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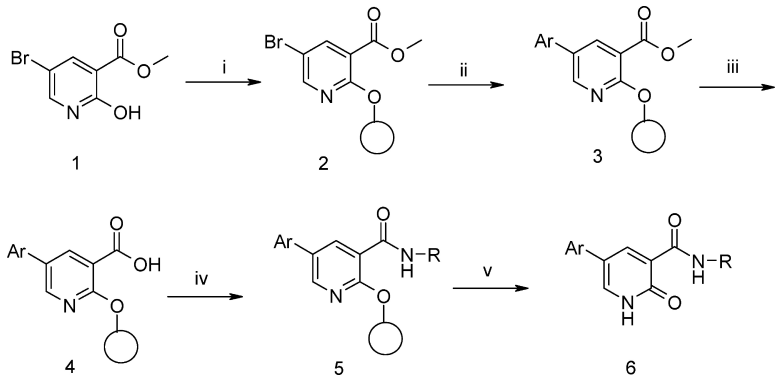

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Polymer-Supported Synthesis of Pyridone-Focused Libraries as Inhibitors of Anaplastic Lymphoma Kinase

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The optimization of screening hits on a promising new target for therapy of certain cancers involving anaplastic lymphoma kinase (ALK) inspired the development of this efficient solid-phase chemistry. A series of novel pyridones have been recently discovered as inhibitors of ALK, which led to the design of focused libraries around the pyridone scaffold. A stepwise process involving iterative template modification based on both medicinal chemistry insights and computational ranking of virtual libraries was employed in the design. The unique solid-phase chemistry has addressed the need for rapid optimization of this "early lead" series. Herein the methodology and scope of the chemistry, as well as its application for library synthesis, are discussed.

Introduction

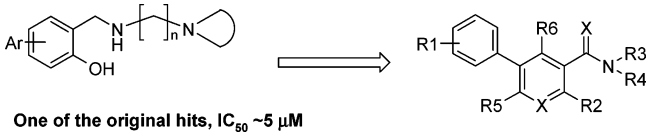
High-throughput medicinal chemistry serves as a powerful tool in lead discovery and optimization that promotes the rapid generation of relevant molecules and potential drug candidates. Efficient synthesis of well-designed compound libraries requires a knowledge-based strategy of both solution- and solid-phase syntheses with appropriate combinations of both.[1] Screening well-designed, small-molecule libraries that utilize drug-relevant building blocks and biologically privileged scaffolds can provide better coverage of druglike chemically accessible space, which will enhance the probability of successful lead discovery.

Anaplastic lymphoma kinase (ALK) is a promising new target for therapy of certain cancers, such as anaplastic large-cell lymphoma (ALCL) and inflammatory myofibroblastic tumors (IMT).[2] We have recently identified a series of novel pyridones as inhibitors of ALK by application of a stepwise process involving in vitro screening of a novel targeted library, followed by iterative template modification based on medicinal chemistry insights and the computational ranking of virtual libraries. The preliminary screening of this library yielded hits (Chart 1) as an ALK inhibitor with an IC_{50} of 5 μM. As a first step toward developing those hits into viable leads, compound libraries were designed around a novel pyridone scaffold, and synthesis of a focused library was accomplished as shown in Scheme 1. Herein, we report a highly efficient synthesis of pyridone libraries targeting ALK. The methodology and scope of the chemistry, as well as their application toward library synthesis, are discussed in detail.

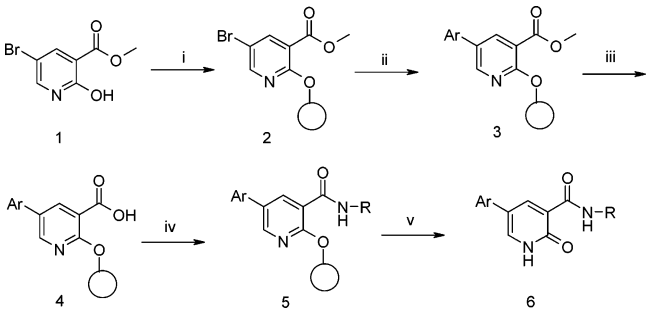
Results and Discussion

Design and Synthesis of Pyridone Focused Library. A focused library was designed around 5-arylpyridone-3-carboxamide scaffold as shown in Chart 2.[3] The synthetic route for the library employed solid support due to its high efficiency and versatility. Optimization of screening hits necessitates the use of the following strategies for a focused library design: (a) incorporation of an additional nitrogen atom in the center aromatic ring to acquire additional potential hydrogen bonding interactions; (b) conversion of a methylene into a carbonyl group to increase the rigidity of the molecule; (c) incorporation of pharmacophoric groups

Chart 1



Scheme 1. Solid-Phase Synthesis of Pyridone-Focused Library[a]



[a] Reagents and conditions: (i) Wang resin, PPh_3, DEAD, THF; (ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, toluene/water (3/1, v/v), 80 °C; (iii) aq NaOH (1 M), THF, 50 °C; (iv) RNH_2, HATU, DIEA, DMF; (v) TFA/DCM (10%), 2h.

Chart 2

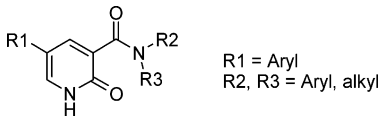


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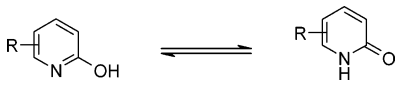
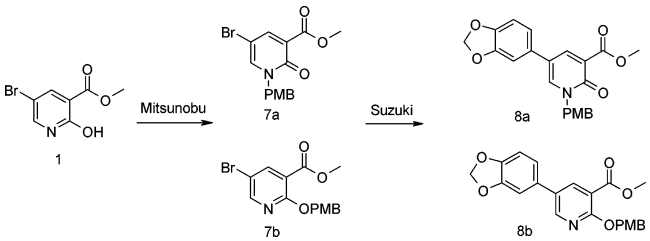
Chart 3



Scheme 2. Model Study in Solution Phase[a]



[a] Reagents and conditions: (i) *p*-methoxybenzyl alcohol, PPh_3, DEAD, THF, 0 °C or *p*-methoxybenzyl chloride, Cs_2CO_3, DMF; (ii) 3,4-methylenedioxyphenyl boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene/water (3/1, v/v), 80 °C.

from known kinase inhibitors to enhance a chance of obtaining the desired activity and selectivity; (d) identification of appropriate spacers to link the aromatic core with the basic moiety; and (e) creation of a novel scaffold. Solid-phase methodology permits the rapid synthesis of a wide range of individual compounds in a short time and provides a flexible means to introduce the desired diversity. One of the challenges in solid-phase synthesis of heterocyclic compounds is to find an access point to tether the starting material to the solid support. The hydroxyl of nicotinic acid provides an excellent handle to immobilize the template. Wang resin[4] was the solid support of choice, since the basic synthetic conditions required should be compatible with the acid-sensitive linker. Methyl ester **1** was readily linked to the Wang resin under standard Mitsunobu conditions.[5] The synthetic route is outlined in Scheme 1.

