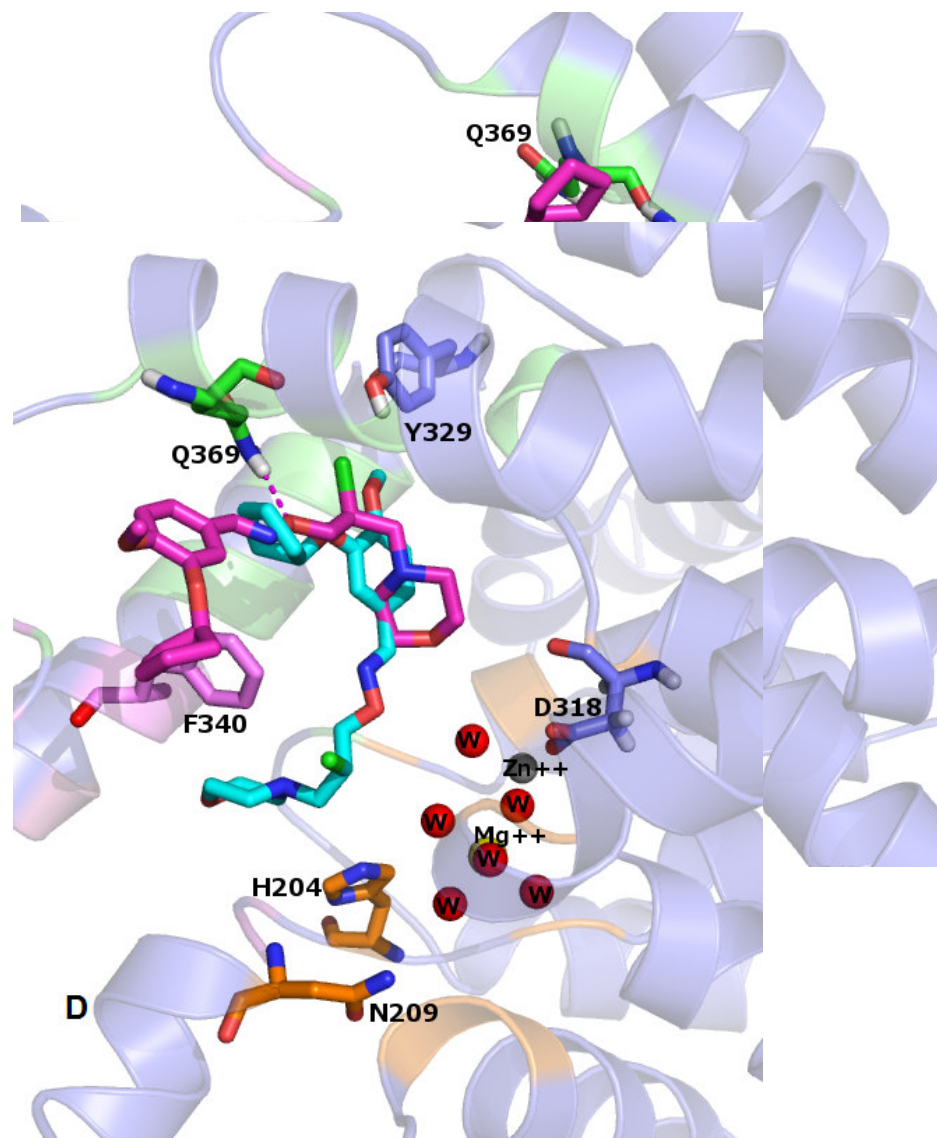
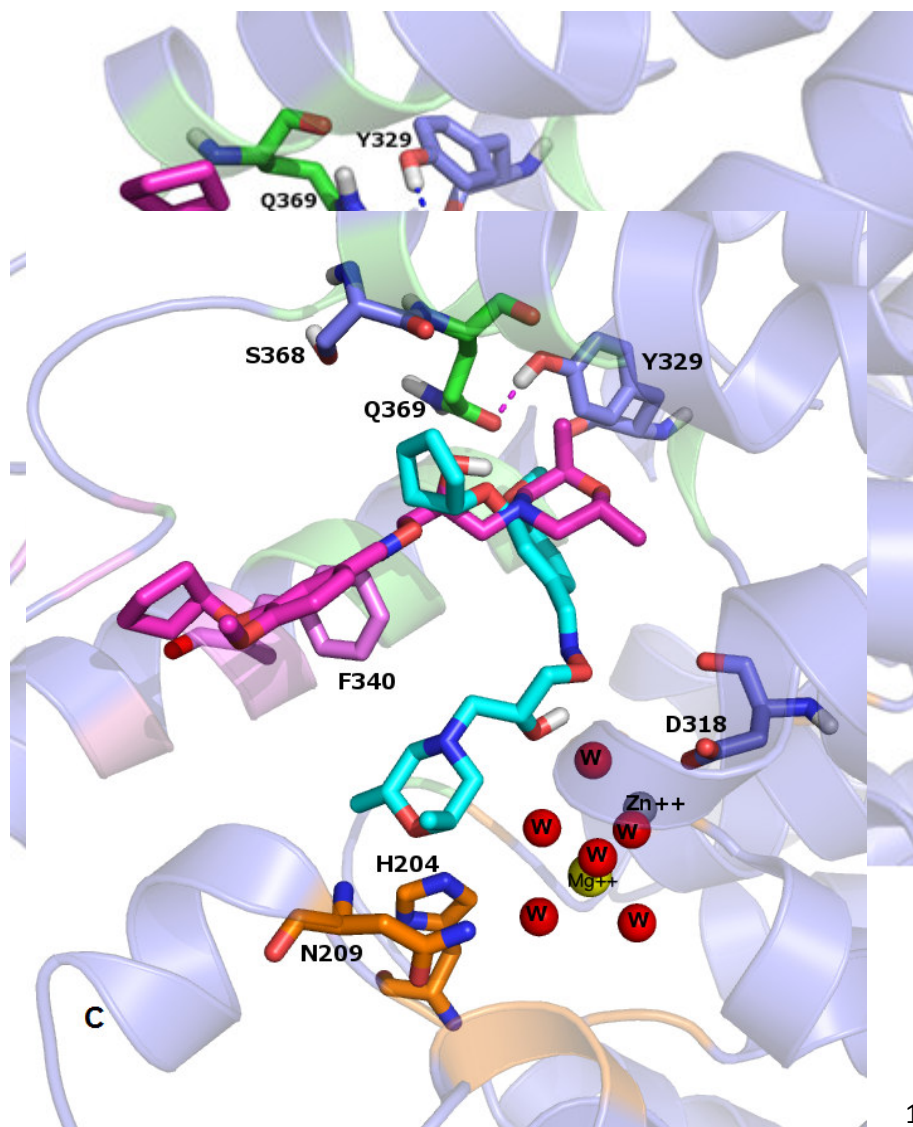


