Supplemental Material

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

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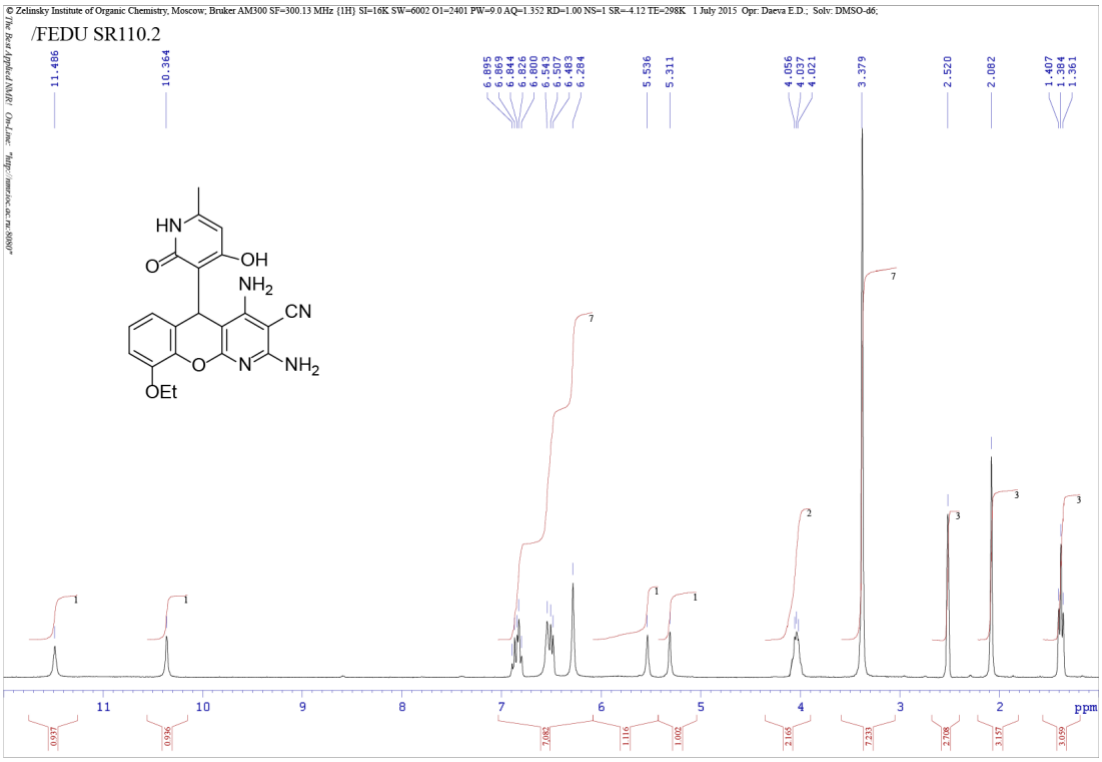
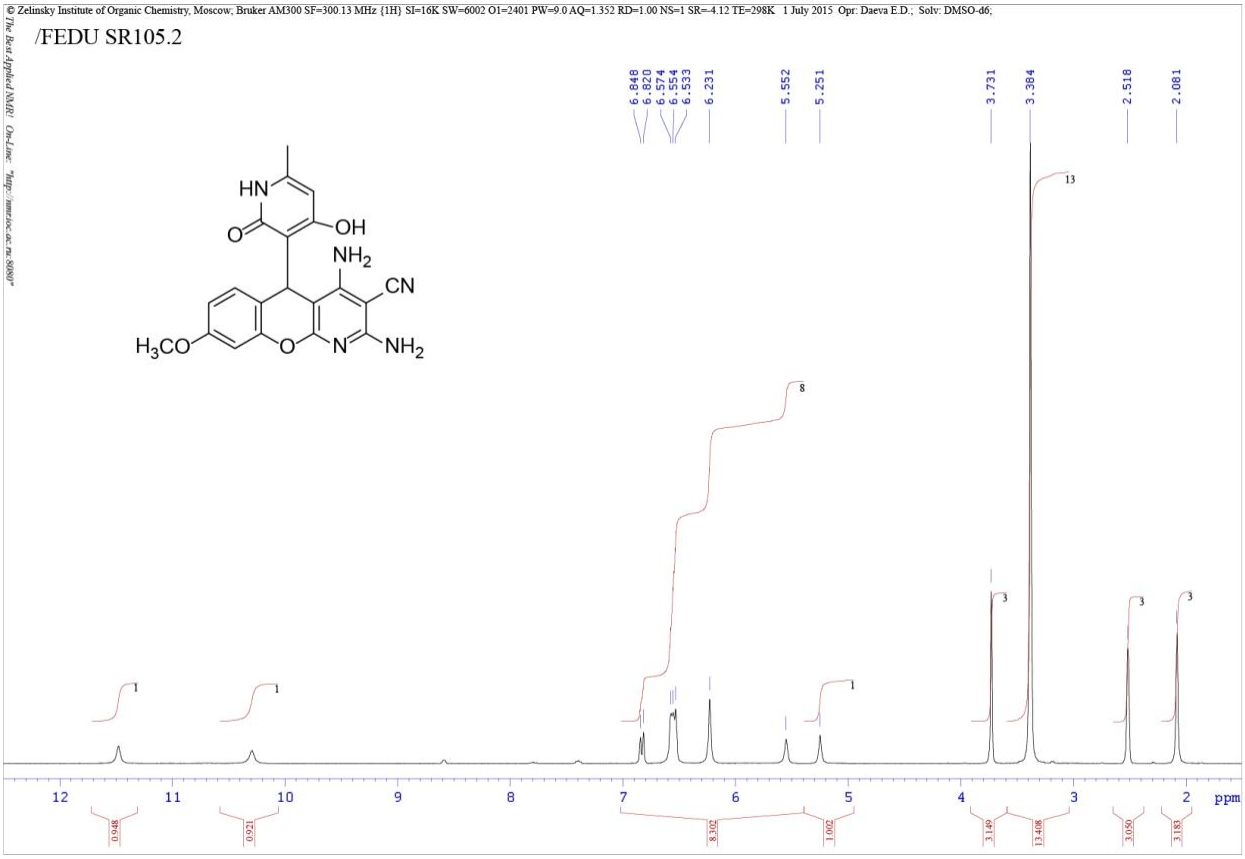
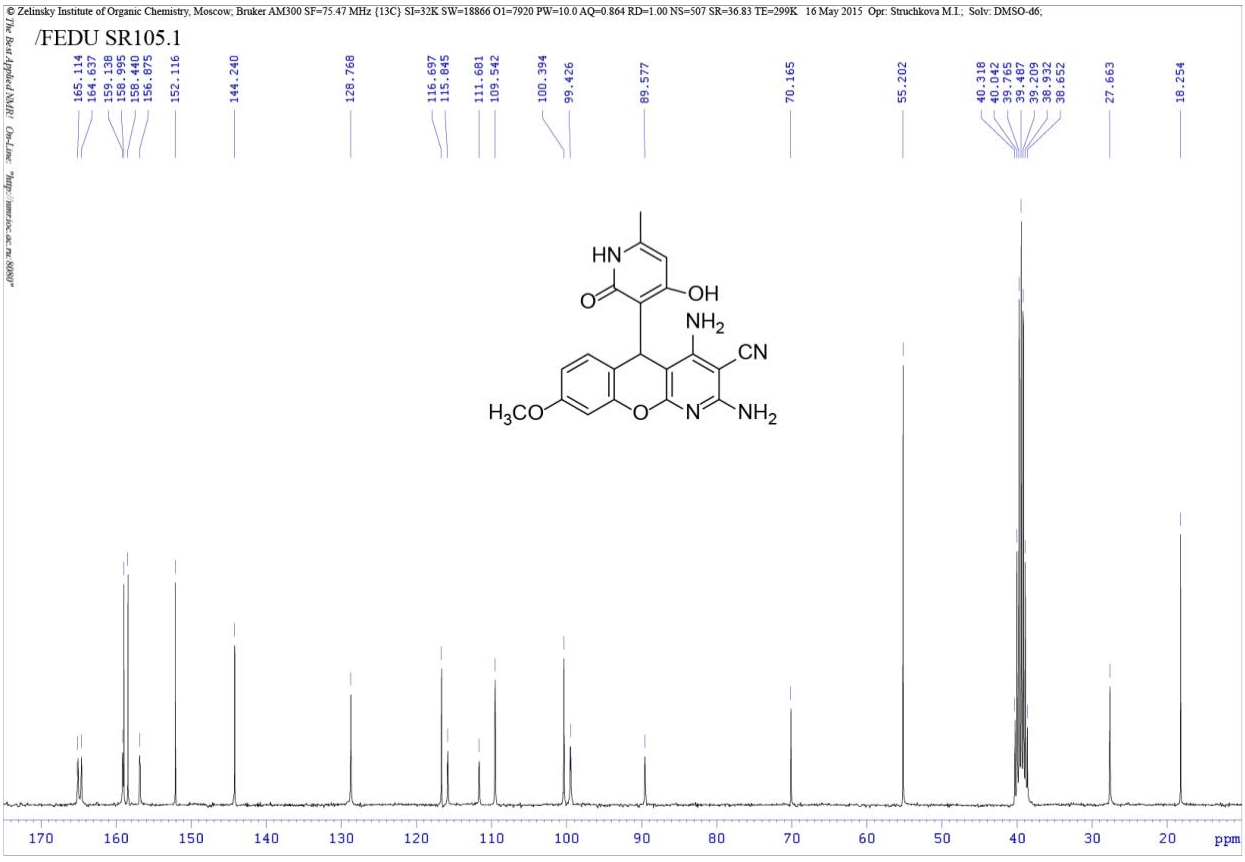
