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

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Abstract

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 heterocylic 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

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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 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, Scheme 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.[1]

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**.[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 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 **13** 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 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 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 chloroace- tone 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.

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-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 on-going 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 (Figure 1).[29]

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 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-heterocyclic 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$_4$Si (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 electronic supplementary information.

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

Methyl 2-formylbenzoate **8b** (0.250 mmol), R$_1$NH$_2$ **6** (0.250 mmol), TMSN$_3$ (0.250 mmol) and R$_2$NC **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$_3$) 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$_3$) 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$_5$O$_2$): 352.1768; found: 352.1772.

3-(1-cyclopentyl-1H-tetrazol-5-yl)-2-(2,5-dimethoxybenzyl) isoindolin-1-one (10c)—yellow solid (m.p. 118–119 °C); 51% yield (one step); ^{1}H NMR (400 MHz, CDCl$_3$) 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$_3$) 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-1H-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$_3$)   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$_3$) 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)-1H-tetrazol-5-yl)isoindolin-1-one (10e)—
white solid (m.p. 167–169 °C); 66% yield (one step); ^{1}H NMR (400 MHz, CDCl$_3$)   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$_3$)   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-(1H-indol-3-yl)ethyl)-3-(1-(tert-butyl-1H-tetrazol-5-yl)isoindolin-1-one (10f)
—white solid (m.p. 108–110 °C); 43% yield (one step); ^{1}H NMR (400 MHz, DMSO$_{d6}$) 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$_{d6}$)   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-1H-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$_3$)   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$_3$)   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)-1H-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$_3$)   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$_3$)   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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_1$NH$_2$ (0.250 mmol), TMSN$_3$ (0.250 mmol) and R$_2$NC (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$_2$O (0.5 ml) were added, followed by 0.03 ml of a 1g/1ml solution of KOH in H$_2$O 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$_2$SO$_4$ 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_5$O$_2$S): 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$_3$) 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$_3$) 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$_7$OS): 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$_3$) 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$_3$) 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$_5$O$_2$S): 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$_3$) 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$_3$) 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$_5$OS): 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$_3$) 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$_3$) 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$_6$O$_5$S): 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$_3$) 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$_3$) 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$_6$O$_3$S$_2$): 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$_3$) 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$_3$) 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$_6$O$_4$S): 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$_3$) 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$_3$) 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$_6$O$_3$S): 473.1766; found: 473.1761.

6-(1-isopropyl-1*H*-tetrazol-5-yl)-6-methyl-4-(methylsulfo-nyl)-1-(3-(trifluoromethyl)benzyl)piperazin-2-one (22e)—viscous liquid; 43% (three steps); ^{1}H NMR (400 MHz, CDCl$_3$) 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$_3$) 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$_3$N$_6$O$_3$S): 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$_3$) 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$_3$) 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$_6$O$_4$S): 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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-(trifluoro-methyl)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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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-(trifluoro-methyl)benzyl)-1,4-thiazepan-3-one (29e)**—viscous liquid; 38% (three steps); ^{1}H NMR (400 MHz, CDCl$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_3$) 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$_5$O$_2$): 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$_3$) 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$_3$) 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$_5$O$_2$): 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(2*H*)-one (31d)—viscous liquid; 55% (three steps); ^{1}H NMR (400 MHz, CDCl$_3$) 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$_3$) 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$_5$O$_2$): 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$_3$) 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$_3$) 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$_5$O$_4$): 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$_3$) 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$_3$) 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$_5$O$_4$): 422.18228; found: 422.8213.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Notes and references

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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 Marcos CF, Marcaccini S, Menchi G, Pepino R, Torroba T. 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 supplementary information.

