# Mutual relations between substituent effect, hydrogen bonding and aromaticity in adenine-uracil and adenine-adenine base pairs

## Supplementary Materials

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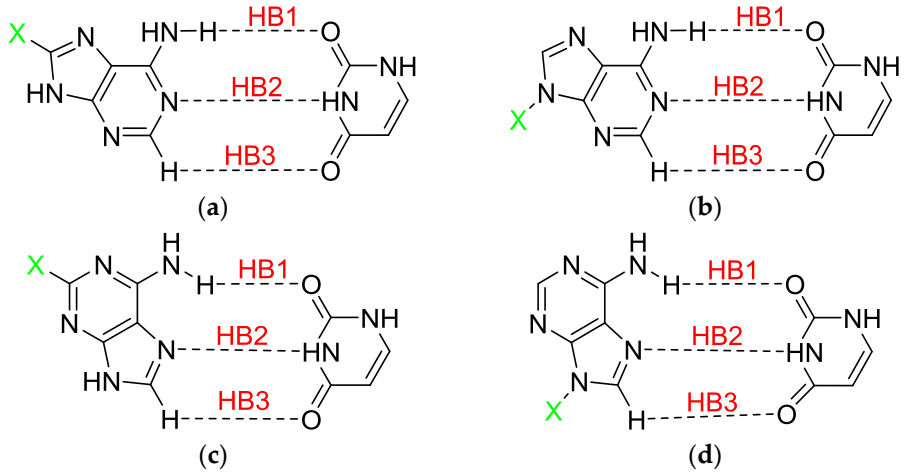


**Figure S1.** Studied substituted adenine-uracil base pairs: (**a**) WC C8-X, (**b**) WC N9-X, (**c**) HG C2-X, (**d**) HG N9-X.

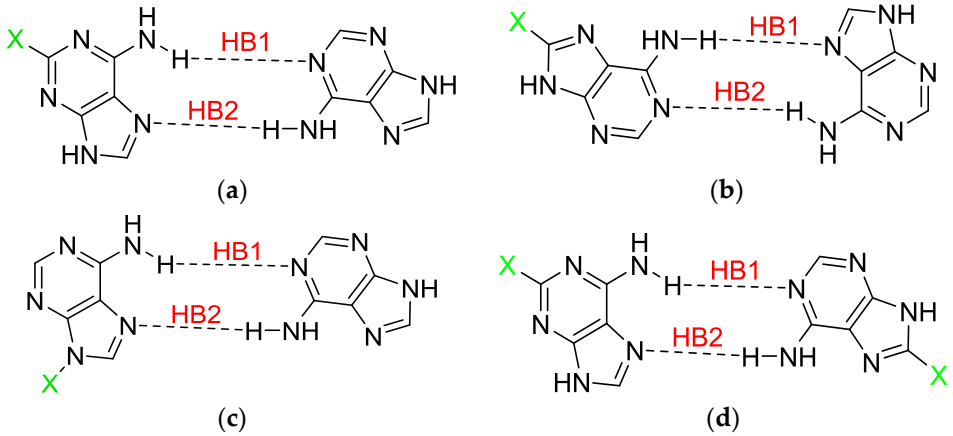


**Figure S2.** Studied substituted adenine-adenine AA2 base pairs: (**a**) AA2 C2-X, (**b**) AA2 C8-X, (**c**) AA2 N9-X, (**d**) double substituted AA2 C2-X, C8-X.

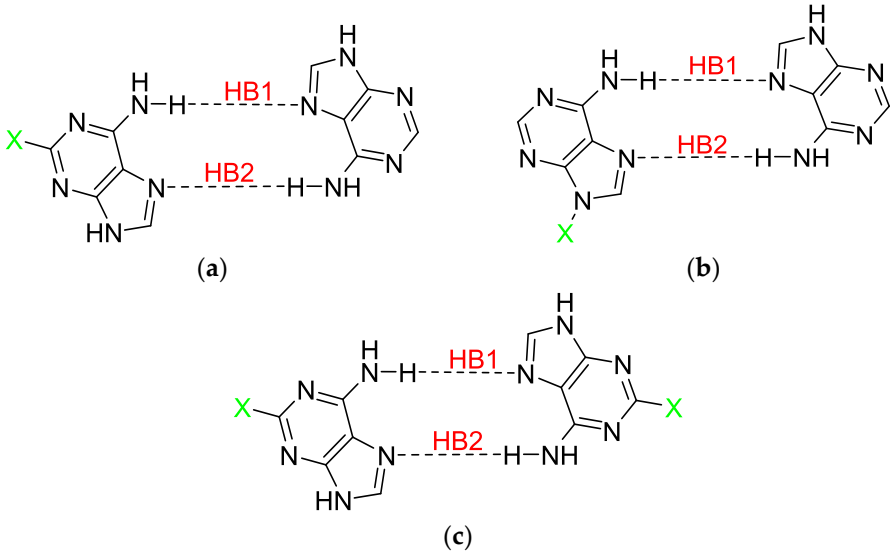


**Figure S3.** Studied substituted adenine-adenine AA3 base pairs: (**a**) AA3 C2-X, (**b**) AA3 N9-X, (**c**) double substituted AA3 C2-X, C2-X.

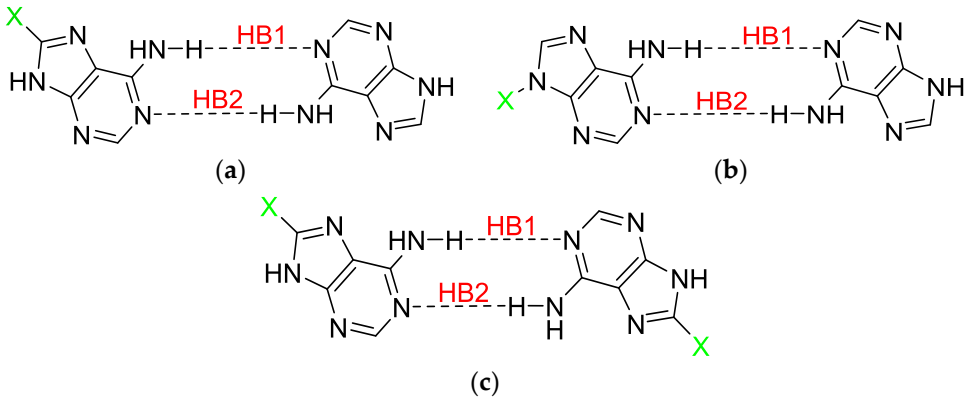


**Figure S4.** Studied substituted adenine-adenine AA4 base pairs: (a) AA4 C8-X, (b) AA4 N9-X, (c) double substituted AA4 C8-X, C8-X.

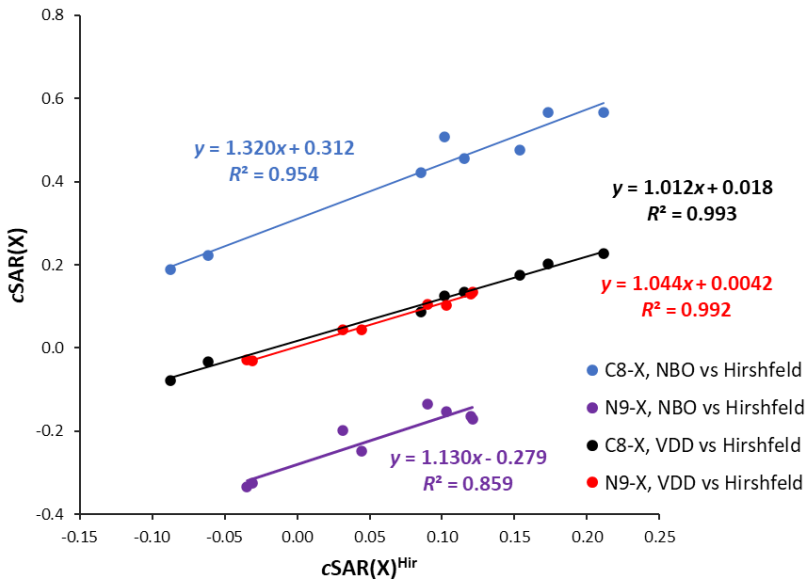


**Figure S5.** Linear regressions between cSAR(X) values calculated by Hirshfeld (Hir) method and data from the VDD and NBO approaches for derivatives of the WC base pair substituted in positions C8-X and N9-X by X = NO, $NO_2$, Cl, F, H, Me, OH, $NH_2$.

