Molecular and Distributional Properties of Tanimoto Similarities for Hypoxia-inducible Factor Prolyl Hydroxylase Inhibitors

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The Mathematical Learning Space Research Portfolio

1 Abstract

The cancer cell is very adapative to resist the immune system response and chemotherapy with neoplastic cells of altered lipid metabolism that generates cellular wall diversity with outlier membrane compositional chemical arrangements. These cells have higher concentrations of cholesterol and increase the membrane thickness and rigidity along with a greater number of gangliosides in the lipid bilayer with enhanced invasive properties.

Hypoxia changes the equilibrium of energy supply and demand and can cause cell death and organ failure with production increases in reactive oxygen (O2) and nitrogen species and limitations on antioxidant capacity in a red blood cell (RBC). B cells can produce lymphotoxin for angiogenesis in tumor growth. Tumor-derived extracellular vesicles (tEVs) can activate B cells to produce antibodies that bind antigen and form immune complexes.

L-lactate dehydrogenase (EC 1.1.1.27) is an Oxidoreductases for the CH-OH group of donors with NAD+ or NADP+. Based on the HIF-1 Pathway several molecular properties with respect to stability, binding potential, temperature and charge at three different pH values were calculated. For a collection of Tanimoto similarities for Roxadustat a hypoxia-inducible factor prolyl hydroxylase inhibitor, Pearson type distributions were identiified based on maximum likelihood estimation with moments for 4 different atom types.

2 Introduction

B cells are in bone marrow hypoxic (pO2 1.3 percent) with extravascular oxygen tension ranging between pO2 0.6–2.8 percent. The B-cells present in secondary lymphoid tissue like the spleen(i.e hypoxic environment (pO2 0.5–4.5 percent) along with the concentration of oxygen within lymph nodes where T cells are primed has an interval of 0.5 and 6 percent. [1A]

L-lactate dehydrogenase(EC 1.1.1.27) is an oxidoreductases that acts on the CH-OH group of donors with NAD+ or NADP+ as acceptor sysname (S)-lactate:NAD+ oxidoreductase with reaction(IUBMB) (S)-lactate + NAD+ = pyruvate + NADH + H+ [RN:R00703] with pathways listed as [401]

1. ec00010 Glycolysis / Gluconeogenesis
2. ec00270 Cysteine and methionine metabolism
3. ec00620 Pyruvate metabolism
4. ec00640 Propanoate metabolism
5. ec01100 Metabolic pathways
6. ec01110 Biosynthesis of secondary metabolites
7. ec01120 Microbial metabolism in diverse environments

Figure 1 has an example of the pathway for Pyruvate metabolism.

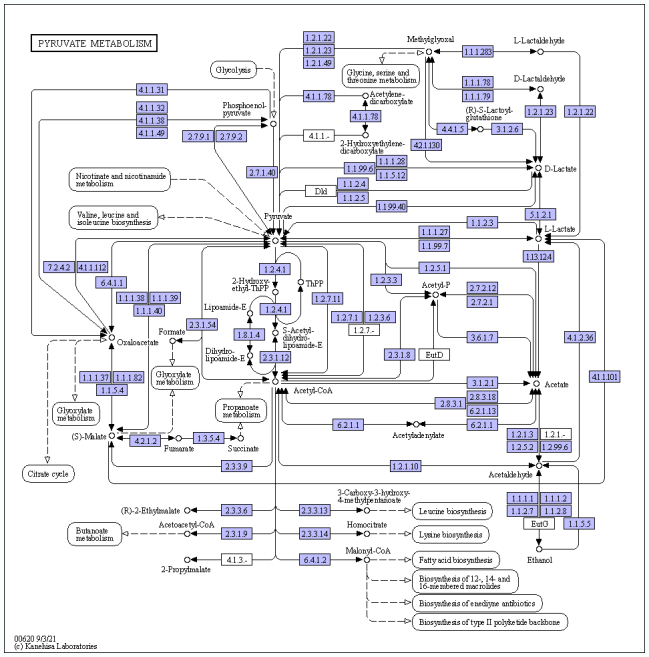

Figure 1: Pyruvate metabolism is part of overall Metabolism and Carbohydrate metabolism with ec00620 [401]

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor master regulator of oxygen homeostasis with two subunits: an (1) inducibly-expressed HIF-1alpha subunit and a (2) constitutively-expressed HIF-1beta subunit. Under normoxia, HIF-1 alpha undergoes hydroxylation at specific prolyl residues with immediate ubiquitination and subsequent proteasomal degradation of the subunit. In hypoxia, HIF-1 alpha subunit becomes stable and interacts with coactivators such as p300/CBP to modulate its transcriptional activity. The target genes of HIF-1 encode proteins to increase O2 delivery and mediate adaptive responses to O2 deprivation. HIF-1 is induced in response to reduced oxygen availability and stimulants, such as nitric oxide, or various growth factors. [401]

HIF-1 is one the primary genes involved in the homeostatic process to increase vascularization in hypoxic areas such as localized ischemia and tumors. [1A] Figure 2 has the HIF-1 pathway.