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29. CCDC 936637 (**31c**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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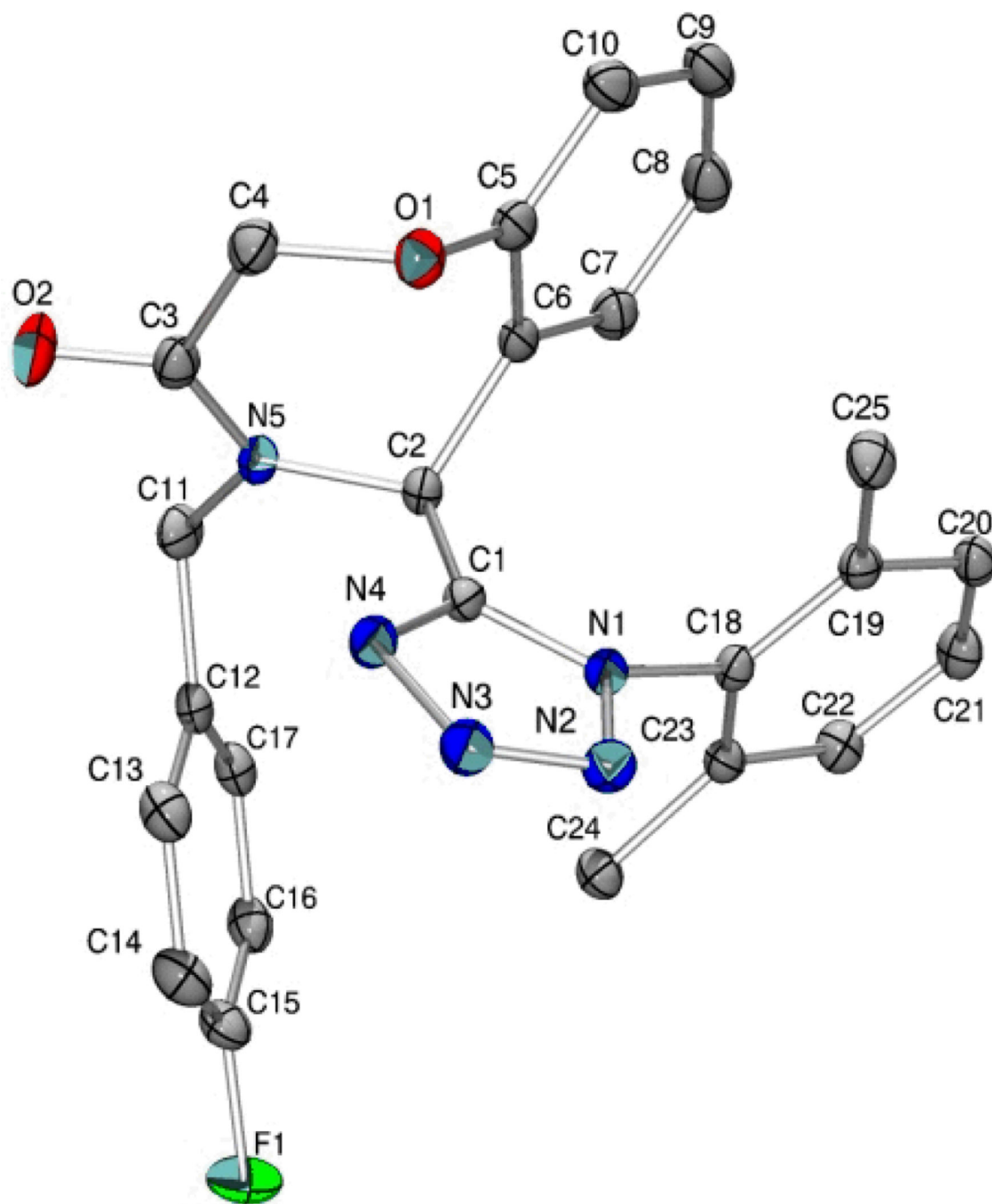
Figure 1.
X-Ray crystal structure of **31c**
