

## Synthesis, Characterization, and Molecular Docking of Casiopeinas® with Dipeptides as Secondary Ligand; Potential Inhibitors of SARS-Cov-2 Transcendental Proteins

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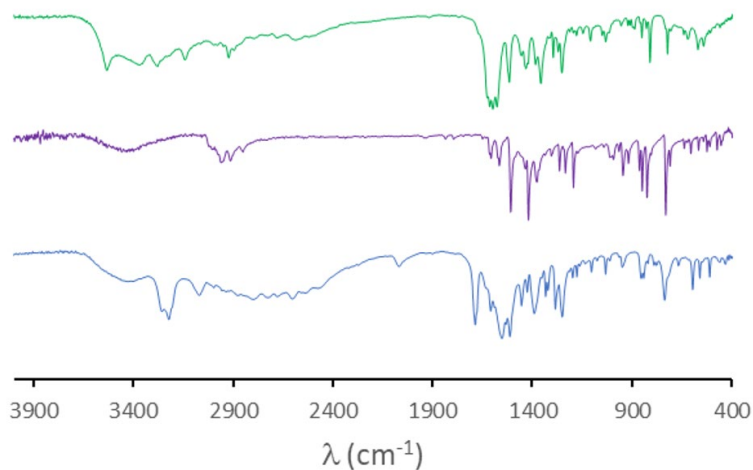
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## Supplementary Information



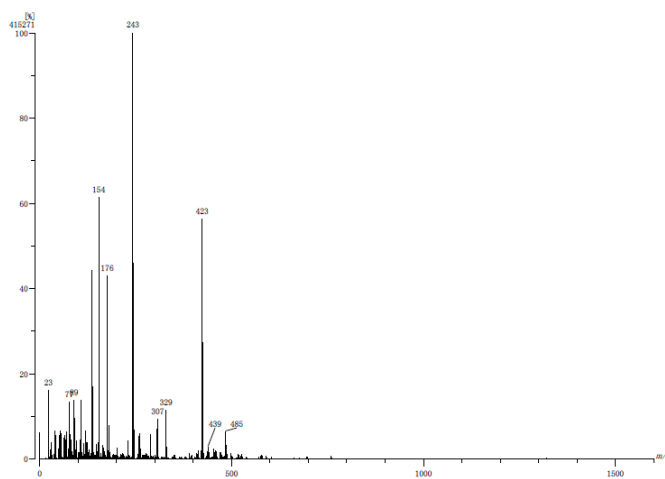
**Fig. S1.** Comparative FT-IR Spectra of L-Tyrosil-Glicinate (Blue), 3,4,7,8-tetramethyl-1,10-phenanthroline (purple) and compound **14** (green).

**Table S1.** Selected vibrational frequencies for bipeptides and Casiopeinas®.

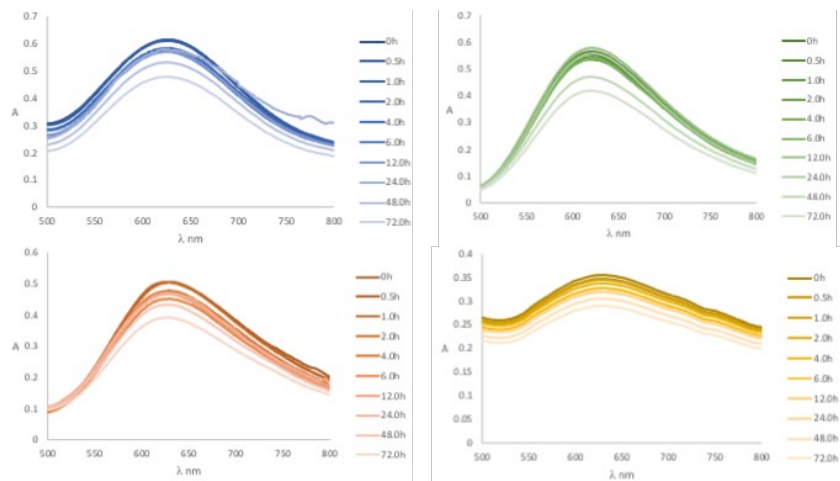
Code compound	Selected vibrational frequencies (cm <sup>-1</sup> )			
	NH <sub>2</sub> , NH	CONR	C=N	NO <sub>3</sub> <sup>-</sup>
GY	3220, 3247	1670	1610	---
YG	3222, 3257	1687	1630	---
<b>1</b>	3257	1683	1622	1384
<b>2</b>	3265	1685	1636	1384
<b>3</b>	3251	1685	1622	1384
<b>4</b>	3222, 3259	1685	1654	1384
<b>5</b>	3251	1691	1623	1384
<b>6</b>	3222, 3253	1683	1654	1384
<b>7</b>	3245	1700	----	1384
<b>8</b>	3216, 3259	1685	1633	1384
<b>9</b>	3253	1685	1625	1384
<b>10</b>	3223, 3252	1685	1631	1384
<b>11</b>	3249	1678	1636	1384
<b>12</b>	3232, 3279	1675	1625	1384
<b>13</b>	3249	1685	1631	1384
<b>14</b>	3220, 3252	1687	1631	1384

**Table S2.** Characterization of Casiopeinas®

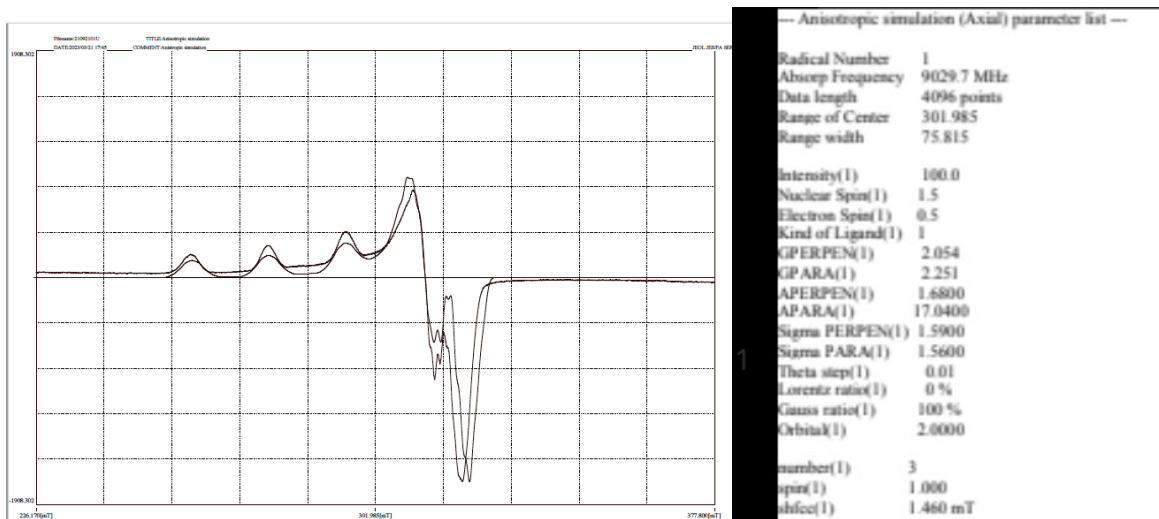
Code compound	$\mu_{\text{eff}}$ (MB)	Molar conductivity $\Lambda_m$ ( $\text{Scm}^2\text{mol}^{-1}$ )	Molecular Ion. (M/Z) <sup>+</sup>
1	1.86	132.63	456
2	2.12	141.85	456
3	1.80	136.10	485
4	2.08	144.80	485
5	2.02	141.49	485
6	1.90	152.99	485
7	1.81	152.72	482
8	2.04	158.37	482
9	2.14	140.39	510
10	1.98	158.45	510
11	1.86	139.40	510
12	2.01	157.40	510
13	2.16	151.28	538
14	2.06	158.46	538



**Fig. S2.** FAB<sup>+</sup> Spectrum of compound **3** acquired in nitrobenzyl alcohol.



**Fig. S3.** Stability of coordination compounds determined in aqueous solution [ $10^{-3}$ ] M. Upper left: Electronic Spectrum of **3**. Upper Right: Electronic Spectrum of **4**. Lower left: Electronic Spectrum of **9**. Lower Right: Electronic Spectrum of **10**.