^{1}H and ^{13}C NMR spectra of novel substituted 2,4-diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles (**3b, c, e, i and j**) with tetramethylsilane (TMS) as internal standard. Chemical shifts (*δ*) are reported in parts per million (ppm) downfield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

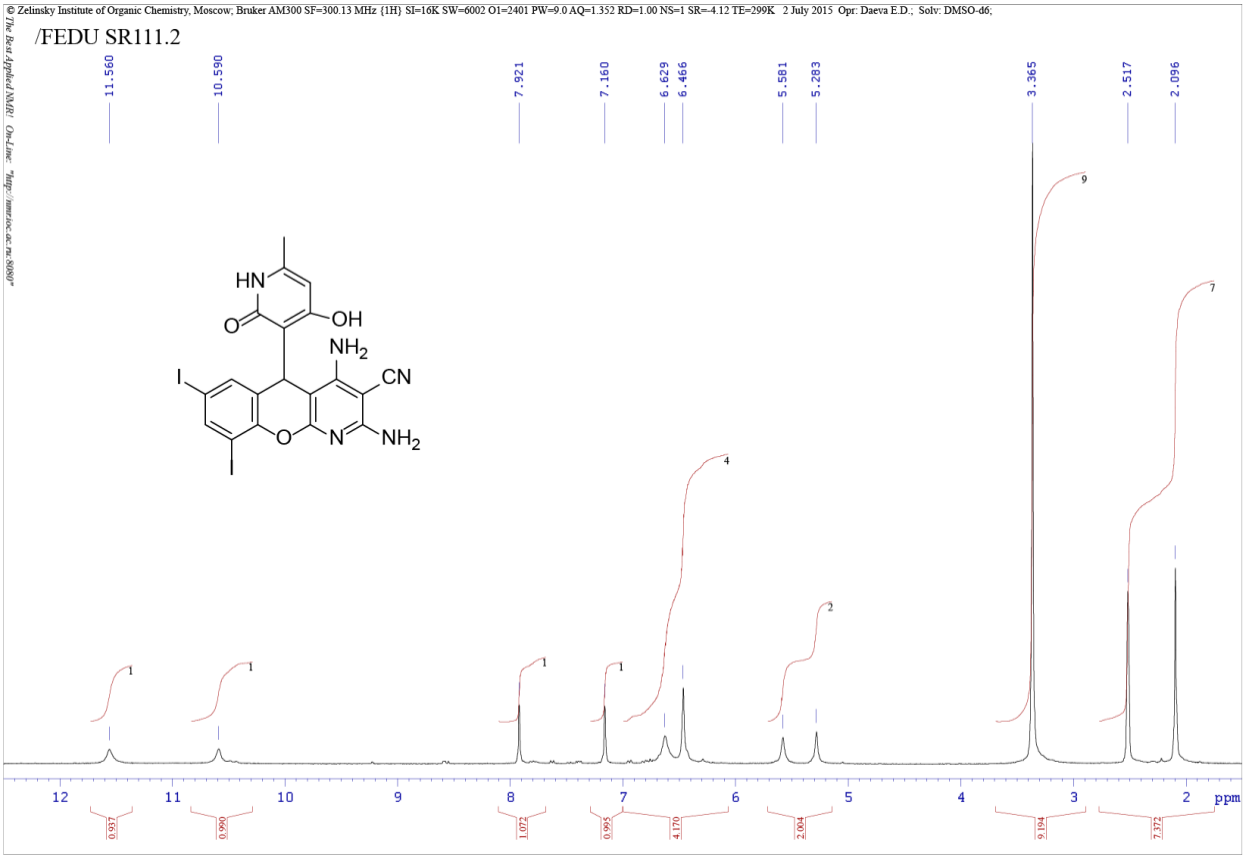


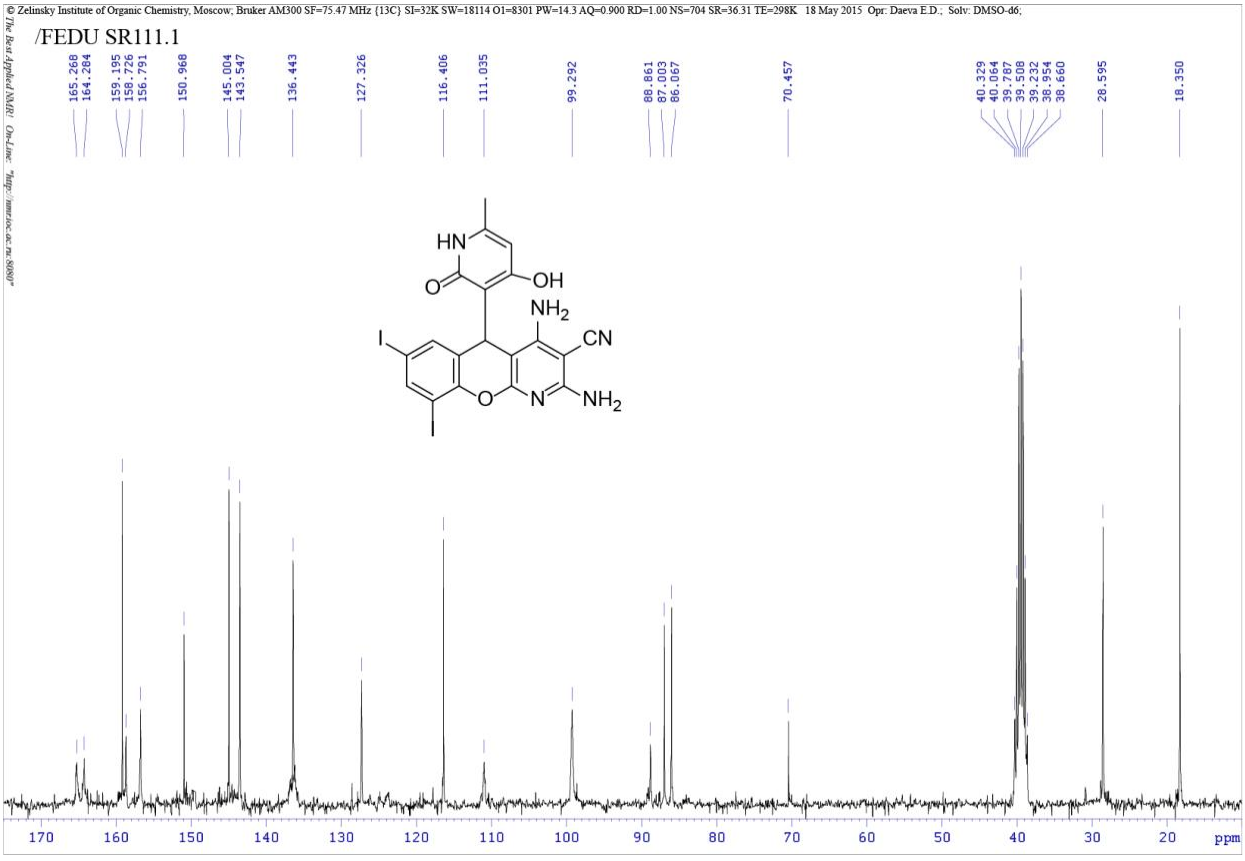
S2: 2,4-Diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (3c)



