Discovery and Synthesis of Novel *N*-Cyanopyrazolidine and *N*-Cyanohexahydropyridazine Derivatives as Cathepsin Inhibitors

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The design, synthesis, and biological evaluation of structurally novel *N*-cyanopyrazolidine and *N*-cyanohexahydropyridazine derivatives as cathepsin inhibitors are described. *In vitro* assay reveals that several compounds exhibit highly potent and selective profiles against cathepsins K or S.

Key Words : Cathepsins, Rheumatoid arthritis, *N*-Cyanopyrazolidine, *N*-Cyanohexahydropyridazine

Introduction

Cathepsins are lysosomal cysteine proteases of the papain family and have been recognized to play a crucial role in a variety of biological processes.[1] For example, cathepsins B, L, and S are implicated in immunological responses[2] while cathepsin K is a crucial enzyme for bone resorption.[3] Thus, investigation of these enzymes as potential drug targets for several diseases such as rheumatoid arthritis, osteoporosis, various types of cancers, stroke, and Alzheimer's disease has been actively pursued. Given the structural homology of cathepsin enzymes, however, selective inhibition of the target cathepsin over other cathepsin family is a prerequisite for further biological evaluation. In the course of our research program directed towards the development of anti-rheumatoid arthritis agents *via* inhibition of cathepsin B, *N*-cyanopyrazolidine compound **1** was identified as a hit as a consequence of HTS utilizing the in-house library. Here we wish to report our design, synthesis, and biological evaluation of *N*-cyanopyrazolidine and *N*-cyanohexahydropyridazine derivatives for selective cathepsin inhibitors.

As described in Figure 1, isoleucine-derived compound **1** exhibits potent and selective inhibition of cathepsin B while displaying no acute toxicity. Based upon these initial data, we decided to investigate the synthesis and biological activity of a series of *N*-cyanopyrazolidines and *N*-cyanohexahydropyridazines for selective cathepsin B inhibitors as shown in Scheme 1. For α-amino acid part, isoleucine, leucine, valine, phenylalanine, and tyrosine were employed.

Synthesis of *N*-cyanopyrazolidine and *N*-cyanohexahydro-

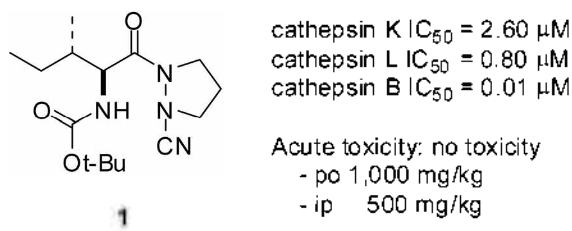
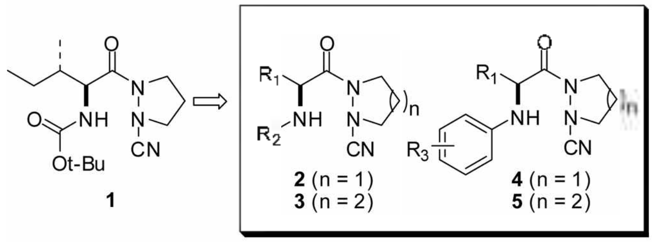


Figure 1



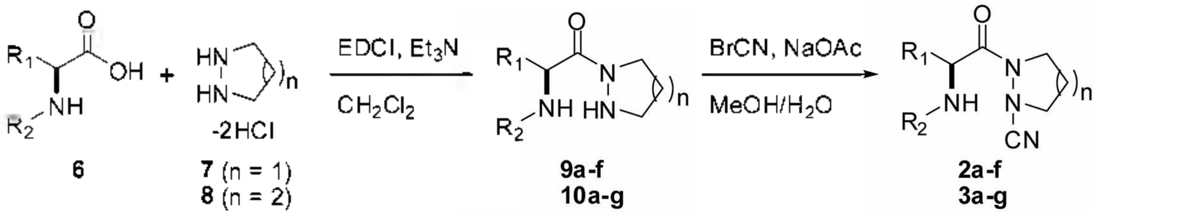
Scheme 1

pyridazine derivatives are outlined in Schemes 2 and 3. Coupling of amino acids **6** with the known pyrazolidine **7** and hexahydropyridazine **8**[4] in the presence of EDCI and Et_3N afforded the acylated pyrazolidines **9** and hexahydropyridazines **10**, respectively. The resulting amides **9** and **10** were then treated with cyanogen bromide and sodium acetate to give *N*-cyanopyrazolidines **2** and *N*-cyanohexahydropyridazines **3** in good to excellent yields.

