Supporting Information

Gram Scale Synthesis of 1,8-Naphthyridines in Water: Friedlander Reaction Revisited

Shubhranshu Shekhar Choudhury\textsuperscript{1,2}, Subhrakant Jena\textsuperscript{1,2}, Dipak Kumar Sahoo\textsuperscript{1,2}, Shamasoddin Shekh\textsuperscript{3}, Rajiv K. Kar\textsuperscript{4}, Ambuj Dhakad\textsuperscript{1,2}, Konkallu Hanumae Gowd\textsuperscript{3}, and Himansu S. Biswal\textsuperscript{1,2,*}

\textsuperscript{1}School of Chemical Sciences, National Institute of Science Education and Research (NISER), PO-Bhimpur-Padanpur, Via-Jatni, District- Khurda, PIN - 752050, Bhubaneswar, India

\textsuperscript{2}Homi Bhabha National Institute, Training School Complex, Anushakti Nagar, Mumbai 400094, India

\textsuperscript{3}Department of Chemistry, School of Chemical Sciences, Central University of Karnataka, Kalaburagi-585367, Karnataka, India.

\textsuperscript{4}Fritz Haber Center for Molecular Dynamics, Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem-9190401, Israel

* Corresponding Author’s E-mail: himansu@niser.ac.in, Phone No: +91-674-2494 185/
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**2-methyl-1,8-naphthyridine (10).** A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and acetone (9) (111µL, 1.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol %). The reaction mixture was stirred under N₂ condition at 50°C temperature for 6 h. After workup, the catalyst was separated and the desire product 2-methyl-1,8-naphthyridine (10) was obtained as a cream solid (71mg, 99%). **¹H NMR (400 MHz, CDCl₃) δ 9.04 (dd, J = 4.0, 2.0 Hz, 1H), 8.11 (dd, J = 2.0, 2.0 Hz, 1H), 8.04 (d, J = 8.4Hz, 1H), 7.40 (dd, J = 4.4, 4.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 2.80 (s, 3H); **¹³C NMR (100MHz, CDCl₃) δ 163.0, 155.9, 153.3, 136.8, 136.6, 123.0, 121.3, 120.7, 25.6.

**Figure S1.** ¹H and ¹³C NMR spectra of 2-methyl-1,8-naphthyridine (10) in CDCl₃.
2,3-dimethyl-1,8-naphthyridine (10a). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and butan-2-one (9a) (45µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10a as a yellowish orange solid (76mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 8.96 (dd, J= 2.0, 2.0 Hz, 1H), 8.03 (dd, J= 2.0, 2.0 Hz, 1H), 7.81 (s, 1H), 7.34 (dd, J=4.0, 4.0 Hz, 1H), 2.72 (s, 3H), 2.44 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 162.8, 154.8, 152.2, 135.8, 135.6, 131.4, 121.5, 121.2, 23.9, 19.3.

Figure S2. ¹H and ¹³C NMR spectra of 2,3-dimethyl-1,8-naphthyridine (10a) in CDCl₃.
1-(2-methyl-1,8-naphthyridin-3-yl)ethanone (10b). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and pentane-2,4-dione (9b) (51µL, 0.5mmol) was stirred in H2O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N2 condition at 50°C temperature for 6 h. After work up, separated the desire product 10b as a colourless solid (92mg, 98%). 1H NMR (400 MHz, CDCl3) δ 9.14 (dd, J= 4.0, 4.0 Hz, 1H), 8.49 (s, 1H), 8.22 (dd, J=4.0, 4.0 Hz, 1H), 7.50 (dd, J=8.0, 4.0 Hz, 1H), 2.97 (s, 3H), 2.72 (s, 3H); 13C NMR (100MHz, CDCl3) δ 199.3, 161.6, 155.8, 155.3, 138.6, 137.4, 132.2, 122.3, 120.0, 29.4, 25.8.

Figure S3. 1H and 13C NMR spectra of 1-(2-methyl-1,8-naphthyridin-3-yl)ethanone (10b) in CDCl3.
Methyl 2-methyl-1,8-naphthyridine-3-carboxylate (10c). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and methyl 3-oxobutanoate(9c) (54µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of CHOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 6 h. After work up, separated the desire product 10c as reddish brown colour solid (98mg, 97%). ¹H NMR (400 MHz, CDCl₃) δ 9.14 (dd, J= 4.0, 4.0 Hz, 1H), 8.75 (s, 1H), 8.21 (dd, J=4.0, 4.0 Hz, 1H), 7.47 (dd, J=4.0, 4.0 Hz, 1H), 3.98 (s, 3H), 3.04 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 166.2, 162.6, 156.2, 155.5, 141.9, 137.5, 124.7, 122.2, 120.1, 52.5, 26.0.

Figure S4. ¹H and ¹³C NMR spectra of Methyl 2-methyl-1,8-naphthyridine-3-carboxylate (10c) in CDCl₃.
**Ethyl 2-methyl-1,8-naphthyridine-3-carboxylate (10d).** A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and ethyl 3-oxobutanoate (9d) (64µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol %). The reaction mixture was stirred under N₂ condition at 50°C temperature for 10 h. And the reaction was monitored through TLC. After completed the reaction, desire product 10d was separated by work up as an orange colour solid (103mg, 95%). ¹H NMR (400 MHz, CDCl₃) δ 9.09 (dd, J= 2.0, 4.0 Hz, 1H), 8.70 (s, 1H), 8.18 (dd, J=2.0, 2.0 Hz, 1H), 7.43 (dd, J=4.0, 4.0 Hz, 1H), 4.38 (dd, J=4.0, 4.0 Hz, 1H), 3.01 (s, 3H), 1.39 (t, J=8.0, 3H); ¹³C NMR (100MHz, CDCl₃) δ 165.8, 162.4, 156.1, 155.3, 140.7, 137.5, 125.0, 122.1, 120.0, 61.6, 25.9, 14.2.

Figure S5. ¹H and ¹³C NMR spectra of Ethyl 2-methyl-1,8-naphthyridine-3-carboxylate (10d) in CDCl₃.
**7,8-dihydro-6H-cyclopenta[b][1,8]naphthyridine (10e).** A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and cyclopentanone (9e) (45µL, 0.5mmol) was stirred in H$_2$O (1ml) followed by the addition of ChOH (3µL, 1 mol %). The reaction mixture was stirred under N$_2$ condition at 50°C temperature for 9 h. And the reaction was monitored through TLC. After completed the reaction, desire product 10e was separated by work up as an black brown colour solid (77mg, 91%). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.99 (dd, J = 4.0, 4.0 Hz, 1H), 8.08 (dd, J=4.0, 4.0 Hz, 1H), 7.89 (s, 1H), 7.38 (dd, J=4.0, 4.0 Hz, 1H), 3.21 (t, J=8.0 Hz, 2H), 3.09 (t, J=8.0 Hz, 2H), 2.19 (m, 2H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 172.1, 155.9, 152.0, 136.9, 136.6, 130.8, 121.6, 121.1, 34.9, 30.4, 23.6.

![Figure S6](image-url). $^1$H and $^{13}$C NMR spectra of 7,8-dihydro-6H-cyclopenta[b][1,8]naphthyridine (10e) in CDCl$_3$.