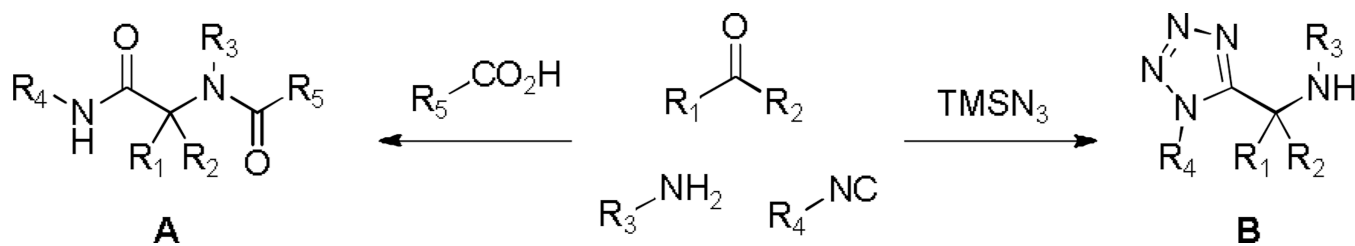
Scheme 1.
Ugi and Ugi-azide MCR
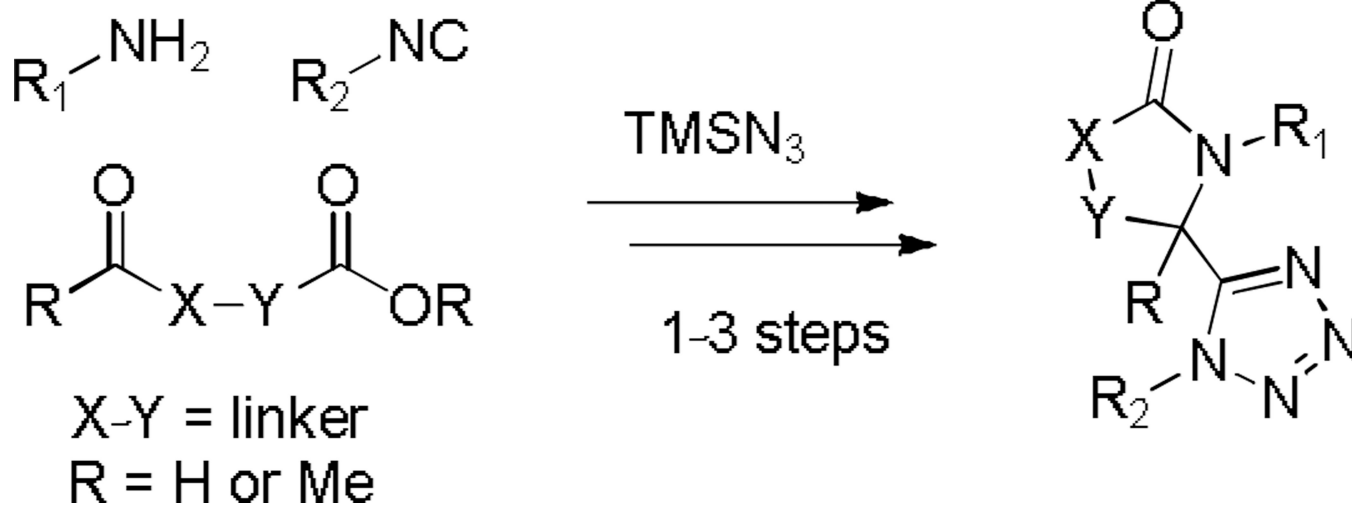
Scheme 2.
General strategy to lactam-tetrazoles
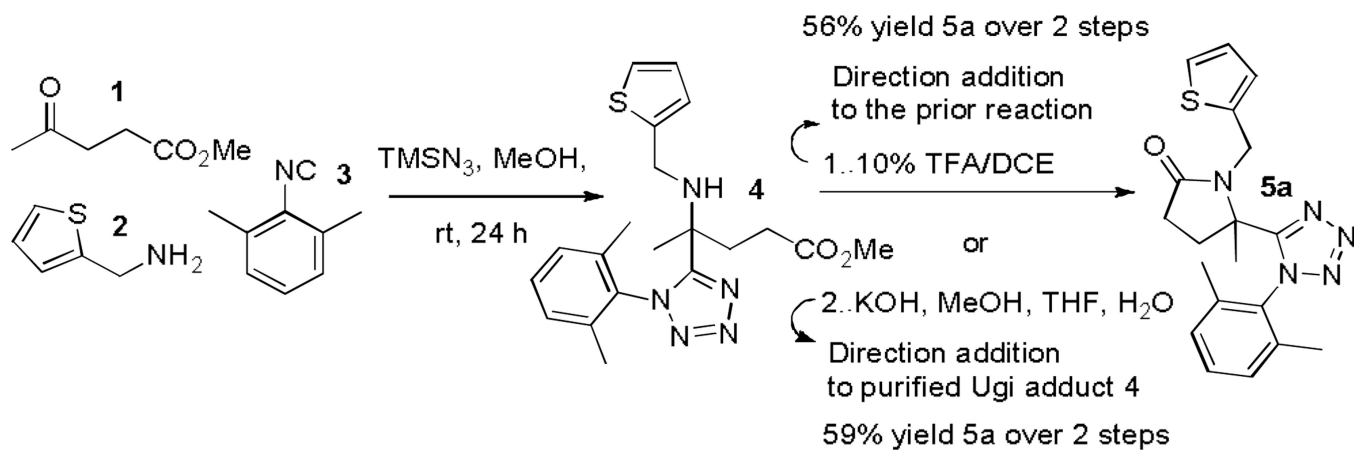
Scheme 3.
Access to tetrazolyl-pyrrolidinone **5a**

