Note

A Protocol for the Direct Conversion of Lactones to Lactams Mediated by 1,5,7-Triazabicyclo[4.4.0]dec-5-ene: Synthesis of Pyridopyrazine-1,6-diones

Danica A Rankic, Cory M. Stiff, Christopher W. am Ende, and John M. Humphrey

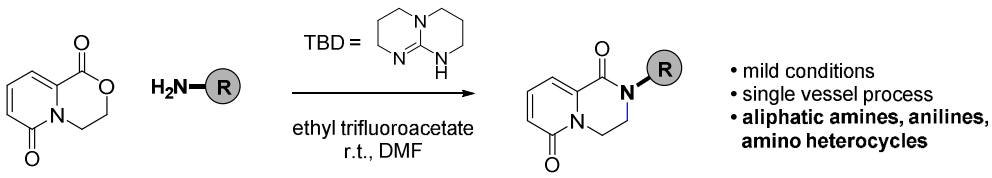
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02079 • Publication Date (Web): 19 Oct 2017

A Protocol for the Direct Conversion of Lactones to Lactams Mediated by 1,5,7-Triazabicyclo[4.4.0]dec-5-ene: Synthesis of Pyridopyrazine-1,6-diones

Danica A. Rankic,* Cory M. Stiff, Christopher W. am Ende, and John M. Humphrey

Pfizer Worldwide Research and Development, Eastern Point Road, Groton, Connecticut 06340, United States
danica.rankic@pfizer.com

Supporting Information Placeholder

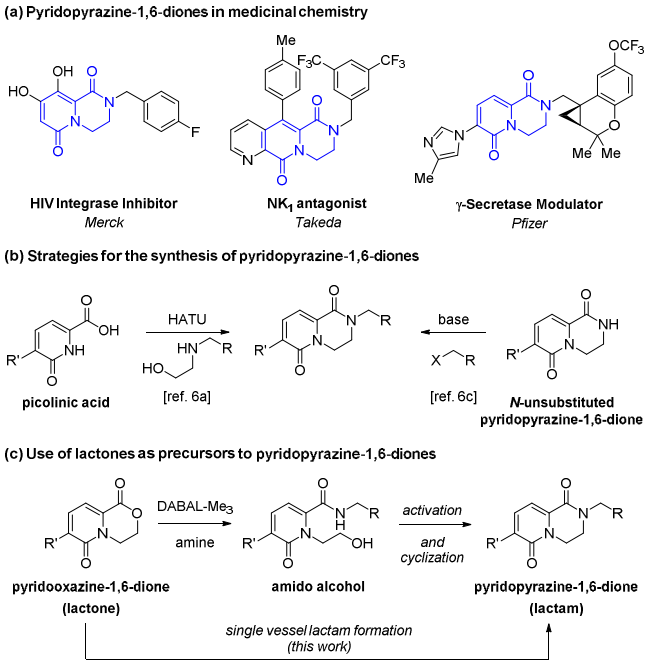


ABSTRACT: We present an operationally simple lactone-to-lactam transformation utilizing diverse amine nucleophiles. The key steps of amidation, alcohol activation and cyclization are all mediated by one reagent (TBD) in a single vessel at room temperature. We illustrate the convenience of this protocol by synthesizing a wide range of *N*-alkyl, *N*-aryl and *N*-hetereoaryl pyridopyrazine-1,6-diones, an important class of medicinally significant lactams. Furthermore, the reported methodology can be applied to the synthesis of milligram to hundred gram quantities of pyridopyrazine-1,6-diones without the use of specialized equipment.

Lactams are important substructures in natural products and biologically active compounds.[1] Although multiple methods for lactam synthesis exist, a highly atom and step economical approach is the direct conversion of a lactone to its corresponding cyclic amide via reaction with amines. This strategy is efficient for rapidly accessing structural diversity as nitrogen substitution of the final lactam can be varied with different amine nucleophiles. However, few methodologies have been reported for the mild conversion of a lactone to a lactam in a single vessel.[2] Most methods for the synthesis of cyclic amides from lactones in a unit operation rely on extreme reaction temperatures (>200 ˚C) and/or high pressures,[3] expensive stoichiometric additives or solvents,[4] or multistep reactions.[2b] We herein describe a step economical and operationally simple, single vessel synthesis of pyridopyrazine-1,6-diones, a class of lactams critical to the development of neurokinin-1 (NK_1) receptor antagonists,[5] HIV-1 integrase inhibitors[6] and γ-secretase modulators (GSMs) – potential treatments for Alzheimer's disease (Scheme 1a).[7]

A number of strategies have been employed to generate pyridopyrazine-1,6-diones[6,8] such as amidation of picolinic acids with amino alcohols and their subsequent cyclization[6a] and *N*-alkylation of an *N*-unsubstituted pyridopyrazine-1,6-dione[6c] which are complicated by challenges such as custom amino alcohol synthesis and competing elimination reactions, respectively (Scheme 1b). A key approach that we utilized while progressing our GSM program was a lactone-to-lactam conversion strategy. In this effort, a critical lactone (pyridooxazine-1,6-dione) intermediate was reacted with amines in order to generate an amido alcohol intermediate (Scheme 1c). To effect lactone aminolysis, we employed stoichiometric DABAL-Me_3, an air stable DABCO/$AlMe_3$ complex, as a Lewis acid (Scheme 1c).[9–11] The intermediate amido alcohol was then be converted to the pyridopyrazine-1,6-dione (lactam) by activation of the alcohol and subsequent base-mediated ring closure using a strong organic base such as DBU or 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).

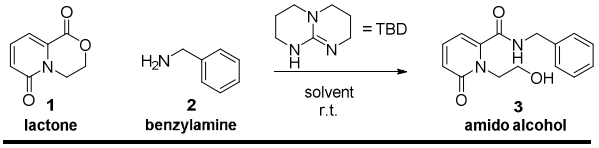
Scheme 1. Pyridopyrazine-1,6-diones: valuable lactam substructures in medicinal chemistry



The lactone-to-lactam conversion strategy proved effective for both non-hindered and hindered amines, enabling the preparation of a variety of pyridopyrazine-1,6-dione GSMs from an easily handled crystalline lactone intermediate. However, required isolation of the intermediate amido alcohol prior to cyclization was time consuming, added to the step-count and generated additional waste. Furthermore, scale-up of the lactone amidation chemistry is complicated by methane off-gassing upon quenching of the stoichiometric DABAL-Me_3 that is used in stoichiometric quantities. In order to address these challenges, we sought alternative reaction conditions to generate the key intermediate amido alcohol (Scheme 1c).