A model study was conducted in solution phase to validate the proposed chemistry. *p*-Methoxybenzyl (PMB) group was chosen to protect the hydroxyl group because it mimics the Wang linker to be used as the solid support. It is well-known that 2-hydroxypyridine coexists with the corresponding 2-pyridone through tautomeric equilibrium (Chart 3). 2-Hydroxypyridine can be alkylated on both the oxygen and the nitrogen, unlike 3-hydroxypyridine as a typical phenol.[6] As postulated in Scheme 2, compound **1** underwent Mitsunobu reaction with *p*-methoxybenzyl alcohol to afford compounds **7a** and **7b** in yields of 56 and 4%, respectively. Our attempts to remove the PMB group from **7a** failed under various conditions (DDQ, CAN, $BF_3 \cdot Et_2O$, TFA, and hydrogenation),[7] whereas PMB on **7b** is extremely sensitive to TFA treatment. NMR analysis indicated that the major product **7a** exists as a pyridone, the PMB group is attached at *N*, and **7b** exists as an O-alkylated pyridine. Both **7a** and **7b** underwent Suzuki coupling reaction with 3,4-methylenedioxyphenyl boronic acid smoothly under standard conditions.[8] As expected, compound **1** without a protecting group failed to react with any boronic acid under various Suzuki coupling conditions. These results led us to determine that the solution-phase approach cannot be utilized due to the inertness of the N-linked PMB group toward chemical manipulations. To our surprise, the treatment of resin-bound **2** with 10% TFA/DCM for 2 h released **1** in >50% yield and excellent purity. This marked difference may have resulted from the predominant formation of acid-sensitive O-alkylated product on the solid support. The solid support, in this case, plays a unique role in the synthesis as a "gatekeeper" in that the undesired N-alkylated compound cannot be cleaved and has no impact on the purity of the final product.

The parallel solid-phase synthesis of the pyridone focused library was executed on Wang resin using IRORI methodology. First, the polymer-bound **2** was distributed to IRORI MiniKans (100 μmol each). The Suzuki reaction with a set of boronic acids (Figure 1) under standard conditions was followed by saponification, which gave polymer-bound acid **4**. Next, HATU-mediated amide coupling with various substituted anilines and amines provided **5**. The final products were released from the solid phase upon treatment with TFA/DCM. The crude products were analyzed by LC/MS and purified by reversed-phase HPLC.

Synthesis of Pyridone Library with *trans*-1,4-Diaminocyclohexane Spacer. In our efforts to find an optimal spacer for pyridone-based ALK inhibitors, compound **9** (Chart 4) was designed, synthesized, and confirmed as a potent ALK inhibitor. A library using *trans*-1,4-diaminocyclohexane spacer was then designed, and the chemistry was developed as shown in Scheme 3. The mono-Dde ((4,4-dimethyl-2,6-dioxocyclohexyl-1-ylidene)ethyl)-protected 1,4-diaminocyclohexane **10** reacted with the polymer-bound nicotinic acid **4** in the presence of PyBop to give the amide **11**, which underwent the treatment with 2% hydrazine hydrate in DMF to reveal the primary amine **12**.[9] The improved monoreductive alkylation[10] with a variety of aldehydes (Figure 2) was performed in IRORI MiniKans to minimize the formation of undesired dialkylated product. In most cases, only monoalkylated products were detected by LC/MS. The crude product **14** was cleaved off the polymer support, followed by high-throughput HPLC purification. All the synthesized compounds which met the purity criteria (>80% by two detectors) are being screened against ALK kinase.

Conclusion

In summary, we have developed an efficient method for preparing structurally diverse, focused pyridone libraries as inhibitors of ALK. It has been demonstrated that the solid-phase approach reported in this paper cannot be replaced by the same chemistry transformation in solution phase. In addition, the following advantages of solid phase over solution phase were realized: (i) achievement of more rapid delivery of the desired products in library format for SAR study; (ii) production of final products with higher purity, since N-alkylated side products are not cleaved from the resin in the last step; (iii) accommodation of a necessary chemical transformation under basic conditions to be compatible with the preferred resin; (iv) accomplishment of higher conversion rates for Suzuki coupling reactions by use of excess boronic acid; (v) avoidance of the tedious purification of removing phosphorus ligands and their byproducts; and (vi) the *p*-methoxy benzyl moiety provides efficient protection for the hydroxyl group of compound **1** as well as acting as the tether to solid support.

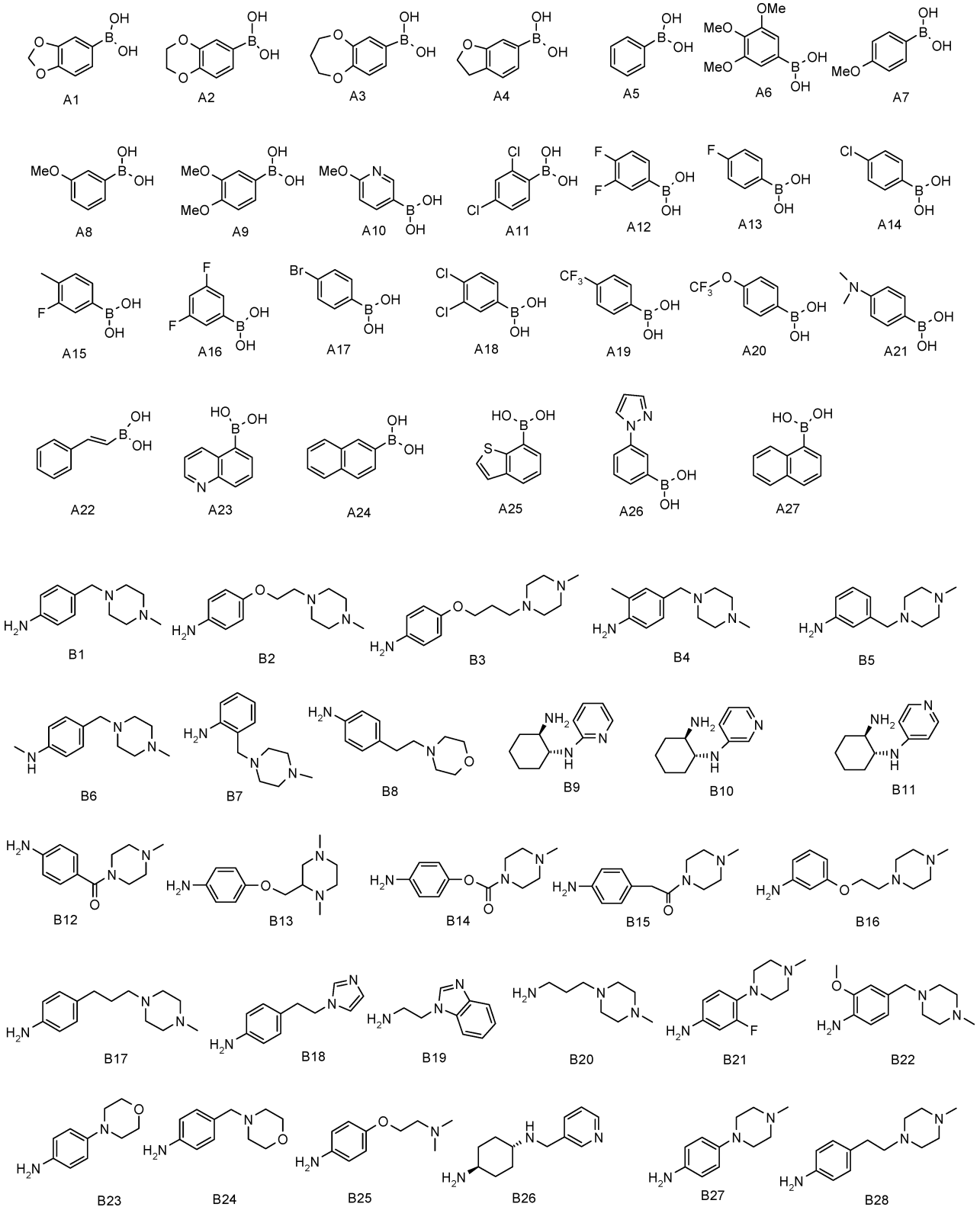
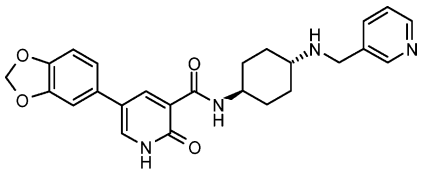


Figure 1. List of boronic acids and amines for pyridone-focused library.

