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An orthogonal protection strategy for the synthesis of 2-substituted piperazines

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Abstract—Tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones are readily prepared from the bis-carbamate protected piperazine-2-carboxylic acids and serve as orthogonally protected piperazines from which a variety of 2-substituted piperazines can be prepared. Sodium benzylate and sodium phenoxides react at the C-5 carbon of the oxazolidinone to yield 2-(benzyloxymethyl)piperazines and 2-(phenoxymethyl)piperazines, respectively. The tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones also provide convenient scaffolds from which 2-benzyl- and 2-phenethylpiperazines are prepared.

1. Introduction

The piperazine ring is found in a number of biologically active compounds, including several marketed drugs,[1] and is considered to be a privileged structure in drug discovery.[2] For an exploratory medicinal chemistry program, we were interested in preparing a diverse set of trisubstituted piperazines, **4**, and required a suitably flexible synthetic route to allow for the introduction of a variety of linkers, X, and aryl groups. An orthogonal protection strategy for the two piperazine nitrogens would also be necessary to facilitate the selective introduction of the R_1 and R_2 groups.

2-Substituted piperazines are commonly prepared by ring construction and reduction of diketopiperazines[3,4] or 2-ketopiperazines,[5] via alkylation and reduction of 2-methylpyrazines,[6] or by α-lithiation and alkylation of *N*-Boc piperazines.[7] In many of these cases, the piperazine derivatives must then be selectively protected prior to further modification. Whereas most of these methods lock in the 2-substituent at an early stage in the synthesis, we were interested in introducing the substituent at a later stage in order to maximize synthetic efficiency. A second strategy involves the elaboration of 2-substituted piperazine derivatives such as piperazin-2-ylmethanol.[8] As this route offered the greatest flexibility for introducing a wide array of linkers and aryl substituents at a later stage in the synthesis, the orthogonally protected 2-(hydroxymethyl)piperazine **3** was initially chosen as a common intermediate from which compounds **4** would be prepared (Scheme 1). Compound **3** is prepared by reduction of the orthogonally protected piperazine-2-carboxylic acid **2**. This, in turn, is readily prepared from piperazine-2-carboxylic acid, which can be selectively Boc-protected at the 4-position, followed by Cbz-protection at the 1-position.[9,1b] The 4-Cbz-1-Boc-protected piperazine-2-carboxylic acid can be prepared in a similar fashion although in somewhat lower yield due to the reduced steric bulk of the Cbz protecting group and resulting formation of the bis-Cbz compound.[10,11]

In our initial attempt at preparing 2-(aryloxymethyl)piperazines via a Mitsunobu reaction between compound **3** and an aryl alcohol, the tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one **5a** was isolated as a major side product. We have since demonstrated that compounds **5** can themselves serve as orthogonally protected piperazine intermediates for the synthesis of a variety of 2-substituted piperazines. As described below, this strategy has the advantage of not requiring selective protection of the piperazine starting material since compounds **5** are prepared from the di-Boc or di-Cbz-protected piperazine-2-carboxylic acids.

2. Results and discussion

Tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones **5a** and **5b** were prepared in three steps as outlined in Scheme 2. Compounds **6**[12] and **7**[13] were readily prepared in identical 96% yields from piperazine-2-carboxylic acid using 2 equiv of di-*tert*-butyldicarbonate and benzyl chloroformate, respectively. The carboxylic acids were reduced to the

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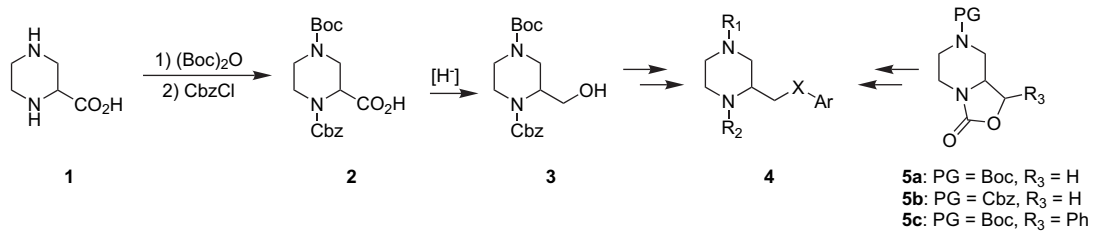
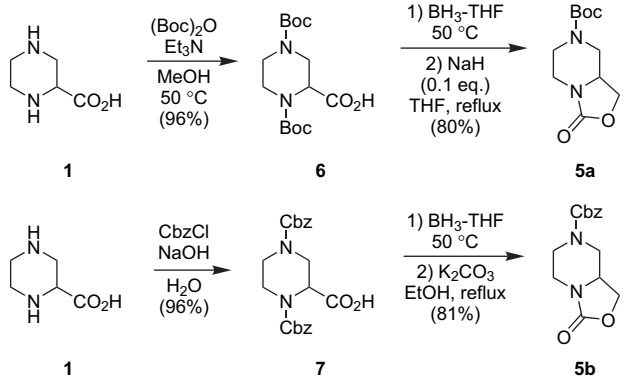


Scheme 1.

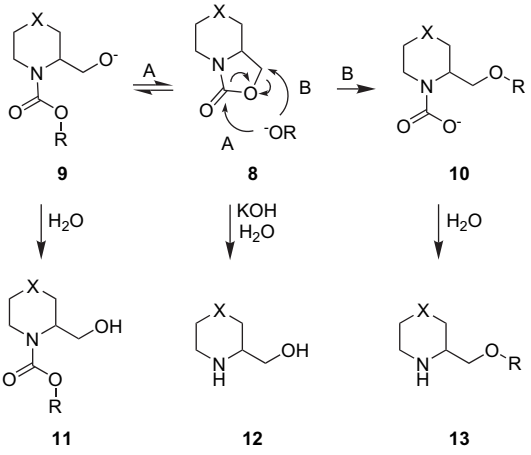
alcohols with borane–THF complex, and the compounds were cyclized to give **5a** and **5b** under basic conditions. The Cbz-protected compound cyclized more easily, requiring only potassium carbonate in refluxing ethanol.[14] The Boc-protected compound was more efficiently prepared by alkoxide formation with catalytic sodium hydride in refluxing THF. Compound **5a** was purified by recrystallization in 80% yield. While compound **5b** was also a crystalline solid, the presence of benzyl alcohol in the crude reaction mixture complicated recrystallization, and the compound was isolated in 81% yield following column chromatography. Both enantiomers of piperazine-2-carboxylic acid are commercially available, and we have applied these routes to the synthesis of both enantiomers of **5a** and **5b**.



