

Supporting Information

Synthesis and Structure-Activity Relationship of Imidazo[1,2-*b*]pyridazines as Ligands for β -Amyloid Plaques

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Experimental Section

Synthesis of 2-(4'-Dimethylaminophenyl)-6-fluoroimidazo[1,2-*b*]pyridazine (2a). **3,6-difluoropyridazine.** A solution of 3,6-dichloropyridazine (447 mg, 3 mmol) and KF (928 mg, 18 mmol) in DMSO (4 mL) was heated at 130 °C in a screw-cap test tube for 15 h. The entire reaction mixture was submitted to flash chromatography and eluting with 3:1 hexane / ethyl acetate gave a white solid (143 mg, 41%). ¹H NMR (400 MHz, CDCl₃): δ 7.38 (t, *J* = 1.4 Hz, 2H).

3-Amino-6-fluoropyridazine. The mixture of 3,6-difluoropyridazine (106 mg, 0.91 mmol) and ammonia (4.55 mL, 9.1 mmol, 2M in ethanol) was heated in a sealed bomb at 120 °C for 15 h. The solvent was removed under vacuo and purification by flash chromatography (hexane: ethyl acetate = 1:1) to afford a light yellow solid (41 mg, 40%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.19 (dd, *J* = 9.7, 2.0 Hz, 1H), 6.95 (dd, *J* = 9.3, 7.3 Hz, 1H), 6.38 (bs, 2H).

2-(4'-Dimethylaminophenyl)-6-fluoroimidazo[1,2-*b*]pyridazine(2a). A mixture of 3-amino-6-fluoropyridazine (10 mg, 0.088 mmol) and 2-bromo-4'-dimethylaminoacetophenone (21 mg, 0.088 mmol) in absolute ethanol (3 mL) was stirred under reflux for 2 h. The mixture was then cooled, and NaHCO₃ (13 mg, 0.15 mmol) was added. The reaction mixture was refluxed for another 4 h. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (12 mg, 52%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.05 (d, *J* = 0.4 Hz, 1H), 7.93 (dd, *J* = 9.5, 7.3 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.5 Hz, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 3.01 (s, 6H). HRMS: *m/z* calcd for C₁₄H₁₄N₄F (M⁺+H) 257.1197, found 257.1194.

6-Chloro-2-(4'-dimethylaminophenyl)imidazo[1,2-*b*]pyridazine (2b). 3-Amino-6-chloropyridazine was prepared by a previously reported method. Yield 71 %. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.33 (d, *J* = 9.3 Hz, 1H), 6.81 (d, *J* = 9.3 Hz, 1H), 6.60 (bs, 2H).

A mixture of 2-bromo-4'-dimethylaminoacetophenone (121 mg, 0.5 mmol) and 3-amino-6-chloropyridazine (65 mg, 0.55 mmol) in absolute ethanol (5 mL) was stirred under reflux for 2 h. The mixture was then cooled, and NaHCO₃ (60 mg, 0.71 mmol) was added. The reaction mixture was refluxed for another 5 h. The mixture was cooled and filtered to give a yellow solid (90 mg, 66%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.12 (d, *J* = 0.6 Hz, 1H), 7.82 (m, 3H), 7.01 (d, *J* = 9.2 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 3.01 (s, 6H). HRMS: *m/z* calcd for C₁₄H₁₄N₄Cl (M⁺+H) 273.0901, found 273.0898.

2-(4'-Dimethylaminophenyl)-6-iodoimidazo[1,2-*b*]pyridazine (2c). A mixture of 3-amino-6-iodopyridazine (68 mg, 0.31 mmol) and 2-bromo-4'-dimethylaminoacetophenone (75

mg, 0.31 mmol) in absolute ethanol (6 mL) was stirred under reflux for 3 h. The mixture was then cooled, and NaHCO₃ (38 mg, 0.45 mmol) was added. The reaction mixture was refluxed for another 5 h. The mixture was cooled and filtered to give a yellow solid (91 mg, 81%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.15 (s, 1H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.27 (d, *J* = 9.2 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.01 (s, 6H). HRMS: *m/z* calcd for C₁₄H₁₄N₄I (M⁺+H) 365.0258, found 365.0253.