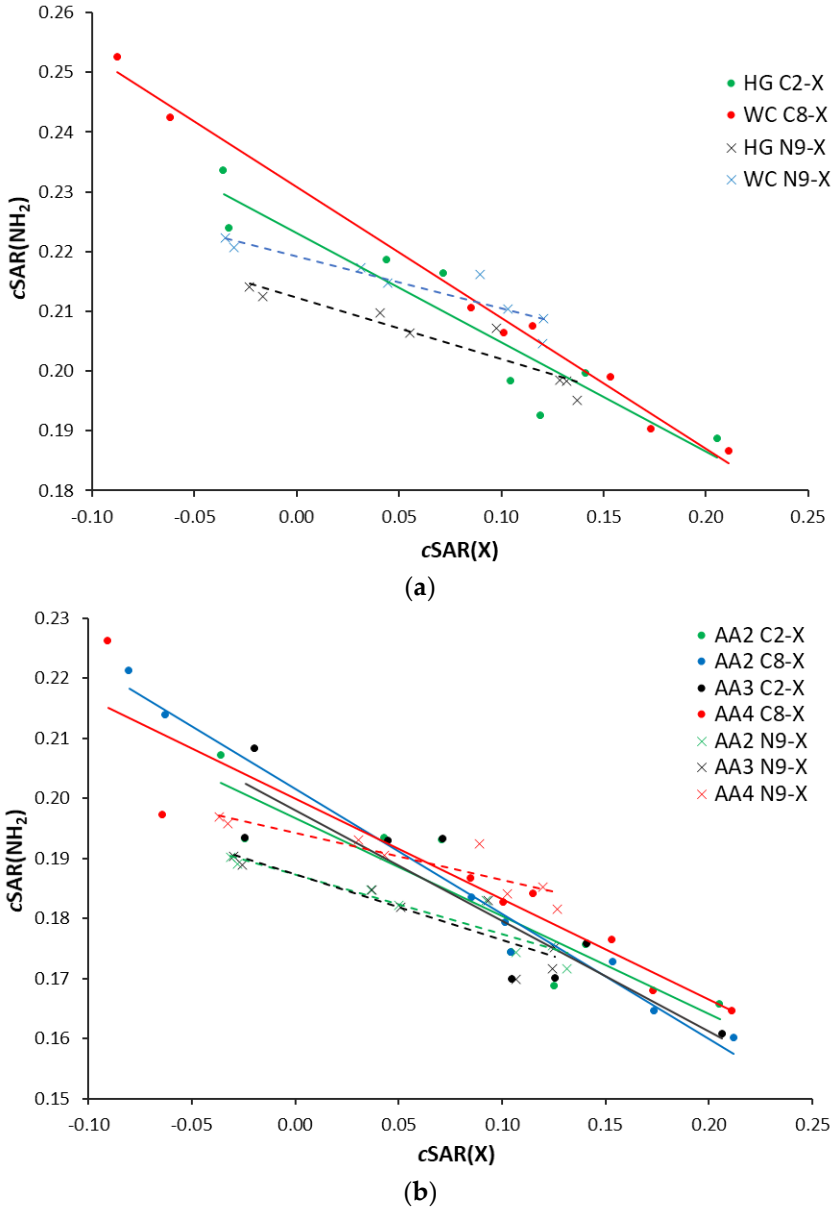


**Figure S6**. Relationships between *c*SAR($NH_2$) and *c*SAR(X) in substituted adenine-uracil (**a**) and adenine-adenine (**b**) systems.

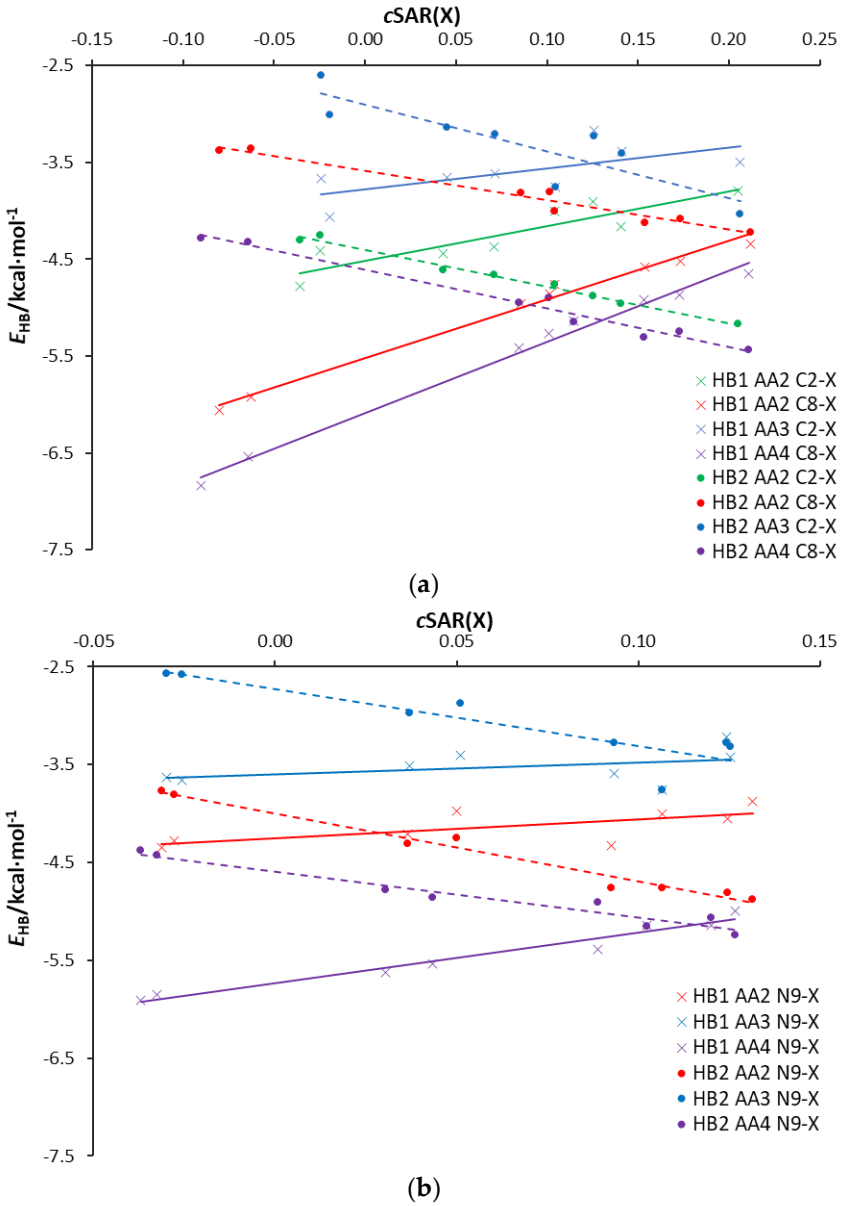


**Figure S7.** Dependence of HB1 and HB2 energies on *c*SAR(X) for adenine dimers substituted in (a) C8 and C2 and (b) N9 positions of one adenine moiety. Parameters of linear regression equations are presented in Table 3.

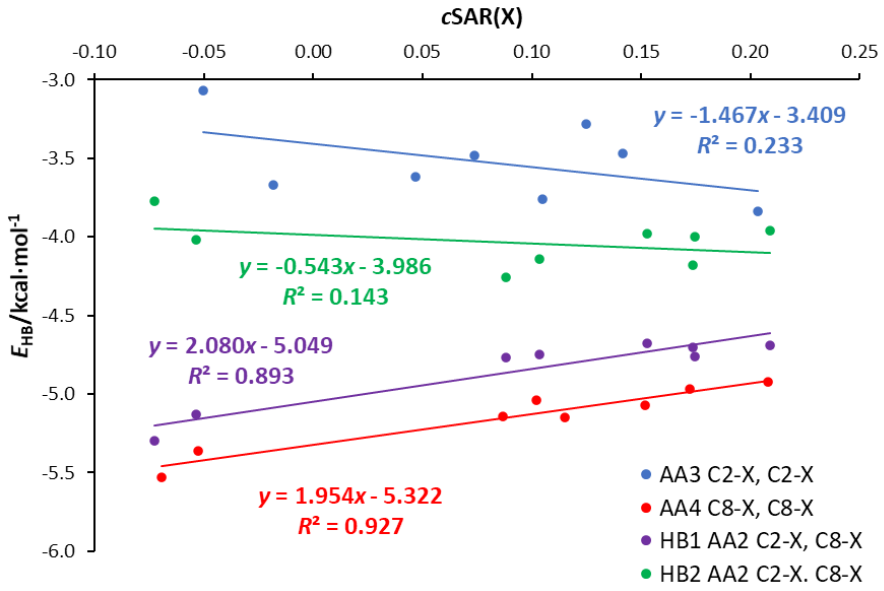


**Figure S8.** Energy of individual H-bonds as a function of *c*SAR(X) for adenine-adenine pairs with the same substituents attached to both adenines.

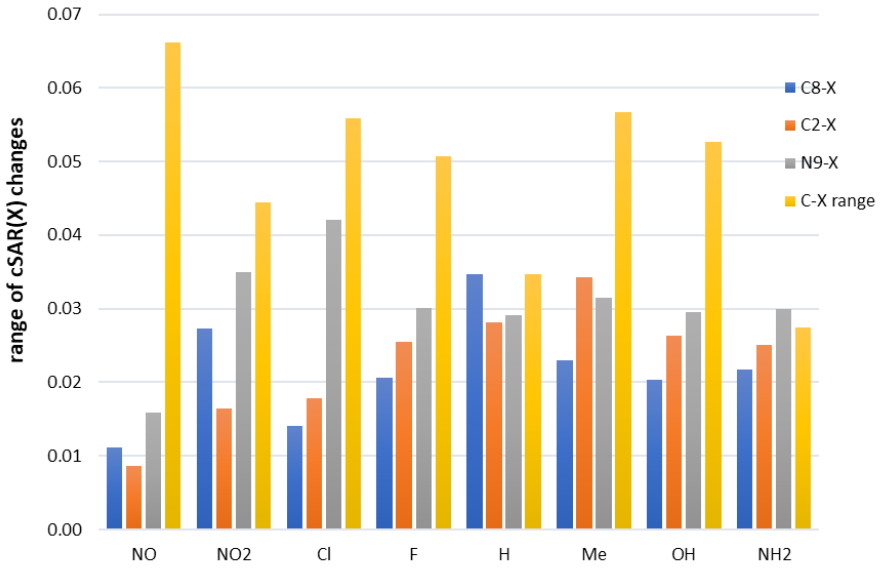


**Figure S9**. Ranges of cSAR(X) changes for the examined X substituent attached to C2, C8, and the nitrogen (N9) and carbon atoms in the adenine monomer and its pairs (WC, HG, and adenine-adenine).