Scheme 2.

2.1. 2-(Benzyloxymethyl)piperazines and 2-(phenoxymethyl)piperazines

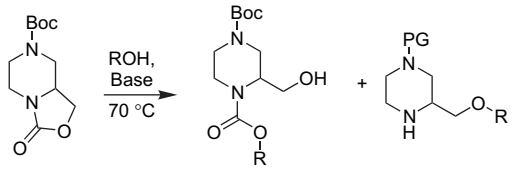
Bicyclic oxazolidinones have been shown to react with alkoxides[15] at the carbonyl carbon (Scheme 3, pathway A) to provide the corresponding *N*-carbamoyl-2-(hydroxymethyl)pyrrolidines **11** (X=bond) or with aqueous hydroxide[16] to yield the corresponding 2-(hydroxymethyl)heterocycles **12** (X=bond, CH_2, NR). There have also been reports of alkoxide ring opening of monocyclic oxazolidinones on the C-5 carbon to form 2-alkoxy-1-aminoethane derivatives (pathway B).[17] While there have been no reports of this type of reaction with aryloxides,[18,19] and no examples with tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones, we were intrigued by the possibility of preparing 2-(aryloxymethyl)-piperazines from **5** by oxazolidinone ring opening via pathway B. Alkoxides were expected to react preferentially via pathway A, establishing an equilibrium between the carbamate **9** and the oxazolidinone **8**. If the alkoxide did react via pathway B, compound **10** would be formed in an irreversible process, driving the reaction toward **13** upon decarboxylation. The ratio of **11** and **13** formed would likely depend on the reaction conditions. In the case of an aryloxide, however, pathway A would not be favorable since the aryloxide is a much better leaving group than the alkoxide of compound **9**. This would leave pathway B as the only productive reaction pathway.



Scheme 3.

In order to explore the differences in reactivity between alkoxides and aryloxides, compound **5a** was reacted with benzyl alcohol or phenol under several conditions (Table 1). Haddad et al reported the reaction of lithium benzylate with a tetrahydropyrrolo[1,2-*c*]oxazol-3(1*H*)-one derivative to proceed via pathway A to provide the corresponding Cbz-protected 2-(hydroxymethyl)pyrrolidine.[15b] Under these conditions, only a trace of compound **3** was observed with lithium benzylate and none of the 2-(benzyloxymethyl)-piperazine **14a** (entry 1) was observed. By increasing to 3 equiv of the alkoxide, compound **3** was isolated in 9% yield while compound **14a** was formed in 8% yield. In both examples, the remainder of the material was the unreacted **5a**. With sodium benzylate, however, only reaction products formed via pathway B were observed, with **14a** isolated in 10% yield and **15a** isolated in 27% yield, arising from reaction of excess sodium benzylate with the Boc group (entry 3). With DMF as solvent, somewhat better yields of 22% and 52% were observed for **14a** and **15a**, respectively. This counterion dependent difference in reactivity may allow for tuning of reactivity between pathways A and B. The less nucleophilic sodium phenoxide gave only an 8% yield of the 2-(phenoxymethyl)piperazine **14b** at 70 °C in THF (entry 5). As expected, neither the compound arising from pathway A nor the exchange of the

Table 1. Reaction of **5a** with oxygen nucleophiles



5a **3** **14**: PG = Boc; **15**: PG = Cbz

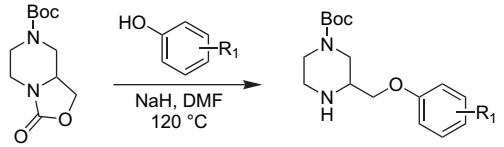
Entry	ROH (equiv)	Base	Solvent	Yield **3**	Yield **14/15**
1	BnOH (1.5)	*n*-BuLi	THF	Trace[a]	None[b]
2	BnOH (3.0)	*n*-BuLi	THF	9%	**14a**: 8%
3	BnOH (3.0)	NaH	THF	None[b]	**14a**: 10%, **15a**: 27%
4	BnOH (3.0)	NaH	DMF	None[b]	**14a**: 22%, **15a**: 52%
5	PhOH (3.0)	NaH	THF	—	**14b**: 8%
6	PhOH (3.0)	NaH	DMF (120 °C)	—	**14b**: 66%

[a] Compound was not isolated, but a small amount was observed by LC–MS during reaction.
[b] Compound was not observed by LC–MS during course of reaction.

Boc group was observed. By heating to 120 °C in DMF, however, compound **14b** was isolated in 66% yield, indicating that this reaction could be a synthetically useful method for the synthesis of 2-(aryloxymethyl)piperazines.

Table 2 illustrates the reaction of several substituted phenoxides with **5a**. Overall, the desired 2-(phenoxymethyl)piperazines **14b** and **16–21** were isolated in good yields, ranging from 48 to 76%. The phenoxides were preformed from 3 equiv of the phenol and sodium hydride in DMF, followed by addition of **5a** and heating at 120 °C overnight. Preforming the phenoxide with sodium hydroxide was not ideal as a significant amount of the hydrolysis product **12** (X=N–Boc) was formed, even when using excess phenol. We are currently exploring the use of other bases and solvent systems. Neither electron rich nor electron deficient substituents had a significant impact on yields (examples **16**, **19**, and **21**). While phenoxides with a methoxy substituent at the 3- or 4-position reacted similarly, a methoxy substituent at the 2-position gave a reduced yield (example **16–18**). Although the full scope of this reaction has yet to be elucidated, this appears to be a convenient and general method for the synthesis of 2-(phenoxymethyl)piperazines. The method is also ideal for the synthesis of our target compounds, **4**, as it allows for the introduction of a variety of substituted aromatic groups while simultaneously unmasking the nitrogen at the 1-position of the piperazines for further elaboration.