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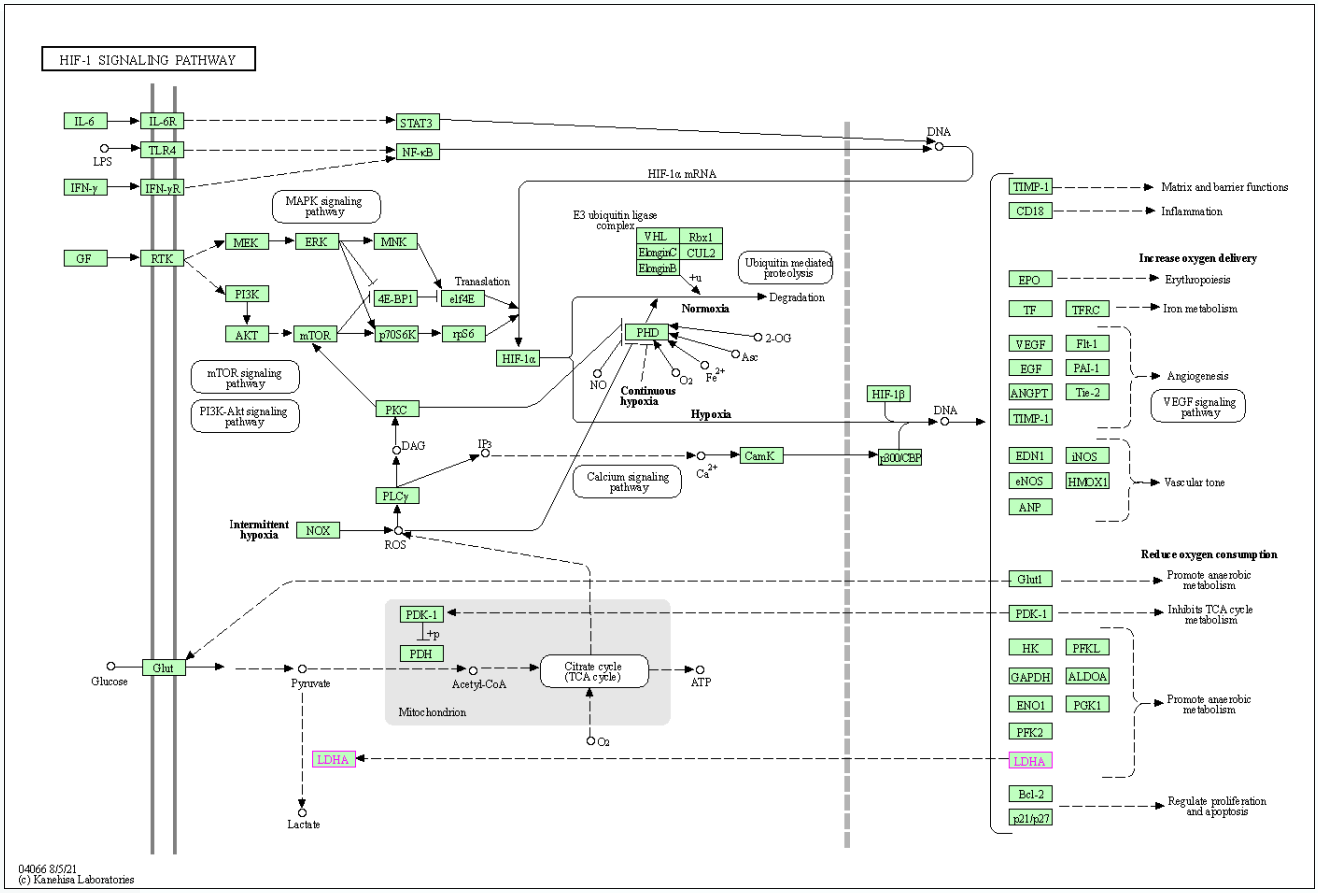

Figure 2: HIF-1 Pathway [401]