2-(4'-Dimethylaminophenyl)-6-methoxyimidazo[1,2-b]pyridazine (3). A mixture **2b** (27 mg, 0.1 mmol) and sodium methoxide (22 mg, 0.4 mmol) in absolute ethanol (7 mL) was stirred under reflux for 18 h. The solvent was removed under reduced pressure and water was added. The mixture was then extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (17 mg, 62%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.42 (s, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 3.91 (s, 3H), 2.91 (s, 6H). HRMS: *m/z* calcd for C₁₅H₁₇N₄O (M⁺+H) 269.1397, found 269.1395.

2-(4'-Dimethylaminophenyl)-6-methylthioimidazo[1,2-b]pyridazine (4). The same procedure described for the preparation of **3** was performed to prepare **4**, starting from **2b** (27 mg) and sodium thiomethoxide (28 mg), to give **4** in 78% yield. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (s, 1H), 7.90 (d, *J* = 9.5 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.5 Hz, 1H), 6.80 (d, *J* = 9.2 Hz, 2H), 3.01 (s, 6H), 2.61 (s, 3H).

6-(2-Fluoroethoxy)-2-(4'-dimethylaminophenyl)imidazo[1,2-b]pyridazine (5). A mixture **2b** (27 mg, 0.1 mmol), 2-fluoroethanol (24 μL, 0.4 mmol), tetrabutylammonium hydroxide (40 wt% in H₂O, 0.26 mL) in DMF (5 mL) was stirred at room temperature for 18 h. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (16 mg, 54%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.41 (s, 1H), 7.95 (d, *J* = 9.5 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 9.5 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 4.84 (t, *J* = 4.1, 3.8 Hz, 1H), 4.72 (t, *J* = 4.1, 3.8 Hz, 1H), 4.55 (t, *J* = 4.1, 3.8 Hz, 1H), 4.47 (t, *J* = 4.1, 3.8 Hz, 1H), 2.91 (s, 6H). HRMS: *m/z* calcd for C₁₆H₁₈N₄FO (M⁺+H) 301.1459, found 301.1458.

6-(3-Fluoropropoxy)-2-(4'-dimethylaminophenyl)imidazo[1,2-b]pyridazine (6). The same procedure described for the preparation of **5** was performed to prepare **6**, starting from **2b** (27 mg, 0.1 mmol), 3-fluoropropanol (31 mg, 0.4 mmol), and tetrabutylammonium hydroxide (40 wt% in H₂O, 0.26 mL), to give **6** in 44% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.41 (s, 1H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 9.5 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 4.66 (t, *J* = 5.7 Hz, 1H), 4.55 (t, *J* = 5.7 Hz, 1H), 4.36 (t, *J* = 6.3 Hz, 2H), 2.91 (s, 6H), 2.19-2.10 (m, 2H). HRMS: *m/z* calcd for C₁₇H₂₀N₄FO (M⁺+H) 315.1616, found 315.1609.

2-(2-(4-(Dimethylamino)phenyl)imidazo[1,2-b]pyridazin-6-ylthio)ethanol (7). A mixture **2b** (54 mg, 0.2 mmol), 2-mercaptoethanol (0.14 mL, 2 mmol), and tetrabutylammonium hydroxide (40 wt% in H₂O, 1.15 mL) in DMF (7 mL) was stirred at room temperature for 1 h. Water was added and the mixture was filtered to give a yellow solid (52 mg, 83%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.06 (s, 1H), 7.79 (d, *J* = 9.2 Hz, 2H), 7.67 (d, *J* = 9.5 Hz, 1H), 6.86 (d, *J* = 9.5 Hz, 1H), 6.78 (d, *J* = 9.2 Hz, 2H), 3.94 (t, *J* = 6.0 Hz, 2H), 3.40 (t, *J* = 6.0 Hz, 2H), 3.00 (s, 6H). HRMS: *m/z* calcd for C₁₆H₁₉N₄OS (M⁺+H) 315.1274, found 315.1268.

