

## ***Supporting Information for:***

**Full Paper** | <http://dx.doi.org/10.17807/orbital.v13i4.1607>

### **Combined Conceptual-DFT, Quantitative MEP Analysis, and Molecular Docking Study of Benzodiazepine Analogs**

Rachida Djebaili <sup>a</sup>, Nadjib Melkemi <sup>a</sup>, Samir Kenouche <sup>b</sup>, Ismail Daoud <sup>c</sup>, Mohammed Bouachrine <sup>d,e</sup>, Halima Hazhazi <sup>a</sup>, and Toufik Salah <sup>a</sup>

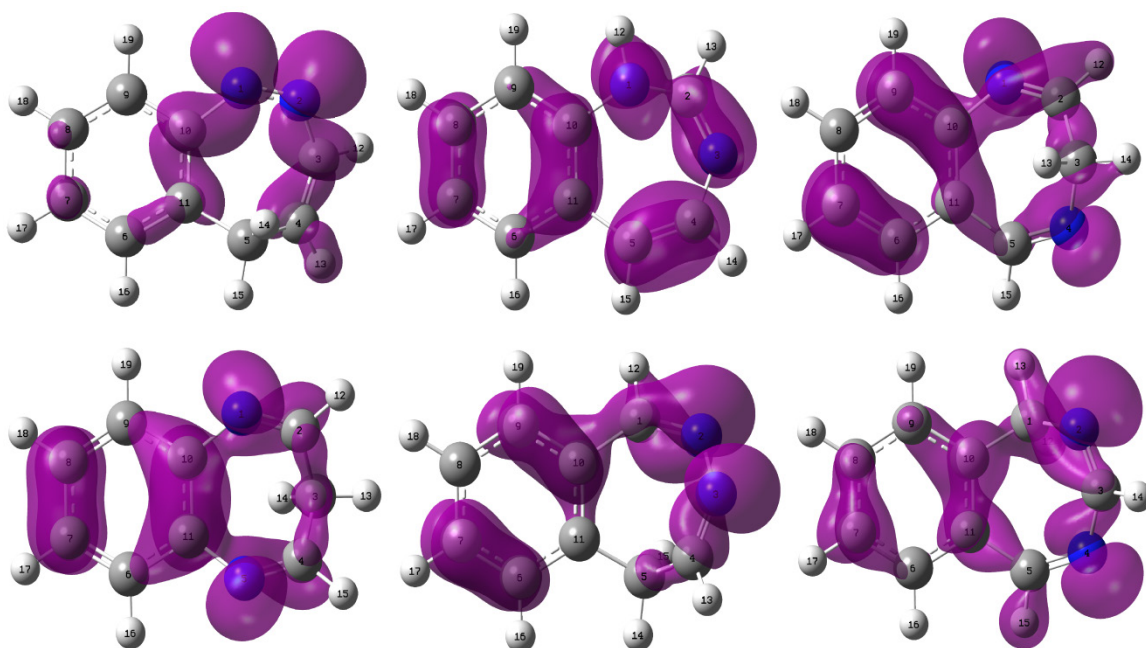
<sup>a</sup>Group of Computational and Pharmaceutical Chemistry, LMCE Laboratory, University Mohamed Khider, 07000 Biskra, Algeria. <sup>b</sup>Group of Modeling of Chemical Systems using Quantum Calculations, Applied Chemistry Laboratory (LCA). University M. Khider of Biskra, 07000 Biskra, Algeria. <sup>c</sup>University Abou-Bakr Belkaid-Faculty of Science- Department of Chemistry- Laboratory of Natural Substances and Bioactive (LASNABIO)-Tlemcen-Algeria. <sup>d</sup>MCNS Laboratory, Faculty of Science, Moulay Ismail University of Meknes, Morocco. <sup>e</sup> EST Khenifra, Sultan Moulay Slimane University, Morocco. \*Corresponding author. E-mail: [bouachrine@gmail.com](mailto:bouachrine@gmail.com)

