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An Ugi Reaction/Intramolecular Cyclization/Oxidation Cascade towards Tetrazole-Linked Dibenzoxazepines

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In memoriam Albert van Leusen

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Abstract A series of tetrazole-linked dibenzo[*b,f*][1,4]oxazepines is synthesized through a short sequence involving an Ugi tetrazole reaction. The intermediate tetrazole undergoes a potassium carbonate mediated S_NAr cyclization, followed by oxidation to afford the target tricyclic heterocyclic scaffold. The optimization, scope and limitations of this two-step and efficient methodology are investigated. A 1000-member library of tetrazole-linked dibenzo[*b,f*][1,4]oxazepines is generated and the physicochemical properties are analyzed. great

Key words dibenzo[*b,f*][1,4]oxazepines, Ugi tetrazole, cyclization, library, drug-like properties

The design and synthesis of dibenzo[*b,f*][1,4]oxazepines is critical in modern drug discovery.¹ The dibenzo[*b,f*][1,4]oxazepine ring system is a common pharmacophore found in CR tear gas (**A**)² and TRPA1 channel activators (**B**).³ It is also found in antipsychotics such as loxapine (**D**)⁴ and amoxapine.⁵ Recently, this heterocycle has been investigated more and more in pharmaceutical chemistry.^{6–9} On the other hand, 1,5-disubstituted tetrazoles are bioisosteres of the *cis*-amide bond of peptides^{10,11} and can also be found in various drugs such as cilostazol¹² and the antibiotics cefonicid¹³ and latamoxef.¹⁴ However, there are few studies on combining dibenzo[*b,f*][1,4]oxazepine and 1,5-disubstituted tetrazoles into a bis-heterocyclic system.^{15–19} Moreover, dibenzo[*b,f*][1,4]oxazepine is an attractive scaffold for *de novo* drug discovery due to its extended flat aromatic ring system, while having superior drug-like properties (such as cLogP and PSA) compared to its congeners (Figure 1).²⁰ Mycemycin (**C**) is an example of an anti-HIV natural product based on the tricyclic ring system.²¹

Multicomponent reactions (MCR) are powerful synthetic tools for the synthesis of complex structures in just one or a few steps and with high atom economy from more than

Figure 1 Examples, applications and properties of dibenzoxazepines and its congeners

two starting materials.^{22–24} In the field of MCRs, the Ugi reaction has become commonplace, and amongst its variations, the Ugi tetrazole version is very popular because of its high convergence in which four components can be combined into a single product through a one-pot reaction.^{25,26} Additionally, combining Ugi/ S_NAr reactions allows for complexity increase and has become a strategy for generating complex skeletons.^{27–31}

Herein, we describe the application of the Ugi tetrazole four-component reaction for the synthesis of a library of diverse analogues of tetrazole-linked dibenzo[*b,f*][1,4]oxazepines. The formation of compound **6a** was selected to establish the methodology. Thus, equimolar amounts of 2-fluoroaniline (**1a**), 2-hydroxybenzaldehyde (**2a**), isocyanide **3a** and trimethylsilyl azide (**4**) were combined sequentially in

methanol (0.5 M) at room temperature for 12 hours, with the Ugi-tetrazole product **5a** being isolated in a good yield (66%) (Table 1).

Next, we investigated the S_NAr cyclization step under different conditions using various bases to form **6a**. Interestingly, we did not observe the direct S_NAr product, even in traces, but instead the oxidized form with an imine in the 7-membered ring. We thus examined conditions described in the literature towards similar compounds.³² In our first attempts we used 4 different bases (potassium carbonate, sodium hydride, cesium carbonate and sodium carbonate) in DMF at 25 °C (Table 1, entries 1–4). However, we did not obtain the desired product. We thus increased the reaction temperature and found that the yields were significantly improved, with the desired compound **6a** being obtained in an excellent yield of 81% (entry 6). On shortening the reaction time to 2 hours, product **6a** was obtained in only 46% yield (entry 7). After prolonging the reaction time to 12 hours, **6a** was again obtained in 81% yield (entry 8). A lower yield of the target product was obtained when the amount of potassium carbonate was decreased to one equivalent (entry 9). Surprisingly, increasing the temperature to 120 °C and extending the reaction time to 12 hours did not im-

prove the yield (entry 10). We also utilized other bases in DMF at 100 °C, but the reaction yields were not as good as those obtained using potassium carbonate. We also used acetonitrile instead of DMF as the solvent, but again a lower yield was obtained (entry 14). Finally, we converted the two-step reaction into a one-pot reaction. Thus we changed the solvent for the first step to DMF and, after 12 hours, added potassium carbonate and continued stirring the reaction for 6 hours at 100 °C. However, the final yield was only 23%, being worse than the overall yield of the 2-step reaction. Thus, the best conditions for the second step were determined to be one equivalent of the Ugi product and two equivalents of potassium carbonate in non-degassed DMF at 100 °C for 6 hours. For the second step, i.e., the cyclization, we used K_2CO_3 as the base and DMF as the solvent, with the reaction being conducted at 100 °C under open-flask conditions. Not surprisingly, we isolated the oxidized dibenzo[*b,f*][1,4]oxazepane and not the 10,11-dihydrodibenzo[*b,f*][1,4]oxazepane. We believe that the oxidation of the final cyclized product occurs in the presence of aerial oxygen. Oxidation of Ugi intermediates at room temperature is unknown. Moreover, oxidation of the Ugi product would likely hinder the cyclization step due to the confor-