The genes involved are: HSA: 160287 (LDHAL6A) 3939(LDHA) 3945(LDHB) 3948(LDHC) 92483(LDHAL6B) [401]

2.1. O2 deprivation

Electrons accumulate in the electron transport system with stoppage of the production of ATP. Oxygen saturation values of 95 to 100 percent are normal with values under 90 percent could quickly deterioratein status and values under 70 percent are life-threatening.The minimum oxygen concentration in the air for a human is 19.5 percent. Tumor hypoxia has (a) uncontrollable cell proliferation, (b) altered metabolism, and (c) abnormal tumor blood vessels from a reduced transport of oxygen and nutrients. Hypoxia is one of the main features of solid tumors and correlates with a poor prognosis of cancer patients. Low oxygen levels in cells can be a primary cause of uncontrollable tumor growth in some cancers. The typical pH for blood in the arteries is 7.35 to 7.45 and healthy cells have a slightly alkaline internal environment with a pH of around 7.2. Cancer cells are more alkaline and have an internal pH that is higher than 7.2. [1B]

When oxygen levels decrease, the HIF protein inhibits oxygen-consuming processes of the cells through gene activity changes and the cells adapt quickly and survive the low oxygen environment. 38 ATP molecules per oxidized glucose molecule during cellular respiration (2 from glycolysis, 2 from the Krebs cycle, and about 34 from the electron transport system). Due to the acid-base properties of ATP, ADP, and inorganic phosphate, the hydrolysis of ATP has the effect of lowering the pH of the reaction medium. ATP is stable in aqueous solutions between pH 6.8 and 7.4 without catalysts. At more extreme pHs, it rapidly hydrolyses to ADP and phosphate with the total quantity of ATP in an adult about 0.10 mol/L. One hundred to 150 mol/L of ATP are required daily so each ATP molecule is recycled some 1000 to 1500 times per day in other words, the human body turns over its weight in ATP daily. ATP is highly soluble in water and is quite stable in solutions between pH 6.8 and 7.4 and rapidly hydrolysed at extreme pH so ATP is best stored as an anhydrous salt. ATP is unstable in unbuffered water and hydrolyses to ADP and phosphate. [1B]

Figure 3 has the chemical arrangement of Cholesterol.

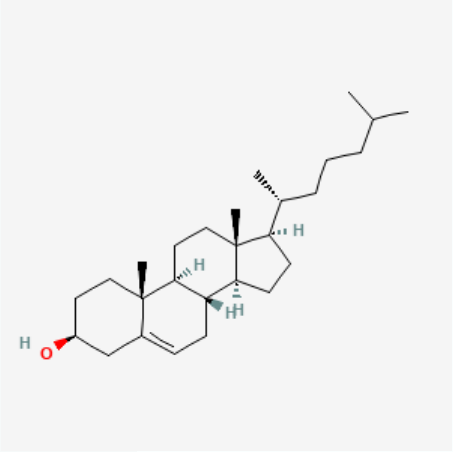

Figure 3: Cholesterol [?key1] [2] [1002]

A greater number of gangliosides in the lipid bilayer is associated with enhanced invasive properties of cancer (Groux-Degroote et al., 2017). [?key1]

3 Molecular Properties of HIF Genes

Molecular properties are abundant in dimensional reduction for collections of sequences. Examples such as stability, binding potential aliphatic and hydrophobicity along with the charge at different pH is a few of available molecular properties to examine based on the gene ontology ids in Table 1. The net charge of a protein sequence based on the Henderson-Hasselbalch equation based on pH 5, 7 and 9. The aliphatic index is the relative volume occupied by aliphatic side chains (Alanine, Valine, Isoleucine, and Leucine) and is a positive factor for the increase of thermostability of globular proteins. The potential protein interaction index proposed by Boman (2003) based in the amino acid sequence of a protein and provides an overall estimate of the potential of a peptide to bind to membranes or other proteins as receptors. A protein have high binding potential if the index value is higher than 2.48. This index predicts the stability of a protein based on its amino acid composition, a protein whose instability index is smaller than 40 is predicted as stable, a value above 40 predicts that the protein may be unstable. Hydrophobicity is an important stabilization force in protein folding; this force changes depending on the solvent in which the protein is found. [1001]

