Substrate exploitation of multicomponent reactions toward diverse scaffolds and applications in medicinal chemistry

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MCR and cyclization
allow for the collective transformation
of a large chemical space
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CHAPTER 3

Scaffolding-induced Property Modulation of Chemical Space

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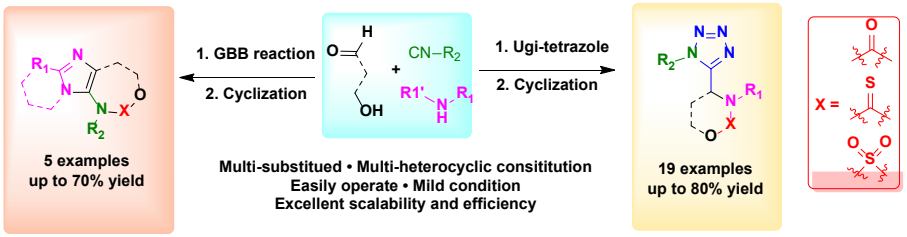
Abstract



Physicochemical property switching of chemical space is of great importance for optimization of compounds, for ex-ample for biological activity. Cyclization is a key method to control 3D and other properties. A two-step approach, which involves a multicomponent reaction followed by cyclization, is reported to achieve the transition from basic moieties to charge neutral cyclic derivatives. A series of multi-substituted oxazolidinones, oxazinanones, oxazepanones as well as their thio- and sulfur-derivatives are synthesized from readily available building blocks with mild conditions and high yields. Like no other method, MCR and cyclization allow for the collective transformation of a large chemical space into a related one with different properties.

KEYWORDS: multicomponent reaction, cyclic carbamate, Ugi reaction, cyclization, tetrazole, scaffolds diversity

Introduction

The property design of organic compounds is of uttermost importance during the process of optimization to obtain compounds with perfect performance. Properties such as charges or neutrality, 3D distribution of lipophilic or hydrogen donor/acceptor moieties are introduced into molecules by an often lengthy, stepwise and sequential pathway. The principles of multicomponent reaction chemistry (MCR) allow for an orthogonally different approach.[1] In an intellectually and operationally easily building block approach, complex molecules are assembled in one-step from a very large number of available building blocks.[2,3,4,5] Amongst, derivatization which often changes the properties dramatically are cyclizations. In the context of medicinal chemistry, cyclizations are often introduced to rigidify and generate a conformation similar to the receptor-bound structure, and also to modify drug-like properties such as stability to metabolism or increasing permeability.[6] By overlapping the 3D structure of cyclic and non-cyclic compounds, stabilization via cyclization and a shift of the terminal moiety was observed (**Figure 1A**). While the number of primary MCRs with useful synthetic properties such as great scope, ease of performance and large number of building blocks (and thus chemical space) is limited, the number of secondary transformations and especially cyclizations is shire infinitely. Hulme and others introduced the very useful concept of UDC (Ugi-deprotection-cyclization) resulting in Epelsiban and Retosiban, which are currently tested in advanced clinical trials.[7,8]

Carbamate containing heterocycles are abundantly present as dominant moieties in plenty of valuable chemicals and therapeutic agents in modern drug discovery and material science development.9 Cyclic carbamate moieties are not only present in many drugs (**Figure 1B**), but also play important roles in several chemicals progresses as chiral auxiliaries[10,11], and in the preparation of hyper branched polymers[12,13]. In particular, 6-membered (2-oxazinanone) cyclic carbamates has cumulatively been regarded as privileged scaffolds in drug discovery due to excellent chemical stability and cell membranes permeability. Owing to the prominent medicinal and industrial applicability of cyclic carbamates, various synthetic routes have been exploited (**Figure 1C**)[14]. The classical approaches generally involve either phosgene and its derivatives[15,16], alkyl halide chemistry[17], or sacrificial rea-gents[18], such as urea and organic carbonates. Shortly afterward, several other synthetic approaches have been developed to supersede these dissipative, costly and environment hazardous methods. Nevertheless, the following

reactions confront various defects, for instance, harsh reaction conditions (0°C or heating)[19], catalyst requirement[20], difficult to access starting materials[21,22], long reaction time[23], multiple steps[24], low yields[25], and limited scope[26].

Our strategy for a cyclization-induced property change based on MCR chemistry was to use bifunctional orthogonal amino and hydroxyl aldehydes in specific variants of the Ugi reaction, GBB-3CR and UT-4CR, followed by a secondary cyclization on the intermediates to yield (thio) carbamates, ureas and amino sulfonic acid esters of 6- and 7-membered ring size (**Figure 1D**).

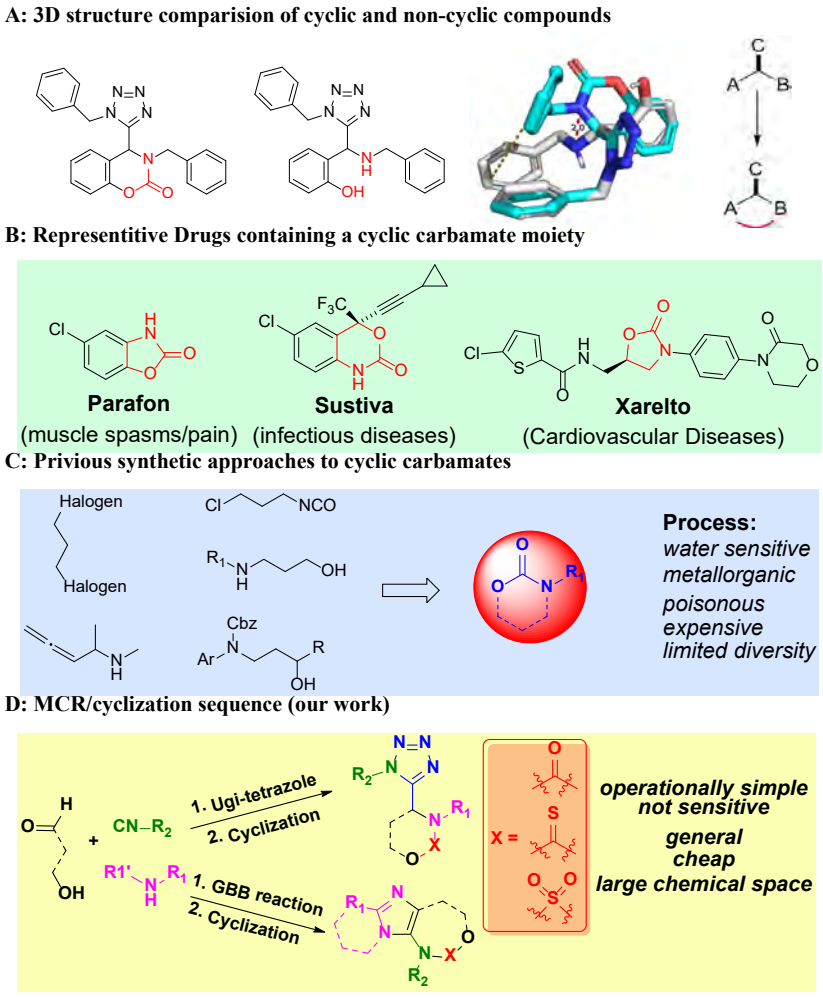
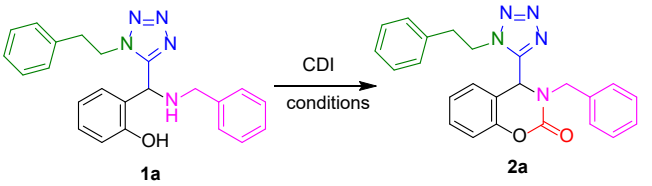


Figure 1. Cyclization strategies in chemistry.

Result and Discussion

The azido-Ugi product **1a**, which features a secondary amine, was chosen as the model substrate to verify this hypothesis. Salicylaldehyde aldehyde was selected in this azido-Ugi reaction as the supplier of the free hydroxyl group. 1,1'-Carbonyldiimidazole (CDI) is a coupling reagent mainly used for the synthesis of amides, peptides, carbamates as well as ureas.[27,28] Therefore, we envisioned that CDI could enable the desired cyclic carbamate formation by affording the carbonyl group to the MCR product.

Table 1. Optimization of reaction conditions[a]



1a 2a

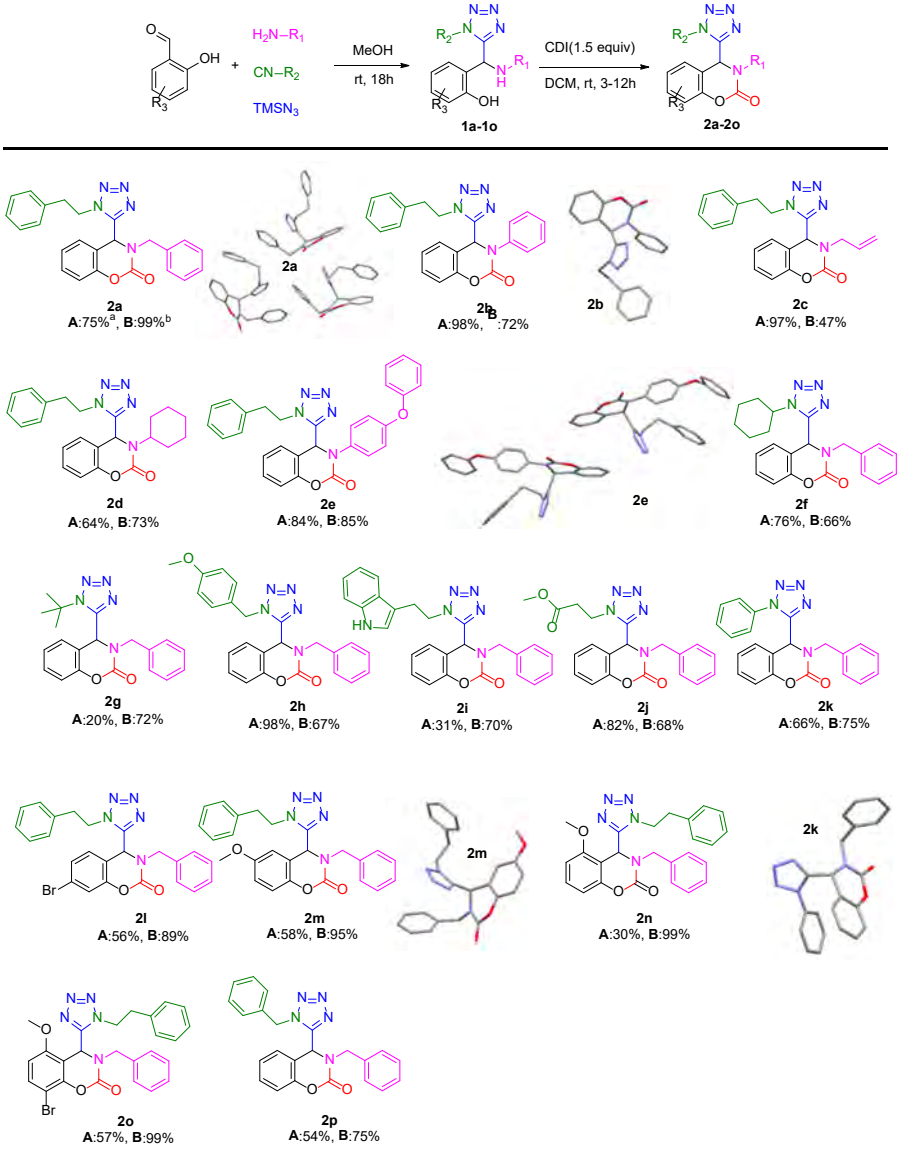
Entry	Equiv. of CDI	Base	Time (h)	Temp. (°C)	yield (%)[b]
1	1	-	3	rt	76
2	1	-	3	50	83
3	2	-	3	rt	93
4	2	-	3	50	88
5	2	TEA	12	rt	61
6	2	DIPEA	12	rt	71
7	2	$NaHCO_3$	12	rt	48
8	1.2	-	3	rt	85
9	1.5	-	3	rt	99

[a] The CDI conducted reaction was carried out in DCM with 1M concentration; [b] Isolated yields.