Table 1 Optimization of the Conditions for the Formation of **6a**

Entry	Base	Amount (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	K_2CO_3	2	DMF	25	6	trace
2	NaH	2	DMF	25	6	trace
3	Cs_2CO_3	2	DMF	25	6	trace
4	Na_2CO_3	2	DMF	25	6	trace
5	K_2CO_3	2	DMF	50	6	21
6	K_2CO_3	2	DMF	100	6	81
7	K_2CO_3	2	DMF	100	2	46
8	K_2CO_3	2	DMF	100	12	81
9	K_2CO_3	1	DMF	100	6	59
10	K_2CO_3	2	DMF	120	12	78
11	NaH	2	DMF	100	6	44
12	Na_2CO_3	2	DMF	100	12	66
13	Cs_2CO_3	2	DMF	100	12	59
14	K_2CO_3	2	MeCN	100	6	34

mational rigidity of the intermediate. Similar spontaneous oxidations leading to highly conjugated systems were previously described in the MCR literature.^{33–35}

With optimized conditions in hand, the scope and limitations of the two-step synthesis was examined. A series of dibenzo[*b,f*][1,4]oxazepines (**6a–l**) was synthesized in good to excellent yields through the cyclization of Ugi-tetrazole products **5a–l**. As shown in Schemes 1 and 2, the scope of the substrates was evaluated using diverse 2-fluoroanilines **1**, 2-hydroxybenzaldehydes **2** and isocyanides **3**. As for the second step, the cyclization, the highest yield of 88% was observed for product **6d**, while the lowest yield of 54% was obtained for compound **6l**. Comparing products **5a–d**, we can see that the presence of an electron-withdrawing group on the 2-fluoroaniline leads to a low yield in the initial Ugi step, while the yield of the second step was satisfactory. In addition, when comparing products **5e** and **5h**, we can deduce that the electron-withdrawing group on the 2-fluoroaniline results in a decreased yield of the initial Ugi step when an aryl isocyanide was used. Surprisingly, the yield of **6g** (84%) was much higher than the yield of **6e** (55%). Amongst the aliphatic isocyanide starting materials, *tert*-

butyl isocyanide and 2,2,4,4-tetramethylbutyl isocyanide performed better than cyclohexyl isocyanide during the initial Ugi step.

Physicochemical properties are of uttermost importance for drug-like compounds.³⁶ Therefore, several physicochemical parameters such as molecular weight, lipophilicity, number of rotatable bonds and the polar surface area were calculated for a random 1000-member virtual library of our novel scaffolds using JChem Reactor and DataWarrior software (see Figure S2 in the Supporting Information).^{37,38} Accordingly, 74% of the compounds were within the rule of five, which is widely used to enrich compounds for oral bioavailability.³⁹ Calculation of cLogP and molecular weight is one of the simplest ways to look into the drug-likeness of a compound library. Figure 2, A shows the distribution of the compounds with respect to the lipophilicity and the molecular weight. Lipophilicity and molecular weight are key parameters determining important drug properties such as oral bioavailability and metabolism. The 'sweet spot' relates to compounds with cLogP ≤ 3 and molecular weight ≤ 500 Daltons, where 48% of the compounds are situated. We analyzed some basic param-

Scheme 1 Synthesis of Ugi-tetrazole products

ters such as the topological polar surface area (TPSA) and cLogP, which are known to describe the molecular polarity and are responsible for solubility and transport (Figure 2, B). Preferred value areas are cLogP ≤ 3 and TPSA $>75 \text{ \AA}$, and 45% of the compounds are in this safe area.

Many of the dibenzoxazepines have been previously used in central nervous system (CNS) applications. Therefore we also used the central nervous system multiparameter optimization (CNS MPO) desirability tool, which has been previously used to increase the percentage of compounds nominated for clinical development that exhibit alignment of ADME (absorption, distribution, metabolism and excretion) attributes, cross the blood–brain barrier, and reside in lower-risk safety space (Figure 2, C).⁴⁰ The CNS MPO desirability score increased from low (≤ 1) to high (>5) scores, and the great majority of the compounds of the virtual library based on our scaffold have a very high score, indicating a high likelihood of CNS permeability.

A simple pharmacophore analysis reveals molecules with a tetrazole moiety featuring 4 hydrogen bond acceptors, a butterfly-shaped extended aromatic π -system, useful for forming π -stacking interactions, and another weak hydrogen bond acceptor introduced by the biphenyl ether oxygen (Figure 2, D).

In summary, a short, two-step, MCR-based synthetic method for the synthesis of 11-(1*H*-tetrazol-5-yl)dibenzo[*b,f*][1,4]oxazepines has been developed. The scope and limitations of the synthesis regarding compatible functional groups and building blocks have been elaborated with the formation of 12 compounds. Chemoinformatic analysis revealed a highly drug-relevant chemical space. The combination of low molecular weight and low hydrogen-bond donor content makes these compounds likely to be CNS permeable. Considering the potential of 11-(1*H*-tetrazol-5-yl)dibenzo[*b,f*][1,4]oxazepine derivatives in drug discovery, this method provides a simple and efficient access to these molecules from rapidly accessible, commercially available building blocks. Efforts to apply our recently developed automated nano synthesis to this two-step sequence are ongoing and will be reported in due course.⁴¹