3-(2-(4-(Dimethylamino)phenyl)imidazo[1,2-b]pyridazin-6-ylthio)propan-1-ol (8). The same procedure described for the preparation of **7** was performed to prepare **8**, starting from

2b (54 mg, 0.2 mmol), 3-mercapto-1-propanol (0.17 mL, 2 mmol), and tetrabutylammonium hydroxide (40 wt% in H₂O, 1.15 mL), to give **8** in 86% yield. ¹H NMR (400 MHz, CD₂Cl₂): δ 8.05 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 9.2 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.33 (t, *J* = 7.0 Hz, 2H), 3.00 (s, 6H), 2.01 (m, 2H). HRMS: *m/z* calcd for C₁₇H₂₁N₄OS (M⁺+H) 329.1431, found 329.1432.

6-(2-Fluoroethylthio)-2-(4'-dimethylaminophenyl)imidazo[1,2-b]pyridazine (9). A solution of DAST (80 μL, 0.6 mmol) in CH₂Cl₂ (1 mL) was slowly added to a solution of compound **7** (31mg, 0.1 mmol) in CH₂Cl₂ (3 mL) cooled to -78 °C. The mixture was stirred at -78 °C for 30 min and then warmed up to room temperature. The mixture was stirred for another 60 min. Water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (6.5 mg, 21%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.07 (s, 1H), 7.81 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 1H), 6.79 (d, *J* = 8.9 Hz, 2H), 4.78 (t, *J* = 6.3 Hz, 1H), 4.67 (t, *J* = 6.3 Hz, 1H), 3.56 (t, *J* = 6.3 Hz, 1H), 3.52 (t, *J* = 6.3 Hz, 1H), 3.01 (s, 6H). HRMS: *m/z* calcd for C₁₆H₁₈N₄FS (M⁺+H) 317.1231, found 317.1224.

6-(3-Fluoropropylthio)-2-(4'-dimethylaminophenyl)imidazo[1,2-b]pyridazine (10). The same procedure described for the preparation of **9** was performed to prepare compound **10**, starting from **2b** (33 mg, 0.1 mmol) and DAST (53 μL, 0.4 mmol), to give **10** in 24% yield. ¹H NMR (400 MHz, CD₂Cl₂): δ 8.07 (s, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 9.4 Hz, 1H), 6.84 (d, *J* = 9.4 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 4.70 (t, *J* = 4.7 Hz, 1H), 4.54 (t, *J* = 5.7 Hz, 1H), 3.33 (t, *J* = 7.1 Hz, 2H), 3.01 (s, 6H), 2.27-2.22 (m, 1H), 2.18-2.13 (m, 1H). HRMS: *m/z* calcd for C₁₇H₂₀N₄FS (M⁺+H) 331.1387, found 331.1381.

6-Fluoro-2-(4'-nitrophenyl)imidazo[1,2-b]pyridazine (11a). A mixture of 3-amino-6-fluoropyridazine (90 mg, 0.8 mmol) and 2-bromo-4'-nitroacetophenone (194 mg, 0.8 mmol) in absolute ethanol (8 mL) was stirred under reflux for 3 h. The mixture was then cooled, and NaHCO₃ (100 mg, 1.19 mmol) was added. The reaction mixture was refluxed for another 5 h. The mixture was cooled and filtered to give a pale yellow solid (128 mg, 62%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.06 (s, 1H), 8.38 (dd, *J* = 9.5, 7.7 Hz, 1H), 8.29 (m, 4H), 7.34 (d, *J* = 9.5 Hz, 1H). HRMS: *m/z* calcd for C₁₂H₈N₄FO₂ (M⁺+H) 259.0626, found 259.0629.