Table 2. Synthesis of 2-(aryloxymethyl)piperazines from **5a**

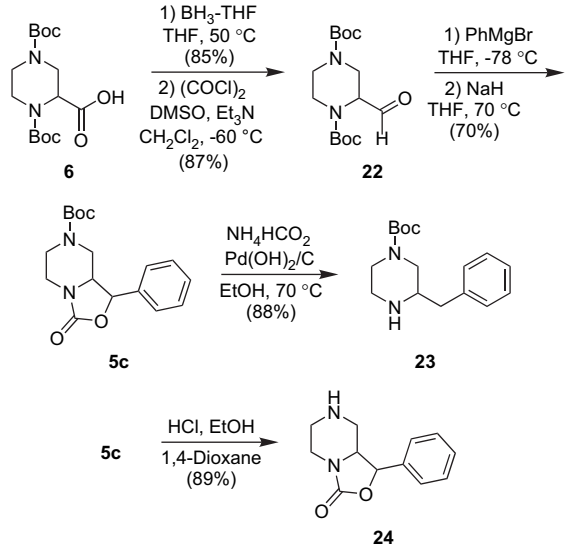


5a **14b, 16-21**

Example	R_1	Yield (%)
14b	H	66
16	4-OMe	63
17	3-OMe	76
18	2-OMe	48
19	4-Cl	75
20	3-F	62
21	4-OCF_3	58

2.2. 2-Benzylpiperazines

Orthogonally protected 2-benzylpiperazines were also prepared in a similar fashion to **5a** and **5b** (Scheme 4). The di-Boc-protected piperazine-2-carboxylic acid was converted to aldehyde **22** by borane reduction followed by Swern oxidation in 74% yield for the two steps. Reaction with phenylmagnesium bromide at −78 °C followed by cyclization with sodium hydride in THF at 70 °C gave **5c** in 70% yield as a 2:1 mixture of diastereomers. Under the Grignard conditions, a small amount of cyclized product was observed, but heating was necessary for complete cyclization. Because excess Grignard reagent was found to react with the carbonyl of the oxazolidinone, the two step sequence was preferred. As demonstrated, compound **5c** serves as an orthogonally protected 2-benzylpiperazine derivative. The nitrogen at the 1-position was deprotected under transfer hydrogenation



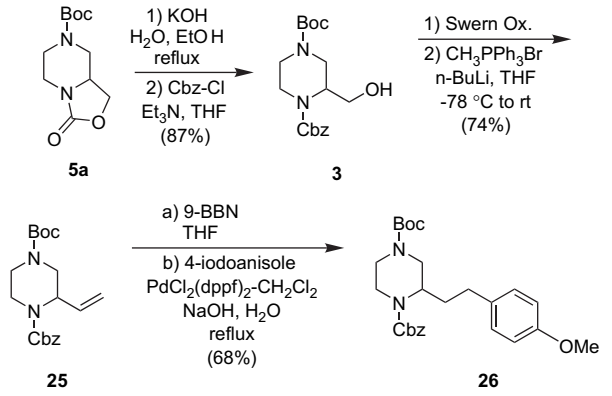
6 **22** **5c** **23** **5c** **24**

Scheme 4.

conditions to give compound **23** in 88% yield. For further reaction of the nitrogen at the 4-position, the Boc group was removed with HCl in 89% yield to give compound **24**. The 1-position could later be deprotected by transfer hydrogenation. With the use of readily available aryl Grignard reagents this route should provide an efficient method for the preparation of orthogonally protected 2-benzylpiperazines.

2.3. 2-Phenethylpiperazines

The tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones also provide a convenient scaffold from which orthogonally protected piperazin-2-ylmethanol derivatives can be prepared. This is demonstrated by the introduction of a Cbz group as found in Scheme 5. Compound **5a** was treated with potassium hydroxide in refluxing ethanol, followed by benzyl chloroformate to give compound **3** in 87% yield. In principle, other nitrogen protecting groups could be introduced as long as they react selectively with the amine over the primary alcohol. We have used compound **3** as the starting point for the synthesis of 2-arylethylpiperazines such as compound **26**. Compound **3** was oxidized by Swern oxidation and converted to the alkene **25** via Witting olefination in 74% yield for the two steps. This was then converted to compound **26** in a hydroboration/Suzuki[20] coupling sequence with 4-iodoanisole in 68% yield.[21] With the use of substituted halobenzenes, this procedure allows for the introduction of a wide range of substitution on the phenyl ring.



Scheme 5.

3. Conclusions

In conclusion, we have demonstrated that tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones **5** can serve as orthogonally protected piperazines from which a variety of 2-substituted piperazines can be conveniently prepared. These compounds are readily prepared from piperazine-2-carboxylic acid without the need for selective protection of the two nitrogens. Sodium benzylate and sodium phenoxides react with **5** to yield 2-(benzyloxymethyl)piperazine and 2-(phenoxymethyl)-piperazines, respectively. In the process, the 1-position of the piperazine is unmasked while the 4-position remains protected, providing a convenient scaffold for further derivatization. The 1-phenyltetrahydro-1*H*-oxazolo[3,4-*a*]-pyrazin-3(5*H*)-one **5c** is also readily prepared from di-Boc-protected piperazine-2-carboxylic acid and serves as an orthogonally protected 2-benzylpiperazine derivative. Finally, tetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-ones **5** provide a scaffold from which orthogonally protected piperazin-2-ylmethanol derivatives can be prepared. These compounds can then be converted to orthogonally protected 2-arylethylpiperazines.

4. Experimental

4.1. General experimental

Air and moisture sensitive liquids and reagents were transferred via syringe or cannula and were introduced into oven-dried glassware under a positive pressure of dry nitrogen through rubber septa. All reactions were stirred magnetically. Commercial reagents were used without further purification. Analytical thin-layer chromatography was performed on EM Science pre-coated glass-backed silica gel 60 Å F_{254} 250 μm plates. Visualization of the plates was effected by one or more of the following techniques: (a) ultraviolet illumination, (b) exposure to iodine vapor, and/or (c) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating. Column chromatography was performed on a FlashMaster™ Personal or FlashMaster Personal Plus™ system using ISOLUTE® Flash Si II silica gel pre-packed cartridges (available from Biotage). Preparative reversed-phase HPLC chromatography (HPLC) was accomplished using an Agilent 1100 Series system and an Agilent Prep-C18 (21.2 mm I.D.×150 mm) column equipped with an Agilent Prep-C18 (21.2 mm I.D.) guard column. The mobile phase used was a mixture of H_2O (A) and MeCN (B) containing 0.1% TFA.

^{1}H NMR spectra were recorded on a Varian Gemini 2400 (400 MHz) spectrometer and are reported in parts per million using residual solvent as the internal standard ($CDCl_3$ at 7.24 ppm or DMSO-d_6 at 2.50 ppm). Data are reported as: br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; coupling constant(s) in hertz, integration. ^{13}C NMR spectra were recorded on a Varian Gemini 2400 (100 MHz) spectrometer and are reported in parts per million using residual solvent as the internal standard ($CDCl_3$ at 77.2 ppm or DMSO-d_6 at 39.5 ppm).

