140.8, 132.8, 131.3, 129.8, 124.4, 124.3, 123.1, 116.7, 114.4, 111.3, 59.3, 55.74, 55.68, 55.4, 39.9, 33.4, 32.6, 24.7, 24.6; $[M + H]^+$ = 420.3; HRMS (ESI): *m*/*z* calcd for ($C_{23}H_{26}N_5O_3$): 420.20302; found: 420.20308.

3-(1-Benzyl-1*H*-tetrazol-5-yl)-2-(thiophen-2-ylmethyl)iso-indolin-1-one (10d). Yellow solid (m.p. 134–136 °C); 58% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 7.95 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.3 Hz, 1H), 7.24–7.18 (m, 2H), 7.16 (td, *J* = 7.3, 1.4 Hz, 2H), 6.97–6.93 (m, 1H), 6.90 (ddd, *J* = 5.1, 3.5, 1.7 Hz, 1H), 6.83–6.79 (m, 1H), 6.68 (d, *J* = 7.9 Hz, 2H), 6.15 (s, 1H), 4.89 (dd, *J* = 15.4, 4.5 Hz, 2H), 4.62 (d, *J* = 15.3 Hz, 1H), 4.12 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 167.5, 150.4, 139.7, 137.3, 132.9, 132.3, 131.2, 130.0, 128.8, 128.7, 127.8, 127.2, 127.1, 126.5, 124.6, 123.1, 54.0, 51.2, 39.3; $[M + H]^+$ = 388.3; HRMS (ESI): *m*/*z* calcd for ($C_{21}H_{18}N_5OS$): 388.12266; found: 388.12239.

2-(2,5-Dimethoxybenzyl)-3-(1-(2,6-dimethylphenyl)-1*H*-tetra-zol-5-yl)isoindolin-1-one (10e). White solid (m.p. 167–169 °C); 66% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 7.61–7.57 (m, 1H), 7.46–7.41 (m, 1H), 7.41–7.36 (m, 1H), 7.30–7.26 (m, 2H), 7.19–7.12 (m, 2H), 6.80–6.73 (m, 4H), 6.09 (s, 1H), 4.95 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 15.0 Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 2.04 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 167.6, 153.6, 152.4, 151.5, 139.7, 135.3, 135.0, 131.7, 131.5, 131.2, 130.7, 129.5, 128.7, 128.3, 124.8, 123.9, 123.2, 116.1, 113.8, 111.4, 55.8, 55.7, 54.4, 39.8, 17.6, 17.0; $[M + H]^+$ = 456.3; HRMS (ESI): *m*/*z* calcd for ($C_{26}H_{26}N_5O_3$): 456.20302; found: 456.20242.

2-(2-(1*H*-Indol-3-yl)ethyl)-3-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-isoindolin-1-one (10f). White solid (m.p. 108–110 °C); 43%

yield (one step); ^{1}H NMR (400 MHz, $DMSO_{d6}$) δ ppm 10.83 (s, 1H), 7.88–7.80 (m, 1H), 7.63–7.56 (m, 2H), 7.37–7.27 (m, 3H), 7.11 (s, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.68 (s, 1H), 3.94–3.83 (m, 1H), 3.15–2.93 (m, 2H), 2.82–2.71 (m, 1H), 1.81 (s, 9H); ^{13}C NMR (100 MHz, $DMSO_{d6}$) δ ppm 167.71, 153.00, 143.32, 136.63, 132.83, 131.69, 129.76, 127.31, 123.80, 123.29, 123.25, 121.51, 118.80, 118.22, 111.94, 111.26, 62.67, 55.24, 42.53, 40.60, 40.39, 40.18, 39.97, 39.76, 39.56, 39.35, 30.27, 24.28; $[M + H]^+$ = 401.4; HRMS (ESI): m/z calcd for ($C_{23}H_{25}N_6O$): 401.20844; found: 401.20824.

3-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-2-(4-hydroxyphenethyl) isoindolin-1-one (10g). White solid (m.p. 162–164 °C); 51% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.04–7.94 (m, 1H), 7.66–7.55 (m, 2H), 7.26–7.22 (m, 1H), 7.06–7.00 (m, 2H), 6.84–6.75 (m, 2H), 6.52–6.40 (m, 1H), 6.09 (s, 1H), 4.22–4.11 (m, 1H), 3.13 (tt, J = 11.6, 3.7 Hz, 1H), 3.05–2.90 (m, 2H), 2.80–2.69 (m, 1H), 2.00–1.49 (m, 8H), 1.15–1.03 (m, 2H), 0.92 (dd, J = 16.4, 11.1 Hz, 1H), 0.68–0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.0, 155.1, 149.5, 140.2, 132.9, 131.6, 130.2, 129.7, 128.9, 124.4, 123.0, 115.7, 58.9, 54.9, 42.7, 33.3, 32.7, 32.6, 25.2, 25.1, 24.4; $[M + H]^+$ = 404.4; HRMS (ESI): m/z calcd for ($C_{23}H_{26}N_5O_2$): 404.20810; found: 404.20828.

3-(1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-tetrazol-5-yl)-2-isobutylisoindolin-1-one (10h). Yellow solid (m. p. 66–67 °C); 58% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70–7.64 (m, 1H), 7.58–7.45 (m, 2H), 7.29 (d, J = 7.4 Hz, 1H), 6.68–6.64 (m, 1H), 6.23 (s, 1H), 6.17–6.14 (m, 1H), 4.32–4.11 (m, 5H), 3.66 (dd, J = 13.9, 9.5 Hz, 1H), 2.48 (dd, J = 13.9, 5.7 Hz, 1H), 2.09–1.96 (m, 1H), 0.94 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.6, 151.7, 145.5, 143.5, 140.2, 132.2, 132.0, 129.6, 125.1, 124.0, 122.8, 118.3, 117.6, 114.6, 64.3, 64.1, 54.6, 48.0, 27.5, 20.3, 19.7; $[M + H]^+$ = 392.3; HRMS (ESI): m/z calcd for ($C_{21}H_{22}N_5O_3$): 392.17172; found: 392.17184.