	Protein	Stability Index	Binding Potential	ALiphatic	f.1	CpH5	CpH7	CpH9
1	(RefSeq) cullin 2	44.6	1.844	84.4	-0.42242	25.1269	-1.00613	-18.672
2	(RefSeq) ring-box 1	38.6	1.620	66.0	-0.27963	4.9946	-0.05752	-7.946
3	(RefSeq) elongin B	63.0	2.124	71.9	-0.49661	-3.1775	-5.82704	-8.416
4	(RefSeq) elongin C	27.8	1.309	74.9	-0.19911	-3.3070	-7.38072	-11.447
5	(RefSeq) vascular endothelial growth factor A	52.3	2.390	57.5	-0.78276	29.0728	18.08444	0.795
6	(RefSeq) egl-9 family hypoxia inducible factor 2	54.0	1.691	72.0	-0.41622	14.8349	4.53108	-8.809
7	(RefSeq) egl-9 family hypoxia inducible factor 3	34.7	1.707	86.5	-0.27992	10.7516	2.40263	-7.622
8	(RefSeq) egl-9 family hypoxia inducible factor 1	40.1	2.027	61.7	-0.65704	24.3588	11.95413	-3.560
9	(RefSeq) von Hippel-Lindau tumor suppressor	68.7	2.515	75.4	-0.77653	-8.9520	-16.84300	-20.713
10	(RefSeq) aryl hydrocarbon receptor nuclear translocator	52.4	2.157	60.8	-0.61445	15.1446	-4.53891	-20.604
11	(RefSeq) CREB binding protein	65.9	1.849	60.9	-0.69034	110.5404	44.96053	-12.504
12	(RefSeq) E1A binding protein p300	67.0	1.866	59.7	-0.72531	113.8659	45.12499	-14.271
13	(RefSeq) hypoxia inducible factor 1 subunit alpha	56.0	2.078	75.0	-0.57288	-0.6261	-28.10190	-47.451
14	(RefSeq) solute carrier family 2 member 1	36.6	0.238	108.9	0.53415	14.0814	7.01605	-0.471
15	(RefSeq) epidermal growth factor	48.7	1.598	77.3	-0.30389	14.5310	-28.77182	-89.371
16	(RefSeq) insulin like growth factor 1	64.1	2.358	51.6	-0.73231	25.4716	20.60987	10.255
17	(RefSeq) insulin	40.3	0.573	102.9	0.19273	0.0165	-2.71938	-8.594
18	(RefSeq) epidermal growth factor receptor	44.6	1.633	80.7	-0.31603	31.1671	-6.30946	-61.899
19	(RefSeq) erb-b2 receptor tyrosine kinase 2	56.1	1.455	82.4	-0.24749	15.3392	-25.30958	-80.635
20	(RefSeq) insulin like growth factor 1 receptor	48.0	1.781	77.6	-0.40080	13.5161	-21.71694	-65.808
21	(RefSeq) insulin receptor	48.3	1.755	80.0	-0.35933	25.8921	-19.43797	-68.129
22	(RefSeq) phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	48.4	1.643	91.4	-0.30609	38.8740	3.30162	-31.943
23	(RefSeq) phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	46.9	1.445	95.9	-0.20056	31.9840	1.10459	-26.874
24	(RefSeq) phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	48.6	1.531	90.6	-0.25498	38.5201	2.60868	-30.606
25	(RefSeq) phosphoinositide-3-kinase regulatory subunit 1	48.9	2.261	81.5	-0.71602	13.1583	-8.52487	-20.819
26	(RefSeq) phosphoinositide-3-kinase regulatory subunit 2	50.4	2.084	79.5	-0.62679	16.4673	-6.03851	-17.608
27	(RefSeq) phosphoinositide-3-kinase regulatory subunit 3	46.9	2.504	73.1	-0.86768	8.8100	-9.52162	-20.112
28	(RefSeq) AKT serine/threonine kinase 3	34.7	2.139	71.8	-0.59854	8.0435	-7.56731	-18.847
29	(RefSeq) AKT serine/threonine kinase 1	35.5	2.071	71.7	-0.57479	9.1766	-8.05164	-18.887
30	(RefSeq) AKT serine/threonine kinase 2	35.1	2.016	77.0	-0.47297	10.7141	-4.53812	-14.891
31	(RefSeq) mechanistic target of rapamycin kinase	40.9	1.537	95.2	-0.19259	95.6477	6.05386	-47.588
32	(RefSeq) cytochrome b-245 beta chain	34.7	0.981	93.7	0.04912	33.2672	15.60213	-2.754
33	(RefSeq) phospholipase C gamma 1	44.4	2.105	74.3	-0.55496	21.1606	-20.13264	-49.994
34	(RefSeq) phospholipase C gamma 2	45.5	2.244	75.4	-0.61257	33.1786	-6.55763	-34.969
35	(RefSeq) protein kinase C alpha	37.4	1.806	71.3	-0.47664	24.8370	0.47611	-22.245