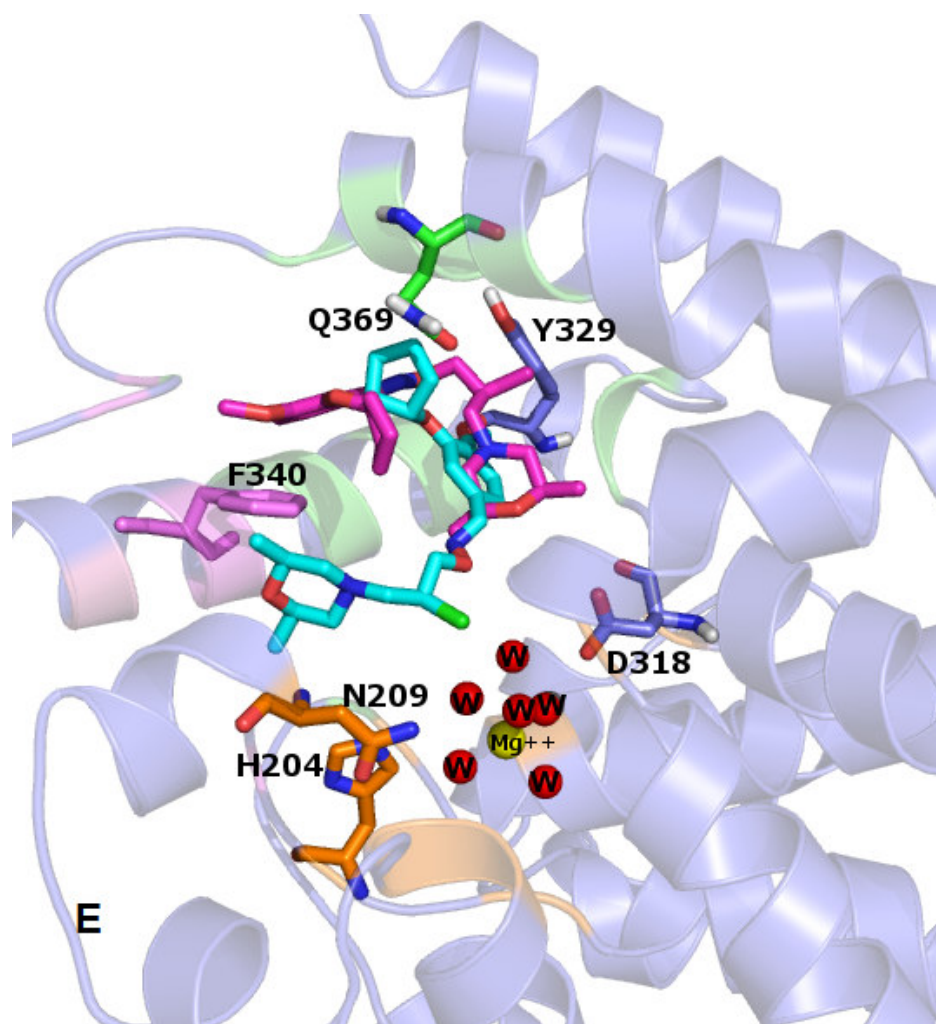
# molecular informatics

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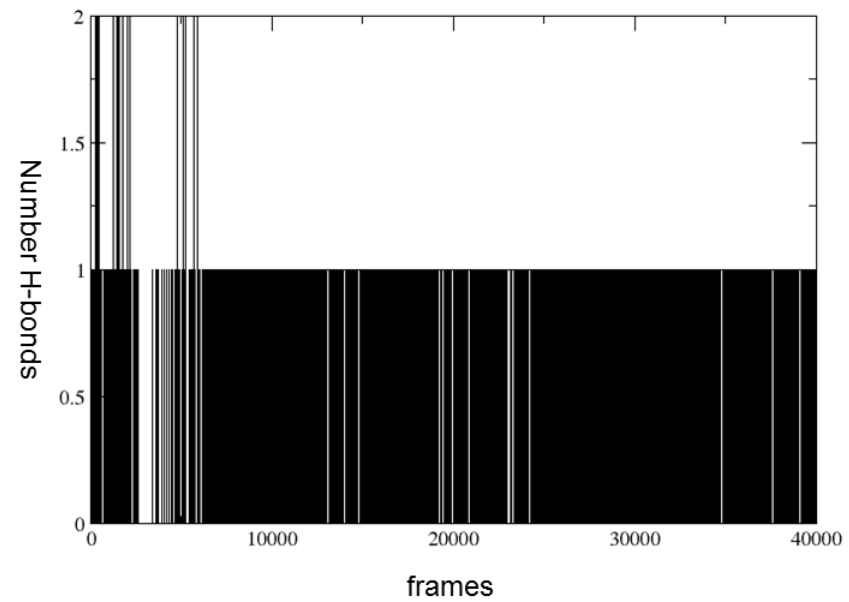
