Supplemental Material

Pseudo-four-component synthesis of 5-(4-hydroxy-2-oxo-1,2-dihydropyridin-3-yl)-substituted 5H-chromeno[2,3-b]pyridines and estimation of its affinity to sirtuin 2

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$^1$H and $^{13}$C NMR spectra of novel substituted 2,4-diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5$H$-chromeno[2,3-b]pyridine-3-carbonitriles (3b, c, e, i and j) with tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) downfield of TMS. Additional information for docking studies (Tables 3-7, references).

S1: 2,4-Diamino-9-ethoxy-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5$H$-chromeno[2,3-b]pyridine-3-carbonitrile (3b)
S2: 2,4-Diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (3c)
S3: 2,4-Diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7,9-diodo-5H-chromeno[2,3-b]pyridine-3-carbonitrile (3e)
S4: 2,4-Diamino-5-(1-benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-5H-chromeno[2,3-b]pyridine-3-carbonitrile (3i)
S5: 2,4-Diamino-5-(1-benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7-chloro-5H-chromeno[2,3-b]pyridine-3-carbonitrile (3j)
S6: Docking studies

For the current docking procedure, Schrodinger Suite Software 2020 was used. Maestro 12.3.013 was employed as the graphical user interface. Structures for all compounds were treated with Lig-Prep (Schrodinger Suite) to obtain possible 3D-forms. The target proteins were retrieved from the RCSB\(^1\) protein databank, and prepared using the Schrodinger Suite protein preparation wizard. Missing chains and loops were filled with Prime (Schrodinger Suite), water, and organic solvents beyond 3A of heteroatoms (if any) were removed. Hydrogen atoms were added and a minimization was performed until the RMSD value of all heavy atoms was within 0.3 Å of the crystal structure. The OPLS3e force field was used. Docking was carried out using the Glide software from Schrodinger Suit in extra-precision (XP)\(^2\) mode using GScore for ligand ranking, Emodel Score for pose ranking, Evdw Score for Van der Waals ranking.

Table S3. Docking of 5H-chromeno[2,3-b]pyridines 3a-j to 5Y0Z

| Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol | Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol |
|----------|---------------------|------------------------|----------------------|----------|---------------------|------------------------|----------------------|
| 3a       | -5,367              | 1,341                  | -24,791              | 3f       | -4,770              | 6,012                  | -29,242              |
| 3b       | -3,157              | 13,372                 | -12,755              | 3g       | -6,146              | 189,477                | -12,879              |
| 3c       | -5,773              | -22,06                 | -29,321              | 3h       | -9,283              | -41,234                | -24,712              |
| 3d       | -4,363              | -1,176                 | -17,889              | 3i       | n/a                 |                        |                      |
| 3e       | -7,299              | 38,625                 | -23,453              | 3j       | -7,235              | 26,796                 | -23,221              |

Presented data for the optimal binding mode.

Table S4. Docking of 5H-chromeno[2,3-b]pyridines 3a-j to 5YQL

| Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol | Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol |
|----------|---------------------|------------------------|----------------------|----------|---------------------|------------------------|----------------------|
| 3f       | -2,594              | -100,296               | -26,799              | 3i       | -7,437              | -5,890                 | -37,648              |
| 3h       | -8,657              | -21,344                | -33,523              | 3j       | -7,973              | 3,082                  | -33,233              |

Presented data for the optimal binding mode.
### Table S5. Docking of 5H-chromeno[2,3-b]pyridines 3a-j to 5DY5

| Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol | Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol |
|----------|---------------------|------------------------|----------------------|----------|---------------------|------------------------|----------------------|
| 3a       | -1,364              | -38,040                | -25,249              | 3f       | -1,489              | -38,681                | -25,525              |
| 3b       | -3,771              | -42,735                | -32,391              | 3g       | n/a                 |                        |                      |
| 3c       | -1,527              | -39,144                | -25,312              | 3h       | -4,450              | -41,868                | -26,662              |
| 3d       | n/a                 |                        |                      | 3i       | -3,127              | -45,280                | -28,938              |
| 3e       | -1,940              | -31,434                | -29,370              | 3j       | -3,163              | -49,836                | -33,205              |

Presented data for optimal binding mode. n/a = not applicable, no bind mode for a protein-ligand combination.

### Table S6. Docking of 5H-chromeno[2,3-b]pyridines 3a-j to 5G4C

| Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol | Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol |
|----------|---------------------|------------------------|----------------------|----------|---------------------|------------------------|----------------------|
| 3a       | -8,772              | -73,748                | -47,471              | 3f       | -8,342              | -87,774                | -55,328              |
| 3b       | -9,720              | -79,423                | -51,666              | 3g       | -11,730             | -84,304                | -42,318              |
| 3c       | -8,125              | -77,013                | -48,496              | 3h       | -10,772             | -92,24                 | -51,879              |
| 3d       | -7,871              | -80,018                | -41,265              | 3i       | -6,588              | -81,757                | -57,053              |
| 3e       | -9,292              | -86,960                | -56,528              | 3j       | -9,732              | -68,797                | -58,936              |

Presented data for the optimal binding mode.
### Table S7. Docking of 5H-chromeno[2,3-b]pyridines 3a-j to 4RMG

| Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol | Compound | XP GScore, kcal/mol | Emodel Score, kcal/mol | Evdw Score, kcal/mol |
|----------|---------------------|------------------------|---------------------|----------|---------------------|------------------------|---------------------|
| 3a       | -7,658              | -58,514                | -31,712             | 3f       | -7,112              | -69,018                | -41,922             |
| 3b       | -9,158              | -54,615                | -42,100             | 3g       | -8,114              | -65,561                | -36,533             |
| 3c       | -7,828              | -57,059                | -32,762             | 3h       | -11,194             | -73,371                | -48,593             |
| 3d       | -7,046              | -60,265                | -36,481             | 3i       | -9,719              | -74,01                 | -47,222             |
| 3e       | -8,010              | -68,023                | -42,218             | 3j       | -10,099             | -76,533                | -44,087             |

Presented data for best binding mode.

### References

1. RCSB Protein Data Bank. Retrieved March 24, 2020, from [https://www.rcsb.org/](https://www.rcsb.org/)
2. Friesner, R. A.; Murphy, R. B.; Repasky, M. P.; Frye, L. L.; Greenwood, J. R.; Halgren, T. A.; Sanschagrin, P. C.; Mainz, D. T. *J. Med. Chem.* 2006, *49*, 6177–6196. [https://doi.org/10.1021/jm051256o](https://doi.org/10.1021/jm051256o)