36	(RefSeq) protein kinase C beta	36.9	1.876	68.7	-0.50134	23.3131	0.00122	-22.178
37	(RefSeq) protein kinase C gamma	43.5	1.664	72.7	-0.34577	28.9934	4.64963	-19.423
38	(RefSeq) lactate dehydrogenase A like 6A	35.1	1.071	107.7	-0.01114	10.3975	-0.01525	-8.184
39	(RefSeq) lactate dehydrogenase A	24.8	1.083	106.8	-0.00633	13.1590	4.53050	-2.521
40	(RefSeq) lactate dehydrogenase B	26.9	1.001	109.3	0.05599	4.5681	-4.46382	-11.415
41	(RefSeq) lactate dehydrogenase C	30.5	0.912	113.6	0.14819	11.1281	1.74121	-6.172
42	(RefSeq) lactate dehydrogenase A like 6B	34.3	1.003	105.6	0.05302	20.1808	9.16195	-0.675
43	(RefSeq) pyruvate dehydrogenase kinase 1	51.4	1.743	82.5	-0.33372	20.8518	8.52125	0.340
44	(RefSeq) pyruvate dehydrogenase E1 subunit alpha 1	33.1	1.726	77.6	-0.31179	16.3178	5.56234	-7.499
45	(RefSeq) pyruvate dehydrogenase E1 subunit alpha 2	37.4	1.701	79.5	-0.28479	20.9161	9.76784	-4.255
46	(RefSeq) pyruvate dehydrogenase E1 subunit beta	41.9	1.094	89.4	0.00167	7.7207	-1.49233	-9.142
47	(RefSeq) calcium/calmodulin dependent protein kinase II alpha	47.5	1.741	84.5	-0.38013	22.5179	0.76570	-13.857
48	(RefSeq) calcium/calmodulin dependent protein kinase II beta	52.7	1.581	80.2	-0.34955	25.4430	2.59058	-16.554
49	(RefSeq) calcium/calmodulin dependent protein kinase II delta	42.5	1.723	81.3	-0.40060	21.4949	2.01227	-12.688
50	(RefSeq) calcium/calmodulin dependent protein kinase II gamma	49.9	1.739	82.2	-0.41132	24.5144	2.70283	-13.513
51	(RefSeq) hexokinase 1	37.8	1.728	89.3	-0.21003	24.9563	-2.49010	-25.327
52	(RefSeq) hexokinase 2	34.9	1.669	87.4	-0.19084	15.9579	-16.42367	-43.606
53	(RefSeq) hexokinase 3	41.6	1.234	97.1	0.09989	1.2049	-23.24994	-50.618
54	(RefSeq) hexokinase domain containing 1	35.2	1.658	90.4	-0.18593	24.4776	0.97968	-22.689
55	(RefSeq) phosphofructokinase, liver type	31.0	1.346	88.8	-0.08064	25.5744	3.93689	-13.579
56	(RefSeq) phosphofructokinase, muscle	32.5	1.529	85.4	-0.17167	30.7967	8.15414	-9.872
57	(RefSeq) phosphofructokinase, platelet	32.3	1.471	88.0	-0.14605	21.9803	3.67848	-13.971
58	(RefSeq) glyceraldehyde-3-phosphate dehydrogenase	15.6	1.195	84.7	-0.10776	15.6558	5.30739	-1.034
59	(RefSeq) aldolase, fructose-bisphosphate A	36.0	1.373	86.9	-0.26209	15.4733	4.91975	-5.131
60	(RefSeq) aldolase, fructose-bisphosphate B	34.7	1.372	85.3	-0.22665	14.2876	3.88895	-6.713
61	(RefSeq) aldolase, fructose-bisphosphate C	33.7	1.496	88.0	-0.24066	8.9411	-0.52490	-9.302
62	(RefSeq) enolase 1	36.5	1.451	88.6	-0.22143	11.0080	1.27579	-6.662
63	(RefSeq) enolase 2	35.3	1.476	92.6	-0.18825	-6.1386	-16.71445	-24.623
64	(RefSeq) enolase 3	29.9	1.358	90.4	-0.19355	12.7537	2.51368	-5.643
65	(RefSeq) enolase 4	46.7	1.331	90.5	-0.25616	8.5357	-11.50883	-27.383
66	(RefSeq) phosphoglycerate kinase 1	27.3	1.123	90.3	-0.07794	12.5940	4.00492	-3.970
67	(RefSeq) phosphoglycerate kinase 2	21.9	1.081	92.4	-0.06930	17.2326	7.48104	-1.053
68	(RefSeq) 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	51.1	2.141	80.4	-0.52096	24.1632	8.47662	-7.696
69	(RefSeq) erythropoietin	42.4	1.139	106.7	0.02746	6.8396	2.56001	-2.928
70	(RefSeq) transferrin	34.9	1.586	73.5	-0.33625	24.4504	1.37318	-35.871
71	(RefSeq) transferrin receptor	21.8	1.494	82.1	-0.24263	14.9445	-3.08433	-15.602
72	(RefSeq) fms related receptor tyrosine kinase 1	46.1	1.750	82.2	-0.35000	61.4303	24.27481	-12.967
73	(RefSeq) serpin family E member 1	35.3	1.217	87.8	-0.05896	14.2354	1.09808	-4.398
