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Research

Molecular Docking Analysis of Novel JAK-2 Inhibitors for Therapy of Myeloproliferative Neoplasms

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Abstract

Background and Objectives: Januskinase-2 (JAK2) is an intracellular, non-receptor tyrosine kinase belonging to the family of Janus kinase that also includes JAK1, JAK3 and TYK2.The recent discovery of JAK2's acquired point mutation V617F led to greater understanding its oncogenic role in Myeloproliferative tumors (MPN'S). At 617 position phenylalanine amino acid was replaced by valine due to mutation. Therefore, aiming abnormal JAK-2 to prevent its essential activation will be an optimistic alterative option in the treatment of Myeloproliferative tumors.

Methods: In this current study, using computational methods we have designed 114 novel Quinazoline JAK2 –inhibitors and evaluated them for interaction with the enzyme JAK2 through insilico analysis like prediction of pharmacokinetics & Molecular docking studies.

Results: Among the designed 114 novel Quinazoline JAK2 – inhibitors 98 compounds were shown good activity with better dock scores and good ADMET properties with no Lipinski rule violation.

Conclusion: Our present study concludes that the designed novel Quinazoline JAK2 –inhibitors are having potent anticancer activity.

Keywords: JAK2, Myeloproliferative Neoplasms, V-617F, Glide algorithm, Prime module.

INTRODUCTION

Januskinase-2(JAK2) is an intracellular, nonreceptor tyrosine kinase belonging to the family of Janus kinase that also includes JAK1, JAK3 and TYK2.The recent discovery of JAK2'S acquired point mutation V617F led to greater understanding of its oncogenic role in Myeloproliferative tumors (MPT'S). At 617 position phenylalanine amino acid was replaced by valine due to mutation. Therefore, aiming abnormal JAK-2 to prevent its essential activation will be an optimistic alterative option in the treatment of Myeloproliferative tumors. In this contemporary study, using computational methods we have drawn 115 novel Quinazoline JAK2 –inhibitors and estimated them for activity with the enzyme JAK2 through in silico study.

MATERIALS AND METHODS

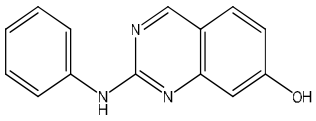
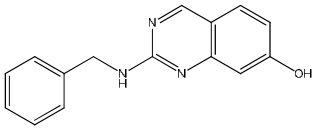
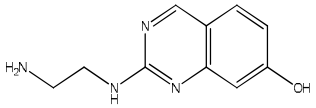
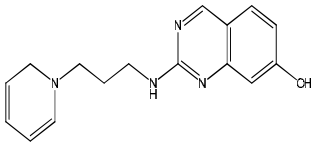
Selection and Preparation of Protein

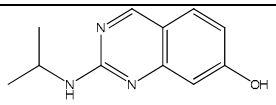
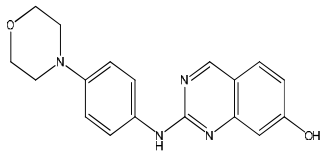
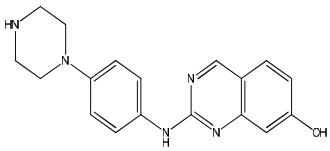
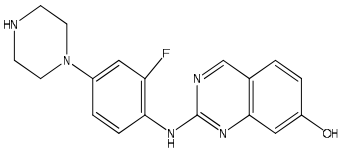
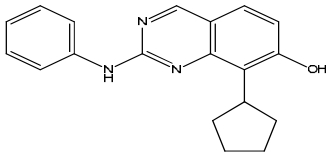
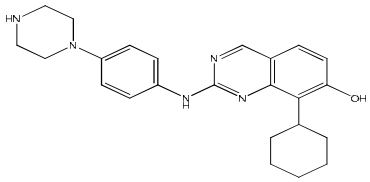
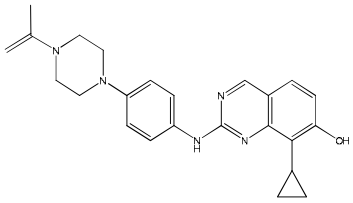
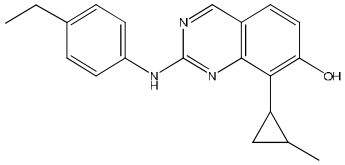
Janus kinase2(JAK2) was retrieved from the RCSB Protein Data Bank(http://www.rcsb.org/pdb/) with X-ray diffraction resolution of 2.00A^0. Preparation of the retrieved protein was performed by using protein preparation wizard of Schrodinger suite 2010. To satisfy the valencies the metal elements, ions, water molecules, and internal ligands were removed, and hydrogens were added in the protein. Perfection of loops was carried out by using PRIME module, and hydrogen bonds were allocated. Energy minimisation /geometrical optimisation of the preprocessed protein structure were done by employing OPLS2005 with RMSD 0.30.