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6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridine (10f). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and cyclohexanone (9f) (52µL, 0.5mmol) was stirred in H2O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N2 condition at 50°C temperature for 6 h. And the reaction was monitored through TLC. After completed the reaction, desire product 10f was separated by work up as an orange colour solid (88mg, 96%). 1H NMR (400 MHz, CDCl3) δ 8.98 (dd, J= 2.0, 2.0 Hz, 1H), 8.04 (dd, J=4.0, 4.0 Hz, 1H), 7.81 (s, 1H), 7.35 (dd, J=4.0, 4.0 Hz, 1H), 3.18 (t, J=8.0 Hz, 2H), 2.97 (t, J=8.0 Hz, 2H), 1.96 (m, 2H), 1.87 (m, 2H); 13C NMR (100MHz, CDCl3) δ 163.2, 154.7, 152.5, 136.0, 135.5, 132.3, 121.4, 121.2, 33.8, 29.0, 22.8, 22.7.

Figure S7. 1H and 13C NMR spectra of 6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridine (10f) in CDCl3.
7,8,9,10-tetrahydro-6H-cyclohepta[b][1,8]naphthyridine (10g). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and cycloheptanone (9g) (59µL, 0.5mmol) was stirred in H$_2$O (1ml) followed by the addition of CH$_2$OH (3µL, 1 mol%). The reaction mixture was stirred under N$_2$ condition at 50°C temperature for 10 h. And the reaction was monitored through TLC. After completed the reaction, desire product 10g was separated by work up as a yellow colour solid (93mg, 94%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.97 (d, $J$ = 4.0 Hz, 1H), 8.03 (d, $J$=8.0 Hz, 1H), 7.79 (s, 1H), 7.36 (dd, $J$=4.0, 4.0 Hz, 1H), 3.25 (t, $J$=8.0 Hz, 2H), 2.93 (t, $J$=8.0 Hz, 2H), 1.87 (m, 2H), 1.79 (m, 2H), 1.72 (m, 2H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 168.4, 154.6, 152.2, 137.8, 135.9, 135.0, 121.4, 121.3, 40.1, 35.0, 32.1, 28.7, 26.7.

**Figure S8.** $^1$H and $^{13}$C NMR spectra of 7,8,9,10-tetrahydro-6H-cyclohepta[b][1,8]naphthyridine (10g) in CDCl$_3$. S10
6,7,8,9,10,11-hexahydrocycloocta[b][1,8]naphthyridine (10h). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and cycloctanone (9h) (66µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol %). The reaction mixture was stirred under N₂ condition at 50°C temperature for 9 h. And the reaction was monitored through TLC. After completed the reaction, desire product 10h was separated by work up as a cream colour solid (96mg, 90%). ¹H NMR (400 MHz, CDCl₃) δ 8.98 (dd, J=2.0, 2.0 Hz, 1H), 8.06 (dd, J=2.0, 2.0 Hz, 1H), 7.82 (s, 1H), 7.35 (dd, J=4.0, 4.0 Hz, 1H), 3.19 (t, J=8.0 Hz, 2H), 2.94 (t, J=8.0 Hz, 2H), 1.91 (m, 2H), 1.76 (m, 2H), 1.38 (m, 2H); ¹³C NMR (100MHz, CDCl₃) δ 177.0, 155.0, 152.3, 136.5, 136.9, 135.4, 121.6, 121.1, 35.3, 32.5, 31.8, 30.6, 25.9, 25.8.

Figure S9. ¹H and ¹³C NMR spectra of 6,7,8,9,10,11-hexahydrocycloocta[b][1,8]naphthyridine (10h) in CDCl₃.
7-methyl-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridine (10i). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-methylpiperidin-4-one (9i) (62µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 11 h. And the reaction was monitored through TLC. After completion of reaction, desire product 10i was separated by work up as a brawn colour solid (92mg, 92%). Rₚ = 0.55 (10% methanol/dichloromethane). ¹H NMR (400 MHz, CDCl₃) δ 9.01 (d, J=4.0 Hz, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.79 (s, 1H), 7.38 (dd, J=4.0, 4.0 Hz, 1H), 3.78 (s, 2H), 3.33 (t, J=8.0 Hz, 2H), 2.86 (t, J=8.0 Hz, 2H), 2.52 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 160.0, 155.0, 153.0, 136.3, 133.4, 129.7, 121.4, 121.1, 57.4, 52.9, 46.0, 33.5; HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₁₂H₁₃N₃Na, 222.1002; Found 222.1019. mp = 115 °C. IR (KBr thin film, cm⁻¹) ν 2956, 2910, 2845, 2789, 1610, 1552, 1480, 1125, 900, 796. Uv-Vis λ_{abs} (max) 320 nm.

Figure S10. ¹H and ¹³C NMR spectra of 7-methyl-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridine (10i) in CDCl₃.
7-ethyl-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridine (10j). A mixture of 2-aminonicotinaldehyde (8) (61.6 mg, 0.5 mmol) and 1-ethylpiperidin-4-one (9j) (68 µL, 0.5 mmol) was stirred in H₂O (1 ml) followed by the addition of CHOH (3 µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 10 h. And the reaction was monitored through TLC. After completion of reaction, desire product 10j was separated by work up as a red colour solid (102 mg, 96%). Rᵣ = 0.42 (10% methanol/dichloromethane). ¹H NMR (400 MHz, CDCl₃) δ 9.0 (dd, J=2.0, 2.0 Hz, 1H), 8.05 (d, J=8.0 Hz, 1H), 7.79 (s, 1H), 7.36 (dd, J=4.0, 4.0 Hz, 1H), 3.82 (s, 2H), 3.31 (t, J=8.0 Hz, 2H), 2.89 (t, J=8.0 Hz, 2H), 2.61 (m, 2H), 1.19 (t, J=8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.5, 155.0, 152.9, 136.3, 133.6, 129.8, 121.4, 121.1, 55.1, 52.0, 50.4, 33.5, 12.3; HRMS (ESI) m/z: [M+Na]⁺ Calcd for C₁₃H₁₅N₃Na, 236.1158; Found 236.1176. mp = 110 °C. IR (KBr thin film, cm⁻¹) ν 2972, 2938, 2816, 2766, 1620, 1560, 1483, 1140, 910, 792. Uv-Vis λₑₐₑₛ (max) 320 nm.

![Figure S11](image-url). ¹H and ¹³C NMR spectra of 7-ethyl-6,7,8,9-tetrahydropyrido[2,3-b][1,6]naphthyridine (10j) in CDCl₃.
**2-phenyl-1,8-naphthyridine (10k).** A mixture of 2-aminonicotinaldehyde (8) (61.6 mg, 0.5 mmol) and acetophenone (9k) (59 µL, 0.5 mmol) was stirred in H₂O (1 ml) followed by the addition of CHOH (3 µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10k as a colourless solid (99 mg, 96%). ^1^H NMR (400 MHz, CDCl₃) δ 9.11 (dd, J = 2.0, 2.0 Hz, 1H), 8.32-8.29 (m, 2H), 8.21 (d, J = 8.0 Hz, 1H), 8.15 (dd, J = 4.0, 4.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.532-7.43 (m, 4H); ^13^C NMR (100 MHz, CDCl₃) δ 160.2, 156.0, 153.8, 138.4, 137.7, 136.7, 130.0, 128.8, 127.9, 121.7, 121.6, 119.6.

**Figure S12.** ^1^H and ^13^C NMR spectra of 2-phenyl-1,8-naphthyridine (10k) in CDCl₃.
2-(4-chlorophenyl)-1,8-naphthyridine (10l). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(4-chlorophenyl)ethanone (9l) (61µL, 0.5mmol) was stirred in H2O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N2 condition at 50°C temperature for 8 h. After work up, separated the desire product 10l as a pale yellow colour solid (117mg, 97%). 1H NMR (400 MHz, CDCl3) δ 9.13 (dd, J = 2.0, 2.0 Hz, 1H), 8.24 (d, J=8.0Hz, 3H), 8.18 (dd, J=4.0, 4.0 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.46 (m, 3H); 13C NMR (100MHz, CDCl3) δ 159.0, 156.0, 154.0,138.0, 136.9, 136.8, 136.4, 129.1,129.0, 121.9, 121.8, 119.3.