**Fig. S4.** EPR spectra experimental and simulated of **1**.

**Table S3.** Energies and atomic coordinates for DFT M06/LanL2DZ optimized structures.

CasX-GY (1) : $E_{\text{tot}}$ : -1527.934383 a. u.				CasX-YG (2) : $E_{\text{tot}}$ : -1527.937329 a. u.			
C	-5.36789500	0.10159500	0.51387100	C	-2.53850300	0.82405000	0.42110000
C	-3.86330800	0.18836000	0.22911200	C	-1.87596500	1.93279800	1.21123000
H	-3.39384000	0.88370600	0.93180100	H	-2.59913200	2.73376800	1.39779900
C	-3.68645200	0.71660000	-1.22626700	N	-0.73778200	2.43044200	0.39115100
H	-4.24096300	0.04129600	-1.89258300	O	-1.85664700	0.20294900	-0.47921100
H	-4.15959100	1.70476900	-1.26694800	H	-0.02655700	2.86824900	0.98412300
C	-2.23853300	0.79813000	-1.63071500	H	-1.05376200	3.11463800	-0.30346700
C	-1.57828500	-0.31643000	-2.17830400	C	0.09284200	-2.03828400	-1.23175000
H	-2.14599400	-1.21740300	-2.40278300	H	-0.98560500	-1.95917400	-1.15121200
C	-0.19899200	-0.29156500	-2.43199400	C	0.73212100	-3.26858200	-1.41951700
H	0.30966300	-1.15862500	-2.84907000	H	0.14442900	-4.17502100	-1.48901300
C	0.52334000	0.88081700	-2.16242500	C	2.12936400	-3.29282000	-1.51058500
C	-0.11974500	2.01927800	-1.65589500	H	2.65244700	-4.23129700	-1.65425600
H	0.45913900	2.91962400	-1.46704700	C	2.85348000	-2.09663300	-1.41275300
C	-1.49078400	1.96639600	-1.38438500	C	4.16935900	0.64227900	-1.13380100
H	-1.98792800	2.83801600	-0.96302800	C	4.65365300	1.94697200	-0.97569900
C	-1.98770000	-1.36847000	0.65043700	H	5.71986300	2.13772500	-1.01443200
C	-1.44859000	-2.76416800	0.45569500	C	3.75354000	2.99941300	-0.76790900
H	-2.02314400	-3.48208200	1.04848800	H	4.09437600	4.01959900	-0.64597800
H	-1.56975500	-3.03490300	-0.59740700	C	2.38674900	2.71312600	-0.71236800
N	-0.00762400	-2.79027100	0.80419900	H	1.65516400	3.49691100	-0.55336200
N	-3.26362800	-1.13977300	0.36357500	C	2.79136700	0.41994400	-1.07570600
H	-3.87608800	-1.91944900	0.11190300	C	2.15715200	-0.90110600	-1.22147700
O	-1.19224400	-0.44295500	1.06564400	Cu	0.03751700	0.86380300	-0.62049800
O	-5.97059100	1.21166900	0.75282100	N	0.79662700	-0.89287100	-1.14454400
O	-5.92391700	-1.05829700	0.43527700	N	1.92699600	1.45408000	-0.86292800
O	1.89546400	0.97919400	-2.40259200	H	3.93469600	-2.10378600	-1.47855500
H	2.29150300	0.12253300	-2.66309400	H	4.85519800	-0.18073200	-1.29535700
H	0.50089500	-3.39657000	0.15856500	N	-3.78967200	0.48374400	0.71345900
H	0.14051100	-3.13093200	1.75841000	H	-4.28836200	1.02735100	1.41486900
C	0.54597900	1.96084300	1.56450500	C	-4.47875700	-0.60271100	0.02973400
H	-0.47061700	1.70337300	1.83758300	H	-3.83789700	-1.49151600	0.00317400
C	1.02144600	3.27213900	1.65432300	H	-5.37665900	-0.85869900	0.59635200
H	0.36844800	4.05675600	2.01481000	C	-4.89715600	-0.28239500	-1.41450700
C	2.33889200	3.53936500	1.26119000	O	-5.44633200	-1.26762700	-2.04028400
H	2.73160300	4.54849800	1.30988600	O	-4.69803500	0.89066600	-1.89676400
C	3.15076300	2.49427500	0.80156800	C	-1.38301300	1.40271800	2.58373200
C	4.69873400	0.05151900	-0.12645300	H	-0.93454000	2.25685100	3.10549200
C	5.31056700	-1.13536000	-0.54669600	H	-2.27070200	1.09839300	3.15031200
H	6.34100400	-1.12593900	-0.88211100	C	-0.39444000	0.26649200	2.48003600
C	4.58090100	-2.32995200	-0.52911600	C	-0.83254000	-1.06936900	2.39680300
H	5.02041300	-3.26686200	-0.84665400	C	0.98996900	0.52168800	2.41972100
C	3.25450600	-2.30192500	-0.09066100	C	0.07683400	-2.12096800	2.22979900
H	2.66598600	-3.21055200	-0.06046000	H	-1.89642600	-1.29094500	2.46095600
C	3.36737000	0.01710700	0.29616600	C	1.91308000	-0.51693700	2.24973300
C	2.62193300	1.20200000	0.74969300	H	1.35015500	1.54587700	2.50493900
Cu	0.73830800	-0.91003300	0.82788900	C	1.44790800	-1.83364100	2.14227400
N	1.33760200	0.95971700	1.12949900	H	-0.26589500	-3.15104500	2.16285200
N	2.66681100	-1.15473600	0.31145000	H	2.98036600	-0.31919400	2.19695700
H	5.25028700	0.98367600	-0.13261600	O	2.40217500	-2.83502700	1.95813700
H	4.17082300	2.68728000	0.49142700	H	1.99612000	-3.71990400	1.85870000