Literature reports of TBD being used to mediate direct ester amidation led us to investigate this reagent in our system.[12] Toward this end, we reacted benzyl amine (**2**) and lactone **1** in the presence of TBD in a variety of solvents (Table 1). Of the solvents utilized, DMF afforded the greatest conversions to amido alcohol **3** at a concentration of 1 M, and a full molar equivalent of TBD proved more effective than sub-stoichiometric amounts (Table 1, entries 5 and 6). Additionally, the reaction was complete in only 1 hour, providing the desired ring-opened product **3** in 83% yield (Table 1, entry 7). Further improvements in yield were realized when excess lactone **1** was employed (Table 1, entry 8, 95% yield). This is attributed to lactone **1** being prone to base-mediated hydrolysis and therefore, a slight excess of lactone was enough to overcome adventitious water.

Table 1. TBD amidation of lactone **1** with benzylamine

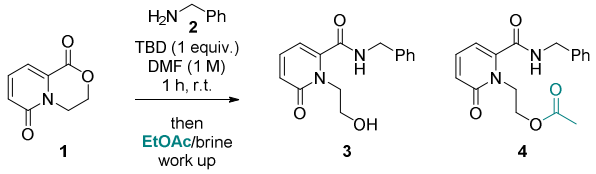


entry[a]	solvent	concentration (M)	TBD loading (equiv.)	time (h)	NMR yield (%)[b]
1	THF	0.5	1.0	18 h	40
2	CH_2Cl_2	0.5	1.0	18 h	66
3	MeCN	0.5	1.0	18 h	68
4	DMF	0.5	1.0	18 h	73
5	DMF	1.0	1.0	18 h	89
6	DMF	1.0	0.5	18 h	66
7	DMF	1.0	1.0	1 h	83
8[c]	**DMF**	**1.0**	**1.0**	**1 h**	**95**

[a] All reactions were performed on a 0.25 mmol scale with 1 equiv. of lactone and 1 equiv. of benzylamine unless otherwise stated. [b] 1,3,5-trimethoxybenzene was used as an internal standard. [c] 1.3 equiv. of lactone and 1 equiv. of benzylamine.

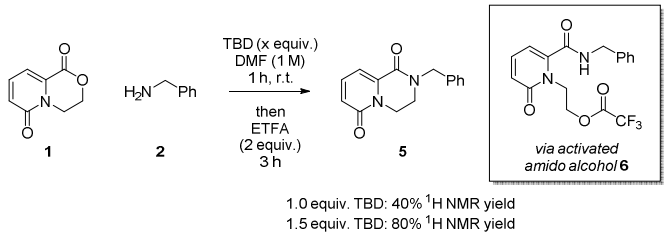
During the course of these early studies, we identified the side product **4** in the crude reaction mixture, a result of acylation of intermediate amido alcohol **3** with the extraction solvent ethyl acetate during work-up (Scheme 2).[13] Although compound **4** was inert to base-promoted cyclization, we surmised that replacement of the "acetate" with an electron-poor surrogate (e.g. trifluoroacetate) might set the stage for an efficient one-pot, direct lactone-to-lactam conversion.[14] In this way, TBD would serve as a catalyst for lactone amidation, a mediator of transesterification (for alcohol activation) as well as a base for the subsequent intramolecular *N*-alkylation.

Scheme 2. Observation of acetylated side product **4** upon workup



To test our hypothesis, the lactone aminolysis reaction (Table 1, entry 8) was run to completion at which point ethyl trifluoroacetate (ETFA) was added. Gratifyingly, the desired lactam was generated in 40% NMR yield (Scheme 3). The low yield was later attributed to insufficient quantities of the stoichiometric base required for the final ring closure. Increasing the amount of TBD from 1 equiv. to 1.5 equiv. afforded the desired pyridopyrazine-1,6-dione **5** in 80% ^{1}H NMR yield.

Scheme 3. Evaluation of conditions for the one-pot synthesis of pyridopyrazine-1,6-dione **5**.[15]

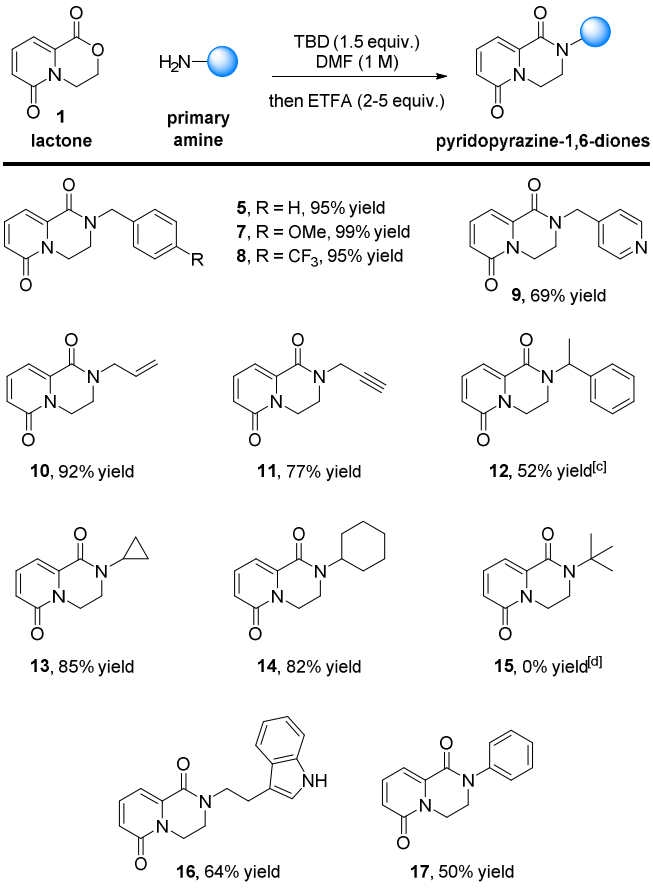


1.0 equiv. TBD: 40% ^{1}H NMR yield
1.5 equiv. TBD: 80% ^{1}H NMR yield

With these results in hand, we proceeded to examine the scope of amine nucleophiles that would be competent in this transformation. Benzyl amines containing electron withdrawing and electron donating groups perform well as nucleophiles in this reaction, providing the corresponding lactams in excellent yields (Table 2, examples **7**–**9**). Aliphatic amines such as allyl and propargyl amine as well as, amines with α-substitution (cyclopropyl, cyclohexyl and α-methyl benzylamine) were well tolerated, providing the desired lactams in 52–92% yield (examples **10–14**). *tert*-Butyl amine, however, did not provide the desired pyridopyrazine-1,6-dione **15**. We attribute this to the inability of the sterically encumbered activated intermediate amido alcohol to undergo deprotonation or cyclization. This hypothesis is supported by the isolation of the intermediate amido alcohol in 89% yield, indicating that *tert*-butyl amine is a viable nucleophile in the amidation step.[16]