Supporting Information

Supporting Information.

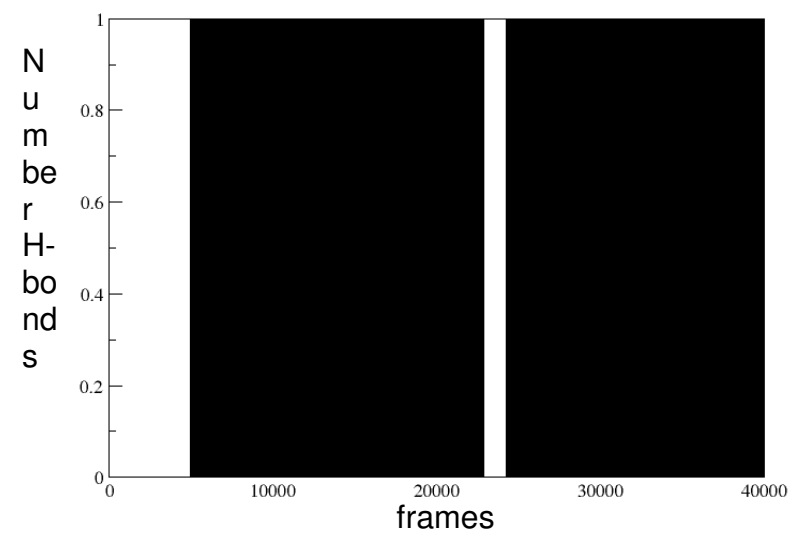
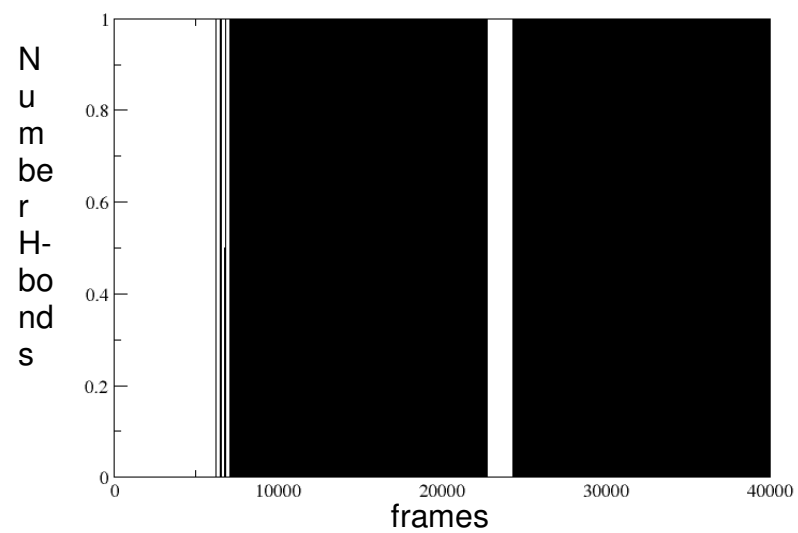