Experimental Section

All anhydrous solvents and reagents were purchased from commercial sources and were used as such without further purification. The Wang resin was purchased from Polymer Labs (1.38 mmol/g). ^{1}H NMR spectra were recorded in 5-mm tubes on a 300 MHz Bruker in DMSO-d_6 unless otherwise specified. Purification of compounds was performed using a Gilson HPLC system equipped with Gilson 306 pumps, a Gilson 215 liquid handler and a Gilson UV/Vis-155 detector. Fraction collection was triggered by UV detection set within the range of 254−320 nm. The injection volume was 2000 μL of sample in DMSO. The mobile phase consisted of 0.1% TFA water and 0.1% TFA acetonitrile (HPLC grade, JT Baker). Chromatographic method A was performed on an

Chart 4



9

Ultra C18Q (250 × 20 mm i.d., 10 μm, Peeke Scientific) column in gradients that ran from 100% to 5% aqueous for up to 43 min at a flow rate of 3 mL/minute. Chromatographic method B was performed on a Kromasil C8 (250 × 20 mm i.d., 10 μm) column in gradients running from 95 to 5% aqueous for up to 19 min at a flow rate of 25 mL/min.

Loading of compound **1** onto Wang resin and the general procedure for preparation of compound **3**, **5**, and **6** were reported earlier.[3]

General Procedure for Preparation of Compound 11. The polymer-bound compound **4** was swollen in DMF (3 mL for each MiniKan) for 30 min. After adding compound **10** (2 equiv) and DIEA (4 equiv), PyBOP (2 equiv) was added, and the mixture was shaken overnight at room temperature. The solvent was drained, and the resin was washed three times with DMF, MeOH, and DCM, successively. Finally, the resin was dried in vacuo.

General Procedure for Preparation of Compound 12 (Removal of Dde). After the solid-supported compound **11** in MiniKans was swollen in DMF for 30 min and the solvent was drained, 2% hydrazine monohydrate in DMF (3 mL for each MiniKan) was added, and the MiniKans were shaken for 20 min. The solvents were drained, and the resin was washed three times with DMF, MeOH, and ether, successively.

General Procedure for Preparation of Compound 13 (Reductive Alkylation). The polymer-bound compound **12** in MiniKans was swollen in anhydrous TMOF (2 mL for each MiniKan) for 15 min. Aldehyde (8 equiv with respect to loading) was added, and the mixture was placed on an orbital shaker and agitated gently for 1 h. After that, a solution of $NaCNBH_3$ (24 equiv with respect to loading) in THF (1 mL for each MiniKan) was added, followed by addition of AcOH/MeOH (1/9, v/v, 0.5 mL for each MiniKan). The mixture was shaken at room temperature for 4 h. The solvents were drained, and the resin was washed three times with MeOH, DCM, and ether, successively, then dried in vacuo.

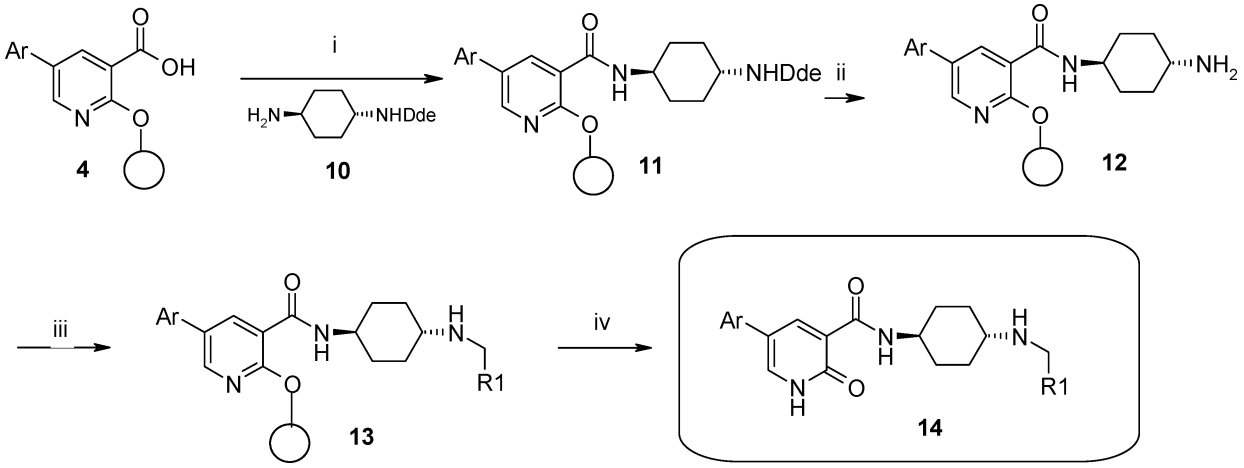
Synthesis of Compounds 7a and 7b. To a cooled and stirred solution of compound **1** (232 mg, 1 mmol), *p*-methoxybenzyl alcohol (276 mg, 2 mmol), and triphenylphosphine (524 mg, 2 mmol) in anhydrous THF (30 mL) under N_2, DEAD (40% solution in toluene, 906 μL, diluted with 5 mL of THF) was added dropwise. After the addition was completed in 15 min, the reaction mixture was allowed to warm to room temperature gradually and the stirring was continued for 16 h. The solvent was evaporated, and the residue was redissolved in DCM (60 mL) and washed with aq $NaHCO_3$ solution (15%, 50 mL), water, and brine. The organic layer was concentrated, and the residue was subject to column chromatography to give compound **7b** as a clear syrup (14 mg, 4%) and compound **7a** as a slightly yellowish solid (197 mg, 56%).

7a. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.15 (d, 1H, J = 2.7 Hz), 7.60 (d, 1H, J = 2.7 Hz), 7.31 (d, 2H, J = 9 Hz), 6.91 (d, 2H, J = 9 Hz), 5.30 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.54, 159.82, 157.97, 147.17, 141.88, 130.27, 128.56, 127.03, 121.69, 114.48, 113.83, 96.37, 55.31, 52.63, 52.41. MS: m/z = 352, 354 $[M + H]^+$.

7b. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.34 (d, 1H, J = 3 Hz), 8.30 (d, 1H, J = 3 Hz), 7.40 (d, 2H, J = 9 Hz), 6.91 (d, 2H, J = 9 Hz), 5.43 (s, 2H), 3.89 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.21, 160.71, 159.29, 151.26, 143.37, 129.18, 128.80, 115.49, 113.83, 111.01, 68.21, 55.27, 52.47. MS: m/z = 352, 354 $[M + H]^+$.

Synthesis of Compound 8a. To a nitrogen-purged suspension of compound **7a** (176 mg, 0.5 mmol), 3,4-methylenedioxyphenyl boronic acid (166 mg, 1 mmol), and sodium carbonate (265 mg, 2.5 mmol) in toluene/water (3/1, v/v) was added tetrakis(triphenylphosphine) palladium (5%, 29 mg). The resulting mixture was heated in a sealed vial at 80 °C for 18 h. Ethyl acetate (50 mL) was added, and the

Scheme 3. Synthesis of Library **14**[a]



[a] Reagents and conditions: (i) PyBOP, DIEA, DMF; (ii) $NH_2NH_2 \cdot H_2O$, DMF; (iii) R_1CHO, TMOF, 1 h; then $NaCNBH_3$, HOAc, MeOH; (iv) TFA, DCM.