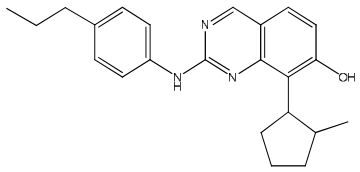
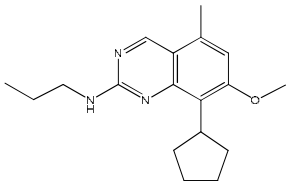
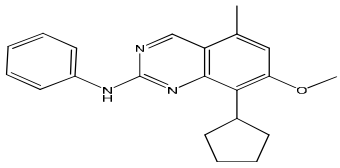
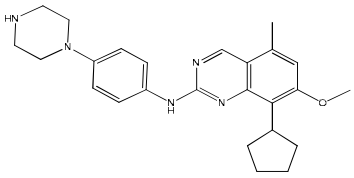
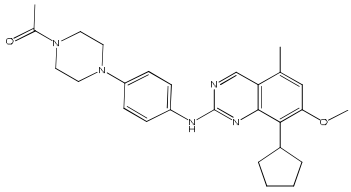
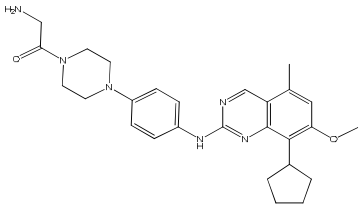
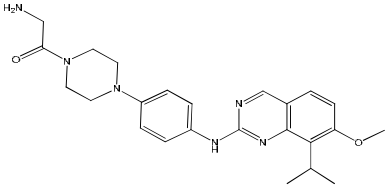
Selection of Lead Moiety & Designing of Ligands

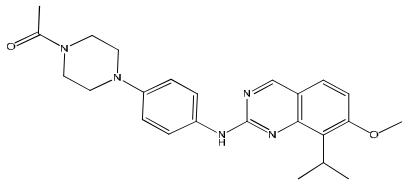
The lead, Quinazoline derivatives of Janus Kinase2 inhibitor is specified as Lead component because of its ideal potency, higher bioavailability and till today a smaller number of compounds were synthesized as JAK2 inhibitors. So, the probability of finding a novel molecule in this category increases.115 ligands were designed from the Lead compound by modifying the non-pharmacophoric groups like R1, R2, R3. To maintain the original biological therapeutic activity, all the modifications were primarily done at the non-pharmacophoric sites of the JAK2 inhibitors. Chem Draw ultra 12.0 was used to draw these novel ligands. By considering the SAR properties of the Quinazoline, the novel ligands were designed as inhibitors of JAK2. The structure of the lead Scaffold and its sites of modification can be seen in FIG-2. A few of the newly designed Ligands along with their XPG score (highest score to least score) were shown in **Table-1.**

Table 1: Newly designed Ligands along with their XPG score

S.NO	NAME	STRUCTURE	XPG score
1	1a1		-2.903096
2	1a2		-1.326136
3	1a3		-7.549078
4	1a4		-5.17451

5	1a5		-7.458065
6	1a6		-4.265179
7	1a7		-4.195146
8	1a8		-3.955364
9	1b1		-6.835722
10	1b2		-2.612678
11	1b3		-8.280792
12	1b4		-6.025372

13	1b5		-4.762857
14	1c1		-8.220343
15	1c2		-7.458454
16	1c3		-6.354576
17	1c4		-6.801976
18	1c5		-6.635429
19	1d3		-8.26312

20	1d5		-8.620195

Preparation of Ligands

Ligprep2.4" module of Schrodinger suite 2010 was used to prepare ligands. Using EPIK2.1 module the ionization in each PH range 7-9 was generated by adding (or) removing protons from the ligand. The glide module was used when docking was in between ligands to metallo proteins. To carryout energy minimization OPLS 2005 forcefield. Molecular properties, partition coefficient of all the newly synthesized 114 ligands and results were tabulated in table 2.