**Table S1.** Mullikan, NPA, ChelpG, and Hirshfeld Partial Charges used in the statistical test.

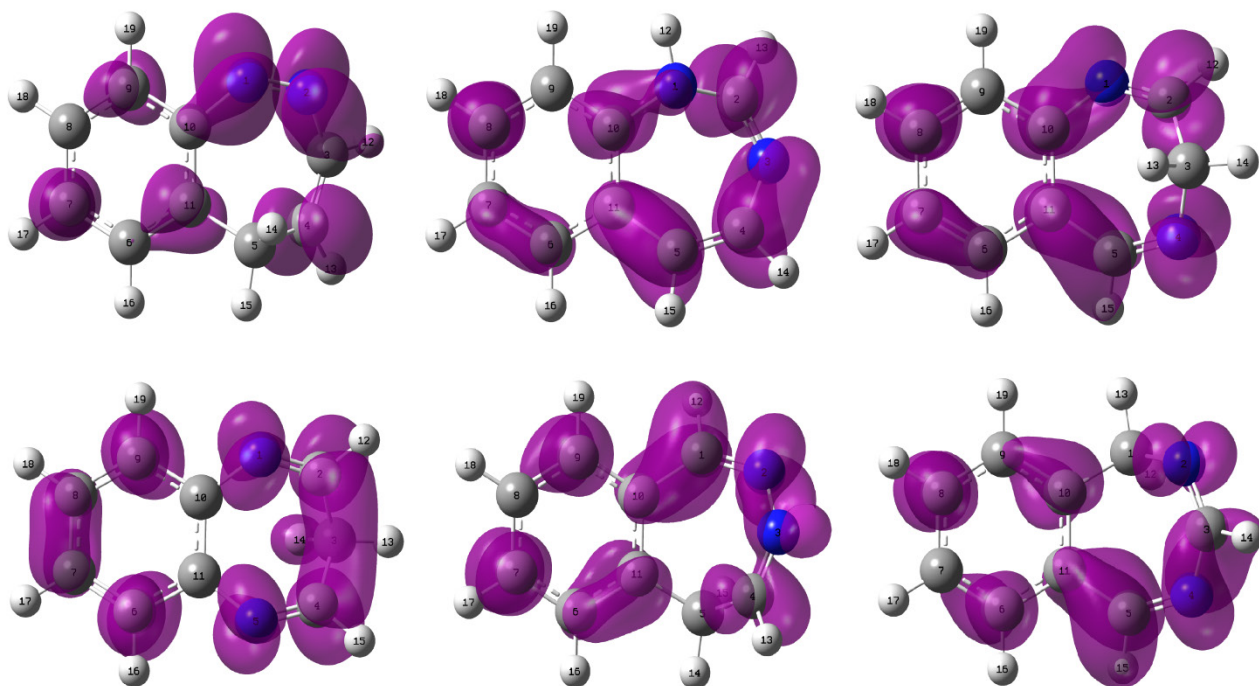
| Atom     | 6-31G  | 6-311<br>G | 6-31+<br>G (d) | 6-311+<br>G (d) | 6-31++<br>G (d,p) | 6-311++<br>G (d,p) | 6-31G  | 6-311<br>G | 6-31+<br>G (d) | 6-311+<br>G (d) | 6-31++<br>G (d,p) | 6-311++<br>G (d,p) |
|----------|--------|------------|----------------|-----------------|-------------------|--------------------|--------|------------|----------------|-----------------|-------------------|--------------------|
| Mullikan |        |            |                |                 |                   | NPA                |        |            |                |                 |                   |                    |
| 1 N      | -0.398 | -0.367     | -0.228         | 0.004           | -0.188            | -0.027             | -0.448 | -0.461     | -0.462         | -0.472          | -0.462            | -0.470             |
| 2 C      | 0.045  | 0.029      | 0.026          | -0.003          | 0.054             | 0.059              | 0.100  | 0.157      | 0.126          | 0.174           | 0.131             | 0.175              |
| 3 C      | -0.226 | -0.375     | -0.407         | -0.637          | -0.205            | -0.426             | -0.395 | -0.297     | -0.381         | -0.290          | -0.365            | -0.294             |
| 4 N      | -0.350 | -0.303     | -0.189         | -0.015          | -0.186            | -0.103             | -0.437 | -0.440     | -0.460         | -0.459          | -0.456            | -0.456             |
| 5 C      | -0.041 | -0.004     | -0.349         | -0.690          | -0.495            | -0.506             | 0.056  | 0.103      | 0.088          | 0.128           | 0.091             | 0.126              |
| 6 C      | -0.181 | -0.160     | -0.781         | -0.438          | -0.212            | -0.267             | -0.207 | -0.169     | -0.201         | -0.165          | -0.198            | -0.165             |
| 7 C      | -0.131 | -0.166     | -0.048         | -0.220          | -0.122            | -0.294             | -0.244 | -0.203     | -0.246         | -0.208          | -0.241            | -0.209             |
| 8 C      | -0.136 | -0.132     | -0.334         | -0.335          | -0.084            | -0.330             | -0.226 | -0.183     | -0.222         | -0.181          | -0.217            | -0.182             |
| 9 C      | -0.121 | -0.157     | -0.619         | -0.267          | -0.444            | -0.360             | -0.231 | -0.194     | -0.233         | -0.199          | -0.232            | -0.200             |
| 10 C     | 0.100  | 0.089      | -0.169         | -0.915          | -0.507            | -0.779             | 0.128  | 0.132      | 0.131          | 0.141           | 0.135             | 0.143              |
| 11 C     | 0.115  | 0.000      | 1.388          | 1.485           | 1.123             | 1.421              | -0.144 | -0.140     | -0.156         | -0.150          | -0.151            | -0.147             |
| 12 H     | 0.176  | 0.201      | 0.212          | 0.242           | 0.162             | 0.217              | 0.241  | 0.193      | 0.236          | 0.189           | 0.228             | 0.188              |
| 13 H     | 0.184  | 0.227      | 0.237          | 0.274           | 0.202             | 0.182              | 0.259  | 0.214      | 0.251          | 0.211           | 0.245             | 0.211              |
| 14 H     | 0.170  | 0.207      | 0.216          | 0.269           | 0.172             | 0.197              | 0.267  | 0.215      | 0.263          | 0.212           | 0.249             | 0.212              |
| 15 H     | 0.168  | 0.198      | 0.206          | 0.240           | 0.159             | 0.213              | 0.242  | 0.196      | 0.236          | 0.191           | 0.229             | 0.191              |
| 16 H     | 0.162  | 0.184      | 0.213          | 0.258           | 0.131             | 0.192              | 0.258  | 0.218      | 0.256          | 0.218           | 0.252             | 0.218              |
| 17 H     | 0.155  | 0.177      | 0.207          | 0.250           | 0.135             | 0.198              | 0.259  | 0.218      | 0.258          | 0.219           | 0.253             | 0.219              |
| 18 H     | 0.156  | 0.177      | 0.207          | 0.250           | 0.143             | 0.196              | 0.259  | 0.218      | 0.258          | 0.218           | 0.253             | 0.219              |
