Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supportive Information

Perception into Hypoxia Selectivity and Electronic features of Symmetrically Substituted Bisthiosemicarbazone ligands and their Copper Complexes: DFT and QM/MM Docking

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Figure S.1

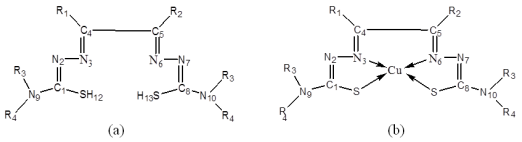

Table S.1: Bisthiosemicarbazone ligands and respective copper complexes

S.No	Name	R_1	R_2	R_3	R_4
1	ATS	CH_3	CH_3	H	H
2	ATSM	CH_3	CH_3	CH_3	H
3	CTS	CH_2CH_3	CH_3	H	H
4	DTSM	CH_2CH_3	CH_2CH_3	CH_3	H
5	ETS	H	CH_2CH_3	H	H
6	*i*PrTSM	H	$CH(CH_3)_2$	CH_3	H
7	*n*BuTS	H	$CH_2CH_2CH_2CH_3$	H	H
8	*n*BuTSM	H	$CH_2CH_2CH_2CH_3$	CH_3	H
9	*n*PrTS	H	$CH_2CH_2CH_3$	H	H
10	*n*PrTSM	H	$CH_2CH_2CH_3$	CH_3	H
11	PhTS	H	C_6H_5	H	H
12	GTSM	H	H	CH_3	H
13	*i*PrTS	H	$CH(CH_3)_2$	CH_3	H
14	ETSM	H	CH_2CH_3	CH_3	H
15	KTS	H	$CH(CH_3)OCH_2CH_3$	H	H

16	$KTSM_2$	H	$CH(CH_3)OCH_2CH_3$	CH_3	CH_3
17	PTS	H	CH_3	C_6H_5	H
18	PTSE	H	CH_3	CH_2CH_3	H
19	PhTSM	H	C_6H_5	CH_3	H
20	$PTSM_2$	H	CH_3	CH_3	CH_3
21	CGTS	Cl	H	H	H
22	DAGTS	NH_2	NH_2	H	H
23	AGTS	NH_2	H	H	H
24	HYGTS	OH	H	H	H
25	NGTS	CN	H	H	H
26	FGTS	F	H	H	H
27	MAGTS	CH_3	NH_2	H	H
28	TFGTS	CF_3	H	H	H
29	THGTS	SH	H	H	H
30	PTSM	H	CH_3	CH_3	H

Figure S.2

Table S.2: Bond lengths and dihedral angle of obtained optimized geometry of BTSC ligand in their respective stable conformer.

Ligand	C_4-N_3	C_5-N_6	C_4-C_5	N_6-N_7	N_2-N_3	N_7-C_8	N_2-C_1	C_1-S	C_8-S	C-I D(N_3=C_4-C_5=N_6)	C-II D (N_3=C_4-C_5=N_6)
ATS	1.280	1.280	1.521	1.430	1.430	1.290	1.290	1.820	1.820	-180.0	-
ATSM	1.280	1.280	1.521	1.430	1.430	1.290	1.290	1.820	1.820	-180.0	-
CTS	1.282	1.281	1.525	1.430	1.432	1.292	1.292	1.820	1.820	-178.7	-
DTSM	1.283	1.282	1.531	1.433	1.432	1.295	1.295	1.820	1.820	179.3	-
ETS	1.273	1.279	1.540	1.432	1.426	1.292	1.292	1.820	1.820	-179.1	-
*i*PrTSM	1.281	1.273	1.509	1.430	1.429	1.295	1.296	1.820	1.820	180.0	-
*n*BuTS	1.283	1.282	1.502	1.430	1.428	1.296	1.296	1.820	1.820	178.8	-
*n*BuTSM	1.273	1.278	1.510	1.433	1.420	1.299	1.296	1.820	1.820	-178.8	-
*n*PrTS	1.275	1.276	1.502	1.431	1.429	1.298	1.296	1.820	1.820	-178.9	-
*n*PrTSM	1.281	1.280	1.503	1.440	1.421	1.296	1.296	1.820	1.820	-178.9	-
PhTS	1.273	1.282	1.508	1.431	1.427	1.292	1.293	1.820	1.820	-	1.2