Table 2: In silico predicted Lipinski's molecular properties of the designed 114 novel Quinazoline JAK2 – inhibitors

S. No	Mole cule Id	Molecular weight (g/mol)	Rota table bonds	H -bond Acceptors	H-bond donors	FISA	VOLUME	MR (cm3/mol)	TPSA	LOGP	Lipinski #violations
1	1a1	237.26	2	3	2	93.811	797.093	71.1	58.04	2.13	0
2	1a2	251.28	3	3	2	95.607	860.717	75.35	58.04	2.26	0
3	1a3	204.23	3	4	3	163.441	703.891	58.38	84.06	1.42	0
4	1a4	282.34	5	3	2	100.653	975.063	88.26	61.28	2.47	0
5	1a5	203.24	2	3	2	91.533	730.771	60.48	58.04	1.97	0
6	1a6	322.36	3	4	2	100.688	1011.628	96.83	70.51	2.46	0
7	1a7	321.38	3	4	3	129.696	1039.69	102.46	73.31	2.4	0
8	1a8	339.37	3	5	3	126.513	1054.818	102.42	73.31	2.74	0
9	1b1	305.37	3	3	2	67.979	1004.319	93.18	58.04	3.11	0
10	1b2	403.52	4	4	3	102.533	1304.383	129.35	73.31	3.63	0
11	1b3	401.5	5	3	2	101.87	1089.084	128.97	64.52	3.73	0
12	1b4	319.4	4	3	2	76.802	1071.811	98.15	58.04	3.58	0
13	1b5	361.48	5	3	2	44.179	1059.053	112.57	58.04	4.05	0
14	1c1	299.41	5	3	1	93.811	797.093	92	47.04	3.71	0
15	1c2	333.43	4	3	1	39.464	1119.464	102.62	47.04	3.56	0
16	1c3	417.55	5	4	2	91.87	1488.826	133.98	62.31	3.84	0
17	1c4	459.58	6	4	1	17.498	1017.133	143.89	70.59	4.05	0

18	1c5	474.6	7	5	2	90.881	1383.874	146.59	96.61	4.08	0
19	1c6	299.41	4	3	1	50.886	610.378	92	47.04	3.68	0
20	1c7	361.48	6	3	1	50.936	727.131	111.68	47.04	3.96	0
21	1d1	259.35	4	3	1	15.042	950.823	79.53	47.04	3.12	0
22	1d2	377.48	5	4	2	72.649	1252.217	121.51	62.31	3.59	0
23	1d3	434.53	7	5	2	147.496	1413.933	134.13	96.61	3.51	0
24	1d4	293.36	4	3	1	76.74	1102.30	90.15	47.04	3.31	0
25	1d5	419.52	6	4	1	77.64	1177.829	131.42	70.59	3.78	0
26	1e1	293.36	3	3	2	60.278	1004.337	90.65	58.04	3.12	0
27	1e2	311.35	3	4	2	58.613	1018.534	90.61	58.04	3.32	0
28	1e3	395.47	4	5	3	98.914	1262.107	121.97	73.31	3.78	0
29	1f1	353.85	3	3	1	76.743	1102.304	101.26	54.88	3.48	0
30	1f2	403.52	4	4	2	115.592	1305.635	127.61	70.15	3.3	0
31	1f3	460.57	6	5	2	194.472	1466.625	140.23	104.5	3.06	0
32	1f4	351.42	4	4	1	78.193	1149.928	100.46	54.88	3.36	0
33	2a	158.2	1	2	0	76.802	1071.811	49.31	25.78	2.07	0
34	2b	206.24	1	2	0	44.179	1059.053	64.97	25.78	2.29	0
35	2c	172.23	1	2	0	93.811	797.093	54.12	25.78	2.32	0
36	2d	172.23	2	2	0	39.464	1119.464	54.12	25.78	2.33	0
37	2e	187.24	3	3	1	114.571	701.228	56.83	51.8	1.98	0
38	2f	201.27	3	3	1	107.981	744.011	61.63	51.8	2.14	0
39	2g	238.26	2	3	0	50.887	791.767	68.95	25.78	2.59	0
40	2h	256.25	2	4	0	50.886	807.709	68.91	25.78	2.67	0
41	2i	272.7	2	3	0	50.886	835.724	73.96	25.78	2.83	0
42	2j	272.7	2	3	0	50.886	835.722	73.96	25.78	2.83	0
43	2k	272.7	2	3	0	67.979	1004.319	73.96	25.78	2.83	0
44	6a	285.69	2	4	1	153.9	836.364	73.46	71.95	1.46	0
45	6b	329.69	2	6	1	168.473	875.062	79.52	90.41	1.75	0
46	6c	325.73	2	4	2	182.379	924.941	87.49	83.98	0	0
47	6d	326.72	2	4	3	229.236	913.173	89.96	96.01	0	0