a R_3 = Me, R_4 = CO_2Me, R_5 = H
b R_3 = H, R_4 = CO_2Me, R_5 = H

a R_3 = Me, R_4 = CO_2Me, R_5 = H
b R_3 = H, R_4 = CO_2Me, R_5 = H

10a R_3 = Me, R_5 = H
10b R_3 = H, R_5 = H; 85%
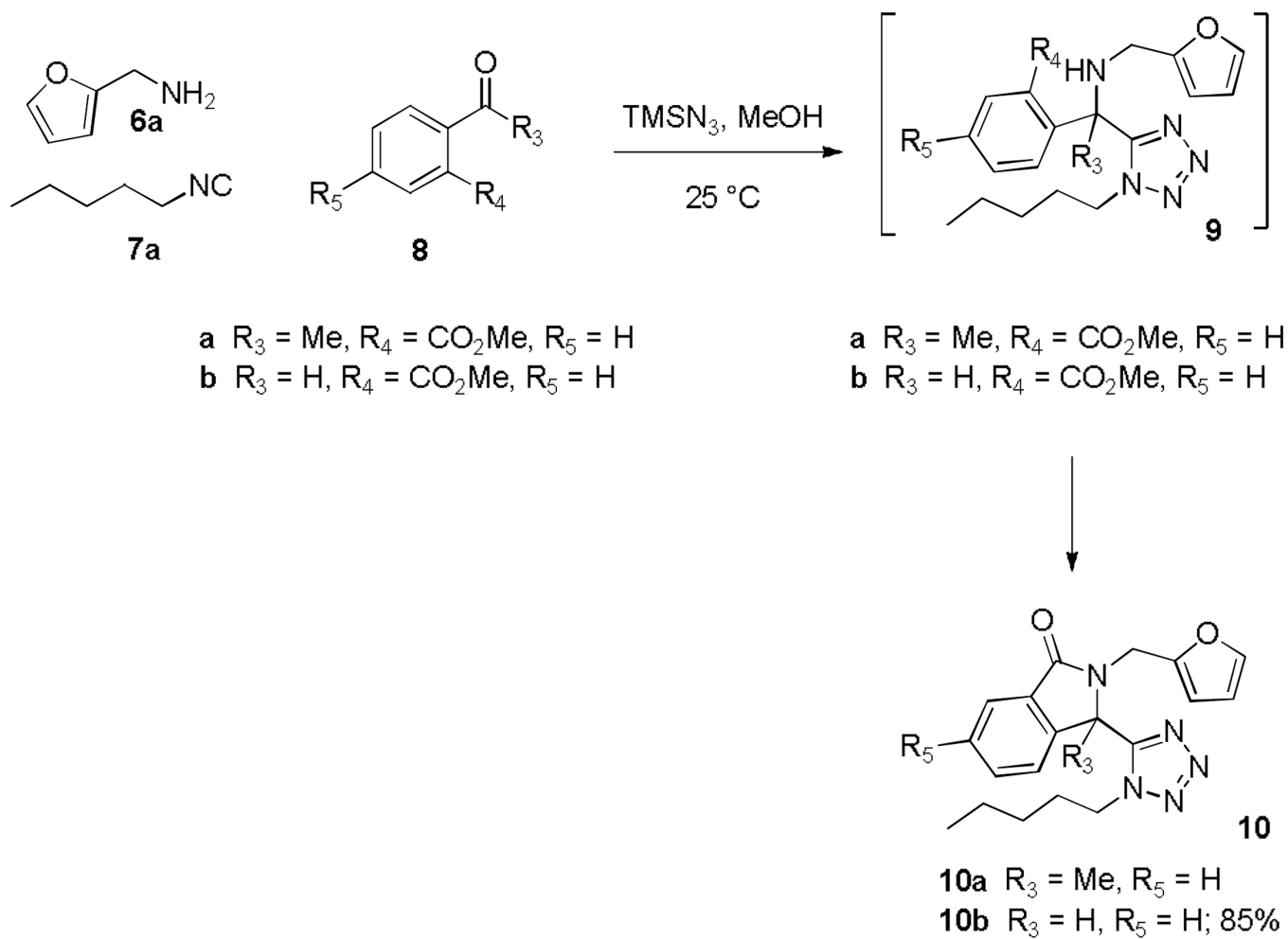
Scheme 4.
Synthesis of 2-(furan-2-ylmethyl)-isoindolin-1-one **10b**
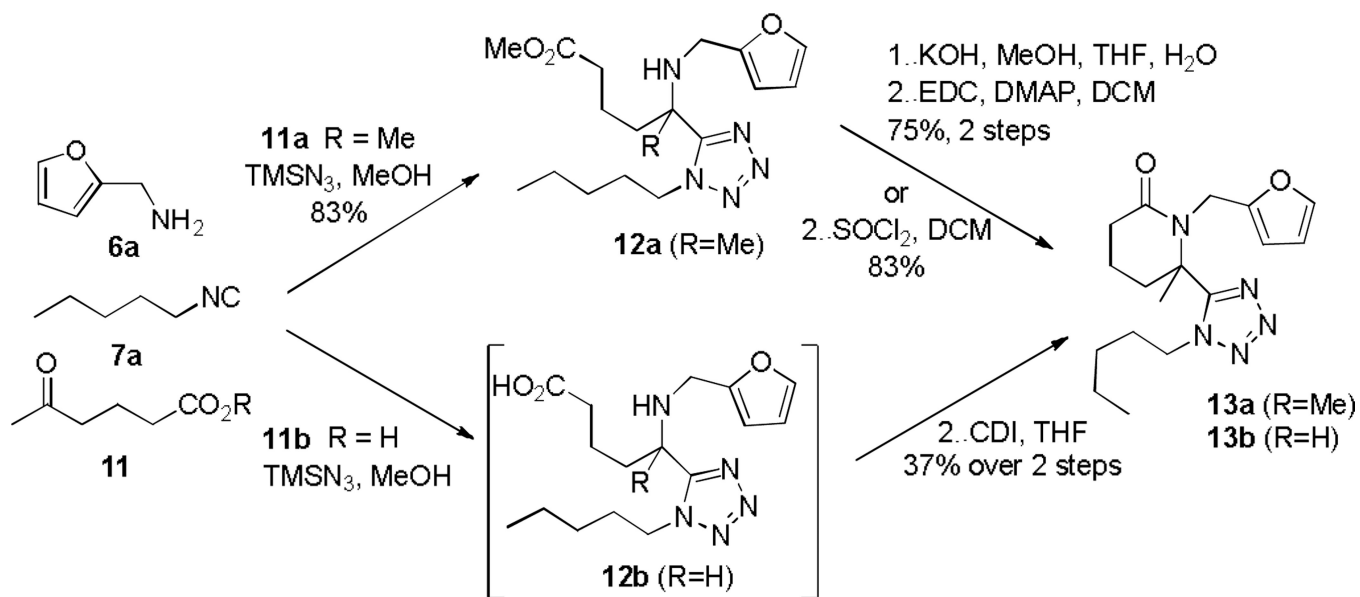
Scheme 5.
Optimization of the preparation of piperidine-tetrazole **13**