We also found that tryptamine could be employed as a nucleophile without requiring a nitrogen protecting group on the indole (Table 2, example **16**). Furthermore, aniline is also a competent substrate in this transformation, providing access to *N*-phenyl pyridopyrazine-1,6-dione **17**. This result prompted us to investigate the use of amino heterocycles in this transformation. Thus, amino heterocycles such as 2- and 4-amino pyridines were employed as potential substrates for the one-pot synthesis of pyridopyrazine-1,6-diones; however, we found that these amines lacked the nucleophilicity needed to engage in the TBD amidation step. On the other hand, 2-ethoxy-4-amino pyridine and other electron rich 5-membered amino heterocycles were found to be sufficiently nucleophilic to afford the corresponding *N*-heteroaryl pyridopyrazine-1,6-diones in 45–81% yield (Table 3, examples **18**–**22**). Again, yields were highly dependent on the nucleophilicity of the amino group, with more electron rich systems providing higher yields. This is exemplified by the comparison of amino isoxazole and *N*-methyl amino pyrazole (examples **19** and **20**).

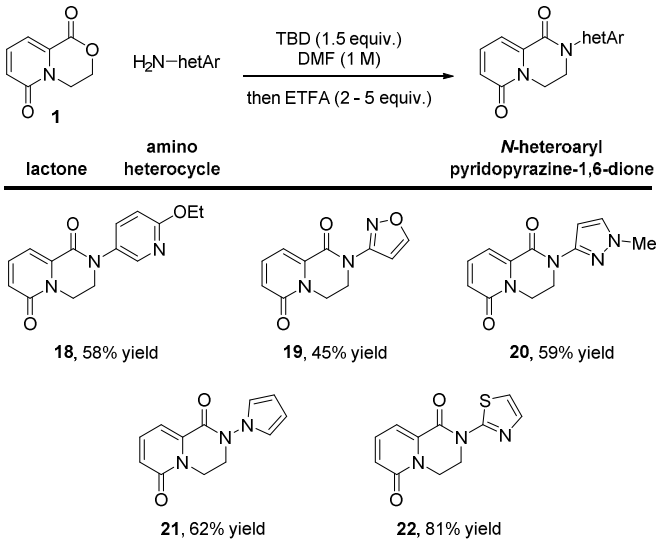
Table 2. Evaluation of primary amine scope for the one-pot synthesis of pyridopyrazine-1,6-diones.[a], [b]



[a] All reactions were performed on a 1 mmol scale with 1.3 equiv. of lactone and 1 equiv. of amine unless otherwise stated. [b] All yields reported are isolated yields. [c] Performed on a 1.3 mmol scale with 2 equiv. of TBD. [d] Intermediate amido alcohol was isolated in 89% yield and no ring closure was observed.[16]

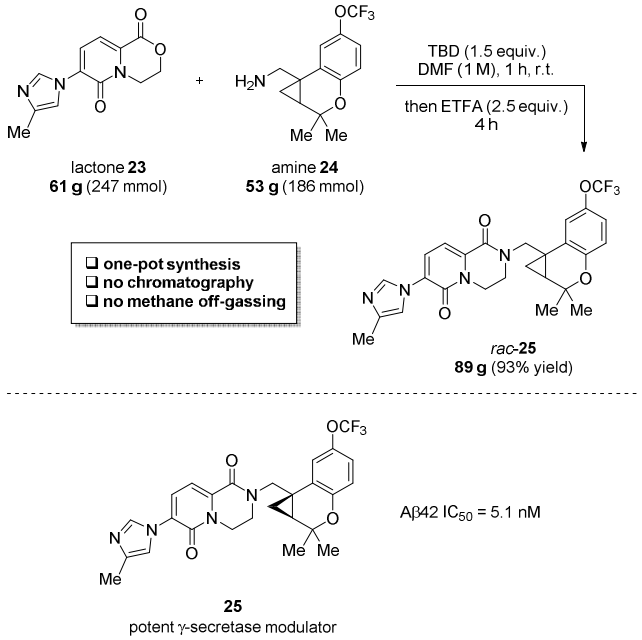
In addition to its broad substrate scope, the TBD-mediated one-pot synthesis of pyridopyrazine-1,6-diones proved highly effective on elevated scales required for exploratory toxicology studies. We demonstrated this with the synthesis of **25**, a highly potent and selective γ-secretase modulator (Scheme 4).[17] Lactone **23** was subjected to TBD-mediated aminolysis with cyclopropyl chromane amine **24**. Consumption of amine **24** and presence of the intermediate amido alcohols was observed after 1 h and at this time ETFA was added to the reaction mixture. After an additional 4 hours, full conversion to *rac*-**25** was observed. By simply diluting the reaction mixture with water, the desired product was precipitated from the reaction mixture and could be collected by vacuum filtration. After washing the collect solids with water, azeotroping with toluene and drying, 89 grams of *rac*-**25** were obtained as a white solid in 93% yield.

Table 3. Evaluation of amino heterocycle nucleophiles in the one-pot synthesis of *N*-heteroaryl pyridopyrazine-1,6-diones.[a], [b]



[a] All reactions were performed on a 1 mmol scale with 1.3 equiv. lactone and 1 equiv. of amine unless otherwise stated. [b] All yields reported are isolated yields.

Scheme 4. Large scale pyridopyrazine-1,6-dione synthesis



In conclusion, we have developed a mild, single vessel lactone-to-lactam conversion for the synthesis of pyridopyrazine-1,6-diones utilizing TBD to mediate all key steps in this transformation: lactone amidation, alcohol activation with ETFA and deprotonative cyclization. The described transformation has a broad substrate scope that is capable of generating *N*-substituted pyridopyrazine-1,6-diones from a wide variety of amines including branched and unbranched aliphatic amines, anilines and amino heterocycles. Furthermore, this method was found to be highly scalable, generating cyclopropyl chromane γ-secretase modulator **26** on an 89 g scale, without the need for specialized equipment, liquid-liquid extraction or chromatography.