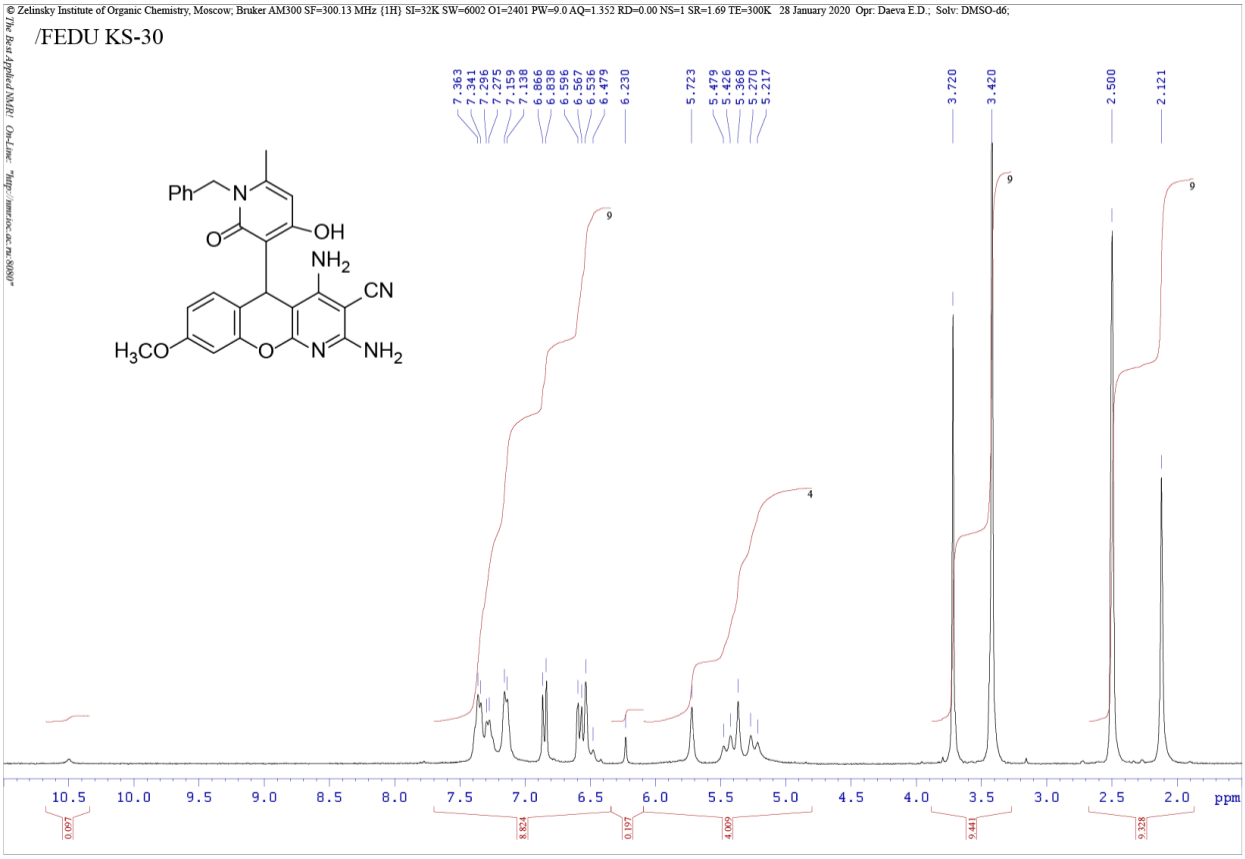


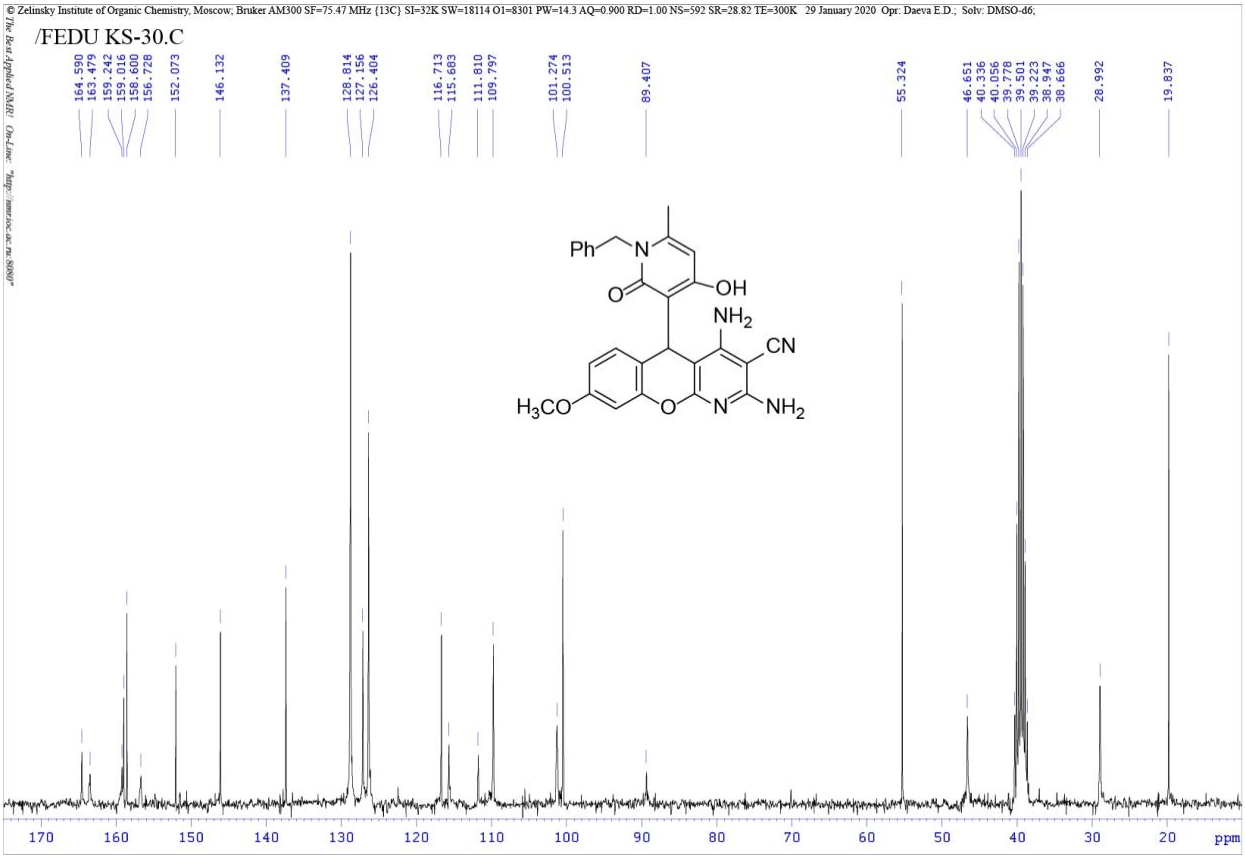
S3: 2,4-Diamino-5-(4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7,9-diiodo-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (3e)