6-Chloro-2-(4'-Nitrophenyl)imidazo[1,2-b]pyridazine (11b). The same procedure described for the preparation of **11a** was performed to prepare **11b**, starting from 3-amino-6-chloropyridazine (260 mg) and 2-bromo-4'-nitroacetophenone (488 mg), to give **11b** in 67% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.14 (s, 1H), 8.34-8.25 (m, 5H), 7.43 (d, *J* = 9.5 Hz, 1H). HRMS: *m/z* calcd for C₁₂H₈ClN₄O₂ (M⁺+H) 275.0330, found 275.0333.

6-Iodo-2-(4'-Nitrophenyl)imidazo[1,2-b]pyridazine (11c). The same procedure described for the preparation of **11a** was performed to prepared **11c**, starting from 3-amino-6-iodopyridazine (442 mg) and 2-bromo-4'-nitroacetophenone (488 mg), to give **11c** in 96% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.08 (s, 1H), 8.31-8.24 (m, 4H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.56 (d, *J* = 9.5 Hz, 1H).

2-(4'-Aminophenyl)-6-fluoroimidazo[1,2-b]pyridazine (12a). To a solution of **11a** (128 mg, 0.5 mmol) in ethanol (15 mL) was added tin (II) chloride dehydrate (1.34 g, 6 mmol). The reaction mixture was refluxed under argon for 2 h. Ethanol was then evaporated, and the residue was dissolved in ethyl acetate. The resulting solution was washed with 1 N NaOH followed by water and dried over MgSO₄. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:5) to afford a

yellow solid (86 mg, 76%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.51 (s, 1H), 8.19 (dd, *J* = 9.5, 7.6 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 2H), 7.16 (d, *J* = 9.5 Hz, 1H), 6.59 (d, *J* = 7.3 Hz, 2H), 5.32 (s, 2H).

2-(4'-Aminophenyl)-6-chloroimidazo[1,2-*b*]pyridazine (12b). The same procedure described for the preparation of **12a** was performed to give **12b** in 61% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.60 (s, 1H), 8.07 (d, *J* = 9.2 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 9.5 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 2H), 5.41 (s, br, 2H).

2-(4'-Aminophenyl)-6-iodoimidazo[1,2-*b*]pyridazine (12c). The same procedure described for the preparation of **12a** was performed to give **12c** in 67% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.59 (s, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 9.2 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 2H), 5.39 (s, br, 2H).

6-Fluoro-2-(4'-methylaminophenyl)imidazo[1,2-*b*]pyridazine (13a). A solution of NaOMe (25 wt % in MeOH, 0.31 mL) was added dropwise to a mixture of **3a** (38 mg, 0.17 mmol) and paraformaldehyde (19 mg, 0.63 mmol) in methanol (5 mL). The mixture was then refluxed for 1 h before adding NaBH₄ (16 mg, 0.42 mmol). The reaction mixture was heated under reflux for another 2 h and cooled to room temperature. 1 M NaOH was added and the mixture was extracted with CH₂Cl₂. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (17 mg, 42%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.54 (s, 1H), 8.19 (dd, *J* = 9.5, 7.6 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 9.5 Hz, 1H), 6.57 (d, *J* = 8.6 Hz, 2H), 5.91 (q, *J* = 5.1 Hz, 1H), 2.69 (d, *J* = 5.1 Hz, 3H). HRMS: *m/z* calcd for C₁₃H₁₂N₄F (M⁺+H) 243.1041, found 243.1043.

6-Iodo-2-(4'-methylaminophenyl)imidazo[1,2-*b*]pyridazine (13c). The same procedure described for the preparation of **13a** was performed to give **13c** in 57% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.60 (s, 1H), 7.76-7.72 (m, 3H), 7.41 (dd, *J* = 9.2, 1.3 Hz, 1H), 6.57 (d, *J* = 7.6 Hz, 2H), 5.93 (q, *J* = 4.1 Hz, 1H), 2.69 (d, *J* = 4.1 Hz, 3H). HRMS: *m/z* calcd for C₁₃H₁₂N₄I (M⁺+H) 351.0101, found 351.0101.