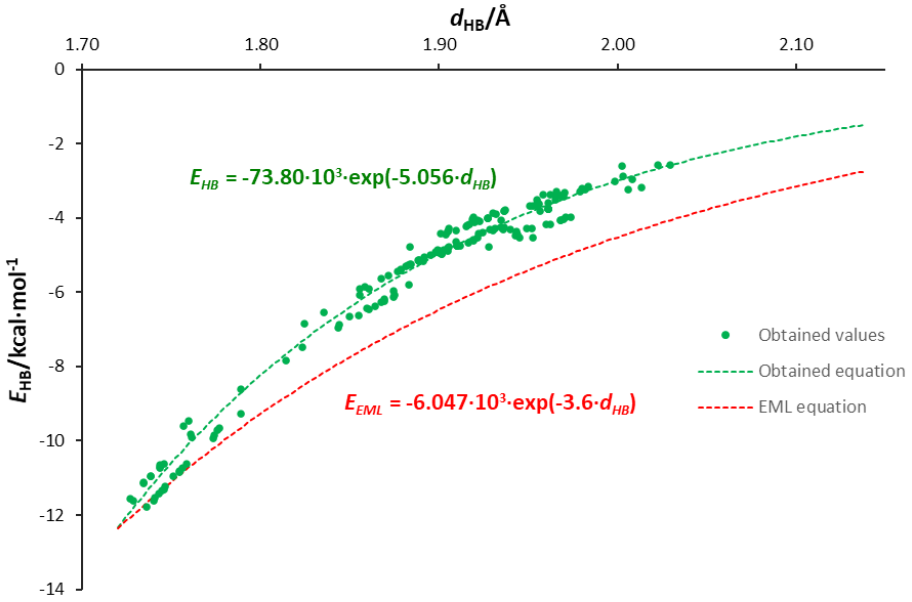


**Figure S10**. Dependence of H-bond energies, $E_{HB}$, on their lengths, $d_{HB}$, for all hydrogen bonds in studied adenine-uracil and adenine-adenine base pairs.

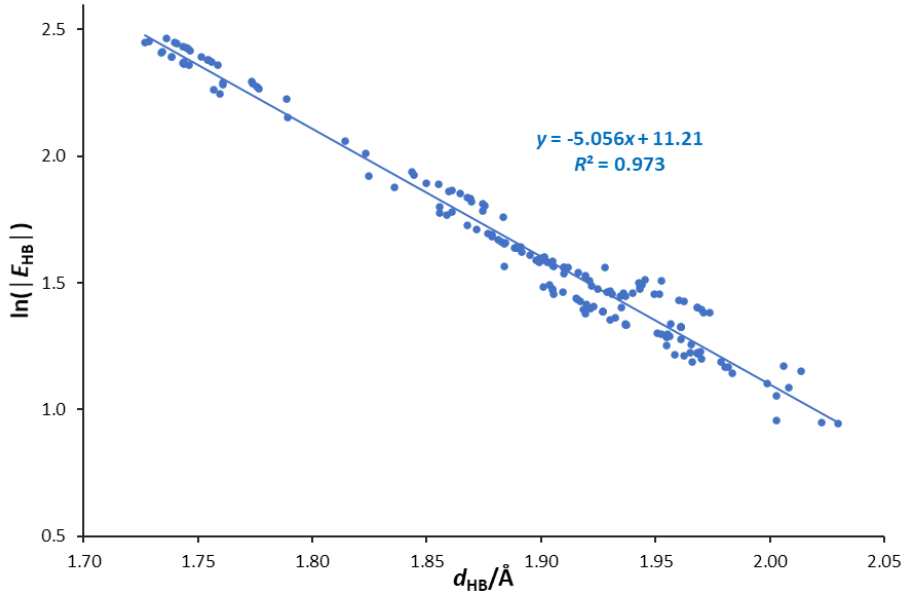


**Figure S11**. Relationship between ln($E_{HB}$) and H-bond lengths, $d_{HB}$, for all hydrogen bonds in studied adenine-uracil and adenine-adenine base pairs.

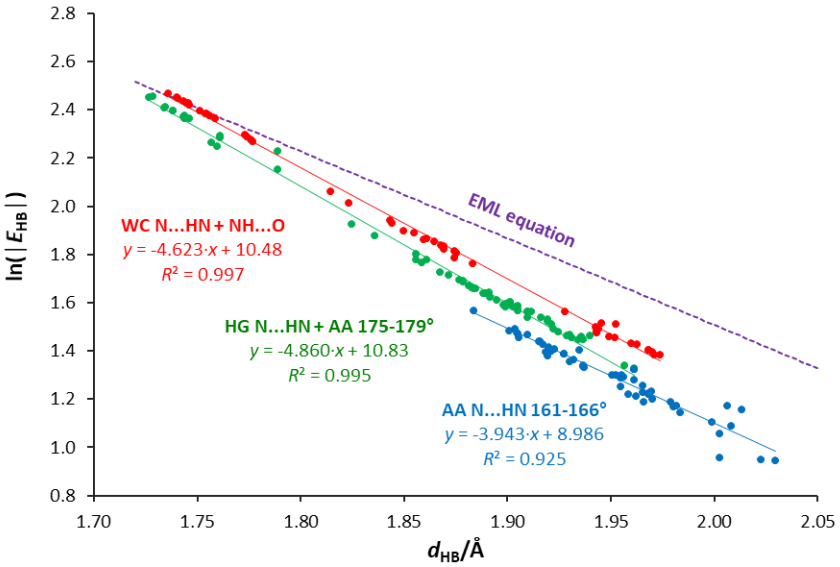


**Figure S12**. Relationships between ln(|$E_{HB}$|) and hydrogen bond lengths, $d_{HB}$, for the groups shown in Figure 8.

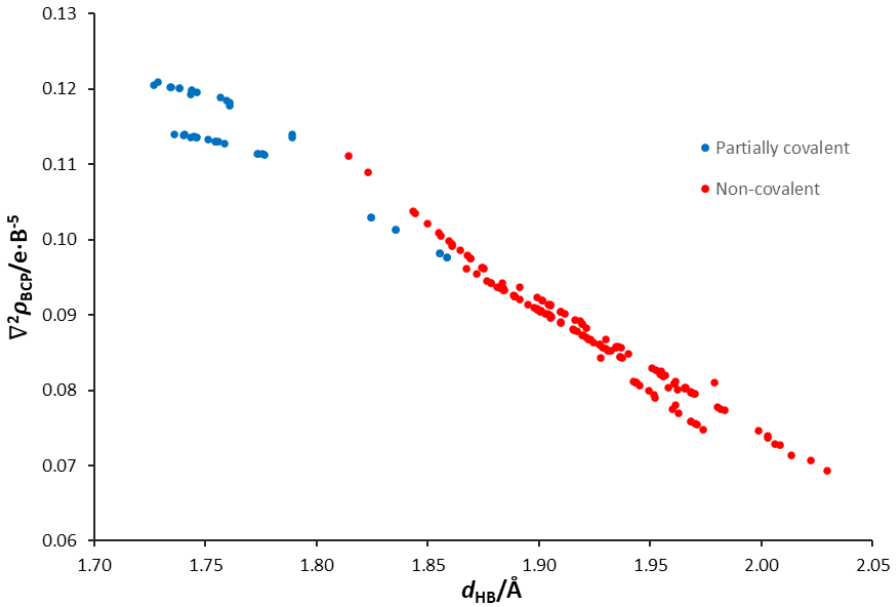


**Figure S13**. Dependence of Laplacian electron density, $\nabla^2\rho_{BCP}$, on the length of the H-bond, $d_{HB}$, for all hydrogen bonds in studied adenine-uracil and adenine-adenine base pairs.

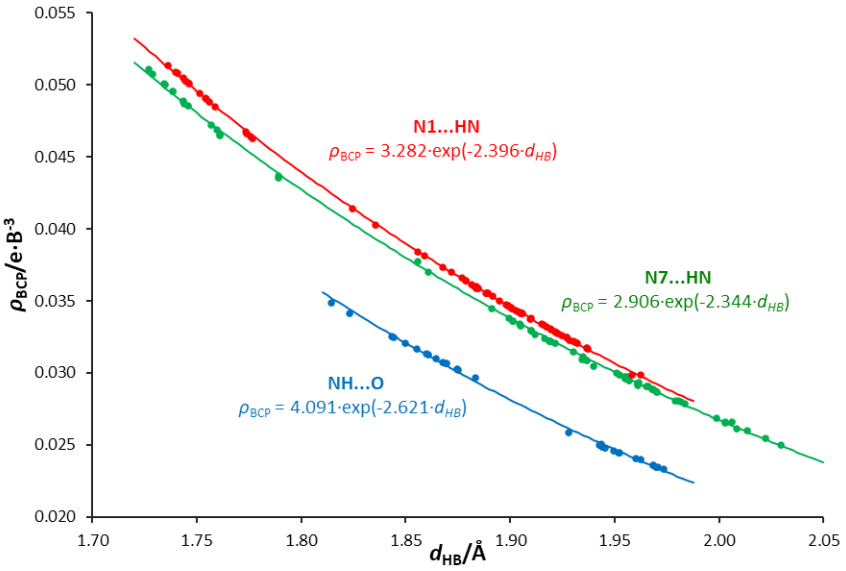


**Figure S14**. Dependences of electron density at the H-bond critical points, $\rho_{BCP}$, on their lengths, $d_{HB}$, in the studied adenine-uracil and adenine-adenine base pairs.

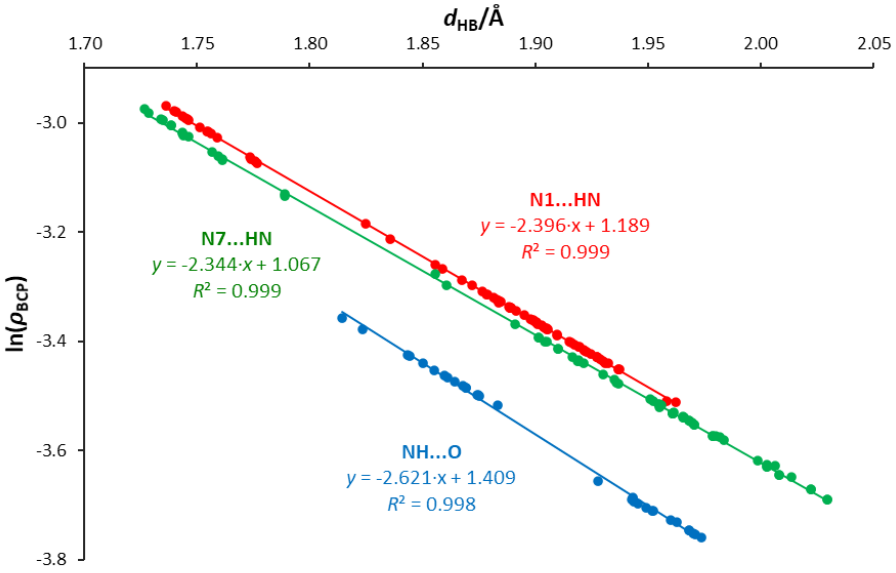


**Figure S15**. Relationships between ln($\rho_{BCP}$) and H-bond lengths, $d_{HB}$, for all hydrogen bonds in studied adenine-uracil and adenine-adenine base pairs.