Reagents were obtained from commercial suppliers and were used without any purification unless otherwise noted. All isocyanides were prepared in-house from their formamides using our recently published improved procedure.⁴¹ Other reagents were purchased from Sigma Aldrich, ABCR, Acros, Fluorochem and AK Scientific, and were used without further purification. Flash chromatography was performed on a Grace Reveleris X2 using Grace Reveleris Silica

Figure 2 Some chemoinformatic and topological features of a random 1000-compound tetrazolo-dioxazepine library. (A) Distribution of the tetrazolo-dibenzoxazepine library across cLogP and molecular weight (dark green dots indicate 'preferred' property values). (B) Distribution of the tetrazolo-dibenzoxazepine library across cLogP and the polar surface area (dark green dots indicate 'preferred' property values). (C) CNS MPO scores for the tetrazolo-dibenzoxazepine library. (D) General pharmacophore model for the scaffold not including the variable substituents, exemplified for compound **6k**.

columns (12 g) and a gradient of petroleum ether/ethyl acetate (0–100%) or dichloromethane/methanol (0–10%) was applied. Thin-layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μ m). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were determined using an OEM Electrothermal melting point apparatus 1A 8103 and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts for ^1H NMR spectra are reported relative to TMS (0 ppm) or the internal solvent peak (CDCl_3 : 7.26 ppm, $\text{DMSO}-d_6$: 2.50 ppm, methanol- d_4 : 3.31 ppm). Coupling constants (J) are given in hertz (Hz). The following abbreviations are used for spin multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dt = doublet triplet, dd = doublet of doublets and m = multiplet. Chemical shifts for ^{13}C NMR spectra are reported in ppm relative to the solvent peak (CDCl_3 : 77.23 ppm, $\text{DMSO}-d_6$: 39.52 ppm, methanol- d_4 : 49.00 ppm). Mass spectra were measured on a Waters Investigator Supercritical Fluid Chromatograph with a 3100 MS Detector (ESI) and using a solvent system of methanol and CO_2 on a Viridis silica gel column (4.6 $\times$ 250 mm, 5 μ m particle size). High-resolution mass spectra (HRMS) were recorded using a QTOF Bruker Maxis Plus; mass range = 100–1500 m/z , spectra rate = 2.00 Hz. Electrospray ionization mass spectra (ESI-MS) were recorded on a Waters Investigator Semi-prep 15 SFC-MS instrument.

Ugi-Tetrazole Adducts **5a–l**; General Procedure

A solution of amine **1** (1.0 mmol) and aldehyde **2** (1.0 mmol) in methanol (1 mL) was stirred at room temperature for 30 min. Next, TMSN_3 (**4**) (1.1 mmol) followed by isocyanide **3** (1.1 mmol) were added and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo and the residue purified by column chromatography to give the desired products (silica gel, PE/EtOAc, 10:1 to 2:1).

2-[[2-(2-Fluorophenyl)amino][1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]methyl]phenol (**5a**)

Yield: 296 mg (66%); yellow solid; mp 156–158 $^\circ\text{C}$.

^1H NMR (500 MHz, CDCl_3): δ = 7.68 (s, 1 H), 7.15 (td, J = 7.8, 1.6 Hz, 1 H), 7.01 (dd, J = 7.7, 1.6 Hz, 1 H), 6.97–6.92 (m, 1 H), 6.89 (dd, J = 8.2, 1.1 Hz, 1 H), 6.85–6.75 (m, 2 H), 6.73–6.61 (m, 1 H), 6.44–6.26 (m, 3 H), 6.13 (d, J = 8.5 Hz, 1 H), 5.62 (d, J = 15.2 Hz, 1 H), 5.40 (d, J = 15.2 Hz, 1 H), 5.02 (dd, J = 8.6, 2.8 Hz, 1 H), 3.81 (s, 3 H), 3.67 (s, 6 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 155.3, 154.1, 153.6, 130.4, 128.4, 128.0, 124.5, 122.6, 121.1, 119.7, 116.9, 115.1 (d, J = 18.9 Hz), 114.3, 104.8, 104.4, 60.8, 56.0, 51.6, 48.5.

HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{24}\text{FN}_5\text{O}_4$: 466.1812; found: 466.1890.

2-[[1-(3,4-Dimethoxybenzyl)-1H-tetrazol-5-yl][(2-fluorophenyl)amino]methyl]phenol (**5b**)

Yield: 305 mg (70%); yellow solid; mp 161–163 $^\circ\text{C}$.

¹H NMR (500 MHz, CDCl₃): δ = 7.81 (s, 1 H), 7.19–7.06 (m, 1 H), 7.02 (dd, J = 7.7, 1.6 Hz, 1 H), 6.95–6.88 (m, 2 H), 6.85–6.72 (m, 4 H), 6.69–6.65 (m, 1 H), 6.63 (d, J = 1.8 Hz, 1 H), 6.38–6.25 (m, 1 H), 6.13 (d, J = 8.2 Hz, 1 H), 5.63 (d, J = 15.1 Hz, 1 H), 5.39 (d, J = 15.1 Hz, 1 H), 5.02 (d, J = 5.7 Hz, 1 H), 3.84 (s, 3 H), 3.68 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 155.2, 154.1, 152.2 (d, J = 240.5 Hz), 149.5 (d, J = 8.3 Hz), 133.6, 133.7, 130.3, 128.0, 125.2, 124.4 (d, J = 3.6 Hz), 122.6, 121.1, 120.7, 119.5 (d, J = 7.0 Hz), 117.0, 115.0 (d, J = 18.6 Hz), 114.3 (d, J = 2.6 Hz), 111.2, 110.6, 55.9, 55.8, 51.3, 48.6.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₃H₂₃FN₅O₃: 436.1707; found: 436.1797.