High-performance liquid chromatography–electrospray mass spectra (LC–MS) were obtained using an Agilent 1100 Series HPLC equipped with a binary pump, a diode array detector monitored at 254 and 214 nm, an Agilent Zorbax Eclipse XDB-C8 (4.6 mm I.D.×150 mm, 5 micron) column, and an Agilent 1100 Series LC/MSD mass spectrometer with electrospray ionization. Spectra were scanned from 100 to 1000 amu. The eluant was a mixture of H_2O (A) and MeCN (B) containing 0.1% AcOH at a flow rate of 1 mL/min. A typical gradient was: (a) time=0 min, 90% A, 10% B; (b) time=9 min, 10% A, 90% B; (c) time=9.5 min, 90% A, 10% B; (d) time=12 min, 90% A, 10% B.

Elemental analysis (C, H, N) was performed by Atlantic Microlab, Inc. (Norcross, Georgia).

4.2. Experimental details

4.2.1. 1,4-Bis(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (6). According to the literature procedure,[12a]

a solution of di-*tert*-butyldicarbonate (63 g, 290 mmol) in MeOH (100 mL) was added portionwise to a solution of piperazine-2-carboxylic acid dihydrochloride (25.0 g, 123 mmol) and triethylamine (48 mL, 340 mmol) in MeOH (150 mL) over 30 min. Upon complete addition, the reaction mixture was heated to 50 °C for 2 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The material was dissolved in water (300 mL) and the solution was brought to pH 2 with 1 M aqueous HCl. This was extracted with EtOAc (4×200 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure until ~100 mL EtOAc remained. The solution was diluted with hexanes (150 mL) and cooled to 0 °C. The resulting solid was collected by filtration, washed with hexanes (2×), and air-dried. This gave 38.9 g (96%) of the title compound as a white solid. Analytical data for **6**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.02–12.80 (br, 1H), 4.50–4.24 (m, 2H), 3.94–3.72 (br, 1H), 3.66 (d, J=12.8 Hz, 1H), 3.22–2.92 (m, 2H), 2.90–2.68 (br, 1H), 1.42–1.34 (m, 18H).

4.2.2. *tert*-Butyl 3-oxotetrahydro-1*H*-oxazolo[3,4-*a*]pyrazine-7(3*H*)-carboxylate (5a). Borane–THF complex (1.0 M solution in THF, 200 mL, 200 mmol) was added slowly to a solution of 1,4-bis(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (35.2 g, 106 mmol) in THF (200 mL). Upon complete addition, the reaction mixture was heated to 50 °C for 3 h. Upon cooling to rt, the reaction mixture was carefully quenched by the dropwise addition of MeOH (25 mL). After gas evolution ceased, the reaction mixture was heated to reflux for 1 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The material was dissolved twice in THF (50 mL) and concentrated under reduced pressure. The material was dissolved in THF (200 mL) and NaH (60% dispersion in mineral oil, 4.24 g, 106 mmol) was added portionwise. The reaction mixture was heated to reflux overnight. Upon cooling to rt, the reaction mixture was quenched with NH_4Cl (saturated, aqueous, 100 mL) and diluted with water (100 mL). The solution was extracted with EtOAc (3×300 mL), and the combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was recrystallized from EtOAc/hexanes (1:4) to give 17.6 g (68%) of the title compound as a white solid. Analytical data for **5a**: R_f=0.43 in 80% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (t, J=8.4 Hz, 1H), 4.35–3.98 (br, 2H), 3.92 (dd, J=5.6 and 8.8 Hz, 1H), 3.80–3.72 (m, 2H), 2.98 (dt, J=3.6 and 12.4 Hz, 1H), 2.86–2.70 (br, 1H), 2.70–2.55 (br, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 154.2, 81.1, 65.5, 52.9, 47.7 (br), 43.4 (br), 41.1, 28.7. LC–MS: t_R=6.46 min; $[M+Na]^+$=264.9. Anal. Calcd for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.49; N, 11.56. Found: C, 54.38; H, 7.44; N, 11.35.

4.2.3. 1,4-Bis(benzyloxycarbonyl)piperazine-2-carboxylic acid (7). According to the literature procedure,[13a] piperazine-2-carboxylic acid dihydrochloride (10.0 g, 49.2 mmol) was dissolved in H_2O (125 mL) and 1,4-dioxane (200 mL), and the solution was brought to pH 11 with 50% NaOH in H_2O. Benzyl chloroformate (14 mL, 98 mmol) was added while maintaining the pH at 11 with 50% NaOH in H_2O. After 1 h, an additional portion of benzyl chloroformate (2 mL, 14 mmol) was added. After 30 min, the solution was extracted with Et_2O (3×100 mL). The aqueous layer was brought to pH 2 with concentrated HCl and extracted with EtOAc (3×200 mL). The combined EtOAc extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 18.9 g (96%) of the desired product as a thick oil. The material was used without further purification. Analytical data for **7**: LC–MS: t_R=9.250 min; $[M+H]^+$=421.1.

4.2.4. Benzyl 3-oxotetrahydro-1*H*-oxazolo[3,4-*a*]pyrazine-7(3*H*)-carboxylate (5b). Borane–THF complex (1.0 M solution in THF, 100 mL, 100 mmol) was added slowly to a solution of **7** (18.9 g, 47.4 mmol) in THF (200 mL). Upon complete addition, the reaction mixture was heated to 50 °C for 3 h. Upon cooling to rt, the reaction mixture was carefully quenched by the dropwise addition of MeOH. After gas evolution ceased, the reaction mixture was heated to 50 °C for 1 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The material was dissolved in EtOH (200 mL) and K_2CO_3 (6.9 g, 49.9 mmol) was added. The reaction mixture was heated to 70 °C overnight. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure, diluted with water (200 mL), and extracted with EtOAc (3×200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by column chromatography (10–40% EtOAc in hexanes gradient) to give 10.7 g (81%) of the title compound as a white solid. Analytical data for **5b**: R_f=0.53 in 80% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 5.12 (s, 2H), 4.44–4.04 (br m, 3H), 3.96–3.85 (br, 1H), 3.84–3.70 (br, 2H), 3.08–2.93 (br m, 1H), 2.93–2.62 (br m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 154.9, 136.1, 128.7, 128.4, 128.2, 68.0, 65.4, 52.8, 47.9, 43.4, 41.0. LC–MS: t_R=7.85 min; $[M+Na]^+$=299.1. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.85; H, 5.83; N, 10.09.