For the synthesis of *N*-cyano derivatives bearing *N*-aryl-substituted amino acyl groups, CuI catalyzed *N*-arylation of amino acids was first conducted with various aryl bromides under the Ma's condition[5] to furnish *N*-arylated amino acids **11**. By following the similar sequence as above, *N*-cyanopyrazolidine and *N*-cyanohexahydropyridazine analogues possessing *N*-arylaminoacyl groups, **4** and **5** were prepared without any event.

In vitro inhibition assays of cathepsins B, L, K, and S with these compounds were conducted.[6] As shown in Tables 1-4, several compounds were identified to possess a good selectivity profile over these cathepsins.

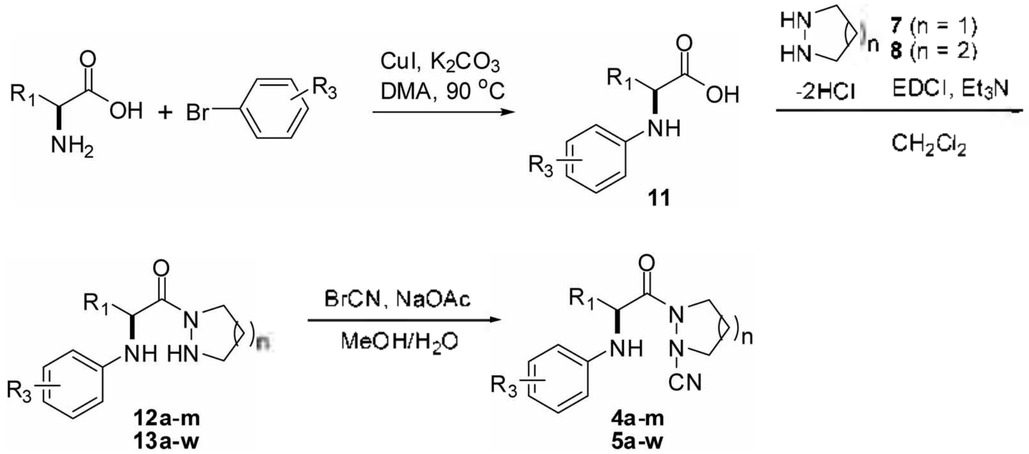
Interestingly, rather cathepsin K- or cathepsin S-selective compounds were discovered. Particularly, both potent inhibition and excellent selectivity against cathepsin K were observed in case of several *N*-cyanohexahydropyridazine derivatives (**3b**, **5f**, and **5j**) whereas compounds such as **2c**, **2f**, **3e**, **4g**, **4l**, and **4m** exhibit great potency and selectivity against cathepsin S. It seemed that hexahydropyridazine ring is better than pyrazolidine for cathepsin K selectivity. As an R_1 part, sterically bulky groups such as benzyl moiety decrease not only selectivity but also potency for cathepsin



2a: R_1 = sec-butyl, R_2 = Cbz
2b: R_1 = isobutyl, R_2 = Cbz
2c: R_1 = isobutyl, R_2 = Boc
2d: R_1 = isopropyl, R_2 = Boc
2e: R_1 = isopropyl, R_2 = Cbz
2f: R_1 = benzyl, R_2 = Boc

3a: R_1 = sec-butyl, R_2 = Boc
3b: R_1 = sec-butyl, R_2 = Cbz
3c: R_1 = isobutyl, R_2 = Boc
3d: R_1 = isobutyl, R_2 = Cbz
3e: R_1 = isopropyl, R_2 = Boc
3f: R_1 = isopropyl, R_2 = Cbz
3g: R_1 = benzyl, R_2 = Boc

Scheme 2



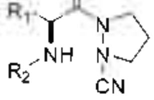
4a: R_1 = sec-butyl, R_3 = 4-Cl
4b: R_1 = sec-butyl, R_3 = 3-Cl
4c: R_1 = sec-butyl, R_3 = 4-CF_3
4d: R_1 = sec-butyl, R_3 = 3-CF_3
4e: R1 = isobutyl, R_3 = 4-Cl
4f: R_1 = isobutyl, R_3 = 4-CF_3
4g: R_1 = isobutyl, R_3 = 4-CN
4h: R_1 = isopropyl, R_3 = 4-CF_3
4i: R_1 = isopropyl, R_3 = 3-CF_3
4j: R_1 = benzyl, R_3 = 4-CF_3
4k: R_1 = benzyl, R_3 = 3-CF_3
4l: R_1 = benzyl, R_3 = 4-CN
4m: R_1 = 4-hydroxybenzyl, R_3 = 4-CN