2-[[2-(2-Fluorophenyl)amino][1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]methyl]-3-methoxyphenol (5c)

Yield: 320 mg (64%); yellow solid; mp 155–157 °C.

¹H NMR (500 MHz, CDCl₃): δ = 6.94 (dd, J = 11.5, 8.1 Hz, 1 H), 6.85–6.76 (m, 2 H), 6.71–6.68 (m, 2 H), 6.60 (d, J = 3.5 Hz, 1 H), 6.35 (s, 1 H), 6.11 (s, 2 H), 5.61 (d, J = 15.2 Hz, 1 H), 5.42 (d, J = 15.2 Hz, 1 H), 5.07 (s, 1 H), 3.80 (s, 3 H), 3.68 (s, 6 H), 3.63 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 155.2, 153.9, 153.6, 152.2 (d, J = 240.3 Hz), 147.5, 138.1, 133.6 (d, J = 11.5 Hz), 128.4, 124.5 (d, J = 3.5 Hz), 123.6, 117.8, 115.3, 115.1 (d, J = 18.7 Hz), 114.2, 113.4, 104.8, 60.8, 56.0, 55.6, 51.5, 48.4.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₆H₂₇FN₅O₅: 496.1918; found: 496.1998.

2-[[2-(2-Fluoro-5-nitrophenyl)amino][1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]methyl]-3-methoxyphenol (5d)

Yield: 142 mg (30%); yellow solid; mp 171–174 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.71 (dd, J = 7.3, 2.7 Hz, 1 H), 7.66–7.56 (m, 1 H), 7.37 (s, 1 H), 7.07 (dd, J = 10.3, 8.8 Hz, 1 H), 6.87 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 3.0 Hz, 1 H), 6.73 (d, J = 3.0 Hz, 1 H), 6.44 (s, 2 H), 6.37 (d, J = 7.4 Hz, 1 H), 5.87 (dd, J = 7.5, 3.0 Hz, 1 H), 5.61 (d, J = 15.1 Hz, 1 H), 5.41 (d, J = 15.2 Hz, 1 H), 3.80 (s, 3 H), 3.74 (s, 6 H), 3.66 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃): δ = 154.8, 154.8 (d, J = 252.0 Hz), 154.3, 153.8, 153.6, 147.0, 144.7, 138.1, 134.6 (d, J = 12.9 Hz), 128.4, 122.8, 117.2, 116.3, 115.0 (d, J = 21.2 Hz), 114.1 (d, J = 8.5 Hz), 113.0, 107.8 (d, J = 5.3 Hz), 104.8, 103.6, 60.8, 56.0, 55.6, 51.2, 45.8.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₅H₂₆FN₆O₇: 541.1769; found: 541.1840.

2-[[2-(2-Fluorophenyl)amino][1-(2-isopropylphenyl)-1H-tetrazol-5-yl]methyl]phenol (5e)

Yield: 280 mg (69%); yellow semi-solid.

¹H NMR (500 MHz, DMSO-*d*₆): δ = 9.79 (s, 1 H), 7.61–7.48 (m, 2 H), 7.39–7.33 (m, 1 H), 7.27 (s, 1 H), 7.10 (t, J = 7.7 Hz, 1 H), 7.00 (dd, J = 12.1, 8.2 Hz, 1 H), 6.77–6.66 (m, 3 H), 6.57 (t, J = 6.4 Hz, 1 H), 6.43 (t, J = 9.0 Hz, 1 H), 6.38 (dd, J = 8.3, 2.2 Hz, 1 H), 5.97 (s, 1 H), 2.20 (s, 1 H), 1.06 (s, 6 H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 156.8, 155.1, 151.5 (d, J = 239.2 Hz), 145.9, 134.9, 134.8, 131.9, 131.1, 129.5, 128.6, 127.4, 127.1, 125.0, 123.6, 119.5, 117.8, 115.5, 115.2, 115.1, 113.4, 46.4, 28.1.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₃H₂₃FN₅O: 404.1808; found: 404.1888.

2-[[1-(1-Cyclohexyl-1H-tetrazol-5-yl)][2-fluoro-4-(trifluoromethyl)phenyl]amino]methyl]-5-methylphenol (5f)

Yield: 180 mg (40%); yellow solid; mp 179–182 °C.

¹H NMR (500 MHz, CDCl₃): δ = 9.47 (s, 1 H), 7.22–7.17 (m, 2 H), 7.15 (d, J = 7.9 Hz, 1 H), 6.99 (d, J = 1.6 Hz, 1 H), 6.92 (t, J = 8.5 Hz, 1 H), 6.68 (d, J = 6.5 Hz, 1 H), 6.51 (d, J = 6.9 Hz, 1 H), 5.94 (dd, J = 7.0, 3.1 Hz, 1 H), 4.66 (t, J = 4.2 Hz, 1 H), 2.24 (s, 3 H), 2.17–2.07 (m, 2 H), 2.01–1.90 (m, 2 H), 1.75–1.69 (m, 3 H), 1.57–1.45 (m, 1 H), 1.42–1.33 (m, 2 H).