Experimental Section

General. All solvents and reagents were obtained from commercial sources and were used as received. All reactions were monitored by TLC (TLC plates F254, Merck) or UPLC-MS analysis (Waters Acquity, ESCI +/–, APCI +/–). ^{1}H NMR and ^{13}C NMR spectra were obtained using deuterated solvent on a Varian or Bruker 400 MHz instrument. All ^{1}H NMR shifts are reported in δ units (ppm) relative to the signals for chloroform (7.27 ppm) or methanol (3.31 ppm). All ^{13}C shifts are reported in δ units (ppm) relative to the signals for chloroform (77.0 ppm) or methanol (49.1 ppm) with ^{1}H-decoupled observation. All coupling constants (J values) are reported in hertz (Hz). NMR abbreviations are as follows: br, broadened; s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets. High-resolution mass spectra (HRMS) were acquired on an Agilent model 6220 MS (ESI-TOF). Column chromatography was carried out on silica gel 60 (32-60 mesh, 60 Å) or on pre-packed Biotage™ or ISCO columns.

Synthesis of Lactone 1: *3,4-dihydropyrido[2,1-c][1,4]oxazine-1,6-dione* (**1**): To 6-oxo-1,6-dihydropyridine-2-carboxylic acid (5.00 g, 34.1 mmol, 95% purity) in anhydrous DMSO (18 mL) was added cesium carbonate (17.6 g, 53.9 mmol) followed by 1,2-dibromoethane (16.0 g, 85.4 mmol). The resultant slurry was heated to 85 °C for 1.5 h, and the resultant dark solution was then cooled to rt and partitioned between dichloromethane (4 × 40 mL) and 10% saturated sodium bicarbonate (1 × 40 mL). The combined cloudy extracts were treated with solid sodium chloride (5.0 g) and decolorizing carbon (3.4 g) with stirring for 20 min. The mixture was filtered through celite and the dichloromethane was removed under reduced pressure to afford a slurry of product in residual DMSO. The slurry was triturated with ethanol (4 mL) in an ice bath for 20 min, and the solid was collected via filtration and rinsed with ethyl ether to afford 4.77 g (85%) of the title compound as an off-white crystalline solid. The material may be recrystallized from ethyl acetate to afford off-white prisms. m.p. 178.2 – 180.4 °C; LCMS m/z 166 $[M + H]^+$; IR (thin film) ν_{max} 1649 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (dd, J = 7.0, 9.4 Hz, 1H), 7.08 (dd, J = 1.2, 7.0 Hz, 1H), 6.76 (dd, J = 1.2, 9.4 Hz, 1H), 4.64 (t, J = 5.1 Hz, 2H), 4.15 (t, J = 5.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) 159.4, 159.0, 138.6, 133.4, 124.9, 65.6, 38.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_8NO_3$ 166.0498, found 166.0496.

Synthesis and characterization of intermediate amido alcohol 3. *N-benzyl-1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-2-carboxamide* (**3**): To a suspension of lactone **1** (215.0 mg, 1.3 mmol) and TBD (220.0 mg, 1.5 mmol) in DMF (1.0 mL) was added benzylamine (0.11 mL, 1.00 mmol) and the reaction mixture was stirred at room temperature for 2 h. The reaction was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined EtOAc layers were washed with water, brine and then dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the product as a white solid (0.207 g, 0.76 mmol, 76%). LCMS m/z 273.5 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 6H), 7.00 (s, 1H), 6.61 (dd, J = 9.2, 1.3 Hz, 1H), 6.36 (dd, J = 6.8, 1.4 Hz, 1H), 4.59 (d, J = 5.8 Hz, 2H), 4.26 (dd, J = 5.6, 4.4 Hz, 2H), 3.95 (dd, J = 5.6, 4.4 Hz, 2H), 3.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 163.1, 144.3, 138.7, 137.0, 128.9, 128.0, 127.9, 122.3, 122.3, 106.8, 60.5, 48.9, 44.2.; IR (thin film) ν_{max} 3199 (O–H), 1644 (C=O), 1053 (C–O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}N_2O_3Na$ 295.1053, found 295.1049.

General procedure for the synthesis of *N*-alkyl, *N*-aryl and *N*-heteroaryl pyridopyrazine-1,6-diones. Note that this general procedure was followed unless otherwise stated. To a suspension of lactone **1** (215.0 mg, 1.3 mmol) and TBD (220.0 mg, 1.5 mmol) in DMF (1.0 mL) was added nitrogen nucleophile (1.00 mmol) and the reaction mixture was stirred at room temperature.

The reaction was monitored by LCMS for consumption of nitrogen nucleophile and the presence of the corresponding intermediate amido alcohol. ETFA (0.24 mL, 2.00 mmol) was added to the reaction mixture and stirring was continued at room temperature. The ring closure was monitored by LCMS for consumption of amido alcohol intermediate and presence of pyridopyrazine-1,6-dione. The reaction was quenched with aqueous 1N NaOH (2 mL) and extracted into either DCM or EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine and then dried over $MgSO_4$, filtered and evaporated. The resulting residue was purified by silica gel chromatography.

Synthesis and characterization of pyridopyrazine-1,6-diones 5, 7–14, 16-22: *2-benzyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione* (**5**): The general procedure was followed using benzylamine (0.11 mL, 1.00 mmol) and the reaction mixture was stirred at room temperature for 1 h. ETFA was added and the reaction was stirred for 1 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the title compound as a white solid (0.241 mg, 0.95 mmol, 95%). The spectral data matched that reported in the literature.[8a] LCMS m/z 255.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, J = 8.1 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.22 (d, J = 6.8 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 4.77 (s, 2H), 4.26 – 4.11 (m, 2H), 3.54 (dd, J = 6.7, 5.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.3, 138.7, 136.8, 135.5, 129.0, 128.2, 124.1, 109.3, 50.7, 43.3, 39.0.

2-(4-methoxybenzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**7**): The general procedure was followed using 4-methoxybenzyl amine (137.0 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 1 h. ETFA was added and the reaction was stirred overnight prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (50 – 100% EtOAc in heptane) to afford the title product as a thick oil that slowly solidified to an off-white solid (0.281 g, 0.99 mmol, 99%). LCMS m/z 285.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 9.0, 7.1 Hz, 1H), 7.25 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 7.9 Hz, 2H), 6.76 (d, J = 9.2 Hz, 1H), 4.70 (s, 2H), 4.18 (t, J = 5.9 Hz, 2H), 3.82 (d, J = 1.5 Hz, 3H), 3.52 (t, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 159.5, 158.2, 138.6, 136.8, 129.7, 127.6, 124.1, 114.3, 109.2, 55.3, 50.0, 43.0, 39.0.; IR (thin film) ν_{max} 1636 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{17}N_2O_3$ ($[M + H]^+$) 285.1234, found 285.1231.