CasIV-GY(3) $E_{\text{tot}} = -1606.501774$ a.u.				CasIV-YG (4) $E_{\text{tot}} = -1606.402694$ a.u.			
C	5.70061400	0.32524400	-0.22465100	C	5.24818600	-0.40239700	0.50601600
C	4.17859700	0.27931500	-0.03940700	C	4.08310000	-0.16811800	-0.38294400
H	3.71586300	1.13932400	-0.53285800	H	3.83353300	0.81641100	-0.76580400
C	3.88463700	0.32845000	1.48941500	C	2.26139600	-1.20095100	-1.62815800
H	4.40985000	-0.51758000	1.95396800	C	1.68180200	-2.54691100	-1.97407600
H	4.32842300	1.25673200	1.86864100	H	1.65668000	-3.18385800	-1.08444200
C	2.41175000	0.27948000	1.80296000	N	0.31671600	-2.40333400	-2.51848500
C	1.74255500	-0.94606000	1.97144700	N	3.37713000	-1.24710600	-0.79344100
H	2.30869700	-1.87580600	1.94065700	H	3.68831800	-2.15368500	-0.42365500
C	0.35452600	-0.99368600	2.17292300	O	1.83144800	-0.11417300	-2.08167100
H	-0.15922100	-1.94519500	2.30207600	O	5.99156200	0.61474200	0.78084800
C	-0.36980500	0.20553900	2.23186200	O	5.41549400	-1.61369000	0.93282700
C	0.27648100	1.44161200	2.08281200	H	-0.06099300	-3.32800900	-2.73552700
H	-0.30703700	2.35762700	2.12847000	H	0.33879000	-1.85234900	-3.38184500
C	1.65822400	1.46830100	1.86428000	C	-1.50366900	1.37694300	-2.38158800
H	2.16206200	2.42394500	1.73353300	H	-0.77855900	1.11159600	-3.14487400
C	2.42245400	-1.13377200	-1.05195200	C	-2.05842000	2.65960800	-2.32508400
C	1.95308200	-2.51661400	-1.43192300	H	-1.76148500	3.41270500	-3.04708000
H	2.03944400	-2.62572500	-2.51672900	C	-2.99595700	2.96000000	-1.32248000
H	2.56040500	-3.29275800	-0.95927300	C	-3.32925500	1.94316200	-0.40737000
N	0.52156300	-2.62494300	-1.04667400	C	-3.96645100	-0.36543800	1.43833200
N	3.66090000	-0.96353900	-0.61241600	C	-4.15156000	-1.45091400	2.31259500
H	4.30661000	-1.75599300	-0.57897700	C	-3.33059700	-2.57930800	2.13827800
O	1.58359900	-0.15910900	-1.17180300	H	-3.42576100	-3.43864100	2.79342700
O	6.25928100	1.47609800	-0.10213800	C	-2.38425000	-2.58618400	1.11277700
O	6.30782800	-0.79273700	-0.43042600	H	-1.73638100	-3.44152500	0.95354100
O	-1.74466300	0.23010000	2.47328400	C	-2.99837400	-0.42972300	0.43057400
H	-2.14176800	-0.66554200	2.47058400	C	-2.73651100	0.68191900	-0.51712400
H	0.42350900	-2.98576700	-0.09184900	Cu	-0.94852000	-1.48273200	-1.29297600
H	0.00647400	-3.23364900	-1.68709700	N	-1.83941200	0.40630800	-1.50651500
C	-0.35966300	2.17291700	-1.28193600	N	-2.22134900	-1.54037600	0.27069000
H	0.67551000	2.05471800	-1.58059500	C	-3.62872600	4.31506500	-1.21564000
C	-0.94458000	3.43357000	-1.15555700	H	-3.16947100	5.02694300	-1.90686400
H	-0.35936400	4.32081600	-1.36996000	H	-4.69935400	4.25737600	-1.44518300
C	-2.28538100	3.54254300	-0.74580400	H	-3.54035200	4.70774600	-0.19670700
C	-2.99546300	2.35363200	-0.49138200	C	-5.20402800	-1.41179800	3.37909500
C	-4.31805300	-0.32621400	0.05553700	H	-5.39245200	-0.38791800	3.71569500
C	-4.82876200	-1.60743900	0.32760500	H	-6.14997400	-1.80971000	2.99130900
C	-3.97064800	-2.70848300	0.14778800	H	-4.91971900	-2.02381400	4.24033000
H	-4.31432700	-3.71577500	0.35505400	H	-4.58541800	0.51800100	1.55670700
C	-2.66660200	-2.50247800	-0.29901400	H	-4.03818900	2.16031700	0.38537700
H	-1.99493700	-3.33942300	-0.44856200	C	1.36251100	-1.32061000	1.33878300
C	-3.00109600	-0.17858300	-0.37962200	H	0.49112600	-1.72205400	0.81513200
C	-2.36122600	1.12175600	-0.64069200	H	2.02473900	-2.02710500	1.83659700
Cu	-0.31221000	-0.78534300	-1.00930600	C	1.59714500	0.03783200	1.39985700
N	-1.05820100	1.04670300	-1.03281000	C	2.75112500	0.55670500	2.09026600
N	-2.19563900	-1.26461300	-0.56558100	C	0.73070200	0.96776200	0.71763400
H	-4.03253400	2.40387700	-0.17603700	C	2.99709100	1.91642200	2.13697200
H	-4.94820700	0.54545500	0.19961100	H	3.40091100	-0.14064300	2.61322300
C	-6.24299300	-1.79605200	0.78017400	C	0.98356100	2.31821700	0.74863000
H	-6.63687900	-0.88985100	1.24851900	H	-0.12439200	0.57614400	0.17017400
H	-6.88265900	-2.03139600	-0.07939800	C	2.11296900	2.79518900	1.46734600
H	-6.32533700	-2.62940400	1.48437500	H	3.85326500	2.31962200	2.66877600

C	-2.93848200	4.87704200	-0.56005300	H	0.34484100	3.03435400	0.24191500
H	-3.97578300	4.86127700	-0.90860400	O	2.29280500	4.14331300	1.47163100
H	-2.95905300	5.13973300	0.50480200	H	3.08301700	4.44296800	1.97043900
H	-2.39537800	5.66512400	-1.08832200	H	2.36153800	-3.02445200	-2.69532700
<b>CasVV-GY (5) : E<sub>tot</sub> : -1606.498781 a. u.</b>				<b>CasVV-YG (6) : E<sub>tot</sub> : -1606.495269 a. u.</b>			
C	5.56684600	-0.64208600	-0.47944300	C	3.91594100	2.09709700	0.82443600
C	4.09203300	-0.33285500	-0.18013500	C	3.62125000	3.22964300	-0.17881500
H	3.77779600	0.55601200	-0.73675800	H	4.11169800	2.98261600	-1.12474400
C	3.96094700	-0.06887000	1.34679600	C	1.41272700	2.44776400	-0.77583000
H	4.28605300	-0.97680300	1.87269500	C	-0.09348000	2.59452900	-0.78536500
H	4.66241200	0.73826400	1.59038500	H	-0.39212200	3.57400300	-1.17340900
C	2.55839800	0.31311100	1.73843600	N	-0.59977200	1.48983700	-1.64536400
C	1.62696200	-0.64786900	2.16710800	N	2.19195200	3.45100600	-0.39086900
H	1.94407600	-1.68072600	2.29990500	H	1.76751500	4.34351000	-0.14884100
C	0.28902400	-0.30028800	2.41273600	O	1.90852000	1.29389100	-1.07410100
H	-0.43372900	-1.04660900	2.73794900	O	5.06869500	1.53527300	0.69292800
C	-0.11209100	1.03228000	2.24080600	O	3.04543300	1.80674800	1.72381000
C	0.80943300	2.01690700	1.85350000	H	-0.37817100	1.65276400	-2.63277700
H	0.47604100	3.04582900	1.74426900	H	-1.61332300	1.38791800	-1.54501900
C	2.13319900	1.64915700	1.59892600	C	2.99041300	-1.35213700	-0.17076100
H	2.84820400	2.40331000	1.27512400	H	3.42768700	-0.42312400	-0.52633700
C	2.00369600	-1.48184200	-0.90094400	C	3.78514800	-2.35113600	0.41399600
C	1.31358400	-2.79880300	-1.15652800	C	3.13574600	-3.52745500	0.82468500
H	1.32201600	-2.98670100	-2.23406700	H	3.71429400	-4.32897400	1.27376200
H	1.82749600	-3.62636900	-0.66178400	C	1.75297800	-3.67401700	0.66234900
N	-0.09371900	-2.66984500	-0.70108800	C	-1.28119300	-3.67994700	0.24131600
N	3.28685100	-1.49081600	-0.57158300	C	-2.65531400	-3.55036400	0.02042600
H	3.79644300	-2.37894000	-0.54311700	H	-3.32781800	-4.35537900	0.30101900
O	1.30718900	-0.40138600	-1.02918500	C	-3.17736200	-2.38042900	-0.55873000
O	6.37641000	0.35522400	-0.48580200	C	-2.26311200	-1.37471200	-0.90481700
O	5.89024800	-1.87876500	-0.64676900	H	-2.61879500	-0.45876900	-1.36718400
O	-1.42864000	1.44654700	2.45332000	C	-0.43092100	-2.63190500	-0.12248700
H	-2.01782300	0.70526000	2.70103200	C	1.02448000	-2.63206400	0.08400300
H	-0.19089000	-2.94562800	0.28194600	Cu	0.45736100	-0.11313400	-1.05215200
H	-0.71889800	-3.24455200	-1.27081900	N	1.66078700	-1.49912400	-0.32298500
C	-0.29112100	2.17619600	-1.16463500	N	-0.93745000	-1.50314700	-0.69700200
H	0.73058400	1.89434900	-1.40082900	C	5.25706000	-2.13640900	0.59911000
C	-0.68244700	3.52208200	-1.12469500	H	5.45100900	-1.59674800	1.53456300
C	-2.03043800	3.79177400	-0.82797400	H	5.79098800	-3.08996400	0.64733600
H	-2.37347400	4.82134900	-0.78972600	H	5.67539100	-1.53702600	-0.21588200
C	-2.92464900	2.74818400	-0.57197900	C	-4.64632600	-2.19728600	-0.79137800
C	-4.62992700	0.28181300	0.00993500	H	-5.19866600	-2.23997400	0.15497700
C	-5.29998800	-0.91430400	0.27589200	H	-4.85743600	-1.23669100	-1.27195500
H	-6.35792500	-0.90183700	0.51972700	H	-5.04133500	-2.99535900	-1.43020000
C	-4.61404100	-2.14109100	0.22974100	C	-0.58165900	2.41887000	0.67852700
C	-3.24813800	-2.09976400	-0.08372400	H	-0.37873900	3.36420000	1.19665100
H	-2.67577800	-3.02078100	-0.12364400	H	0.02924000	1.64510600	1.16523500
C	-3.26805100	0.24544300	-0.30400500	C	-2.03749000	2.03179700	0.78550100
C	-2.45496500	1.43172400	-0.60402800	C	-3.05016300	2.79346300	0.17190000
Cu	-0.65799100	-0.73447500	-0.78481100	C	-2.40512000	0.87122800	1.49164100
N	-1.15565200	1.17467600	-0.91239900	C	-4.39305700	2.40402000	0.24890100
N	-2.60192700	-0.94384400	-0.34363000	H	-2.79037300	3.69690400	-0.37655200
H	-5.15989000	1.22592500	0.04609400	C	-3.74276500	0.47248000	1.58666200
H	-3.96056500	2.96036300	-0.33598700	H	-1.63308100	0.27097700	1.96907800