4.2.5. 1-Benzyl 4-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (3) and *tert*-butyl 3-(benzyloxymethyl)piperazine-1-carboxylate (14a).

4.2.5.1. Reaction of 5a with 3 equiv of benzyl alcohol and *n*-BuLi in THF. *n*-BuLi (2.5 M solution in hexanes, 1.25 mL, 3.13 mmol) was added to a solution of benzyl alcohol (0.32 mL, 3.1 mmol) at 0 °C. The reaction mixture was allowed to warm to rt for 30 min. Compound **5a** (0.250 g, 1.03 mmol) was added, and the reaction mixture was heated to reflux overnight. Upon cooling to rt, the reaction mixture was diluted with water (1 mL) and concentrated under reduced pressure. The material was purified by HPLC (5–50% CH_3CN in H_2O, 0.1% TFA gradient), yielding two major fractions. The fraction containing **3** was concentrated under reduced pressure, yielding 0.033 g (9%) of **3** as a thick, colorless oil. Analytical data for compound **3** are given in Section 4.3.13. The fraction containing **14a** was brought to pH ~12 with 1 N NaOH and extracted with EtOAc (3×). The extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, yielding 0.025 g (8%) of **14a** as a thick, colorless oil. Analytical data for **14a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 4.49 (s, 2H), 4.01–3.75 (br, 2H), 3.46 (dd, J=3.8 and 9.0 Hz, 1H), 3.32 (dd, J=7.8 and 9.0 Hz, 1H), 3.00–2.76 (m, 3H), 2.76–2.65 (m, 1H), 2.65–2.45 (br, 1H), 2.15 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 138.0, 128.5, 127.8, 79.9, 73.7, 72.1, 54.7, 48.0–45.8 (br), 45.3, 45.3–44.0 (br),

28.7. LC–MS: t_R=5.45 min; $[M+H]^+$=307.2. Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.63; H, 8.64; N, 9.10.

4.2.6. *tert*-Butyl 3-(benzyloxymethyl)piperazine-1-carboxylate (14a) and benzyl 3-(benzyloxymethyl)piperazine-1-carboxylate (15a).

4.2.6.1. Reaction of 5a with 3 equiv of benzyl alcohol and NaH in THF. Benzyl alcohol (0.32 mL, 3.1 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.124 g, 3.09 mmol) in THF (5 mL) at 0 °C. The reaction mixture was allowed to warm to rt for 30 min. Compound **5a** (0.250 g, 1.03 mmol) was added, and the reaction mixture was heated to reflux overnight. Upon cooling to rt, the reaction mixture was diluted with water (1 mL) and concentrated under reduced pressure. The material was purified by HPLC (5–50% CH_3CN in H_2O, 0.1% TFA gradient), yielding two major fractions corresponding to **14a** and **15a**. The fractions were independently brought to pH ~12 with 1 N NaOH and extracted with EtOAc (3×). The extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave 0.030 g (10%) of **14a** as a thick, colorless oil and 0.095 g (27%) of **15a** as a thick, colorless oil. Analytical data for **15a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10H), 5.18–5.06 (br m, 2H), 4.49 (s, 2H), 4.09–3.88 (br, 2H), 3.52–3.40 (br, 1H), 3.38–3.29 (br, 1H), 3.03–2.82 (br m, 3H), 2.81–2.59 (br m, 2H), 2.27–2.12 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 137.9, 136.8, 128.6, 128.1, 128.0, 127.9, 127.8, 73.8, 71.9, 67.4, 54.7, 46.6 (br), 45.3, 44.8. LC–MS: t_R=5.48 min; $[M+H]^+$=341.1. Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.56; H, 7.11; N, 8.23. Found: C, 70.26; H, 7.16; N, 8.21.

4.2.6.2. Reaction of 5a with 3 equiv of benzyl alcohol and NaH in DMF. Benzyl alcohol (0.64 mL, 6.18 mmol) was added portionwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.247 g, 6.18 mmol) in DMF (5 mL). Compound **5a** (0.500 g, 2.06 mmol) was added, and the reaction mixture was heated to 70 °C overnight. Upon cooling to rt, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3×). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by HPLC (5–50% CH_3CN in H_2O, 0.1% TFA gradient), yielding two major fractions corresponding to **14a** and **15a**. The fractions were independently brought to pH ~12 with 1 N NaOH and extracted with EtOAc (3×). The extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave 0.139 g (22%) of **14a** and 0.365 g (52%) of **15a**.

4.2.7. *tert*-Butyl 3-(phenoxymethyl)piperazine-1-carboxylate (14b).

4.2.7.1. Reaction of 5a with phenol and NaH in THF at 70 °C. Phenol (0.291 g, 3.09 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.124 g, 3.09 mmol) in THF (5 mL) at 0 °C. After warming to rt for 30 min, **5a** (0.250 g, 1.03 mmol) was added and the reaction mixture was heated to reflux overnight. Upon cooling to rt, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3×25 mL). The combined extracts were washed with 1 N NaOH (2×30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by column chromatography (0–3% MeOH in CH_2Cl_2 gradient) to give 0.025 g (8%) of the title compound as a tan solid. Analytical data for **14b**: R_f=0.51 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 2H), 6.96–6.91 (m, 1H), 6.90–6.85 (m, 2H), 4.12–3.80 (m, 4H), 3.12–3.03 (m, 1H), 3.03–2.86 (m, 3H), 2.84–2.60 (m, 1H), 2.40–2.20 (br, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 154.8, 129.6, 121.2, 114.7, 80.1, 69.5, 54.3, 48.0–45.3 (br), 45.2, 45.2–43.8 (br), 28.8. LC–MS: t_R= 5.15 min; $[M+H]^+$=293.1. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.56; H, 8.27; N, 9.49.

4.3. General procedure for the reaction of 5a with phenols

Phenol (6.18 mmol) was added portionwise to a suspension of sodium hydride (60% dispersion in mineral oil, 0.247 g, 6.18 mmol) in DMF (5 mL). Compound **5a** (0.500 g, 2.06 mmol) was added, and the reaction mixture was heated to 120 °C overnight. Upon cooling to rt, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3×25 mL). The combined extracts were washed with 1 N NaOH (2×40 mL) and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by column chromatography (0–3% MeOH in CH_2Cl_2 gradient) to give **14b** and **16**–**21**.