2-(1-Benzylpiperidin-4-yl)-3-(1-(4-methoxyphenyl)-1*H*-tetrazol-5-yl)isoindolin-1-one (10i). Light tangerine solid (m.p. 83–84 °C); 29% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62 (d, J = 7.4 Hz, 1H), 7.52 (td, J = 7.5, 1.3 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.35–7.22 (m, 7H), 6.70–6.64 (m, 2H), 6.63–6.57 (m, 2H), 6.29 (s, 1H), 4.15–4.03 (m, 1H), 3.77 (s, 3H), 3.47 (s, 2H), 2.97–2.89 (m, 1H), 2.88–2.80 (m, 1H), 2.08–1.99 (m, 3H), 1.69 (d, J = 9.4 Hz, 1H), 1.72–1.64 (m, 1H), 1.48–1.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.2, 160.9, 153.2, 141.1, 138.3, 132.4, 132.1, 129.7, 128.9, 128.2, 127.0, 126.7, 125.3, 124.0, 122.7, 114.3, 62.6, 55.6, 52.8, 52.7, 51.6, 30.1, 29.9; $[M + H]^+$ = 481.3; HRMS (ESI): m/z calcd for ($C_{28}H_{29}N_6O_2$): 481.23465; found: 481.23441.

2-Cyclopropyl-3-(1-(naphthalen-2-yl)-1*H*-tetrazol-5-yl)iso-indolin-1-one (10j). Light tangerine solid (m.p. 88–89 °C); 36% yield (one step); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.59–7.51 (m, 4H), 7.46 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.6, H), 7.10 (d, J = 2.0 Hz, 1H), 6.96 (dd, J = 8.7, 2.2 Hz, 1H), 6.17 (s, 1H), 2.47–2.39 (m, 1H), 0.95–0.88 (m, 1H), 0.81–0.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 168.4, 152.3, 140.4, 133.5, 132.5, 132.2, 129.8, 129.8, 128.3, 128.2, 128.0, 127.7, 124.7, 124.0, 122.8, 121.7, 55.8, 24.2, 6.6, 5.1; $[M + H]^+$ = 368.3; HRMS (ESI): m/z calcd for ($C_{22}H_{18}N_5O$): 368.1506; found: 368.1513.

General experimental procedure for synthesis of tetrazolyl-thiomorpholinones (20a–e), tetrazolyl ketopiperazines (22a–f and 24a–e), tetrazolyl-thiazepanones (29a–e), and tetrazolyl-benzoxazepinones (31a–f)

Bifunctional reagents (**20**, **22**, **24**, **29** or **31**, 0.250 mmol), R_1NH_2 (0.250 mmol), $TMSN_3$ (0.250 mmol) and R_2NC (0.250 mmol) were dissolved in MeOH (1.0 ml) in a 10 ml vial. The reaction was allowed to run at room temperature for 24 h. The crude mixture was concentrated *in vacuo* and purified by flash chromatography (hexane–EtOAc) to afford the Ugi-tetrazoles. Subsequently, MeOH (1.5 ml), THF (0.75 ml), and H_2O (0.5 ml) were added, followed by 0.03 ml of a 1 g/1 ml solution of KOH in H_2O and the reaction mixture was irradiated in a microwave initiator at 100 °C for 5 min. Upon acidification with 1 M HCl solution to pH 2, the hydrolyzed product was then extracted with EtOAc (3 × 2 ml) and the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in DCE (2 ml) followed by addition of $SOCl_2$ (1.5 eq.) and the reaction was refluxed at 85 °C. When completed, TEA (0.5 ml) was added and the mixture was stirred for 2 h before being purified by flash chromatography (hexane–EtOAc) on silica gel to afford final products.

5-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-4-(2,5-dimethoxybenzyl)-5-methylthiomorpholin-3-one (20a). Viscous liquid; 69% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.76–6.66 (m, 3H), 4.98 (d, J = 16.5 Hz, 1H), 4.88–4.77 (m, 1H), 3.80–3.70 (m, 4H), 3.67 (s, 3H), 3.63 (d, J = 17.2 Hz, 1H), 3.53 (d, J = 17.2 Hz, 1H), 3.20 (d, J = 14.4 Hz, 1H), 3.08 (d, J = 14.3 Hz, 1H), 2.31–2.20 (m, 1H), 2.20–2.02 (m, 5H), 1.98 (s, 3H), 1.83–1.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 166.5, 155.8, 153.5, 150.2, 125.9, 114.4, 111.5, 110.6, 63.1, 60.6, 55.6, 55.5, 43.6, 40.0, 35.2, 34.4, 32.7, 27.1, 25.2, 25.1; $[M + H]^+$ = 418.2; HRMS (ESI): m/z calcd for ($C_{20}H_{28}N_5O_3S$): 418.19074; found: 418.19068.

5-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-4-(4-hydroxyphenethyl)-5-methylthiomorpholin-3-one (20b). Viscous liquid; 40% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00 (dd, J = 8.3, 1.6 Hz, 2H), 6.78 (dd, J = 8.3, 1.6 Hz, 2H), 4.51 (tt, J = 11.7, 3.8 Hz, 1H), 4.19–4.06 (m, 1H), 3.81 (td, J = 11.9, 4.3 Hz, 1H), 3.55 (d, J = 17.3 Hz, 1H), 3.45 (d, J = 17.3 Hz, 1H), 3.18–2.98 (m, 2H), 2.65 (td, J = 12.0, 5.2 Hz, 1H), 2.42 (td, J = 11.8, 5.0 Hz, 1H), 2.27 (d, J = 11.4 Hz, 1H), 2.19 (s, 3H), 2.14–1.67 (m, 4H), 1.57–1.42 (m, 1H), 1.40–1.21 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.9, 155.2, 155.0, 140.5, 129.8, 115.6, 62.4, 60.2, 58.9, 49.0, 39.7, 34.0, 33.8, 33.0, 27.3, 25.7, 25.4, 24.8, 24.6; $[M + H]^+$ = 402.2; HRMS (ESI): m/z calcd for ($C_{20}H_{28}N_5O_2S$): 402.1958; found: 402.1957.