C	0.31523300	4.61553900	-1.35682200	C	-4.73076000	1.23944600	0.95623900
H	1.31667100	4.20789400	-1.52547600	H	-5.17266200	2.99228700	-0.22877300
H	0.03968800	5.22503300	-2.22478600	H	-4.02539500	-0.42422400	2.13099300
H	0.35852400	5.28632000	-0.49083700	O	-6.04856100	0.79281600	1.06563100
C	-5.30466500	-3.44381200	0.49728700	H	-6.68387400	1.38962500	0.62102300
H	-6.09290700	-3.62209400	-0.24281300	H	4.06050300	4.15475600	0.20112300
H	-4.60343200	-4.28222800	0.45894800	H	-0.88097000	-4.57946900	0.69385000
H	-5.78248400	-3.43678000	1.48296000	H	1.25752600	-4.58275700	0.98281700
<b>CasVII-GY (7) : E<sub>tot</sub> : -1604.101645 a. u.</b>				<b>CasVII-YG (8) : E<sub>tot</sub> : -1604.090493 a. u.</b>			
C	-5.59912600	0.57571000	0.27353500	C	-2.23103600	2.31826800	-0.13301900
C	-4.07696700	0.48756600	0.09353100	H	-1.23003700	2.67131600	-0.36151300
H	-3.58499200	1.25026400	0.70488300	C	-3.28410900	3.21553100	0.15377100
C	-3.76285400	0.73788000	-1.41033400	H	-3.08441200	4.27945000	0.14417000
H	-4.33118700	0.00041200	-1.99384800	C	-4.55051800	2.72173900	0.44084800
H	-4.15049300	1.73514500	-1.65037800	H	-5.37310300	3.39443900	0.66248800
C	-2.29345900	0.64952100	-1.73065700	C	-4.77379100	1.32056900	0.44730100
C	-1.70531100	-0.57080700	-2.10912500	C	-6.04190100	0.70487100	0.73597900
H	-2.33097200	-1.45367400	-2.22825200	H	-6.88673800	1.34754600	0.96432100
C	-0.32440200	-0.67161100	-2.33590000	C	-6.17972700	-0.66016500	0.72392300
H	0.12655800	-1.61871500	-2.62683900	H	-7.13657100	-1.12549300	0.94104500
C	0.47664000	0.47131900	-2.20009800	C	-5.06158400	-1.51503600	0.42264700
C	-0.08721600	1.70284600	-1.83515400	C	-5.13192600	-2.93116100	0.39326400
H	0.55380600	2.57572200	-1.74190000	H	-6.07476300	-3.42477600	0.60753700
C	-1.46441300	1.78084500	-1.59882600	C	-3.99444300	-3.66778900	0.09010800
H	-1.90577900	2.73141000	-1.30551400	H	-4.01673300	-4.74961200	0.05910300
C	-2.40888800	-1.13887100	0.92171100	C	-2.78037000	-3.00024600	-0.18319000
C	-2.02431100	-2.58062100	1.14598500	H	-1.88287100	-3.55924700	-0.42203500
H	-2.14973200	-2.80888700	2.20838100	C	-3.81257400	-0.92652200	0.13720300
H	-2.65911600	-3.26043200	0.57216800	C	-3.67147300	0.49453100	0.14954600
N	-0.58884900	-2.72736700	0.78734500	Cu	-1.11436200	-0.46507800	-0.49535300
N	-3.62828300	-0.84620600	0.49626300	N	-2.43286900	0.99504300	-0.13445500
H	-4.32199500	-1.58767800	0.37027900	N	-2.69625000	-1.66355400	-0.15838700
O	-1.51905300	-0.23295400	1.16305100	C	1.52352000	0.35843100	-0.65805300
O	-6.11165700	1.75402200	0.26850100	C	1.66351700	-1.10393000	-0.27241600
O	-6.25157800	-0.53236900	0.35975500	H	1.70312700	-1.13028800	0.82396600
O	1.84941200	0.44452900	-2.45213600	N	0.39417900	-1.77617200	-0.67485100
H	2.18344300	-0.46633300	-2.59039000	N	2.58084100	1.15772800	-0.74987100
H	-0.47982200	-2.98080700	-0.20030500	H	3.51230700	0.78021200	-0.58121900
H	-0.12906000	-3.43455100	1.36538100	O	0.33876200	0.82959800	-0.86004300
C	0.53900600	1.99821100	1.61321500	H	0.23835600	-2.61218400	-0.10481900
H	-0.49250300	1.92889500	1.94026700	H	0.42832100	-2.05595000	-1.66197700
C	1.22569700	3.23258000	1.59234200	C	2.41471900	2.58842800	-0.99321100
H	0.71098500	4.12608800	1.92214700	H	3.40671900	3.03938700	-1.07052000
C	2.53923600	3.28216800	1.14159200	H	1.89394800	2.75389200	-1.94100200
C	3.17846800	2.09199200	0.70894500	C	1.63435700	3.31914400	0.11389800
C	4.52117600	2.03744400	0.19312800	O	1.54758600	2.79295100	1.28243500
H	5.09302200	2.95940200	0.14845200	O	1.13986000	4.45835500	-0.23294200
C	5.06093700	0.85259400	-0.23959300	C	2.88905000	-1.83811100	-0.84955100
H	6.07077400	0.81274800	-0.63676300	H	2.71737900	-2.90525100	-0.65524300
C	4.30207200	-0.36952100	-0.18817000	H	2.90657200	-1.70365000	-1.93865800
C	4.77919800	-1.61835600	-0.65880100	C	4.21375500	-1.42351000	-0.24694100
C	3.95506300	-2.73549300	-0.59799900	C	5.26998300	-0.99067700	-1.06736000
H	4.28939400	-3.70092500	-0.95575600	C	4.42751900	-1.49110600	1.14517000
C	2.65416300	-2.61552100	-0.06324400	C	6.51143000	-0.63209200	-0.52328200