48	6e	310.26	2	5	3	219.427	884.685	85.21	96.01	0	0
49	6f	309.27	2	5	2	187.131	898.299	82.75	83.98	0	0
50	6g	313.24	2	7	1	158.55	846.031	74.77	90.41	1.56	0
51	6h	269.23	2	5	1	158.698	809.944	68.71	71.95	1.48	0
52	6i	330.14	2	4	1	153.275	845.3	76.53	71.95	1.67	0
53	6j	374.15	2	6	1	153.137	881.168	82.59	90.41	1.93	0
54	6k	370.18	2	4	2	181.741	934.032	90.57	83.98	0	0
55	6l	371.17	2	4	3	214.004	919.709	93.03	96.01	0	0
56	6m	313.74	3	4	1	153.898	954.583	83.23	71.95	1.95	0
57	6n	345.74	4	6	1	146.718	984.442	86.44	90.41	2.18	0
58	6o	364.58	2	4	1	153.636	889.254	81.16	71.95	1.91	0
59	6p	313.74	3	4	1	142.447	914.288	83.23	71.95	1.96	0
60	6q	299.71	2	4	1	145.868	875.4	78.42	71.95	1.72	0
61	6r	299.71	2	4	1	153.637	896.172	78.42	71.95	1.75	0
62	6s	299.71	2	4	1	153.913	896.367	78.42	71.95	1.81	0
63	6t	313.74	2	4	1	153.838	946.48	83.39	71.95	1.93	0
64	6u	313.74	2	4	1	145.868	935.435	83.39	71.95	2.03	0
65	6v	378.61	2	4	1	146.122	935.035	86.12	71.95	2.31	0
66	6w	329.74	4	5	1	147.319	965.241	84.75	81.18	2.14	0
67	6x	364.58	2	4	1	146.121	875.003	81.16	71.95	1.92	0
68	6y	320.13	2	4	1	153.687	880.438	78.47	71.95	1.82	0
69	7a	513.39	11	4	3	115.322	1502.484	141.17	82.18	3.84	2
70	7b	529.85	11	3	3	114.066	1514.439	146.23	82.18	3.84	2
71	7c	574.3	11	3	3	113.758	1520.893	148.92	82.18	4.11	2
72	7d	563.4	12	6	3	104.591	1541.707	146.22	82.18	4.03	2
73	7e	513.39	11	4	3	121.673	1503.039	141.17	82.18	3.95	2
74	7f	574.3	11	3	3	107.486	1517.12	148.92	82.18	4.29	2
75	7g	513.39	11	4	3	115.793	1496.159	141.17	82.18	3.95	2
76	7h	547.84	11	4	3	109.144	1512.349	146.18	82.18	4.3	2
77	7i	547.84	11	4	3	122.388	1545.404	146.18	82.18	4.04	2