4-(3-(1*H*-Imidazol-1-yl)propyl)-5-(1-(2,6-dimethylphenyl)-1*H*-tetrazol-5-yl)-5-methylthiomorpholin-3-one (20c). Viscous liquid; 9% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.46–7.38 (m, 2H), 7.24 (d, J = 7.6 Hz, 2H), 7.03 (s, 1H), 6.87 (s, 1H), 4.08–3.96 (m, 1H), 3.96–3.83 (m, 1H), 3.55–3.44 (m, 1H), 3.37 (d, J = 17.0 Hz, 1H), 3.12 (d, J = 15.7 Hz, 1H), 3.05 (d, J =

15.7 Hz, 1H), 2.85 (d, J = 14.1 Hz, 1H), 2.73–2.58 (m, 1H), 2.39–2.23 (m, 1H), 1.87 (s, 3H), 1.86 (s, 3H), 1.56 (s, 3H), 1.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.7, 157.4, 137.0, 136.1, 135.8, 132.8, 131.3, 129.7, 129.24, 129.21, 118.6, 62.5, 45.0, 44.0, 38.4, 32.0, 30.4, 24.9, 17.8, 17.5; $[M + H]^+$ = 412.1; HRMS (ESI): m/z calcd for ($C_{20}H_{26}N_7OS$): 412.1914; found: 412.1916.

4-(Furan-2-ylmethyl)-5-methyl-5-(1-pentyl-1*H*-tetrazol-5-yl)-thiomorpholin-3-one (20d). White solid (m.p. 134–135 °C); 63% yield (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25–7.21 (m, 1H), 6.32–6.22 (m, 1H), 6.16–6.11 (m, 1H), 4.39 (d, J = 15.4 Hz, 1H), 4.28 (d, J = 15.4 Hz, 1H), 4.18–4.04 (m, 1H), 3.86–3.73 (m, 1H), 3.50 (q, J = 17.2 Hz, 2H), 3.22 (d, J = 14.3 Hz, 1H), 2.95 (d, J = 14.3 Hz, 1H), 2.20 (s, 3H), 2.06–1.91 (m, 2H), 1.44–1.28 (m, 4H), 0.93 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.5, 155.4, 149.7, 141.7, 110.8, 109.7, 61.8, 48.8, 41.3, 39.0, 32.5, 29.2, 28.9, 2637, 22.1, 13.8; $[M + H]^+$ = 350.2; HRMS (ESI): m/z calcd for ($C_{16}H_{24}N_5O_2S$): 350.16452; found: 350.1645.

4-Cyclopropyl-5-methyl-5-(1-(naphthalen-2-yl)-1*H*-tetrazol-5-yl)-thiomorpholin-3-one (20e). Light tangerine solid (m.p. 164–165 °C); 59% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.06 (d, J = 8.7 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 9.6 Hz, 2H), 7.76–7.61 (m, 2H), 7.44 (dd, J = 8.7, 1.6 Hz, 1H), 3.22 (d, J = 16.2 Hz, 1H), 2.94 (dd, J = 15.0, 5.9 Hz, 2H), 2.84 (d, J = 14.0 Hz, 1H), 2.44–2.32 (m, 1H), 2.07 (s, 3H), 1.03–0.87 (m, 2H), 0.80–0.68 (m, 1H), 0.67–0.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 167.5, 158.0, 133.8, 132.5, 131.6, 130.2, 128.6, 128.5, 128.2, 128.1, 126.4, 123.3, 63.0, 38.4, 31.4, 28.5, 26.2, 9.0, 7.7; $[M + H]^+$ = 366.1; HRMS (ESI): m/z calcd for ($C_{19}H_{20}N_5OS$): 366.1383; found: 366.1383.

6-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-1-(2,5-dimethoxybenzyl)-6-methyl-4-(methylsulfonyl)piperazin-2-one (22a). Viscous liquid; 12% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.83 (s, 1H), 6.80–6.66 (m, 2H), 4.98 (d, J = 16.3 Hz, 1H), 4.77–4.67 (m, 1H), 4.26 (d, J = 16.8 Hz, 1H), 4.10–3.95 (m, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.47 (d, J = 12.9 Hz, 1H), 2.77 (s, 3H), 2.31–2.17 (m, 1H), 2.14–1.96 (m, 5H), 1.85 (s, 3H), 1.78–1.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.2, 154.4, 153.6, 150.3, 126.0, 115.4, 112.1, 110.8, 60.8, 60.4, 55.7, 55.6, 54.0, 49.0, 42.0, 35.9, 35.2, 34.2, 25.2, 25.1, 24.4; $[M + H]^+$ = 479.2; HRMS (ESI): m/z calcd for ($C_{21}H_{31}N_6O_5S$): 479.2071; found: 479.2066.

6-(1-Benzyl-1*H*-tetrazol-5-yl)-6-methyl-4-(methylsulfonyl)-1-(thiophen-2-ylmethyl)piperazin-2-one (22b). Viscous liquid; 25% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42–7.32 (m, 3H), 7.28–7.22 (m, 1H), 7.07 (d, J = 7.4 Hz, 2H), 6.88–6.80 (m, 1H), 6.43–6.36 (m, 1H), 5.30 (d, J = 16.1 Hz, 1H), 4.96 (d, J = 16.2 Hz, 1H), 4.51 (d, J = 15.3 Hz, 1H), 4.41 (d, J = 15.3 Hz, 1H), 4.18 (d, J = 16.7 Hz, 1H), 3.75 (d, J = 16.7 Hz, 1H), 3.34 (d, J = 12.7 Hz, 1H), 3.11 (d, J = 12.7 Hz, 1H), 2.52 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.5, 154.0, 138.4, 133.5, 129.5, 129.2, 127.6, 127.5, 127.2, 127.1, 126.4, 59.5, 52.0, 51.7, 49.0, 43.1, 35.1, 24.0; $[M + H]^+$ = 447.0; HRMS (ESI): m/z calcd for ($C_{19}H_{23}N_6O_3S_2$): 447.1268; found: 447.1265.