H	1.99660500	-3.47549500	-0.00915500	H	5.11971500	-0.93389700	-2.14292900
C	2.99041800	-0.33448800	0.32950200	C	5.65743700	-1.13406800	1.70376200
C	2.42776200	0.90059400	0.77435900	H	3.62954700	-1.83675000	1.79888300
Cu	0.33476000	-0.94056800	0.99094500	C	6.69607900	-0.70629300	0.86337500
N	1.13763400	0.86713200	1.22194100	H	7.32575600	-0.29926200	-1.16209400
N	2.19171000	-1.44382500	0.39408700	H	5.82641000	-1.18549800	2.77503400
H	3.08153800	4.22200100	1.10865300	O	7.90622600	-0.36522800	1.46976000
H	5.78165700	-1.68796500	-1.06939000	H	8.58531000	-0.09868200	0.81734000
<b>CasII-GY (9) <math>E_{\text{tot}} = -1682.668648</math> a. u.</b>				<b>CasII-YG (10) <math>E_{\text{tot}} = -1682.661466</math> a. u.</b>			
C	-0.22839500	2.08468900	-1.31703000	C	2.27737500	-2.08506400	0.88532800
H	0.81379700	2.06076900	-1.61630800	H	1.54344000	-2.87856800	0.96495700
C	-0.92483600	3.30059800	-1.17174400	C	3.59973900	-2.26378700	1.33441300
H	-0.40751400	4.23050600	-1.37949900	H	3.88203700	-3.21676800	1.76717000
C	-2.25730500	3.31756100	-0.75865400	C	4.53878700	-1.23864100	1.22422100
C	-2.89262500	2.06217400	-0.49652800	C	4.11249300	-0.00144300	0.64424100
C	-4.25105900	1.92209800	-0.04524400	C	4.96630400	1.14188200	0.47017600
H	-4.85115700	2.81440000	0.10238700	H	6.00058000	1.08051300	0.79333700
C	-4.79356600	0.68631500	0.20746300	C	4.49480900	2.30204500	-0.09208400
H	-5.81900200	0.60930800	0.55472200	H	5.15900700	3.15214900	-0.21040900
C	-4.02772700	-0.51774200	0.02861000	C	3.13069700	2.41912600	-0.53153700
C	-4.52224500	-1.82918900	0.31297200	C	2.58198300	3.60216900	-1.11970500
C	-3.65626800	-2.90590400	0.12086900	C	1.24098600	3.57517800	-1.49970100
H	-3.98804300	-3.91645900	0.33059300	H	0.78360600	4.44908000	-1.94948300
C	-2.34250500	-2.70314900	-0.34239000	C	0.45905900	2.41947500	-1.31227600
H	-1.67343200	-3.54336100	-0.48896000	H	-0.58040500	2.40898900	-1.61844300
C	-2.69975200	-0.39771000	-0.42886700	C	2.28178500	1.30463100	-0.37294300
C	-2.13270100	0.89026000	-0.68340400	C	2.77288200	0.09899100	0.21865200
Cu	-0.00774800	-0.89861000	-1.04718800	Cu	0.09205800	-0.47154700	-0.39321200
N	-0.82570800	0.91060900	-1.08372800	N	1.87752500	-0.92907000	0.34244500
N	-1.87826600	-1.47767000	-0.62088000	N	0.96730300	1.30815500	-0.76382700
C	5.88796800	0.60408300	-0.17059300	C	-1.38684000	-5.33796300	-0.93504000
C	4.36710000	0.46909700	-0.01918800	C	-2.04834200	-4.74060900	0.31814500
H	3.86462300	1.27894400	-0.55669900	H	-1.28499000	-4.67310500	1.09972900
C	4.03198500	0.55772500	1.49969000	C	-1.95669000	-2.32854000	-0.06741200
H	4.62473400	-0.21302200	2.01181900	C	-2.67920900	-1.01408800	-0.26136200
H	4.37955500	1.53933800	1.84333100	H	-3.63987700	-1.16954100	-0.76641700
C	2.56510100	0.37982000	1.79755700	N	-1.77902400	-0.14730100	-1.06474900
C	2.01511300	-0.90340100	1.96990200	N	-2.66601000	-3.43744000	0.10837200
H	2.66745200	-1.77503800	1.94738700	H	-3.67765900	-3.37907300	0.01432100
C	0.63796100	-1.08287300	2.16615500	O	-0.66723900	-2.31515400	-0.01560600
H	0.21490800	-2.07799100	2.29495500	O	-0.79734200	-6.46788000	-0.73896200
C	-0.19819000	0.04189400	2.22045900	O	-1.45661700	-4.71599300	-2.05587400
C	0.32698400	1.33330000	2.06771800	H	-2.06213500	0.83423700	-0.97800200
H	-0.33988500	2.19078000	2.11034000	H	-1.78769000	-0.40895000	-2.05584200
C	1.70088400	1.49137500	1.85102400	H	-2.81439300	-5.43728000	0.66492900
H	2.11174900	2.49032800	1.71867600	C	3.41706200	4.82710300	-1.31805900
C	2.73285100	-1.08671200	-1.01786800	H	3.79508400	5.20125300	-0.35918800
C	2.36091200	-2.50426500	-1.37896900	H	4.29129800	4.60838100	-1.94240700
H	2.51340700	-2.63737100	-2.45393000	H	2.83842200	5.62111000	-1.79583800
H	2.98826100	-3.22802200	-0.85242100	C	5.94540000	-1.42751800	1.69706900
N	0.91919600	-2.69442300	-1.06684900	H	6.65735400	-1.28833600	0.87503000
N	3.94826600	-0.82435800	-0.56133100	H	6.20050700	-0.69294300	2.46986200
H	4.64881900	-1.56689300	-0.49643900	H	6.08646300	-2.42856100	2.11120500
O	1.83963200	-0.16638200	-1.17365300	C	-2.92465600	-0.37627700	1.12900700

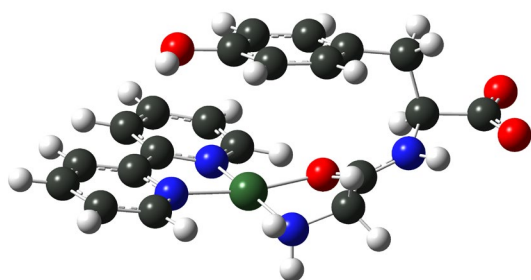
O	6.37640100	1.78702600	-0.05421900	H	-3.62885700	-1.02420800	1.66368600
O	6.56439500	-0.47877600	-0.34735900	H	-1.97737300	-0.37000600	1.68538000
O	-1.56978900	-0.06843500	2.45828700	C	-3.46541800	1.02517500	1.00378200
H	-1.87611200	-0.99891400	2.43970600	C	-2.62397100	2.13665800	1.18559800
H	0.79223000	-3.07042400	-0.12139000	C	-4.81239800	1.24587900	0.65603600
H	0.46886100	-3.32046900	-1.73804600	C	-3.10724300	3.44328600	1.03216300
C	-5.91679100	-2.04036100	0.81145600	H	-1.58270600	1.97927200	1.46225200
H	-6.08125800	-1.50620100	1.75476000	C	-5.31129200	2.54228000	0.50043200
H	-6.65193300	-1.65593800	0.09465900	H	-5.47354100	0.39355800	0.51336400
H	-6.11528400	-3.10196700	0.97608400	C	-4.45209700	3.63556500	0.68822700
C	-2.99831400	4.60618300	-0.59128200	H	-2.45464200	4.30077200	1.17676900
H	-3.89092600	4.62885600	-1.22766300	H	-6.34987000	2.72100200	0.23917300
H	-3.34096600	4.72890400	0.44302000	O	-4.99849100	4.90919100	0.52050800
H	-2.36520900	5.45787400	-0.85025100	H	-4.34160900	5.61708300	0.67758500
<b>CasVI-GY (11): -1682.655996 a. u.</b>				<b>CasVI-YG (12): -1682.660794 a. u.</b>			
C	-5.99078100	0.10544500	0.96867100	C	5.35668500	1.52848400	-1.04801400
C	-4.54004400	0.26032000	0.49160200	C	4.96830400	1.17385400	0.39751700
H	-3.94620300	0.75359300	1.26772700	H	4.19751100	1.88169400	0.72167500
C	-4.55161500	1.13607400	-0.79244900	C	3.31491600	-0.59520100	0.10919200
H	-5.12813000	0.59955700	-1.55820100	C	2.88008300	-2.02609300	0.34653600
H	-5.08624700	2.06126500	-0.54455800	H	3.74318700	-2.69112400	0.23516200
C	-3.15816500	1.44297700	-1.27080500	N	1.84021900	-2.33013400	-0.67543400
C	-2.48669900	0.59656500	-2.17114800	N	4.49377000	-0.19306700	0.57362000
H	-3.01472700	-0.24720400	-2.61136600	H	5.10150500	-0.88036100	1.01388200
C	-1.14040900	0.81398600	-2.50166500	O	2.51497800	0.20727000	-0.50555200
H	-0.61746600	0.14793400	-3.18435700	O	5.64199700	2.77205800	-1.23537200
C	-0.46870500	1.90806500	-1.93839000	O	5.38700900	0.61113400	-1.94552000
C	-1.13526800	2.80254300	-1.08924900	H	1.26312100	-3.12361300	-0.38129000
H	-0.60375000	3.66641400	-0.70097000	H	2.26459700	-2.54564300	-1.58278400
C	-2.47007200	2.55697100	-0.75347700	C	0.25752700	2.26073600	-0.42050600
H	-2.98646900	3.23032100	-0.07253700	H	1.33673800	2.36217700	-0.43637600
C	-2.71513100	-1.42055200	0.27642300	C	-0.58576500	3.34902100	-0.11783500
C	-2.34075600	-2.77709700	-0.27107000	H	-0.14607300	4.31624100	0.09023400
H	-2.98974100	-3.54964200	0.15139100	C	-1.96260300	3.16820000	-0.09018300
H	-2.50958000	-2.76343800	-1.35214200	H	-2.59909100	4.01406500	0.14221100
N	-0.91004500	-3.05591500	-0.00399200	C	-2.52742400	1.89225500	-0.36377500
N	-3.99209500	-1.06584800	0.20311200	C	-3.95041600	1.59753400	-0.33945300
H	-4.68542600	-1.74478900	-0.12291100	C	-4.39550800	0.31933300	-0.64555300
O	-1.79770900	-0.65958400	0.76902300	C	-3.44603400	-0.73522300	-0.94623000
O	-6.49804900	1.10223300	1.60146100	C	-3.81773900	-2.07996800	-1.21568000
O	-6.60762200	-0.98131100	0.65169300	H	-4.86293100	-2.36911400	-1.21461600
O	0.88251200	2.15999200	-2.18797200	C	-2.84117800	-3.03297800	-1.47356000
H	1.27790900	1.49128000	-2.78287700	H	-3.10387100	-4.06313300	-1.67824100
H	-0.47526000	-3.50182300	-0.81421600	C	-1.48077000	-2.66024200	-1.47018900
H	-0.78939700	-3.66385900	0.81097900	H	-0.70535600	-3.39023300	-1.67111600
C	0.32892300	1.47861500	1.40663000	C	-2.06536800	-0.45411700	-0.95553300
H	-0.73407000	1.43163900	1.61497200	C	-1.60718500	0.86536200	-0.66741500
C	1.07397300	2.65945400	1.61820600	Cu	0.73374600	-0.65773000	-0.90561300
H	0.56798700	3.54009900	1.99378500	N	-0.25541200	1.05763400	-0.69663000
C	2.43178700	2.67765600	1.33430900	N	-1.11010300	-1.39817500	-1.22278100
H	3.00118600	3.58703800	1.49190500	C	-5.85667000	-0.03866900	-0.69038700
C	3.07525800	1.50651000	0.84609500	H	-6.11075000	-0.50500600	-1.64988900
C	4.48651700	1.42983600	0.53373700	H	-6.11056100	-0.76196600	0.09492800
C	5.04045600	0.24172400	0.07777600	H	-6.50464300	0.82964200	-0.56970000