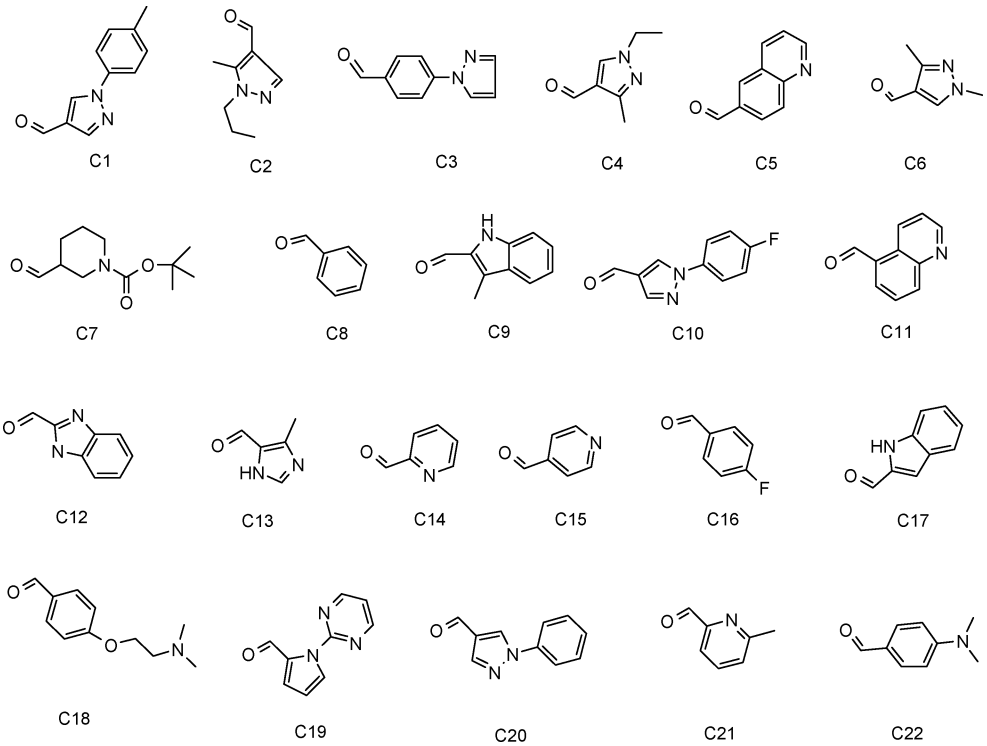


Figure 2. List of aldehydes for pyridone library with *trans*-1,4-diaminocyclohexane spacer.

mixture was washed with saturated aqueous sodium bicarbonate solution (30 mL) and brine (30 mL). The organic layer was concentrated under reduced pressure, and the residue was purified by column chromatography to afford the title compound as a white solid (167 mg, 85%). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.34 (d, 1H, J = 2.7 Hz), 7.63 (d, 1H, J = 2.7 Hz), 7.36−7.32 (m, 2H), 6.91−6.79 (m, 5H), 6.00 (s, 2H), 5.17 (s, 2H), 3.94 (s, 3H), 3.80 (s, 3H). MS: m/z = 394 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[2-(4-Methylpiperazin-1-yl)-ethoxy]-phenyl}-amide (6A1B2). ^{1}H NMR δ (ppm): 8.64 (s, 1H), 8.05 (m, 1H), 7.66 (d, 2H, J = 9 Hz), 7.28 (s, 1H), 7.11 (d, 1H, J = 9 Hz), 7.02−6.99 (m, 3H), 6.07 (s, 2H), 4.16 (m, 2H), 3.70 (m, 2H), 3.40 (m, 2H), 3.21 (m, 2H), 3.10 (m, 2H), 3.03 (m, 2H), 2.78 (s, 3H). MS: m/z = 477 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[3-(4-Methylpiperazin-1-yl)-propoxy]-phenyl}-amide (6A1B3). ^{1}H NMR δ (ppm): 8.64 (s, 1H), 8.05 (m, 1H), 7.65 (d, 2H, J = 9 Hz), 7.28 (s, 1H), 7.11 (d, 1H, J = 9 Hz), 7.02−6.93 (m, 3H), 6.07 (s, 2H), 4.02 (m, 2H), 3.68−2.84 (m, 10H), 2.74 (s, 3H), 1.98 (m, 2H). MS: m/z = 491 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [3-(4-Methylpiperazin-1-ylmethyl)-phenyl]-amide (6A1B5). ^{1}H NMR δ (ppm): 8.66 (s, 1H), 8.08 (m, 1H), 7.68 (m, 2H), 7.37 (m, 1H), 7.28 (s, 1H), 7.10 (d, 2H, J = 6 Hz), 7.00 (d, 2H, J = 6 Hz), 6.07 (s, 2H), 3.53 (m, 6H), 3.17 (m, 4H), 2.77 (s, 3H). MS: m/z = 447 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [2-(4-Methylpiperazin-1-ylmethyl)-phenyl]-amide (6A1B7). ^{1}H NMR δ (ppm): 8.69 (s, 1H), 8.34 (d, 1H, J = 6 Hz), 8.06 (m, 2H), 7.39−6.99 (m, 6H), 6.07 (s, 2H), 3.66 (m, 2H), 3.40 (m, 2H), 3.10 (m, 4H), 2.86 (s, 3H), 2.42 (m, 2H). MS: m/z = 447 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(2-Morpholin-4-ylethyl)-phenyl]-amide (6A1B8). ^{1}H NMR δ (ppm): 9.90 (brs, 1H), 8.66 (s, 1H), 8.08 (br, 1H), 7.72 (d, 2H, J = 6 Hz), 7.28 (m, 3H), 7.10 (d, 1H, J = 6 Hz), 7.00 (d, 1H, J = 6 Hz), 6.07 (s, 2H), 4.00 (m, 2H), 3.67 (m, 2H), 3.54 (m, 2H), 3.35 (m, 2H), 3.17 (m, 2H), 3.00 (m, 2H). MS: m/z = 448 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [*trans*-2-(pyridin-2-ylamino)-cyclohexyl]-amide (6A1B9). ^{1}H NMR δ (ppm): 9.88 (d, 1H, J = 6 Hz), 8.40 (s, 1H), 7.90 (m, 1H), 7.80 (d, 1H, J = 6 Hz), 7.67 (m, 2H), 7.17(s, 1H), 6.98 (s, 1H), 6.90 (m, 2H), 6.64 (m, 1H), 6.05 (s, 2H), 3.92 (m, 2H), 1.98 (m, 1H), 1.75 (m, 2H), 1.40 (m, 4H). MS: m/z = 433 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [*trans*-2-(pyridin-3-ylamino)-cyclohexyl]-amide (6A1B10). ^{1}H NMR δ (ppm): 9.88 (d, 1H, J = 6 Hz), 8.44 (s, 1H), 8.21 (s, 1H), 7.90 (m, 2H), 7.77 (d, 1H, J = 6 Hz), 7.58(m, 1H), 7.19 (s, 1H), 7.00 (m, 3H), 6.06 (s, 2H), 3.90 (m, 1H), 3.69 (m, 1H), 1.95 (m, 2H), 1.76 (m, 2H), 1.48−1.35 (m, 4H). MS: m/z = 433 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [*trans*-2-(pyridin-4-ylamino)-cyclohexyl]-amide (6A1B11). ^{1}H NMR δ (ppm): 9.90 (d, 1H, J = 6 Hz), 8.50 (d, 1H, J = 6 Hz), 8.43 (s, 1H), 8.10 (t, 1H, J = 6 Hz), 7.92 (m, 2H), 7.18(m, 2H), 6.99 (m, 2H), 6.75 (m, 1H), 6.05 (s, 2H), 3.90 (m, 2H), 1.90 (m, 2H), 1.74 (m, 2H), 1.42 (m, 4H). MS: m/z = 433 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Methylpiperazine-1-carbonyl)-phenyl]-amide (6A1B12). ^{1}H NMR δ (ppm): 9.80 (brs, 1H), 8.67 (s, 1H), 8.10 (m, 1H), 7.83 (d, 2H, J = 6 Hz), 7.51 (d,

2H, $J = 6$ Hz), 7.29 (s, 1H), 7.13 (d, 1H, $J = 6$ Hz), 7.00 (m, 2H), 6.07 (s, 2H), 3.37 (m, 4H), 3.10 (m, 4H), 2.81 (s, 3H). MS: $m/z = 461$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(1,4-Dimethylpiperazin-2-ylmethoxy)-phenyl]-amide (6A1B13). ^{1}H NMR δ (ppm): 9.65 (s, 1H), 8.06 (brs, 1H), 7.70 (d, 2H, $J = 6$ Hz), 7.28 (s, 1H), 7.12−6.99 (m, 5H), 6.07 (s, 2H), 4.23 (m, 2H), 3.67−3.06 (m, 7H), 2.82 (s, 3H), 2.73 (s, 3H). MS: $m/z = 477$ $[M + H]^+$.