1-(Furan-2-ylmethyl)-6-methyl-4-(methylsulfonyl)-6-(1-pentyl-1*H*-tetrazol-5-yl)piperazin-2-one (22c). Viscous liquid; 48% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.25–7.21 (m, 1H), 6.30–6.25 (m, 1H), 6.19 (d, J = 3.2 Hz, 1H), 4.60 (d, J = 15.7 Hz, 1H), 4.36 (d, J = 15.7 Hz, 1H), 4.17 (d, J = 16.7 Hz, 1H), 4.13–4.07 (m, 1H), 4.01 (d, J = 16.7 Hz, 1H), 3.96–3.85 (m, 1H), 3.81 (d, J = 12.9 Hz, 1H), 3.50 (d, J = 13.0 Hz, 1H), 2.80 (s, 3H), 2.07 (s, 3H), 2.04–1.92 (m, 2H), 1.45–1.29 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.3, 154.3, 149.1, 142.1, 110.8, 110.0, 59.4, 53.5, 49.2, 49.0, 39.8, 36.1, 29.2, 28.8, 24.4, 22.1, 13.8; $[M + H]^+$ = 410.9; HRMS (ESI): m/z calcd for ($C_{17}H_{27}N_6O_4S$): 411.1809; found: 411.1803.

6-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-1-(4-fluoro-benzyl)-6-methyl-4-(methylsulfonyl)piperazin-2-one (22d). Viscous liquid; 47% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43 (td, J = 7.7, 2.5 Hz, 1H), 7.34–7.20 (m, 2H), 7.12–7.05 (m, 2H), 6.96 (td, J = 8.7, 2.7 Hz, 2H), 4.99 (d, J = 16.1 Hz, 1H), 4.23–4.08 (m, 2H), 4.05 (d, J = 13.0 Hz, 1H), 3.58 (d, J = 16.2 Hz, 1H), 3.37 (d, J = 13.0 Hz, 1H), 2.81 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.6, 160.7, 156.4, 135.6, 135.5, 133.1, 132.9, 131.4, 129.3, 129.1, 128.5, 128.4, 115.7, 115.5, 60.2, 53.9, 48.4, 47.3, 37.9, 22.8, 17.7, 17.6; $[M + H]^+$ = 472.8; HRMS (ESI): m/z calcd for ($C_{22}H_{26}FN_6O_3S$): 473.1766; found: 473.1761.

6-(1-Isopropyl-1*H*-tetrazol-5-yl)-6-methyl-4-(methylsulfonyl)-1-(3-(trifluoromethyl)benzyl)piperazin-2-one (22e). Viscous liquid; 43% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.53 (d, J = 7.6 Hz, 1H), 7.48–7.41 (m, 2H), 7.38 (d, J = 7.7 Hz, 1H), 5.40 (d, J = 16.1 Hz, 1H), 4.69–4.58 (m, 1H), 4.30 (d, J = 16.9 Hz, 1H), 4.12–3.94 (m, 2H), 3.82 (d, J = 16.1 Hz, 1H), 3.48 (d, J = 13.1 Hz, 1H), 2.77 (s, 3H), 1.78 (s, 3H), 1.68 (d, J = 6.4 Hz, 3H), 1.62 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 165.4, 153.8, 138.5, 130.5, 129.3, 124.5, 123.7, 60.6, 53.5, 53.3, 48.8, 47.9, 35.9, 24.8, 23.8, 23.0; $[M + H]^+$ = 461.2; HRMS (ESI): m/z calcd for ($C_{18}H_{24}F_3N_6O_3S$): 461.1577; found: 461.1582.

6-(1-Cyclohexyl-1*H*-tetrazol-5-yl)-1-(4-methoxybenzyl)-6-methyl-4-(methylsulfonyl)piperazin-2-one (22f). Viscous liquid; 41% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.11 (d, J = 8.1 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.26 (d, J = 15.4 Hz, 1H), 4.28 (d, J = 16.7 Hz, 1H), 4.22–4.11 (m, 1H), 4.01 (d, J = 16.7 Hz, 1H), 3.89 (d, J = 12.9 Hz, 1H), 3.78 (s, 3H), 3.59 (d, J = 15.4 Hz, 1H), 3.41 (d, J = 12.9 Hz, 1H), 2.78 (s, 3H), 2.17–1.88 (m, 4H), 1.81 (s, 3H), 1.48–1.20 (m, 4H), 0.95–0.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.9, 159.0, 154.0, 129.4, 128.6, 114.1, 60.6, 60.5, 55.3, 54.0, 49.3, 47.6, 35.4, 34.0, 33.5, 29.7, 25.7, 25.5, 24.6; $[M + H]^+$ = 463.2; HRMS (ESI): m/z calcd for ($C_{21}H_{31}N_6O_4S$): 463.2122; found: 463.2118.

6-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-5-(2,5-dimethoxybenzyl)-6-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (24a). Light brown solid (m.p. 171–172 °C); 38% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.61–7.58 (m, 1H), 7.03 (d, J = 2.6 Hz, 1H), 7.01–6.98 (m, 1H), 6.75 (dd, J = 9.0, 2.9 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 5.04 (d, J = 15.8 Hz, 1H), 4.76 (d, J = 13.3 Hz, 1H), 4.76–4.67 (m, 1H), 4.43 (d, J = 13.3 Hz, 1H), 4.38 (d, J = 15.8 Hz, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 2.09–1.92 (m, 4H), 1.89

(s, 3H), 1.86–1.76 (m, 2H), 1.72–1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.9, 153.7, 153.5, 150.6, 140.5, 133.0, 126.0, 116.0, 113.2, 111.0, 109.2, 60.8, 59.9, 55.8, 55.7, 55.6, 55.5, 40.2, 35.1, 33.5, 24.9, 24.1; $[M + H]^+$ = 438.3; HRMS (ESI): *m*/*z* calcd for ($C_{22}H_{28}N_7O_3$): 438.2248; found: 438.2242.