C	4.20152700	-0.93260600	-0.08901000	C	-4.92228300	2.69275300	0.02107500
C	4.66747600	-2.20103500	-0.53128200	H	-5.40193200	3.10502600	-0.87569500
H	5.71157200	-2.35094600	-0.77880100	H	-5.71596300	2.31946000	0.67416200
C	3.78998400	-3.26927200	-0.65038100	H	-4.44089800	3.52064800	0.54554700
H	4.13535700	-4.24057500	-0.98067800	C	2.32230400	-2.21421800	1.78313500
C	2.42594200	-3.09395000	-0.34409700	H	2.11155300	-3.28460200	1.89542800
H	1.73287500	-3.92159700	-0.43190600	H	3.13333300	-1.96404200	2.47724800
C	2.81939700	-0.85058700	0.20008000	C	1.08281500	-1.40673300	2.08811100
C	2.25836400	0.37362700	0.66790800	C	-0.19532300	-1.97237300	1.92553100
Cu	0.05851300	-1.34869900	0.44999000	C	1.17082700	-0.06202800	2.50436000
N	0.91899800	0.37120200	0.94744000	C	-1.35810700	-1.22347400	2.15055500
N	1.95735900	-1.90922200	0.06586800	H	-0.28347100	-3.01232300	1.61464600
C	5.30692900	2.67576200	0.72800900	C	0.02083900	0.70206200	2.73097300
H	4.90056200	3.50660000	0.13836700	H	2.14984400	0.39185100	2.65181600
H	5.29214400	2.99236100	1.77853400	C	-1.24025500	0.11838600	2.53987600
H	6.34878300	2.54097800	0.46332200	H	-2.34331200	-1.66953000	2.02616600
C	6.51250700	0.16572500	-0.24310500	H	0.08636400	1.73797700	3.05133100
H	6.77640300	0.87823200	-1.03307700	O	-2.35584500	0.92263800	2.77859500
H	7.11796400	0.41908600	0.63458800	H	-3.19611800	0.47376800	2.55157200
H	6.82588800	-0.82294200	-0.58023800	H	5.84410400	1.32373300	1.03253300
<b>CasVIII-GY (13) : E<sub>tot</sub> : -1761.227525 a. u.</b>				<b>CasVIII-YG (14) : E<sub>tot</sub> : -1761.230225 a. u.</b>			
C	6.01431800	-0.03771400	-0.13632200	C	5.50737700	0.12010800	-1.40678700
C	4.48930700	-0.03041300	0.03088100	C	5.13852600	0.17033200	0.08578000
H	4.05686900	0.80160800	-0.53353900	H	4.54934800	1.07854000	0.25543600
C	4.17942000	0.14725200	1.54548600	C	3.13434700	-1.21177400	0.22828900
H	4.66602300	-0.67940600	2.08146400	C	2.43045800	-2.43559600	0.77545400
H	4.65511500	1.08439500	1.85899600	H	3.12756500	-3.28053600	0.78827600
C	2.70301100	0.17890800	1.84389400	N	1.28342300	-2.71191200	-0.13272900
C	1.99263400	-1.00187900	2.12562800	N	4.40301100	-0.99425400	0.56158600
H	2.52916500	-1.94657400	2.19284500	H	4.88488700	-1.69837200	1.11651700
C	0.60387300	-0.98463800	2.32754900	O	2.47305900	-0.38904100	-0.51124700
H	0.05910800	-1.90041200	2.54875500	O	6.08276400	1.18560700	-1.84996500
C	-0.07991400	0.23891900	2.26701100	O	5.24340000	-0.92945400	-2.09745300
C	0.60978900	1.43298400	2.01151000	H	0.56557700	-3.26559100	0.34519800
H	0.05974700	2.37005600	1.98088900	H	1.58874600	-3.21904100	-0.96910200
C	1.99100100	1.39362700	1.79413400	C	0.64170500	2.07761900	-0.74703600
H	2.52654600	2.31668200	1.57769100	H	1.72199100	1.97010400	-0.78723100
C	2.70709000	-1.45749100	-0.91254700	C	0.05753000	3.35849700	-0.60318200
C	2.19786500	-2.85952500	-1.14970300	C	-1.34178900	3.46129800	-0.54256200
H	2.73112000	-3.30577000	-1.99419100	C	-2.11856400	2.26544500	-0.63353400
H	2.41069300	-3.46974900	-0.26790300	C	-3.55592200	2.23379900	-0.56844600
N	0.73305200	-2.82576700	-1.39914000	H	-4.09966600	3.16813200	-0.47145700
N	3.94237200	-1.29838300	-0.45502100	C	-4.24831800	1.05040300	-0.61749000
H	4.55635600	-2.10833000	-0.34126500	H	-5.33147100	1.07027600	-0.56432600
O	1.92514900	-0.45774700	-1.14414200	C	-3.57292800	-0.21853900	-0.73102300
O	6.60103300	1.10497400	-0.08964000	C	-4.22868700	-1.48752800	-0.76073100
O	6.59444500	-1.18248300	-0.25234100	C	-3.43843600	-2.64825200	-0.85653100
O	-1.45612000	0.33354400	2.48611100	C	-2.03462700	-2.52356300	-0.91456600
H	-1.89079200	-0.54313800	2.52945900	H	-1.41571400	-3.41320100	-0.98339300
H	0.25343300	-3.50684700	-0.80773300	C	-2.16287200	-0.19836400	-0.80299100
H	0.51314600	-3.02771200	-2.37778900	C	-1.44476600	1.03711600	-0.75921400
C	0.15563600	2.02753600	-1.19560300	Cu	0.53990000	-0.92684500	-0.73276100
H	1.19087700	1.88637300	-1.49184500	N	-0.08376900	0.95785800	-0.82559800
C	-0.35773200	3.33024600	-0.99796400	N	-1.41404800	-1.33676300	-0.89489900