5a: R_1 = sec-butyl, R_3 = 4-F
5b: R_1 = sec-butyl, R_3 = 3-F
5c: R_1 = sec-butyl, R_3 = 4-Cl
5d: R_1 = sec-butyl, R_3 = 3-Cl
5e: R_1 = sec-butyl, R_3 = 4-CF_3
5f: R_1 = sec-butyl, R_3 = 3-CF_3
5g: R_1 = isobutyl, R_3 = 4-F
5h: R_1 = isobutyl, R_3 = 3-F
5i: R_1 = isobutyl, R_3 = 4-Cl
5j: R_1 = isobutyl, R_3 = 3-Cl
5k: R_1 = isobutyl, R_3 = 4-CF_3
5l: R_1 = isobutyl, R_3 = 3-CF_3

5m: R_1 = isopropyl, R_3 = 4-F
5n: R_1 = isopropyl, R_3 = 3-F
5o: R_1 = isopropyl, R_3 = 4-Cl
5p: R_1 = isopropyl, R_3 = 3-Cl
5q: R_1 = isopropyl, R_3 = 4-CF_3
5r: R_1 = isopropyl, R3 = 3-CF_3
5s: R_1 = benzyl, R_3 = 4-F
5t: R_1 = benzyl, R_3 = 3-F
5u: R_1 = benzyl, R_3 = 3-Cl
5v: R_1 = benzyl, R_3 = 4-CF_3
5w: R_1 = benzyl, R_3 = 3-CF_3

Scheme 3

Table 1

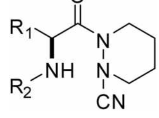


2a-f

compounds	IC$_{50}$ (μM)			
	Cat B	Cat L	Cat K	Cat S
2a	0.049	1.100	>1	0.255
2b	0.027	0.175	0.007	0.009
2c	0.680	0.755	–	0.003
2d	0.037	0.925	0.031	0.023
2e	0.028	0.095	0.029	0.032
2f	0.120	>10	0.093	0.004

–: No data available for this compound

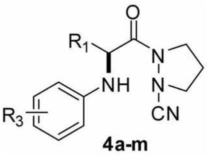
Table 2



3a-g

compounds	IC$_{50}$ (μM)			
	Cat B	Cat L	Cat K	Cat S
3a	0.017	0.185	0.008	0.018
3b	0.039	0.380	0.001	0.040
3c	0.021	0.085	0.028	0.004
3d	0.032	0.180	0.007	0.008
3e	0.056	0.435	0.055	0.004
3f	0.011	0.145	0.009	0.031
3g	0.495	2.150	0.325	0.023

Table 3

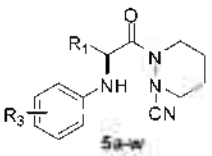


4a-m

compounds	IC_{50} (μM)			
	Cat B	Cat L	Cat K	Cat S
4a	0.037	0.360	>1	0.027
4b	0.015	0.100	0.040	0.005
4c	0.017	0.980	0.170	0.033
4d	0.092	0.046	–	0.031
4e	0.056	0.690	>1	0.013
4f	0.083	0.490	>1	0.007
4g	0.525	1.250	1.000	0.013
4h	0.045	0.470	>1	0.039
4i	0.022	0.100	>1	0.021
4j	0.300	>10	–	0.024
4k	0.053	1.200	>1	0.010
4l	>10	>10	–	0.033
4m	5.100	>10	–	0.037

–: No data available for this compound

Table 4



5a-w

compounds	IC_{50} (μM)			
	Cat B	Cat L	Cat K	Cat S
5a	0.185	0.340	–	0.024
5b	0.135	0.370	–	0.050
5c	0.120	0.343	0.056	0.030
5d	0.043	0.210	0.004	0.007
5e	0.096	0.210	0.024	0.045
5f	0.044	0.046	0.003	0.019
5g	0.052	0.180	0.036	0.016
5h	0.046	0.300	0.042	0.006
5i	0.039	0.150	0.012	0.005
5j	0.028	0.086	0.002	0.016
5k	0.037	0.100	0.015	0.005
5l	0.015	0.032	0.005	0.003
5m	0.056	0.435	0.052	0.035
5n	0.046	0.900	0.135	0.044
5o	0.110	0.610	0.024	0.038
5p	0.032	0.240	0.011	0.029
5q	0.041	0.430	0.040	0.036
5r	0.023	0.048	0.023	0.019
5s	0.180	0.850	–	0.035
5t	0.077	1.300	0.700	0.031
5u	0.053	0.530	0.560	0.016
5v	0.165	0.223	–	0.041
5w	0.042	0.090	0.140	0.007