| 19 H     | 0.152  | 0.173      | 0.212          | 0.247           | 0.161             | 0.218              | 0.262  | 0.223      | 0.259          | 0.222           | 0.256             | 0.221              |
| ChelpG   |        |            |                |                 |                   | Hirshfeld          |        |            |                |                 |                   |                    |
| 1 N      | -0.659 | -0.696     | -0.651         | -0.649          | -0.650            | -0.653             | -0.167 | -0.166     | -0.167         | -0.164          | -0.167            | -0.163             |
| 2 C      | 0.268  | 0.288      | 0.224          | 0.227           | 0.225             | 0.242              | 0.056  | 0.057      | 0.063          | 0.062           | 0.064             | 0.064              |
| 3 C      | 0.412  | 0.445      | 0.547          | 0.524           | 0.551             | 0.515              | -0.018 | -0.019     | -0.019         | -0.021          | -0.019            | -0.020             |
| 4 N      | -0.709 | -0.725     | -0.748         | -0.736          | -0.750            | -0.736             | -0.189 | -0.185     | -0.191         | -0.187          | -0.190            | -0.185             |
| 5 C      | 0.477  | 0.458      | 0.462          | 0.447           | 0.464             | 0.458              | 0.032  | 0.032      | 0.039          | 0.038           | 0.040             | 0.039              |
| 6 C      | -0.159 | -0.178     | -0.178         | -0.190          | -0.177            | -0.177             | -0.035 | -0.034     | -0.033         | -0.034          | -0.032            | -0.032             |
| 7 C      | -0.103 | -0.091     | -0.086         | -0.088          | -0.080            | -0.085             | -0.041 | -0.041     | -0.042         | -0.043          | -0.041            | -0.041             |
| 8 C      | -0.042 | -0.055     | -0.053         | -0.069          | -0.056            | -0.074             | -0.033 | -0.032     | -0.032         | -0.033          | -0.031            | -0.031             |
| 9 C      | -0.266 | -0.269     | -0.252         | -0.255          | -0.245            | -0.229             | -0.049 | -0.049     | -0.051         | -0.051          | -0.050            | -0.049             |
| 10 C     | 0.488  | 0.508      | 0.474          | 0.471           | 0.468             | 0.463              | 0.036  | 0.034      | 0.039          | 0.037           | 0.040             | 0.038              |
| 11 C     | -0.168 | -0.149     | -0.124         | -0.115          | -0.125            | -0.125             | -0.025 | -0.024     | -0.020         | -0.021          | -0.019            | -0.019             |
| 12 H     | 0.045  | 0.045      | 0.054          | 0.056           | 0.053             | 0.051              | 0.059  | 0.059      | 0.056          | 0.057           | 0.056             | 0.055              |
| 13 H     | -0.035 | -0.046     | -0.082         | -0.075          | -0.082            | -0.073             | 0.046  | 0.045      | 0.045          | 0.045           | 0.044             | 0.044              |
| 14 H     | -0.034 | -0.041     | -0.065         | -0.057          | -0.066            | -0.057             | 0.049  | 0.050      | 0.045          | 0.046           | 0.045             | 0.045              |
| 15 H     | -0.020 | -0.006     | -0.009         | -0.003          | -0.009            | -0.007             | 0.051  | 0.052      | 0.049          | 0.050           | 0.049             | 0.048              |
| 16 H     | 0.139  | 0.144      | 0.139          | 0.145           | 0.137             | 0.138              | 0.058  | 0.057      | 0.056          | 0.057           | 0.055             | 0.054              |
| 17 H     | 0.112  | 0.110      | 0.104          | 0.109           | 0.101             | 0.105              | 0.058  | 0.057      | 0.056          | 0.057           | 0.055             | 0.054              |
| 18 H     | 0.111  | 0.115      | 0.110          | 0.118           | 0.109             | 0.115              | 0.059  | 0.058      | 0.058          | 0.059           | 0.056             | 0.056              |
| 19 H     | 0.141  | 0.142      | 0.134          | 0.140           | 0.131             | 0.130              | 0.053  | 0.050      | 0.048          | 0.049           | 0.046             | 0.046              |