Having synthesized the corresponding Ugi-tetrazole in hand, the optimization started with 1 equivalent of CDI in DCM at room temperature, giving a moderate yield of 76% (**Table 1**, **entry 1**) after 3 h. Further optimization was conducted by increasing either temperature or the equivalent of CDI. As expected, both conditions performed better yields of 83% (**Table 1**, **entry 2**) and 93% (**Table 1**, **entry 3**), respectively. Several researches indicated that a catalytic amount of base in CDI reaction will accelerate the formation of the corresponding product.[29] However, subsequent attempts have shown that the utilization of base (**Table 1**, **entry 5-6**) restrict the reaction process, even with longer

reaction time. To our delight, superior conditions were found with shorter reaction time without heating. In the optimal protocol, 1.5 equivalent of CDI was added to a solution of azido-Ugi product in DCM at room temperature under air, and the corresponding oxazinanone was formed with nearly quantitative yield in a few hours (**Table1**, **entry 9**).

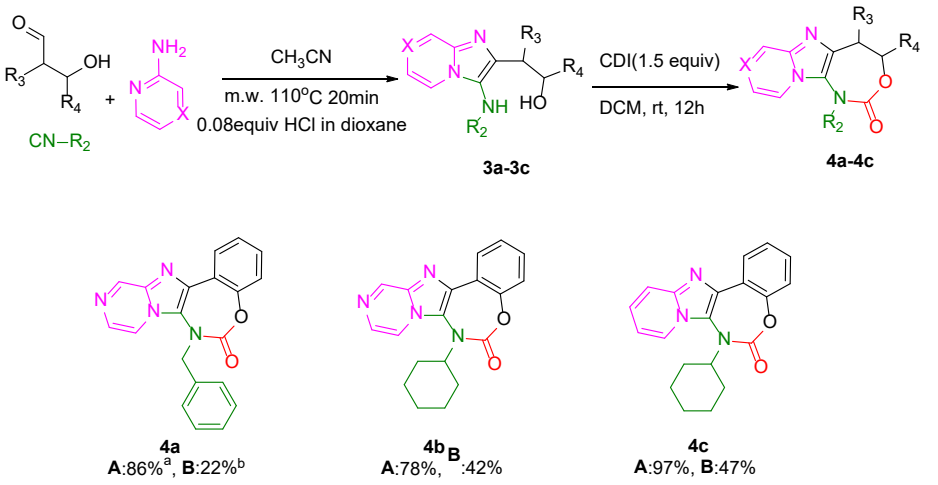
Scheme 1. Yields of the Ugi Products (**1**) and cyclized 1.3-oxazinan-2-one (**2**)



[a] Isolated yield of 1; [b] Isolated yield of 2

Under optimized conditions, we next examined the substrate scope of cyclization with various amines, isocyanides, and salicylaldehydes with diverse substitutions (**Scheme 1**). The majority of the corresponding oxazinanones resulted in moderate to good yields over two steps. First of all, amino substituents have obvious influences on synthetic conversion. Compounds synthesized by aromatic amines exhibited excellent overall yields, including phenox phenyl substituted **2e** despite the possible steric hindrance. On the contrary, aliphatic amine substitutions reduced the yield of the cyclization. For instance, compound **2c** with allyl substitution affords only 47% yield. In addition, changes in the isocyanide components were well-tolerated. Most of the isolated products have approximately 70% yield. It is noteworthy that the desired compound **2i** was obtained in high yield in the presence of a competitive amino group in the indole ring. Furthermore, aldehydes with methoxyl and halogen substituents on ortho- or meta- positions were evaluated in the scope as well. Surprisingly, most of the cyclization products with either mono- or multi- substituents on the salicylaldehydes gave extraordinary quantitive yields.

Scheme 2. Yields of the GBB Products (**3**) and cyclized oxazepanones (**4**)

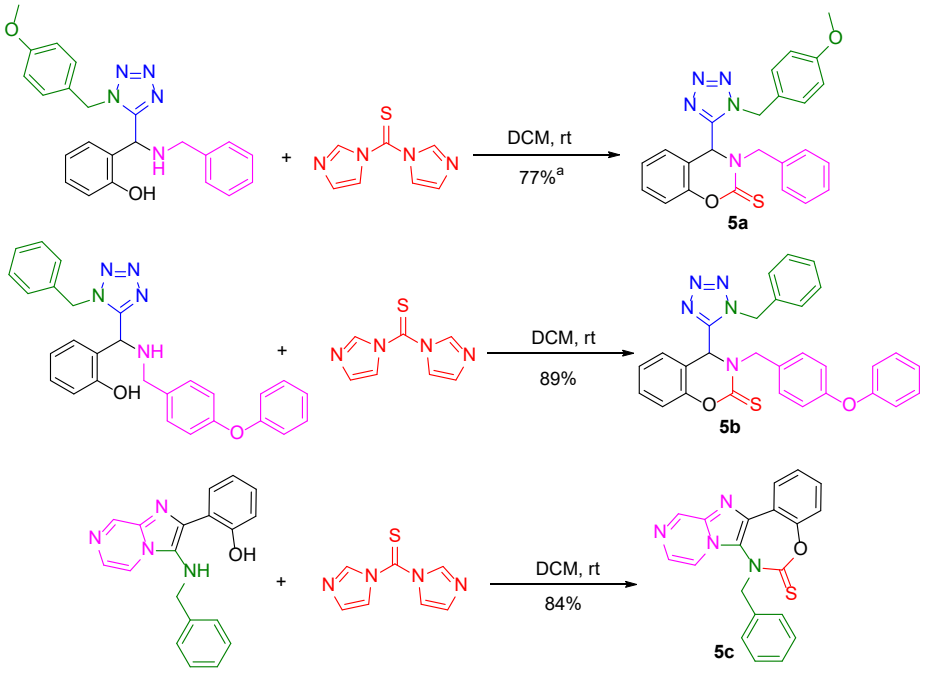


[a] Isolated yield of 3; [b] Isolated yield of 4

Encouraged by the initial results, we investigated the potential of the cyclization strategy based on Groebke-Blackburn-Bienaymé reactions (GBB reactions) which could afford secondary amines on imidazole heterobicyclic rings (**Scheme 2**).[2,3,4] Equimolar amounts of aldehyde, amino amine and isocyanide, as well as 0.08 equivalent of HCl in dioxane, were combined in CH_3CN (1 M) in microwave at 110 °C for 20 min. The corresponding imida-

zole-heterobicyclic product **3** was isolated by column chromatography with excellent yields (for example, **3c**, 97%). The identical cyclization approach as above was employed. Not surprisingly, the carbamate formation of the 7-membered 1,3-oxazepan-2-one appeared more difficult than the 6-membered 1.3-oxazinan-2-ones. The overall yields of the cyclized GBB products are below 50%. A large amount of imidazole-1-carboxylate intermediates were observed even with longer reaction time.

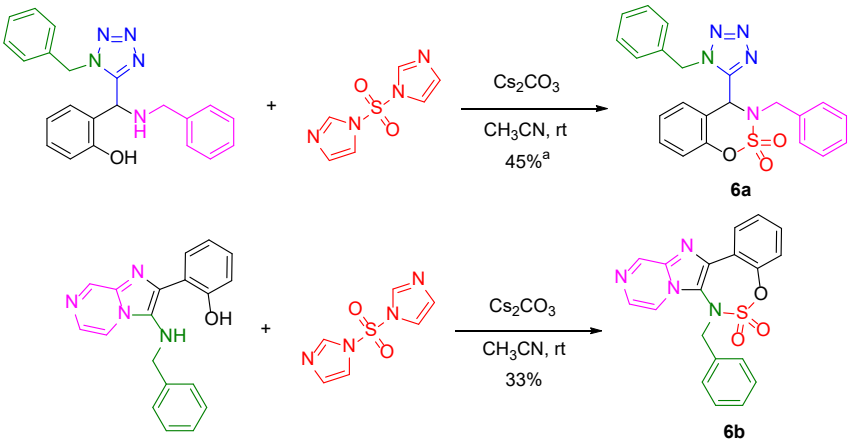
Scheme 3. Substrate Scope of cyclized 1,3-oxazinane-2-thiones and 1,3-oxazepane-2-thiones (**5**)



[a] Isolated yield of cyclic thiocarbamate 5.

In light of the aforementioned results, we next explored the synthesis of thiocarbamate derivatives (**Scheme 3**). 1,1'-Thiocarbonyldiimidazole (TCDI), the sulfur analog of CDI, was employed as the thiocarbonyl donor. Accordingly, the reaction was conducted with 2 equivalents of TCDI in room temperature for 12h in DCM. To our delight, the overall cyclization exhibited good to excellent yields. Positively, enhanced conversion to the thiocarbamate compounds was observed in the Ugi products, compared with the carbamate formation. Furthermore, it is noteworthy that the thiocarbamate GBB product (**5c**, 84%) went better than carbamate GBB (**4a**, 22%), effectively comparable with the Ugi product yields (**5a**, 77%; **5b**, 89%).

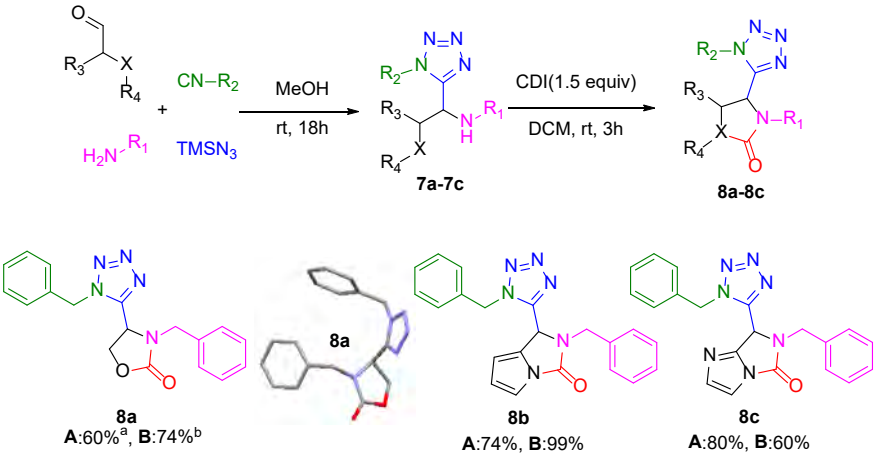
Scheme 4. Substrate Scope of cyclized 1,2,3-oxathiazinane-2,2-dioxides and 1,2,3-oxathiazepane-2,2-dioxides (**6**)



[a] Isolated yield of cyclic thiocarbamate 6.

Next, we attempted to use the uniform approach with the sulfonyl donor 1,1′-Sulfonyldiimidazole (SDI), for the synthesis of sulfamate derivatives (**Scheme 4**). However, under the previous conditions, the reaction remained at the stage of the imidazole-1-sulfonyl intermediate instead of cyclization to the sulfamate product. In order to push the reaction to the desired cyclization, excess amount of Cs_2CO_3 was added to the reaction solution. Under base-catalysis, 6-membered and 7-membered cyclized sulfamate derivatives were then synthesized in 45% (**6a**) and 33% (**6b**) yield, respectively.

Scheme 5. Substrate Scope of 5-membered CDI cyclization of MCR products (**8**)



[a] Isolated yield of 7; bIsolated yield of 8

As an application of this methodology, we next investigated the scope of 5-membered carbamate cyclization and urea cyclization with CDI as the carbonyl donor (**Scheme 5**). The main innovation of 5-membered ring formation is the employment of various aldehydes. Glycolaldehyde dimer, providing a free hydroxyl group, was used in the azido-Ugi reaction. CDI afforded oxazolidin-2-one **8a** with 74% yield. Pyrrole-2-carboxaldehyde and 2-imidazolecarboxaldehyde, which provided secondary amines, were employed to the formation of heterobicyclic ureas with 99% (**8b**) and 60% (**8c**) yield, respectively. For better yields, a catalytic amount of DIPEA was added in the urea formation.

Additionally, five oxazinanone derivatives (**2a**, **2b**, **2e**, **2k**, **2m**) and one oxazolidinone derivative (**8a**) have been confirmed by X-ray single-crystal analysis (**Scheme1**, **Scheme 5** and **Supporting Information**).

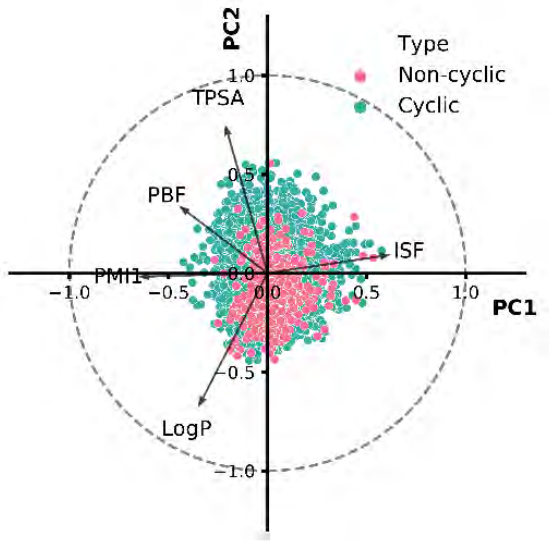


Figure 2. Normalized PC1 vs PC2 plot of cyclic and non-cyclic molecules. Cyclic molecules (green) showed a different distribution against non-cyclic molecules (pink).