Figure S13. 1H and 13C NMR spectra of 2-(4-chlorophenyl)-1,8-naphthyridine (10l) in CDCl3.
2-(4-fluorophenyl)-1,8-naphthyridine (10m). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(4-fluorophenyl)ethanone (9m) (65µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol %). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10m as a red colour solid (105mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.13 (dd, J= 2.0, 2.0 Hz, 1H), 8.30 (m, 2H), 8.24 (d, J=8.0 Hz, 1H), 8.19 (dd, J=4.0, 4.0 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.46 (m, 2H), 7.18 (dd, J=4.0, 4.0 Hz, 1H); ¹³C NMR (100MHz, CDCl₃) δ 165.5, 163.0, 159.1, 156.0, 153.9, 137.8, 136.7, 134.6, 129.8, 121.7, 119.3, 115.6.

Figure S14. ¹H and ¹³C NMR spectra of 2-(4-fluorophenyl)-1,8-naphthyridine (10m) in CDCl₃.
2-(4-bromophenyl)-1,8-naphthyridine (10n). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(4-bromophenyl)ethanone (9n) (65µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of CHOH (3µL, 1 mol %). The reaction mixture was stirred under N₂ condition at 50°C temperature for 7 h. After work up, separated the desire product 10n as a red colour solid (136 mg, 96%). ¹H NMR (400 MHz, CDCl₃) δ 9.11 (dd, J= 2.0, 2.0 Hz, 1H), 8.21 (d, J=8.0 Hz, 1H), 8.15 (m, 3H), 7.92 (d, J=8.0 Hz, 1H), 7.61 (m, 2H), 7.44 (dd, J=4.0, 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 156.0, 154.0, 138.0, 137.3, 136.8, 131.9, 129.3, 124.8, 121.9, 121.7, 119.2.

Figure S15. ¹H and ¹³C NMR spectra of 2-(4-bromophenyl)-1,8-naphthyridine (10n) in CDCl₃.
2-(p-tolyl)-1,8-naphthyridine (10o). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(p-tolyl)ethanone (9o) (65µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10o as a red colour solid (105mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.09 (dd, J= 2.0, 2.0 Hz, 1H), 8.23-8.13 (m, 4H), 7.96 (d, J= 8.0 Hz, 1H), 7.41 (dd, J= 4.0, 4.0 Hz, 1H), 7.31 (d, J= 8.0 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 160.2, 156.1, 153.7, 140.3, 137.5, 136.6, 135.6, 129.5, 127.8, 121.5, 119.5, 21.3.

Figure S16. ¹H and ¹³C NMR spectra of 2-(p-tolyl)-1,8-naphthyridine (10o) in CDCl₃.
2-(4-methoxyphenyl)-1,8-naphthyridine (10p). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(4-methoxyphenyl)ethanone (9p) (65µL, 0.5mmol) was stirred in H2O (1ml) followed by the addition of CHOH (3µL, 1 mol %). The reaction mixture was stirred under N2 condition at 50°C temperature for 8 h. After work up, separated the desire product 10p as a red colour solid (105mg, 94%). 1H NMR (400 MHz, CDCl3) δ 9.09 (dd, J = 2.0, 2.0 Hz, 1H), 8.31-8.29 (m, 2H), 8.18 (d, J = 12.0 Hz, 1H), 8.15 (dd, J = 2.0, 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 4.0, 4.0 Hz, 1H), 3.89 (s, 3H); 13C NMR (100MHz, CDCl3) δ 161.5, 159.9, 156.2, 153.7, 137.5, 136.7, 131.0, 129.4, 121.4, 121.3, 119.2, 114.18.

Figure S17: 1H and 13C NMR spectra of 2-(4-methoxyphenyl)-1,8-naphthyridine (10p) in CDCl3.
2-(2-methoxyphenyl)-1,8-naphthyridine (10q). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 1-(2-methoxyphenyl)ethanone (9q) (65µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of CHOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10q as a red colour solid (105mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.11 (dd, J= 2.0, 2.0 Hz, 1H), 8.20-8.11 (m, 4H), 7.48-7.42 (m, 2H), 7.12 (t, J=8.0 Hz, 1H), 7.03 (d, J=4.0 Hz, 1H), 3.90 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 160.2, 157.5, 156.2, 153.2, 136.5, 135.9, 132.3, 131.0, 128.8, 124.6, 121.6, 121.5, 121.3, 111.5, 55.7.

**Figure S18.** ¹H and ¹³C NMR spectra of 2-(2-methoxyphenyl)-1,8-naphthyridine (10q) in CDCl₃.
3-phenyl-1,8-naphthyridine (10r). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and 2-phenylacetaldehyde (9r) (57µL, 0.5mmol) was stirred in H$_2$O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N$_2$ condition at 50°C temperature for 6 h. After work up, separated the desire product 10r as a colourless solid (99mg, 96%). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.40 (d, $J$=4.0 Hz, 1H) 9.12 (dd, $J$= 4.0, 4.0 Hz, 1H), 8.33 (d, $J$=2.0 Hz, 1H), 8.25 (dd, $J$=4.0, 4.0 Hz, 1H), 7.74-7.72 (m, 2H), 7.55-7.52 (m, 3H), 7.49-7.47 (m, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 155.4, 153.4,153.1, 137.2, 136.9, 134.9, 134.0, 129.3, 128.5, 127.5, 122.5.

Figure S19. $^1$H and $^{13}$C NMR spectra of 3-phenyl-1,8-naphthyridine (10r) in CDCl$_3$. 

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3-methyl-2-phenyl-1,8-naphthyridine (10s). A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and propiophenone (9s) (45µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 9 h. After work up, separated the desire product 10s as a yellow colour solid (104mg, 94%). ¹H NMR (400 MHz, CDCl₃) δ 9.05 (dd, J= 2.0, 2.0 Hz, 1H), 8.12 (dd, J= 2.0, 2.0 Hz, 1H), 8.02 (d, J= 4.0, 1H), 7.70-7.68 (m, 2H), 7.49-7.42 (m, 4H), 2.53 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 163.3, 154.7, 152.9, 140.0, 137.7, 135.9, 130.5, 129.2, 128.5, 128.0, 121.9, 121.6, 20.5.

Figure S20. ¹H and ¹³C NMR spectra of 3-methyl-2-phenyl-1,8-naphthyridine (10s) in CDCl₃.
**(E)-2-styryl-1,8-naphthyridine (10t).** A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and (E)-4-phenylbut-3-en-2-one (9t) (74µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 7 h. After work up, separated the desire product 10t as a red colour solid (113mg, 97%). ¹H NMR (400 MHz, CDCl₃) δ 9.06 (dd, J= 2.0, 2.0 Hz, 1H), 8.11-8.08 (m, 2H), 7.96 (d, J=16.0 Hz, 1H), 7.64-7.61 (d, J=4.0, 4.0 Hz, 3H), 7.40-7.36 (m, 4H), 7.34-7.32 (m, 1H); ¹³C NMR (100MHz, CDCl₃) δ 158.9, 156.1, 153.8,137.2, 136.5, 136.3, 136.2, 128.9, 128.8, 127.4, 121.8, 121.4, 121.2.