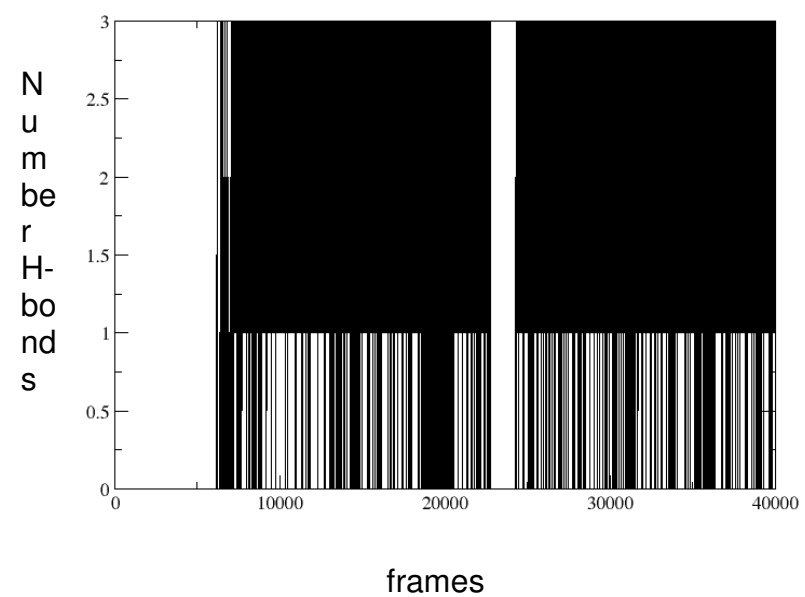
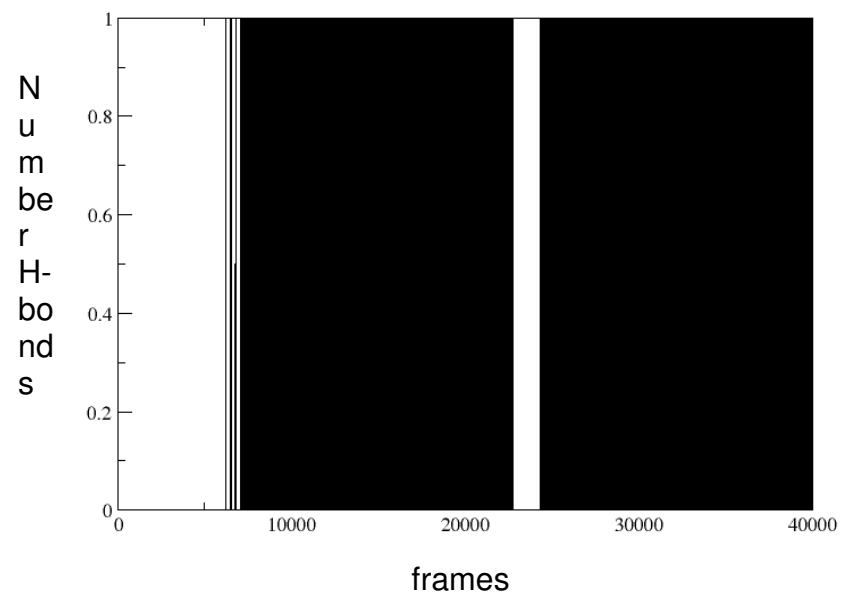
**Figure 1S.** The overlay of both conformations A and B, for compounds **1-5**. Panel A. Compound **1**; Panel B. Compound **2**, Panel C. Compound **3**; Panel D. Compound **4**; Panel E. Compound **5**.