–: No data available for this compound

K. It should be mentioned that *N*-cyanopyrazolidine ring seemed crucial for cathepsin S selectivity. For selectivity against cathepsin S, isobutyl and isopropyl groups as well as benzyl and 4-hydroxybenzyl groups can be employed for R_1 part, implying more structural flexibility for this region. In addition, cyano group attached to the para position of the phenyl group in the series of **4** (**4g**, **4l**, and **4m**) is conceived to play a role in the selectivity against cathepsin S. Although potency of these derivatives against cathepsin B did not increase much compared with that of hit compound **1**, two compounds (**4b** and **5n**) having selective inhibitory activity against cathepsins B and S were elected for further biological evaluation.[7]

In conclusion, a series of *N*-cyanopyrazolidine and *N*-cyanohexahydropyridazine compounds were synthesized in search for potent and selective cathepsin B inhibitors. However, contrary to our expectation, several compounds with promising inhibitory activity and selectivity against cathepsins K or S were discovered, respectively. Given the fact that cathepsin K is a good target for curing osteoporosis whereas cathepsin S is an attractive target for various inflammatory diseases, these compounds might be a useful lead for these therapeutic areas. Further studies are ongoing along this line and will be reported in due course.

Experimental Section

General procedure for the synthesis of 9, 10, 12, and 13: To a stirred solution of acid **6** (6 mmol) in dichloromethane (20 mL) at rt were added triethylamine (12 mmol), pyrazolidine **7** (6 mmol), and EDCI (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride, 6 mmol) successively. After being stirred at rt for 16 h, the reaction mixture was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (hexanes:ethyl acetate) to afford the corresponding amide **9**. Compounds **10**, **12**, and **13** were prepared by following the similar procedure above.

General procedure for the synthesis of 2, 3, 4, and 5: To a stirred solution of amide **9** (1 mmol) in 5 mL of MeOH/H_2O (1:1) were added NaOAc (2 mmol) and CNBr (3 mmol) at rt. After being stirred at rt for 3 h, the reaction mixture was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2 one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (hexanes:ethyl acetate) to give **2**. Compounds **3**, **4**, and **5** were prepared by following the similar procedure above.