**Figure S21.** ¹H and ¹³C NMR spectra of (E)-2-styryl-1,8-naphthyridine (10t) in CDCl₃.
**3-methyl-2-(thiophen-2-yl)-1,8-naphthyridine (10u).** A mixture of 2-aminonicotinaldehyde (8) (61.6mg, 0.5mmol) and (1-(thiophen-2-yl)propan-1-one (9u) (74µL, 0.5mmol) was stirred in H₂O (1ml) followed by the addition of ChOH (3µL, 1 mol%). The reaction mixture was stirred under N₂ condition at 50°C temperature for 8 h. After work up, separated the desire product 10u as a yellow colour solid (110 mg, 98%). ¹H NMR (400 MHz, CDCl₃) δ 9.02 (dd, J= 2.0, 2.0 Hz, 1H), 8.05 (dd, J=4.0, 4.0 Hz, 1H), 7.96 (s, 1H), 7.74 (d, J=2.0 Hz, 1H), 7.52 (d, J=4.0 Hz, 1H), 7.37 (dd, J=4.0, 4.0 Hz, 1H), 7.15 (dd, J=4.0, 4.0 Hz, 1H), 2.76 (s, 3H); ¹³C NMR (100MHz, CDCl₃) δ 155.3, 154.4, 153.2, 144.9, 138.6, 135.7, 129.6, 129.4, 128.7, 127.7, 121.6, 121.4, 21.9.

**Figure S22.** ¹H and ¹³C NMR spectra of 3-methyl-2-(thiophen-2-yl)-1,8-naphthyridine (10u) in CDCl₃.
Computational Method:

The geometry optimization and frequency calculations were performed using density functional theory (DFT) with the B3LYP functional and 6-31+G(d,p) basis set. Solvent effects were incorporated by using PCM solvation model. The structures of reactants, intermediates, transition-states and products were optimized in solution phase taking H2O as the solvent through PCM model, without symmetry constraints. Single-point energies of all the structures were calculated at higher basis set i.e. at B3LYP-PCM(water)/6-311++G(d,p)//B3LYP-PCM(water)/6-31+G(d,p) level of theory. The Gibbs free energy corrections from the smaller basis set calculations were added to the single-point electronic energies calculated with the larger basis to obtain the free energies and construct reaction path at 50°C (1 atm, 323 K) as per the experimental reaction condition. All the calculations were performed with Gaussian-16 software package.1 Optimized Cartesian coordinates, electronic energies, Gibbs energies of all reactants, transition states and products are provided. The wave functions obtained at same level of theory were used for non-covalent interaction (NCI) index analysis.

Crystal structures of proteins were retrieved from the protein databank (PDB). The PDB codes 3EFL2, and 6AWO3 were used in the studies. Three-dimensional structures of proteins were processed using the Maestro Version 12.0.012 platform of Schrödinger software. The alignment of structures of proteins and measurement of the distance between the atoms was achieved using option quick align and measurement of distance, respectively.

Molecular docking: The crystal structure of each protein was processed using the protein preparation wizard.4 Hydrogen atoms were added, sample water orientations were achieved using PROPKA at pH 7, and waters with less than three hydrogen bonds to non-waters were removed from the proteins. The restrained minimization of protein -ligand complex was achieved using OPLS3e force field.5 Docking simulations were achieved using the default option of the Glide docking process of Schrödinger software. Receptor grid was generated by choosing the centroid of the workspace ligand. Molecule’s docking was performed using extra precision (XP) mode with flexible ligand sampling by adding Epik state penalties for the docking score.

The Prime-MMGBSA Simulation: To calculate the relative binding energies and ligand strain energies of protein-ligand complexes, the Prime-MMGBSA (Molecular Mechanics Generalized Born Surface Area) of Maestro Version 12.0.012 platform of Schrödinger software was used. The protein-ligand complexes which were obtained from XP docking were subjected to Prime/MMGBSA simulation. The relative binding free energy $\Delta G_{\text{bind}}$ was estimated according to the following equation.
Toxicity prediction: The ligand molecules used for docking simulation were subjected to ADME/Tox module in Maestro Version 12.0.012. Schrodinger software to predict the toxicity of each ligand molecule. And calculated the ADME properties, 2D and 3D QSAR descriptors.

Molecular Dynamics Simulation: The low-energy protein-ligand complex obtained from the docking calculations was subjected to molecular dynamics (MD) simulations. The system under investigation includes: (i) 10j with human serotonin transporter (PDB code: 6AWO), and (ii) 10r with thioredoxin glutathione reductase (3EFL). The missing residues in the three-dimensional structures were remodeled using the SWISS MODELLE.6 The objective of using classical simulation in explicit solvent condition is to access the interaction pairs and their dynamics within the protein active site, as well as the energetics. All the calculations were performed using Amber18 program. Standard parameters from ff14SB force-fields7 were used for protein, whereas generalized (GAFF) parameters8 for the small molecules, which have been benchmarked to predict accurate thermodynamic parameters.9

The protein complex was solvated in an octahedral water box of 9 Å edge-length from solute atom. Simulating system comprises of 66,194 and 68,495 atoms for 10j and 10r, respectively. Neutralization was achieved by adding the counter ions with respect to the net protein charges. TIP3P water models were used along with the periodic boundary conditions.10 Particle mesh Ewald summation with grid spacing of 1 Å was used to account the electrostatic condition. A cutoff value of 10 Å was used for correction of van der Waal interaction with Lennard-Jones potential and direct space interaction. Hydrogen bonds were re-positioned with SHAKE algorithm using integration time step of 2 fs.11 System heating was performed for a time scale of 1 ns using Langevin dynamics and a constant temperature of 300 K was applied. A systematic protocol was used to equilibrate the system which aims to gradually relax the water molecules, ions and biomolecules from high force constants to equilibrium. Details of the simulation protocol are reported in previous work.12 The discrete equilibration steps were performed for a time scale of 25 ns, followed by a pre-production run of 5 ns. The production trajectories were calculated for a time scale of 200 ns and structural snapshots were collected at an interval of 20 ps. Additionally, trajectories were also calculated up to same time scale, for the protein macromolecules without 10j and 10r. The objective here was to compare their perturbative effect onto the secondary structures. Thermodynamic parameters including binding free energy was calculated using MM-
PBSA method. Normal mode analysis was used to calculate the entropic contributions. These calculations were performed on the snapshots obtained from last 50 ns trajectory.

![RMSD plot of protein-ligand complex obtained from classical simulations.](image)

**Figure S23.** RMSD plot of protein-ligand complex obtained from classical simulations. (A) molecule 10j in complex with human serotonin transporter, (B) molecule 10r in complex with thioredoxin glutathione reductase.

**Table S1.** Lipinski’s “rule of five” molecular descriptors for drug likeness.

| Molecule | mol_MW | donorHB | acceptHB | QPlogPo/w |
|----------|--------|---------|----------|-----------|
| 10       | 144    | 0.0     | 2.0      | 1.4       |
| 10a      | 158    | 0.0     | 2.0      | 2.2       |
| 10b      | 186    | 0.0     | 4.0      | 1.2       |
| 10c      | 202    | 0.0     | 4.0      | 1.3       |
| 10d      | 216    | 0.0     | 4.0      | 2.0       |
| 10e      | 170    | 0.0     | 2.0      | 2.3       |
| 10f      | 184    | 0.0     | 2.0      | 2.7       |
| 10g      | 198    | 0.0     | 2.0      | 3.0       |
| 10h      | 212    | 0.0     | 2.0      | 3.2       |
| 10i      | 199    | 0.0     | 4.0      | 1.4       |
| 10j      | 213    | 0.0     | 4.0      | 1.8       |
| 10k      | 206    | 0.0     | 2.0      | 3.4       |
| 10l      | 241    | 0.0     | 2.0      | 3.8       |
| 10m      | 224    | 0.0     | 2.0      | 3.6       |
| 10n      | 285    | 0.0     | 2.0      | 3.9       |
| 10o      | 220    | 0.0     | 2.0      | 3.7       |
Table S2. Jorgensen’s “rule of three” molecular descriptors for bioavailability prediction.