6-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-5-(4-fluoro-benzyl)-6-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (24b). White solid (m.p. 163–164 °C); 42% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51–7.48 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 7.4, 5.5 Hz, 2H), 7.05–6.93 (m, 2H), 6.86 (d, *J* = 1.4 Hz, 1H), 5.41 (d, *J* = 16.4 Hz, 1H), 4.76 (d, *J* = 13.7 Hz, 1H), 4.29 (d, *J* = 13.7 Hz, 1H), 3.87 (d, *J* = 16.4 Hz, 1H), 1.89 (s, 5H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 163.2, 160.7, 158.7, 156.5, 140.4, 136.1, 136.0, 134.1, 133.2, 132.3, 131.5, 129.3, 128.4, 115.7, 115.5, 109.0, 105.5, 59.8, 55.7, 45.6, 23.7, 17.7, 17.5; $[M + H]^+$ = 432.2; HRMS (ESI): *m*/*z* calcd for ($C_{23}H_{23}FN_7O$): 432.19426; found: 432.19474.

5-(Furan-2-ylmethyl)-6-methyl-6-(1-pentyl-1*H*-tetrazol-5-yl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (24c). Viscous liquid; 38% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62–7.57 (m, 1H), 7.28–7.25 (m, 1H), 7.00–6.97 (m, 1H), 6.34–6.24 (m, 1H), 6.15–6.10 (m, 1H), 4.76–4.63 (m, 2H), 4.57–4.46 (m, 2H), 4.04–3.90 (m, 1H), 3.88–3.73 (m, 1H), 2.08 (s, 3H), 1.92–1.79 (m, 1H), 1.77–1.63 (m, 1H), 1.40–1.17 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 157.8, 153.8, 149.4, 142.2, 140.6, 132.8, 110.9, 109.7, 109.4, 59.1, 55.3, 48.8, 39.1, 29.4, 28.6, 23.9, 22.0, 13.7; $[M + H]^+$ = 370.1; HRMS (ESI): *m*/*z* calcd for ($C_{19}H_{22}N_5O_2$): 352.1768; found: 352.1772.

6-(1-Isopropyl-1*H*-tetrazol-5-yl)-6-methyl-5-(3-(trifluoromethyl)-benzyl)-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (24d). White solid (m.p. 187–188 °C); 37% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.57 (t, *J* = 1.9 Hz, 1H), 7.56–7.49 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 6.98 (t, *J* = 2.0 Hz, 1H), 5.38 (d, *J* = 16.1 Hz, 1H), 4.83 (d, *J* = 13.6 Hz, 1H), 4.61–4.52 (m, 2H), 4.25 (d, *J* = 16.1 Hz, 1H), 1.90 (s, 3H), 1.52 (d, *J* = 6.5 Hz, 3H), 1.42 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.0, 153.4, 140.7, 140.6, 138.9, 132.8, 130.7, 129.4, 124.6, 124.1, 124.1, 109.5, 60.1, 55.6, 53.1, 46.7, 24.4, 23.6, 22.8; $[M + H]^+$ = 420.2; HRMS (ESI): *m*/*z* calcd for ($C_{19}H_{21}F_3N_7O$): 420.1754; found: 420.1751.

6-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-5-(4-methoxy-benzyl)-6-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-4(5*H*)-one (24e). Viscous liquid; 23% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.49 (d, *J* = 2.0 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.35 (d, *J* = 16.2 Hz, 1H), 4.80 (d, *J* = 13.6 Hz, 1H), 4.28 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.75 (d, *J* = 16.2 Hz, 1H), 1.89 (d, *J* = 12.0 Hz, 6H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.8, 158.7, 156.7, 140.3, 136.2, 135.9, 133.3, 132.3, 131.5, 130.4, 129.3, 128.1, 114.1, 108.9, 59.7, 55.9, 55.3, 45.6, 23.8, 17.7, 17.5; $[M + H]^+$ = 443.8; HRMS (ESI): *m*/*z* calcd for ($C_{24}H_{26}N_7O_2$): 444.21425; found: 444.215.

5-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-4-(2,5-dimethoxybenzyl)-5-methyl-1,4-thiazepan-3-one (29a). Viscous liquid; 39% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.23 (d, *J* = 2.6 Hz, 1H), 6.86–6.76 (m, 2H), 5.39 (d, *J* = 16.4 Hz, 1H), 4.84–4.72 (m, 1H), 4.54 (d, *J* = 16.3 Hz, 1H), 4.06–3.93 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.15 (d, *J* = 15.0 Hz, 1H), 2.82–2.61 (m, 3H), 2.32–1.89 (m, 7H), 1.83–1.66 (m, 2H), 1.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.3, 157.7, 153.8, 145.0, 126.5, 114.0, 111.8, 60.1, 58.9, 56.0, 55.9, 41.4, 39.6, 34.6, 34.3, 30.1, 27.3, 25.1, 25.1; $[M + H]^+$ = 432.2; HRMS (ESI): *m*/*z* calcd for ($C_{21}H_{30}N_5O_3S$): 432.20639; found: 432.2064.

5-(1-Benzyl-1*H*-tetrazol-5-yl)-5-methyl-4-(thiophen-2-ylmethyl)-1,4-thiazepan-3-one (29b). White solid (m.p. 192–193 °C); 46% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43–7.31 (m, 3H), 7.26–7.22 (m, 1H), 7.13–7.01 (m, 2H), 6.93–6.87 (m, 1H), 6.80–6.74 (m, 1H), 5.42 (d, *J* = 15.8 Hz, 1H), 5.32–5.12 (m, 2H), 4.39 (d, *J* = 15.6 Hz, 1H), 3.59–3.44 (m, 1H), 3.12 (d, *J* = 15.3 Hz, 1H), 2.76 (d, *J* = 15.3 Hz, 1H), 2.67–2.52 (m, 2H), 2.00–1.87 (m, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 172.9, 157.9, 139.5, 133.2, 129.2, 129.1, 127.1, 127.0, 126.4, 126.3, 59.3, 51.8, 44.0, 39.0, 33.9, 28.2, 26.1; $[M + H]^+$ = 400.2; HRMS (ESI): *m*/*z* calcd for ($C_{19}H_{22}N_5OS_2$): 400.12603; found: 400.12546.