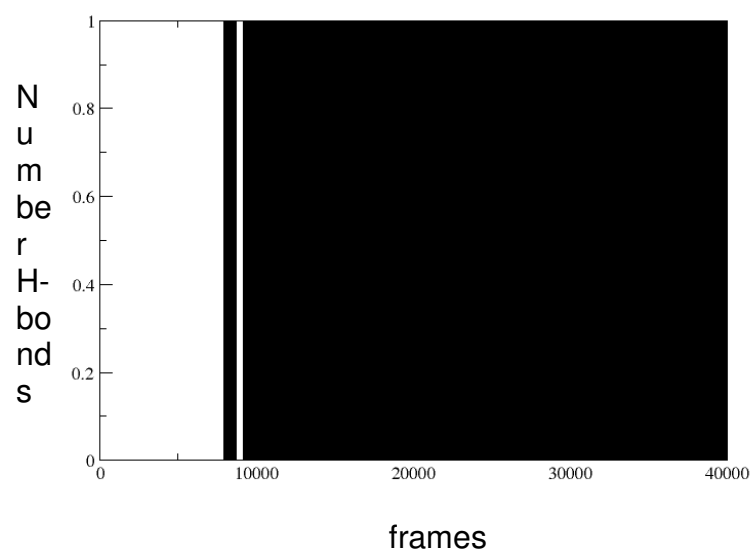
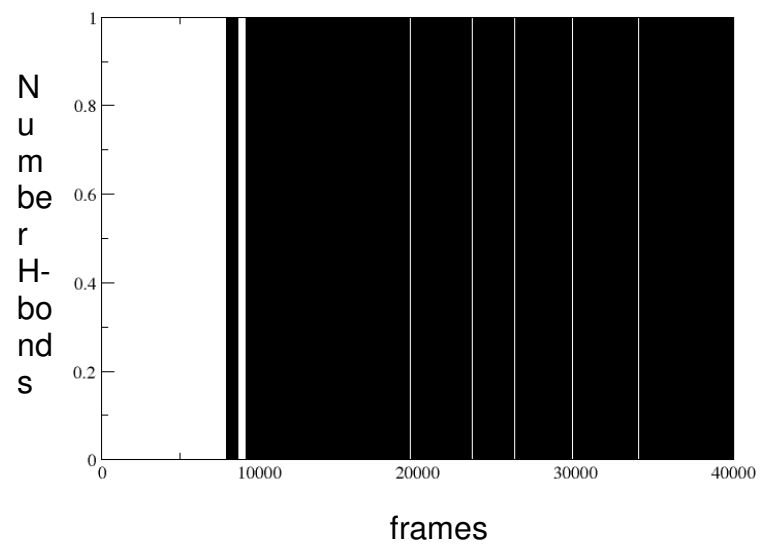
**Figure 2S.** Stability plotting of the H-bond between Q369-O2 compound **1** along the MD.



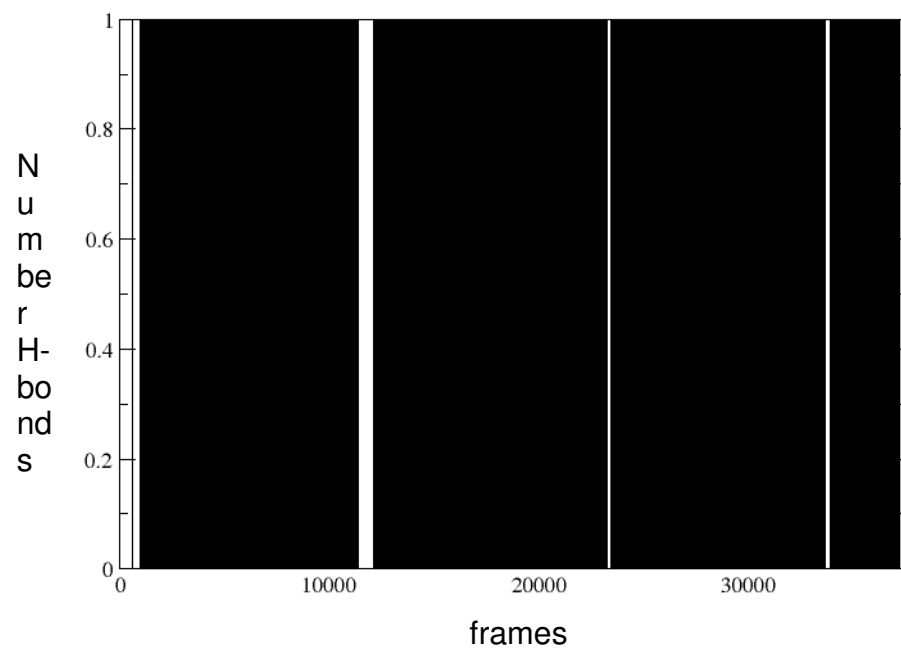
**Figure 3S.** Stability plotting of the water bridge along the MD for compound **1** and Q369. Left, compound **1** and water. Right, Q369 and water.