| Molecule | QPlogS | QPPCaco | #metab |
|----------|--------|---------|--------|
| 10       | -1.6   | 4049    | 2      |
| 10a      | -2.1   | 4077    | 3      |
| 10b      | -1.7   | 1466    | 2      |
| 10c      | -2.2   | 1628    | 2      |
| 10d      | -2.6   | 1957    | 2      |
| 10e      | -2.6   | 3812    | 3      |
| 10f      | -3.1   | 4118    | 3      |
| 10g      | -3.4   | 4225    | 3      |
| 10h      | -3.6   | 4469    | 3      |
| 10i      | -1.1   | 885     | 4      |
| 10j      | -1.5   | 951     | 4      |
| 10k      | -3.7   | 4247    | 1      |
| 10l      | -4.4   | 4248    | 1      |
| 10m      | -4.0   | 4249    | 1      |
| 10n      | -4.5   | 4254.2  | 1      |
| 10o      | -4.3   | 4245    | 2      |
| 10p      | -3.7   | 4259    | 2      |
| 10q      | -3.7   | 4806    | 2      |
| 10r      | -3.5   | 3429    | 2      |
| 10s      | -3.9   | 4768    | 2      |
| 10t      | -4.4   | 4753    | 1      |
| 10u      | -4.0   | 5024.8  | 3      |

Table S3. Summary of important pharmacokinetic property distribution of naphthyridine substituted molecules by QuikProp program.

| Molecule | A  | SASA | FOS | B | C  | glob | D  | E  | F  | G   | H  | I   |
|----------|----|------|-----|---|----|------|----|----|----|------|----|-----|
| 10       | 0  | 359.3| 91.6| 558.3 | 0  | 0.91 | 18.4 | -  | 0.24 | 2243. | 2  | 1.48 | 0.30 |
| 10a      | 0  | 382.7| 154.6| 608.8 | 0  | 0.91 | 20.0 | -  | 0.23 | 2259. | 8  | 1.61 | 0.15 |
| 10b      | 1  | 410.1| 142.6| 665.9 | 0  | 0.90 | 21.6 | -  | 0.22 | 748.1  | -  | 2.40 | 0.56 |
| Drug targets | Compound | ΔG | ΔG\text{Coul} | ΔG\text{Cov} | ΔG\text{H-bond} | ΔG\text{Lipo} | ΔG\text{Packing} | ΔG\text{Solv} | ΔG\text{Vdw} |
|-------------|----------|----|---------------|-------------|----------------|-------------|----------------|-------------|-------------|
| 10c         | 433.6    | 169.1 | 704.2        | 0.88        | 23.1           | 4.3         | 0.20           | 838.0       | 2.31         | 0.45        |
| 10d         | 464.1    | 208.0 | 763.2        | 0.87        | 24.8           | 4.5         | 0.21           | 1022.2      | 2.06         | 0.32        |
| 10e         | 391.7    | 163.2 | 627.7        | 0.91        | 20.7           | 3.9         | 0.21           | 2101.2      | 1.68         | 0.10        |
| 10f         | 415.8    | 192.0 | 676.9        | 0.90        | 22.7           | 4.1         | 0.23           | 2284.6      | 1.61         | 0.05        |
| 10g         | 435.9    | 219.4 | 723.1        | 0.89        | 24.5           | 4.1         | 0.24           | 2348.8      | 1.61         | 0.18        |
| 10h         | 445.5    | 236.4 | 760.9        | 0.90        | 25.9           | 3.9         | 0.27           | 2495.6      | 1.58         | 0.29        |
| 10i         | 432.7    | 200.8 | 725.2        | 0.90        | 24.6           | 4.7         | 0.58           | 479.8       | 3.80         | 0.35        |
| 10j         | 462.9    | 234.3 | 782.6        | 0.89        | 26.3           | 5.0         | 0.53           | 518.1       | 3.64         | 0.22        |
| 10k         | 455.3    | 0.0   | 742.9        | 0.87        | 26.9           | 5.6         | 0.16           | 2361.8      | 0.67         | 0.20        |
| 10l         | 479.5    | 0.0   | 787.4        | 0.86        | 28.2           | 5.6         | 0.33           | 5852.1      | 0.84         | 0.33        |
| 10m         | 463.8    | 0.0   | 758.4        | 0.87        | 27.2           | 5.5         | 0.27           | 4256.7      | 0.81         | 0.24        |
| 10n         | 483.8    | 0.0   | 795.3        | 0.86        | 28.5           | 5.6         | 0.34           | 6281.3      | 0.84         | 0.35        |
| 10o         | 487.9    | 89.0  | 803.6        | 0.86        | 28.8           | 5.6         | 0.15           | 2360.5      | 0.87         | 0.37        |
| 10p         | 488.6    | 92.1  | 817.8        | 0.87        | 28.7           | 5.4         | 0.10           | 2368.9      | 0.78         | 0.17        |
| 10q         | 487.9    | 90.0  | 813.2        | 0.86        | 28.6           | 5.5         | 0.15           | 2699.5      | 0.65         | 0.16        |
| 10r         | 447.5    | 0.0   | 733.0        | 0.88        | 26.3           | 5.4         | 0.08           | 1874.4      | 0.91         | 0.17        |
| 10s         | 470.0    | 69.6  | 782.1        | 0.87        | 28.0           | 5.3         | 0.21           | 2676.6      | 0.75         | 0.31        |
| 10t         | 515.1    | 32.9  | 848.0        | 0.84        | 30.1           | 6.2         | 0.07           | 2667.2      | 0.27         | 0.42        |
| 10u         | 454.5    | 70.4  | 750.2        | 0.88        | 26.8           | 5.0         | 0.40           | 4806.0      | 1.00         | 0.26        |

\(^\text{A}:\) rotor, B: volume, C: ACxDN^\text{A}/SA, D: QPpolrz, E: QPlogHERG, F: QPlogBB, G: QPPMDCK, H: QPlogKp, I: QPlogKhsa

**Table S4.** Binding free energies and its constituent energy components (kJ mol\(^{-1}\)) for different synthesized inhibitors are presented with their respective target enzymes.
|        | Molecule 10j | Molecule 10r |
|--------|--------------|--------------|
| ΔE elec | -9.4±2.6     | -2.4±2.5     |
| ΔE vdw  | -34.7±1.7    | -36.7±1.6    |
| ΔE mm (ΔE elec + ΔE vdw) | -44.1±3.4 | -39.1±3.7 |
| ΔPB cal | 24.1±2.2     | 21.7±4.5     |
| ΔPB np  | -22.7±0.6    | -25.2±0.5    |
| ΔPB solv (ΔPB cal + ΔPB PB) | 1.4±0.9     | -3.5±1.9    |
| ΔG PB (ΔE mm + ΔPB solv) | -42.7±2.5     | -42.6±1.7    |
| TΔS    | -20.4±5.6    | -22.7±3.2    |
| Translational | -12.5±0.0 | -12.5±0.0 |
| Rotational | -9.6±0.0    | -9.8±0.0     |
| Vibrational | 1.7±5.5    | -0.4±3.2     |
| ΔG bind (ΔG PB - TΔS) | -22.3±2.6     | -19.9±1.4    |