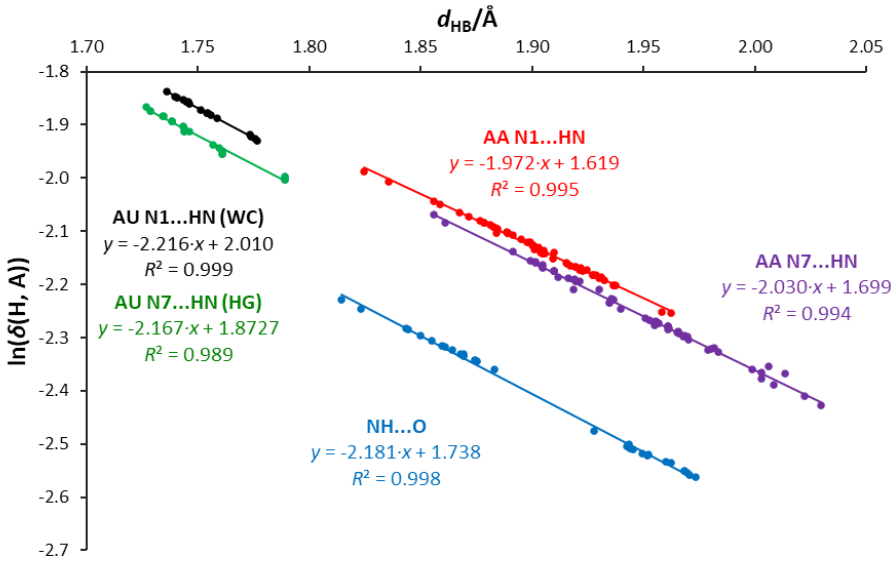


**Figure S16**. Relationships between ln(DI) and H-bond lengths, $d_{HB}$, for all hydrogen bonds in studied adenine-uracil and adenine-adenine base pairs.

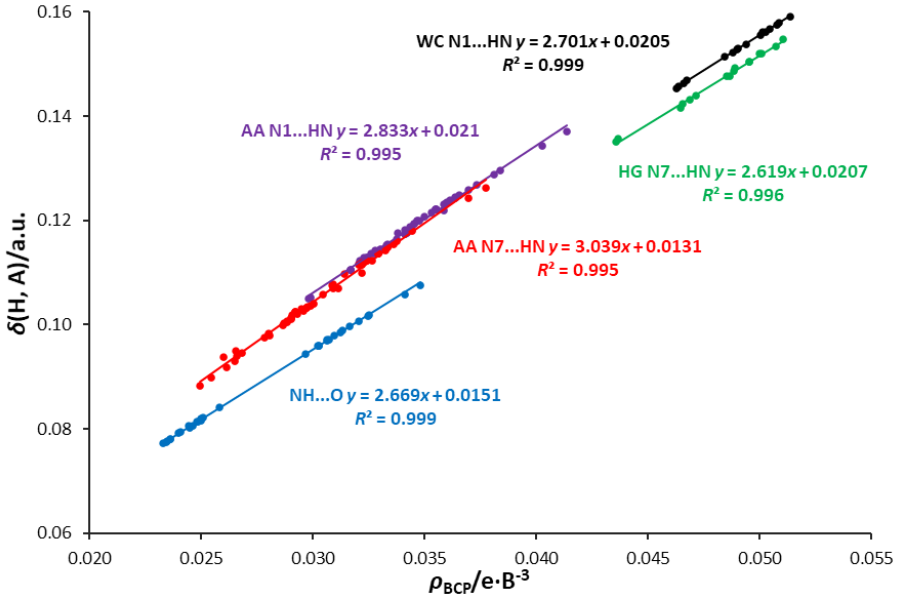


**Figure S17**. Delocalization index δ(H,A) between H and A atoms, where A is the acceptor of H-bond as a function of electron density $\rho_{BCP}$ at H-bond critical point for AU and AA dimers.

**Table S1**. Values of cSAR(X), cSAR($NH_2$) and HOMA. Substituted adenine-uracil Hoogsteen (HG) and Watson-Crick (WC) pairs. HOMA values of five-membered adenine ring (HOMA AD5) and six-membered adenine ring (HOMA AD6).

| HG C8-X | X= | *c*SAR(X) | *c*SAR($NH_2$) | HOMA AD5 | HOMA AD6 |
|---|---|---|---|---|---|
| | NO | -0.063 | 0.125 | 0.807 | 0.828 |
| | $NO_2$ | -0.055 | 0.117 | 0.815 | 0.863 |
| | Cl | 0.110 | 0.088 | 0.781 | 0.910 |
| | F | 0.126 | 0.088 | 0.758 | 0.920 |
| | H | 0.132 | 0.097 | 0.816 | 0.918 |
| | $CH_3$ | 0.133 | 0.077 | 0.788 | 0.911 |
| | OH | 0.100 | 0.079 | 0.780 | 0.936 |
| | $NH_2$ | 0.185 | 0.069 | 0.771 | 0.933 |
| | ***Range*** | ***0.248*** | ***0.056*** | ***0.057*** | ***0.108*** |
| **HG C2-X** | NO | -0.033 | 0.224 | 0.829 | 0.899 |
| | $NO_2$ | -0.036 | 0.234 | 0.828 | 0.911 |
| | Cl | 0.044 | 0.219 | 0.823 | 0.923 |
| | F | 0.072 | 0.216 | 0.821 | 0.920 |
| | H | 0.105 | 0.198 | 0.816 | 0.918 |
| | $CH_3$ | 0.119 | 0.193 | 0.817 | 0.919 |
| | OH | 0.141 | 0.200 | 0.814 | 0.922 |
| | $NH_2$ | 0.206 | 0.189 | 0.807 | 0.912 |
| | ***Range*** | ***0.262*** | ***0.045*** | ***0.022*** | ***0.024*** |
| **HG N9-X** | NO | -0.017 | 0.212 | 0.693 | 0.924 |
| | $NO_2$ | -0.023 | 0.214 | 0.700 | 0.918 |
| | Cl | 0.055 | 0.206 | 0.794 | 0.916 |
| | F | 0.041 | 0.210 | 0.823 | 0.909 |
| | H | 0.132 | 0.198 | 0.816 | 0.918 |
| | $CH_3$ | 0.137 | 0.195 | 0.809 | 0.920 |
| | OH | 0.098 | 0.207 | 0.861 | 0.914 |
| | $NH_2$ | 0.129 | 0.198 | 0.820 | 0.919 |
| | ***Range*** | ***0.160*** | ***0.019*** | ***0.167*** | ***0.015*** |
| **WC C8-X** | NO | -0.087 | 0.253 | 0.806 | 0.836 |
| | $NO_2$ | -0.062 | 0.242 | 0.825 | 0.875 |
| | Cl | 0.085 | 0.211 | 0.790 | 0.920 |
| | F | 0.101 | 0.206 | 0.767 | 0.927 |
| | H | 0.115 | 0.207 | 0.809 | 0.916 |
| | $CH_3$ | 0.154 | 0.199 | 0.799 | 0.922 |
| | OH | 0.173 | 0.190 | 0.782 | 0.931 |
| | $NH_2$ | 0.211 | 0.187 | 0.781 | 0.932 |
| | ***Range*** | ***0.299*** | ***0.066*** | ***0.058*** | ***0.096*** |
| **WC N9-X** | NO | -0.031 | 0.221 | 0.924 | 0.927 |
| | $NO_2$ | -0.035 | 0.222 | 0.918 | 0.921 |
| | Cl | 0.045 | 0.215 | 0.916 | 0.916 |
| | F | 0.032 | 0.217 | 0.909 | 0.909 |
| | H | 0.103 | 0.210 | 0.918 | 0.916 |
| | $CH_3$ | 0.120 | 0.205 | 0.920 | 0.917 |
| | OH | 0.090 | 0.216 | 0.914 | 0.912 |
| | $NH_2$ | 0.121 | 0.209 | 0.919 | 0.919 |
| | ***Range*** | ***0.156*** | ***0.018*** | ***0.015*** | ***0.019*** |

**Table S2**. Values of cSAR(X), cSAR($NH_2$) and HOMA. Substituted adenine-adenine AA2 and AA3 pairs. HOMA values of five-membered adenine ring (HOMA AD5) and six-membered adenine ring (HOMA AD6).