To exemplify the scaffolding induced property modulation, we compared 14 physicochemical properties of each 1000 compound virtual libraries[30,31] of the cyclized and non-cyclized structures (**Figure 2** and **Supporting Information**). PCA of five non-redundant physicochemical properties included 3D descriptors allowed us to identify interesting differences between non-cyclic and cyclic molecules. Topological

polar surface area (TPSA) and logP, which are important values in medicinal chemistry, were identified as the most relevant descriptors (black arrows) to explain the variance among the cyclic and non-cyclic molecules, indicating drug-likeliness of all herein described cyclic scaffolds.

Conclusion

In summary, a MCR-based synthesis of 5-membered, 6-membered and 7-membered cyclic carbamate derivatives with at least 4 substitutions has been developed with the purpose to modify physicochemical properties. Both the azido-Ugi reaction and the GBB reaction are instrumental in this approach, leading to potentially bioactive bis-heterocyclic or multi-heterocyclic scaffold constructs. Furthermore, their thio- and sulfur- scaffolds are investigated along with the achievement of extraordinary scaffold diversity. The cheminformatics analysis clearly shows we are addressing a drug-like chemical space. Our protocol, utilizing mild condition and readily available building blocks, is of excellent maneuverability, scalability, and efficiency. It will add to a growing body in the development of material and organic synthesis, as well as medicinal chemistry.

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Experimental section

Experimental procedures

Procedure A: General procedure for the synthesis of Ugi-tetrazole products 1 and 7:

A solution of aldehyde (1 mmol) and amine (1 mmol) in methanol (1 mL) was stirred at room temperature for 15 minutes. Subsequently, isocyanide (1 mmol) and TMS azide (1 mmol) were added and the reaction was stirred at room temperature for 18 hours. The reaction was concentrated in vacuo and purified by column chromatography (EtOAc/ PE).

Procedure B: General procedure for the synthesis of 2, 4 and 8a:

A solution of 1 or 7 (1 equiv.) and Carbonyldiimidazole (1.5 equiv.) in DCM (0.5 mL) was stirred at room temperature for 3-12 hours. The reaction was concentrated in vacuo and purified by column chromatography (EtOAc/PE).

Procedure C: General procedure for the synthesis of GBB Products 3:

To a solution of aldehyde (1 mmol) in acetonitrile (1 mL) were added amine (1 mmol), isocyanide (1 mmol) and 4 N HCl/dioxane (0.02ml, 0.008mmol). The reaction mixture was then heated under microwave conditions (110 °C) in a sealed vial for 20 minutes. After the reaction mixture was cooled to room temperature, the reaction was concentrated in vacuo and purified by column chromatography (EtOAc/PE).

Procedure D: General procedure for the synthesis of 5:

A solution of 1 or 3 (1 equiv.) and 1,1′-Thiocarbonyldiimidazole (2 equiv.) in DCM (0.5 mL) was stirred at room temperature for 12 hours. The reaction was concentrated in vacuo and purified by column chromatography (EtOAc/PE).

Procedure E: General procedure for the synthesis of 6:

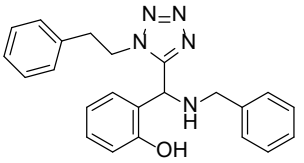
A solution of 1 or 3 (1 equiv.), 1,1′-Sulfonyldiimidazole (2 equiv.) and cesium carbonate (5 euqiv.) in acetonitrile (1 mL) was stirred at room temperature for 12 hours. The reaction was concentrated in vacuo and purified by column chromatography (EtOAc/PE).

Procedure F: General procedure for the synthesis of 8b and 8c:

A solution of 1 (1 euqiv.), Carbonyldiimidazole (1.5 equiv.), N,N-Diisopropylethylamine (2 equiv.) in DCM (0.5 mL) was stirred at room temperature for 12 hours. The reaction was concentrated in vacuo and purified by column chromatography (EtOAc/ PE).

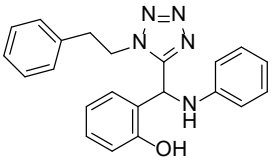
Characterization data

2-((benzylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)phenol (1a)



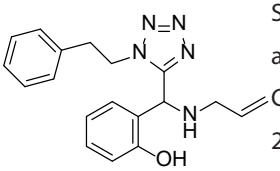
Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 289mg (75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.22 (m, 3H), 7.21 – 7.11 (m, 6H), 6.97 – 6.85 (m, 3H), 6.77 (td, *J* = 7.5, 1.2 Hz, 1H), 6.66 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.88 (s, 1H), 4.41 – 4.30 (m, 1H), 4.28 – 4.16 (m, 1H), 3.57 (d, *J* = 13.0 Hz, 1H), 3.50 (d, *J* = 13.0 Hz, 1H), 3.02 – 2.94 (m, 1H), 2.93 – 2.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 154.6, 137.7, 136.4, 130.6, 129.0, 128.9, 128.8, 128.6, 128.4, 127.8, 127.4, 120.8, 120.0, 117.8, 54.5, 50.7, 49.0, 35.9. MS (ESI) m/z calculated for $C_{23}H_{24}N_5O$ $[M+H]^+$: 386.19; found $[M+H]^+$: 386.30.

2-((1-phenethyl-1H-tetrazol-5-yl)(phenylamino)methyl)phenol (1b)



Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 364mg (98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.17 (m, 3H), 7.17 – 7.07 (m, 3H), 7.07 – 6.96 (m, 3H), 6.88 (d, *J* = 8.1 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 7.9 Hz, 2H), 5.78 (s, 1H), 4.85 (s, 1H), 4.63 – 4.45 (m, 2H), 3.17 – 3.05 (m, 1H), 3.05 – 2.93 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.3, 154.4, 145.3, 136.3, 130.3, 129.4, 129.0, 128.7, 128.4, 127.4, 122.9, 121.2, 120.1, 117.3, 115.0, 50.1, 49.0, 35.9. MS (ESI) m/z calculated for $C_{22}H_{22}N_5O$ $[M+H]^+$: 372.17; found $[M+H]^+$: 372.24.

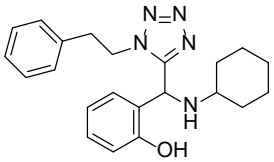
2-((allylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)phenol (1c)



Synthesized according to procedure A from 1 mmol reaction as pale yellow solid, yield: 325mg (97%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 3H), 7.26 – 7.22 (m, 1H), 7.02 – 6.95 (m, 2H), 6.90 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.78 (td, *J* = 7.5, 1.2 Hz, 1H), 6.54 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.83 – 5.70 (m, 1H), 5.20 – 5.07 (m, 2H), 4.83 (s, 1H), 4.52 – 4.42 (m, 1H), 4.28 – 4.18 (m, 1H), 3.16 – 3.08 (m, 1H), 3.07 – 2.96 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 154.1, 136.3, 134.0, 130.7, 129.0, 128.8, 128.1, 127.5, 120.1, 119.9, 118.2, 118.1, 55.2, 49.0, 36.0, 33.1. MS (ESI) m/z calculated for $C_{19}H_{22}N_5O$ $[M+H]^+$: 336.17; found $[M+H]^+$: 336.30.

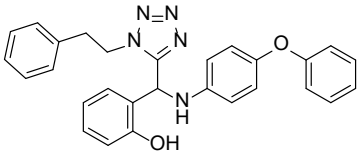
2-((cyclohexylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)phenol (1d)

Synthesized according to procedure A from 1 mmol reaction as pale yellow solid, yield:



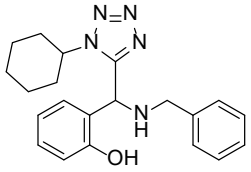
242mg (64%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 3H), 7.19 (td, *J* = 7.8, 1.7 Hz, 1H), 6.99 (d, *J* = 6.1 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.61 (dd, *J* = 7.6, 1.5 Hz, 1H), 5.14 (s, 1H), 4.48 – 4.39 (m, 1H), 4.34 – 4.23 (m, 1H), 3.12 – 3.04 (m, 1H), 3.02 – 2.93 (m, 1H), 2.37 – 2.26 (m, 1H), 1.89 – 1.79 (m, 1H), 1.77 – 1.71 (m, 1H), 1.71 – 1.61 (m, 2H), 1.61 – 1.50 (m, 1H), 1.21 – 1.09 (m, 4H), 1.08 – 1.00 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 154.8, 136.3, 130.4, 128.9, 128.8, 127.9, 127.4, 121.0, 119.7, 117.9, 53.9, 52.7, 49.0, 35.8, 32.9, 32.6, 25.7, 24.7, 24.6. MS (ESI) m/z calculated for $C_{22}H_{28}N_5O$ $[M+H]^+$: 378.22; found $[M+H]^+$: 378.51.

2-((1-phenethyl-1H-tetrazol-5-yl)((4-phenoxyphenyl)amino)methyl)phenol (1e)



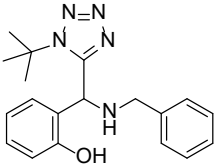
Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 389mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.12 (m, 5H), 7.11 – 7.03 (m, 2H), 7.01 – 6.95 (m, 3H), 6.93 – 6.88 (m, 1H), 6.87 – 6.83 (m, 2H), 6.78 (dd, *J* = 7.5, 1.0 Hz, 1H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.9 Hz, 2H), 5.82 (s, 1H), 4.59 – 4.46 (m, 2H), 3.14 – 3.03 (m, 1H), 2.98 – 2.86 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 156.1, 154.4, 149.5, 141.9, 136.3, 130.3, 129.6, 129.0, 128.8, 128.3, 127.4, 123.1, 122.5, 120.8, 120.7, 117.7, 117.6, 116.9, 115.8, 115.7, 49.3, 49.1, 35.9. MS (ESI) m/z calculated for $C_{28}H_{26}N_5O_2$ $[M+H]^+$: 464.21; found $[M+H]^+$: 464.25.

2-((benzylamino)(1-cyclohexyl-1H-tetrazol-5-yl)methyl)phenol (1f)



Synthesized according to procedure A from 1 mmol reaction as pale yellow solid, yield: 276mg (76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.30 – 7.25 (m, 3H), 7.24 – 7.20 (m, 1H), 6.92 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 (td, *J* = 7.4, 1.2 Hz, 1H), 6.76 (dd, *J* = 7.7, 1.7 Hz, 1H), 5.30 (s, 1H), 3.96 (tt, *J* = 11.6, 3.7 Hz, 1H), 3.89 – 3.78 (m, 2H), 2.00 – 1.90 (m, 1H), 1.89 – 1.80 (m, 2H), 1.77 – 1.69 (m, 2H), 1.68 – 1.60 (m, 1H), 1.49 – 1.39 (m, 1H), 1.30 – 1.17 (m, 2H), 1.16 – 1.04 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 153.3, 137.5, 130.5, 128.8, 128.6, 128.2, 127.9, 121.1, 119.8, 117.8, 58.2, 54.5, 50.8, 32.7, 25.1, 24.7.MS (ESI) m/z calculated for $C_{21}H_{26}N_5O$ $[M+H]^+$: 364.21; found $[M+H]^+$: 364.28.

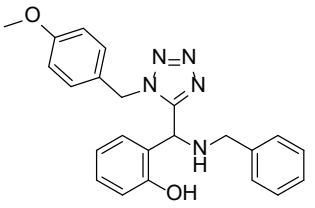
2-((benzylamino)(1-(tert-butyl)-1H-tetrazol-5-yl)methyl)phenol (1g)



Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 64mg (20%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 3H), 7.21 (td, *J* = 7.7, 1.6 Hz, 1H), 6.94 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.71 (td, *J* = 7.6, 1.3 Hz, 1H), 6.13 (dt, *J* = 7.7, 1.2 Hz, 1H), 5.59 (s, 1H), 3.82 (d, *J* = 12.6 Hz, 1H), 3.72 (d, *J* = 12.6 Hz, 1H), 1.62 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 153.8, 137.2, 130.3, 128.9, 128.6, 128.0, 127.6, 123.3, 119.7, 117.7, 62.1, 55.2, 51.1, 30.1.MS (ESI) m/z calculated for $C_{23}H_{24}N_5O_2$ $[M+H]^+$: 338.19; found $[M+H]^+$: 338.25.