GTSM	1.271	1.271	1.487	1.429	1.429	1.296	1.296	1.820	1.820	180	-
*i*PrTS	1.281	1.273	1.509	1.428	1.426	1.292	1.292	1.820	1.820	180	-
ETSM	1.279	1.273	1.504	1.433	1.429	1.295	1.296	1.820	1.820	-179.1	-
KTS	1.281	1.274	1.507	1.427	1.437	1.292	1.292	1.820	1.820	-	1.0
$KTSM_2$	1.284	1.272	1.505	1.431	1.435	1.300	1.299	1.833	1.835	-	-0.3
PTS	1.281	1.277	1.500	1.432	1.435	1.301	1.298	1.820	1.830	179.9	-
PTSE	1.273	1.277	1.503	1.434	1.429	1.296	1.296	1.820	1.820	179.9	-
PhTSM	1.273	1.283	1.500	1.429	1.433	1.296	1.295	1.821	1.821	-	1.2
$PTSM_2$	1.277	1.273	1.503	1.431	1.436	1.399	1.299	1.823	1.823	180	-
CGTS	1.270	1.274	1.510	1.437	1.427	1.293	1.289	1.820	1.820	180	-
DAGTS	1.298	1.468	1.438	1.438	1.438	1.293	1.280	1.820	1.820	153.8	-
AGTS	1.290	1.270	1.500	1.420	1.437	1.294	1.293	1.820	1.820	-	-0.3
HYGTS	1.281	1.278	1.540	1.424	1.421	1.287	1.287	1.801	1.799	-	-7.8
NGTS	1.288	1.272	1.516	1.421	1.433	1.287	1.295	1.837	1.805	-	2.1
FGTS	1.275	1.278	1.498	1.428	1.432	1.291	1.293	1.821	1.821	-	0
MAGTS	1.298	1.283	1.515	1.432	1.411	1.292	1.292	1.820	1.820	-179.7	-
TFGTS	1.281	1,284	1.488	1.353	1.483	1.299	1.299	1.807	1.870	-180.0	0
THGTS	1.272	1.280	1.496	1.280	1.272	1.436	1.426	1.820	1.820	180.0	0
PTSM	1.273	1.277	1.503	1.429	1.434	1.296	1.296	1.820	1.820	-180.0	0

Table s. 3 Correlation coefficient r^2 matrices for the descriptors used in different MLR analysis

	Alpha HOMO Energy	Alpha LUMO Energy	Chemical Potential	Electrophilicity	Hardness	LogPo/w	Softness	Total Energy
Alpha HOMO Energy	1	0.442897	-0.650968	-0.439036	0.0938674	0.256082	-0.140522	-0.487615
Alpha LUMO Energy	0.44289	1	-0.950616	-0.988704	0.932714	-0.0695989	-0.94267	-0.110943
Chemical Potential	-0.65096	-0.95061	1	0.953818	-0.795014	-0.005633	0.813055	0.251103
Electrophilicity	-0.43903	-0.98870	0.953818	1	-0.919623	0.0919458	0.941064	0.140184
Hardness	0.09386	0.932714	-0.795014	-0.919623	1	-0.159337	-0.989045	0.0633417
LogPo/w	0.25608	-0.069598	-0.0056334	0.0919458	-0.159337	1	0.173061	-0.749883
Softness	-0.14052	-0.94267	0.813055	0.941064	-0.989045	0.173061	1	-0.0238096
Total Energy	-0.48761	-0.11094	0.251103	0.140184	0.0633417	-0.749883	-0.023809	1

TABLE S.4: Representing statistical parameters. (SD is standard deviation, R^2-vlaue for R-squared for

regression,R^2 CV-cross validated R^2 values computed from predictions obtained by leave-out approach, F-variance ratio, P-significance level of variance ratio, RMSE-root-mean-square-error)

PLS Factors	SD	R^2	R^2 CV	R^2 Scramble	Stability	F	P	RMSE	Q^2	Pearson-r
1	0.5137	0.6045	0.4679	0.2828	0.87	16.8	0.00176	0.78	0.877	0.4428
2	0.3642	0.8192	0.7105	0.1544	0.518	22.7	0.000193	0.77	0.9149	0.7517

Coordinates and Dihedral angles of Ligands

Coordinate	ETS	CTS	ATSM	KTSM2	nPrTSM	ATS
0	-146.92625	-141.877	-39.394344	-102.6659	-39.53986	-15.939005
30	-125.1016	-115.2850	-13.617641	-81.78154	-17.96579	6.265354
60	-70.360855	-38.58394	60.481094	-26.72821	36.213509	60.299255
90	-30.575834	53.878609	151.07034	17.465866	77.117302	100.55152
120	-72.857956	-55.88962	44.730194	-9.282027	33.384403	57.533081
150	-127.56783	-131.2037	-30.249317	-68.71504	-21.15421	2.082425
180	-150.86466	-160.0409	-55.791084	-92.28125	-42.34631	-19.072346
210	-129.3757	-134.3328	-30.246672	-73.28241	-21.18208	4.503428
240	-73.749413	-57.89114	44.727051	-21.21128	33.611023	59.221275
270	-30.792019	39.845818	140.77891	20.542046	77.378777	101.19535
300	-70.893562	-35.54072	60.465515	-23.36406	36.39913	60.920174
330	-124.79399	-110.9132	-13.610358	-79.00495	-17.88998	5.939544
360	-146.9243	-141.8758	-39.381237	-102.6657	-39.51310	-15.929008
Coordinate	Energy8	Energy9	Energy10	Energy11	Energy12	Energy13