2-(4-(trifluoromethyl)benzyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**8**): The general procedure was followed using 4-(trifluoromethyl)benzylamine (175 mg, 1.00 mmol) and the reaction mixture was stirred at room temperature for 1 h. ETFA was added and the reaction was stirred for an additional hour prior to work up using EtOAc and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 10% MeOH in DCM) to afford the title product as a white solid (0.306 g, 0.95 mmol, 95%). LCMS m/z 323.4 $[M + H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (d, J = 8.2 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.20 (dd, J = 1.6, 7.0 Hz, 1H), 6.72 (dd, J = 1.2, 9.0 Hz, 1H), 4.81 (s, 2H), 4.24 – 4.15 (m, 2H), 3.70 – 3.61 (m, 2H).; ^{13}C NMR (100 MHz, CD_3OD) δ 163.1, 160.3, 142.1, 141.0, 138.5, 131.2 (q, $^2J_{C-F}$ = 32.1 Hz), 129.8, 126.9 (q, $^3J_{C-F}$ = 3.51 Hz), 125.8 (q, $^1J_{C-F}$ = 271.1 Hz), 124.6, 111.1, 51.4, 45.1, 40.7; IR (thin film) ν_{max} 1641 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{14}F_3N_2O_2$ 323.1002, found 323.1000.

2-(pyridin-4-ylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**9**): The general procedure was followed using 4-pyridine methanamine (108 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. ETFA was added and the reaction was stirred for 2 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the title compound as an off-white solid (0.177 g, 0.69 mmol, 69%). LCMS m/z 256.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.55 (m, 3H), 7.47 (ddd, J = 8.7, 7.1, 1.1 Hz, 1H), 7.25 (d, J = 5.2 Hz, 2H), 7.22 (d, J = 6.9 Hz, 1H), 6.79 (d, J = 9.3 Hz, 1H), 4.78 (s, 2H), 4.26 (t, J = 5.9 Hz, 2H), 3.60 (t, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 158.6, 150.1, 145.0, 138.6, 136.2, 124.6, 122.8, 109.5, 50.0, 44.1, 38.9.; IR (thin film) ν_{max} 1633 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_3O_2$ 256.1081, found 256.1076.

2-allyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**10**): The general procedure was followed using allyl amine (57.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 10 min. ETFA was added and the reaction was stirred overnight prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (50 – 100% EtOAc in heptane) to afford the title compound as an off-white solid (0.188 g, 0.92 mmol, 92%). LCMS m/z 205.1 $[M + H]^+$; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.45 (dd, J = 7.0, 9.2 Hz, 1H), 7.18 (dd, J = 1.4, 7.0 Hz, 1H), 6.77 (dd, J = 1.4, 9.2 Hz, 1H), 5.88 – 5.76 (m, 1H), 5.34 – 5.31 (m, 1H), 5.29 (qd, J = 1.3, 8.0 Hz, 1H), 4.29 – 4.23 (m, 2H), 4.19 (td, J = 1.4, 6.1 Hz, 2H), 3.62 – 3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 158.0, 138.6, 136.7, 131.4, 124.1, 119.2, 109.1, 49.7, 43.3, 39.0.; IR (thin film) ν_{max} 1632 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_2$ 205.0972, found 205.0966.

2-(prop-2-yn-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**11**): The general procedure was followed using propargylamine (55.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 30 min. ETFA was added and the reaction was stirred overnight prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (50 – 100% EtOAc in heptane) to afford the title compound as an off-white solid (0.155 g, 0.77 mmol, 77%). LCMS m/z 203.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 9.2, 6.9 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 9.2 Hz, 1H), 4.43 (d, J = 2.5 Hz, 2H), 4.34 – 4.26 (m, 2H), 3.84 – 3.72 (m, 2H), 2.34 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 157.9, 138.6, 136.3, 124.5, 109.4, 76.8, 73.5, 43.1, 38.9, 36.1.; IR (thin film) ν_{max} 3232, 2125, 1633 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}N_2O_2$ 203.0815, found 203.0808.

2-(1-phenylethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**12**): To a suspension of lactone **1** (280.0 mg, 1.7 mmol) in DMF (1.3 mL) was added α-methyl benzylamine (0.17 mL, 1.3 mmol) followed by TBD (272.0 mg, 1.95 mmol). The reaction mixture was stirred at room temperature for 2 h after which ethyl trifluoroacetate (0.24 mL, 1.3 mmol) was added to the reaction mixture and stirring was continued at room temperature for an additional 1 h. TLC analysis revealed that major product was the intermediate amido alcohol. An additional portion of ethyl trifluoroacetate (0.54 mL, 5.2 mmol) was added to the reaction mixture and stirring was continued overnight. TLC analysis revealed that some intermediate amido alcohol still remained. An additional portion of TBD (90.6 mg, 0.65 mmol) was added and complete conversion was realized by TLC analysis after 2 h. The reaction was quenched with aqueous 1N NaOH (2 mL) and stirred for 15 min. The mixture was partitioned between water and ethyl acetate. The layers were separated and the organic layer was washed with brine and dried over $MgSO_4$. Filtered and evaporated to afford a colorless oil that was purified by silica gel chromatography (100% EtOAc). The title compound was obtained as an off-white solid (0.180 g, 0.68 mmol, 52%). The spectral data matched that reported in the literature.[8a] LCMS m/z 269.5 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 9.2, 6.9 Hz, 1H), 7.30 – 7.42 (m, 5H), 7.23 (dd, J = 6.9, 1.4 Hz, 1H), 6.75 (dd, J = 9.2, 1.4 Hz, 1H), 6.11 (q, J = 7.1 Hz, 1H), 4.28 (ddd, J = 14.2, 6.4, 3.9 Hz, 1H),

3.88 (ddd, J = 14.2, 8.9, 4.0 Hz, 1H), 3.45 (ddd, J = 13.0, 8.9, 3.9 Hz, 1H), 3.18 (ddd, J = 13.4, 6.5, 4.0 Hz, 1H), 1.61 (d, J = 7.1 Hz, 3H).