4-Methylpiperazine-1-carboxylic Acid 4-[(5-Benzo[1,3]-dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carbonyl)-amino]-phenyl Ester (6A1B14). ^{1}H NMR δ (ppm): 10.00 (br s, 1H), 8.66 (s, 1H), 8.10 (m, 1H), 7.72 (d, 2H, $J = 6$ Hz), 7.28 (s, 1H), 7.18−6.99 (m, 5H), 6.07 (s, 2H), 4.20 (m, 2H), 3.10 (m, 2H), 2.85 (s, 3H). MS: $m/z = 477$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[2-(4-Methylpiperazin-1-yl)-2-oxo-ethyl]-phenyl}-amide (6A1B15). ^{1}H NMR δ (ppm): 9.90 (brs, 1H), 8.66 (s, 1H), 8.07 (m, 1H), 7.66 (d, 2H, $J = 6$ Hz), 7.28−7.21 (m, 3H), 7.10 (d, 1H, $J = 6$ Hz), 7.01 (d, 1H, $J = 6$ Hz), 6.57 (s, 1H), 6.07 (s, 2H), 3.75 (m, 2H), 3.00 (m, 8H), 2.76 (s, 3H). MS: $m/z = 475$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {3-[2-(4-Methylpiperazin-1-yl)-ethoxy]-phenyl}-amide (6A1B16). ^{1}H NMR δ (ppm): 8.64 (s, 1H), 8.08 (m, 1H), 7.52 (m, 1H), 7.28−7.00 (m, 5H), 6.73 (m, 1H), 6.07 (s, 2H), 4.15 (m, 2H), 3.70−3.00 (m, 10H), 2.77 (s, 3H). MS: $m/z = 477$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(2-Imidazol-1-ylethyl)-phenyl]-amide (6A1B18). ^{1}H NMR δ (ppm): 8.41 (d, 1H, $J = 9$ Hz), 8.75 (s, 1H), 8.64−8.61 (m, 3H), 8.22−8.06 (m, 3H), 7.59 (m, 2H), 7.27 (s, 1H), 7.18−6.99 (m, 4H), 6.07 (s, 2H), 4.72 (m, 2H), 3.16 (m, 2H). MS: $m/z = 429$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (4-Morpholin-4-ylphenyl)-amide (6A1B23). ^{1}H NMR δ (ppm): 8.64 (s, 1H), 8.57 (s, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.60 (d, 1H, $J = 9$ Hz), 7.27 (d, 1H, $J = 9$ Hz), 7.13 (d, 1H, $J = 9$ Hz), 7.00 (m, 2H), 6.07 (s, 2H), 3.76 (m, 4H), 3.09 (m, 4H). MS: $m/z = 420$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (4-morpholin-4-ylmethylphenyl)-amide (6A1B24). ^{1}H NMR δ (ppm): 9.95 (brs, 1H), 8.67 (s, 1H), 8.10 (s, 1H), 7.83 (d, 2H, $J = 6$ Hz), 7.50 (d, 2H, $J = 6$ Hz), 7.29 (s, 1H), 7.10 (d, 1H, $J = 6$ Hz), 7.01 (d, 1H, $J = 6$ Hz), 6.07 (s, 2H), 4.62 (m, 2H), 4.00 (m, 2H), 3.63 (m, 2H), 3.27 (m, 2H), 3.14 (m, 2H). MS: $m/z = 434$ $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A1B26). ^{1}H NMR δ (ppm): 8.90 (brs, 2H), 8.65 (s, 1H), 8.70 (m, 1H), 8.54 (s, 1H), 7.98 (m, 2H), 7.56 (m, 1H), 7.23 (s, 1H), 7.06 (d, 1H, $J = 9$ Hz), 7.00 (d, 1H, $J = 6$ Hz), 6.06 (s, 2H), 4.28 (m, 4H), 3.77 (m, 2H), 3.17 (m, 2H), 2.21−2.17 (m, 2H), 2.07−2.03 (m, 2H), 1.58−1.35 (m, 4H). MS: $m/z = 447$ $[M + H]^+$.

5-(3,4-Dihydro-2H-benzo[*b*][1,4]dioxepin-7-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A3B26). ^{1}H NMR δ (ppm): 9.80 (d, 1H, $J = 6$ Hz), 8.85 (br, 2H), 8.71 (m, 1H), 8.64 (s, 1H), 8.54 (s, 1H), 8.00 (m, 2H), 7.50 (m, 1H), 7.21−7.16 (m, 2H), 7.03 (d, 1H, $J = 6$ Hz), 4.26 (m, 2H), 4.15 (t, 4H, $J = 6$ Hz), 3.80 (m, 1H), 3.20 (m, 1H), 2.17−2.07 (m, 6H), 1.50−1.40 (m, 4H). MS: $m/z = 475$ $[M + H]^+$.

5-(2,3-Dihydrobenzofuran-5-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A4B26). ^{1}H NMR δ (ppm): 9.85 (d, 1H, $J = 9$ Hz), 8.85 (m, 2H), 8.71 (s, 1H), 8.64 (s, 1H), 8.55 (s, 1H), 7.93 (m, 2H), 7.53−7.47 (m, 2H), 7.30 (d, 1H, $J = 9$ Hz), 6.83 (d, 1H, $J = 9$ Hz), 4.56 (t, 2H, $J = 9$ Hz), 4.25 (m, 2H), 3.78−3.60 (m, 4H), 3.22 (t, 2H, $J = 9$ Hz), 2.21−2.03 (m, 4H), 1.53−1.35 (m, 4H). MS: $m/z = 445$ $[M + H]^+$.

2-Oxo-5-phenyl-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Methylpiperazin-1-ylmethyl)-phenyl]-amide (6A5B1). ^{1}H NMR δ (ppm): 8.47 (m, 1H), 7.85 (m, 1H), 7.83 (d, 2H, $J = 6$ Hz), 7.43 (d, 2H, $J = 6$ Hz), 6.59 (m, 1H), 4.05 (m, 2H), 3.70−3.10 (m, 8H), 2.83 (s, 3H). MS: $m/z = 403$ $[M + H]^+$.

5-(4-Methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A7B26). ^{1}H NMR δ (ppm): 9.83 (d, 1H, $J = 6$ Hz), 8.91 (br, 2H), 8.73 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 7.98 (m, 2H), 7.53 (m, 3H), 7.03 (m, 2H), 4.27 (m, 2H), 4.02 (m, 1H), 3.79 (s, 3H), 3.17 (m, 1H), 2.21−2.18 (m, 2H), 2.08−2.04 (m, 2H), 1.55−1.36 (m, 4H). MS: $m/z = 433$ $[M + H]^+$.

5-(3-Methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A8B26). ^{1}H NMR δ (ppm): 9.80 (d, 1H, $J = 6$ Hz), 8.91 (br, 2H), 8.74 (s, 1H), 8.67 (s, 1H), 8.65 (s, 1H), 8.09 (br, 1H), 7.98 (d, 1H, $J = 6$ Hz), 7.56 (m, 1H), 7.37 (m, 1H), 7.17 (m, 2H), 6.91 (d, 1H, $J = 6$ Hz), 4.27 (m, 2H), 3.82 (s, 3H), 3.79 (m, 1H), 3.16 (m, 1H), 2.21−2.18 (m, 2H), 2.08−2.04 (m, 2H), 1.54−1.35 (m, 4H). MS: $m/z = 433$ $[M + H]^+$.