2a: 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.29 (m, 5H), 5.49 (m, 1H), 5.08 (m, 2H), 4.98 (m, 1H), 3.60 (m, 1H), 3.46 (m, 1H), 2.06 (m, 2H), 1.75 (m, 1H), 1.50 (m, 1H), 1.12 (m, 1H), 0.94 (d, 3H, J = 6.7 Hz), 0.88 (t, 3H, J = 7.4 Hz); **2b:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.66-7.30 (m, 5H), 4.72-4.62 (m, 2H), 3.86-3.82 (m, 1H), 3.68-3.56 (m, 2H), 3.46-3.42 (m, 1H), 2.39-2.33 (m, 2H), 2.02 (m, 2H), 1.70-1.66 (m, 2H), 1.27-1.14 (m, 1H), 0.95 (m, 6H); **2c:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.95 (d, 1H, J = 8.5 Hz), 4.69 (m, 1H), 4.09 (m, 1H), 3.60 (m, 1H), 3.49 (m, 1H), 2.30 (m, 2H), 1.76 (m, 1H), 1.52 (m, 1H), 1.42 (s, 9H), 1.20 (m, 1H), 1.02 (d, 3H, J = 6.8 Hz), 0.92 (t, 3H, J = 7.5 Hz); **2d:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 4.69 (d, 1H, J = 9.7 Hz), 4.45 (m, 1H), 3.90 (m, 1H), 3.66-3.55 (m, 2H), 3.34 (m, 1H), 2.36 (m 2H), 1.41 (s, 9H), 1.08 (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz); **2e:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.29 (m, 5H), 5.32 (d, 1H, J = 8.7 Hz), 4.73 (q. 2H. J = 20.7 Hz), 4.79 (m. 1H). 4.12-4.03 (m. 1H), 3.67-3.39 (m. 2H). 2.35-2.14 (m. 2H). 1.06 (d. 3H, J = 6.6 Hz). 0.94 (d, 3H, J = 6.6 Hz): **3b:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.34-7.26 (m. 5H), 5.29 (d. 1H, J = 9.0 Hz), 5.14-5.02 (m, 2H). 4.81 (m, 1H), 4.51 (d. 1H, J = 13.2), 3.55 (m. 2H). 3.19-3.15 (m. 1H), 2.03 (m. 1H). 1.82-1.65 (m, 3H), 1.56-1.49 (m. 1H). 1.32 (m, 1H), 1.01 (d, 3H. J = 6.6 Hz), 0.91 (t. 3H. J = 7.4 Hz): **3c:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.25 (d, 1H, J = 8.7 Hz), 4.96-4.91 (m. 1H). 4.49 (d, 1H. J = 13.8 Hz). 3.53-3.50 (m, 2H). 3.16-3.08 (m, 1H). 1.83-1.68 (m, 4H). 1.52-1.48 (m, 2H). 1.44 (s. 9H), 1.02 (d. 3H. J = 6.3 Hz). 0.91 (d, 3H, J = 6.6 Hz): **3d:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.29 (m. 5H), 5.25 (d, 1H. J = 8.7 Hz). 5.14-4.99 (m, 2H). 4.96-4.91 (m. 1H). 4.49 (d, 1H. J = 13.8 Hz), 3.53-3.50 (m. 2H), 3.16-3.08 (m, 1H), 1.83-1.68 (m. 4H), 1.52-1.48 (m. 2H). 1.02 (d, 3H, J = 6.3 Hz), 0.91 (d. 3H, J = 6.6 Hz): **3e:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 5.03-5.00 (d, 1H, J = 9.0 Hz). 4.73-4.68 (m. 1H), 4.53-4.49 (d. 1H, J = 9.9 Hz). 3.60-3.52 (m. 2H). 3.18-3.10 (m. 1H). 2.13-2.01 (m. 2H), 1.99-1.84 (m, 2H). 1.80 (m, 1H). 1.43 (s, 9H). 1.03-1.01 (d, 3H. J = 6.6 Hz). 0.93 (d. 3H, J = 6.9 Hz): **3f:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.36-7.34 (m. 5H), 5.28 (d. 1H, J = 9.6 Hz). 5.15-5.03 (m. 2H), 4.78-4.75 (m, 1H), 4.51 (d. 1H, J = 12.0 Hz), 3.53-3.50 (m. 2H), 3.20- 3.11 (m, 1H). 2.06-1.99 (m, 2H). 1.83-1.79 (m. 1H), 1.05-1.03 (d. 3H, J = 6.6 Hz), 0.93 (d. 3H. J = 6.9 Hz): **3g:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.18 (m. 5H). 5.09-5.05 (m. 2H). 