**Table S2.** The bond lengths, bond angles, and dihedral angles calculated in water, using, DFT (Ub3lyp)/6-311<sup>++</sup>G(d,p)/Hirshfeld/PCM model/Gaussian W09 software.

| system                     | 5H-1,2-<br>bpdz | 1H-1,3-<br>bpdz | 3H-1,4-<br>bpdz | 3H-1,5-<br>bpdz | 5H-2,3-<br>bpdz | 1H-2,4-bpdz |
|----------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-------------|
| <b>Bond Length (Å)</b>     |                 |                 |                 |                 |                 |             |
| 1-2                        | 1.263           | 1.392           | 1.276           | 1.278           | 1.294           | 1.470       |
| 2-3                        | 1.408           | 1.279           | 1.509           | 1.508           | 1.383           | 1.276       |
| 3-4                        | 1.342           | 1.403           | 1.468           | 1.508           | 1.279           | 1.400       |
| 4-5                        | 1.503           | 1.345           | 1.281           | 1.278           | 1.507           | 1.289       |
| 5-11                       | 1.509           | 1.468           | 1.469           | 1.402           | 1.511           | 1.464       |
| 11-6                       | 1.397           | 1.402           | 1.409           | 1.410           | 1.397           | 1.404       |
| 6-7                        | 1.393           | 1.395           | 1.385           | 1.383           | 1.393           | 1.390       |
| 7-8                        | 1.397           | 1.391           | 1.401           | 1.403           | 1.398           | 1.397       |
| 8-9                        | 1.388           | 1.396           | 1.385           | 1.383           | 1.389           | 1.394       |
| 9-10                       | 1.405           | 1.394           | 1.407           | 1.410           | 1.405           | 1.395       |
| 10-11                      | 1.411           | 1.409           | 1.419           | 1.423           | 1.412           | 1.412       |
| 10-1                       | 1.422           | 1.429           | 1.403           | 1.402           | 1.466           | 1.508       |
| <b>Bond Angle (°)</b>      |                 |                 |                 |                 |                 |             |
| 10-1-2                     | 124.534         | 123.236         | 122.027         | 121.790         | 129.543         | 110.744     |
| 1-2-3                      | 124.619         | 128.798         | 124.382         | 124.103         | 120.943         | 117.115     |
| 2-3-4                      | 126.815         | 122.508         | 109.533         | 105.232         | 121.709         | 130.372     |
| 3-4-5                      | 121.910         | 129.591         | 116.732         | 124.103         | 124.800         | 122.214     |
| 4-5-11                     | 107.613         | 127.853         | 128.586         | 121.790         | 106.517         | 128.385     |
| 11-6-7                     | 121.068         | 121.965         | 121.344         | 121.563         | 120.501         | 120.392     |
| 6-7-8                      | 120.070         | 119.281         | 119.519         | 119.723         | 120.270         | 119.690     |
| 7-8-9                      | 119.653         | 119.822         | 120.127         | 119.723         | 119.789         | 120.325     |
| 8-9-10                     | 120.584         | 120.761         | 121.058         | 121.563         | 120.498         | 120.650     |
| 1-10-9                     | 114.049         | 118.242         | 116.614         | 116.231         | 119.676         | 122.150     |
| 1-10-11                    | 126.016         | 121.526         | 124.013         | 124.824         | 120.718         | 118.767     |