| AA2 C2-X | X | *c*SAR(X) | *c*SAR($NH_2$) | HOMA AD5 | HOMA AD6 |
|---|---|---|---|---|---|
| | NO | -0.024 | 0.193 | 0.807 | 0.890 |
| | $NO_2$ | -0.036 | 0.207 | 0.819 | 0.894 |
| | Cl | 0.043 | 0.193 | 0.814 | 0.908 |
| | F | 0.071 | 0.193 | 0.812 | 0.905 |
| | H | 0.104 | 0.174 | 0.807 | 0.905 |
| | $CH_3$ | 0.125 | 0.169 | 0.808 | 0.906 |
| | OH | 0.141 | 0.176 | 0.805 | 0.909 |
| | $NH_2$ | 0.205 | 0.166 | 0.799 | 0.899 |
| | ***Range*** | ***0.241*** | ***0.041*** | ***0.020*** | ***0.019*** |
| **AA2 C8-X** | NO | -0.080 | 0.221 | 0.812 | 0.837 |
| | $NO_2$ | -0.063 | 0.214 | 0.829 | 0.874 |
| | Cl | 0.086 | 0.184 | 0.792 | 0.920 |
| | F | 0.101 | 0.179 | 0.769 | 0.926 |
| | H | 0.104 | 0.174 | 0.810 | 0.913 |
| | $CH_3$ | 0.154 | 0.173 | 0.800 | 0.922 |
| | OH | 0.173 | 0.165 | 0.783 | 0.931 |
| | $NH_2$ | 0.212 | 0.160 | 0.782 | 0.932 |
| | ***Range*** | ***0.292*** | ***0.061*** | ***0.060*** | ***0.095*** |
| **AA2 N9-X** | NO | -0.028 | 0.189 | 0.683 | 0.911 |
| | $NO_2$ | -0.031 | 0.190 | 0.689 | 0.905 |
| | Cl | 0.050 | 0.182 | 0.786 | 0.902 |
| | F | 0.036 | 0.185 | 0.812 | 0.893 |
| | H | 0.107 | 0.174 | 0.807 | 0.905 |
| | $CH_3$ | 0.131 | 0.172 | 0.811 | 0.905 |
| | OH | 0.092 | 0.183 | 0.853 | 0.900 |
| | $NH_2$ | 0.124 | 0.175 | 0.802 | 0.907 |
| | ***Range*** | ***0.163*** | ***0.019*** | ***0.170*** | ***0.018*** |
| **AA3 C2-X** | NO | -0.024 | 0.193 | 0.809 | 0.896 |
| | $NO_2$ | -0.020 | 0.208 | 0.817 | 0.900 |
| | Cl | 0.045 | 0.193 | 0.814 | 0.914 |
| | F | 0.072 | 0.193 | 0.812 | 0.911 |
| | H | 0.105 | 0.170 | 0.807 | 0.912 |
| | $CH_3$ | 0.126 | 0.170 | 0.812 | 0.911 |
| | OH | 0.141 | 0.176 | 0.806 | 0.914 |
| | $NH_2$ | 0.206 | 0.161 | 0.800 | 0.900 |
| | ***Range*** | ***0.231*** | ***0.047*** | ***0.017*** | ***0.018*** |
| **AA3 N9-X** | NO | -0.026 | 0.189 | 0.686 | 0.917 |
| | $NO_2$ | -0.030 | 0.190 | 0.690 | 0.911 |
| | Cl | 0.051 | 0.182 | 0.786 | 0.908 |
| | F | 0.037 | 0.185 | 0.813 | 0.899 |
| | H | 0.107 | 0.170 | 0.807 | 0.912 |
| | $CH_3$ | 0.124 | 0.172 | 0.813 | 0.913 |
| | OH | 0.093 | 0.183 | 0.854 | 0.906 |
| | $NH_2$ | 0.125 | 0.175 | 0.803 | 0.913 |
| | ***Range*** | ***0.155*** | ***0.020*** | ***0.168*** | ***0.018*** |

**Table S3.** Values of cSAR(X), cSAR($NH_2$) and HOMA. Substituted adenine-adenine AA4 pairs. HOMA values of five-membered adenine ring (HOMA AD5) and six-membered adenine ring (HOMA AD6).

| AA4 C8-X | X | *c*SAR(X) | *c*SAR($NH_2$) | HOMA AD5 | HOMA AD6 |
|---|---|---|---|---|---|
| | NO | -0.090 | 0.226 | 0.810 | 0.832 |
| | $NO_2$ | -0.064 | 0.197 | 0.829 | 0.870 |
| | Cl | 0.085 | 0.187 | 0.791 | 0.917 |
| | F | 0.101 | 0.183 | 0.769 | 0.924 |
| | H | 0.115 | 0.184 | 0.811 | 0.912 |
| | $CH_3$ | 0.153 | 0.176 | 0.800 | 0.919 |
| | OH | 0.173 | 0.168 | 0.783 | 0.929 |
| | $NH_2$ | 0.211 | 0.165 | 0.782 | 0.929 |
| | ***Range*** | ***0.301*** | ***0.062*** | ***0.060*** | ***0.097*** |
| **AA4 N9-X** | NO | -0.032 | 0.196 | 0.677 | 0.923 |
| | $NO_2$ | -0.037 | 0.197 | 0.689 | 0.917 |
| | Cl | 0.043 | 0.190 | 0.790 | 0.912 |
| | F | 0.030 | 0.193 | 0.821 | 0.905 |
| | H | 0.102 | 0.184 | 0.811 | 0.912 |
| | $CH_3$ | 0.127 | 0.182 | 0.815 | 0.912 |
| | OH | 0.089 | 0.192 | 0.856 | 0.908 |
| | $NH_2$ | 0.120 | 0.185 | 0.806 | 0.915 |
| | ***Range*** | ***0.163*** | ***0.015*** | ***0.179*** | ***0.018*** |

**Table S4.** Values of cSAR(X) and cSAR($NH_2$). Symmetrically substituted adenine-adenine AA3 and AA4 pairs.

| AA3 C2-X+C2-X | X | *c*SAR(X) | *c*SAR($NH_2$) |
|---|---|---|---|
| | NO | -0.018 | 0.191 |
| | $NO_2$ | -0.050 | 0.209 |
| | Cl | 0.047 | 0.194 |
| | F | 0.074 | 0.194 |
| | H | 0.105 | 0.170 |
| | $CH_3$ | 0.125 | 0.168 |
| | OH | 0.142 | 0.176 |
| | $NH_2$ | 0.203 | 0.159 |
| | ***Range*** | ***0.253*** | ***0.050*** |
| **AA4 C8-X+C8-X** | NO | -0.069 | 0.228 |
| | $NO_2$ | -0.053 | 0.221 |
| | Cl | 0.087 | 0.188 |
| | F | 0.102 | 0.184 |
| | H | 0.115 | 0.184 |
| | $CH_3$ | 0.152 | 0.175 |
| | OH | 0.172 | 0.167 |
| | $NH_2$ | 0.208 | 0.163 |
| | ***Range*** | ***0.277*** | ***0.065*** |

**Table S5.** Values of cSAR(X) and cSAR($NH_2$). Asymmetrically substituted adenine-adenine AA2 pairs.

| AA2 C2-X+C8-X | X | $cSAR(X)_{C8X}$ | $cSAR(NH_2)_{C8X}$ | $cSAR(NH_2)_{C2X}$ | $cSAR(NH2)_{C8X}$ |
|---|---|---|---|---|---|
| | NO | -0.015 | -0.072 | 0.196 | 0.223 |
| | $NO_2$ | -0.049 | -0.053 | 0.210 | 0.217 |
| | Cl | 0.045 | 0.088 | 0.194 | 0.185 |
| | F | 0.072 | 0.103 | 0.194 | 0.181 |
| | H | 0.104 | 0.174 | 0.181 | 0.181 |
| | $CH_3$ | 0.124 | 0.153 | 0.168 | 0.172 |
| | OH | 0.140 | 0.174 | 0.176 | 0.176 |
| | $NH_2$ | 0.202 | 0.209 | 0.165 | 0.160 |
| | ***Range*** | ***0.252*** | ***0.281*** | ***0.045*** | ***0.064*** |

**Table S6.** HOMA values of uracil ring in adenine-uracil Hoogsteen (HG) and Watson-Crick (WC) pairs with substituents at C2, C8, N9 position of adenine moiety.

| X | WC C8-X | HG C2-X | WC N9-X |
|---|---|---|---|
| NO | 0.572 | 0.530 | 0.565 |
| $NO_2$ | 0.570 | 0.530 | 0.565 |
| Cl | 0.559 | 0.526 | 0.561 |
| F | 0.558 | 0.526 | 0.562 |
| H | 0.556 | 0.524 | 0.556 |
| $CH_3$ | 0.554 | 0.523 | 0.555 |
| OH | 0.555 | 0.523 | 0.560 |
| $NH_2$ | 0.552 | 0.523 | 0.557 |
| ***Range*** | ***0.020*** | ***0.007*** | ***0.011*** |

**Table S7.** Calculated hydrogen bond parameters of all studied base pairs. Energy of individual hydrogen bond obtained with NBO approach $E_{HB}$/kcal·mol$^{-1}$; Interaction energy obtained with supermolecular method $E_{SM}$/kcal·mol$^{-1}$; total deformation energy $E_{def}$/kcal·mol$^{-1}$; hydrogen bond length $d$/Å; electron density at hydrogen bond critical point $\rho_{BCP}$/e·B$^{-3}$; Laplacian of electron density at hydrogen bond critical point $L_{BCP}$/ e·B$^{-5}$; delocalization index between hydrogen atom and hydrogen bond acceptor atom $\delta$(H, A)/a.u.