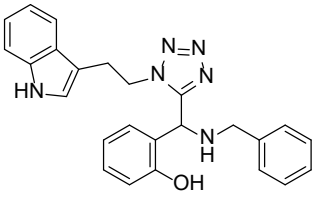
3

2-((benzylamino)(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)methyl)phenol (1h)



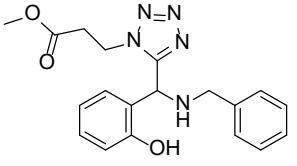
Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 393mg (98%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 4H), 7.16 (td, *J* = 7.7, 1.7 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.91 – 6.86 (m, 3H), 6.74 – 6.68 (m, 3H), 6.53 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.32 (d, *J* = 15.3 Hz, 1H), 5.24 (s, 1H), 5.20 (d, *J* = 15.3 Hz, 1H), 3.71 (s, 3H), 3.63 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 157.0, 154.3, 137.5, 130.4, 129.2, 128.8, 128.5, 128.2, 127.8, 124.9, 120.8, 119.9, 117.8, 114.5, 55.4, 55.3, 54.1, 50.8. MS (ESI) m/z calculated for $C_{19}H_{24}N_5O$ $[M+H]^+$: 402.19; found $[M+H]^+$: 402.26.

2-((1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)(benzylamino)methyl)phenol (1i)



Synthesized according to procedure A from 1 mmol reaction as pale yellow solid, yield: 132g (31%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.35 – 7.22 (m, 6H), 7.21 – 7.14 (m, 2H), 7.12 – 7.06 (m, 3H), 6.84 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.74 – 6.65 (m, 2H), 6.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.56 (s, 1H), 4.52 – 4.46 (m, 1H), 4.34 – 4.24 (m, 1H), 3.31 – 3.12 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 154.5, 137.5, 136.2, 130.5, 128.7, 128.4, 128.0, 127.7, 126.6, 123.0, 122.9, 122.7, 120.4, 120.2, 119.8, 117.8, 111.7, 110.2, 54.9, 50.3, 48.4, 25.9.MS (ESI) m/z calculated for $C_{25}H_{25}N_6O$ $[M+H]^+$: 425.20; found $[M+H]^+$: 425.27.

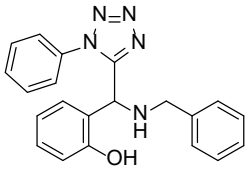
Methyl 3-(5-((benzylamino)(2-hydroxyphenyl)methyl)-1H-tetrazol-1-yl)propanoate (1j)



Synthesized according to procedure A from 1 mmol reaction as pale yellow solid, yield: 301mg (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.25 – 7.20 (m, 1H),

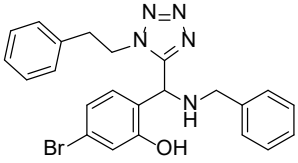
6.90 (d, *J* = 8.1 Hz, 1H), 6.83 – 6.79 (m, 2H), 5.47 (s, 1H), 4.40 – 4.32 (m, 1H), 4.29 – 4.22 (m, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 3.60 (s, 3H), 2.95 – 2.86 (m, 1H), 2.72 – 2.62 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 157.3, 154.5, 137.6, 130.6, 128.8, 128.6, 128.3, 127.8, 120.6, 119.9, 117.9, 54.8, 52.2, 50.8, 43.0, 33.1. MS (ESI) m/z calculated for $C_{19}H_{22}N_5O_3$ $[M+H]^+$: 368.16; found $[M+H]^+$: 368.24.

2-((benzylamino)(1-phenyl-1H-tetrazol-5-yl)methyl)phenol (1k)



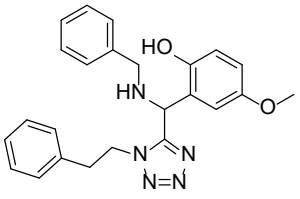
Synthesized according to procedure A from 1 mmol reaction as orange solid, yield: 236mg (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 1H), 7.59 – 7.54 (m, 1H), 7.53 – 7.48 (m, 1H), 7.45 – 7.39 (m, 2H), 7.28 – 7.25 (m, 1H), 7.20 – 7.13 (m, 5H), 6.86 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.62 (td, *J* = 7.5, 1.2 Hz, 1H), 6.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.25 (s, 1H), 3.80 – 3.69 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.1, 154.6, 140.7, 137.1, 133.2, 130.8, 130.4, 130.2, 130.0, 129.9, 128.8, 128.6, 128.3, 127.9, 125.2, 121.2, 120.8, 119.6, 117.7, 54.5, 50.7.MS (ESI) m/z calculated for $C_{21}H_{20}N_5O$ $[M+H]^+$: 358.16; found $[M+H]^+$: 358.25.

2-((benzylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)-5-bromophenol (1l)



Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 260mg (56%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 4H), 7.23 – 7.15 (m, 5H), 6.95 – 6.83 (m, 2H), 6.79 – 6.69 (m, 2H), 4.72 (s, 1H), 4.44 – 4.35 (m, 1H), 4.32 – 4.23 (m, 1H), 3.59 (d, *J* = 13.0 Hz, 1H), 3.48 (d, *J* = 13.0 Hz, 1H), 3.09 – 2.91 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 153.0, 150.7, 137.5, 136.2, 128.9, 128.8, 128.7, 128.5, 127.9, 127.4, 121.2, 118.7, 115.1, 114.7, 55.0, 50.8, 49.0, 36.0. MS (ESI) m/z calculated for $C_{23}H_{23}BrN_5O$ $[M+H]^+$: 464.10; found $[M+H]^+$: 464.26.

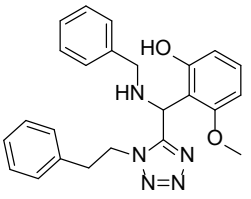
2-((benzylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)-5-methoxyphenol (1m)



Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 241mg (58%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 4H), 7.24 – 7.19 (m, 4H), 7.19 – 7.15 (m, 1H), 6.94 – 6.90 (m, 2H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.80 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.22 (d, *J* = 2.8 Hz, 1H), 4.76 (s, 1H), 4.45 – 4.36 (m, 1H), 4.28 – 4.18 (m, 1H), 3.68 (s, 3H), 3.60 (d, *J* = 13.0 Hz, 1H), 3.53 (d, *J* = 13.0 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.96 – 2.85 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$)

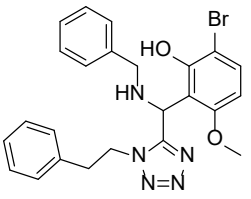
δ 154.2, 153.0, 150.7, 137.5, 136.2, 128.9, 128.8, 128.7, 128.5, 127.9, 127.4, 121.2, 118.8, 115.1, 114.7, 55.8, 55.0, 50.8, 49.0, 36.0. MS (ESI) m/z calculated for $C_{24}H_{26}N_5O_2$ $[M+H]^+$: 416.20; found $[M+H]^+$: 416.26.

2-((benzylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)-3-methoxyphenol (1n)



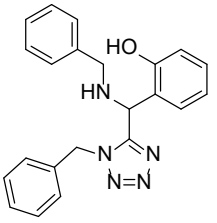
Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 125mg (30%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.24 (m, 3H), 7.24 – 7.14 (m, 5H), 6.95 – 6.89 (m, 2H), 6.50 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 2.6 Hz, 1H), 6.34 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.77 (s, 1H), 4.41 – 4.32 (m, 1H), 4.25 – 4.16 (m, 1H), 3.73 (s, 3H), 3.61 (d, *J* = 13.1 Hz, 1H), 3.53 (d, *J* = 13.1 Hz, 1H), 3.06 – 2.98 (m, 1H), 2.97 – 2.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.7, 158.5, 154.5, 137.5, 136.3, 129.2, 129.1, 128.9, 128.8, 128.5, 127.8, 127.4, 112.5, 106.1, 103.2, 55.4, 54.5, 50.5, 48.9, 35.9. MS (ESI) m/z calculated for $C_{24}H_{26}N_5O_2$ $[M+H]^+$: 416.20; found $[M+H]^+$: 416.26.

2-((benzylamino)(1-phenethyl-1H-tetrazol-5-yl)methyl)-6-bromo-3-methoxyphenol (1o)



Synthesized according to procedure A from 1 mmol reaction as yellow solid, yield: 282mg (57%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 6H), 7.23 – 7.15 (m, 3H), 6.94 – 6.89 (m, 2H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.64 (d, *J* = 2.2 Hz, 1H), 5.03 (s, 1H), 4.45 – 4.28 (m, 2H), 3.76 (s, 3H), 3.65 – 3.54 (m, 2H), 3.07 – 2.88 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 148.6, 143.9, 137.9, 136.3, 129.0, 128.9, 128.8, 128.7, 128.6, 127.7, 127.5, 127.3, 124.0, 122.5, 114.6, 111.7, 56.2, 51.2, 51.1, 48.7, 36.0. MS (ESI) m/z calculated for $C_{24}H_{25}BrN_5O_2$ $[M+H]^+$: 494.11; found $[M+H]^+$: 494.39.

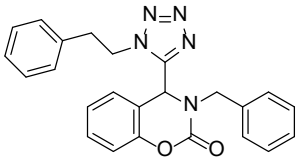
2-((1-benzyl-1H-tetrazol-5-yl)(benzylamino)methyl)phenol (1p)



Synthesized according to procedure A from 1 mmol reaction as off white solid, yield: 200mg (54%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 6H), 7.25 – 7.20 (m, 1H), 7.16 – 7.10 (m, 2H), 6.98 – 6.93 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.43 (d, *J* = 7.5 Hz, 1H), 5.43 (d, *J* = 15.5 Hz, 1H), 5.19 (d, *J* = 15.5 Hz, 1H), 5.13 (s, 1H), 3.64 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 154.0, 137.1, 132.9, 130.7, 129.2, 129.0, 128.8, 128.5, 128.1, 127.9, 127.3, 120.1, 119.8, 118.1, 54.7, 51.1, 50.7. MS (ESI) m/z calculated for $C_{22}H_{22}N_5O$ $[M+H]^+$: 372.44; found $[M+H]^+$: 372.36.

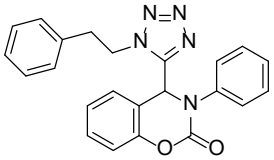
3-benzyl-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one

(2a)



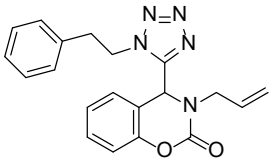
Synthesized according to procedure B from 0.26 mmol reaction as white solid, yield: 106mg (99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.33 – 7.27 (m, 5H), 7.26 – 7.19 (m, 3H), 7.17 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 6.97 – 6.90 (m, 2H), 6.82 – 6.75 (m, 1H), 6.26 (s, 1H), 4.86 (d, *J* = 14.9 Hz, 1H), 4.17 – 3.99 (m, 2H), 3.87 (d, *J* = 14.9 Hz, 1H), 2.96 – 2.85 (m, 1H), 2.68 – 2.56 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.7, 148.9, 148.5, 135.5, 134.1, 131.1, 129.0, 128.9, 128.7, 128.6, 127.4, 126.5, 126.4, 125.5, 117.0, 114.4, 52.0, 50.8, 49.3, 35.2. HRMS calculated for $C_{24}H_{22}N_5O_2$ $[M+H]^+$: 412.1768; found $[M+H]^+$: 412.1771.

4-(1-phenethyl-1H-tetrazol-5-yl)-3-phenyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2b)



Synthesized according to procedure B from 0.25 mmol reaction as off white solid, yield: 71mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (td, *J* = 7.9, 1.5 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.28 – 7.25 (m, 3H), 7.24 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 7.06 – 7.00 (m, 2H), 6.99 – 6.92 (m, 2H), 6.48 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.27 (s, 1H), 4.25 – 4.11 (m, 2H), 3.16 – 3.03 (m, 1H), 2.82 – 2.71 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 149.2, 148.6, 139.1, 135.8, 131.0, 130.1, 129.1, 129.0, 128.7, 127.5, 127.1, 126.0, 125.2, 117.2, 115.8, 55.7, 49.0, 35.5. HRMS calculated for $C_{23}H_{20}N_5O_2$ $[M+H]^+$: 398.1612; found $[M+H]^+$: 398.1615.