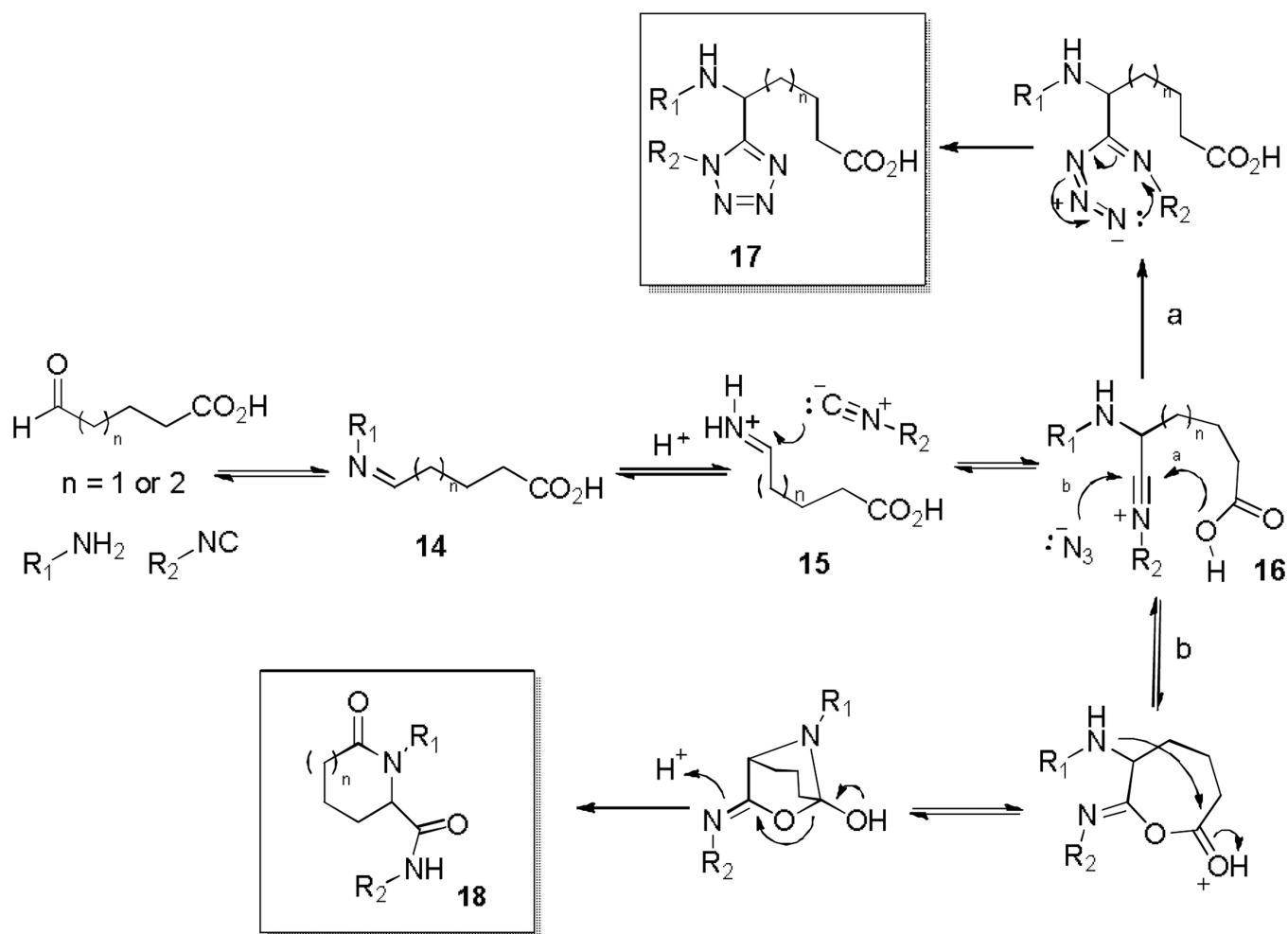
Scheme 6.
Ugi-azide condensation to afford **17**
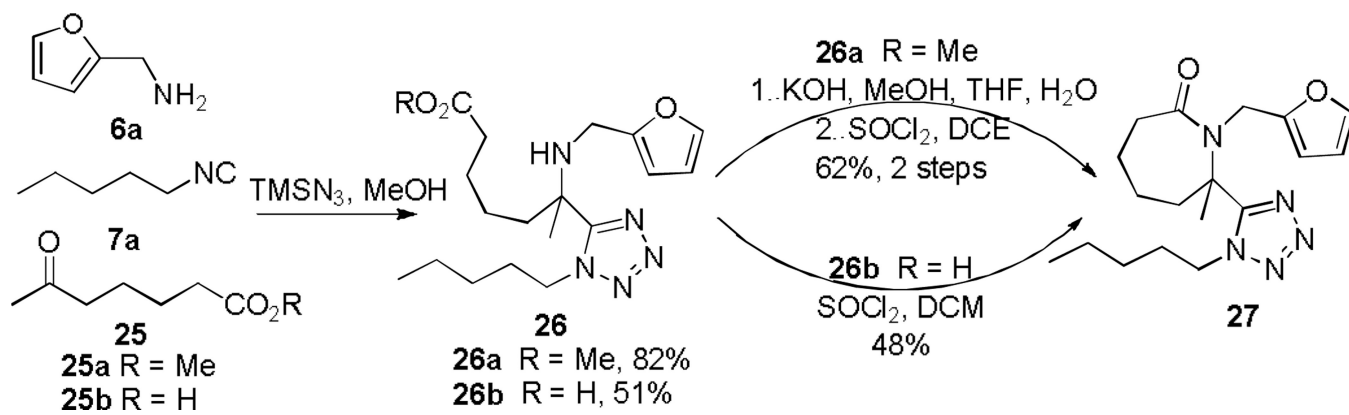
Scheme 7.
Optimization of azepinone-tetrazoles **27**