4-(Furan-2-ylmethyl)-5-methyl-5-(1-pentyl-1*H*-tetrazol-5-yl)-1,4-thiazepan-3-one (29c). Viscous liquid; 38% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.39–7.34 (m, 1H), 6.50–6.43 (m, 1H), 6.40–6.37 (m, 1H), 5.08 (d, *J* = 15.8 Hz, 1H), 4.55 (d, *J* = 15.8 Hz, 1H), 4.02 (t, *J* = 7.7 Hz, 2H), 3.97–3.83 (m, 1H), 3.04 (d, *J* = 14.8 Hz, 1H), 2.87 (dt, *J* = 14.8, 3.9 Hz, 1H), 2.64 (dt, *J* = 14.6, 4.4 Hz, 1H), 2.56 (d, *J* = 14.8 Hz, 1H), 2.14 (ddd, *J* = 15.1, 11.2, 4.0 Hz, 1H), 1.93 (s, 3H), 1.98–1.77 (m, 2H), 1.41–1.18 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.2, 157.7, 150.5, 141.6, 112.0, 110.0, 58.4, 48.6, 40.8, 39.5, 34.4, 30.5, 29.1, 28.7, 27.0, 22.1, 13.8; $[M + H]^+$ = 364.2; HRMS (ESI): *m*/*z* calcd for ($C_{17}H_{26}N_5O_2S$): 364.18017; found: 364.18077.

5-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-4-(4-methoxy-benzyl)-5-methyl-1,4-thiazepan-3-one (29d). White solid (m.p. 182–184 °C); 27% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.45 (t, *J* = 7.6 Hz, 1H), 7.33–7.27 (m, 2H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.09 (d, *J* = 16.3 Hz, 1H), 3.89–3.79 (m, 1H), 3.76 (s, 3H), 3.16–2.97 (m, 3H), 2.88 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.76 (dd, *J* = 12.5, 5.7 Hz, 1H), 2.20–2.08 (m, 1H), 1.94 (s, 3H), 1.93 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.2, 159.3, 158.5, 136.6, 135.9, 132.5, 131.2, 130.6, 129.3, 129.1, 127.7, 114.0, 58.7, 55.2, 47.1, 41.3, 36.6, 33.8, 28.6, 18.0, 17.9; $[M + H]^+$ = 438.0; HRMS (ESI): *m*/*z* calcd for ($C_{23}H_{28}N_5O_2S$): 438.19582; found: 438.19671.

5-(1-Isopropyl-1*H*-tetrazol-5-yl)-5-methyl-4-(3-(trifluoromethyl)-benzyl)-1,4-thiazepan-3-one (29e). Viscous liquid; 38% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.74 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 5.58 (d, *J* = 16.0 Hz, 1H), 4.63–4.49 (m, 1H), 4.39 (d, *J* = 15.9 Hz, 1H), 4.00 (ddd, *J* = 14.5, 11.2, 2.9 Hz, 1H), 3.17 (d, *J* = 15.0 Hz, 1H), 2.86–2.68 (m, 2H), 2.69 (d, *J* = 15.0 Hz, 1H), 2.16–2.05 (m, 1H), 1.76 (s, 3H), 1.62–1.48 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.2, 156.8, 138.9, 131.1, 131.0, 129.4, 125.3, 124.5, 122.6, 59.1, 52.2, 47.6, 39.5, 34.5, 30.1,

27.2, 23.2, 23.1; $[M + H]^+$ = 302.1; HRMS (ESI): *m*/*z* calcd for ($C_{18}H_{23}N_5OS$): 414.15699; found: 414.15684.

5-(1-Cyclopentyl-1*H*-tetrazol-5-yl)-4-(2,5-dimethoxybenzyl)-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one (31a). Viscous liquid; 23% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 (tt, *J* = 8.0, 1.9 Hz, 1H), 7.21–7.05 (m, 3H), 6.87–6.77 (m, 3H), 5.62 (s, 1H), 5.39 (d, *J* = 15.1 Hz, 1H), 4.98 (d, *J* = 16.7 Hz, 1H), 4.43 (d, *J* = 16.7 Hz, 2H), 4.15–4.03 (m, 1H), 3.74 (s, 3H), 3.67 (s, 3H), 2.15–1.85 (m, 3H), 1.85–1.72 (m, 1H), 1.66–1.63 (m, 1H), 1.50–1.32 (m, 1H), 1.30–1.22 (m, 1H), 1.18–1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.8, 157.6, 153.8, 153.5, 151.8, 132.0, 130.6, 128.7, 125.1, 122.1, 115.9, 114.3, 111.8, 110.0, 73.4, 59.6, 56.1, 55.7, 55.6, 47.1, 32.9, 32.8, 24.5, 24.3; $[M + H]^+$ = 450.3; HRMS (ESI): *m*/*z* calcd for ($C_{24}H_{28}N_5O_4$): 450.2136; found: 450.213.

4-Cyclopropyl-5-(1-(naphthalen-2-yl)-1*H*-tetrazol-5-yl)-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one (31b). Viscous liquid; 20% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.88 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.66–7.56 (m, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.10 (td, *J* = 7.6, 2.0 Hz, 1H), 7.00 (dd, *J* = 8.6, 2.1 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.60–6.45 (m, 2H), 5.63 (s, 1H), 4.92 (d, *J* = 16.5 Hz, 1H), 4.33 (d, *J* = 16.5 Hz, 1H), 3.08–2.97 (m, 1H), 1.05–0.76 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 171.25, 156.90, 156.02, 133.45, 132.38, 131.43, 130.51, 130.04, 129.75, 128.83, 128.18, 128.13, 127.89, 127.67, 125.42, 124.35, 122.42, 121.38, 77.31, 76.99, 76.68, 73.58, 58.71, 33.47, 8.77, 7.83; $[M + H]^+$ = 398.2; HRMS (ESI): *m*/*z* calcd for ($C_{23}H_{20}N_5O_2$): 398.16115; found: 398.16105.