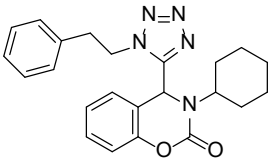
3-allyl-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2c)



Synthesized according to procedure B from 0.28 mmol reaction as pale yellow solid, yield: 48mg (47%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 1H), 7.29 – 7.22 (m, 3H), 7.18 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.93 – 6.88 (m, 1H), 6.33 (s, 1H), 5.79 – 5.66 (m, 1H), 5.29 – 5.22 (m, 1H), 5.22 – 5.13 (m, 1H), 4.32 – 4.16 (m, 3H), 3.33 (dd, *J* = 15.3, 7.4 Hz, 1H), 3.09 – 2.98 (m, 1H), 2.75 – 2.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 148.7, 148.4, 135.5, 131.2, 129.6, 129.0, 128.6, 127.4, 126.5, 125.6, 121.0, 117.0, 114.5, 52.0, 49.9, 49.4, 35.4. HRMS calculated for $C_{20}H_{20}N_5O_2$ $[M+H]^+$: 362,1612; found $[M+H]^+$: 362,1614.

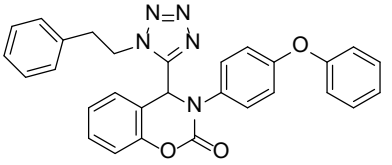
3-cyclohexyl-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]

oxazin-2-one (2d)



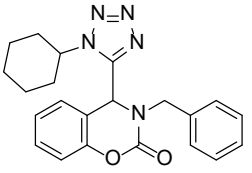
Synthesized according to procedure B from 0.25 mmol reaction as pale yellow solid, yield: 74mg (73%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 1H), 7.29 – 7.19 (m, 3H), 7.16 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.12 (td, *J* = 7.5, 1.1 Hz, 1H), 7.07 – 7.01 (m, 3H), 6.40 (s, 1H), 4.44 – 4.33 (m, 1H), 4.30 – 4.20 (m, 1H), 3.94 (tt, *J* = 12.3, 3.6 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.74 – 2.64 (m, 1H), 1.99 – 1.86 (m, 1H), 1.86 – 1.76 (m, 1H), 1.66 – 1.61 (m, 1H), 1.61 – 1.51 (m, 2H), 1.47 – 1.38 (m, 1H), 1.34 – 1.26 (m, 1H), 1.25 – 1.17 (m, 1H), 1.09 – 1.01 (m, 1H), 1.01 – 0.91 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 148.5, 148.4, 135.5, 131.0, 128.9, 128.7, 127.3, 126.5, 125.4, 116.8, 115.4, 59.6, 50.2, 49.2, 35.4, 29.8, 29.1, 25.8, 25.7, 24.9. HRMS calculated for $C_{23}H_{26}N_5O_2$ $[M+H]^+$:404.2081; found $[M+H]^+$: 404.2079.

4-(1-phenethyl-1H-tetrazol-5-yl)-3-(4-phenoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazin-2-one (2e)



Synthesized according to procedure B from 0.20 mmol reaction as off white solid, yield: 83mg (85%); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.45 – 7.39 (m, 1H), 7.38 – 7.31 (m, 2H), 7.28 – 7.24 (m, 3H), 7.24 – 7.21 (m, 1H), 7.19 – 7.13 (m, 1H), 7.11 – 7.06 (m, 1H), 7.02 – 6.98 (m, 2H), 6.98 – 6.94 (m, 2H), 6.94 – 6.87 (m, 4H), 6.54 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.28 (s, 1H), 4.30 – 4.16 (m, 2H), 3.17 – 3.05 (m, 1H), 2.81 – 2.72 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 155.8, 153.2, 149.1, 148.7, 135.7, 133.5, 131.1, 130.0, 129.2, 128.7, 128.5, 127.5, 126.0, 125.3, 124.3, 119.8, 119.2, 117.2, 115.6, 56.0, 49.1, 35.5. HRMS calculated for $C_{29}H_{24}N_5O_3$ $[M+H]^+$: 490.1879; found $[M+H]^+$: 490.1876.

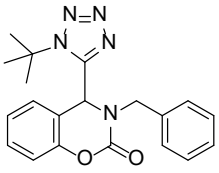
3-benzyl-4-(1-cyclohexyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2f)



Synthesized according to procedure B from 0.26 mmol reaction as white solid, yield: 67mg (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 6H), 7.16 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.30 (s, 1H), 5.07 (d, *J* = 14.7 Hz, 1H), 4.02 (d, *J* = 14.8 Hz, 1H), 3.83 (tt, *J* = 11.7, 3.8 Hz, 1H), 1.92 – 1.81 (m, 2H), 1.66 – 1.61 (m, 2H), 1.61 – 1.51 (m, 2H), 1.35 – 1.26 (m, 1H), 1.21 – 1.11 (m, 1H), 1.01 – 0.89 (m, 1H), 0.88 – 0.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.0, 149.0, 148.6, 134.2, 131.0, 129.1, 129.0, 128.6, 126.6, 125.3, 116.7, 114.7, 59.1, 52.0, 51.0,

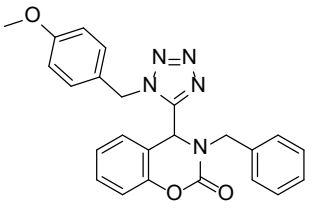
32.7, 32.4, 25.3, 24.6. HRMS calculated for $C_{22}H_{24}N_5O_2$ $[M+H]^+$: 390.1925; found $[M+H]^+$: 390.1927.

3-benzyl-4-(1-(tert-butyl)-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2g)



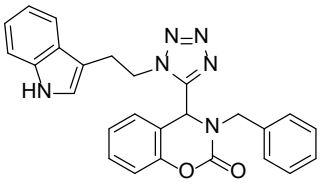
Synthesized according to procedure B from 0.28 mmol reaction as off white solid, yield: 73mg (72%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 4H), 7.29 – 7.27 (m, 1H), 7.27 (s, 1H), 7.16 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H), 6.83 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.44 (s, 1H), 5.15 (d, *J* = 15.1 Hz, 1H), 3.96 (d, *J* = 15.1 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.0, 149.9, 148.8, 134.3, 130.8, 129.0, 128.7, 128.5, 125.5, 124.8, 117.3, 116.6, 63.2, 53.3, 51.0, 30.0. HRMS calculated for $C_{20}H_{22}N_5O_2$ $[M+H]^+$: 364.1768; found $[M+H]^+$: 364.1770.

3-benzyl-4-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2h)



Synthesized according to procedure B from 0.23 mmol reaction as off white solid, yield: 66mg (67%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 3H), 7.28 – 7.23 (m, 3H), 7.04 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.95 (td, *J* = 7.6, 1.2 Hz, 1H), 6.79 – 6.74 (m, 2H), 6.73 – 6.69 (m, 2H), 6.61 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.23 (s, 1H), 5.20 (d, *J* = 15.3 Hz, 1H), 4.96 (d, *J* = 15.3 Hz, 1H), 4.88 (d, *J* = 15.0 Hz, 1H), 3.81 (d, *J* = 14.0 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9, 152.5, 149.1, 148.5, 134.1, 130.8, 129.0, 128.9, 128.7, 128.6, 126.3, 125.1, 124.0, 116.9, 114.4, 55.3, 51.9, 51.2, 50.9. HRMS calculated for $C_{24}H_{22}N_5O_3$ $[M+H]^+$: 428,1717; found $[M+H]^+$: 428,1717.

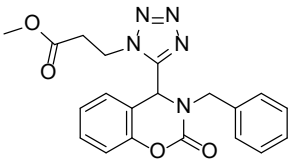
4-(1-(2-(1H-indol-3-yl)ethyl)-1H-tetrazol-5-yl)-3-benzyl-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2i)



Synthesized according to procedure B from 0.22 mmol reaction as off white solid, yield: 69mg (70%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.34 – 7.27 (m, 5H), 7.25 – 7.16 (m, 3H), 7.09 (td, *J* = 7.5, 6.9, 1.0 Hz, 1H), 7.05 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.95 (td, *J* = 7.6, 1.2 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 6.64 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.12 (s, 1H), 4.78 (d, *J* = 15.1 Hz, 1H), 4.26 – 4.15

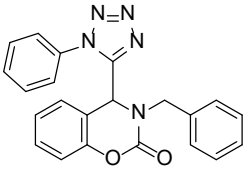
(m, 1H), 4.13 – 4.00 (m, 1H), 3.70 (d, *J* = 15.1 Hz, 1H), 3.23 – 3.08 (m, 1H), 3.03 – 2.90 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.9, 149.1, 148.5, 136.1, 134.1, 130.8, 129.0, 128.8, 128.6, 126.6, 126.2, 125.2, 122.7, 122.5, 120.0, 118.0, 116.8, 114.5, 111.4, 110.1, 51.8, 50.6, 49.0, 25.2. HRMS calculated for $C_{26}H_{23}N_6O_2$ $[M+H]^+$: 451,1877; found $[M+H]^+$: 451,1879.

Methyl 3-(5-(3-benzyl-2-oxo-3,4-dihydro-2H-benzo[e][1,3]oxazin-4-yl)-1H-tetrazol-1-yl) propanoate (2j)



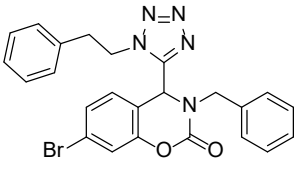
Synthesized according to procedure B from 0.25 mmol reaction as off white solid, yield: 67mg (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 1H), 7.35 – 7.29 (m, 5H), 7.16 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.11 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.29 (s, 1H), 5.03 (d, *J* = 15.1 Hz, 1H), 4.24 – 4.17 (m, 2H), 4.07 – 4.01 (m, 1H), 3.64 (s, 3H), 2.80 – 2.73 (m, 1H), 2.65 – 2.56 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 153.0, 149.5, 148.9, 134.4, 131.1, 129.0, 128.8, 128.5, 126.2, 125.3, 117.0, 114.8, 52.3, 51.9, 51.2, 43.2, 32.3. HRMS calculated for $C_{20}H_{20}N_5O_4$ $[M+H]^+$: 394.1510; found $[M+H]^+$: 394.1513.

3-benzyl-4-(1-phenyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2k)



Synthesized according to procedure B from 0.26 mmol reaction as yellow solid, yield: 75mg (75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.31 (m, 4H), 7.29 – 7.22 (m, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.21 (s, 1H), 5.19 (d, *J* = 14.8 Hz, 1H), 3.91 (d, *J* = 14.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 148.8, 148.7, 134.0, 132.5, 131.4, 130.7, 130.2, 130.1, 129.8, 129.1, 128.7, 126.1, 125.7, 124.9, 121.2, 116.6, 114.8, 51.5, 50.6. HRMS calculated for $C_{22}H_{18}N_5O_2$ $[M+H]^+$: 384.1455; found $[M+H]^+$: 384.1457.

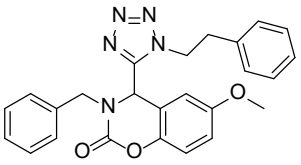
3-benzyl-7-bromo-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3] oxazin-2-one (2l)



Synthesized according to procedure B from 0.20 mmol reaction as white solid, yield: 87mg (89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.26 – 7.16 (m, 5H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.95 – 6.90 (m, 2H), 6.87 (d, *J* = 2.3 Hz, 1H), 6.13 (s, 1H), 4.85 (d, *J* = 15.0

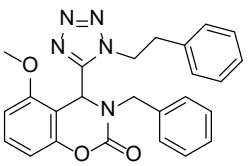
Hz, 1H), 4.20 – 4.00 (m, 2H), 3.84 (d, *J* = 15.0 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.87 – 2.80 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 148.5, 147.7, 135.5, 134.2, 133.8, 129.1, 129.1, 129.1, 128.8, 128.8, 128.6, 127.5, 118.7, 117.9, 116.5, 51.4, 50.9, 49.4, 35.2. HRMS calculated for $C_{24}H_{21}BrN_5O_2$ $[M+H]^+$: 490,0873; found $[M+H]^+$: 490,0877.