74	(RefSeq) angiopoietin 1	39.8	2.068	73.1	-0.68092	16.4579	-2.20118	-16.236
75	(RefSeq) angiopoietin 2	36.5	1.940	75.5	-0.59899	2.7666	-9.33338	-20.581
76	(RefSeq) angiopoietin 4	52.3	2.002	84.0	-0.52942	27.9877	13.09819	1.166
77	(RefSeq) TEK receptor tyrosine kinase	37.2	1.544	85.6	-0.27562	33.2805	-1.88545	-41.182
78	(RefSeq) TIMP metallopeptidase inhibitor 1	70.5	1.107	82.0	-0.01981	11.3364	5.06005	-6.383
79	(RefSeq) endothelin 1	48.3	2.605	63.0	-0.82547	25.1594	17.33913	6.248
80	(RefSeq) nitric oxide synthase 2	49.0	1.687	79.6	-0.38517	57.1275	14.85501	-18.890
81	(RefSeq) nitric oxide synthase 3	53.5	1.664	79.5	-0.34929	34.6250	3.20061	-27.481
82	(RefSeq) heme oxygenase 1	60.8	1.807	83.0	-0.42674	10.4235	2.44671	-0.688
83	(RefSeq) natriuretic peptide A	60.6	1.655	81.5	-0.26689	0.6018	-1.82975	-4.444
84	(RefSeq) lymphotoxin beta receptor	47.4	1.258	68.7	-0.36759	4.8002	-10.39016	-33.608
85	(RefSeq) toll like receptor 4	43.0	1.154	101.9	0.03278	15.3453	-10.07716	-33.876
86	(RefSeq) nuclear factor kappa B subunit 1	38.1	1.542	84.7	-0.33936	1.3484	-33.04840	-51.806
87	(RefSeq) RELA proto-oncogene, NF-kB subunit	54.4	1.808	73.2	-0.46352	3.7657	-9.08377	-19.699
88	(RefSeq) interferon gamma	30.3	2.127	75.2	-0.57771	13.7179	10.37478	6.167
89	(RefSeq) interferon gamma receptor 1	48.7	1.470	88.8	-0.23906	-9.5360	-25.45220	-39.574
90	(RefSeq) interferon gamma receptor 2	52.5	0.932	94.0	0.03056	0.8186	-6.74531	-14.344
91	(RefSeq) interleukin 6	57.7	1.609	87.5	-0.27075	3.3532	-0.64437	-5.190
92	(RefSeq) interleukin 6 receptor	61.4	1.667	74.6	-0.32842	19.6287	7.28475	-5.704
93	(RefSeq) signal transducer and activator of transcription 3	48.2	1.706	83.5	-0.40338	12.5868	-6.25461	-22.599
94	(RefSeq) eukaryotic translation initiation factor 4E binding protein 1	78.9	2.272	52.0	-0.70085	0.3046	-1.83289	-4.428
95	(RefSeq) eukaryotic translation initiation factor 4E	52.0	2.201	71.4	-0.69677	3.9263	-2.91905	-8.433
96	(RefSeq) eukaryotic translation initiation factor 4E family member 1B	45.7	2.119	83.4	-0.56612	9.4655	0.60041	-4.537
97	(RefSeq) eukaryotic translation initiation factor 4E family member 2	47.6	2.543	64.1	-0.87306	12.8199	5.38125	1.056
98	(RefSeq) ribosomal protein S6 kinase B1	51.0	1.870	73.4	-0.49105	14.8108	-2.78118	-12.816
99	(RefSeq) ribosomal protein S6 kinase B2	58.7	1.669	80.4	-0.37614	17.4669	1.93643	-8.217
100	(RefSeq) ribosomal protein S6	51.8	3.086	77.9	-0.94538	47.5082	42.62344	38.076
101	(RefSeq) mitogen-activated protein kinase 1	39.7	1.563	95.9	-0.28667	13.7514	-0.08872	-10.755
102	(RefSeq) mitogen-activated protein kinase 3	43.1	1.621	91.6	-0.31398	11.2249	-1.53278	-10.898
103	(RefSeq) mitogen-activated protein kinase kinase 1	43.9	1.504	87.1	-0.30458	9.5864	-2.00379	-10.350
104	(RefSeq) mitogen-activated protein kinase kinase 2	49.6	1.652	91.1	-0.31850	10.0415	-2.72599	-10.453
105	(RefSeq) MAPK interacting serine/threonine kinase 2	58.1	1.870	80.6	-0.39677	9.6207	-7.85493	-24.884
106	(RefSeq) MAPK interacting serine/threonine kinase 1	55.0	1.848	78.4	-0.42428	11.4805	-1.96884	-15.757
107	(RefSeq) BCL2 apoptosis regulator	51.6	1.259	78.0	-0.13598	9.7627	1.09193	-3.863
108	(RefSeq) cyclin dependent kinase inhibitor 1A	80.9	2.785	56.5	-0.84512	7.1264	3.32435	-1.755
109	(RefSeq) cyclin dependent kinase inhibitor 1B	66.1	3.205	44.4	-1.26111	6.8528	0.08300	-5.167