4.3.1. *tert*-Butyl 3-(phenoxymethyl)piperazine-1-carboxylate (14b).

Compound **14b** (0.398 g, 66%) was prepared from phenol (0.581 g, 6.18 mmol) and isolated as a tan solid. For analytical data of compound **14b**, see Section 4.2.7.1.

4.3.2. *tert*-Butyl 3-((4-methoxyphenoxy)methyl)piperazine-1-carboxylate (16).

Compound **16** (0.421 g, 63%) was prepared from 4-methoxyphenol (0.767 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **16**: R_f=0.49 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84–6.77 (m, 4H), 4.12–3.84 (m, 3H), 3.82–3.72 (m, 4H), 3.09–2.96 (m, 2H), 2.96–2.84 (m, 1H), 2.84–2.60 (m, 2H), 2.16–1.96 (br, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.2, 152.8, 115.7, 114.8, 80.0, 70.5, 56.0, 54.4, 48.0–45.3 (br), 45.3, 45.3–43.8 (br), 28.8. LC–MS: t_R=4.98 min; $[M+H]^+$=323.5. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.60; H, 8.14; N, 8.66.

4.3.3. *tert*-Butyl 3-((3-methoxyphenoxy)methyl)piperazine-1-carboxylate (17).

Compound **17** (0.505 g, 76%) was prepared from 3-methoxyphenol (0.767 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **17**: R_f=0.52 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J=8.0 Hz, 1H), 6.52–6.41 (m, 3H), 4.12–3.85 (m, 3H), 3.81 (dd, J=7.2 and 8.8 Hz, 1H), 3.75 (s, 3H), 3.10–2.95 (m, 2H), 2.95–2.82 (m, 1H), 2.82–2.58 (m, 2H), 2.15–2.05 (br, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 159.9, 154.8, 130.0, 106.84, 106.76, 101.2, 80.0, 69.6, 55.5, 54.2, 48.0–45.3 (br), 45.2, 45.2–43.8 (br), 28.7. LC–MS: t_R=5.31 min; $[M+H]^+$=323.5. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.01; H, 8.27; N, 8.64.

4.3.4. *tert*-Butyl 3-((2-methoxyphenoxy)methyl)piperazine-1-carboxylate (18).

Compound **18** (0.320 g, 48%)

was prepared from 2-methoxyphenol (0.767 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **18**: R_f=0.47 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96–6.84 (m, 4H), 4.06–3.80 (m, 7H), 3.16–3.06 (m, 1H), 3.04–2.84 (m, 2H), 2.84–2.60 (m, 2H), 2.44–2.28 (br, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 150.0, 148.3, 122.1, 121.1, 115.0, 112.3, 80.0, 71.5, 56.1, 54.3, 48.0–45.2 (br), 45.2, 45.2–43.8 (br), 28.8. LC–MS: t_R=5.20 min; $[M+H]^+$=323.5. Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 63.17; H, 8.04; N, 8.65.

4.3.5. *tert*-Butyl 3-((4-chlorophenoxy)methyl)piperazine-1-carboxylate (19). Compound **19** (0.505 g, 75%) was prepared from 4-chlorophenol (0.795 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **19**: R_f=0.57 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J=9.0 Hz, 2H), 6.79 (d, J=9.0 Hz, 2H), 4.10–3.84 (m, 3H), 3.79 (dd, J=7.6 and 8.8 Hz, 1H), 3.08–2.83 (m, 3H), 2.83–2.58 (m, 2H), 2.18–2.04 (br, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 154.8, 129.4, 126.1, 115.9, 80.0, 70.0, 54.1, 48.0–45.2 (br), 45.2, 45.2–43.8 (br), 28.7. LC–MS: t_R=5.52 min; $[M+H]^+$=327.5. Anal. Calcd for $C_{16}H_{23}ClN_2O_3$: C, 58.80; H, 7.09; N, 8.57. Found: C, 59.06; H, 7.22; N, 8.61.

4.3.6. *tert*-Butyl 3-((3-fluorophenoxy)methyl)piperazine-1-carboxylate (20). Compound **20** (0.397 g, 62%) was prepared from 3-fluorophenol (0.693 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **20**: R_f=0.51 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (q, J=7.9 Hz, 1H), 6.67–6.55 (m, 3H), 4.10–3.85 (m, 3H), 3.80 (dd, J=7.6 and 8.8 Hz, 1H), 3.10–2.83 (m, 3H), 2.83–2.58 (m, 2H), 2.18–2.04 (br, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J=244 Hz), 159.9 (d, J=10.6 Hz), 154.8, 130.3 (d, J=9.9 Hz), 110.3 (d, J=2.2 Hz), 108.1 (d, J=21.2 Hz), 102.5 (d, J=25.0 Hz), 80.1, 69.9, 54.1, 48.0–45.2 (br), 45.2, 45.2–43.8 (br), 28.7. LC–MS: t_R=5.30 min; $[M+H]^+$=311.5. Anal. Calcd for $C_{16}H_{23}FN_2O_3$: C, 61.92; H, 7.47; N, 9.03. Found: C, 62.17; H, 7.53; N, 9.03.

4.3.7. *tert*-Butyl 3-((4-(trifluoromethoxy)phenoxy)-methyl)piperazine-1-carboxylate (21). Compound **21** (0.454 g, 58%) was prepared from 4-(trifluoromethoxy)phenol (1.10 g, 6.18 mmol) and isolated as a thick oil. Analytical data for **21**: R_f=0.56 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J=9.0 Hz, 2H), 6.86 (d, J=9.0 Hz, 2H), 4.13-3.86 (m, 3H), 3.82 (dd, J=7.2 and 8.8 Hz, 1H), 3.12–2.85 (m, 3H), 2.85–2.60 (m, 2H), 2.25–1.95 (br, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 154.8, 143.1, 122.6, 120.7 (q, J=254 Hz), 115.4, 80.1, 70.1, 54.2, 48.0–45.2 (br), 45.2, 45.2–43.8 (br), 28.8. LC–MS: t_R=6.07 min; $[M+H]^+$=377.6. Anal. Calcd for $C_{17}H_{23}F_3N_2O_4$: C, 54.25; H, 6.16; N, 7.44. Found: C, 54.24; H, 6.15; N, 7.43.