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)·10$^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)·10$^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **Hoogsteen C2-X** | NO | 1.952 | 2.447 | 7.897 | 8.052 | -4.52 | 1.760 | 4.689 | 11.85 | 14.32 | -9.45 | -13.97 | 1.48 | -15.50 |
| | $NO_2$ | 1.928 | 2.585 | 8.437 | 8.410 | -4.77 | 1.757 | 4.718 | 11.89 | 14.40 | -9.60 | -14.37 | 0.70 | -16.67 |
| | Cl | 1.945 | 2.481 | 8.056 | 8.129 | -4.54 | 1.746 | 4.854 | 11.96 | 14.77 | -10.61 | -15.15 | 1.63 | -15.78 |
| | F | 1.943 | 2.498 | 8.121 | 8.167 | -4.48 | 1.744 | 4.883 | 11.98 | 14.86 | -10.73 | -15.21 | 1.67 | -15.82 |
| | H | 1.968 | 2.361 | 7.587 | 7.801 | -4.07 | 1.738 | 4.955 | 12.01 | 15.05 | -10.95 | -15.02 | 1.70 | -15.61 |
| | $CH_3$ | 1.974 | 2.330 | 7.483 | 7.717 | -3.99 | 1.734 | 5.009 | 12.03 | 15.20 | -11.11 | -15.1 | 1.76 | -15.60 |
| | OH | 1.952 | 2.449 | 7.933 | 8.029 | -4.28 | 1.735 | 5.002 | 12.02 | 15.19 | -11.15 | -15.43 | 1.67 | -15.98 |
| | $NH_2$ | 1.971 | 2.346 | 7.548 | 7.745 | -3.98 | 1.727 | 5.107 | 12.05 | 15.47 | -11.57 | -15.55 | 1.92 | -15.69 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | *d* | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | *d* | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **Hoogsteen N9-X** | NO | 1.943 | 2.502 | 8.110 | 8.191 | -4.37 | 1.789 | 4.369 | 11.36 | 13.57 | -9.27 | -13.64 | 1.34 | -14.54 |
| | $NO_2$ | 1.943 | 2.508 | 8.105 | 8.210 | -4.41 | 1.789 | 4.356 | 11.39 | 13.50 | -8.61 | -13.02 | 1.36 | -14.53 |
| | Cl | 1.960 | 2.408 | 7.751 | 7.937 | -4.18 | 1.761 | 4.656 | 11.78 | 14.23 | -9.90 | -14.08 | 1.44 | -14.99 |
| | F | 1.963 | 2.398 | 7.688 | 7.922 | -4.16 | 1.761 | 4.649 | 11.82 | 14.17 | -9.81 | -13.97 | 1.43 | -15.04 |
| | H | 1.968 | 2.361 | 7.587 | 7.801 | -4.07 | 1.738 | 4.955 | 12.01 | 15.05 | -10.95 | -15.02 | 1.70 | -15.61 |
| | $CH_3$ | 1.970 | 2.349 | 7.554 | 7.766 | -4.03 | 1.729 | 5.074 | 12.10 | 15.34 | -11.62 | -15.65 | 1.83 | -15.81 |
| | OH | 1.944 | 2.488 | 8.099 | 8.143 | -4.44 | 1.744 | 4.868 | 11.99 | 14.77 | -10.64 | -15.08 | 1.66 | -15.49 |
| | $NH_2$ | 1.949 | 2.462 | 7.995 | 8.064 | -4.29 | 1.743 | 4.890 | 11.926 | 14.923 | -10.69 | -14.98 | 1.74 | -15.38 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | *d* | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | *d* | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **Watson-Crick C8-X** | NO | 1.814 | 3.484 | 11.11 | 10.76 | -7.85 | 1.777 | 4.627 | 11.13 | 14.53 | -9.65 | -17.5 | 1.78 | -16.07 |
| | $NO_2$ | 1.823 | 3.412 | 10.89 | 10.58 | -7.48 | 1.776 | 4.640 | 11.13 | 14.58 | -9.72 | -17.20 | 1.76 | -15.92 |
| | Cl | 1.861 | 3.124 | 9.946 | 9.85 | -6.46 | 1.755 | 4.899 | 11.30 | 15.29 | -10.83 | -17.29 | 1.91 | -15.64 |
| | F | 1.864 | 3.099 | 9.860 | 9.788 | -6.37 | 1.754 | 4.904 | 11.30 | 15.29 | -10.82 | -17.19 | 1.91 | -15.60 |
| | H | 1.868 | 3.075 | 9.786 | 9.722 | -6.27 | 1.745 | 5.026 | 11.37 | 15.62 | -11.34 | -17.61 | 2.03 | -15.68 |
| | $CH_3$ | 1.875 | 3.023 | 9.611 | 9.589 | -6.07 | 1.740 | 5.087 | 11.39 | 15.79 | -11.60 | -17.67 | 2.09 | -15.65 |
| | OH | 1.875 | 3.028 | 9.627 | 9.604 | -5.95 | 1.743 | 5.044 | 11.36 | 15.67 | -11.41 | -17.36 | 2.11 | -15.55 |
| | $NH_2$ | 1.883 | 2.967 | 9.423 | 9.442 | -5.81 | 1.736 | 5.137 | 11.40 | 15.92 | -11.79 | -17.6 | 2.22 | -15.51 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **Watson-Crick N9-X** | NO | 1.844 | 3.247 | 10.35 | 10.17 | -6.87 | 1.773 | 4.674 | 11.14 | 14.69 | -9.93 | -16.8 | 1.74 | -15.60 |
| | $NO_2$ | 1.843 | 3.254 | 10.37 | 10.19 | -6.96 | 1.774 | 4.663 | 11.14 | 14.64 | -9.85 | -16.81 | 1.74 | -15.59 |
| | Cl | 1.855 | 3.167 | 10.09 | 9.965 | -6.61 | 1.756 | 4.881 | 11.30 | 15.23 | -10.74 | -17.35 | 1.90 | -15.71 |
| | F | 1.850 | 3.205 | 10.22 | 10.06 | -6.65 | 1.759 | 4.846 | 11.28 | 15.14 | -10.61 | -17.26 | 1.88 | -15.73 |
| | H | 1.869 | 3.065 | 9.746 | 9.722 | -6.25 | 1.746 | 5.013 | 11.36 | 15.62 | -11.31 | -17.56 | 2.00 | -15.68 |
| | $CH_3$ | 1.874 | 3.028 | 9.624 | 9.601 | -6.12 | 1.741 | 5.078 | 11.40 | 15.75 | -11.54 | -17.66 | 2.11 | -15.66 |
| | OH | 1.860 | 3.134 | 9.976 | 9.881 | -6.43 | 1.751 | 4.941 | 11.34 | 15.38 | -10.96 | -17.39 | 1.95 | -15.78 |
| | $NH_2$ | 1.869 | 3.063 | 9.744 | 9.692 | -6.17 | 1.746 | 5.005 | 11.36 | 15.56 | -11.23 | -17.4 | 1.98 | -15.71 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA2 C2-X** | NO | 1.901 | 3.446 | 9.063 | 11.83 | -4.41 | 1.937 | 3.087 | 8.562 | 10.76 | -4.25 | -8.66 | 1.48 | -13.10 |
| | $NO_2$ | 1.884 | 3.586 | 9.358 | 12.19 | -4.78 | 1.936 | 3.093 | 8.584 | 10.78 | -4.30 | -9.08 | 1.22 | -13.85 |
| | Cl | 1.904 | 3.423 | 9.014 | 11.77 | -4.44 | 1.919 | 3.218 | 8.877 | 11.15 | -4.61 | -9.05 | 1.49 | -13.48 |
| | F | 1.905 | 3.415 | 8.997 | 11.74 | -4.37 | 1.916 | 3.242 | 8.930 | 11.22 | -4.66 | -9.03 | 1.48 | -13.54 |
| | H | 1.927 | 3.244 | 8.605 | 11.28 | -4.00 | 1.910 | 3.294 | 9.039 | 11.37 | -4.76 | -8.76 | 1.43 | -13.21 |
| | $CH_3$ | 1.932 | 3.206 | 8.525 | 11.17 | -3.90 | 1.905 | 3.334 | 9.125 | 11.49 | -4.88 | -8.78 | 1.45 | -13.22 |
| | OH | 1.917 | 3.319 | 8.787 | 11.47 | -4.16 | 1.901 | 3.361 | 9.196 | 11.56 | -4.96 | -9.12 | 1.41 | -13.73 |
| | $NH_2$ | 1.937 | 3.169 | 8.436 | 11.06 | -3.79 | 1.891 | 3.445 | 9.376 | 11.80 | -5.17 | -8.96 | 1.55 | -13.38 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta(H, A)\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta(H, A)\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA2 C8-X** | NO | 1.856 | 3.775 | 10.05 | 12.63 | -6.06 | 1.958 | 2.989 | 8.036 | 10.52 | -3.38 | -9.44 | 1.49 | -13.61 |
| | $NO_2$ | 1.861 | 3.700 | 9.917 | 12.43 | -5.92 | 1.962 | 2.984 | 8.009 | 10.51 | -3.36 | -9.28 | 1.44 | -13.45 |
| | Cl | 1.901 | 3.361 | 9.194 | 11.55 | -4.96 | 1.937 | 3.170 | 8.443 | 11.05 | -3.81 | -8.77 | 1.41 | -13.15 |
| | F | 1.904 | 3.337 | 9.140 | 11.48 | -4.86 | 1.937 | 3.171 | 8.443 | 11.06 | -3.80 | -8.66 | 1.42 | -13.08 |
| | H | 1.910 | 3.294 | 9.039 | 11.37 | -4.76 | 1.927 | 3.244 | 8.605 | 11.28 | -4.00 | -8.76 | 1.43 | -13.21 |
| | $CH_3$ | 1.919 | 3.222 | 8.873 | 11.18 | -4.58 | 1.920 | 3.302 | 8.736 | 11.44 | -4.12 | -8.70 | 1.46 | -13.18 |
| | OH | 1.921 | 3.208 | 8.829 | 11.15 | -4.52 | 1.923 | 3.276 | 8.680 | 11.36 | -4.08 | -8.60 | 1.51 | -13.01 |
| | $NH_2$ | 1.930 | 3.143 | 8.677 | 10.97 | -4.34 | 1.915 | 3.337 | 8.810 | 11.54 | -4.22 | -8.56 | 1.53 | -13.02 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta(H, A)\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta(H, A)\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA2 N9-X** | NO | 1.906 | 3.412 | 8.970 | 11.75 | -4.28 | 1.957 | 2.949 | 8.200 | 10.31 | -3.81 | -8.09 | 1.35 | -12.90 |
| | $NO_2$ | 1.905 | 3.419 | 8.987 | 11.75 | -4.35 | 1.961 | 2.911 | 8.114 | 10.18 | -3.77 | -8.12 | 1.36 | -12.78 |
| | Cl | 1.919 | 3.305 | 8.736 | 11.45 | -3.97 | 1.935 | 3.091 | 8.578 | 10.70 | -4.25 | -8.22 | 1.35 | -12.86 |
| | F | 1.916 | 3.332 | 8.797 | 11.52 | -4.21 | 1.940 | 3.048 | 8.481 | 10.58 | -4.31 | -8.52 | 1.33 | -12.82 |
| | H | 1.927 | 3.244 | 8.605 | 11.28 | -4.00 | 1.910 | 3.294 | 9.039 | 11.37 | -4.76 | -8.76 | 1.43 | -13.21 |
| | $CH_3$ | 1.930 | 3.222 | 8.555 | 11.22 | -3.88 | 1.899 | 3.377 | 9.238 | 11.60 | -4.88 | -8.76 | 1.50 | -13.35 |
| | OH | 1.910 | 3.376 | 8.912 | 11.64 | -4.33 | 1.912 | 3.265 | 9.019 | 11.22 | -4.76 | -9.09 | 1.48 | -13.55 |
| | $NH_2$ | 1.921 | 3.287 | 8.705 | 11.39 | -4.05 | 1.905 | 3.328 | 9.140 | 11.43 | -4.81 | -8.86 | 1.49 | -13.47 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA3 C2-X** | NO | 1.951 | 3.003 | 8.287 | 10.41 | -3.67 | 2.003 | 2.662 | 7.394 | 9.390 | -2.6 | -6.27 | 1.84 | -10.86 |
| | $NO_2$ | 1.935 | 3.114 | 8.568 | 10.70 | -4.06 | 1.999 | 2.685 | 7.466 | 9.453 | -3.01 | -7.07 | 1.20 | -11.94 |
| | Cl | 1.953 | 2.989 | 8.263 | 10.36 | -3.66 | 1.983 | 2.784 | 7.731 | 9.757 | -3.14 | -6.80 | 1.29 | -11.76 |
| | F | 1.955 | 2.975 | 8.218 | 10.32 | -3.62 | 1.980 | 2.804 | 7.782 | 9.819 | -3.21 | -6.83 | 1.28 | -11.82 |
| | H | 1.961 | 2.924 | 8.084 | 10.24 | -3.76 | 1.961 | 2.924 | 8.084 | 10.24 | -3.76 | -7.52 | 1.36 | -11.84 |
| | $CH_3$ | 2.014 | 2.602 | 7.139 | 9.377 | -3.17 | 2.006 | 2.658 | 7.283 | 9.499 | -3.23 | -6.40 | 1.25 | -11.58 |
| | OH | 1.968 | 2.885 | 7.983 | 10.06 | -3.39 | 1.965 | 2.904 | 8.041 | 10.12 | -3.41 | -6.80 | 1.20 | -11.95 |
| | $NH_2$ | 1.955 | 2.959 | 8.255 | 10.27 | -3.50 | 1.919 | 3.219 | 8.925 | 10.98 | -4.03 | -7.53 | 1.44 | -12.01 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA3 N9-X** | NO | 1.955 | 2.975 | 8.199 | 10.34 | -3.66 | 2.022 | 2.544 | 7.066 | 8.979 | -2.58 | -6.24 | 1.15 | -11.16 |
| | $NO_2$ | 1.956 | 2.971 | 8.185 | 10.31 | -3.63 | 2.030 | 2.496 | 6.936 | 8.823 | -2.57 | -6.20 | 1.16 | -11.03 |
| | Cl | 1.968 | 2.887 | 7.974 | 10.07 | -3.40 | 2.003 | 2.651 | 7.368 | 9.289 | -2.87 | -6.27 | 1.17 | -11.17 |
| | F | 1.965 | 2.906 | 8.025 | 10.13 | -3.51 | 2.008 | 2.614 | 7.277 | 9.178 | -2.97 | -6.48 | 1.14 | -11.11 |
| | H | 1.961 | 2.924 | 8.084 | 10.24 | -3.76 | 1.961 | 2.924 | 8.084 | 10.24 | -3.76 | -7.52 | 1.36 | -11.84 |
| | $CH_3$ | 1.982 | 2.802 | 7.745 | 9.828 | -3.22 | 1.966 | 2.905 | 8.030 | 10.11 | -3.28 | -6.50 | 1.34 | -11.66 |
| | OH | 1.961 | 2.930 | 7.802 | 10.21 | -3.59 | 1.979 | 2.807 | 8.097 | 9.792 | -3.28 | -6.87 | 1.28 | -11.79 |
| | $NH_2$ | 1.970 | 2.874 | 7.952 | 10.04 | -3.42 | 1.970 | 2.868 | 7.951 | 9.987 | -3.32 | -6.74 | 1.29 | -11.78 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA4 C8-X** | NO | 1.825 | 4.138 | 10.30 | 13.70 | -6.84 | 1.931 | 3.210 | 8.524 | 11.23 | -4.28 | -11.12 | 1.58 | -14.68 |
| | $NO_2$ | 1.836 | 4.029 | 10.12 | 13.44 | -6.54 | 1.929 | 3.229 | 8.568 | 11.28 | -4.32 | -10.86 | 1.52 | -14.49 |
| | Cl | 1.879 | 3.638 | 9.426 | 12.43 | -5.42 | 1.900 | 3.456 | 9.053 | 11.93 | -4.95 | -10.37 | 1.45 | -14.11 |
| | F | 1.883 | 3.603 | 9.354 | 12.34 | -5.27 | 1.901 | 3.454 | 9.047 | 11.93 | -4.90 | -10.17 | 1.44 | -14.04 |
| | H | 1.889 | 3.550 | 9.244 | 12.20 | -5.14 | 1.889 | 3.551 | 9.247 | 12.21 | -5.15 | -10.29 | 1.46 | -14.14 |
| | $CH_3$ | 1.899 | 3.469 | 9.077 | 11.99 | -4.92 | 1.881 | 3.616 | 9.376 | 12.38 | -5.31 | -10.23 | 1.49 | -14.10 |
| | $O_H$ | 1.899 | 3.468 | 9.075 | 11.99 | -4.87 | 1.885 | 3.589 | 9.323 | 12.30 | -5.25 | -10.12 | 1.53 | -13.99 |
| | $NH_2$ | 1.910 | 3.382 | 8.889 | 11.76 | -4.65 | 1.877 | 3.658 | 9.453 | 12.50 | -5.44 | -10.09 | 1.56 | -13.94 |