5-(1-(2,6-Dimethylphenyl)-1*H*-tetrazol-5-yl)-4-(4-fluoro-benzyl)-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one (31c). White solid (m.p. 178–179 °C); 62% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.26–7.14 (m, 4H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.04–6.96 (m, 3H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.70–6.62 (m, 1H), 5.96 (d, *J* = 7.4 Hz, 1H), 5.62 (d, *J* = 15.3 Hz, 1H), 5.11 (dd, *J* = 16.8, 2.2 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 4.50 (dd, *J* = 16.8, 2.5 Hz, 1H), 4.25 (d, *J* = 15.3 Hz, 1H), 1.77 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.1, 163.7, 161.3, 157.1, 154.7, 136.9, 133.7, 131.7, 131.4, 131.3, 131.1, 130.7, 130.1, 130.0, 129.3, 128.8, 128.3, 124.8, 121.4, 115.9, 115.7, 73.3, 55.1, 50.9, 16.8, 16.4; $[M + H]^+$ = 444.1; HRMS (ESI): *m*/*z* calcd for ($C_{25}H_{23}FN_5O_2$): 444.18303; found: 444.18303.

5-(1-Isopropyl-1*H*-tetrazol-5-yl)-4-(3-(trifluoromethyl)benz-yl)-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(*2H*)-one (31d). Viscous liquid; 55% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63–7.56 (m, 1H), 7.52–7.42 (m, 4H), 7.24–7.17 (m, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 5.83 (d, *J* = 16.0 Hz, 1H), 5.32 (s, 1H), 4.99 (d, *J* = 16.9 Hz, 1H), 4.52 (d, *J* = 16.9 Hz, 1H), 4.32 (d, *J* = 15.7 Hz, 1H), 3.97–3.82 (m, 1H), 1.43 (d, *J* = 5.6 Hz, 3H), 0.86 (d, *J* = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 170.1, 157.6, 152.5, 137.1, 132.5, 131.6, 130.2, 129.4, 128.5, 125.6, 124.8, 124.5, 122.3, 73.5, 55.5, 51.5, 51.4, 22.3, 21.7; $[M + H]^+$ = 432.2; HRMS (ESI): *m*/*z* calcd for ($C_{21}H_{21}N_5O_2$): 432.16419; found: 432.16378.

5-(1-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-1*H*-tetrazol-5-yl)-4-isopentyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one (31e). White solid (m.p. 209–210 °C); 27% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31–7.22 (m, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 6.82–6.75 (m, 2H), 6.50–6.35 (m, 2H), 5.37 (s, 1H), 4.86 (dd, *J* = 16.6, 1.0 Hz, 1H), 4.38–4.18 (m, 5H), 4.16–4.04 (m, 1H), 3.34–3.21 (m, 1H), 1.65–1.53 (m, 1H), 1.53–1.43 (m, 2H), 0.92 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.2, 156.9, 155.5, 145.5, 143.7, 131.5, 130.4, 128.9, 126.2, 124.5, 121.5, 118.9, 117.7, 115.3, 73.3, 64.4, 64.2, 56.7, 48.3, 36.7, 25.9, 22.6, 22.5; $[M + H]^+$ = 436.3; HRMS (ESI): *m*/*z* calcd for ($C_{23}H_{26}N_5O_4$): 436.19793; found: 436.19759.

4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-5-(1-butyl-1*H*-tetrazol-5-yl)-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one (31f). Viscous liquid; 41% (three steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.48–7.40 (m, 1H), 7.22–7.09 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.77 (dd, *J* = 7.7, 2.0 Hz, 1H), 6.73–6.67 (m, 2H), 6.02–5.92 (m, 2H), 5.70 (d, *J* = 15.0 Hz, 1H), 5.37 (s, 1H), 4.97 (dd, *J* = 16.8, 1.9 Hz, 1H), 4.46 (dd, *J* = 16.8, 2.2 Hz, 1H), 4.06 (d, *J* = 15.1 Hz, 1H), 3.82–3.59 (m, 2H), 1.52–1.36 (m, 1H), 1.19–0.94 (m, 3H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 169.7, 157.7, 153.5, 148.2, 147.5, 132.3, 130.3, 129.5, 128.6, 125.4, 122.2, 121.9, 108.9, 108.3, 101.2, 73.5, 54.3, 51.2, 47.6, 30.9, 19.4, 13.3; $[M + H]^+$ = 422.1; HRMS (ESI): *m*/*z* calcd for ($C_{22}H_{24}N_5O_4$): 422.18228; found: 422.8213.

Acknowledgements

The authors thanked the National Institutes of Health (P41GM086190) for funding, Dr Sue Roberts for the X-Ray crystallography work, Kristen Keck for compound purification, Alex Laetsch for compound management, and Dr Fabio De Moliner for proof-reading.

Notes and references

1 A. Giannis and T. Kolter, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1244–1267.
2 J. Zabrocki, G. D. Smith, J. B. Dunbar Jr., H. Iijima and G. R. Marshall, *J. Am. Chem. Soc.*, 1988, **110**, 5875–5880.
3 C. J. Creighton, G. C. Leo, W. Du and A. B. Reitz, *Bioorg. Med. Chem.*, 2004, **12**, 4375–4385.
4 S. Y. Kang, S.-H. Lee, H. J. Seo, M. E. Jung, K. Ahn, J. Kim and J. Lee, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 2385–2389.
5 J. P. Alexander and B. F. Cravatt, *J. Am. Chem. Soc.*, 2006, **128**, 9699–9704.
6 (*a*) C. Hulme, P. Tempest, V. Ma, T. Nixey and G. Balow, *PCT Int. Appl*, WO 2005019167, 2005, 260 pp; (*b*) P. Tempest, T. Nixey, V. Ma, G. Balow, C. van Staden, J. Salon, K. Rorer, J. Baumgartner, C. Hale, T. Bannon, R. Hungate and C. Hulme, *Abstract of Papers*, 227th National Meeting of the American Chemical Society, Anaheim, CA, March 28–April 1, 2004; MEDI 298.
7 T. Nixey, J. Boylan, C. Hulme, D. Powers, A. Smith and A. Wong, *Abstract of Papers*, 231st National Meeting of the