| 9-10-11                    | 119.796         | 120.197         | 118.957         | 118.634         | 119.505         | 119.045     |
| 5-11-6                     | 122.087         | 119.186         | 117.735         | 116.231         | 122.555         | 119.124     |
| 5-11-10                    | 119.189         | 122.834         | 123.336         | 124.824         | 118.076         | 121.034     |
| 6-11-10                    | 118.714         | 117.961         | 118.828         | 118.634         | 119.367         | 119.834     |
| <b>Dihedral Angles (°)</b> |                 |                 |                 |                 |                 |             |
| 10-1-2-3                   | -1.941          | -48.360         | -3.526          | 3.309           | -9.725          | 65.764      |
| 1-2-3-4                    | -41.680         | -1.721          | 70.545          | -66.577         | 51.130          | 2.408       |
| 2-3-4-5                    | 4.371           | 29.382          | -65.391         | 66.577          | -3.827          | -43.474     |
| 3-4-5-11                   | 59.751          | -1.834          | 3.152           | -3.309          | -67.406         | 2.598       |
| 11-6-7-8                   | -0.793          | 0.189           | 2.783           | -3.287          | 0.214           | 1.195       |
| 6-7-8-9                    | 0.107           | 0.277           | 1.030           | 0.000           | -0.533          | 0.537       |
| 7-8-9-10                   | 2.370           | -1.070          | -3.208          | 3.287           | -1.011          | -0.577      |
| 8-9-10-11                  | -4.153          | 1.395           | 1.572           | -3.253          | 2.843           | -1.096      |
| 8-9-10-1                   | 179.877         | -176.478        | 174.464         | -177.161        | 179.219         | 176.623     |
| 2-1-10-11                  | 41.170          | 47.717          | -38.468         | 38.445          | -36.503         | -66.431     |
| 2-1-10-9                   | -143.155        | -134.440        | 149.038         | -148.070        | 147.166         | 115.844     |
| 7-6-11-10                  | -0.976          | 0.125           | -4.358          | 3.253           | 1.622           | -2.875      |
| 7-6-11-5                   | 177.823         | 178.613         | 179.174         | 177.161         | -177.743        | 178.170     |
| 4-5-11-10                  | -61.114         | -24.718         | 33.322          | -38.444         | 61.602          | 33.308      |
| 4-5-11-6                   | 120.092         | 156.871         | -150.381        | 148.070         | -119.025        | -147.749    |
| 1-10-11-5                  | 0.027           | -1.536          | 6.081           | 0.000           | -0.071          | 3.941       |
| 1-10-11-6                  | 178.861         | 176.893         | -170.178        | 173.341         | -179.465        | -174.994    |
| 9-10-11-6                  | 3.412           | -0.908          | 2.152           | 0.000           | -3.127          | 2.802       |
| 9-10-11-5                  | -1.941          | -48.360         | -3.526          | 3.309           | -9.725          | 65.764      |



**Figure S1. a-** Condensed Fukui function ( $f^-(r)$ ) 3D-mapped surface, calculated in water using DFT (Ub3lyp)/6-311<sup>++</sup>G(d,p)/Hirshfeld/PCM model/Gaussian W09 software, visualized in term of FMO theory using gaussview 5.0.8, Isovalue MO = 0.0015 a.u, purple color indicate the regions of electrophilic attacks.



**Figure S1: b-** Condensed Fukui function ( $f^+(r)$ ) 3D-mapped surface, calculated in water using DFT (Ub3lyp)/6-311<sup>++</sup>G(d,p)/Hirshfeld/PCM model/Gaussian W09 software, visualized in term of FMO theory using gaussview 5.0.8, Isovalue MO = 0.0015 a.u, purple color indicate the regions of nucleophilic attacks.