**Table S5**: Binding free energy components of molecule 10j and 10r in protein calculated from MD trajectories.

ΔE elec and ΔE vdw corresponds to the electrostatic and van der Waals interaction calculated by the MM force field. The sum of these two molecular mechanic energies is denoted by ΔE mm. ΔG PB is the free energy calculated using the Poison Boltzmann method. TΔS is the entropic contribution. ΔG bind denotes the total energy of binding with solute entropic contribution. All the values reported are in kcal.mol⁻¹.
| Molecule | E (au)    | G (au) | E+G (au) |
|----------|-----------|--------|----------|
| ChOH     | -404.833839378 | 0.164916 | -404.668923378 |
| C        | -1.819828000  | -0.253249000 | 0.354577000   |
| H        | -2.030311000  | -1.327524000 | 0.415847000   |
| H        | -1.711384000  | 0.141632000  | 1.370821000   |
| C        | -0.581785000  | 0.042782000  | -0.489927000  |
| H        | -0.755685000  | -0.295022000 | -1.514352000  |
| H        | -0.354999000  | 1.116074000  | 0.415847000   |
| O        | -2.882173000  | 0.419717000  | -0.328568000  |
| H        | -3.696471000  | 0.310089000  | 0.183793000   |
| N        | 0.700897000   | -0.631810000 | -0.026943000  |
| C        | 1.059092000   | -0.178848000 | 1.368625000   |
| H        | 2.033550000   | -0.598580000 | 1.620285000   |
| H        | 1.091336000   | 0.915027000  | 1.348767000   |
| H        | 0.310362000   | -0.550806000 | 2.069582000   |
| C        | 0.598993000   | -2.130565000 | -0.079478000  |
| H        | -0.134262000  | -2.474457000 | 0.647767000   |
| H        | 0.300960000   | -2.428478000 | -1.084928000  |
| H        | 1.575366000   | -2.551079000 | 0.160701000   |
| C        | 1.798655000   | -0.171185000 | -0.957960000  |
| H        | 1.548242000   | -0.488519000 | -1.972629000  |
| H        | 1.848986000   | 0.919090000  | -0.881757000  |
| H        | 2.732178000   | -0.638158000 | -0.644642000  |
| O        | 1.012445000   | 2.688568000  | 0.040204000   |
| H        | 0.958417000   | 3.653493000  | 0.089356000   |

| Molecule      | E (au)    | G (au) | E+G (au) |
|----------------|-----------|--------|----------|
| Reactant-1 (8) | -417.113427701 | 0.079544 | -417.033883701 |
| O              | 2.725514000 | -0.355709000 | 0.001006000 |
| N              | -1.264300000 | 1.280274000 | 0.000373000 |
| C              | 0.339139000 | -0.553919000 | -0.000550000 |
| C              | -0.725819000 | -1.469404000 | -0.000477000 |
| C              | 0.017238000 | 0.844621000  | -0.000264000 |
| C              | -2.038039000 | -1.017393000 | 0.000028000  |
| C              | -2.240522000 | 0.370157000  | 0.000526000  |
| C              | 1.703524000 | -1.052438000 | -0.000383000 |
| H              | -0.504054000 | -2.533774000 | -0.000774000 |
| H              | -2.880543000 | -1.698774000 | 0.000193000  |
| Molecule          | E (au)       | G (au)  | E+G (au)   |
|-------------------|--------------|---------|------------|
| Reactant-2 (9)    | -193.2255707| 0.054338| -193.171233|
| C                 | 0.0000000000| 0.0000000000| 0.176979000|
| O                 | 0.0000000000| 0.0000000000| 1.404032000|
| C                 | 0.0000000000| 1.2898380000| -0.612529000|
| C                 | 0.0000000000| -1.2898380000| -0.612529000|
| H                 | 0.0000000000| 2.1503920000| 0.058363000|
| H                 | 0.0000000000| -2.1503920000| 0.058363000|
| H                 | -0.8796660000| 1.3293790000| -1.265128000|
| H                 | 0.8796660000| 1.3293790000| -1.265128000|
| H                 | 0.8796660000| -1.3293790000| -1.265128000|
| H                 | -0.8796660000| -1.3293790000| -1.265128000|
| C                 | 0.7359600000| -1.7634380000| 0.197041000|
| C                 | 1.2207640000| -0.4985050000| -0.526880000|
| O                 | -0.3414290000| -2.3191420000| -0.545973000|
| N                 | 2.4376320000| 0.1946220000| 1.460824000|
| C                 | 2.1143680000| 0.7072890000| 1.460824000|
| C                 | 3.6299790000| -0.7176660000| 0.124271000|
| C                 | 2.7480580000| 1.3879270000| -0.795806000|
| O                 | -0.1772750000| 2.3281130000| -0.000136000|
| H                 | 1.5189320000| -2.5255840000| 0.236682000|
| H                 | 0.4244540000| -1.5423670000| 1.224372000|
| H                 | 1.4958920000| -0.7609750000| -1.551185000|
| H                 | 0.4399340000| 0.2670780000| -0.541120000|
| H                 | -1.1760290000| -1.8656410000| -0.291131000|
| H                 | 2.9825210000| 1.2551070000| 1.828987000|
| H                 | 1.2450910000| 1.3660750000| 1.357565000|
| H                 | 1.9128670000| -0.1371620000| 2.118203000|
| H                 | 3.4410840000| -1.5327280000| 0.820797000|
| H                 | 3.8132610000| -1.1107680000| -0.876380000|
| H                 | 4.4915690000| -0.1422270000| 0.462690000|
| H                 | 2.9787740000| 1.0315450000| -1.800229000|
| H                 | 1.8575250000| 2.0259410000| -0.783924000|

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| Molecule | E (au) | G (au) | E+G (au) |
|----------|-------|-------|---------|
| TS-1     | -598.061692244 | 0.238187 | -597.823505244 |

C  -0.789413000  1.822916000  0.082645000
C  -1.257667000  0.523513000  -0.590196000
O  0.282871000  2.354580000  -0.678734000
N  -2.349252000  -0.258616000  0.134844000
C  -1.834953000  -0.781400000  1.455168000
C  -3.577274000  0.580884000  0.350994000
C  -2.695977000  -1.445821000  -0.731799000
O  0.528417000  -2.199316000  -0.252828000
H  -1.586439000  2.571871000  0.090489000
H  -0.478408000  1.646818000  1.119342000
H  -1.652437000  0.753590000  -1.582484000
H  -0.426512000  -0.176782000  -0.689383000
H  1.120750000  1.900770000  -0.396505000
H  -2.615016000  -1.397328000  1.903676000
H  -0.940635000  -1.373276000  1.242835000
H  -1.612985000  0.057581000  2.112260000
H  -3.349909000  1.385619000  1.048395000
H  -3.897960000  0.990401000  -0.607022000
H  -4.361000000  -0.052194000  0.766770000
H  -3.079380000  -1.081613000  -1.685144000
H  -1.780209000  -2.025184000  -0.867357000
H  -3.459721000  -2.034594000  -0.223161000
H  1.610527000  -1.461637000  -0.647891000
C  4.089661000  -0.459952000  0.936804000
C  3.008746000  0.089730000  0.022708000
O  2.497006000  1.200800000  0.321830000
C  2.575474000  -0.715585000  -1.093654000
H  3.924113000  -0.129911000  1.965816000
H  4.144816000  -1.551142000  0.898228000
H  5.060112000  -0.066054000  0.608710000
H  2.122858000  -0.136783000  -1.902936000
| Molecule | E (au)   | G (au)  | E+G (au)  |
|----------|---------|--------|----------|
| INT-2    | -598.079575382 | 0.240403 | -597.839172382 |
| C        | 0.777174000   | -1.806940000 | 0.107430000 |
| C        | 1.251450000   | -0.514987000 | -0.579275000 |
| O        | -0.341714000  | -2.293442000 | -0.602407000 |
| N        | 2.392984000   | 1.419081000  | -0.784060000 |
| C        | 1.960960000   | 0.770012000  | 1.442728000  |
| C        | 3.607517000   | -0.631577000 | 0.254588000  |
| C        | 2.739559000   | 0.107430000  | -0.784060000 |
| O        | -0.623988000  | 2.347721000  | -0.081235000 |
| H        | 1.559964000   | -2.571925000 | 0.077009000  |
| H        | 0.524044000   | -1.623558000 | 1.159806000  |
| H        | 1.593094000   | -0.746607000 | -1.590450000 |
| H        | 0.426163000   | 0.194684000  | -0.641352000 |
| H        | -1.176880000  | -1.812470000 | -0.261483000 |
| H        | 2.777137000   | 1.362985000  | 1.855842000  |
| H        | 1.073762000   | 1.386290000  | 1.295791000  |
| H        | 1.746911000   | -0.066543000 | 2.104889000  |
| H        | 3.386356000   | -1.434278000 | 0.955911000  |
| H        | 3.874658000   | -1.042579000 | -0.718825000 |
| H        | 4.424939000   | -0.022607000 | 0.639902000  |
| H        | 3.075862000   | 1.045458000  | -1.750988000 |
| H        | 1.845080000   | 2.031319000  | -0.897545000 |
| H        | 3.535617000   | 1.989979000  | -0.306370000 |
| H        | -1.381524000  | 1.796249000  | -0.404937000 |
| C        | -4.123549000  | 0.430488000  | 0.880652000  |
| C        | -3.034783000  | -0.118829000 | -0.033022000 |
| O        | -2.413689000  | -1.170366000 | 0.421765000  |
| C        | -2.766777000  | 0.518005000  | -1.227058000 |
| H        | -4.884858000  | -0.340542000 | 1.050916000  |
| H        | -3.698024000  | 0.681094000  | 1.860041000  |
| H        | -4.611981000  | 1.319821000  | 0.471697000  |
| H        | -2.050344000  | 0.100114000  | -1.930602000 |
| H        | -3.391287000  | 1.337375000  | -1.570455000 |
| H        | -0.833744000  | 3.253168000  | -0.346657000 |