	iPrTSM	THGTS	TFGTS	AGTS	PHTS	iPrTS
0	-91.943069	4.607391	-174.02164	-34.47359	-253.7159	-117.12515
30	-69.010811	26.241171	-151.12894	-18.33877	-231.1950	-95.559616
60	-10.865919	80.220963	-93.376678	27.115244	-175.1592	-41.806793
90	39.644131	119.72399	-45.445251	64.750443	-136.4950	-2.735753
120	-8.923925	78.515907	-93.675163	27.18709	-193.2170	-44.220196
150	-67.801537	25.092018	-152.53711	-23.87650	-253.4451	-97.783371
180	-91.074272	3.554456	-175.90149	-44.43367	-276.5627	-119.27749
210	-67.795662	25.106016	-152.53706	-24.04888	-253.4158	-97.778946
240	-8.918989	78.523384	-93.675468	26.941599	-193.2090	-44.216232
270	39.641235	119.72277	-45.439877	66.564796	-136.5012	-2.732561
300	-10.873932	80.211922	-93.379326	27.116474	-175.1671	-41.807098
330	-69.013275	26.229946	-151.13181	-18.34377	-231.2081	-95.576553
360	-91.939415	4.619007	-174.01988	-34.57157	-253.7141	-117.11656
Coordinate	Energy15	Energy	Energy	Energy	Energy	Energy
	PHTSM	PTSM2	NGTS	nBuTS	PTSM	nBuTSM
0	68.295563	-54.074158	47.464462	-95.691139	-141.44322	-52.307514
30	89.113083	-33.325165	69.065262	-76.496353	-119.27249	-30.744736
60	143.550842	20.914053	123.231079	-28.259497	-65.419769	23.419743
90	184.272415	61.278294	164.008774	14.406268	-25.745682	64.286652
120	153.389771	30.191917	120.161156	-29.038733	-69.364777	20.513868
150	95.88475	-27.550636	65.417496	-83.966316	-124.91761	-34.291969
180	70.595398	-52.813232	44.326778	-105.76382	-145.98589	-55.356556
210	90.765038	-32.608929	65.398064	-83.967049	-122.16538	-34.291069
240	145.671158	22.457373	120.092041	-29.067945	-67.22036	20.515463
270	186.867111	64.094391	164.017944	14.677241	-24.967772	64.282906
300	148.851395	26.246023	123.184631	-28.26231	-64.825455	23.411217
330	92.681587	-29.75704	69.024834	-76.517143	-119.60699	-30.747513
360	68.320396	-54.054424	47.472019	-95.68988	-141.42067	-52.304726
Coordinate	Energy	Energy	Energy	Energy	Energy	Energy
	GTSM	PTSE	DAGTS	ETSM	GTS	DTSM
0	-138.0612	-41.533646	-48.050308	-490.90598	-24.724552	-98.130768
30	-116.23258	-25.630411	-26.485735	-477.10892	-2.847827	-87.7808
60	-61.446388	9.901303	27.675184	-499.04254	52.096962	-62.430302
90	-21.572691	29.909637	68.543259	-495.78189	92.27417	-50.083965
120	-63.802544	8.033851	24.775557	-498.10562	50.26231	-75.186272
150	-118.70449	-29.214706	-30.019558	-501.3674	-4.263749	-113.68472
180	-142.37228	-45.727386	-51.06881	-499.6958	-27.476833	-130.16173
210	-121.138	-29.212107	-30.016666	-500.07721	-6.053674	-113.59404
240	-65.5233	8.037754	24.778862	-498.10062	49.406216	-75.019379
270	-22.204401	29.896711	68.541359	-495.79929	92.052116	-49.596302
300	-62.038708	9.897018	27.667824	-499.04172	51.527115	-62.43045

330	-115.91211	-25.635214	-26.488403	-498.66495	-2.543231	-87.892609
360	-138.06027	-41.531647	-48.04446	-490.80664	-24.721689	-98.090866
Coordinate	Energy HYGTS	Energy CGTS	Energy KTS	Energy nPrTS	Energy14 MAGTS	Energy7 FGTS
0	-154.54393	-123.88163	50.686169	-19.40011	-287.79141	-173.04817
30	-150.77327	-104.13136	86.223335	2.496899	-259.76096	-147.43036
60	-117.05648	-53.857533	167.354355	57.491009	-183.77701	-73.446671
90	-77.010933	-8.452398	223.752197	97.741486	-91.29599	16.932539
120	-114.26485	-57.819546	130.964401	55.731689	-205.42412	-89.647385
150	-162.05563	-114.57355	52.354385	0.982031	-283.57568	-164.58443
180	-180.95195	-136.8909	23.246414	-22.722664	-311.16574	-190.34027
210	-162.25674	-114.57674	56.053871	-1.736149	-281.8255	-164.74695
240	-114.70486	-57.868786	141.382828	53.62051	-205.35919	-89.645531
270	-71.952225	-7.878363	241.394531	96.928284	-104.69791	6.418213
300	-117.05653	-53.858593	158.386261	56.818405	-183.79031	-73.449837
330	-150.79596	-104.24204	77.660828	2.789661	-259.7999	-147.43304
360	-154.54443	-123.88419	50.685253	-19.400032	-287.79572	-173.17859