American Chemical Society, Atlanta, GA, March 26–30, 2006; MEDI 277.
8 J. Li, S. Y. Chen, J. J. Li, H. Wang, A. S. Hernandez, S. Tao, C. M. Musial, F. Qu, S. Swartz, S. T. Chao, N. Flynn, B. J. Murphy, D. A. Slusarchyk, R. Seethala, M. Yan, P. Sleph, G. Grover, M. A. Smith, B. Beehler, L. Giupponi, K. E. Dickinson, H. Zhang, W. G. Humphreys, B. P. Patel, M. Schwinden, T. Stouch, P. T. W. Cheng, S. A. Biller, W. R. Ewing, D. Gordon, J. A. Robl and J. A. Tino, *J. Med. Chem.*, 2007, **50**, 5890–5893.
9 (*a*) L. Weber, *Curr. Opin. Chem. Biol.*, 2000, **4**, 295–302; (*b*) C. Hulme and V. Gore, *Curr. Med. Chem.*, 2003, **10**, 51–80; (*c*) C. Hulme and J. Dietrich, *Mol. Diversity*, 2009, **13**, 195–207.
10 I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 8–21.
11 T. Nixey, M. Kelly and C. Hulme, *Tetrahedron Lett.*, 2000, **41**, 8729–8733.
12 (*a*) T. Nixey, M. Kelly, D. Semin and C. Hulme, *Tetrahedron Lett.*, 2002, **43**, 3681–3684; (*b*) M. Nayak and S. Batra, *Tetrahedron Lett.*, 2010, **51**, 510–516.
13 R. S. Borisov, A. I. Polyakov, L. A. Medvedeva, V. N. Khrustalev, N. I. Guranova and L. G. Voskressensky, *Org. Lett.*, 2010, **12**, 3894–3897.
14 C. Kalinski, M. Umkehrer, S. Gonnard, N. Jager, G. Ross and W. Hiller, *Tetrahedron Lett.*, 2006, **47**, 2041–2044.
15 S. Gunawan, J. Petit and C. Hulme, *ACS Comb. Sci.*, 2012, **14**, 160–163.
16 S. Gunawan, K. Keck, A. Laetsch and C. Hulme, *Mol. Diversity*, 2012, **16**, 601–606.
17 Details of the nine compounds with all characterization data and reagents diversity for the four 24-well plates production can be found in ref. 15.
18 (*a*) While the manuscript was in preparation, it was realized a very close MCR based methodology to prepare compounds **10** had already been reported in C. F. Marcos, S. Marcos, G. Menchi, R. Pepino and T. Torroba, *Tetrahedron Lett.*, 2008, **49**, 149–152. However, unprecedented significant scope expansion and combinatorial applications are herein described for this series (*b*) Details of the reagents diversity for the four 24-well plates production along with purity and yield can be found in the ESI.†
19 J. Zhang, A. Jacobson, J. R. Rusche and W. Herlihy, *J. Org. Chem.*, 1999, **64**, 1074–1076.
20 Y. Watanabe, K. Osanai, T. Osanai, N. Miyawaki, D. Shii, T. Honda and T. Shibano, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1923–1926.
21 (*a*) Y. M. Choi-Sledeski, R. Kearner, G. Poli, H. Pauls, C. Gardner, Y. Gong, M. Becker, R. Davis, A. Spada, G. Liang, V. Chu, K. Brown, D. Brown, R. Leadley Jr., S. Rebello, P. Moxey, S. Morgan, R. Bentley, C. Kasiewski, S. Mignan, J.-P. Guilloteau and V. Mikol, *J. Med. Chem.*, 2003, **46**, 681–684; (*b*) H. Nishida, Y. Miyazaki, T. Mukaihira, F. Saitoh, M. Fukui, K. Harada, M. Itoh, A. Muraoka, T. Matsusue, A. Okamoto, Y. Hasaka, M. Matsumoto, S. Ohnishi and H. Mochizuki, *Chem. Pharm. Bull.*, 2002, **50**, 1187–1194.
22 D. Boger, J. Goldberg, A. Shigeki, C. Yves and P. Vogt, *Helv. Chim. Acta*, 2000, **83**, 1825–1845.
23 A. P. Ilyin, A. S. Trifilenkov, I. D. Kurashvili, M. Krasavin and A. V. Ivachtchenko, *J. Comb. Chem.*, 2005, **7**, 360–363.
24 B. C. Askew, C. J. McIntyre, C. A. Hunt, D. A. Claremon, J. J. Baldwin, P. S. Anderson, R. J. Gould, R. J. Lynch, C. C.-T. Chang, J. J. Cook, J. J. Cook, M. A. Holahan, G. R. Sitko and M. T. Stranieri, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1531–1536.
25 V. Wehner, H.-U. Stilz, A. Peyman, J. Knolle, J.-M. Ruxer, D. Carniato, J.-M. Lefrancois, T. R. Gadek and R. McDowell, *DE Patent*, 19653647, 1998; V. Wehner, H.-U. Stilz, A. Peyman, J. Knolle, J.-M. Ruxer, D. Carniato, J.-M. Lefrancois, T. R. Gadek and R. McDowell, *Chem. Abstr.*, 1998, **129**, 81970.
26 A. P. Ilyn, A. S. Trifilenkov, S. A. Tsirulnikov, I. D. Kurashvily and A. V. Ivachtchenko, *J. Comb. Chem.*, 2005, **7**, 806–808.
27 J. A. Robl, L. M. Simpkins and M. M. Asaad, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 257–260.
28 (*a*) J. M. Klunder, K. D. Hargrave, M. West, E. Cullen, K. Pal, M. L. Behnke, S. R. Kapadia, D. W. McNeil, J. C. Wu and G. C. Chow, *J. Med. Chem.*, 1992, **35**, 1887–1897; (*b*) F. Aiello, A. Brizzi, A. Garofalo, F. Grande, G. Ragno, R. Dayam and N. Neamati, *Bioorg. Med. Chem.*, 2004, **15**, 4459–4466.
29 CCDC 936637 (**31c**) contains the supplementary crystallographic data for this paper.
30 J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734–736.