4.51-4.47 (m. 1H), 3.53-3.50 (d. 1H, J = 9.0 Hz), 3.53-3.50 (m, 2H). 3.20-3.11 (m, 1H). 3.17-3.08 (m, 4H), 3.06-2.98 (m. 1H). 2.80-2.03 (m. 1H), 1.37 (s. 9H). **4a:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.10 (d. 2H, J = 8.7 Hz), 6.60 (d, 2H. J = 9.0 Hz). 4.40-4.34 (m. 1H), 4.11 (d, 1H. J = 10.5 Hz). 3.89 (m, 1H). 3.58 (m, 2H). 3.23 (m. 2H). 3.22 (m, 1H), 2.25 (m, 2H). 1.88 (m, 2H), 1.33-1.17 (m, 1H). 1.03 (d, 3H. J = 7.2 Hz). 0.94 (t. 3H. J = 7.2 Hz); **4b:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.05 (t. 1H, J = 7.8 Hz), 6.68 (d. 1H. J = 8.1 Hz). 6.61 (s. 1H). 6.54 (d, 1H, J = 8.1 Hz), 4.41 (m, 1H), 4.21 (d. 1H. J = 10.8 Hz). 3.95 (m, 1H). 3.58 (m. 2H). 3.30 (m, 1H). 2.21 (m. 2H). 1.75 (m, 2H). 1.29 (m. 1H). 1.05 (d. 3H. J = 6.9 Hz). 0.94 (t. 3H. J = 7.5 Hz): **4c:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (d. 2H. J = 8.5 Hz). 6.61 (d. 2H. J = 8.5 Hz). 4.42-4.34 (m. 2H). 3.89-3.79 (m. 1H). 3.59-3.43 (m. 2H). 3.27-3.18 (m, 1H). 2.32-2.15 (m, 2H). 1.85-1.58 (m. 2H). 1.25-1.12 (m, 1H). 0.98 (d. 3H. J = 6.8 Hz). 0.87 (t. 3H. J = 7.4 Hz): **4d:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.26-7.21 (m. 1H), 6.96 (d, 1H. J = 7.5 Hz). 6.83-6.81 (m. 2H), 4.47 (dd. 2H. J = 10.5, 6.9 Hz). 4.33 (d. 1H. J = 10.5 Hz). 3.99-3.90 (m. 1H). 3.61-3.52 (m. 2H). 3.29-3.20 (m. 1H). 2.38-2.20 (m. 2H). 1.90-1.68 (m. 2H). 1.33-1.24 (m, 1H). 1.07 (d, 3H. J = 6.8 Hz). 0.95 (t, 3H, J = 7.4 Hz): **4e:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.10 (d. 2H. J = 8.7 Hz). 6.56 (d, 2H. J = 8.7 Hz). 4.65-4.56 (m, 1H), 4.08 (d. 1H, J = 10.5 Hz). 3.91-3.79 (m. 2H). 1.96-1.81 (m. 1H). 1.69-1.50 (m. 2H). 1.04-0.98 (m. 6H): **4f:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.49 (d. 2H, J = 8.7 Hz). 6.64 (d. 2H. J = 8.7 Hz). 4.73-4.69 (m, 1H), 4.39 (d, 1H, J = 9.9 Hz), 3.88-3.85 (m. 1H). 3.84-3.54 (m. 2H). 3.43-3.39 (m. 1H). 2.37-2.30 (m. 2H). 1.67-1.65 (m. 1H). 1.64-1.55 (m. 2H). 1.02 (m, 6H); **4g:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 2H. J = 8.7 Hz). 6.59 (d. 2H. J = 8.7 Hz), 4.72-4.62 (m, 2H), 3.86-3.82 (1H, m). 3.68-3.56 (m, 2H), 3.46-3.42 (m. 1H). 2.39-2.33 (m. 2H), 1.70-1.66 (m, 1H). 1.27-1.14 (m. 2H). 0.95 (m, 6H); **4h:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.38 (d. 2H. J = 8.4 Hz). 6.69 (d. 2H, J = 8.4 Hz). 4.55 (d. 1H. J = 10.2 Hz). 4.47-4.42 (m, 1H). 3.89-3.88 (m, 1H), 3.63-3.53 (m, 2H). 3.34-3.30 (m, 1H). 2.35-2.28 (m, 2H), 2.14-2.10 (m, 1H). 1.07 (m. 6H); **4i:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.26-7.21 (m, 1H), 6.96 (d, 1H, J = 7.5 Hz). 6.83-6.81 (m. 2H). 4.47-4.37 (m, 2H). 3.96-3.93 (m, 1H), 3.60-3.55 (m. 1H). 3.29-3.25 (m. 1H). 2.27-2.09 (m, 2H). 1.10 (m, 6H): **4j:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.32 (d, 2H. J = 8.7 Hz), 7.25-7.14 (m, 1H). 4.58 (d. 1H, J = 9.9 Hz). 