78	7j	564.29	11	3	3	113.06	1547	151.24	82.18	4.18	2
79	7k	592.29	11	4	3	113.192	1532.803	148.87	82.18	4.13	2
80	7l	559.87	12	4	3	113.194	1591.89	152.72	91.41	4.41	2
81	7m	525.43	12	4	3	122.993	1554.889	147.71	91.41	4.14	1
82	7n	585.48	14	6	3	101.314	1669.511	160.69	109.9	4.57	1
83	7o	523.46	12	3	3	105.186	1551.321	150.99	82.18	4.37	2
84	7p	587.5	13	4	3	104.348	1662.755	167.73	91.41	4.39	2
85	7q	559.87	12	4	3	111.723	1502.898	152.72	91.41	4.41	2
86	9a	412.49	5	6	1	136.663	1137.442	109.33	130.7	2.61	0
87	9b	352.39	4	5	1	58.169	1055.145	96.19	88.17	3.38	0
88	9c	352.39	4	5	1	58.15	1063.387	96.19	88.17	3.17	0
89	9d	446.93	5	6	1	126.999	1226.336	114.34	130.7	2.98	0
90	9e	446.93	5	6	1	128.525	1243.511	114.34	130.7	2.93	0
91	9f	491.38	5	6	1	127.407	1234.444	117.03	130.7	2.78	0
92	9g	413.29	4	4	1	58.151	1100.343	103.94	88.17	3.51	0
93	10a	395.43	5	6	1	143.817	1126.566	105.74	107.4	1.96	0
94	10b	353.33	4	6	1	87.553	989.45	92.56	64.86	3.15	0
95	10c	413.43	5	7	1	144.233	1135.718	105.7	107.4	1.86	0
96	10d	429.88	5	6	1	146.486	1154.956	110.75	107.4	1.94	0
97	10e	409.46	5	6	1	146.043	1162.413	110.7	107.4	2.16	0
98	10f	409.46	5	6	1	144.786	1166.749	110.7	107.4	2.51	0
99	10g	356.38	4	5	1	151.257	1065.533	102.33	88.65	2.72	0
100	10h	318.33	4	5	1	112.987	968.741	90.44	77.75	2.37	0
101	10i	319.32	4	6	1	132.145	955.799	88.23	90.64	1.9	0
102	10j	319.32	4	6	1	138.556	955.194	88.23	90.64	2.03	0
103	10k	336.32	4	6	1	110.409	968.124	90.4	77.75	2.25	0
104	10l	352.78	4	5	1	98.648	999.539	95.45	77.75	2.38	0
105	10m	397.23	4	5	1	107.972	994.787	98.14	77.75	2.54	0
106	10n	389.41	6	6	1	116.706	1149.018	108.34	98.06	2.66	0
107	13a1	427.45	6	7	1	128.516	1162.207	110.5	107.4	2.31	0

108	13a2	402.42	5	8	3	140.042	1108.115	108.29	113.6	0	0
109	13a3	402.42	5	8	3	155.847	1105.431	108.29	113.6	0	0
110	13a4	425.44	5	8	1	137.559	1128.14	109.21	115.3	2.18	0
111	13b1	411.41	5	8	1	140.042	1108.115	104.24	115.3	2.34	0
112	13b2	445.85	5	8	1	152.847	1131.122	109.25	115.3	2.3	0
113	13b3	431.46	5	8	1	152.283	1134.265	107.08	143.6	2.54	0
114	13b4	410.42	5	7	1	141.496	1115.359	106.44	102.5	2.21	0

RECEPTOR-LIGAND INTERACTIONS

GLIDE 5.6 was generally used to perform docking studies. Includes two steps, grid generation and ligand docking. Three-dimensional grid generation was done by selecting a particular protein residue. Once the grid was created, molecular docking studies were performed to analyze the protein ligand interactions. Then the docking score for the energy minimized poses was calculated and tabulated in Table 1.

GScore=0.065*VanderWallsEnergy+0.130*Coulombenergy+Lipophilicterm(hydrophobicinteractions) +H-bonding+Metalbinding+BuryP (Penalty for buried polar groups) + RotB (Penalty for freezing rotatable bonds) + Site (Polar interactions in the active site)

RESULTS AND DISCUSSIONS

Drug likeliness of All the Ligands: Insilico drug likeliness was performed using Swiss ADME. All the ligands showed good Lipinski properties with no violation of Lipinski rule, The results are displayed in table 2.