Table 1

Tetrazolyl-pyrrolidinones series
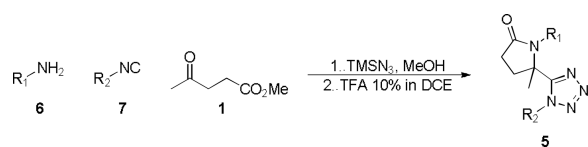
R$_1$	R$_2$	Product	Yield (%)
		5b	78
		5c	54
		5d	69
		5e	59
		5f	52
		5g	64
		5h	40
		5i	48

Table 2

Indolinone tetrazole series
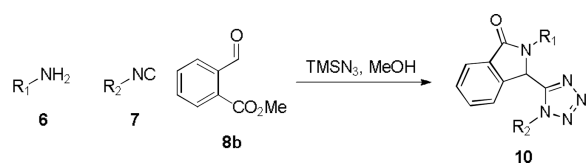
R$_1$	R$_2$	Product	Yield (%)
		10c	51
		10d	58
		10e	66
		10f	43
		10g	51
		10h	**58**
		10i	**29**
		10j	36

Table 3

Array of thiomorpholinone-tetrazole derivatives **20**
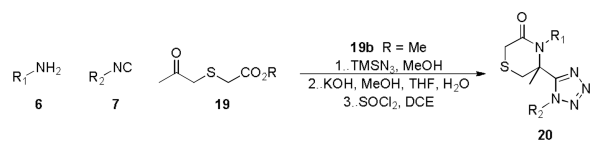
R₁	R₂	Product	Ugi (%)	Final Steps* (%)
		20a	**78**	88
		20b	61	66
		20c	42	22
		20d	86	73
		20e	61	96

*
Basic hydrolysis and SOCl₂ activation

Table 4

Array of 4-sulfonyl-2-piperazinone-tetrrazole derivatives
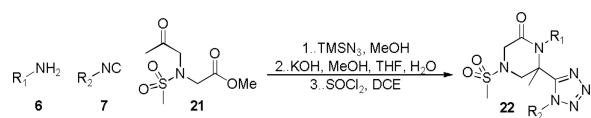
R₁	R₂	Product	Ugi (%)	Final Steps* (%)
		22a	16	78
		22b	27	93
		22c	59	82
		22d	55	86
		22e	74	58
		22f	64	64

*Basic hydrolysis and $SOCl_2$ activation

Table 5

Array of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]-pyrazine-4-one tetrazole derivatives **24**
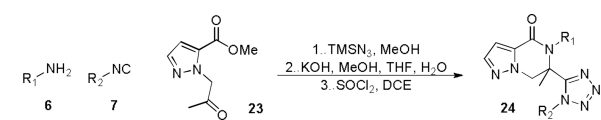
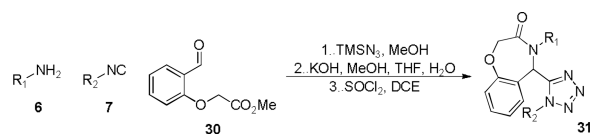| R₁	R₂	Product	Ugi (%)	Final Steps* (%)
		24a	74	51
		24b	73	57
		24c	67	78
		24d	51	72
		24e	42	55

*
Basic hydrolysis and SOCl₂ activation

Table 6

Array of [1,4]thiazepanone derivatives **29**
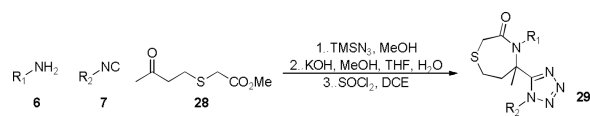
R₁	R₂	Product	Ugi (%)	Final Steps* (%)
		29a	68	57
		29b	70	66
		29c	70	54
		29d	61	45
		29e	75	51

*Basic hydrolysis and SOCl₂ activation

Table 7

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

R₁	R₂	Product	Ugi e(%)	Final Steps* (%)
		31a	80	29
		31b	63	31
		31c	74	84
		31d	78	70
		31e	77	35
		31f	66	62

*Basic hydrolysis and SOCl₂ activation