3.62-3.57 (m. 2H). 3.20-3.12 (m, 1H). 3.02 (d, 2H. J = 6.9 Hz), 2.60 (m, 1H). 2.13-2.00 (m, 2H): **4k:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.34-7.22 (m, 6H). 6.97 (d. 1H, J = 7.5 Hz). 6.80-6.77 (m. 2H). 4.93-4.88 (m, 1H), 4.48 (d, 1H, J = 9.9 Hz). 3.71-3.62 (m. 2H). 3.29-3.21 (m, 1H). 3.12-3.08 (m, 2H), 2.88-2.85 (m. 1H). 2.24-2.15 (m, 2H); **4l:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.42 (d, 2H, J = 8.7 Hz). 7.33-7.20 (m. 5H), 6.60 (d, 2H. J = 9.0 Hz), 4.93-4.91 (m. 1H), 4.83 (d. 1H, J = 9.3 Hz), 3.71-3.67 (m. 2H). 3.31-3.23 (m, 1H), 3.10 (d. 2H, J = 6.9 Hz). 2.73 (m, 1H). 2.24-2.14 (m. 2H): **4m:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.39 (d, 2H. J = 8.1 Hz), 7.03 (d. 2H. J = 8.1 Hz), 6.74 (d, 2H. J = 8.1 Hz). 6.58 (d. 2H. J = 8.1 Hz). 4.92-4.89 (m. 2H), 3.69-3.35 (m, 2H). 3.33-3.27 (m, 1H), 3.02-3.01 (m, 2H), 2.96-2.90 (m. 1H). 2.25-2.19 (m. 2H); **5a:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.91-6.82 (m, 2H), 6.68-6.63 (m, 2H), 4.54-4.49 (m, 1H). 4.34 (m, 1H), 3.98 (m. 1H), 3.55-3.40 (m, 1H), 3.15-2.74 (m. 2H), 2.02-1.57 (m. 5H), 1.28-1.22 (m, 2H), 1.01 (d. 3H. J = 6.6 Hz), 0.94 (t. 3H. J = 7.2 Hz); **5b:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.13-7.05 (m, 1H). 6.45-6.34 (m. 3H). 4.55-4.44 (m, 2H). 4.26 (d, 1H. J = 9.9 Hz). 3.55-3.50 (m, 1H), 3.18-2.98 (m. 2H). 2.11-1.97 (m, 1H), 1.83-1.57 (m. 4H), 1.26-1.15 (m. 2H). 1.02 (d, 3H. J = 6.6 Hz), 0.93 (t. 3H. J = 7.5 Hz): **5c:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.11 (d, 2H. J = 6.9 Hz), 6.62 (d, 2H, J = 6.9 Hz), 4.54-4.35 (m, 2H). 4.13 (m. 1H). 3.59-3.44 (m. 1H). 3.22-2.89 (m, 2H). 2.06-1.95 (m, 1H). 1.82-1.54 (m. 5H). 1.26-1.19 (m, 1H). 1.01 (d. 3H. J = 6.6 Hz). 0.95 (t. 3H, J = 7.2 Hz); **5d:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.07 (t, 1H. J = 8.1 Hz), 6.70-6.64 (m. 2H), 6.55 (d, 1H, J = 9.6 Hz), 3.55-3.52 (m. 1H). 4.49 (m. 2H). 4.22 (d. 1H. J = 9.6 Hz). 3.53 (m. 1H). 3.15 (m. 2H). 2.10-1.99 (m. 1H). 1.75 (m. 5H). 1.24 (m. 1H). 1.02 (d. 3H, J = 6.6 Hz). 0.93 (t. 3H, J = 7.5 Hz): **5e:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.40 (d. 2H. J = 8.6 Hz). 6.68 (d. 2H, J = 8.2 Hz), 4.57-4.45 (m, 3H), 3.60-3.49 (m. 1H). 3.23-2.99 (m, 2H). 2.09-2.00 (m, 1H). 1.88-1.56 (m, 5H). 1.26-1.15 (m. 1H). 1.02 (d. 3H. J = 6.7 Hz). 0.93 (t. 3H. J = 7.4 Hz): **5f:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.29-7.23 (m, 1H). 6.97 (d. 1H, J = 7.2 Hz). 6.88-6.82 (m. 2H). 4.54-4.34 (m. 3H). 3.56-3.51 (m. 1H). 3.23-2.97 (m. 2H). 2.06-2.02 (m. 1H). 1.83-1.51 (m, 4H). 1.30-1.17 (m. 2H). 1.05 (d. 3H. J = 6.9 Hz). 0.94 (t. 3H, J = 7.2 Hz): **5g:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.91-6.83 (m, 2H), 6.64-6.59 (m. 2H). 4.61-4.47 (m, 2H). 3.92 (m, 1H). 3.62-3.52 (m. 1H), 3.29-3.06 (m.