**Figure 4S.** Stability plotting of the water bridge along the MD for compound **1** and Y329. Left, compound **1** and water. Right, Y329 and water. In the case of Y329 plot, the number of 3 represents the H-bonds made by the water molecule and the residue (see Figure 1S, panel A).



**Figure 5S.** Stability plotting of the water bridge along the MD for compound **1** and D318. Left, compound **1** and water. Right, D318 and water.



**Figure 6S.** Stability plotting of the H-bond between Y329-O2 compound **2** along the MD.



**Table 1S.** The list of the H bonds between the 35 PDE4 inhibitors and the five selected X rays, reporting the residue, followed by the amino acid atom, the compound atom involved and the distance in Å, in brackets.

Compd.	X-rays, PDB code				
	1MKD	1OYN	1XOQ	1Y2E	3IAK
1	H160 (Nε-O, 3.19); Q369 (Nε-O, 3.63); Q369 (Nε-O, 2.62); H <sub>2</sub> O (O-O, 2.56)	H204 (Nε-O, 3.01); Q369 (Nε-O, 2.88); Q369 (Nε-O, 2.99)	Q369 (Nε-O, 3.06); Q369 (Nε-O, 2.99); H204 (Nε-O, 2.85)	N209 (N-O, 3.51); Q369 (Nε-O, 2.84)	Q369 (Nε-O, 3.31)
2	H160 (Nε-O, 2.93); Q369 (Nε-O, 2.68); Q369 (Nε-O, 3.66); H <sub>2</sub> O (O-O, 2.92)	Q369 (Nε-O, 3.03); Q369 (Nε-O, 3.03)	N209 (N-O, 3.11); Q369 (Nε-O, 2.66); Q369 (Nε-O, 3.25)	N209 (N-O, 3.06); Q369 (Nε-O, 2.87); H <sub>2</sub> O (O-O, 2.80)	H204 (Nε-O, 2.97); Q369 (Nε-O, 3.13); H <sub>2</sub> O (O-O, 3.03); H <sub>2</sub> O (O-O, 2.30)
4	Q369 (Nε-O, 2.72)	Q369 (Nε-O, 2.97); Q369 (Nε-O, 2.98)	Q369 (Nε-O, 2.62)	-	-
5	H160 (Nε-O, 3.20); Q369 (Nε-O, 3.55); Q369 (Nε-O, 2.70); H <sub>2</sub> O (O-O, 3.09)	H160 (Nε-O, 3.16); Q369 (Nε-O, 2.78); Q369 (Nε-O, 3.12)	Q369 (Nε-O, 2.95); Q369 (Nε-O, 2.80)	H160 (Nε-O, 3.24); Q369(Nε-O, 3.08)	Q369 (Nε-O, 3.10)
6	M273 (N-N, 3.13); H <sub>2</sub> O (O-O, 2.80)	Y159 (O-N, 2.80)	-	Q369 (Nε-N, 3.12)	Q369 (Nε-N, 3.14)