¹³C NMR (126 MHz, CDCl₃): δ = 155.1, 153.7, 151.6, 149.7, 140.9, 137.1 (d, J = 11.2 Hz), 127.6, 123.9 (d, J = 271.0 Hz), 122.2, 119.7, 119.5, 116.8, 112.2, 111.9 (d, J = 21.6 Hz), 59.2, 58.2, 45.6, 33.0, 32.7, 25.2, 24.7, 21.1.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₂H₂₄F₄N₅O: 450.1839; found: 450.1890.

2-[[2-(2-Fluoro-5-nitrophenyl)amino][1-(2-isopropylphenyl)-1H-tetrazol-5-yl]methyl]-5-methylphenol (5g)

Yield: 174 mg (38%); yellow solid; mp 197–199 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.63–7.50 (m, 5 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.10–7.05 (m, 2 H), 6.95–6.90 (m, 2 H), 6.62 (d, J = 7.8 Hz, 1 H), 5.99 (d, J = 8.0 Hz, 1 H), 5.90 (s, 1 H), 2.20 (s, 3 H), 1.14 (s, 6 H).

¹³C NMR (126 MHz, CDCl₃): δ = 156.2, 156.1, 154.1, 153.7, 146.3, 144.8 (d, J = 2.7 Hz), 141.1, 134.9 (d, J = 13.2 Hz), 131.8, 131.7, 130.4, 128.5, 127.2, 127.0, 122.2, 121.1, 117.3, 114.1 (d, J = 8.5 Hz), 108.0 (d, J = 5.2 Hz), 57.5, 47.6, 28.3, 21.1.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₄H₂₄FN₆O₃: 463.1816; found: 463.1895.

2-[[2-(1-Cyclohexyl-1H-tetrazol-5-yl)][2-(2-fluoro-5-nitrophenyl)amino]methyl]phenol (5h)

Yield: 156 mg (38%); yellow solid; mp 200–202 °C.

¹H NMR (500 MHz, DMSO-*d*₆): δ = 10.34 (s, 1 H), 7.75 (dd, J = 7.5, 2.8 Hz, 1 H), 7.57 (dd, J = 8.9, 3.3 Hz, 1 H), 7.45–7.32 (m, 2 H), 7.16 (t, J = 7.7 Hz, 1 H), 6.90 (t, J = 8.3 Hz, 2 H), 6.82 (t, J = 7.5 Hz, 1 H), 6.58 (d, J = 8.0 Hz, 1 H), 4.51 (s, 1 H), 2.06–2.08 (m, 1 H), 1.88–1.84 (m, 2 H), 1.74–1.51 (m, 3 H), 1.32–1.20 (m, 4 H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 155.2, 155.0, 154.7, 145.0, 135.9 (d, J = 13.4 Hz), 128.9, 123.2, 120.0, 116.0, 115.9, 115.8, 113.6, 108.7, 57.4, 46.1, 32.7, 26.2, 24.0.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₀H₂₂FN₆O₃: 413.1659; found: 413.1740.

2-[[2-(2-Fluorophenyl)amino][1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl]methyl]phenol (5i)

Yield: 296 mg (66%); yellow solid; mp 217–219 °C.

¹H NMR (500 MHz, methanol-*d*₄): δ = 7.44 (dd, J = 8.2, 1.6 Hz, 1 H), 7.18 (td, J = 7.7, 1.7 Hz, 1 H), 7.02–6.97 (m, 1 H), 6.94 (td, J = 7.9, 1.5 Hz, 1 H), 6.89–6.85 (m, 2 H), 6.81 (td, J = 8.4, 1.6 Hz, 1 H), 6.73–6.66 (m, 2 H), 2.31–1.99 (m, 2 H), 1.91 (s, 6 H), 0.74 (s, 9 H).

¹³C NMR (126 MHz, methanol-*d*₄): δ = 155.2, 155.0, 154.7, 145.0, 135.9 (d, J = 13.4 Hz), 128.9, 123.2, 120.0, 116.0, 115.9, 115.8, 113.6, 108.7, 57.4, 46.1, 32.7, 26.2, 24.0.

HRMS (ESI-TOF): m/z [M + H]⁺ calcd for C₂₂H₂₉FN₅O: 398.2278; found: 398.2512.

2-[[1-(*tert*-Butyl)-1H-tetrazol-5-yl][(2-fluoro-5-methoxyphenyl)amino]methyl]-5-methylphenol (5j)

Yield: 288 mg (75%); yellow solid; mp 176–179 °C.

^1H NMR (500 MHz, methanol- d_4): δ = 9.47 (s, 1 H), 7.22–7.17 (m, 2 H), 7.15 (d, J = 7.9 Hz, 1 H), 6.99 (d, J = 1.6 Hz, 1 H), 6.92 (t, J = 8.5 Hz, 1 H), 6.68 (d, J = 6.5 Hz, 1 H), 6.51 (d, J = 6.9 Hz, 1 H), 5.94 (dd, J = 7.0, 3.1 Hz, 1 H), 4.66 (t, J = 4.2 Hz, 1 H), 2.24 (s, 3 H), 2.17–2.07 (m, 2 H), 2.01–1.90 (m, 2 H), 1.75–1.69 (m, 3 H), 1.57–1.45 (m, 1 H), 1.42–1.33 (m, 2 H).