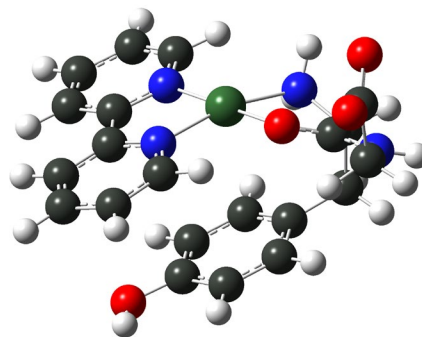
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C	-2.48252400	2.30187400	-0.39609600	H	2.01252000	4.25032100	-0.58137100
C	-3.85021300	2.31115000	0.05357400	H	0.76050800	5.27750600	-1.30047600
H	-4.33545500	3.26399000	0.23987200	H	0.83139900	5.07405100	0.45150600
C	-4.54393000	1.14428900	0.25564800	C	-2.03279500	4.77700500	-0.35485000
H	-5.57235700	1.18607900	0.59951600	H	-2.75053800	4.96175300	-1.16272100
C	-3.93857700	-0.14268300	0.02561100	H	-2.60226900	4.77597800	0.58407800
C	-4.60777700	-1.38673800	0.24007500	H	-1.33133100	5.61201100	-0.32564400
C	-3.89924000	-2.57556500	-0.00022200	C	-4.05071000	-4.01726500	-0.89777300
C	-2.55632900	-2.49487500	-0.43477000	H	-3.28095600	-4.78828700	-0.99464300
H	-2.00260300	-3.41038800	-0.61679500	H	-4.62756000	-4.22144800	0.01277500
C	-2.60279200	-0.16602300	-0.41941400	H	-4.74249100	-4.11671400	-1.74301800
C	-1.88190000	1.04996500	-0.62733700	C	-5.71860300	-1.62460300	-0.69957800
Cu	0.00542000	-0.96444000	-1.07358900	H	-6.10024500	-2.02352300	-1.64829900
N	-0.58516600	0.92706100	-1.02998500	H	-6.00577700	-2.34042800	0.07943800
N	-1.92275800	-1.33256200	-0.64120300	H	-6.23002700	-0.68220000	-0.50075500
C	-4.51037000	-3.93561000	0.18761900	H	6.06122600	0.26130200	0.66283100
H	-3.79292800	-4.72174100	-0.06469500	C	1.94737300	-2.20140300	2.23156500
H	-4.83166000	-4.09010000	1.22408600	H	1.51004600	-3.14954000	2.56777300
H	-5.39316900	-4.06561200	-0.44873100	H	2.83963400	-2.01527200	2.84087200
C	-6.02967200	-1.39439200	0.71144000	C	0.94699300	-1.08078000	2.38603000
H	-6.67686800	-0.87744800	-0.00737400	C	-0.43701900	-1.34211500	2.34691800
H	-6.41430500	-2.40622300	0.84650600	C	1.37047500	0.25483800	2.53026000
H	-6.12585700	-0.86343200	1.66593800	C	-1.37576900	-0.30651100	2.42893000
C	-2.30564500	4.82572700	-0.35283700	H	-0.78500200	-2.36950500	2.24965200
H	-3.20036400	4.96255800	-0.97164700	C	0.44613400	1.30365100	2.61183900
H	-2.62353000	4.92259100	0.69253500	H	2.43476800	0.47945100	2.58217800
H	-1.61153000	5.63819600	-0.57238200	C	-0.92579500	1.01494500	2.54852700
C	0.56439100	4.49930300	-1.19930100	H	-2.44340100	-0.50956500	2.40395900
H	1.55780200	4.15952800	-1.50684500	H	0.77783200	2.33402300	2.72306000
H	0.18670800	5.18337300	-1.96805000	O	-1.89638900	2.01461100	2.62904200
H	0.67630900	5.07878200	-0.27514400	H	-1.50449400	2.91146100	2.65726400

## GY derivatives

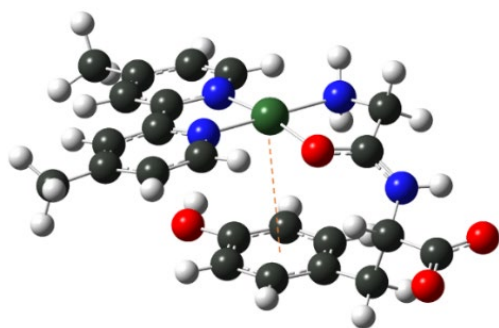
## YG derivatives



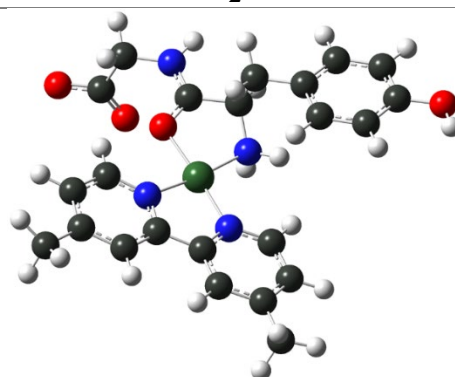
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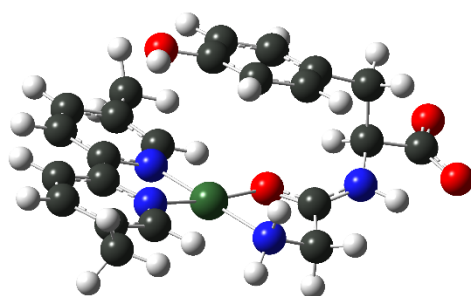
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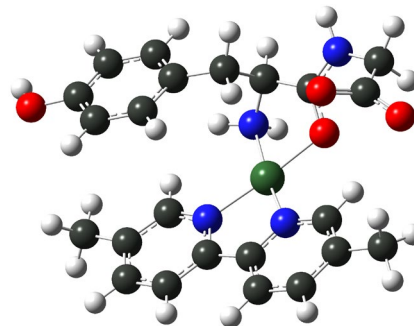
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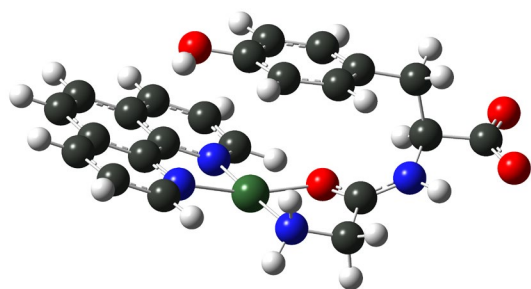
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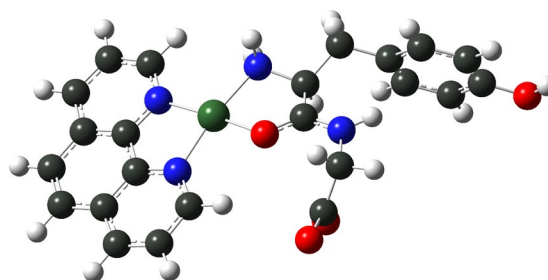
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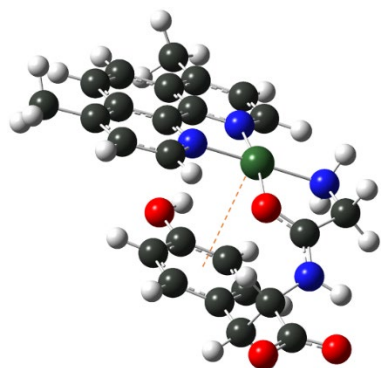
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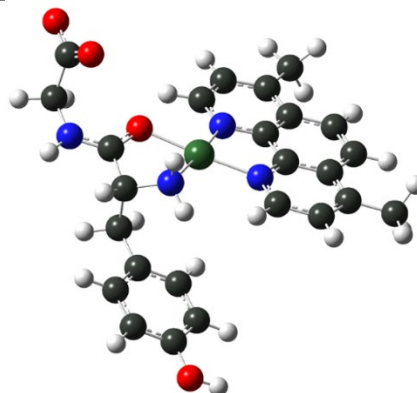
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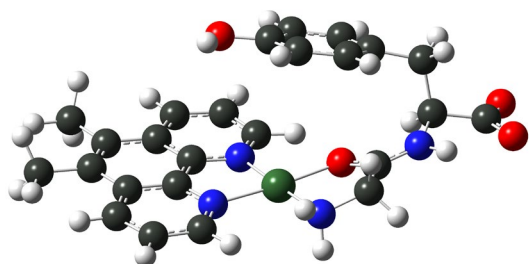
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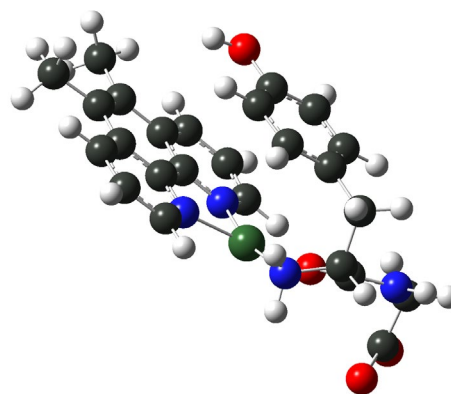
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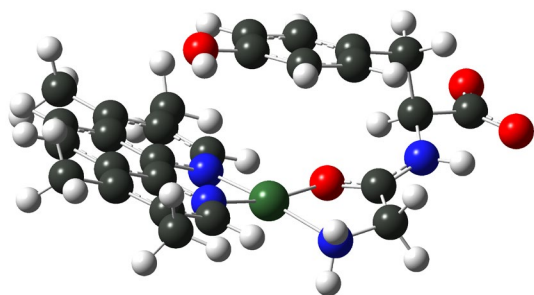
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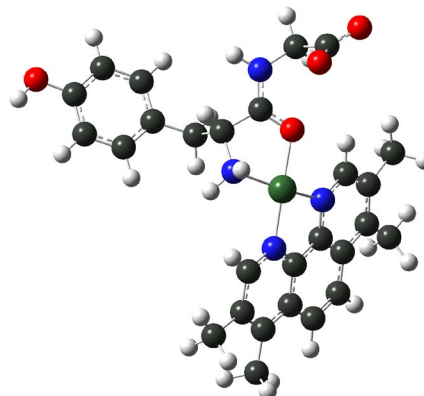
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13