4.3.8. Di-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate. Borane–THF complex (1.0 M solution in THF, 6.0 mL, 6.0 mmol) was added slowly to a solution of **6** (1.00 g, 3.03 mmol) in THF (10 mL). Upon complete addition, the reaction mixture was heated to 50 °C for 2 h. Upon cooling to rt, the reaction mixture was carefully quenched by the dropwise addition of MeOH (10 mL). After gas evolution ceased, the reaction mixture was heated to reflux for 1 h. Upon cooling to rt, the reaction mixture was concentrated under reduced pressure. The material was purified by column chromatography (0–40% EtOAc in hexanes gradient) to give 0.819 g (85%) of the title compound as a white solid. Analytical data:[22] R_f=0.22 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.76 (t, J=5.0 Hz, 1H), 4.04–3.85 (m, 2H), 3.85–3.64 (m, 2H), 3.42–3.26 (m, 2H), 3.00–2.64 (m, 3H), 1.39 (s, 18H). LC–MS: t_R=8.27 min; $[M+Na]^+$=339.6.

4.3.9. Di-*tert*-butyl 2-formylpiperazine-1,4-dicarboxylate (22). A solution of DMSO (0.20 mL, 2.9 mmol) in CH_2Cl_2 (2 mL) was added to a solution of oxalyl chloride (0.124 mL, 1.43 mmol) in CH_2Cl_2 (10 mL) at −60 °C. After 5 min, a solution of di-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (0.410 g, 1.30 mmol) in CH_2Cl_2 (2 mL) was added. After 15 min, triethylamine (0.91 mL, 6.5 mmol) was added and the reaction mixture was allowed to warm to rt. After 1 h, water (25 mL) was added, the organics were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organics were washed with brine (3×50 mL), 1% HCl (3×50 mL), water (50 mL), and 5% $NaHCO_3$ (3×50 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by column chromatography (10–20% EtOAc in hexanes gradient) to give 0.354 g (87%) of the title compound as a white solid. Analytical data for **22**:[23] R_f=0.53 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (br, 1H), 4.64–4.37 (m, 1H), 4.42 (d, J=14 Hz, 1H), 3.80–3.62 (m, 2H), 3.24–3.08 (m, 1H), 3.02–2.74 (m, 2H), 1.44–1.34 (m, 18H).

4.3.10. *tert*-Butyl 3-oxo-1-phenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazine-7(3*H*)-carboxylate (5c). Phenylmagnesium bromide (1.0 M solution in THF, 0.66 mL, 0.66 mmol) was added dropwise to a solution of **22** (0.208 g, 0.662 mmol) in THF (5 mL) at −78 °C over ~2 min. After 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride and allowed to warm to rt. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was dissolved in THF (5 mL) and sodium hydride (60% dispersion in mineral oil, 0.026 g, 0.66 mmol) was added in one portion. The reaction mixture was heated to reflux for 1 h. Upon cooling to rt, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by HPLC (10–90% CH_3CN in H_2O, 0.1% TFA gradient) to give 0.147 g (70%) of the title compound as a white solid. The material was isolated as a 2:1 ratio of diastereomers. Analytical data for **5c**:[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.24 (m, 5H), 5.67 (d, J=8.4 Hz, 0.33H), 5.03 (d, J=6.8 Hz, 0.67H), 4.54–4.3 (br, 0.67H), 4.20–3.88 (m, 1.33H), 3.86–3.76 (m, 1H), 3.60–3.52 (m, 0.67H), 3.06–2.92 (m, 1H), 2.90–2.64 (br, 2H), 2.18–2.06 (m, 0.33H), 1.43 (s, 6H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 156.1, 154.4, 154.2, 137.3, 134.0, 129.2, 129.1, 128.9, 128.8, 125.6, 125.4, 81.2, 80.9, 79.1, 76.7, 60.3, 56.6, 48.0–47.0 (br), 45.5–44.4 (br), 44.2–42.8 (br), 41.6, 41.1, 28.6, 28.6. LC–MS: t_R=8.72 min; $[M+Na]^+$=341.1.

4.3.11. *tert*-Butyl 3-benzylpiperazine-1-carboxylate (23). Palladium hydroxide on carbon (~20% Pd, 7 mg, 0.01 mmol) was added to a solution of **5c** (35 mg, 0.11 mmol) and ammonium formate (14 mg, 0.22 mmol) in EtOH (1 mL). The reaction mixture was heated to 70 °C for 2 h. Upon cooling to rt, the reaction mixture was filtered through Celite®, and the filtrate was concentrated under reduced pressure. The material was purified by column chromatography (0–4% MeOH in CH_2Cl_2 gradient), yielding 26.8 mg (88%) of the title compound. Analytical data for **23**:[25] R_f=0.44 in 10% MeOH/CH_2Cl_2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.32–7.16 (m, 5H), 4.15–3.80 (br, 2H), 3.00–2.50 (m, 8H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.7, 129.3, 128.7, 126.7, 80.0, 56.4, 50.0–48.6 (br), 45.7, 45.7–43.8 (br), 40.2, 28.7. LC–MS: t_R=5.34 min; $[M+H]^+$=277.1.

4.3.12. 1-Phenyltetrahydro-1*H*-oxazolo[3,4-*a*]pyrazin-3(5*H*)-one (24). HCl (4.0 M solution in 1,4-dioxane, 2 mL, 8 mmol) was added to a solution of **23** (0.035 g, 0.11 mmol) in EtOH (1 mL). After 1 h, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (20 mL), and washed with 1 N NaOH (2×10 mL) and brine (10 mL). The EtOAc layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave 21.3 mg (89%) of the title compound as a 2:1 ratio of diastereomers. Analytical data for **24**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.24 (m, 5H), 5.63 (d, J=8.8 Hz, 0.3H), 5.00 (d, J=7.2 Hz, 0.7H), 4.04 (ddd, J=4.0, 8.6, and 11.8 Hz, 0.3H), 3.86–3.76 (m, 1H), 3.59 (ddd, J=4.0, 7.0, and 10.6 Hz, 0.7H), 3.24 (dd, J=4.0 and 11.4 Hz, 0.7H), 3.13 (ddd, J=3.8, 12.4, and 13.4 Hz, 0.3H), 3.04–2.96 (m, 1.4H), 2.92 (dd, J=4.0 and 12.4 Hz, 0.3H), 2.76–2.66 (m, 1.4H), 2.64–2.54 (m, 1.3H), 2.42 (dd, J=3.6 and 12.0 Hz, 0.3H), 2.09 (t, J=11.6 Hz, 0.3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 156.3, 137.7, 134.3, 129.0, 128.9, 128.7, 128.1, 125.6, 125.5, 79.6 (br), 76.8 (br), 61.3, 57.5, 50.1, 47.0, 44.8, 44.6, 42.2, 42.1. LC–MS: t_R=3.17 min, $[M+H]^+$=339.6 and t_R=3.45 min, $[M+H]^+$=219.1. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.13; H, 6.76; N, 12.82.