3-benzyl-7-methoxy-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2m)



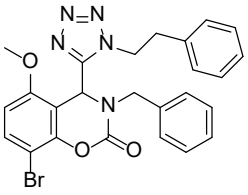
Synthesized according to procedure B from 0.23 mmol reaction as white solid, yield: 96mg (95%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.25 (m, 5H), 7.25 – 7.16 (m, 3H), 7.09 (d, *J* = 9.1 Hz, 1H), 6.96 – 6.91 (m, 2H), 6.89 (dd, *J* = 9.1, 2.9 Hz, 1H), 6.23 (d, *J* = 2.9 Hz, 1H), 6.22 (s, 1H), 4.86 (d, *J* = 14.9 Hz, 1H), 4.24 – 4.01 (m, 2H), 3.87 (d, *J* = 14.9 Hz, 1H), 3.61 (s, 3H), 2.99 – 2.85 (m, 1H), 2.78 – 2.66 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.8, 152.6, 149.2, 142.3, 135.5, 134.2, 129.0, 128.9, 128.9, 128.6, 127.3, 118.1, 117.7, 114.8, 109.8, 55.7, 52.2, 50.8, 49.2, 35.1. HRMS calculated for $C_{25}H_{24}N_5O_3$ $[M+H]^+$: 442.1874; found $[M+H]^+$: 442.1875

3-benzyl-5-methoxy-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2n)



Synthesized according to procedure B from 0.23 mmol reaction as off white solid, yield: 100mg (99%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.27 – 7.18 (m, 5H), 6.97 – 6.91 (m, 2H), 6.68 – 6.63 (m, 2H), 6.59 (dd, *J* = 8.6, 2.5 Hz, 1H), 6.18 (s, 1H), 4.84 (d, *J* = 15.0 Hz, 1H), 4.14 – 3.99 (m, 2H), 3.88 (d, *J* = 15.0 Hz, 1H), 3.79 (s, 3H), 2.99 – 2.87 (m, 1H), 2.74 – 2.64 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.5, 152.9, 149.5, 148.9, 135.7, 134.2, 129.0, 128.9, 128.6, 128.6, 127.3, 112.4, 106.2, 101.5, 55.7, 51.8, 50.9, 49.2, 35.2. HRMS calculated for $C_{25}H_{24}N_5O_3$ $[M+H]^+$: 442.1874 ; found $[M+H]^+$: 442.1876.

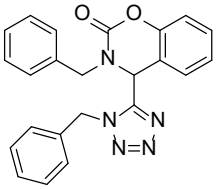
3-benzyl-8-bromo-5-methoxy-4-(1-phenethyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2o)



Synthesized according to procedure B from 0.19 mmol reaction as off white solid, yield: 98mg (99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 3H), 7.26 – 7.17 (m, 5H), 6.99 (d, *J* = 2.1 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.12

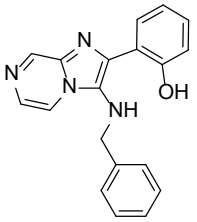
(s, 1H), 4.85 (d, *J* = 15.0 Hz, 1H), 4.19 – 4.06 (m, 2H), 3.90 (s, 3H), 3.79 (d, *J* = 15.0 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.84 – 2.73 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.3, 148.2, 137.5, 135.5, 133.9, 129.0, 129.0, 128.9, 128.7, 128.6, 128.5, 127.4, 119.7, 117.8, 116.8, 116.4, 56.4, 51.5, 50.8, 49.4, 35.3. HRMS calculated for $C_{25}H_{23}BrN_5O_3$ $[M+H]^+$: 520.0979; found $[M+H]^+$: 520.0981.

3-benzyl-4-(1-benzyl-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (2p)



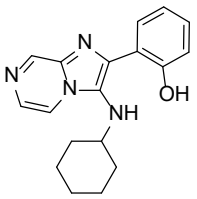
Synthesized according to procedure B from 0.27 mmol reaction as white solid, yield: 80mg (75%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 3H), 7.30 – 7.14 (m, 6H), 7.01 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.93 (td, *J* = 7.6, 1.2 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.65 – 6.55 (m, 1H), 6.23 (s, 1H), 5.29 (d, *J* = 15.6 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.83 (d, *J* = 15.0 Hz, 1H), 3.78 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.6, 149.0, 148.5, 134.0, 132.1, 130.8, 129.0, 128.9, 128.9, 128.7, 127.0, 126.3, 125.1, 116.9, 114.1, 51.8, 51.5, 50.8. HRMS calculated for $C_{23}H_{20}N_5O_2$ $[M+H]^+$: 398.1612; found $[M+H]^+$: 398.1608.

2-(3-(benzylamino)imidazo[1,2-a]pyrazin-2-yl)phenol (3a)



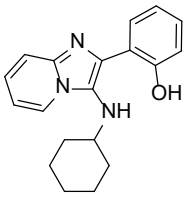
Synthesized according to procedure C from 1 mmol reaction as brown solid, yield: 272mg (86%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, *J* = 1.4 Hz, 1H), 7.95 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.83 – 7.69 (m, 2H), 7.34 – 7.26 (m, 5H), 7.25 – 7.19 (m, 1H), 7.02 (dd, *J* = 8.3, 1.3 Hz, 1H), 6.87 (td, *J* = 7.5, 1.3 Hz, 1H), 4.19 (d, *J* = 5.7 Hz, 2H), 3.59 (t, *J* = 6.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 142.1, 138.4, 137.8, 134.4, 130.1, 129.7, 129.0, 128.2, 128.0, 126.2, 125.7, 119.2, 117.8, 116.2, 114.9, 52.1. MS (ESI) m/z calculated for $C_{19}H_{17}N_4O$ $[M+H]^+$: 317.13; found $[M+H]^+$: 317.34.

2-(3-(cyclohexylamino)imidazo[1,2-a]pyrazin-2-yl)phenol (3b)



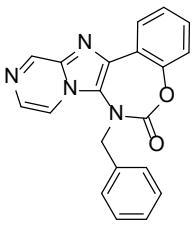
Synthesized according to procedure C from 1 mmol reaction as brown solid, yield: 240mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.03 – 7.97 (m, 2H), 7.88 (d, *J* = 4.6 Hz, 1H), 7.26 – 7.20 (m, 1H), 7.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.89 (td, *J* = 7.6, 1.3 Hz, 1H), 3.24 (s, 1H), 3.06 – 2.96 (m, 1H), 1.82 – 1.75 (m, 2H), 1.74 – 1.67 (m, 2H), 1.63 – 1.56 (m, 1H), 1.34 – 1.27 (m, 2H), 1.22 – 1.09 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.4, 142.0, 138.3, 134.6, 130.0, 129.6, 126.6, 125.1, 119.0, 117.8, 116.5, 115.3, 56.9, 34.1, 25.5, 24.8. MS (ESI) m/z calculated for $C_{18}H_{21}N_4O$ $[M+H]^+$: 309.16; found $[M+H]^+$: 309.36.

2-(3-(cyclohexylamino)imidazo[1,2-a]pyridin-2-yl)phenol (3c)



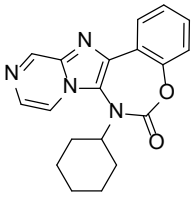
Synthesized according to procedure C from 1 mmol reaction as brown solid, yield: 298mg (97%);^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 6.8, 1.3 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.41 (dd, *J* = 9.0, 1.2 Hz, 1H), 7.21 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.14 (ddd, *J* = 9.0, 6.8, 1.3 Hz, 1H), 7.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.89 (td, *J* = 7.5, 1.3 Hz, 1H), 6.80 (td, *J* = 6.7, 1.2 Hz, 1H), 2.99 (tt, *J* = 10.6, 3.8 Hz, 1H), 1.83 – 1.73 (m, 2H), 1.73 – 1.62 (m, 2H), 1.60 – 1.52 (m, 1H), 1.34 – 1.22 (m, 2H), 1.21 – 1.07 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 139.4, 136.0, 129.1, 126.3, 124.6, 123.4, 122.5, 118.7, 117.7, 117.4, 116.6, 112.3, 56.9, 34.1, 25.7, 24.8. MS (ESI) m/z calculated for $C_{19}H_{22}N_3O$ $[M+H]^+$: 308.17; found $[M+H]^+$: 308.38.

7-benzylbenzo[f]pyrazino[2',1':2,3]imidazo[4,5-d][1,3]oxazepin-6(7H)-one (4a)



Synthesized according to procedure B from 0.32 mmol reaction as brown solid, yield: 24mg (22%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.96 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.92 (d, *J* = 4.7 Hz, 1H), 7.82 (dt, *J* = 4.7, 1.1 Hz, 1H), 7.55 – 7.48 (m, 1H), 7.47 – 7.39 (m, 2H), 7.21 – 7.11 (m, 3H), 7.00 – 6.93 (m, 2H), 5.04 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.7, 151.8, 144.6, 137.8, 135.9, 134.5, 131.5, 130.0, 128.9, 128.4, 127.2, 126.9, 126.9, 124.7, 122.4, 122.0, 115.6, 51.9. HRMS calculated for $C_{20}H_{15}N_4O_2$ $[M+H]^+$: 343.1190; found $[M+H]^+$: 343.1189.

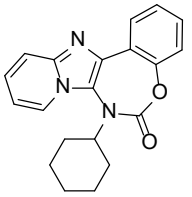
7-cyclohexylbenzo[f]pyrazino[2',1':2,3]imidazo[4,5-d][1,3]oxazepin-6(7H)-one (4b)



Synthesized according to procedure B from 0.32 mmol reaction as brown solid, yield: 45mg (42%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.11 – 7.96 (m, 2H), 7.82 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.52 (td, *J* = 7.7, 1.8 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 (dd, *J* = 8.1, 1.3 Hz, 1H), 3.32 (tt, *J* = 12.1, 3.7 Hz, 1H), 2.62 – 2.46 (m, 1H), 2.14 (m, 1H), 2.03 – 1.91 (m, 2H), 1.84 – 1.71 (m, 1H), 1.68 – 1.61 (m, 1H), 1.59 – 1.48 (m, 1H), 1.35 – 1.28 (m, 1H), 1.24 – 1.09 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.4, 152.2, 144.6, 137.8, 135.8, 131.4, 130.2, 127.0, 126.9, 124.7, 123.0, 122.4, 115.4, 62.6, 30.6, 28.8, 26.2, 25.7, 24.8. HRMS calculated for $C_{19}H_{19}N_4O_2$ $[M+H]^+$: 335.1503 ; found $[M+H]^+$: 335.1504.

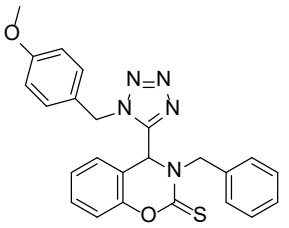
7-cyclohexylbenzo[f]pyrido[2',1':2,3]imidazo[4,5-d][1,3]oxazepin-6(7H)-one (4c)

Synthesized according to procedure B from 0.33 mmol reaction as off white solid, yield: 51mg (47%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.4, 1.9 Hz, 1H), 7.91 – 7.84 (m, 1H),



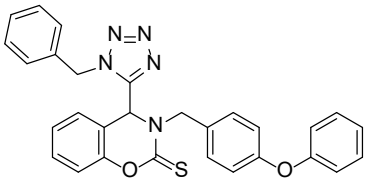
7.70 (dd, *J* = 9.1, 1.2 Hz, 1H), 7.49 – 7.36 (m, 3H), 7.31 – 7.23 (m, 1H), 6.96 (td, *J* = 6.9, 1.2 Hz, 1H), 3.28 (tt, *J* = 12.1, 3.7 Hz, 1H), 2.61 – 2.49 (m, 1H), 2.20 – 2.10 (m, 1H), 1.99 – 1.87 (m, 2H), 1.75 – 1.66 (m, 1H), 1.64 – 1.56 (m, 1H), 1.56 – 1.47 (m, 1H), 1.33 – 1.22 (m, 2H), 1.15 – 1.07 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 151.9, 143.0, 133.5, 130.5, 126.7, 126.6, 125.5, 124.5, 122.3, 121.9, 118.5, 113.2, 62.5, 30.6, 28.6, 26.2, 25.7, 24.9. HRMS calculated for $C_{20}H_{20}N_3O_2$ $[M+H]^+$: 334.1550; found $[M+H]^+$: 334.1550.

3-benzyl-4-(1-(4-methoxybenzyl)-1H-tetrazol-5-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-2- thione (5a)



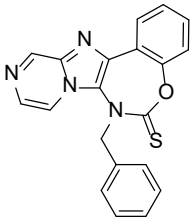
Synthesized according to procedure D from 0.25 mmol reaction as pale yellow solid, yield: 85mg (77%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 2H), 7.36 – 7.32 (m, 3H), 7.31 – 7.27 (m, 1H), 7.08 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.98 (td, *J* = 7.6, 1.2 Hz, 1H), 6.82 – 6.75 (m, 2H), 6.73 – 6.66 (m, 2H), 6.61 (dt, *J* = 7.7, 1.1 Hz, 1H), 6.23 (s, 1H), 5.95 (d, *J* = 15.0 Hz, 1H), 5.24 (d, *J* = 15.4 Hz, 1H), 5.15 (d, *J* = 15.4 Hz, 1H), 4.21 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 159.9, 152.0, 147.3, 133.0, 131.1, 129.1, 128.9, 128.7, 128.6, 126.1, 125.9, 123.9, 116.5, 114.4, 114.2, 56.8, 55.4, 51.3, 51.1. HRMS calculated for $C_{24}H_{22}N_5O_2S$ $[M+H]^+$: 444.1489; found $[M+H]^+$: 444.1493.