<b>7</b>	N209 (N-O, 2.95); H <sub>2</sub> O (O-O, 2.91)	Y159 (O-N, 2.68); N321 (Oδ-N, 2.68)	-	-	-
<b>8</b>	H <sub>2</sub> O (O-O, 2.58)	E230 (Oε-O, 3.09); M273 (N-O, 3.17)	-	D318 (O-O, 2.95)	H160 (Nε-O, 2.83)
<b>9</b>	Y159 (O-N, 3.14); S368 (O-O, 2.66); H <sub>2</sub> O (O-N, 2.89)	Y159 (O-N, 2.86); Q369 (Nε-O, 2.93)	N321 (Oδ-N, 3.32); S368 (O-N, 3.07); Y329 (O-O, 3.73); Q369 (Nε-N, 3.32); Q369 (Nε-O, 3.19)	E339 (Oε-O, 2.78); Q369 (Nε-N, 2.99)	N321 (Oδ-N, 2.69); Q369 (Oε-N, 2.97); Q369 (Nε-N, 2.92)
<b>10</b>	S368 (O-N, 2.92); Q369 (Oε-N, 3.15); Q369 (Nε-N, 2.78)	Y159 (O-N, 2.66); N321 (Oδ-N, 2.73)	N321 (Oδ-N, 3.04); Q369 (Nε-N, 3.43); Q369 (Nε-O, 3.09)	-	Q369 (Oε-N, 3.08); Q369 (Nε-N, 2.83)
<b>11</b>	S368 (O-N, 2.66); Q369 (Nε-N, 2.92)	Q369 (Nε-O, 3.04); N321 (Oδ-N, 2.65); H160 (Nε-O, 2.94)	S368 (O-N, 3.05); Q369 (Nε-N, 2.94); Q369 (Nε-O, 3.23)	-	S368 (O-N, 2.78); Q369 (Nε-N, 3.00)
<b>12</b>	S368 (O-N, 2.71); Q369 (Nε-N, 2.78)	Y159 (O-N, 2.64); N321 (Oδ-N, 2.69)	N321 (Oδ-N, 2.89); Q369 (Nε-O, 3.37)	-	S368 (O-N, 2.84); Q369 (Nε-N, 2.92)
<b>13</b>	N321 (Oδ-N, 3.10); H <sub>2</sub> O (O-O, 2.66)	N321 (Oδ-N, 2.73); Q369 (Nε-N, 3.15); H <sub>2</sub> O (O-O, 2.69)	N321 (Oδ-N, 3.38); S368 (O-N, 2.97); Q369 (Nε-N, 3.20); Q369 (Nε-O, 3.06)	D318 (O-N, 3.25); Q369 (Nε-O, 2.86)	Q369 (Oε-N, 3.11); Q369 (Nε-N, 2.85)

<b>14</b>	S368 (O-N, 2.70); Q369 (Ne-N, 2.95)	Y159 (O-N, 3.21); Q369 (Ne-O, 2.80)	S368 (O-N, 2.99); Q369 (Ne-N, 2.99); Q369 (Ne-O, 3.11)	D318 (O-N, 3.40); Q369 (Ne-O, 2.91)	Q369 (Ne-O, 3.15)
<b>15</b>	S368 (O-N, 2.60); Q369 (Ne-N, 2.85)	M273 (N-O, 2.89); H <sub>2</sub> O (O-O, 2.82)	S368 (O-N, 2.94); Q369 (Ne-N, 2.87); Q369 (Ne-O, 3.07)	D318 (O-N, 3.30); Q369 (Ne-O, 2.91)	Q369 (Ne-N, 2.82); Q369 (Ne-O, 3.37)
<b>16</b>	Q369 (Ne-N, 2.82)	Y159 (O-N, 2.93);	N321 (O $\delta$ -N, 3.17); S368 (O-N, 2.97); Q369 (Ne-N, 3.20); Q369 (Ne-O, 3.01)	Q369 (Ne-N, 2.93)	Q369 (Ne-N, 2.78)
<b>17</b>	Q369 (Ne-N, 2.82)	Y159 (O-N, 2.92)	N321 (O $\delta$ -N, 3.16); S368 (O-N, 2.97); Q369 (Ne-N, 3.20); Q369 (Ne-O, 3.01)	Q369 (Ne-N, 2.94)	Q369 (Ne-N, 2.79)
<b>18</b>	Q369 (Ne-N, 2.82)	Y159 (O-N, 2.82)	S368 (O-N, 3.07); Q369 (Ne-N, 2.87); Q369 (Ne-O, 3.16)	-	S368 (O-N, 3.09); Q369 (Ne-N, 2.90); Q369 (Ne-O, 3.35)
<b>19</b>	-	Q369 (Ne-N, 2.62)	Q369 (Ne-N, 2.70)	H <sub>2</sub> O (O-O, 3.19)	H <sub>2</sub> O (O-O, 2.87); H204 (Ne-O, 3.22); Q369 (Ne-N, 2.91)