2-(cyclopropylmethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**13**): The general procedure was followed using cyclopropylamine (57.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. ETFA was added and the reaction was stirred for 2 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the title compound as an off-white solid (0.173 g, 0.85 mmol, 85%). LCMS m/z 205.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.8, 7.1 Hz, 1H), 7.19 (d, J = 6.9 Hz, 1H), 6.77 (d, J = 9.2 Hz, 1H), 4.23 (t , J = 5.9 Hz, 2H), 3.63 (t, J = 5.9 Hz, 2H), 2.91 (dt, J = 7.4, 3.6 Hz, 1H), 0.98 (q, J = 6.6 Hz, 2H), 0.83 – 0.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 159.8, 138.7, 137.0, 124.0, 108.9, 44.6, 39.6, 30.3, 7.0.; IR (thin film) ν_{max} 1637 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}N_2O_2$ 205.0972, found 205.0966.

2-cyclohexyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**14**): The general procedure was followed using cyclohexylamine (99.2 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 2 h. ETFA was added and the reaction was stirred overnight prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the title compound as an off-white solid (0.201 g, 0.82 mmol, 82%). LCMS m/z 247.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, J = 9.2, 6.9 Hz, 1H), 7.16 (d, J = 6.9 Hz, 1H), 6.75 (d, J = 9.2 Hz, 1H), 4.68 – 4.41 (m, 1H), 4.21 (dd, J = 6.7, 4.9 Hz, 2H), 3.54 (dd, J = 6.7, 4.9 Hz, 2H), 1.95 – 1.81 (m, 2H), 1.81 – 1.68 (m, 3H), 1.55 – 1.34 (m, 4H), 1.20 – 1.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.6, 138.8, 137.3, 123.7, 109.1, 53.1, 39.4, 38.7, 29.8, 25.4, 25.3.; IR (thin film) ν_{max} 1635 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{19}N_2O_2$ 247.1441, found 247.1436.

2-(2-(1H-indol-3-yl)ethyl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**16**): The general procedure was followed using tryptamine (0.160 g, 1.00 mmol) and the reaction mixture was stirred at room temperature for 1 h. ETFA was added and the reaction was stirred for 1 h prior to work up using EtOAc and 1N NaOH as described. The resulting beige solid was recrystallized from EtOAc to afford the title compound as a crystalline white solid (0.196 g, 0.64 mmol, 64%). m.p. 209.0 – 214.1 ˚C (decomp.); LCMS m/z 308.4 $[M + H]^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.84 (br. s., 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.54 (dd, J = 7.0, 9.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 2.4 Hz, 1H), 7.12 – 7.04 (m, 1H), 7.02 – 6.93 (m, 2H), 6.62 (dd, J = 1.2, 9.3 Hz, 1H), 4.03 – 3.97 (m, 2H), 3.77 – 3.66 (m, 2H), 3.65 – 3.56 (m, 2H), 2.99 (t, J = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 157.3, 138.9, 137.4, 136.3, 127.1, 123.0, 122.7, 121.0, 118.3, 118.2, 111.5, 111.0, 107.3, 47.9, 43.8, 38.6, 22.8; IR (thin film) ν_{max} 3281 (N–H), 1639 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}N_3O_2$ 308.1394, found 308.1390.

2-phenyl-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**17**): The general procedure was followed using aniline (0.09 mL, 93.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature overnight. ETFA was added and the reaction was stirred for 2 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford an off-white solid containing residual DMF. The solid was azeotroped with heptane (3 × 20 mL) to afford the title compound as an off-white solid (0.120 g, 0.50 mmol, 50%). LCMS m/z 241.5 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 3H), 7.41 – 7.36 (m, 2H), 7.35 – 7.29 (m, 1H), 7.26 (partially obscured by solvent, dd, J = 9.2, 1.4 Hz, 1H), 6.82 (dd, J = 9.2, 1.4 Hz, 1H), 4.47 – 4.39 (m, 2H), 4.11 – 4.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 157.8, 141.1, 138.7, 137.1, 129.3, 127.3, 124.6, 124.4, 109.7, 47.2, 39.5.; IR (thin film) ν_{max} 1640 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{13}N_2O_2$ 241.0972, found 241.0969.

2-(6-ethoxypyridin-3-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**18**): The general procedure was followed using 6-ethoxypyridin-3-amine (138.0 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 6 h. ETFA was added and the reaction was stirred overnight prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0% – 10% MeOH in DCM) to afford the title compound as a pink solid (0.162 g, 0.57 mmol, 57%). LCMS m/z 286.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 2.7 Hz, 1H), 7.61 (dd, J = 8.9, 2.8 Hz, 1H), 7.48 (dd, J = 9.2, 6.9 Hz, 1H), 7.22 (dd, J = 6.9, 1.3 Hz, 1H), 6.84 – 6.74 (m, 2H), 4.44 – 4.33 (m, 5H), 4.05 – 4.00 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 160.7, 158.1, 142.8, 138.6, 136.7, 135.7, 131.5, 124.5, 111.3, 109.8, 62.2, 47.5, 39.3, 14.5.; IR (thin film) ν_{max} 1648 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{16}N_3O_3$ 286.1186, found 286.1184.

2-(isoxazol-3-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**19**): The general procedure was followed using 3-amino isoxazole (84.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature overnight. ETFA was added and the reaction was stirred for 1.5 h prior to work up using DCM and 1N NaOH as described. Due to the presence of residual DMF, the resulting residue was taken up in DCM and the solution was re-washed with water then brine. The resulting solution was dried over Na_2SO_4, filtered and evaporated to afford the title compound as a white solid (0.105 g, 0.45 mmol, 45%). LCMS m/z 232.3 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 1.8 Hz, 1H), 7.49 (dd, J = 9.2, 6.9 Hz, 1H), 7.27 – 7.23 (m, 2H), 6.84 (dd, J = 9.2, 1.3 Hz, 1H), 4.45 – 4.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.6, 159.0, 156.8, 138.4, 136.1, 125.3, 110.5, 100.6, 43.7, 38.7; IR (thin film) ν_{max} 1651 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{10}N_3O_3$ 232.0717, found 232.0709.