| | | HB1 | | | | | HB2 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}\cdot10^2$ | $L_{BCP}\cdot10^2$ | $\delta$(H, A)$\cdot10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA4 N9-X** | NO | 1.859 | 3.813 | 9.757 | 12.89 | -5.85 | 1.922 | 3.281 | 8.679 | 11.43 | -4.43 | -10.28 | 1.44 | -14.18 |
| | $NO_2$ | 1.856 | 3.840 | 9.806 | 12.96 | -5.91 | 1.925 | 3.261 | 8.636 | 11.38 | -4.38 | -10.29 | 1.46 | -14.20 |
| | Cl | 1.872 | 3.697 | 9.542 | 12.59 | -5.54 | 1.903 | 3.435 | 9.011 | 11.88 | -4.86 | -10.40 | 1.48 | -14.21 |
| | F | 1.868 | 3.734 | 9.613 | 12.69 | -5.62 | 1.905 | 3.414 | 8.968 | 11.82 | -4.78 | -10.40 | 1.47 | -14.26 |
| | H | 1.889 | 3.550 | 9.244 | 12.20 | -5.14 | 1.889 | 3.551 | 9.247 | 12.21 | -5.15 | -10.29 | 1.46 | -14.14 |
| | $CH_3$ | 1.895 | 3.501 | 9.143 | 12.07 | -5.00 | 1.884 | 3.597 | 9.335 | 12.33 | -5.24 | -10.24 | 1.50 | -14.09 |
| | OH | 1.879 | 3.639 | 9.424 | 12.44 | -5.39 | 1.898 | 3.476 | 9.095 | 11.99 | -4.91 | -10.30 | 1.47 | -14.10 |
| | $NH_2$ | 1.888 | 3.555 | 9.256 | 12.22 | -5.14 | 1.892 | 3.531 | 9.202 | 12.15 | -5.06 | -10.20 | 1.47 | -14.06 |

| | | HB1 | | | | HB2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA2 C2-X+C8-X** | NO | 1.886 | 3.482 | 9.481 | -5.30 | 1.936 | 3.171 | 8.469 | -3.77 | -9.07 | 1.99 | -12.36 |
| | NO2 | 1.894 | 3.413 | 9.337 | -5.13 | 1.925 | 3.247 | 8.645 | -4.02 | -9.15 | 1.39 | -12.98 |
| | Cl | 1.911 | 3.343 | 9.019 | -4.77 | 1.914 | 3.279 | 8.850 | -4.26 | -9.03 | 1.47 | -13.34 |
| | F | 1.911 | 3.328 | 9.034 | -4.75 | 1.916 | 3.285 | 8.809 | -4.14 | -8.89 | 1.45 | -13.37 |
| | H | 1.910 | 3.294 | 9.039 | -4.76 | 1.927 | 3.244 | 8.605 | -4.00 | -8.76 | 1.43 | -13.21 |
| | CH3 | 1.913 | 3.269 | 8.981 | -4.68 | 1.927 | 3.249 | 8.617 | -3.98 | -8.66 | 1.48 | -13.16 |
| | OH | 1.911 | 3.289 | 9.034 | -4.70 | 1.916 | 3.331 | 8.802 | -4.18 | -8.88 | 1.47 | -13.56 |
| | NH2 | 1.912 | 3.247 | 8.608 | -4.69 | 1.927 | 3.284 | 9.008 | -3.96 | -8.65 | 1.63 | -13.09 |