5-(2,4-Dichlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A11B26). ^{1}H NMR δ (ppm): 9.75 (d, 1H, $J = 6$ Hz), 8.90 (m, 2H), 8.73 (m, 1H), 8.66 (m, 1H), 8.40 (m, 1H), 7.99 (m, 1H), 7.89 (m, 1H), 7.79 (m, 1H), 7.55 (m, 3H), 4.27 (m, 2H), 3.77 (m, 1H), 3.18 (m, 1H), 2.20 (m, 2H), 2.07 (m, 2H), 1.53−1.36 (m, 4H). MS: $m/z = 471$ $[M + H]^+$.

5-(3,4-Difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A12B26). ^{1}H NMR δ (ppm): 9.77 (d, 1H, $J = 9$ Hz), 8.93 (m, 2H), 8.74 (s, 1H), 8.67 (s, 1H), 8.59 (s, 1H), 8.11 (m, 1H), 8.00 (d, 1H, $J = 9$ Hz), 7.78 (m, 1H), 7.50 (m, 3H), 4.28 (m, 2H), 3.78 (m, 1H), 3.17 (m, 1H), 2.21−2.04 (m, 4H), 1.55−1.36 (m, 4H). MS: $m/z = 439$ $[M + H]^+$.

5-(4-Fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A13B26). ^{1}H NMR δ (ppm): 9.80 (d, 1H, $J = 6$ Hz), 8.88 (m 1H), 8.73 (s, 1H), 8.65 (d, 1H, $J = 6$ Hz), 8.58 (s, 1H), 8.05−8.97 (m, 2H), 7.66 (m, 2H), 7.55 (m,

1H), 7.29 (m, 2H), 4.26 (m, 2H), 3.79 (m, 1H), 3.15 (m, 1H), 2.21−2.04 (m, 4H), 1.55−1.36 (m, 4H). MS: m/z = 421 $[M + H]^+$.

5-(4-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Methylpiperazin-1-ylmethyl)-phenyl]-amide (6A14B1). ^{1}H NMR δ (ppm): 8.35 (s, 1H), 8.31 (s, 1H), 7.74 (d, 2H, J = 6 Hz), 7.42 (d, 2H, J = 6 Hz), 3.93 (m, 2H), 3.31 (m, 4H), 3.04 (m, 4H), 2.81 (s, 3H). MS: m/z = 437 $[M + H]^+$.

5-(4-Chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A14B26). ^{1}H NMR δ (ppm): 9.78 (d, 1H, J = 6.0 Hz), 8.90 (m, 2H), 8.74 (s, 1H), 8.66 (d, 1H, J = 3 Hz), 8.60 (d, 1H, J = 3 Hz), 8.10 (brs, 1H), 8.00 (d, 1H, J = 6 Hz), 7.66 (d, 2H, J = 6 Hz), 7.57−7.49 (m, 3H), 4.27 (m, 2H), 3.77 (m, 1H), 3.17 (m, 1H), 2.21−2.04 (m, 4H), 1.55−1.36 (m, 4H). MS: m/z = 437 $[M + H]^+$.

5-(4′-Fluoro-3′-methylbiphenyl-4-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A15B26). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 9 Hz), 8.92 (m, 2H), 8.73 (s, 1H), 8.66 (s, 1H), 8.58 (s, 1H), 7.99 (m, 2H,), 7.47 (m, 1H), 7.21 (m, 1H), 4.27 (m, 2H), 3.77 (m, 1H), 3.13 (m, 1H), 2.29 (s, 3H), 2.21−2.04 (m, 4H), 1.58−1.20 (m, 4H). MS: m/z = 511 $[M + H]^+$.

5-(3,5-Difluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A16B26). ^{1}H NMR δ (ppm): 9.73 (d, 1H, J = 6.0 Hz), 8.84 (m, 2H), 8.71 (s, 1H), 8.64 (d, 1H, J = 6 Hz), 8.61 (s, 1H), 8.20 (m, 1H), 7.96 (d, 1H, J = 6 Hz), 7.54 (m, 1H), 7.42 (d, 2H, J = 6 Hz), 7.21 (m, 1H), 4.26 (m, 2H), 3.75 (m, 1H), 3.15 (m, 1H), 2.17−2.04 (m, 4H), 1.50−1.41 (m, 4H). MS: m/z = 439 $[M + H]^+$.

5-(4-Bromophenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Methylpiperazin-1-ylmethyl)-phenyl]-amide (6A17B1). ^{1}H NMR δ (ppm): 8.41 (s, 1H), 8.14 (s, 1H), 7.72 (d, 2H, J = 6 Hz), 7.39 (d, 2H, J = 6 Hz), 4.00 (m, 4H), 3.40 (m, 2H), 3.10 (m, 4H), 2.78 (s, 3H). MS: m/z = 481, 483 $[M + H]^+$.

2-Oxo-5-(4-trifluoromethyl-phenyl)-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A19B26). ^{1}H NMR δ (ppm): 9.77 (d, 1H, J = 6 Hz), 8.95 (m, 2H), 8.75 (s, 1H), 8.67 (d, 1H, J = 6 Hz), 8.65 (s, 1H), 8.24 (m, 1H), 8.04−7.93 (m, 3H), 7.72 (m, 2H), 7.57 (m, 1H), 4.30 (m, 2H), 3.78 (m, 1H), 3.17 (m, 1H), 2.22−2.05 (m, 4H), 1.59−1.41 (m, 4H). MS: m/z = 471 $[M + H]^+$.

2-Oxo-5-(4-trifluoromethoxyphenyl)-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A20B26). ^{1}H NMR δ (ppm): 9.77 (d, 1H, J = 6 Hz), 8.85 (m, 2H), 8.71 (s, 1H), 8.64 (d, 1H, J = 6 Hz), 8.61 (s, 1H), 8.11 (m, 1H), 7.96 (d, 1H, J = 6 Hz), 7.74 (d, 2H, J = 6 Hz), 7.54 (m, 1H), 7.46 (d, 2H, J = 6 Hz), 4.27 (m, 2H), 3.80 (m, 1H), 3.15 (m, 1H), 2.20−2.03 (m, 4H), 1.50−1.40 (m, 4H). MS: m/z = 487 $[M + H]^+$.

5-(4′-Dimethylaminobiphenyl-4-yl)-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A21B26). ^{1}H NMR δ (ppm): 9.87 (d, 1H, J = 9 Hz), 8.91 (m, 2H), 8.74 (s, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.00 (m, 1H), 7.90 (m, 1H), 7.58 (m, 1H), 7.43 (d, 2H, J = 9 Hz), 6.83 (d, 2H, J = 9 Hz), 4.28 (m, 2H), 3.78 (m, 1H), 3.16 (m, 1H), 2.95 (s, 6H), 2.21−2.04 (m, 4H), 1.58−1.40 (m, 4H). MS: m/z = 522 $[M + H]^+$.

2-Oxo-5-[4-((*E*)-styryl)-phenyl]-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A22B26). ^{1}H NMR δ (ppm): 9.67 (d, 1H, J = 6 Hz), 8.82 (m, 2H), 8.71 (s, 1H), 8.64 (s, 1H), 8.21 (s, 1H), 7.95 (d, 1H, J = 6 Hz), 7.60 (m, 1H), 7.51 (m, 1H), 7.30 (m, 5H), 6.61 (d, 1H, J = 12 Hz), 6.45 (d, 1H, J = 12 Hz), 4.24 (m, 2H), 3.75 (m, 1H), 3.15 (m, 1H), 2.16 (m, 2H), 1.97 (m, 2H), 1.49−1.30 (m, 4H). MS: m/z = 505 $[M + H]^+$.