2-(1-methyl-1H-pyrazol-3-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**20**): The general procedure was followed using 1-methyl-1*H*-pyrazol-3-amine (84.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature overnight. ETFA was added and the reaction was stirred for 5 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (0% – 10% MeOH in DCM) to afford the title compound as a white solid (0.155 g, 0.64 mmol, 64%). LCMS m/z 245.1 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 9.2, 6.9 Hz, 1H), 7.33 (d, J = 2.3 Hz, 1H), 7.23 (dd, J = 7.0, 1.3 Hz, 1H), 6.88 (d, J = 2.3 Hz, 1H), 6.78 (dd, J = 9.2, 1.3 Hz, 1H), 4.39 – 4.29 (m, 4H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 156.3, 148.0, 138.6, 137.1, 131.2, 124.2, 109.5, 99.4, 43.3, 39.0.; IR (thin film) ν_{max} 1644 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}N_4O_2$ 245.1033, actual 245.1034.

2-(1H-pyrrol-1-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**21**): The general procedure was followed using 1-amino pyrrole (82.1 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature overnight. ETFA was added and the reaction was stirred for 1.5 h. The reaction was quenched with aqueous 1N NaOH (1 mL) and stirred for 10 min upon which a white precipitate formed. Water (1 mL) was added to the slurry and stirring continued for 5 min. The slurry was filtered on a glass frit. The filter cake was washed with water, ether and heptane and allowed to dry on the frit to afford the title product as a white powder (0.143 g, 0.62 mmol, 62%). LCMS m/z 230.4 $[M + H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 9.3, 6.9 Hz, 1H), 7.25 (dd, J =

6.9, 1.4 Hz, 1H), 6.84 (dd, *J* = 9.3, 1.4 Hz, 1H), 6.74 (t, *J* = 2.3 Hz, 2H), 6.26 (t, *J* = 2.3 Hz, 2H), 4.50 (t, *J* = 5.8 Hz, 2H), 4.09 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 157.7, 138.7, 135.8, 125.4, 119.5, 110.4, 108.7, 49.8, 40.0; IR (thin film) ν_{max} 1651 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{12}H_{12}N_3O_2$ 230.0924, found 230.0923.

2-(thiazol-2-yl)-3,4-dihydro-2H-pyrido[1,2-a]pyrazine-1,6-dione (**22**): The general procedure was followed using 2-amino thiazole (100.0 mg, 1.0 mmol) and the reaction mixture was stirred at room temperature for 1 h. ETFA was added and the reaction was stirred for 2 h prior to work up using DCM and 1N NaOH as described. The resulting residue was purified by silica gel chromatography (30 – 100% EtOAc in heptane) to afford the title compound as a white solid (0.20 g, 0.8 mmol, 80%). LCMS m/z 248.4 [M + H] $^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 3.5 Hz, 1H), 7.52 (dd, *J* = 9.3, 6.9 Hz, 1H), 7.32 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.17 (d, *J* = 3.6 Hz, 1H), 6.87 (dd, *J* = 9.2, 1.3 Hz, 1H), 4.73 – 4.62 (m, 2H), 4.47 – 4.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 158.0, 156.5, 138.5, 137.6, 135.6, 125.5, 116.4, 110.5, 43.7, 38.8. IR (thin film) ν_{max} 1640 (C=O) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{10}N_3O_2S$ 248.0488, found 248.0481.

Synthesis and characterization of intermediate amido alcohol 15a – precursor to targeted pyridopyrazine-1,6-dione 15: *N-(t-butyl)-1-(2-hydroxyethyl)-6-oxo-1,6-dihydropyridine-2-carbox-amide* (**15a**): To a suspension of lactone 1 (215.0 mg, 1.3 mmol) and TBD (220.0 mg, 1.5 mmol) in DMF (1.0 mL) was added tert-butyl amine (0.11 mL, 1.00 mmol) and the reaction mixture was stirred at room temperature for 24 h. The reaction was partitioned between water and EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined EtOAc layers were washed with water, brine and then dried over Na_2SO_4, filtered and evaporated. The resulting residue was purified by silica gel chromatography (0 – 5% MeOH in DCM) to afford the product as a white solid (0.213 g, 0.89 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 9.2, 6.8 Hz, 1H), 6.64 (dd, *J* = 9.2, 1.4 Hz, 1H), 6.29 (dd, *J* = 6.7, 1.4 Hz, 1H), 6.27 (br s, 1H, N–H), 4.31 – 4.22 (m, 2H), 4.00 (q, *J* = 4.8 Hz, 2H), 3.84 (t, *J* = 5.0 Hz, 1H, O–H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 145.2, 138.7, 122.1, 105.9, 60.7, 52.8, 49.0, 28.5.; IR (thin film) ν_{max} 3200 (O–H), 1647 (C=O), 1053 (C–O) cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{12}H_{19}N_2O_3$ 239.1390, found 239.1385.

Procedure for the large scale preparation of γ-secretase modulator *rac*-25: To a suspension of lactone **23**[10b] (60.6 g, 0.247 mol) and amine **24**[17] (53.3 g, 0.186 mol) in DMF (200 mL) was added TBD (39.9 g, 0.278 mol) and the reaction mixture was stirred at room temperature. After 1 h, LCMS analysis revealed consumption of amine **24** and the presence of the corresponding intermediate amido alcohol. ETFA (55 mL, 0.460 mol) was added dropwise to the reaction mixture over 30 minutes and stirring was continued at room temperature for an additional hour. The reaction was quenched with aqueous 1N NaOH (200 mL). The resulting suspension was stirred at room temperature for 30 min and then filtered. The obtained solids were washed with water, azeotroped with toluene (3 × 500 mL) and dried under vacuum to afford the product as a white solid (88.9 g, 173 mmol, 93% yield). Analytical data matched that reported in the literature.[17] LCMS m/z 515.2 (M + H)$^+$; ^{1}H NMR (400 MHz, CD_3OD-d_4) δ 8.29 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.49 (s, 1H), 7.26 – 7.33 (m, 2H), 6.95 (d, *J* = 9.8 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 5.11 (d, *J* = 14.8 Hz, 1H), 4.20 – 4.26 (m, 2H), 3.77 – 3.84 (m, 2H), 3.01 (d, *J* = 14.8 Hz, 1H), 2.23 (s, 3H), 2.02 (t, *J* = 7.2 Hz, 1H), 1.50 (s, 3H), 1.28 (s, 3H), 1.08 (d, *J* = 7.4 Hz, 2H).

ASSOCIATED CONTENT

Supporting Information

Experimental details including ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: danica.rankic@pfizer.com

Author Contributions

The manuscript was written through contributions of all authors and all authors have given approval to the final version of the manuscript.

Notes

The authors have no competing financial interests.