| | | HB1 | | | | HB2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA3 C2-X+C2-X** | NO | 1.964 | 2.896 | 8.034 | -3.67 | 1.964 | 2.895 | 8.032 | -3.67 | -7.34 | 2.58 | -10.12 |
| | NO2 | 1.968 | 2.877 | 7.986 | -3.07 | 1.969 | 2.882 | 8.004 | -3.07 | -6.14 | 1.25 | -11.29 |
| | Cl | 1.962 | 2.918 | 8.091 | -3.62 | 1.963 | 2.923 | 8.107 | -3.61 | -7.23 | 1.33 | -11.86 |
| | F | 1.961 | 2.922 | 8.095 | -3.48 | 1.962 | 2.929 | 8.114 | -3.48 | -6.96 | 1.30 | -12.00 |
| | H | 1.961 | 2.924 | 8.084 | -3.76 | 1.961 | 2.924 | 8.084 | -3.76 | -7.52 | 1.36 | -11.84 |
| | CH3 | 1.975 | 2.846 | 7.876 | -3.28 | 1.975 | 2.844 | 7.870 | -3.28 | -6.56 | 1.32 | -11.56 |
| | OH | 1.959 | 2.945 | 8.150 | -3.47 | 1.961 | 2.937 | 8.124 | -3.46 | -6.93 | 1.15 | -12.37 |
| | NH2 | 1.953 | 2.983 | 8.234 | -3.84 | 1.954 | 2.977 | 8.215 | -3.84 | -7.68 | 1.49 | -12.09 |

| | | HB1 | | | | HB2 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | X | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $d$ | $\rho_{BCP}*10^2$ | $L_{BCP}*10^2$ | $E_{HB}$ | $\sum E_{HB}$ | $E_{def}$ | $E_{SM}$ |
| **AA4 C8-X+C8-X** | NO | 1.872 | 3.686 | 9.534 | -5.53 | 1.872 | 3.687 | 9.537 | -5.53 | -11.06 | 1.48 | -14.17 |
| | NO2 | 1.879 | 3.619 | 9.401 | -5.36 | 1.880 | 3.624 | 9.415 | -5.37 | -10.73 | 1.40 | -13.98 |
| | Cl | 1.890 | 3.535 | 9.221 | -5.14 | 1.891 | 3.540 | 9.234 | -5.15 | -10.29 | 1.42 | -14.03 |
| | F | 1.893 | 3.513 | 9.176 | -5.04 | 1.893 | 3.517 | 9.186 | -5.04 | -10.08 | 1.43 | -13.90 |
| | H | 1.889 | 3.551 | 9.247 | -5.15 | 1.889 | 3.550 | 9.244 | -5.14 | -10.29 | 1.46 | -14.14 |
| | CH3 | 1.891 | 3.531 | 9.203 | -5.07 | 1.892 | 3.531 | 9.203 | -5.07 | -10.14 | 1.50 | -14.04 |
| | OH | 1.895 | 3.504 | 9.152 | -4.97 | 1.895 | 3.503 | 9.148 | -4.97 | -9.94 | 1.59 | -14.38 |
| | NH2 | 1.897 | 3.488 | 9.111 | -4.92 | 1.897 | 3.486 | 9.105 | -4.92 | -9.84 | 1.65 | -13.65 |

**Table S8.** Changes in aromaticity expressed by the HOMA index for (a) AD6 and (b) AD5 rings due to substitution in WC and HG pairs.

| (a) | **WC C8-X** | **HG C2-X** | **HG N9-X** | **WC N9-X** |
|---|---|---|---|---|
| **X** | Differences in HOMA index between substituted and unsubstituted systems* | | | |
| NO | 0.079 | 0.019 | -0.006 | -0.011 |
| $NO_2$ | 0.041 | 0.007 | 0.000 | -0.005 |
| Cl | -0.005 | -0.005 | 0.002 | -0.001 |
| F | -0.011 | -0.002 | 0.009 | 0.007 |
| **H** | **0.000** | **0.000** | **0.000** | **0.000** |
| $CH_3$ | -0.007 | -0.001 | -0.002 | -0.001 |
| OH | -0.016 | -0.004 | 0.004 | 0.004 |
| $NH_2$ | -0.016 | 0.006 | -0.001 | -0.003 |
| Differences in HOMA and cSAR(X) values for X=$NH_2$ and $NO_2$ systems** | | | | |
| **ΔHOMA** | 0.057 | 0.001 | 0.001 | -0.002 |
| **ΔcSAR(X)** | 0.273 | 0.241 | 0.155 | 0.157 |
| **ΔHOMA/ ΔcSAR(X)** | 0.210 | 0.006 | 0.004 | -0.015 |

| (b) | **WC C8-X** | **HG C2-X** | **HG N9-X** | **WC N9-X** |
|---|---|---|---|---|
| **X** | Differences in HOMA index between substituted and unsubstituted systems* | | | |
| NO | 0.003 | -0.013 | 0.122 | 0.133 |
| $NO_2$ | -0.016 | -0.012 | 0.116 | 0.121 |
| Cl | 0.019 | -0.007 | 0.021 | 0.022 |
| F | 0.042 | -0.005 | -0.007 | -0.009 |
| **H** | **0.000** | **0.000** | **0.000** | **0.000** |
| $CH_3$ | 0.011 | -0.001 | 0.006 | -0.004 |
| OH | 0.027 | 0.002 | -0.045 | -0.045 |
| $NH_2$ | 0.028 | 0.009 | -0.004 | 0.005 |
| Differences in HOMA and cSAR(X) values for X=$NH_2$ and $NO_2$ systems** | | | | |
| **ΔHOMA** | -0.044 | -0.021 | 0.120 | 0.116 |
| **ΔcSAR(X)** | 0.273 | 0.241 | 0.152 | 0.156 |
| **ΔHOMA/ ΔcSAR(X)** | -0.163 | -0.086 | 0.792 | 0.748 |

* HOMA(unsubstituted)-HOMA(substituted)

** ΔHOMA = HOMA($NH_2$) - HOMA($NO_2$); ΔcSAR(X) = cSAR($NH_2$) - cSAR($NO_2$).

**Table S9.** Changes in aromaticity expressed by the HOMA index for (a) AD6 and (b) AD5 rings due to substitution in AA dimers.

| (a) | AA2 C2-X | AA3 C2-X | AA2 C8-X | AA4 C8-X | AA2 N9-X | AA3 N9-X | AA4 N9-X |
|---|---|---|---|---|---|---|---|
| **X** | Differences in HOMA index between substituted and unsubstituted systems* | | | | | | |
| NO | 0.027 | 0.016 | 0.071 | 0.083 | 0.007 | -0.005 | -0.008 |
| $NO_2$ | 0.023 | 0.012 | 0.034 | 0.045 | 0.014 | 0.003 | -0.002 |
| Cl | 0.008 | -0.003 | -0.014 | -0.004 | 0.015 | 0.004 | 0.001 |
| F | 0.010 | -0.001 | -0.021 | -0.010 | 0.024 | 0.013 | 0.009 |
| **H** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** |
| $CH_3$ | 0.008 | 0.002 | -0.018 | -0.008 | 0.009 | -0.002 | 0.000 |
| OH | 0.006 | -0.005 | -0.027 | -0.017 | 0.015 | 0.003 | 0.005 |
| $NH_2$ | 0.014 | 0.005 | -0.028 | -0.018 | 0.007 | -0.004 | -0.002 |
| Differences in HOMA and cSAR(X) values for X=$NH_2$ and $NO_2$ systems** | | | | | | | |
| **ΔHOMA** | 0.005 | 0.000 | 0.058 | 0.059 | 0.002 | 0.003 | -0.002 |
| **ΔcSAR(X)** | 0.241 | 0.226 | 0.274 | 0.275 | 0.152 | 0.156 | 0.156 |
| **ΔHOMA/ ΔcSAR(X)** | 0.020 | -0.001 | 0.210 | 0.214 | 0.016 | 0.016 | -0.010 |

| (b) | AA2 C2-X | AA3 C2-X | AA2 C8-X | AA4 C8-X | AA2 N9-X | AA3 N9-X | AA4 N9-X |
|---|---|---|---|---|---|---|---|
| **X** | Differences in HOMA index between substituted and unsubstituted systems* | | | | | | |
| NO | 0.005 | -0.001 | -0.003 | 0.003 | 0.129 | 0.122 | 0.135 |
| $NO_2$ | -0.006 | -0.009 | -0.021 | -0.016 | 0.124 | 0.118 | 0.123 |
| Cl | -0.002 | -0.006 | 0.015 | 0.020 | 0.026 | 0.022 | 0.022 |
| F | 0.000 | -0.005 | 0.037 | 0.042 | -0.001 | -0.005 | -0.009 |
| **H** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** | **0.000** |
| $CH_3$ | 0.003 | 0.001 | 0.006 | 0.010 | 0.000 | -0.005 | -0.004 |
| OH | 0.006 | 0.002 | 0.023 | 0.028 | -0.041 | -0.047 | -0.044 |
| $NH_2$ | 0.012 | 0.006 | 0.024 | 0.028 | 0.009 | 0.004 | 0.005 |
| Differences in HOMA and cSAR(X) values for X=$NH_2$ and $NO_2$ systems** | | | | | | | |
| **ΔHOMA** | -0.020 | -0.017 | -0.047 | -0.046 | 0.113 | 0.112 | 0.117 |
| **ΔcSAR(X)** | 0.241 | 0.226 | 0.274 | 0.275 | 0.156 | 0.155 | 0.157 |
| **ΔHOMA/ ΔcSAR(X)** | -0.083 | -0.076 | -0.172 | -0.169 | 0.729 | 0.725 | 0.745 |

* HOMA(unsubstituted)-HOMA(substituted)

** ΔHOMA = HOMA($NH_2$) - HOMA($NO_2$); ΔcSAR(X) = cSAR($NH_2$) - cSAR($NO_2$).