4-(1-benzyl-1H-tetrazol-5-yl)-3-(4-phenoxybenzyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-2- thione (5b)



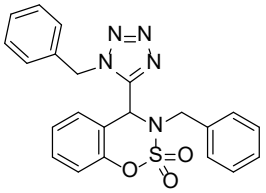
Synthesized according to procedure D from 0.22 mmol reaction as pale brown solid, yield: 97mg (89%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.22 (m, 3H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.08 – 6.97 (m, 4H), 6.96 – 6.87 (m, 2H), 6.86 – 6.71 (m, 2H), 6.51 (d, *J* = 7.7 Hz, 1H), 6.27 (s, 1H), 4.24 (t, *J* = 7.3 Hz, 2H), 3.21 – 3.09 (m, 1H), 2.90 – 2.78 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.2, 158.2, 155.6, 152.8, 148.0, 136.9, 135.7, 131.4, 130.1, 129.2, 128.8, 128.5, 127.5, 126.0, 124.5, 120.0, 119.2, 116.8, 115.1, 56.0, 49.2, 35.4. HRMS calculated for $C_{29}H_{24}N_5O_2S$ $[M+H]^+$: 506.1645; found $[M+H]^+$: 506.1647.

7-benzylbenzo[f]pyrazino[2',1':2,3]imidazo[4,5-d][1,3]oxazepine-6(7H)-thione (5c)



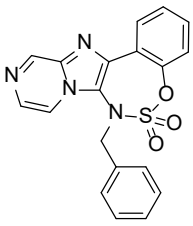
Synthesized according to procedure D from 0.32 mmol reaction as brown solid, yield: 95mg (84%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.97 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.90 (d, *J* = 4.8 Hz, 1H), 7.81 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.8 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.23 – 7.13 (m, 3H), 7.06 – 6.98 (m, 2H), 5.78 – 5.58 (m, 1H), 5.40 – 5.23 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.7, 154.0, 144.6, 137.5, 137.1, 133.4, 132.1, 130.3, 128.8, 128.3, 127.5, 126.7, 126.7, 125.5, 123.5, 122.1, 115.9, 56.1. HRMS calculated for $C_{20}H_{15}N_4OS$ $[M+H]^+$: 359.0961; found $[M+H]^+$: 359.0962.

3-benzyl-4-(1-benzyl-1H-tetrazol-5-yl)-3,4-dihydrobenzo[e][1,2,3]oxathiazine 2,2-dioxide (6a)



Synthesized according to procedure E from 0.27 mmol reaction as yellow solid, yield: 53mg (45%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 1H), 7.58 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 – 7.30 (m, 2H), 7.30 – 7.29 (m, 2H), 7.21 – 7.17 (m, 3H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.08 (d, *J* = 1.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.2, 1.2 Hz, 1H), 5.54 (d, *J* = 15.4 Hz, 1H), 5.48 (d, *J* = 15.4 Hz, 1H), 5.38 (s, 1H), 3.58 (d, *J* = 12.8 Hz, 1H), 3.55 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 147.2, 138.2, 137.5, 133.2, 131.7, 131.0, 130.4, 130.1, 129.2, 129.1, 128.9, 128.7, 128.5, 127.6, 127.5, 120.6, 118.3, 51.6, 51.0, 49.8. HRMS calculated for $C_{22}H_{20}N_5O_3S$ $[M+H]^+$: 434.1281; found $[M+H]^+$: 434.1284.

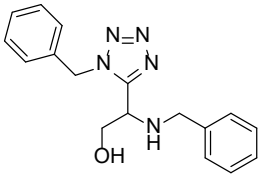
7-benzyl-7H-benzo[f]pyrazino[2',1':2,3]imidazo[4,5-d][1,2,3]oxathiazepine 6,6-dioxide (6b)



Synthesized according to procedure E from 0.32 mmol reaction as brown solid, yield: 39mg (33%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.37 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.69 (d, *J* = 4.7 Hz, 1H), 7.46 (td, *J* = 7.6, 1.9 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (dd, *J* = 4.6, 1.5 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.19 – 7.12 (m, 2H), 7.07 – 6.98 (m, 2H), 4.79 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.2, 144.0, 138.6, 132.9, 131.1, 129.9, 129.6, 129.3, 129.2, 129.0, 127.1, 122.5, 121.8, 119.1, 115.2, 58.9. HRMS calculated for $C_{19}H_{15}N_4O_3S$ $[M+H]^+$: 379.0859; found $[M+H]^+$: 379.0859.

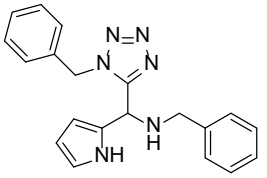
2-(1-benzyl-1H-tetrazol-5-yl)-2-(benzylamino)ethan-1-ol (7a)

Synthesized according to procedure A from 1 mmol reaction as brown solid, yield:



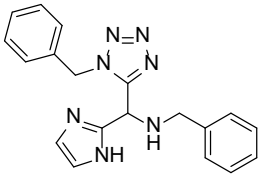
186mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 6H), 7.19 – 7.15 (m, 2H), 7.11 – 7.04 (m, 2H), 5.60 (d, *J* = 15.2 Hz, 1H), 5.49 (d, *J* = 15.2 Hz, 1H), 4.00 (t, *J* = 5.4 Hz, 1H), 3.84 (dd, *J* = 11.3, 5.4 Hz, 1H), 3.78 (dd, *J* = 11.3, 5.4 Hz, 1H), 3.65 (d, *J* = 13.1 Hz, 1H), 3.53 (d, *J* = 13.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.1, 138.8, 133.7, 129.1, 128.8, 128.6, 128.3, 127.7, 127.5, 62.3, 53.4, 51.1, 51.0. MS (ESI) m/z calculated for $C_{17}H_{20}N_5O$ $[M+H]^+$: 310.06; found $[M+H]^+$: 310.27.

N-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-1-(1H-pyrrol-2-yl)methanamine (7b)



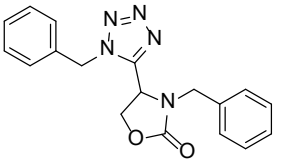
Synthesized according to procedure A from 1 mmol reaction as brown solid, yield: 255mg (74%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 7H), 7.16 – 7.12 (m, 2H), 6.98 – 6.94 (m, 2H), 6.76 (s, 1H), 6.09 (d, *J* = 3.2 Hz, 1H), 6.00 (d, *J* = 3.4 Hz, 1H), 5.38 (d, *J* = 15.3 Hz, 1H), 5.32 (d, *J* = 15.3 Hz, 1H), 5.10 (s, 1H), 3.66 – 3.52 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.4, 155.2, 138.8, 133.4, 129.1, 128.8, 128.6, 128.5, 127.7, 127.4, 126.3, 119.7, 111.3, 108.5, 108.1, 51.0, 50.6, 49.6. MS (ESI) m/z calculated for $C_{20}H_{21}N_6$ $[M+H]^+$: 345.17; found $[M+H]^+$: 345.29.

N-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-1-(1H-imidazol-2-yl)methanamine (7c)



Synthesized according to procedure A from 1 mmol reaction as brown solid, yield: 276mg (80%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 3H), 7.21 – 7.15 (m, 3H), 7.13 – 7.02 (m, 4H), 6.97 (s, 2H), 5.62 (d, *J* = 2.3 Hz, 2H), 5.43 (s, 1H), 3.62 – 3.51 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 143.9, 138.4, 133.3, 129.0, 128.8, 128.5, 128.4, 128.1, 127.4, 51.3, 50.9, 50.7. MS (ESI) m/z calculated for $C_{19}H_{20}N_7$ $[M+H]^+$: 346.17; found $[M+H]^+$: 346.36.

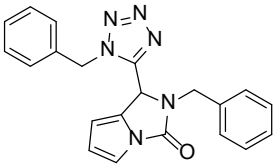
3-benzyl-4-(1-benzyl-1H-tetrazol-5-yl)oxazolidin-2-one (8a)



Synthesized according to procedure B from 0.32 mmol reaction as off white solid, yield: 80mg (74%);^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 6H), 7.11 – 6.98 (m, 4H), 5.45 (d, *J* = 15.5 Hz, 1H), 4.94 (dd, *J* = 9.3, 6.6 Hz, 1H), 4.90 (d, *J* = 15.5 Hz, 1H), 4.72 (d, *J* = 15.0 Hz, 1H), 4.14 (t, *J* = 9.3 Hz, 1H), 3.87 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.82 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.9, 151.8, 134.0, 132.7, 129.6, 129.5, 129.2, 128.7, 128.6, 127.3, 65.1, 51.5, 49.2, 47.1. HRMS calculated

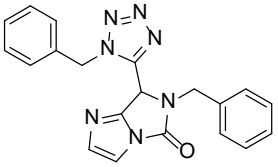
for $C_{18}H_{18}N_5O_2$ $[M+H]^+$: 336.1455; found $[M+H]^+$: 336.1460.

2-benzyl-1-(1-benzyl-1H-tetrazol-5-yl)-1,2-dihydro-3H-pyrrolo[1,2-c]imidazol-3-one (8b)



Synthesized according to procedure F from 0.29 mmol reaction as brown solid, yield: 106mg (99%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.28 (m, 6H), 7.22 (d, *J* = 3.0 Hz, 1H), 7.16 (dd, *J* = 6.6, 3.0 Hz, 2H), 6.85 (d, *J* = 1.8 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 6.37 (t, *J* = 3.1 Hz, 1H), 5.95 (s, 1H), 5.89 – 5.85 (m, 1H), 5.22 (d, *J* = 15.3 Hz, 1H), 4.53 (d, *J* = 5.6 Hz, 1H), 4.50 (d, *J* = 5.6 Hz, 1H), 3.62 (d, *J* = 15.3 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 150.0, 134.6, 132.4, 129.1, 129.1, 129.0, 128.8, 128.5, 127.1, 126.8, 116.3, 113.2, 105.1, 51.6, 49.2, 45.9. HRMS calculated for $C_{21}H_{19}N_6O$ $[M+H]^+$: 371.1615 ; found $[M+H]^+$: 371.1617.

6-benzyl-7-(1-benzyl-1H-tetrazol-5-yl)-6,7-dihydro-5H-imidazo[1,5-a]imidazol-5-one (8c)



Synthesized according to procedure F from 0.29 mmol reaction as pink solid, yield: 65mg (60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 1.5 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.29 – 7.24 (m, 3H), 7.24 – 7.18 (m, 3H), 7.06 – 7.01 (m, 2H), 6.96 – 6.91 (m, 2H), 5.74 (d, *J* = 15.6 Hz, 1H), 5.57 (s, 1H), 5.26 (d, *J* = 15.6 Hz, 1H), 4.94 (d, *J* = 15.0 Hz, 1H), 4.08 (d, *J* = 15.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 148.3, 146.5, 135.1, 134.1, 132.0, 129.3, 129.2, 129.2, 128.7, 128.6, 127.1, 112.7, 51.8, 49.2, 46.0. HRMS calculated for $C_{20}H_{18}N_7O$ $[M+H]^+$: 372.1567; found $[M+H]^+$: 372.1567.

X-RAY STRUCTURE DETERMINATION

X-ray diffraction data for single crystals of compounds **2a**, **2b**, **2e**, **2k**, **2m**, and **8a** was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.71073 Å) for **2b**, **2m**, and **8a**, and CuKα radiation source (λ = 1.54184 Å) for **2a**, **2e**, and **2k**. Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments, performed at 130(2) K for all but **2m**, in case of which temperature 120(2) K was applied. The obtained data set was processed with CrysAlisPro software[S1]. The phase problem was solved by direct methods using SUPERFLIP[S2] or SIR2004[S3]. Parameters of obtained models were refined by full-matrix least-squares on F2 using SHELXL-2014/6[S4]. Calculations were performed using WinGX integrated system (ver. 2014.1)[S5]. Figure was prepared with Mercury 3.7 software[S6].

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter Uiso[H] = 1.2 (or 1.5 (methyl groups only)) Ueq[C]. The molecular geometry (asymmetric unit for all but **2a** and**2e**) observed in the crystal structure is shown in **Figure S1**.