14

**Scheme S1.** Optimized M06/LanL2DZ structures of Casiopeinas®

**Table S3.** Binding affinities, inhibition constants and potential interactions for the M<sup>pro</sup>-Cas adducts.

Compound	$\Delta G_u$ (Kcal/mol)	$K_i$ ( $\mu$ M) [log Ki]	AA's (M <sup>pro</sup> -Cas)
1	-7.75	(2.07) [0.32]	His41, Tyr54, Gly143, Cys145, His163, Met165, Glu166, Gln189
2	-7.84	(1.80) [0.26]	His41, Met49, Phe140, Gly143, Cys145, Met165, Gln189
3	-8.38	(0.72) [-0.15]	Thr26, His41, Met49, Asn142, Gly143, Ser144, Cys145, Met165
4	-7.26	(4.79) [0.68]	His41, Met49, Pro52, Ser144, Cys145, Met165, Arg188, Gln189
5	-8.41	(0.69) [-0.16]	His41, Tyr54, Cys145, Gly143, His163, Met165, Glu166, His172, Gln189
6	-8.08	(1.19) [0.07]	His41, Leu141, Gly143, Ser144, Cys145, His164, Met165, Glu166
7	-7.25	(4.82) [0.68]	His41, Met49, Gly143, Cys145, His163, Met165, Glu166
8	-8.21	(0.72) [-0.14]	Cys44, Met49, Cys145, His163, His164, Glu166, Thr190, Gln192
9	-8.07	(1.21) [0.08]	His41, Met49, Asn142, Cys145, His163, Met165, Glu166
10	-9.02	(0.25) [-0.61]	His41, Met49, Phe140, Cys145, Met165, Glu166, Gln189
11	-7.48	(3.29) [0.52]	Met49, Cys145, His163, Met165, Glu166, Asp187, Arg188
12	-8.21	(0.96) [-0.02]	Thr26, His41, Leu141, Asn142, Gly143, Cys145, Met165, Glu166
13	-6.62	(13.98) [1.15]	His41, Met49, Leu141, Gly143, Cys145, Met165, Glu166, Gln189
14	-9.57	(0.10) [-1.01]	Leu27, His41, Met49, Tyr54, Gly143, Cys145, His163, Met165, Glu166, Asp187, Arg188, Gln189, Thr190, Gln192
Boceprevir	-8.44	(0.65*) [-0.19]	His41, Met49, Asn142, Ser144, Gly143, Cys145, His164, Met165, Glu166, Gln189
Remdesevir	-7.17	(5.53) [0.74]	His 41, Met49, Leu141, Gly143, His164, Met165, Glu166.

**Table S4.** Binding affinities, inhibitions constants and potential interactions for the Spike-ACE2 RBD domain C-terminal-Cas-adducts.

Compound	$\Delta G_u$ (Kcal/mol)	$K_i$ ( $\mu$ M) [log $K_i$ ]	AA's (Spike-ACE2 complex-Cas)	
			Spike Chain E	ACE2 Chain B
1	-4.44	(559.58) [2.75]	Ala475, Gly476, Ser477, Thr478, Cys480, Phe486, Cys488	Ile21, Gln24
2	-4.08	(1020.00) [3.01]	Ser477, Phe486	Ile21, Met82, Glu87,
3	-4.09	(1010.00) [3.00]	Ala475, Gly476, Ser477, Cys480, Phe486, Asn487, Cys488	Ile21, Gln24, Pro84
4	-5.01	(214.45) [2.33]	Ala475, Ser477, Cys480, Cys488	Ile21, Pro84, Glu87
5	-4.61	(421.15) [2.62]	Ala475, Gly476, Ser477, Thr478, Cys480, Phe486, Asn487, Cys488	Ile21, Pro84
6	-6.69	(12.47) [1.10]	Ala475A, Thr478, Cys480, Phe486, Asn487, Cys488	Ile21, Met82
7	-5.28	(133.98) [2.13]	Ala475, Gly476, Thr478, Cys480, Phe486, Asn487, Cys488	Ile21, Met82
8	-4.28	(725.61) [2.86]	Ala475, Thr478, Phe486, Asn487	Met82
9	-5.27	(137.53) [2.14]	Thr478, Phe486, Asn487	Ile21, Gln24, Tyr83, Pro84, Glu87
10	-2.64	(11650.00) [4.07]	Ala475, Ser477, Thr478, Phe486	Ile21, Gln24, Pro84
11	-4.48	(518.31) [2.71]	Ser477, Phe486, Asn487	Ile21, Pro84
12	-1.24	(12327.00) [4.09]	Phe486	Ile21, Met82, Pro84, Glu87
13	-3.15	(4910.00) [3.69]	Phe486	Ile21, Met82, Pro84, Glu87
14	-3.55	(2500.00) [3.39]	Ala475, Thr478, Cys480, Phe486, Cys488	Ile21, Met82, Pro84
Boceprevir	-1.98	(35280) [4.55]	Thr478, Phe486	Gln24, Ala25, Met82, Tyr83, Pro84, Glu87, Ile88
Remdesivir	>0	---	---	---



**Table S5.** Binding affinities, inhibitions constants and potential interactions for the Spike-ACE2 RBD domain Middle region-Cas-adducts.

Compound	$\Delta G_u$ (Kcal/mol)	$K_i$ ( $\mu$ M) [log Ki]	AA's (Spike-ACE2 complex-Cas)	
			Spike Chain E	ACE2 Chain B
1	-5.73	(62.91) [1.79]	Asp405,Gly416, Lys417	Pro389
2	-5.79	(56.6) [1.75]	Lys417	Asp30, Gln388, Pro389
3	-6.45	(18.75) [1.27]	Arg402, Asp405, Glu406	Asn33, Glu37, Ala387, Gln388, Pro389, Arg393
4	-4.76	(214.45) [2.33]	Arg403	Asp30, Glu37, Pro389
5	-5.36	(117.42) [2.07]	Arg403, Lys417	Asp30, Asn33, Glu37, Gln388, Pro389, Arg393,
6	-5.54	(86.72) [1.94]	Lys417	Asp30, Asn33, His34, Glu37, Gln96
7	-5.58	(80.98) [1.91]	Arg403, Lys417, Tyr505	Ala387, Arg393
8	-6.34	(22.38) [1.35]	Non interactions	Lys26, Leu29, Asn33, Glu37, Thr92, Val93, Ala387, Pro389
9	-6.78	(10.7) [1.03]	Arg403, Asp405, Lys417, Tyr453, Tyr495, Tyr505	Asn33, His34, Glu37, Pro389, Arg393
10	-6.02	(38.74) [1.59]	Lys417	Lys26, Asp30, His34, Glu37, Gln96, Pro389
11	-5.89	(48.3) [1.68]	Non interactions	Lys26, Asp30, Gln96, Ala387, Gln388, Pro389
12	-6.34	(22.63) [1.35]	Arg403, Lys417	Leu29, Asp30, Asn33, His34, Glu37, Gln388, Pro389
13	-8.27	(0.86) [-0.07]	Arg403, Asp 405, Tyr453,Tyr505	Asp30, Glu37, Gln388, Pro389, Arg393
14	-5.94	(43.91) [1.64]	Asp405, Glu406, Arg408, Lys417	His34, Glu37, Ala387, Gln388, Pro389
Boceprevir	-4.97	(227.27) [2.36]	Arg403, Glu406, Lys417, Tyr453, Tyr505	Asp30, His34, Pro389
Remdesivir	-3.37	(3400) [3.53]	Arg403, Asp405, Glu406, Gln409, Lys417	Non interactions