Drugs for HIF-1 are as follows: [?key1]

1. D09926 Icrucumab (USAN/INN)
2. D10334 Rebastinib (USAN)
3. D10386 Cindunistat (USAN/INN)
4. D10395 Nesvacumab (USAN)
5. D10399 Rebastinib Tosylate (USAN)
6. D10419 Cindunistat hydrochloride maleate (USAN)
7. D10464 Firtecan pegol (USAN/INN)
8. D10593 Roxadustat (JAN/USAN/INN)
9. D10874 Daprodustat (JAN/USAN/INN)
10. D11078 Vadadustat (JAN/USAN/INN)
11. D11273 Molidustat sodium (JAN/USAN)
12. D11452 Tomivosertib (USAN/INN)
13. D11481 Tomivosertib hydrochloride (USAN)
14. D11523 Enarodustat (JAN)
15. D11540 Razuprotafib (USAN)
16. D11812 Pabinafusp alfa (genetical recombination) (JAN)
17. D12122 Molidustat (USAN/INN)

Table 2 has the Drug name and the efficacy.

	Name	EFF
1	Icrucumab (USAN/INN)	Antineoplastic, Angiogenesis inhibitor, Anti-vascular endothelial growth factor receptor-1 antibody
2	Rebastinib (USAN)	Antineoplastic, Tyrosine kinase inhibitor
3	Cindunistat (USAN/INN)	Anti-inflammatory, Inducible nitric oxide synthase inhibitor
4	Nesvacumab (USAN)	Antineoplastic, Angiogenesis inhibitor
5	Rebastinib Tosylate (USAN)	Antineoplastic, Tyrosine kinase inhibitor
6	Cindunistat hydrochloride maleate (USAN)	Anti-inflammatory, Inducible nitric oxide synthase inhibitor
7	Firtecan pegol (USAN/INN)	Antineoplastic, Topoisomerase I inhibitor
8	Roxadustat (JAN/USAN/INN);	Anti-anemic, Prolyl hydroxylase inhibitor
9	Daprodustat (JAN/USAN/INN);	Anti-anemic, Prolyl hydroxylase inhibitor
10	Vadadustat (JAN/USAN/INN);	Anti-anemic, Prolyl hydroxylase inhibitor
11	Molidustat sodium (JAN/USAN);	Anti-anemic, Hypoxia inducible factor-prolyl hydroxylase (HIF-PH) inhibitor
12	Tomivosertib (USAN/INN)	Antineoplastic, MAP kinase interacting serine/threonine kinase inhibitor
13	Tomivosertib hydrochloride (USAN)	Antineoplastic, MAP kinase interacting serine/threonine kinase inhibitor
14	Enarodustat (JAN);	Anti-anemic, Hypoxia inducible factor-prolyl hydroxylase (HIF-PH) inhibitor
15	Razuprotafib (USAN)	Angiopoietin modulator, TIE2 receptor agonist
16	Pabinafusp alfa (genetical recombination) (JAN);	Fusion protein
17	Molidustat (USAN/INN)	Anti-anemic, Hypoxia inducible factor-prolyl hydroxylase (HIF-PH) inhibitor