^{13}C NMR (126 MHz, methanol- d_4): δ = 156.5, 155.4, 154.2, 147.5, 140.9, 139.5, 135.0, 127.6, 121.0, 120.4, 115.3, 114.2 (d, J = 17.4 Hz), 101.0, 100.1, 62.2, 54.5, 28.5, 28.3, 19.9.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{20}\text{H}_{25}\text{FN}_5\text{O}_2$: 386.1914; found: 386.2020.

2-[[1-(2-Fluoro-4-methoxyphenyl)amino][1-(2-isopropylphenyl)-1H-tetrazol-5-yl]methyl]-5-methylphenol (5k)

Yield: 160 mg (36%); yellow semi-solid.

^1H NMR (500 MHz, methanol- d_4): δ = 7.61–7.46 (m, 2 H), 7.31 (d, J = 8.8 Hz, 2 H), 7.04 (d, J = 7.9 Hz, 1 H), 6.81 (dd, J = 11.3, 9.1 Hz, 1 H), 6.56 (d, J = 8.0 Hz, 1 H), 6.52 (s, 1 H), 6.15–6.07 (m, 2 H), 6.02 (s, 1 H), 3.56 (s, 3 H), 2.18 (s, 3 H), 1.36–1.20 (m, 1 H), 1.11 (d, J = 6.8 Hz, 3 H), 0.94–0.88 (m, 3 H).

^{13}C NMR (126 MHz, methanol- d_4): δ = 158.6, 157.7, 148.8, 147.5 (d, J = 231.8 Hz), 147.0, 141.0, 136.2, 136.1, 132.7, 132.6, 132.2, 129.0, 128.2, 128.0 (d, J = 16.9 Hz), 127.8, 121.6 (d, J = 16.8 Hz), 121.2, 116.7 (d, J = 16.0 Hz), 102.6, 101.1, 55.8, 47.6, 29.4, 21.2.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{25}\text{H}_{27}\text{FN}_5\text{O}_2$: 448.2071; found: 448.2154.

2-[[1-(tert-Butyl)-1H-tetrazol-5-yl][(4-chloro-2-fluorophenyl)amino]methyl]-5-methylphenol (5l)

Yield: 201 mg (52%); yellow semi-solid.

^1H NMR (500 MHz, CDCl_3): δ = 7.56 (s, 1 H), 7.00 (d, J = 13.2 Hz, 1 H), 6.90 (d, J = 8.6 Hz, 1 H), 6.84 (d, J = 7.8 Hz, 1 H), 6.77–6.70 (m, 2 H), 6.67 (d, J = 7.8 Hz, 1 H), 6.34 (d, J = 8.6 Hz, 1 H), 4.90 (s, 1 H), 2.26 (s, 3 H), 1.71 (s, 9 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 154.7, 153.9, 146.5, 140.9, 132.4, 128.4, 124.6, 121.9, 120.5, 118.3, 116.8, 116.2, 116.1, 62.0, 50.5, 29.9, 21.1.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{19}\text{H}_{22}\text{ClFN}_5\text{O}$: 390.1419; found: 390.1499.

Dibenzo[b,f][1,4]oxazepines 6a–l; General Procedure

To a stirred solution of the Ugi product **5** (0.5 mmol) in DMF (5 mL) was added K_2CO_3 (0.75 mmol). The mixture was stirred overnight 6 h at 100 °C. After completion of the reaction, the mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with saturated NaHCO_3 and dried over anhydrous Na_2SO_4 . After removal of the EtOAc, the residue was purified by column chromatography to afford the corresponding products **6**.

11-[1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6a)

Yield: 180 mg (81%); yellow solid; mp 155–158 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.56–7.52 (m, 2 H), 7.45 (dd, J = 7.7, 1.7 Hz, 1 H), 7.35 (td, J = 7.7, 1.7 Hz, 1 H), 7.27 (dd, J = 7.5, 1.6 Hz, 1 H), 7.26–7.19 (m, 3 H), 6.62 (s, 2 H), 6.03 (s, 2 H), 3.78 (s, 3 H), 3.68 (s, 6 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 161.5, 154.1, 153.5, 152.3, 151.5, 139.2, 138.2, 134.5, 130.8, 130.2, 129.8, 128.2, 126.0, 125.6, 125.2, 121.5, 121.0, 105.4, 60.8, 56.0, 53.2.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{24}\text{H}_{22}\text{N}_5\text{O}_4$: 444.1594; found: 444.1673.

11-[1-(3,4-dimethoxybenzyl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6b)

Yield: 350 mg (85%); yellow semi-solid.

^1H NMR (500 MHz, CDCl_3): δ = 7.53–7.46 (m, 3 H), 7.33 (td, J = 7.7, 1.7 Hz, 1 H), 7.28–7.20 (m, 3 H), 7.18 (td, J = 7.7, 1.2 Hz, 1 H), 6.99–6.93 (m, 2 H), 6.78 (d, J = 8.2 Hz, 1 H), 6.06 (s, 2 H), 3.81 (s, 3 H), 3.71 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 161.5, 154.0, 152.3, 151.5, 149.2, 149.1, 139.2, 134.4, 130.8, 130.2, 128.3, 126.9, 126.0, 125.6, 125.1, 121.4, 121.0, 120.9, 111.4, 111.3, 55.8, 55.7, 52.8.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}_3$: 414.1488; found: 414.1567.

1-Methoxy-11-[1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6c)

Yield: 180 mg (80%); yellow solid; mp 160–162 °C.