ACKNOWLEDGMENT

The authors would like to thank Martin Pettersson, Akshay Shah, Christopher Helal, Patrick Verhoest, Anabella Villalobos and Prof. E. J. Corey for their useful discussions and feedback during the preparation of this manuscript.

REFERENCES

(1) (a) Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams (1993)*; John Wiley & Sons, Inc.; West Sussex, England, 2010; p 1-268. (b) *Natural Lactones and Lactams; Synthesis, Occurrence and Biological Activity*; Janecki, T., Ed Wiley-VCH: Weinheim, Germany, 2013.

(2) (a) For an Ir-catalyzed hydrogen autotransfer/transamidation approach, see: Kim, K.; Hong, S. H. *J. Org. Chem.* **2015**, *80,* 4152. (b) For an approach using solid supported reagents and scavengers, see: Kawahata, N. H.; Brookes, J.; Makara, G. M. *Tetrahedron Lett.***2002**, *43*, 7221.

(3) (a) Decker, M.; Nguyen, T. T. H.; Lehmann, J. *Tetrahedron* **2004**, *60*, 4567. (b) Zienty, F. B.; Steahly, G. W. *J. Am. Chem. Soc.* **1947**, *69*, 715. (c) Späth, E.; Lintner, J. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 2727.

(4) Orrling, K. M.; Wu, X.; Russo, F.; Larhed, M. *J. Org. Chem.* **2008**, *73*, 8627.

(5) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fuishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Doi, T. *J. Med. Chem.* **1999**, *42*, 3982.

(6) Wai, J. S.; Kim, B.; Fisher, T. E.; Zuang, L.; Embrey, M. W.; Williams, P. D.; Staas, D. D.; Culberson, C.; Lyle, T. A.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Schleif, W. A.; Gabryelski, L. J.; Jin, L.; Chen, I.-W.; Ellis, J. D.; Mallai, R.; Young, S. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5595.

(7) For recent reviews on γ-secretase modulators as potential therapeutics in Alzheimer's Disease including examples of pyridopyrazine-1,6-diones see: (a) Johnson, D. S.; Pettersson, M. *Top. Med. Chem.* **2017**, *24*, 87. (b) Bursavich, M. G.; Harrison, B. A.; Blain, J.-F. *J. Med. Chem.* **2016**, *59*, 7389.

(8) (a) Tran, T. P.; Mullins, P. B.; am Ende, C. W.; Pettersson, M. *Org. Lett.* **2013**, *15*, 642. (b) *Janssen Pharmaceuticals, Inc.* WO 2014096212; **2014** (c) *Janssen Pharmaceuticals, Inc.* WO 2014111457 A1; **2014** (d) for related cyclization with bis (2-chloroethyl amine) see: Pettersson, M.; Johnson, D. S.; Subramanyam, C.; Bales, K. R.; am Ende, C. W.; Fish, B. A.; Green, M. A.; Kauffman, G. W.; Mullins, P. B.; Navaratnam, T.; Sakya, S. M.; Stiff, C. M.; Tran, T. P. Xie, L.; Zhang, L.; Pustilnik, L. R.; Vetelino, B. C.; Wood, K. M.; Pozdnyakov, N.; Verhoest, P. R.; O'Donnell, C. J. *J. Med. Chem.* **2014**, *57*, 1046.

(9) A number of conditions were evaluated for efficient lactone amidation. Of these, two reagents were found to be superior: DABAL-Me_3 (which even outperformed related $AlMe_3$) and triazabicyclodecene (TBD). Direct aminolysis with amines at elevated temperatures

was successful, with the caveat that a large excess of amine was required to drive the reaction beyond ~60% conversion. While acceptable for simple and readily available amines, an alternative approach is required when both coupling partners are precious.

(10) For examples of lactone amidation with DABAL-Me_3 see: (a) Pettersson, M.; Johnson, D. S.; Humphrey, J. M.; am Ende, C. W.; Evrard, E.; Efremov, I.; Kauffman, G. W.; Stepan, A. F.; Stiff, C. M.; Xie, L.; Bales, K. R.; Hajos-Korcsok, E.; Murrey, H. E.; Pustilnik, L. R.; Steyn, S. J.; Wood, K. M.; Verhoest, P. R. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 908. (b) Pettersson, M.; Johnson, D. S.; Humphrey, J. M.; Butler, T. W.; am Ende, C. W.; Fish, B. A.; Green, M. E.; Kauffman, G. W.; Mullins, P. B.; O'Donnell, C. J.; Stepan, A. F.; Stiff, C. M.; Subramanyam, C.; Tran, T. P.; Vetelino, B. C.; Yang, E.; Xie, L.; Bales, K. R.; Pustilnik, L. R.; Steyn, S. J.; Wood, K. M.; Verhoest, P. R. *ACS Med Chem Lett.* **2015**, 6, 596. (c) *Pfizer, Inc.*US9193726 B2.

(11) (a) For an initial report of DABAL-Me_3 see: Bradford, A. M.; Bradley, D. C.; Hursthouse, M. B.; Motevalli, M. *Organometallics* **1992**, *11*, 111. (b) For a review on the initial discovery and uses of DABAL-Me_3 as a reagent that can be used in the absence of an inert atomosphere see: Woodward, S. *Synlett* **2007**, *10*, 1490. (c) For the use of DABAL-Me_3 in amide bond formation see: Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Tetrahedron Lett.* **2006**, *47*, 5767.

(12) Sabot, C.; Kumar, K. A.; Meunier, S.; Mioskowski, C.; *Tetrahedron Lett.***2007**, *48*, 3863.

(13) TBD is known to mediate transesterification, see: Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556.

(14) It has previously been demonstrated that the amido alcohol activation with trifluoromethyl acetic anhydride and subsequent deprotonation with DBU mediates lactam formation. See reference 10b for more details.

(15) 1,3,5-trimethoxy benzene was used as a standard for reported ^1H NMR yields.

(16) See supporting information for more detail.

(17) Pettersson, M.; Johnson, D. S.; Rankic, D. A.; Kauffman, G. W.; am Ende, C. W.; Butler, T. W.; Boscoe, B.; Evrard, E.; Helal, C. J.; Humphrey, J. M.; Stepan, A. F.; Stiff, C. M.; Yang, E.; Xie, L.; Bales, K. R.; Hajos-Korcsok, E.; Jenkinson, S.; Pettersen, B.; Pustilnik, L. R.; Ramirez, D. S.; Steyn, S. J.; Wood, K. M.; Verhoest, P. R. *MedChemCommun.* **2017**, *8*, 730.