2-Oxo-5-quinolin-5-yl-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A23B26). ^{1}H NMR δ (ppm): 9.85 (d, 1H, J = 9 Hz), 8.99 (s, 1H), 8.98 (m, 2H), 8.71 (s, 1H), 8.65 (s, 1H), 8.38 (s, 1H), 8.26 (d, 1H, J = 9 Hz), 8.10 (d, 1H, J = 9 Hz), 7.97−7.85 (m, 2H), 7.60 (m, 3H), 4.26 (m, 2H), 3.20 (m, 2H), 2.18−2.04 (m, 4H), 1.46 (m, 2H). MS: m/z = 454 $[M + H]^+$.

5-Naphthalen-2-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A24B26). ^{1}H NMR δ (ppm): 9.83 (d, 1H, J = 6 Hz), 8.92 (m, 1H), 8.79 (s, 1H), 8.74 (s, 1H), 8.66 (m, 1H), 8.22 (m, 1H), 8.18 (s, 1H), 8.02−7.93 (m, 4H), 8.79 (d, 1H, J = 6 Hz), 7.55 (m 3H), 4.28 (m, 2H), 3.80 (m, 1H), 3.18-(m, 1H), 2.20−2.06 (m, 4H), 1.59−1.34 (m, 4H). MS: m/z = 453 $[M + H]^+$.

5-Benzo[*b*]thiophen-7-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A25B26). ^{1}H NMR δ (ppm): 9.79 (brs, 1H), 8.88 (m, 2H), 8.72 (m, 2H), 8.64 (m, 1H), 8.08 (m, 1H), 7.96−7.84 (m, 3H), 7.60−7.43 (m, 4H), 4.27 (m, 2H), 3.79 (m, 1H), 3.17 (m, 1H), 2.19−2.07 (m, 4H), 1.53−1.42 (m, 4H). MS: m/z = 459 $[M + H]^+$.

2-Oxo-5-(3-pyrazol-1-yl-phenyl)-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-3-ylmethyl)-amino]-cyclohexyl}-amide (6A26B26). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 6 Hz), 8.85 (m, 2H), 8.72−8.63 (m, 4H), 8.20 (m, 1H), 8.06 (s, 1H), 7.90 (d, 1H, J = 6 Hz), 7.82 (d, 1H, J = 6 Hz), 7.78 (s, 1H), 7.58 (m, 3H), 6.58 (s, 1H), 4.26 (m, 2H), 3.85 (m, 1H), 3.15 (m, 1H), 2.20−2.10 (m, 4H), 1.63−1.42 (m, 4H). MS: m/z = 469 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1-*p*-tolyl-1*H*-pyrazol-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C1). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.85 (br, 2H), 8.54 (s, 1H), 7.97 (s, 1H), 7.85 (s, 1H), 7.70 (d, 2H, J = 6 Hz), 7.33 (d, 2H, J = 6 Hz), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.15 (m, 1H), 3.12 (m, 1H), 2.35 (s, 3H), 2.06−2.16 (m, 2H), 2.06−2.03 (m, 2H), 1.48−1.36 (m, 4H). MS: m/z = 526 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(5-Methyl-1-propyl-1*H*-pyrazol-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C2). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.62 (br, 2H), 8.54 (s, 1H), 7.97 (s, 1H), 7.49 (s, 1H), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 3.99 (m, 4H), 3.76 (m, 1H), 3.10 (m, 1H),