^1H NMR (500 MHz, CDCl_3): δ = 7.45 (dd, J = 7.7, 1.7 Hz, 1 H), 7.35 (td, J = 7.7, 1.7 Hz, 1 H), 7.27 (dd, J = 7.5, 1.6 Hz, 1 H), 7.26–7.19 (m, 1 H), 7.14 (d, J = 10.0 Hz, 1 H), 7.08–7.04 (m, 2 H), 6.62 (s, 2 H), 6.03 (s, 2 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.68 (s, 6 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 156.4, 155.1, 153.7, 153.4, 152.5, 151.5, 139.2, 138.1, 130.2, 129.7, 128.2, 125.8, 121.6, 121.2, 120.4, 114.5, 105.4, 60.8, 56.0, 55.8, 53.2.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{25}\text{H}_{24}\text{N}_5\text{O}_5$: 474.1699; found: 474.1781.

1-Methoxy-8-nitro-11-[1-(3,4,5-trimethoxybenzyl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6d)

Yield: 84 mg (88%); yellow oil.

^1H NMR (500 MHz, CDCl_3): δ = 8.28 (d, J = 2.7 Hz, 1 H), 8.22 (dd, J = 8.8, 2.7 Hz, 1 H), 7.37 (d, J = 8.9 Hz, 1 H), 7.18 (d, J = 9.8 Hz, 1 H), 7.13–7.08 (m, 2 H), 6.56 (s, 2 H), 6.08 (s, 2 H), 3.82 (s, 3 H), 3.78 (s, 6 H), 3.77 (s, 3 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 156.4, 155.1, 153.7, 153.4, 152.5, 151.5, 139.2, 138.1, 130.2, 129.7, 128.2, 125.8, 121.6, 121.2, 120.4, 114.5, 105.4, 60.8, 56.0, 55.8, 53.2.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{N}_5\text{O}_7$: 519.1550; found: 519.1627.

11-[1-(2-Isopropylphenyl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6e)

Yield: 130 mg (55%); yellow oil.

^1H NMR (500 MHz, CDCl_3): δ = 7.61–7.45 (m, 4 H), 7.33 (dd, J = 7.7, 1.6 Hz, 1 H), 7.30–7.24 (m, 1 H), 7.24–7.17 (m, 3 H), 7.12 (dd, J = 8.1, 1.4 Hz, 1 H), 7.03–6.98 (m, 1 H), 6.40 (dd, J = 7.8, 1.7 Hz, 1 H), 2.52 (quin, J = 6.9 Hz, 1 H), 1.14 (d, J = 6.9 Hz, 6 H).

^{13}C NMR (126 MHz, CDCl_3): δ = 161.3, 153.2, 152.0, 151.8, 145.8, 139.2, 134.4, 133.6, 130.8, 130.4, 129.9, 128.4, 127.0, 126.6, 126.3, 125.8, 125.7, 125.3, 121.2, 121.0, 28.5, 23.3.

HRMS (ESI-TOF): m/z [M + H] $^+$ calcd for $\text{C}_{23}\text{H}_{20}\text{N}_5\text{O}$: 382.1590; found: 382.1668.

11-(1-Cyclohexyl-1H-tetrazol-5-yl)-3-methyl-7-(trifluoromethyl)dibenzo[b,f][1,4]oxazepine (6f)

Yield: 100 mg (78%); yellow solid; mp 171–173 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.55–7.47 (m, 2 H), 7.43 (dd, *J* = 14.2, 8.1 Hz, 2 H), 7.12–7.07 (m, 2 H), 5.38–4.82 (m, 1 H), 2.42 (s, 3 H), 2.26 (dd, *J* = 12.8, 3.7 Hz, 2 H), 2.16–1.95 (m, 4 H), 1.81–1.74 (m, 1 H), 1.44–1.39 (m, 3 H).¹³C NMR (126 MHz, CDCl₃): δ = 161.3, 156.2, 152.2, 151.0, 146.5, 142.3, 131.3 (q, *J* = 33.3 Hz), 131.1, 128.7, 126.4, 123.3 (d, *J* = 273.4 Hz), 123.0, 122.7 (d, *J* = 3.7 Hz), 121.5, 118.8 (d, *J* = 3.7 Hz), 60.3, 32.9, 25.5, 25.0, 21.4.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₂H₂₁F₃N₅O: 428.1260; found: 428.1702.**11-[1-(2-Isopropylphenyl)-1H-tetrazol-5-yl]-3-methyl-8-nitrodibenzo[b,f][1,4]oxazepine (6g)**

Yield: 113 mg (86%); yellow solid; mp 201–204 °C.

¹H NMR (500 MHz, CDCl₃): δ = 8.06 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 1 H), 7.41–7.34 (m, 1 H), 7.22 (dd, *J* = 8.3, 4.4 Hz, 2 H), 7.14 (q, *J* = 10 Hz, 2 H), 7.06 (d, *J* = 1.6 Hz, 1 H), 2.49 (quin, *J* = 6.8 Hz, 1 H), 2.42 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 6 H).¹³C NMR (126 MHz, CDCl₃): δ = 160.4, 156.6, 154.2, 152.7, 147.1, 145.8, 145.4, 139.6, 133.4, 131.2, 130.8, 127.0, 126.9, 126.8, 126.4, 124.5, 123.8, 122.5, 121.9, 121.8, 28.5, 23.3, 21.5.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₄H₂₀N₆O₃: 441.1597; found: 441.1678.**11-(1-Cyclohexyl-1H-tetrazol-5-yl)-8-nitrodibenzo[b,f][1,4]oxazepine (6h)**

Yield: 78 mg (84%); yellow solid; mp 229–232 °C.