6-Chloro-2-(4'-methylaminophenyl)imidazo[1,2-*b*]pyridazine (14). To a solution of **12b** (50 mg, 0.2 mmol) in DMSO (5 mL) were added methyl iodide (25 μL, 0.4 mmol) and K₂CO₃ (166 mg, 1.2 mmol). The reaction mixture was heated at 110 °C for 16 h. The mixture was cooled to room temperature, poured into water and extracted with ethyl acetate. The combined organic extracts were dried (MgSO₄) and concentrated, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (13 mg, 24%). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.02 (d, *J* = 9.2 Hz, 1H), 6.69 (d, *J* = 8.7 Hz, 2H), 5.94 (q, *J* = 4.5 Hz, 1H), 2.2.68 (d, *J* = 4.5 Hz, 3H). HRMS: *m/z* calcd for C₁₃H₁₂N₄Cl (M⁺+H) 259.0745, found 259.0747.

2-Bromo-1-(5-(dimethylamino)pyridin-2-yl)ethanone hydrobromide (15). 1-(5-Nitrothiophen-2-yl)ethanone (200 mg, 1.22 mmol) was dissolved in 48% hydrobromic acid (0.8 mL) and acetic acid (6 mL). The solution was heated to 40 °C and then a solution of pyridinium tribromide (520 mg, 1.62 mmol) in acetic acid (4 mL) was added. The mixture was kept at 50 °C overnight. The reaction mixture was cooled and the precipitate was filtered out and washed with acetic acid to give a yellow solid (147 mg, 37%). ¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 3.1 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 6.95 (dd, *J* = 9.0, 3.1 Hz, 1H), 4.77 (s, 2H), 3.12 (s, 6H).

2-(3'-Dimethylaminopyridinyl)-6-fluoroimidazo[1,2-*b*]pyridazine (16a). A mixture of 2-bromo-1-(5-(dimethylamino)pyridin-2-yl)ethanone hydrobromide (48 mg, 0.15 mmol) and NaHCO₃ (14 mg) in EtOH (5 mL) was added to a warm solution of 3-amino-6-fluoropyridazine

(17 mg, 0.15 mmol) in EtOH (2 mL). The mixture was refluxed overnight and then the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (16 mg, 41%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (s, 1H), 8.28 (dd, *J* = 9.7, 8.0 Hz, 1H), 8.13 (d, *J* = 3.0 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.24 (d, *J* = 9.6 Hz, 1H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.98 (s, 6H). HRMS: *m/z* calcd for C₁₃H₁₃N₅F (M⁺+H) 258.1150, found 258.1150.

2-(3'-Dimethylaminopyridinyl)-6-chloroimidazo[1,2-*b*]pyridazine (16b). The same procedure described for the preparation of **16a** was performed to give **16b** in 56% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.54 (s, 1H), 8.19-8.14 (m, 2H), 7.94 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 9.5 Hz, 1H), 7.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.98 (s, 6H). HRMS: *m/z* calcd for C₁₃H₁₃N₅Cl (M⁺+H) 274.0854, found 274.0855.

2-(3'-Dimethylaminopyridinyl)-6-iodoimidazo[1,2-*b*]pyridazine (16c). The same procedure described for the preparation of **16a** was performed to give **16c** in 47% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.52 (s, 1H), 8.14 (d, *J* = 3.0 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.17 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.98 (s, 6H). HRMS: *m/z* calcd for C₁₃H₁₃N₅I (M⁺+H) 366.0210, found 366.0212.

2-Bromo-1-(5-nitrothiophen-2-yl)ethanone (17). CuBr (111 mg, 0.5 mmol) was suspended in ethyl acetate (2 mL) and heated to reflux. A solution of 1-(5-nitrothiophen-2-yl)ethanone (51 mg, 0.3 mmol) in CHCl₃ (1 mL) was added. The mixture was refluxed overnight and filtered. The solvent was removed and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (45 mg, 60%). ¹H NMR (400 MHz, CD₂Cl₂): δ 7.92 (d, *J* = 4.3 Hz, 1H), 7.70 (d, *J* = 4.3 Hz, 1H), 4.41 (s, 2H).