| Molecule | E (au)   | G (au)  | E+G (au)  |
|----------|---------|--------|----------|
| TS-2     | -1015.173615790 | 0.341647 | -1014.831968790 |
| C        | -5.218255000   | 1.684808000 | -0.544320000 |
| C        | -5.858663000   | 0.762949000 | 0.279434000  |
| N        | -5.348769000   | -0.440032000 | 0.589032000  |
| Molecule | E (au)         | G (au)          | E+G (au)         |
|----------|---------------|-----------------|-----------------|
| INT-3    | -1015.203006110 | 0.352465        | -1014.850541110 |

C  -5.189229000  0.447358000  -1.503355000
C  -5.019057000  -0.917795000  -1.284089000
N   -4.005390000  -1.437128000  -0.575267000
C  -3.098075000  -0.592027000  -0.049264000
C  -3.183318000   0.815839000  -0.198042000
C  -4.250069000   1.317274000  -0.938210000
N  -2.030029000  -1.176229000   0.615484000
C  -1.212234000  -0.386668000  1.574401000
C  -0.908209000   0.957248000  0.883955000
C  -2.168078000   1.727957000  0.472847000
O   -0.041485000  -1.097411000  1.865675000
C  -1.962577000  -0.209400000   2.903922000
O  -1.842870000   2.868806000  -0.337372000
C   2.505205000  -0.260534000  -0.267722000
C   3.958663000  -0.744255000  -0.090999000
O   1.670762000  -1.338493000  -0.005562000
N   5.079694000   0.278364000  -0.315586000
C   5.037825000   0.820809000  -1.720079000
C   4.971677000   1.415856000   0.665841000
C   6.399871000  -0.417805000  -0.103655000
O  -0.106243000  -2.045672000  -1.773284000
H  -6.026638000   0.815950000  -2.085563000
H  -5.727322000  -1.635811000  -1.692299000
H  -4.341135000   2.391197000  -1.072332000
H   0.647851000  -1.773960000  -1.153840000
H  -0.299229000   1.573365000   1.551441000
H  -0.314010000   0.742959000  -0.012348000
H  -2.628145000   2.175441000  1.361645000
H  -2.105904000  -1.189031000   3.370536000
H  -1.378644000   0.417621000   3.584922000
H  -2.945026000   0.250099000   2.760793000
H  -1.435899000   2.554824000  -1.158909000
H  -2.223756000  -2.123142000   0.928312000
H   2.315824000   0.587647000   0.416064000
H   2.370019000   0.129234000  -1.293702000
H   4.092204000  -1.115574000   0.927252000
H   4.154045000  -1.560586000  -0.789704000
H   0.622466000  -1.138207000   1.072335000
H   5.901041000   1.469469000  -1.867434000
H   5.072740000  -0.014494000  -2.419142000
H   4.120692000   1.388921000  -1.859409000
H   4.048892000   1.962324000   0.483513000

S36
| Molecule | E (au)   | G (au)   | E+G (au)  |
|----------|---------|---------|----------|
| TS-3     | -1015.16966482 | 0.352244 | -1014.81742082 |
| C        | 5.432566000    | 1.352075000 | 0.615026000 |
| C        | 5.338248000    | 0.238825000 | 1.447896000 |
| N        | 4.289281000    | -0.593706000 | 1.481166000 |
| C        | 3.210944000    | -0.344195000 | 0.671982000 |
| C        | 3.248092000    | 0.752660000 | -0.263897000 |
| C        | 4.367595000    | 1.574567000 | -0.271915000 |
| N        | 2.120788000    | -1.138789000 | 0.725161000 |
| C        | 1.018295000    | -1.409857000 | -1.131696000 |
| C        | 0.901329000    | 0.108642000 | -1.171654000 |
| C        | 2.185435000    | 0.933069000 | -1.342484000 |
| O        | 0.011556000    | -2.098054000 | -0.786780000 |
| C        | 2.134289000    | -2.119241000 | -1.871155000 |
| O        | 1.817005000    | 2.323839000 | -1.502595000 |
| C        | -2.799771000   | -0.493413000 | -0.271781000 |
| C        | -4.160662000   | -0.612700000 | 0.426898000 |
| O        | -1.907961000   | -1.298993000 | 0.473165000 |
| N        | -5.144495000   | 0.523609000 | 0.170585000 |
| C        | -4.695543000   | 1.788647000 | 0.861365000 |
| C        | -5.297252000   | 0.774322000 | -1.307698000 |
| C        | -6.483459000   | 0.117219000 | 0.737520000 |
| O        | -0.055475000   | -0.274212000 | 2.405035000 |
| H        | 6.307412000    | 1.993318000 | 0.631819000 |
| H        | 6.158199000    | -0.008474000 | 2.122543000 |
| H        | 4.415797000    | 2.393526000 | -0.985673000 |
| H        | -0.813345000   | -0.568763000 | 1.866176000 |
| H        | 0.248104000    | 0.365883000 | -2.020055000 |
| H        | 0.378468000    | 0.420980000 | -0.265420000 |
| H        | 2.636310000    | 0.692193000 | -2.313008000 |
| H        | 2.264181000    | -3.120671000 | -1.457343000 |
| H        | 1.834903000    | -2.225178000 | -2.924903000 |
| H        | 3.082091000    | -1.581172000 | -1.844538000 |
| H        | 1.522306000    | 2.654681000 | -0.640812000 |
| H        | 2.337349000    | -1.990492000 | 1.246058000 |
| H        | -2.869336000   | -0.857536000 | -1.303511000 |
| H        | -2.455850000   | 0.550518000 | -0.310683000 |
| Molecule | E (au)     | G (au)     | E+G (au)    |
|----------|------------|------------|-------------|
| INT-4    | -1015.18174760 | 0.352559   | -1014.829185760 |
| C        | 4.177839000  | 2.683626000 | -0.058006000 |
| C        | 2.824433000  | 3.013921000 | -0.086922000 |
| N        | 1.818952000  | 2.131388000 | -0.055676000 |
| C        | 2.103468000  | 0.782000000 | 0.015897000  |
| C        | 3.490788000  | 0.359057000 | 0.035759000  |
| C        | 4.491957000  | 1.313525000 | 0.003004000  |
| N        | 1.050904000  | -0.047796000 | 0.071655000 |
| C        | 1.284478000  | -1.458402000 | 0.186999000 |
| C        | 2.609162000  | -1.910233000 | -0.457309000 |
| C        | 3.795383000  | -1.123675000 | 0.101714000 |
| O        | 0.195447000  | -2.097778000 | -0.573480000 |
| C        | 1.158620000  | -1.934594000 | 1.646820000  |
| O        | 5.020756000  | -1.476895000 | -0.564709000 |
| C        | -3.338308000 | -1.592965000 | -0.535533000 |
| C        | -3.605795000 | -0.443243000 | 0.445920000  |
| O        | -2.464313000 | -2.512090000 | 0.104137000  |
| N        | -4.518871000 | 0.673481000  | -0.051405000 |
| C        | -3.958550000 | 1.305576000  | -1.303179000 |
| C        | -5.911021000 | 0.164525000  | -0.310695000 |
| C        | -4.569374000 | 1.726350000  | 1.029034000  |
| O        | -1.073572000 | 1.603095000  | 0.375210000  |
| H        | 4.9455581000 | 3.449392000  | -0.086914000 |
| H        | 2.5245000000 | 4.061286000  | -0.142383000 |
| H        | 5.5300220000 | 0.989517000  | 0.018997000  |
| H        | -0.395330000 | 0.857536000  | 0.278034000  |
| H        | 2.7709500000 | -2.984262000 | -0.309482000 |
| H        | 2.5386890000 | -1.722525000 | -1.536505000 |
| H        | 3.9797520000 | -1.430431000 | 1.139389000  |
| Molecule | E (au)          | G (au)          | E+G (au)         |
|----------|-----------------|-----------------|-----------------|
| TS-4     | -1015.174487450 | 0.348031        | -1014.826456450 |