The presented compounds are chiral. All crystallise as racermic mixtures in centrosymmetric space groups. The only exception is observed for **2e**, which crystalise in the non-centrosymmetric space group Pc, with both enantiomers in the asymmetric unit. This space group is one of known non-centrosymmetric racemates example. [S7]

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1957565 (**2a**), CCDC 1957198 (**2b**), CCDC 1957562 (**2e**), CCDC 1957563 (**2k**), CCDC 1957561 (**2m**) and CCDC 1957199 (**8a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

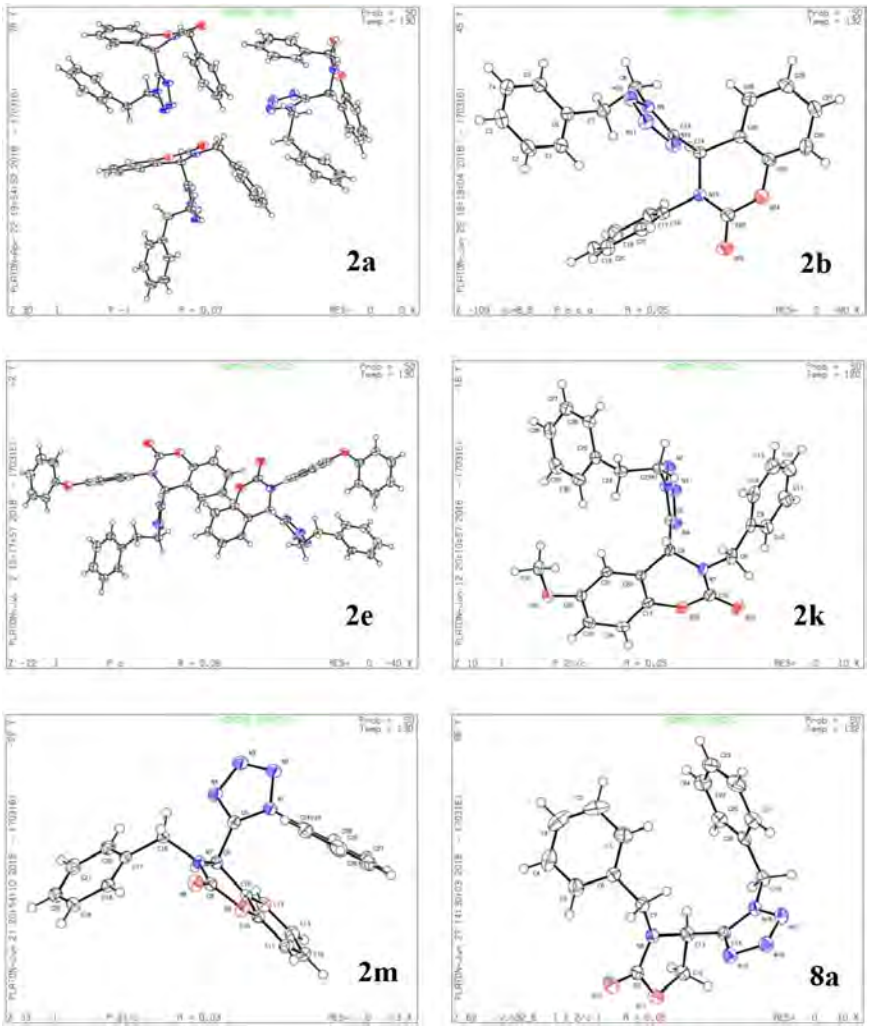


Figure S1. Molecular structure of 2a, 2b, 2e, 2k, 2m, and 8a according to X-ray diffraction study.

Acknowledgements

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Exploration of the chemical space of cyclic and noncyclic molecules

In order to explore the physicochemical differences among the two groups of molecules synthesized in this paper, virtual library synthesis of each 1000 molecules for all scaffold described in the manuscript were formed using ChemaxonR reactor software and a total of 14 descriptors were calculated for each data set using rdkit (https://www.rdkit.org/) (**Figure S3** and **S4**). Major differences of cyclic molecules against their non-cyclic counterparts were a reduction of the number of hydrogen bond donors (NumHDonors) and the number of rotatable bonds (NumRotableBonds), and an increment in the number of heteroatoms (NumHeteroatoms). The explanation of this phenomenon is the loss of hydrogen bond donors in order to the formation of the heterocycle. As a consequence, the number of rotatable bonds decreases and the number of heteroatoms increases. For Instance, an increment in the topological polar surface area (TPSA) and an increment of LogP which have been reported as an enhancement of molecular polarity and improvement to pierce the cell membrane [S8].

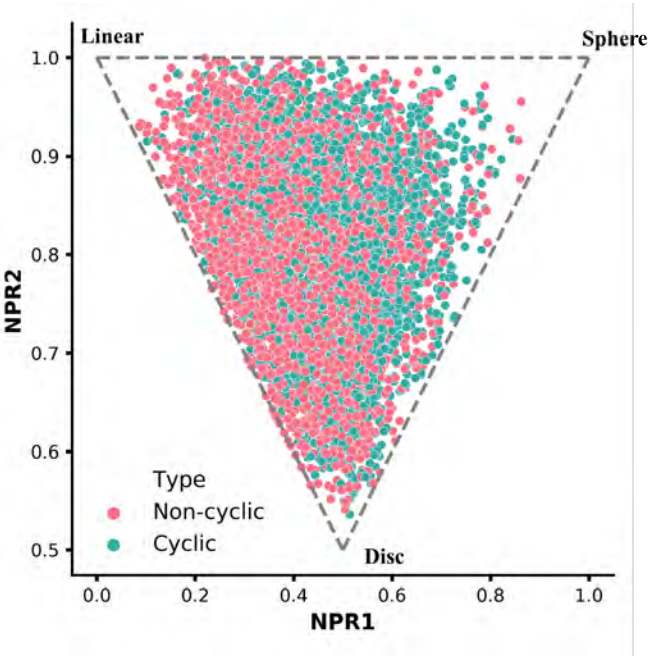

Figure S2. Normalized NPR1 vs NPR2 plot of cyclic and non-cyclic molecules. Cyclic molecules (green) showed a different distribution against no-cyclic molecules (pink).

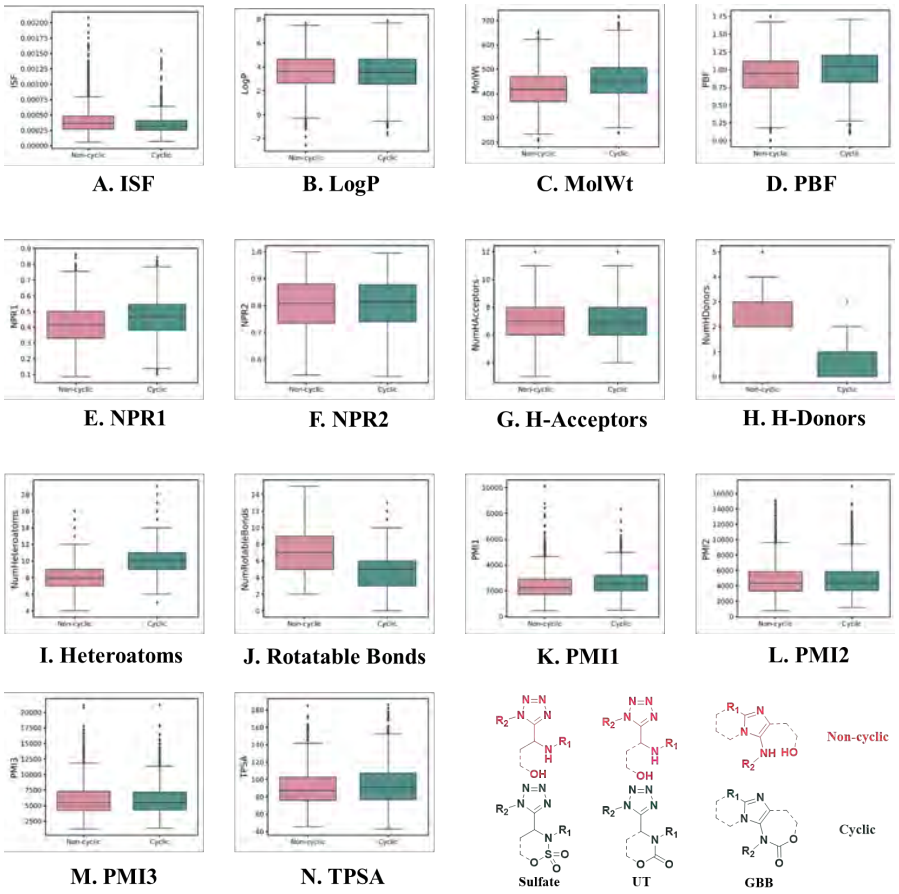

Figure S3. Cheminformatics analysis plot of cyclic and noncyclic molecules. Cyclic molecules (green) showed a different distribution against nocyclic molecules (pink). A: Inertial shape factor; B: LogP; C: Molecular weight; D: Plane of best fit; E: Normalized principal moments ratio 1; F: Normalized principal moments ratio 2; G: Number of hydrogen acceptors; H: Number of Hydrogen donners; I: Number of hetero atoms; *J*: Number of rotatable bonds; K: Principal moments of inertia 1; L: Principal moments of inertia 2; M: Principal moments of inertia 3; N: Topological polar surface area.

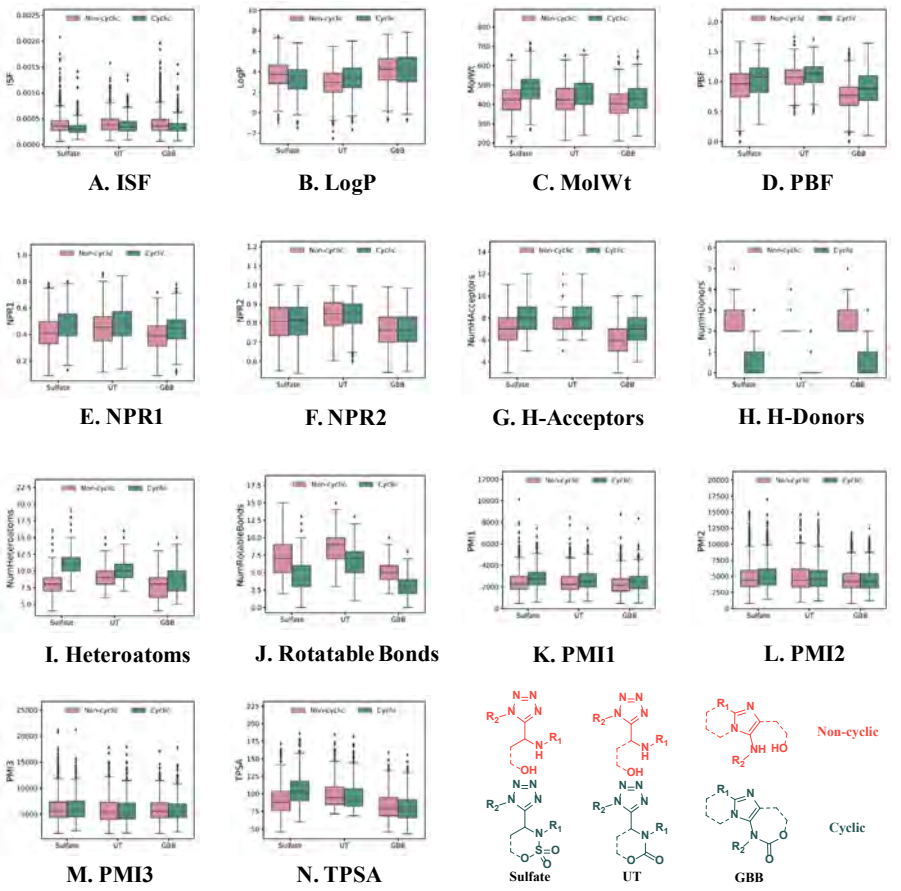

Figure S4. Cheminformatics analysis plot of Sulfate, Ugi-tetrazole (UT) and GBB molecules. Cyclic molecules (green) showed a different distribution against noncyclic molecules (red). A: Inertial shape factor; B: LogP; C: Molecular weight; D: Plane of best fit; E: Normalized principal moments ratio 1; F: Normalized principal moments ratio 2; G: Number of hydrogen acceptors; H: Number of Hydrogen donners; I: Number of hetero atoms; *J*: Number of rotatable bonds; K: Principal moments of inertia 1; L: Principal moments of inertia 2; M: Principal moments of inertia 3; N: Topological polar surface area.

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