6-Chloro-2-(5-nitrothiophen-2-yl)imidazo[1,2-*b*]pyridazine (18b). A mixture of 2-bromo-1-(5-nitrothiophen-2-yl)ethanone (190 mg, 0.76 mmol) and 3-amino-6-chloropyridazine (98 mg, 0.76 mmol) in absolute ethanol (4 mL) was stirred under reflux overnight. The mixture was cooled and filtered to give a brown solid (120 mg, 56%). ¹H NMR (400 MHz, CD₂Cl₂): δ 8.28 (s, 1H), 7.94 (d, *J* = 4.4 Hz, 1H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.41 (d, *J* = 4.4 Hz, 1H), 7.16 (d, *J* = 9.5 Hz, 1H). HRMS: *m/z* calcd for C₁₀H₆N₄ClSO₂ (M⁺+H) 280.9894, found 280.9891.

2-(5-Aminothiophen-2-yl)-6-Chloroimidazo[1,2-*b*]pyridazine (19b). Concentrated HCl solution (1.37 mL) was added dropwise to a mixture of **6b** (116 mmol, 0.41 mL) and tin (II) chloride dehydrate (837 mg, 3.3 mmol) in EtOH (5 mL) at 0 °C. The mixture was stirred at room temperature for 2 h. Ethanol was then evaporated, and the residue was dissolved in ethyl acetate. The resulting solution was washed with 1 N NaOH followed by water and dried over MgSO₄. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a brown solid (59 mg, 57%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.46 (s, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.23 (d, *J* = 9.3 Hz, 1H), 7.11 (d, *J* = 3.7 Hz, 1H), 5.91 (s, 2H), 5.86 (d, *J* = 3.7 Hz, 1H). HRMS: *m/z* calcd for C₁₀H₈N₄ClS (M⁺+H) 251.0153, found 251.0149.

6-Fluoro-2-(5-dimethylaminothiophen-2-yl)imidazo[1,2-*b*]pyridazine (20a). The same procedure described for the preparation of **20b** was performed to give **20a** in 22% yield. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.44 (s, 1H), 8.13 (dd, *J* = 9.5, 8.1 Hz, 1H), 7.25 (d, *J* = 3.8 Hz, 1H), 7.14 (d, *J* = 9.5 Hz, 1H), 5.90 (d, *J* = 3.8 Hz, 1H), 2.89 (s, 6H). HRMS: *m/z* calcd for C₁₂H₁₂N₄FS (M⁺+H) 263.0761, found 263.0758.

6-Chloro-2-(5-dimethylaminothiophen-2-yl)imidazo[1,2-*b*]pyridazine (20b). To a solution of **19b** (25 mg, 0.1 mmol) in DMSO (1.5 mL) was added NaH (60% oil dispersion, 16 mg, 0.4 mmol) followed by MeI (25 μL, 0.4 mmol) at room temperature. The mixture was stirred

for 1 h at room temperature and then water was added to quench the reaction. The mixture was extracted three times with EtOAc, and the extracts were combined and washed twice with H₂O. The organic layer was dried over MgSO₄ and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane: ethyl acetate = 1:1) to afford a yellow solid (9 mg, 32%). ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.51 (s, 1H), 8.01 (d, *J* = 9.3 Hz, 1H), 7.28 (d, *J* = 3.8 Hz, 1H), 7.24 (d, *J* = 9.3 Hz, 1H), 5.91 (d, *J* = 3.8 Hz, 1H), 2.89 (s, 6H). HRMS: *m/z* calcd for C₁₂H₁₂N₄ClS (M⁺+H) 279.0466, found 279.0461.