Roxadustat is an orally bioavailable, hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), with potential anti-anemic activity. Roxadustat binds to and inhibits HIF-PHI, an enzyme responsible for the degradation of transcription factors in the HIF family under normal oxygen conditions. This prevents HIF breakdown and promotes HIF activity where increased HIF activity leads to an increase in endogenous erythropoietin production for erythropoiesis. It also reduces the (a) expression of the peptide hormone hepcidin, (b) improves iron availability, and (c) boosts hemoglobin (Hb) levels and HIF regulates the expression of genes in response to reduced oxygen levels such as genes required for erythropoiesis and iron metabolism. [601]

Figure 4 has the Roxadustat chemical configuration.

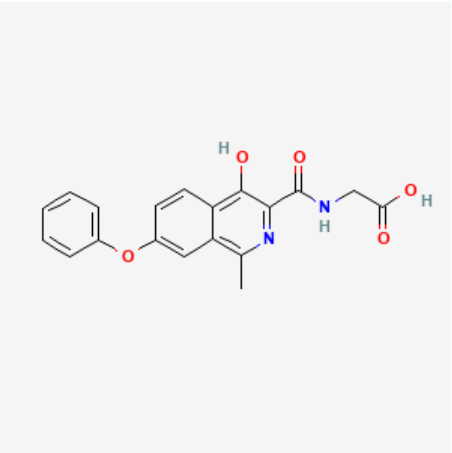

Figure 4: Roxadustat [601]

Roxadustat is an N-acylglycine resulting from the formal condensation of the amino group of glycine with the carboxy group of 4-hydroxy-1-methyl-7-phenoxyisoquinoline-3-carboxylic acid. It is an inhibitor of hypoxia inducible factor prolyl hydroxylase (HIF-PH) and has a role as an EC 1.14.11.2 (procollagen-proline dioxygenase) inhibitor and an EC 1.14.11.29 (hypoxia-inducible factor-proline dioxygenase) inhibitor. It is a member of isoquinolines, an aromatic ether and a N-acylglycine. [601]

Figure 5 has the Tanimoto Structural Similarities N=845 with CID5884 with (a) oxygen (b) carbon (c) hydrogen (d) Nitrogen with a location scale [0,1] with 0=start and 1=end for the SMILE sequence.

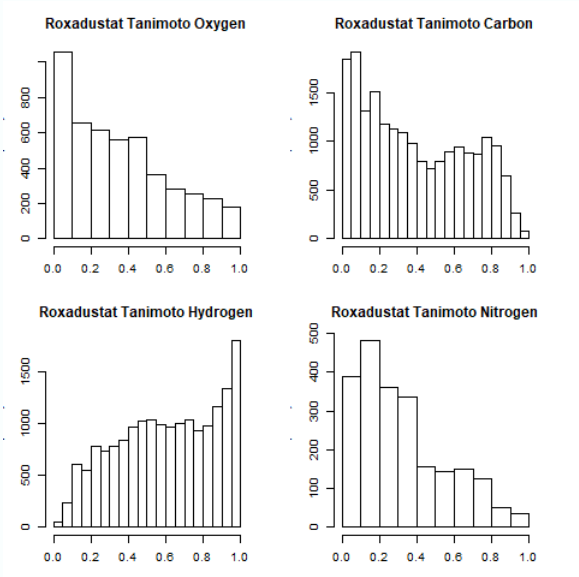

Figure 5: Tanimoto Structural Similarities N=868 with CID11256664 with (a) oxygen (b) carbon (c) hydrogen (d) Nitrogen with a location scale [0,1] with 0=start and 1=end for the SMILE sequence. [601] The Pearson distribution with moments are (a) type 1 a 0.9198973 b=1.711608, location=0.001144165, scale=1.211808, (b) type 3 shape=1.317877, location=0.003236576, scale=0.2965204, (c) type 2, a=0.9742473, location=0.02059497, scale= 0.9783164, and (d) type 3, shape=1.653929, location=0.005221357, scale=0.1935626

4 Conclusion

Based on the HIF-1 Pathway several molecular properties with respect to stability, binding potential, temperature and charge at three different pH values were calculated. For a collection of Tanimoto similarities for Roxadustat a hypoxia-inducible factor prolyl hydroxylase inhibitor, Pearson type distributions were identiified based on maximum likelihood estimation with moments for 4 different atom types.

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