C  4.415527000  2.534703000  -0.128634000
C  3.097850000  2.975661000  -0.221808000
N  2.024592000  2.174015000  -0.195378000
C  2.210168000  0.829677000  -0.065441000
C  3.534331000  0.285175000  0.043253000
C  4.615564000  1.152501000  0.008572000
N  1.084169000  0.068582000  -0.038998000
C  1.162443000  -1.357591000  0.165352000
C  2.487051000  -1.931887000  -0.364609000
C  3.703690000  -1.210711000  0.216545000
O  0.080523000  -1.931865000  -0.642066000
C  0.897850000  -1.738556000  1.632051000
O  4.925238000  -1.706894000  -0.351140000
C  -3.507360000  -1.576483000  -0.611619000
C  -3.653372000  -0.450248000  0.419566000
O  -2.613171000  -2.545124000  -0.076216000
N  -4.479369000  0.756831000  -0.015076000
C  -3.848542000  1.420365000  -1.216297000
C  -5.901040000  0.374864000  -0.317361000
C  -4.455722000  1.741131000  1.128589000
O  -1.059542000  1.290426000  0.521416000
S39
H  5.244781000  3.233092000  -0.160425000
H  2.885293000  4.039219000  -0.328033000
H  5.620268000  0.746192000  0.215168000
H  0.060051000  0.635133000  0.215168000
H  2.550440000  -3.002707000  -0.142542000
H  2.494180000  -1.807749000  -1.455066000
H  3.802026000  -1.456703000  1.281137000
H  0.060051000  -1.339769000  1.942942000
H  2.550440000  -2.286565000  1.762268000
H  1.665480000  -1.315170000  2.287506000
H  4.940838000  -1.473516000  -1.291711000
H  3.802026000  -1.456703000  1.281137000
H  0.892327000  -2.826565000  1.762268000
H  2.494180000  -1.807749000  -1.455066000
H  3.802026000  -1.456703000  1.281137000
H  0.892327000  -2.826565000  1.762268000
H  2.494180000  -1.807749000  -1.455066000
H  3.802026000  -1.456703000  1.281137000
H  0.892327000  -2.826565000  1.762268000
H  2.494180000  -1.807749000  -1.455066000
H  3.802026000  -1.456703000  1.281137000
H  0.892327000  -2.826565000  1.762268000
Molecule | E (au) | G (au) | E+G (au) |
--- | --- | --- | --- |
INT-5  | -1015.173619510 | 0.341213 | -1014.832406510 |
C     | 4.320760000  | -2.556761000  | 0.522491000  |
C     | 5.146287000  | -1.521479000  | 0.082007000  |
N     | 4.703077000  | -0.279651000  | -0.158466000 |
C     | 3.400528000  | -0.099209000  | 0.042411000  |
C     | 2.491082000  | -0.989583000  | 0.488182000  |
C     | 2.968152000  | -2.278377000  | 0.723389000  |
N     | 3.020847000  | 1.315984000   | -0.250971000 |
C     | 1.870692000  | 1.736007000   | 0.160949000  |
C     | 0.918442000  | 0.882996000   | 0.970297000  |
C     | 1.039460000  | -0.606542000  | 0.649930000  |
C     | 1.455166000  | 3.144084000   | -0.139202000 |
O     | 0.281727000  | -0.973784000  | -0.529979000 |
H     | 4.728207000  | -3.545547000  | 0.701638000  |
H     | 6.206404000  | -1.691693000  | -0.087298000 |

S40
| Molecule | E (au)       | G (au)     | E+G (au)    |
|----------|-------------|------------|-------------|
| TS-5     | -1015.174613760 | 0.344049   | -1014.830564760 |

C    -3.672117000 -2.810302000 0.679878000
C    -4.569342000 -1.783253000 0.974381000
N    -4.345939000 -0.496370000 0.678650000
C    -3.188952000 -0.164749000 0.065094000
C    -2.206142000 -1.132909000 -0.260259000
C    -2.474019000 -2.465027000 0.049697000
N    -3.052131000 1.193316000 -0.235006000

S41
C  2.915615000    0.239453000    0.000006000
C  2.521280000    -1.120818000   0.000003000
N  1.263661000    -1.535144000  -0.000004000
C  0.280169000    -0.590096000  -0.000007000
C  0.576394000    0.808537000  -0.000001000
C  1.935593000    1.207125000   0.000005000
N  -1.001235000   -1.061243000 -0.000007000
C  -2.003362000   -0.194925000  -0.000005000
C  -1.796646000   1.218577000  -0.000007000
C  -0.517754000   1.714224000  -0.000001000
C  -3.408051000   -0.739614000  0.000009000
H  3.969343000    0.496626000  0.000011000
H  3.283932000    -1.897343000  0.000001000
H  2.185493000    2.264704000  0.000008000
H  -2.654535000   1.883409000  -0.000011000
H  -0.329165000   2.784394000  -0.000001000
H  -3.393590000   -1.830754000 -0.0000239000
H  -3.958850000   -0.390761000  0.881095000
H  -3.959043000   -0.390349000  -0.880792000

| Molecule           | E (au)     | G (au)    | E+G (au)   |
|--------------------|------------|-----------|------------|
| H2O (Product-2)    | -76.466454767 | 0.001730  | -76.464724767 |
| O                  | 0.0000000000 | 0.0000000000 | 0.117789000 |
| H                  | 0.0000000000 | 0.766774000 | -0.471155000 |
| H                  | 0.0000000000 | -0.766774000 | -0.471155000 |
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