Molecular Docking Studies

To identify the molecular binding interactions of the analogs with the receptor, all the 114 ligands were docked into the active binding site of the enzyme JAK2 using Glide docking algorithm and the resulting XPG score of the ligands were observed. The docking score of these ligands ranged between -8.620195 (1d5) to -1.326136 (1a2). The docking result revealed that the ligand 1d5 (Fig1) got highest dock score (-8.620195) and next highest dock scores attained by 1d4 (-8.26312), 1b3 (-8.280792) (fig2). Ligand 1d5 has two hydrogen bonds with leucine932 and lysine943 at bond distance of 1.837 and 1.860 respectively. Ligand 1b3 has one hydrogen bond with leucine932 at bond distance of 2.067. All these ligands also showed molecular properties with good values without violating Lipinski rule. Results of 114 ligand moieties showed the receptor-ligand complex was stabilized by hydrogen bonds, hydrophobic and electrostatic interactions.

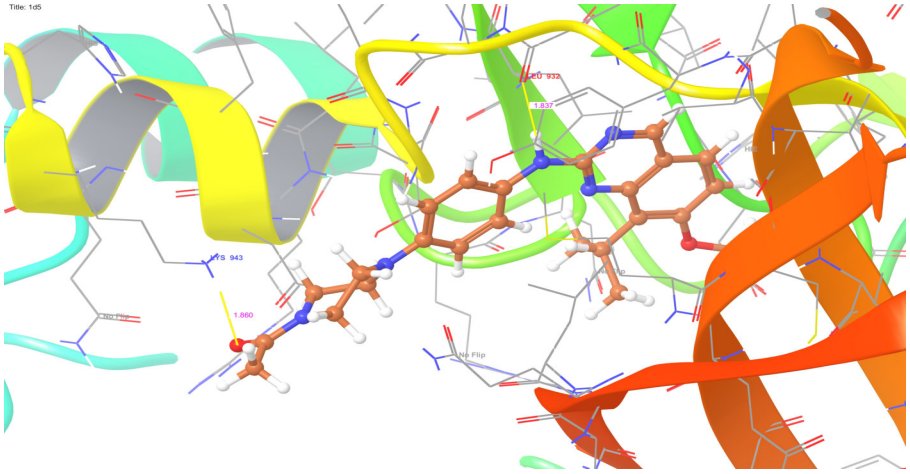


Fig 1:Three dimensional Representation of 1d5 with JAK 2 protein

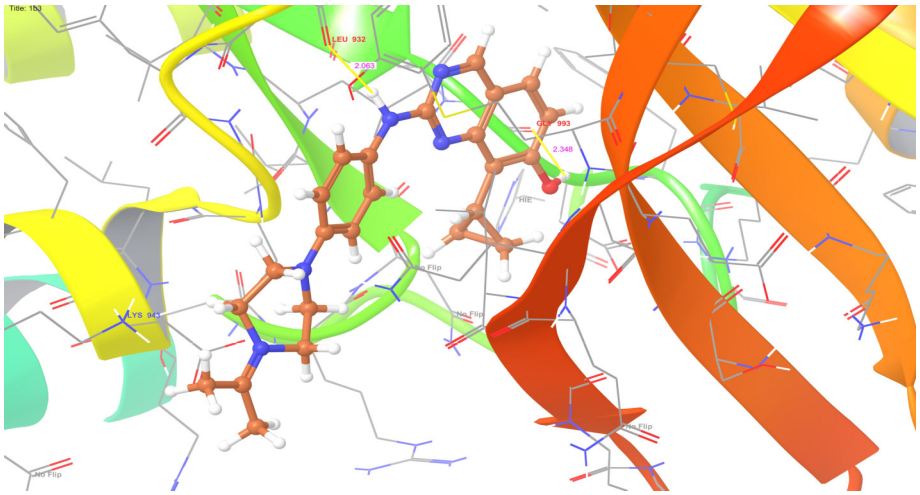


Fig-2: Three dimensional Representation of 1b3 with JAK 2 protein

CONCLUSION

Among the designed 114 novel Quinazoline JAK2 inhibitors 98 compounds were shown good activity with better dock scores and good ADMET properties with no Lipinski rule violation. Among all the compounds the ligands 1d5,1d4,1b3 showed highest dock scores with hydrogen bond formation and has good fit with protein as it showed good molecular properties. Hence these three compounds are considered as lead compounds in this library of compounds to develop novel quinazoline derivatives as JAK2 inhibitors. Our present study concludes that the designed novel Quinazoline JAK2 inhibitors are having potent anticancer activity.

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