4.3.13. 1-Benzyl 4-*tert*-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (3). Sodium hydroxide (1 N aqueous solution, 8.6 mL, 8.6 mmol) was added to a solution of **5a** (1.05 g, 4.32 mmol) in EtOH (10 mL), and the reaction mixture was heated to 70 °C for 1 h. Upon cooling to rt, EtOH was removed under reduced pressure. The aqueous solution was diluted with THF (10 mL) and benzyl chloroformate (0.640 mL, 4.32 mmol) was added. After 2 h, the reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3×25 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The material was purified by column chromatography (20–40% EtOAc in hexane gradient) to give 1.32 g (87%) of the title compound as a thick, colorless oil. Analytical data for **3**:[26] R_f=0.32 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.13 (ABq, J_{AB}=12.4 Hz, 2H), 4.34–3.80 (br m, 4H), 3.74–3.48 (br, 2H), 3.18–2.80 (br m, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8 (br), 136.4, 128.6, 128.2, 128.0, 80.8, 67.8, 60.8–58.2 (br), 52.9, 44.5 (br), 42.9 (br), 39.9, 28.6. LC–MS: t_R=8.63 min; $[M+Na]^+$=373.1.

4.3.14. 1-Benzyl 4-*tert*-butyl 2-vinylpiperazine-1,4-dicarboxylate (25). A solution of DMSO (0.286 mL, 4.03 mmol) in CH_2Cl_2 (2 mL) was added to a solution of oxalyl chloride (0.176 mL, 2.01 mmol) in CH_2Cl_2 (15 mL) at −60 °C. After 5 min, a solution of **3** (0.640 g, 1.83 mmol) in CH_2Cl_2 (2 mL) was added. After 15 min, triethylamine (1.27 mL, 9.15 mmol) was added and the reaction mixture was allowed to warm to rt. After 1 h, water (20 mL) was added, the organics were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organics were washed with brine (3×50 mL), 1% HCl (3×50 mL), water (50 mL), and 5% $NaHCO_3$ (3×50 mL). The organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. This gave 0.626 g of 1-benzyl 4-*tert*-butyl 2-formylpiperazine-1,4-dicarboxylate as a thick oil, which was ~90% pure and used without further purification. R_f=0.10 in 30% EtOAc/hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.57 (br d, J=7.6 Hz, 1H), 7.40–7.24 (m, 5H), 5.14 (br d, J=17 Hz, 2H), 4.75–4.50 (br, 2H), 4.08–3.80 (br, 2H), 3.22–3.05 (br m, 2H), 2.94–2.78 (br, 1H), 1.42 (s, 9H). *n*-Butyl lithium (2.5 M solution in hexane, 0.80 mL, 2.0 mmol) was added to a suspension of methyltriphenylphosphonium bromide (0.832 g, 2.33 mmol) in THF (15 mL) at −78 °C. After 10 min, the reaction mixture was allowed to warm to rt. After 1 h, the reaction mixture was cooled to −78 °C and a solution of 1-benzyl 4-*tert*-butyl 2-formylpiperazine-1,4-dicarboxylate (0.626 g, 1.80 mmol) in THF (5 mL) was added dropwise. After 1 h, the reaction mixture was allowed to warm to rt and quenched with NH_4Cl (saturated, aqueous solution). The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3×50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (0–20% EtOAc in hexane gradient) gave 0.471 g (74%, 2 steps) of the title compound as a thick oil. Analytical data for **25**: R_f=0.48 in 30% EtOAc/hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.74 (ddd, J=4.8, 10.8, and 17.2 Hz, 1H), 5.26–5.10 (m, 4H), 4.77–4.66 (br, 1H), 4.40–3.82 (br m, 3H), 3.16–2.74 (br m, 3H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.7, 136.5, 134.4, 128.6, 128.2, 128.0, 117.6, 80.5, 67.7, 53.4, 46.9–45.0 (br), 44.3–42.2 (br), 39.8, 28.7. LC–MS: t_R=10.3 min, $[M+H]^+$=369.1. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.86; H, 7.56; N, 8.09. Found: C, 65.47; H, 7.49; N, 8.04.

4.3.15. 1-Benzyl 4-*tert*-butyl 2-(4-methoxyphenethyl)-piperazine-1,4-dicarboxylate (26). 9-Borabicyclo[3.3.1]-nonane (0.5 M solution in THF, 2.4 mL, 1.2 mmol) was added to **25** (102 mg, 0.294 mmol). After 2 h, 4-iodoanisole (103 mg, 0.441 mmol) and [1,1′-bis(diphenylphosphino)-ferrocene] dichloropalladium(II) complex with dichloromethane (1:1) (12 mg, 0.015 mmol) were added. Sodium hydroxide (1 N aqueous solution, 0.74 mL, 0.74 mmol) was added dropwise, and the reaction mixture was heated to reflux overnight. Upon cooling to rt, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (3×20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (0–20% EtOAc in hexane gradient) gave 90.6 mg (68%) of the desired product as a thick oil. Analytical data for **26**: R_f=0.13 in 20% EtOAc/hexane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26

(m, 10H), 7.12–6.96 (br, 2H), 6.82–6.72 (br, 2H), 5.12 (ABq, J_{AB}=12.4 Hz, 2H), 4.30–3.82 (br m, 4H), 3.75 (s, 3H), 3.10–2.40 (br m, 5H), 1.87–1.76 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 155.3, 154.9, 136.6, 133.4, 129.2, 128.6, 128.2, 128.0, 113.9, 80.3, 67.5, 55.5, 51.4, 47.0–45.0 (br), 45.0–42.8 (br), 39.2, 31.6, 31.0, 28.7. LC–MS: t_R=11.0 min, $[M+Na]^+$=477.2. Anal. Calcd for $C_{25}H_{32}N_2O_4$: C, 68.70; H, 7.54; N, 6.16. Found: C, 69.00; H, 7.62; N, 6.13.

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