<b>20</b>	H204 (Nε-N, 2.89); S208 (Oγ-O, 3.05); Q343 (Nε-O, 2.84)	H160 (Nε-O, 2.99); Q369 (Nε-N, 2.64)	H160 (Nε-O, 3.34); Q369 (Nε-N, 2.56)	N209 (N-O, 3.13); Q210 (N-O, 2.69); H <sub>2</sub> O (O-O, 2.99);	H <sub>2</sub> O (O-O, 2.89); Q369 (Nε-N, 2.99)
<b>21</b>	H <sub>2</sub> O (O-O, 3.29)	H160 (Nε-O, 2.99); Q369 (Nε-N, 2.61)	H160 (Nε-O, 3.16); Q369 (Nε-N, 2.73)	H160 (Nε-O, 2.89)	H <sub>2</sub> O (O-O, 2.85); Q369 (Nε-N, 3.03)
<b>22</b>	H204 (Nε-O, 3.06); N209 (N-O, 2.98); Q369 (Nε-N, 3.02)	H160 (Nε-O, 2.83); Q369 (Nε-N, 2.58)	H204 (Nε-O, 2.99); N209 (N-O, 2.3); Q369 (Nε-N, 2.73)	H160 (Nε-O, 3.13)	H <sub>2</sub> O (O-O, 3.15); H204 (Nε-O, 3.31)
<b>23</b>	-	Q369 (Nε-N, 2.85)	Q369 (Nε-N, 2.73)	H <sub>2</sub> O (O-O, 2.69)	-
<b>24</b>	Q369 (Nε-O, 2.92)	Q369 (Nε-N, 2.76)	Q369 (Nε-N, 2.67)	H160 (Nε-O, 2.76)	Q369 (Nε-O, 2.83)
<b>25</b>	Q369 (Nε-N, 3.17)	Q369 (Nε-N, 2.84)	Q369 (Nε-N, 2.76)	H160 (Nε-O, 3.10)	Q369 (Nε-O, 3.26)
<b>26</b>	Q369 (Nε-N, 3.09)	M273 (N-N, 3.07); Q369 (Nε-N, 2.84)	M273 (N-N, 3.12); Q369 (Nε-N, 2.78)	H204 (Nε-O, 3.07); N209 (N-O, 2.3)	H <sub>2</sub> O (O-O, 3.10); H204 (Nε-O, 3.18)
<b>27</b>	Q369 (Nε-N, 3.13)	Q369 (Nε-N, 2.77)	H160 (Nε-O, 3.07); N209 (N-N, 3.02)	H160 (Nε-O, 3.12); N209 (N-N, 3.04)	-
<b>28</b>	Q369 (Nε-N, 3.14)	Q369 (Nε-N, 2.75)	H160 (Nε-O, 3.12); N209 (N-N, 3.04)	H160 (Nε-O, 3.09); N209 (N-N, 2.86)	-
<b>29</b>	Q369 (Nε-N, 3.10)	Q369 (Nε-N, 2.67)	H160 (Nε-O, 3.09); N209 (N-N, 2.86)	-	-

<b>30</b>	Q369 (Nε-N,2.63)	Q369 (Nε-N, 2.76)	-	-	H <sub>2</sub> O (O-O, 3.11); H204 (Nε-O, 3.23)
<b>31</b>	Q369 (Nε-N, 3.19)	Q369 (Nε-N, 2.63)	H160 (Nε-O, 2.99)	H160 (Nε-O, 2.99)	-
<b>32</b>	-	Q369 (Nε-N, 2.77)	Q369 (Nε-N, 2.94)	H160 (Nε-O, 3.00); Q369 (Nε-N, 3.07)	-
<b>33</b>	-	H204 (Nε-O, 2.98); N209 (N-O, 3.18); Q369 (Nε-N, 2.97); H <sub>2</sub> O (O-O, 3.02)	H204 (Nε-O, 2.89); N209 (N-O, 3.16); Q369 (Nε-N, 2.81)	Q369 (Nε-O, 2.98)	H <sub>2</sub> O (O-O, 3.10); H <sub>2</sub> O (O-O, 3.39); H204 (Nε-O, 3.14); N209 (N-O, 3.12); Q369 (Nε-N, 3.04)
<b>34</b>	-	Q369 (Nε-N, 2.87); H <sub>2</sub> O (O-O, 2.79)	H204 (Nε-O, 2.82); N209 (N-O, 3.25); Q369 (Nε-N, 2.75);	T271 (O-O, 3.05); M273 (N-O, 3.22); H <sub>2</sub> O (O-O, 2.87)	H <sub>2</sub> O (O-O, 2.65); H <sub>2</sub> O (O-O, 2.64); H204 (Nε-O, 2.92); E230 (Oε-O, 2.97); Q369 (Nε-N, 3.15)
<b>35</b>	T333 (Oγ-O, 2.82); H204 (Nε-O, 2.93)	E230 (Oε-O, 2.89); M273 (N-O, 3.03); Q369 (Nε-N, 2.59); H <sub>2</sub> O (O-O, 2.80)	S208 (Oγ-O, 2.75); Q343 (Nε-O, 2.63); Q369 (Nε-N, 2.76)	H160 (Nε-O, 3.02); Q369 (Nε-O, 2.69)	N321 (Oδ-O, 2.71); H <sub>2</sub> O (O-O, 3.11); H204 (Nε-O, 3.30)