2H), 2.06-2.02 (m, 1H), 1.90-1.75 (m, 4H), 1.60-1.56 (m, 2H), 1.04-0.95 (m, 6H); **5h:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.14-7.06 (m, 1H), 6.45-6.29 (m, 3H), 4.71-4.49 (m, 2H), 4.21 (d, 1H, J = 10.5 Hz), 3.62-3.57 (m, 1H), 3.26-3.09 (m, 2H), 2.09-2.00 (m, 1H), 1.90-1.82 (m, 3H), 1.62-1.58 (m, 3H), 1.04-0.95 (m, 6H); **5i:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 2H, J = 8.7 Hz), 6.58 (d, 2H, J = 8.4 Hz), 4.67-4.48 (m, 2H), 4.08 (m, 1H), 3.59-3.54 (m, 1H), 3.26-3.11 (m, 2H), 2.12-1.98 (m, 1H), 1.90-1.81 (m, 3H), 1.61-1.57 (m, 3H), 1.03-0.98 (m, 3H); **5j:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.08 (t, 1H, J = 7.8 Hz), 6.70 (d, 1H, J = 7.8 Hz), 6.58 (s, 1H), 6.53 (d, 1H, J = 8.1 Hz), 4.70-4.59 (m, 1H), 4.51 (d, 1H, J = 11.7 Hz), 4.1 (m, 1H), 3.61 (m, 1H), 3.18 (m, 2H), 2.13-2.01 (m, 1H), 1.89 (m, 3H), 1.67-1.57 (m, 3H), 1.04-0.98 (m, 6H); **5k:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.41 (d, 2H, J = 8.7 Hz), 6.69-6.63 (m, 2H), 4.77-4.66 (m, 1H), 4.54-4.44 (m, 2H), 3.62-3.58 (m, 1H), 3.26-3.09 (m, 2H), 2.10-2.00 (m, 1H), 1.92-1.80 (m, 3H), 1.68-161 (m, 3H), 1.03-0.97 (m, 6H); **5l:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.29-7.23 (m, 1H), 6.99-6.93 (d, 1H, J = 7.8 Hz) 6.82-6.76 (m, 2H), 4.77-4.67 (m, 1H), 4.53-4.49 (d, 1H, J = 11.7 Hz), 4.29 (m, 1H), 3.64-3.59 (m, 1H), 3.29-3.09 (m, 2H), 2.09-2.05 (m, 1H), 1.94-1.83 (m, 3H), 1.64-1.60 (m, 3H), 1.05-0.96 (m, 6H); **5m:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.91-6.85 (m, 2H), 6.68-6.64 (m, 2H), 4.53-4.49 (m, 1H), 4.30 (m, 1H), 4.04 (m, 1H), 3.47-3.43 (m, 1H), 3.15-2.80 (m, 2H), 2.07-2.00 (m, 1H), 1.80-1.68 (m, 2H), 1.57-1.45 (m, 2H), 1.07-0.99 (m, 6H); **5n:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.13-7.05 (m, 1H), 6.46-6.35 (m, 3H), 4.54-4.31 (m, 3H), 3.56-3.51 (m, 1H), 3.18-3.01 (m, 2H), 2.13-1.98 (m, 2H), 1.83-1.73 (m, 2H), 1.66-1.54 (m, 1H), 1.06 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.9 Hz); **5o:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 2H, J = 9.0 Hz), 6.63 (d, 2H, J = 9.0 Hz), 4.53-4.48 (m, 1H), 4.39-4.32 (m, 1H), 4.20-4.19 (m, 1H), 3.60-3.48 (m, 1H), 3.27-2.92 (m, 2H), 2.11-2.01 (m, 1H), 1.83-1.72 (m, 2H), 1.59-1.51 (m, 2H), 1.06 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.6 Hz); **5p:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.07 (t, 1H, J = 8.1 Hz), 6.70-6.50 (m, 2H), 6.56 (d, 1H, J = 8.1 Hz), 4.54-4.40 (m, 2H), 4.29 (d, 1H, J = 10.2 Hz), 3.54 (m, 1H), 3.18-3.03 (m, 2H), 2.12-2.02 (m, 2H), 1.83-1.74 (m, 2H), 1.65 (m, 1H), 1.06 (d, 3H, J = 6.6 Hz), 1.01 (d, 3H, J = 6.9 Hz); **5q:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.33 (d, 2H, J = 8.4 Hz), 6.66 (d, 2H, J = 7.8 Hz), 4.468 (m, 3H), 3.57-3.45 (m, 1H), 3.17-2.95 (m, 2H), 2.10-1.97 (m, 2H), 1.86-1.69 (m, 2H), 1.52 (m, 1H), 1.00 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz); **5r:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.26 (t, 1H, J = 7.8 Hz), 6.96 (d, 1H, J = 7.5 Hz), 6.85-6.83 (m, 2H), 4.53-4.42 (m, 3H), 3.56-3.52 (m, 1H), 3.18-3.01 (m, 2H), 2.17-1.95 (m, 2H), 1.83-1.73 (m, 2H), 1.56-1.52 (m, 1H), 1.09 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.6 Hz); **5s:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.22 (m, 5H), 6.93-6.83 (m, 2H), 6.70-6.66 (m, 1H), 6.57-6.54 (m, 1H), 4.90-4.78 (m, 1H), 4.52-4.42 (m, 1H), 4.12 (d, 1H, J = 6.9 Hz), 3.16-2.94 (m, 5H), 1.84-1.67 (m, 2H), 1.58-1.41 (m, 2H); **5t:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.24 (m, 5H), 7.16-7.06 (m, 1H), 6.50-6.23 (m, 3H), 4.94-4.82 (m, 1H), 4.53-4.33 (m, 2H), 3.19-2.95 (m, 4H), 1.86-1.33 (m, 5H); **5u:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.23 (m, 5H), 7.13-7.01 (m, 1H), 6.73-6.44 (m, 3H), 4.90-4.86 (m, 1H), 4.49-4.30 (m, 2H), 3.25-2.91 (m, 4H), 2.08-1.33 (m, 5H); **5v:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.44-7.18 (m, 7H), 6.72 (d, 1H, J = 8.4 Hz), 6.57 (d, 1H, J = 8.1 Hz), 4.99-4.92 (m, 1H), 4.68-4.46 (m, 2H), 3.22-2.93 (m, 4H), 2.17-2.1 (m, 1H), 1.88-1.46 (m, 4H); **5w:** 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.33-7.20 (m, 6H), 7.00-6.85 (m, 2H), 6.74-6.69 (m, 1H), 4.97-4.91 (m, 1H), 4.54-4.47 (m, 2H), 3.25-2.95 (m, 4H), 1.88-1.47 (m, 5H).

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References and Notes

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