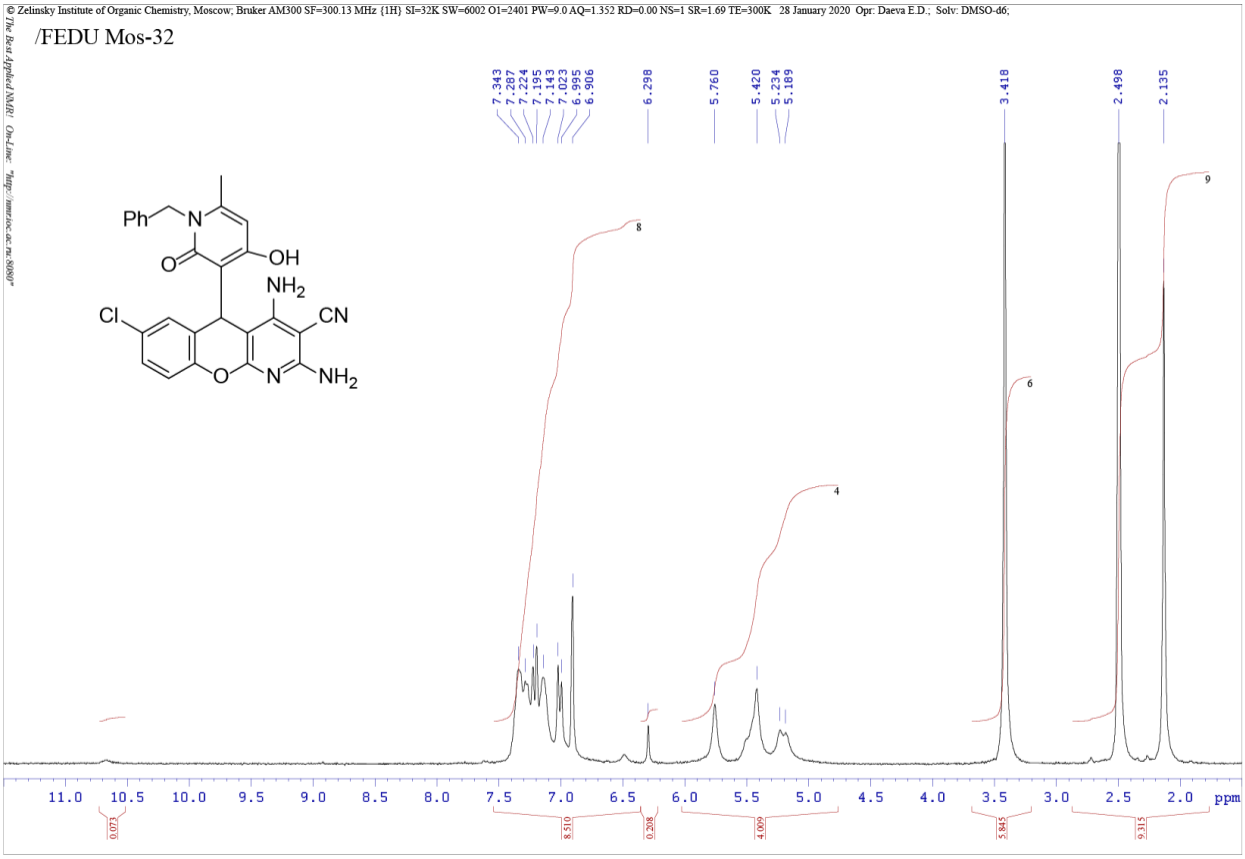


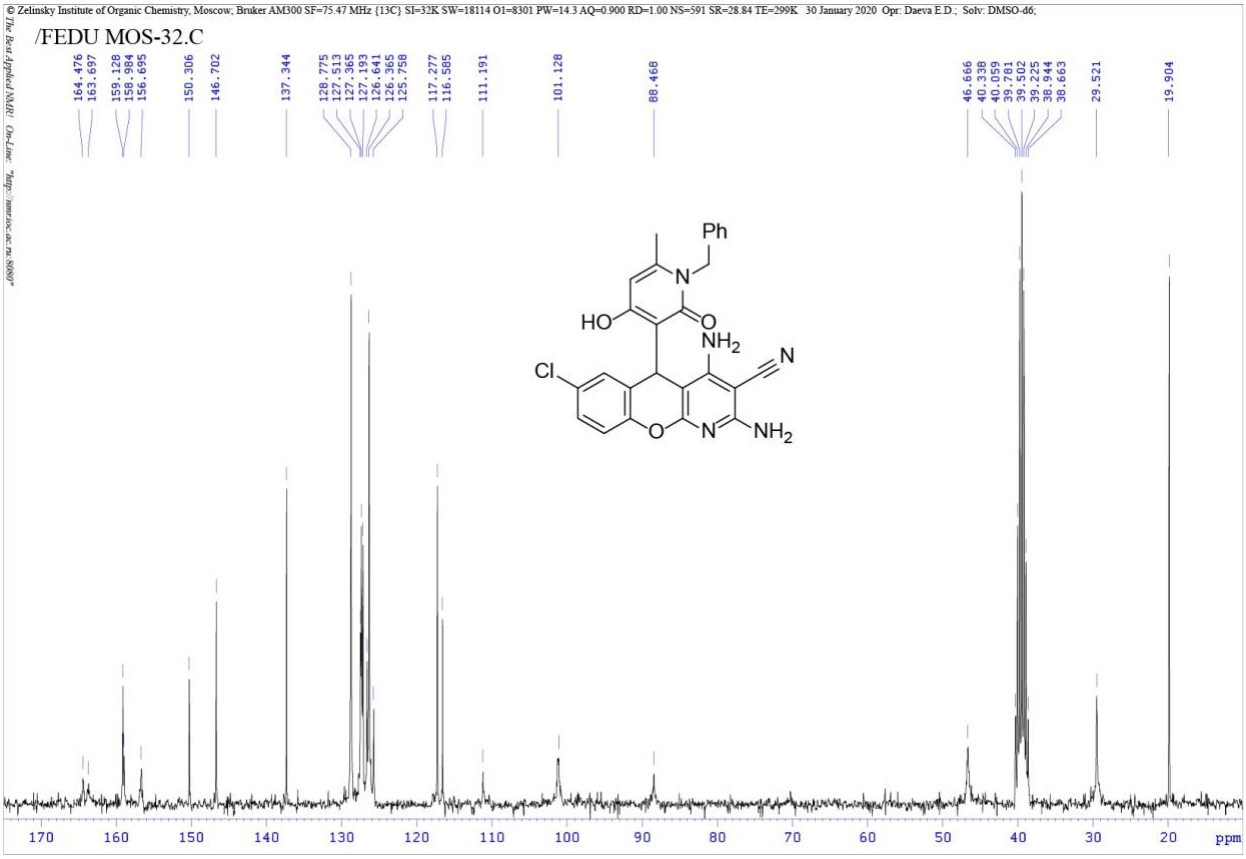
S4: 2,4-Diamino-5-(1-benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-8-methoxy-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitrile (3i)





S5: 2,4-Diamino-5-(1-benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)-7-chloro-5*H*-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 (Shcrodinger 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 A 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 5*H*-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 5*H*-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 5*H*-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 5*H*-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 5*H*-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.

S7: References

1. RCSB Protein Data Bank. Retrieved March 24, **2020**, from 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