¹H NMR (500 MHz, CDCl₃): δ = 8.21 (d, *J* = 9.0 Hz, 2 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.56 (d, *J* = 7.7 Hz, 1 H), 7.39 (d, *J* = 8.6 Hz, 1 H), 7.34–7.24 (m, 2 H), 5.23–5.19 (m, 1 H), 2.29 (d, *J* = 12.6 Hz, 2 H), 2.20–1.96 (m, 4 H), 1.85 (d, *J* = 13.3 Hz, 1 H), 1.57–1.48 (m, 2 H), 1.40–1.36 (m, 1 H).¹³C NMR (126 MHz, CDCl₃): δ = 160.6, 157.0, 156.7, 150.7, 145.5, 139.7, 135.1, 131.6, 126.0, 125.6, 124.7, 123.9, 122.2, 121.1, 60.6, 32.9, 25.5, 25.0.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₀H₁₉N₆O₃: 391.1440; found: 391.1520.**11-[1-(2,4,4-Trimethylpentan-2-yl)-1H-tetrazol-5-yl]dibenzo[b,f][1,4]oxazepine (6i)**

Yield: 148 mg (79%); yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.52–7.48 (m, 1 H), 7.43 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.37–7.31 (m, 2 H), 7.26–7.24 (m, 3 H), 7.18–7.15 (m, 1 H), 2.12 (s, 2 H), 1.81 (s, 6 H), 0.75 (s, 9 H).¹³C NMR (126 MHz, CDCl₃): δ = 160.8, 156.5, 152.0, 151.9, 139.3, 134.5, 130.0, 129.9, 128.8, 126.9, 126.1, 125.5, 121.3, 121.2, 66.3, 53.4, 31.5, 30.6, 30.2.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₂H₂₆N₅O: 376.2059; found: 376.2141.**11-[1-(tert-Butyl)-1H-tetrazol-5-yl]-8-methoxy-3-methyldibenzo[b,f][1,4]oxazepine (6j)**

Yield: 157 mg (62%); yellow oil.

¹H NMR (500 MHz, CDCl₃): δ = 7.13 (d, *J* = 8.8 Hz, 1 H), 7.08–7.03 (m, 2 H), 6.96 (dd, *J* = 8.3, 1.5 Hz, 1 H), 6.92 (d, *J* = 3.0 Hz, 1 H), 6.89–6.83 (m, 1 H), 3.79 (s, 3 H), 2.38 (s, 3 H), 1.74 (s, 9 H).¹³C NMR (126 MHz, CDCl₃): δ = 160.9, 157.3, 156.9, 151.9, 146.2, 145.7, 139.9, 129.6, 126.1, 124.2, 121.6, 115.9, 112.5, 62.7, 55.7, 29.9, 21.4.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₀H₂₂N₅O₂: 364.1695; found: 364.1773.**11-[1-(2-Isopropylphenyl)-1H-tetrazol-5-yl]-7-methoxy-3-methyldibenzo[b,f][1,4]oxazepine (6k)**

Yield: 100 mg (80%); yellow solid; mp 181–184 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.62–7.52 (m, 2 H), 7.40 (d, *J* = 7.9 Hz, 1 H), 7.35–7.31 (m, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.06 (d, *J* = 8.1 Hz, 1 H), 7.03–7.01 (m, 2 H), 6.75 (dd, *J* = 8.8, 3.1 Hz, 1 H), 5.87 (d, *J* = 3.1 Hz, 1 H), 3.64 (s, 3 H), 2.64–2.48 (m, 1 H), 2.39 (s, 3 H), 1.16 (d, *J* = 7.0 Hz, 6 H).¹³C NMR (126 MHz, CDCl₃): δ = 161.6, 157.0, 153.4, 152.3, 146.0, 145.9, 145.6, 139.7, 133.7, 130.6, 130.2, 127.1, 126.6, 126.3, 125.9, 122.9, 121.5, 121.3, 115.5, 112.1, 55.5, 28.5, 23.4, 21.4.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₂₅H₂₄N₅O₂: 426.1852; found: 426.1932.**11-[1-(tert-Butyl)-1H-tetrazol-5-yl]-7-chloro-3-methyldibenzo[b,f][1,4]oxazepine (6l)**

Yield: 88 mg (54%); yellow solid; mp 161–164 °C.

¹H NMR (500 MHz, CDCl₃): δ = 7.34 (d, *J* = 8.1 Hz, 1 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 7.08 (dd, *J* = 4.8, 3.2 Hz, 2 H), 7.01 (dd, *J* = 8.1, 1.6 Hz, 1 H), 2.41 (s, 3 H), 1.76 (s, 9 H).¹³C NMR (126 MHz, CDCl₃): δ = 160.2, 156.6, 152.1, 150.8, 146.5, 138.2, 135.1, 129.7, 129.6, 126.6, 126.3, 124.1, 121.8, 121.7, 62.8, 29.9, 21.5.HRMS (ESI-TOF): *m/z* [M + H]⁺ calcd for C₁₉H₁₉ClN₅O: 368.1200; found: 368.1282.**Funding Information**

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Supporting Information

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