2.28 (s, 3H), 2.19−2.16 (m, 2H), 2.07−2.03 (m, 2H), 1.73 (q, 2H, J = 6 Hz), 1.52−1.35 (m, 4H), 0.85 (t, 3H, J = 6 Hz). MS: m/z = 492 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Pyrazol-1-ylbenzylamino)-cyclohexyl]-amide (14A1C3). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.89 (br, 2H), 8.55 (d, 2H, J = 6 Hz), 7.96 (m, 3H), 7.78 (s, 1H), 7.65 (d, 2H, J = 6 Hz), 7.22 (s, 1H), 7.07−7.97 (m, 2H), 6.58 (s, 1H), 6.06 (s, 2H), 4.24 (m, 2H), 3.76 (m, 1H), 3.14 (m, 1H), 2.22−2.18 (m, 2H), 2.07−2.03 (m, 2H), 1.55−1.35 (m, 4H). MS: m/z = 512 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1-Ethyl-3-methyl-1*H*-pyrazol-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C4). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.59 (br, 2H), 8.54 (s, 1H), 7.96 (s, 1H), 7.74 (s, 1H), 7.07 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.06 (q, 2H, J = 6 Hz), 3.98 (m, 2H), 3.75 (m, 1H), 3.11 (m, 1H), 2.19 (s, 3H), 2.15 (m, 2H), 2.04 (m, 2H), 1.51−1.34 (m, 4H), 1.29 (t, 3H, J = 6 Hz). MS: m/z = 478 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Quinolin-6-ylmethyl)-amino]-cyclohexyl}-amide (14A1C5). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 9.02 (m, 3H), 8.54 (m, 2H), 8.16 (m, 2H), 7.16 m, 1H), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.43 (m, 2H), 3.75 (m, 1H), 3.20 (m, 1H), 2.26−2.22 (m, 2H), 2.08−2.04 (m, 2H), 1.62−1.51 (m, 2H), 1.44−1.28 (m, 2H). MS: m/z = 497 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1,3-Dimethyl-1*H*-pyrazol-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C6). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.54 (m, 3H), 7.95 (m, 1H), 7.70 (s, 1H), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 3.93 (m, 2H), 3.78 (s, 3H), 3.68 (m, 1H), 3.09 (m, 1H), 2.18 (s, 3H), 2.18−2.14 9m, 2H), 2.06−2.02 (m, 2H), 1.54−1.38 (m, 4H). MS: m/z = 464 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Piperidin-3-ylmethyl)-amino]-cyclohexyl}-amide (14A1C7). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 6 Hz), 8.60 (m, 3H), 8.53 (s, 1H), 7.96 (s, 1H), 7.22 (s, 1H), 7.06−6.97 (m, 2H), 6.06 (s, 2H), 3.75 (m, 1H), 3.25 (m, 1H), 3.15−2.60 (m, 6H), 2.07 (m, 4H), 1.85 (m, 2H), 1.45−1.26 (m, 7H). MS: m/z = 453 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (4-Benzylaminocyclohexyl)-amide (14A1C8). ^{1}H NMR δ (ppm): 9.81 (d, 1H, J = 6 Hz), 8.82 (m, 2H), 8.53 (s, 1H), 7.95 (m, 1H), 7.54−7.43 (m, 5H), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.21 (m, 2H), 3.76 (m, 1H), 3.14 (m, 1H), 2.21−2.18 (m, 2H), 2.06−2.03 (m, 2H), 1.54−1.24 (m, 4H). MS: m/z = 446 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(3-Methyl-1*H*-indol-2-ylmethyl)-amino]-cyclohexyl}-amide (14A1C9). ^{1}H NMR δ (ppm): 10.84 (brs, 1H), 9.82 (d, 1H, J = 9 Hz), 8.84 (m, 2H), 8.54 (s, 1H), 7.97 (s, 1H), 7.53 (d, 1H, J = 9 Hz), 7.40 (d, 1H, J = 9 Hz), 7.23 (s, 1H), 7.18 (m, 2H), 7.07−6.97 (m, 4H), 6.57 (s, 1H), 6.06 (s, 2H), 4.30 (m, 2H), 3.80 (m, 1H), 3.15 (m, 1H), 2.31 (s, 3H), 2.23−2.20 (m, 2H), 2.07−2.05 (m, 2H), 1.55−1.37 (m, 4H). MS: m/z = 513 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid (4-{[1-(4-Fluorophenyl)-1*H*-pyrazol-4-ylmethyl]-amino}-cyclohexyl)-amide (14A1C10). ^{1}H NMR δ (ppm): 9.82 (d, 1H, J = 6 Hz), 8.80 (m, 2H), 8.56 (d, 2H, J = 6 Hz), 7.97 (m, 1H), 7.84 (m, 3H), 7.42 (m, 2H), 7.20 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.16 (m, 2H), 3.78 (m, 1H), 3.12 (m, 1H), 2.19−2.16 (m, 2H), 2.08−2.03 (m, 2H), 1.56−1.33 (m, 4H). MS: m/z = 530 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Quinolin-5-ylmethyl)-amino]-cyclohexyl}-amide (14A1C11). ^{1}H NMR δ (ppm): 9.84 (d, 1H, J = 6 Hz), 9.03 (s, 1H), 9.00 (m, 2H), 8.70 (d, 1H, J = 6 Hz), 8.55 (s, 1H), 8.13 (d, 1H, J = 6 Hz), 7.97 (m, 1H), 7.91−7.82 (m, 2H), 7.72 (m, 1H), 7.23 (s, 1H), 7.07−7.00 (m, 2H), 6.06 (s, 2H), 4.73 (m, 2H), 3.77 (m, 1H), 3.36 (m, 1H), 2.32−2.28 (m, 2H), 2.11−2.07 (m, 2H), 1.62−1.58 (m, 2H), 1.46−1.34 (m, 2H). MS: m/z = 497 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1*H*-Benzoimidazol-2-ylmethyl)-amino]-cyclohexyl}-amide (14A1C12). ^{1}H NMR δ (ppm): 9.83 (d, 1H, J = 6 Hz), 9.43 (m, 2H), 8.54 (s, 1H), 7.97 (m, 1H), 7.64 (m, 2H), 7.23 (m, 3H), 7.07−6.96 (m, 2H), 6.06 (s, 2H), 4.51 (m, 2H), 3.77 (m, 1H), 3.28 (m, 1H), 3.23−3.20 (m, 2H), 2.07−2.04 (m, 2H), 1.60−1.53 (m, 2H), 1.49−1.35 (m, 2H). MS: m/z = 486 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(5-Methyl-3*H*-imidazol-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C13). ^{1}H NMR δ (ppm): 9.83 (d, 1H, J = 6 Hz), 9.02 (m, 2H), 8.89 (m, 2H), 8.54 (s, 1H), 7.96 (m, 1H), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.22 (m, 2H), 3.67 (m, 1H), 3.15 (m, 1H), 2.33 (s, 3H), 2.20−2.16 (m, 2H), 2.07−2.03 (m, 2H), 1.53−1.35 (m, 4H). MS: m/z = 450 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-2-ylmethyl)-amino]-cyclohexyl}-amide (14A1C14). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 6 Hz), 9.06 (br, 2H), 8.69 (s, 1H), 8.53 (s, 1H), 7.95−7.90 (m, 2H), 7.54−7.45 (m, 2H), 7.23 (s, 1H), 7.07−6.79 (m, 2H), 6.06 (s, 2H), 4.39 (m, 2H), 3.17 (m, 2H), 2.02−2.17 (m, 2H), 2.06−2.02 (m, 2H), 1.45 (m, 2H), 1.37 (m, 2H). MS: m/z = 447 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(Pyridin-4-ylmethyl)-amino]-cyclohexyl}-amide (14A1C15). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 6 Hz), 8.96 (br, 2H), 8.70 (d, 2H, J = 6 Hz), 8.53 (s, 1H), 7.97 (m, 1H), 7.55 (d, 2H, J = 6 Hz), 7.23 (s, 1H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.28 (m, 2H), 3.17 (m, 2H), 2.19−2.17 (m, 2H), 2.07−2.04 (m 2H), 1.54−1.39 (m, 4H). MS: m/z = 447 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-Fluorobenzylamino)-cyclohexyl]-amide (14A1C16). ^{1}H NMR δ (ppm): 9.82 (br, 1H), 8.84 (br, 2H), 8.53 (s, 1H), 7.97 (s, 1H), 7.58 (m, 2H), 7.34−7.22 (m, 3H), 7.07−6.97 (m, 2H), 6.06 (s, 2H), 4.21 (m, 2H), 3.77 (m, 1H), 3.12 (m, 1H), 2.19−2.17 (m, 2H), 2.06−2.03 (m, 2H), 1.53−1.37 (m, 4H). MS: m/z = 464 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[4-(2-(Dimethylamino)-ethoxy)-benzylamino]-cyclohexyl}-amide (14A1C18). ^{1}H NMR δ (ppm): 9.96 (brs, 1H), 9.80 (d, 1H, J = 9 Hz), 8.85 (m, 2H), 8.53 (s, 1H), 7.47 (d, 2H, J = 9 Hz), 7.23 (s, 1H), 7.09−6.97 (m, 4H), 6.06 (s, 2H), 4.35 (m, 2H), 4.15 (m, 2H), 3.75 (m, 1H), 3.54 (m, 2H), 3.07 (m, 1H), 2.88 (s, 6H), 2.20−1.96 (m, 4H), 1.58−1.28 (m, 4H). MS: m/z = 533 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1-Pyrimidin-2-yl-1*H*-pyrrol-2-ylmethyl)-amino]-cyclohexyl}-amide (14A1C19). ^{1}H NMR δ (ppm): 9.84 (d, 1H, J = *6* Hz), 8.91 (m, 2H), 8.89 (m, 3H), 7.92 (m, 2H), 7.46 (m, 1H), 7.23 (s, 1H), 7.05 (d, 1H, J = *6* Hz), 7.00 (d, 1H, J = 6 Hz), 6.57 (s, 1H), 6.34 (m, 1H), 6.06 (s, 2H), 4.55 (m, 2H), 3.79 (m, 1H), 3.28 (m, 1H), 2.21−2.04 (m, 4H), 1.65−1.36 (m, 4H). MS: m/z = 513 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(1-Phenyl-1*H*-pyrazol-3-ylmethyl)-amino]-cyclohexyl}-amide (14A1C20). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = *6* Hz), 8.53 (m, 3H), 7.95 (s, 1H), 7.83 (m, 3H), 7.54 (m, 2H), 7.35 (s, 1H), 7.22 (s, 1H), 7.00 (m, 2H), 6.56 (s, 1H), 6.06 (s, 2H), 4.10 (m, 2H), 3.75 (m, 1H), 3.05 (m, 1H), 2.20−2.00 (m, 4H), 1.50−1.35 (m, 4H). MS: m/z = 512 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid {4-[(6-Methylpyridin-2-ylmethyl)-amino]-cyclohexyl}-amide (14A1C21). ^{1}H NMR δ (ppm): 9.78 (d, 1H, J = *6* Hz), 8.53 (s, 1H), 7.95 (m, 1H), 7.76 (m, 2H), 7.28−7.22 (m, 4H), 7.07 (d, 1H, J = 6 Hz), 7.00 (d, 1H, J = 6 Hz), 6.05 (s, 2H), 4.57 (s, 2H), 3.84 (m, 1H), 3.44 (m, 1H), 2.20−2.04 (m, 4H), 1.87−1.76 (m, 2H), 1.43−1.32 (m, 2H). MS: m/z = 461 $[M + H]^+$.

5-Benzo[1,3]dioxol-5-yl-2-oxo-1,2-dihydropyridine-3-carboxylic Acid [4-(4-(Dimethylamino)-benzylamino)-cyclohexyl]-amide (14A1C22). ^{1}H NMR δ (ppm): 9.80 (d, 1H, J = 6 Hz), 8.60 (m, 2H), 8.53 (s, 1H), 7.96 (s, 1H), 7.30 (d, 2H, J = 6 Hz), 7.23 (s, 1H), 7.07−7.00 (m, 2H), 6.76 (d, 2H, J = 6 Hz), 6.06 (s, 2H), 4.05 (m, 2H), 3.73 (m, 1H), 3.05 (m, 1H), 2.92 (s, 6H), 2.18−2.15 (m, 2H), 2.05−2.01 (m, 2H), 1.51−1.24 (m, 4H). MS: m/z = 489 $[M + H]^+$.

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Supporting Information Available. Characterization of representative compounds by ^{1}H NMR and LC/MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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