Table 1. Elemental analysis of compounds

Compound	Formula	Calculated			Found		
		C	H	N	C	H	N
2a	C ₁₄ H ₁₃ FN ₄	65.61	5.11	21.86	65.48	5.33	21.92
2b	C ₁₄ H ₁₃ ClN ₄	61.65	4.80	20.54	61.58	4.88	20.44
2c	C ₁₄ H ₁₃ IN ₄	46.17	3.60	15.38	46.27	3.69	15.23
3	C ₁₅ H ₁₆ N ₄ O	67.15	6.01	20.88	67.04	6.05	20.79
4	C ₁₅ H ₁₆ N ₄ S	63.35	5.67	19.70	63.41	5.70	19.63
5	C ₁₆ H ₁₇ FN ₄ O	63.99	5.71	18.66	63.84	5.71	18.62
6	C ₁₇ H ₁₉ FN ₄ O	64.95	6.09	17.82	64.87	6.07	17.85
9	C ₁₆ H ₁₇ FN ₄ S	60.74	5.42	17.71	60.75	5.42	17.67
10	C ₁₇ H ₁₉ FN ₄ S	61.79	5.80	16.96	61.70	5.84	17.03
12b	C ₁₂ H ₉ ClN ₄	58.90	3.71	22.90	59.02	3.73	22.79
12c	C ₁₂ H ₉ IN ₄	42.88	2.70	16.67	42.79	2.70	16.71
13a	C ₁₃ H ₁₁ FN ₄	64.45	4.58	23.13	64.32	4.64	23.24
13c	C ₁₃ H ₁₁ IN ₄	44.59	3.17	16.00	44.62	3.17	15.58
14	C ₁₃ H ₁₁ ClN ₄	60.35	4.29	21.66	60.31	4.26	21.71
16a	C ₁₃ H ₁₂ FN ₅	60.69	4.70	27.22	60.67	4.71	27.18
16b	C ₁₃ H ₁₂ ClN ₅	57.04	4.42	25.59	56.98	4.52	25.53
16c	C ₁₃ H ₁₂ IN ₅	42.76	3.31	19.18	42.66	3.31	19.20
20a	C ₁₂ H ₁₁ FN ₄ S	54.95	4.23	21.36	54.98	4.30	21.26
20b	C ₁₂ H ₁₁ ClN ₄ S	51.70	3.98	20.10	51.76	4.03	20.07

In Vitro Binding Assay. Humane Aβ(1-40) was purchased from Bachem, Inc. (USA). Aggregation was carried out by dissolving 1 mg of peptide in a solution of 2.3 mL of PBS (pH 7.0) containing 1.30 mM of sodium hydroxide. The solution was incubated at room temperature for 56h with constant magnetic stirring (1200 rpm). The aggregate were aliquoted into 170 mL portions and stored at -78 °C for 3-6 months without noticeable change in the binding results. [³H]BTA-1 (82 Ci/mmol and 99% purity) was obtained from American Radiolabeled Chemicals, Inc., St. Louis, MO.

Binding assays were carried out in 12 x 75 mm borosilicate glass tubes. All compounds were prepared as 1mM dimethyl sulfoxide (DMSO) stocks solution before dilution into PBS. The maximum final concentration of DMSO in the assays was 0.25%. The reaction mixture contained 50 mL of Aβ (1-40) aggregates (0.86 mg in the final assay mixture), 100 mL of [³H]BTA-1 (0.8-1 nM diluted in PBS) and 500 mL of inhibitors (3.10⁻⁶ to 10⁻¹¹ M diluted serially in PBS containing 0.5% DMSO) in a final volume of 1 mL. Non specific binding was defined in

the presence of 3 mM of PIB in the same assay tubes. The mixture was incubated at room temperature for 120 min, and the bound and free fractions were separated by vacuum filtration through Whatman GF/B glass filters using a Brandel M-24 cell harvester followed by 2 x 2 mL washes with PBS. Filters containing the bound ligand were counted in a gamma counter. Values for the half-maximum inhibitory concentration (IC_{50}) were determined from displacement curves of three independent experiments in triplicate subject to non linear regression analysis using GraphPad Prism. The inhibition constant (K_i) were calculated using the Cheng-Prusoff equation: $K_i = IC_{50}/(1+[L]/K_d)$, where [L] is the concentration of [3H]BTA-1 used in the assay, and K_d is the dissociation constant of BTA-1.