**Supplementary information**

**Data on molecular properties, OSIRIS toxicity, PASS biological activity and ADMET-sar profile**

**Table S1:** Binding energy scores of the designed trihybridized molecules on AChE (2CMF) and BuChE (4BDS) receptors

|  |  |  |
| --- | --- | --- |
| **Compound**  | **AChE (kcal/mol)** | **BuChE (kcal/mol)** |
| **4a** | -9.1 | -10.5 |
| **4b** | -9.9 | -8.6 |
| **4c** | -10.1 | -9.7 |
| **4d** | -9.6 | -9 |
| **4e** | -10.1 | -9.6 |
| **4f** | -7.8 | -9.2 |
| **4g** | -9.7 | 10 |
| **4h** | -8.2 | -10 |
| **4i** | -8.4 | -6.6 |
| **4j** | -7.3 | -9.3 |
| **4k** | -9 | -9 |
| **4l** | -8.9 | -4.3 |
| **4m** | -12 | -10.7 |
| **4n** | -10.3 | -10.5 |
| **7a** | -7.1 | -10.9 |
| **7b** | -9 | -10.7 |
| **7c** | -7.1 | -9.8 |
| **7d** | -5.8 | -7 |
| **7e** | -7.1 | -9.8 |
| **7f** | -1.3 | -0.2 |
| **7g** | -6.5 | -8.1 |
| **7h** | -5.8 | -10.9 |
| **7i** | -9.2 | -10.5 |
| **7j** | -9.5 | -11.6 |
| **7k** | -6.9 | -10 |
| **7l** | -9.8 | -8.4 |
| **7m** | -8.9 | -11.5 |

**Table S2:** Molecular properties of synthesized compounds

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **miLogP** | **TPSA** | **MW** | **HBA** | **HBD** | **nRot bonds** | **Violation of Lipinski rule** |
| **4a** | 2.79 | 107.83 | 406.39 | 8 | 1 | 6 | 0 |
| **4b** | 2.58 | 98.60 | 378.38 | 7 | 1 | 6 | 0 |
| **4c** | 2.78 | 107.83 | 380.36 | 8 | 1 | 5 | 0 |
| **4d** | 3.09 | 96.84 | 394.38 | 8 | 0 | 6 | 0 |
| **4e** | 2.47 | 118.83 | 366.33 | 8 | 2 | 4 | 0 |
| **4f** | 2.81 | 117.06 | 436.42 | 9 | 1 | 7 | 0 |
| **4g** | 2.18 | 139.05 | 382.33 | 9 | 3 | 4 | 0 |
| **4h** | 2.48 | 118.83 | 392.37 | 8 | 2 | 5 | 0 |
| **4i** | 3.10 | 96.84 | 420.42 | 8 | 0 | 7 | 0 |
| **4j** | 3.34 | 96.84 | 404.38 | 8 | 0 | 5 | 0 |
| **4k** | 2.71 | 96.84 | 422.44 | 8 | 0 | 8 | 0 |
| **4l** | 3.86 | 96.84 | 430.42 | 8 | 0 | 6 | 0 |
| **4m** | 2.93 | 96.84 | 392.37 | 8 | 0 | 5 | 0 |
| **4n** | 3.33 | 96.84 | 378.34 | 8 | 0 | 4 | 0 |
| **7a** | 2.79 | 107.83 | 362.39 | 8 | 1 | 6 | 0 |
| **7b** | 3.25 | 89.36 | 334.36 | 6 | 1 | 4 | 0 |
| **7c** | 2.78 | 107.83 | 336.30 | 8 | 1 | 5 | 0 |
| **7d** | 3.75 | 87.60 | 350.36 | 7 | 0 | 4 | 0  |
| **7e** | 3.14 | 109.59 | 322.30 | 7 | 2 | 2 | 0 |
| **7f** | 3.48 | 107.83 | 392.39 | 8 | 1 | 5 | 0 |
| **7g** | 2.85 | 129.82 | 338.30 | 8 | 3 | 2 | 0 |
| **7h** | 2.77 | 109.59 | 348.31 | 7 | 2 | 3 | 0 |
| **7i** | 3.77 | 87.60 | 376.39 | 7 | 0 | 5 | 0 |
| **7j** | 3.81 | 87.60 | 360.35 | 7 | 0 | 3 | 0 |
| **7k** | 3.37 | 87.60 | 378.41 | 7 | 0 | 6 | 0 |
| **7l** | 4.53 | 87.60 | 386.39 | 7 | 0 | 4 | 0 |
| **7m** | 3.59 | 87.60 | 348.34 | 7 | 0 | 3 | 0 |
| Galantamine | 1.54 | 41.93 | 287.36 | 4 | 1 | 1 | 0 |
| Donepezil | 4.10 | 38.78 | 379.50 | 4 | 0 | 6 | 0 |

TPSA: total polar surface area; HBA: hydrogen bond acceptor; HBD: hydrogen bond donor; MW: molecular weight; nRot bonds: no of rotatable bonds

**Table S3: Prediction of** **bioactivity of coumarin derivatives by PASS**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | P value | MAO B inhibitor | MAO A inhibitor | COX 1 inhibitor | COX 2 inhibitor | Antioxidant | Anti-inflammatory |
| **4a** | Pa  | 0,873 | 0,351 | 0,266 | 0,239 | 0,308 | 0,377 |
| Pi  | 0,002 | 0,004 | 0,018 | 0,009 | 0,022 | 0,108 |
| **4b** | Pa  | 0,772 | 0,423 | - | 0,127 | 0,223 | 0,412 |
| Pi | 0,002 | 0,003 | - | 0,039 | 0,045 | 0,089 |
| **4c** | Pa  | 0,942 | 0,822 | 0,194 | 0,186 | 0,276 | 0,511 |
| Pi  | 0.003 | 0.004 | 0.032 | 0.112 | 0.076 | 0.032 |
| **4d** | Pa  | 0,952 | 0,798 | 0,147 | 0,185 | 0,205 | 0,488 |
| Pi  | 0,001 | 0,002 | 0,038 | 0,018 | 0,052 | 0,061 |
| **4e** | Pa | 0,939 | 0,854 | 0,201 | 0,190 | 0,275 | 0,526 |
| Pi | 0,001 | 0,002 | 0,0272 | 0,016 | 0,028 | 0,049 |
| **4f** | Pa  | 0,826 | 0,281 | 0,247 | 0,247 | 0,321 | 0,367 |
| Pi  | 0,002 | 0,004 | 0,020 | 0,008 | 0,020 | 0,113 |
| **4g** | Pa | 0.862 | 0.879 | 0.272 | 0.244 | 0.312 | 0.377 |
| Pi  | 0.002 | 0.002 | 0.017 | 0.008 | 0.021 | 0.108 |
| **4h** | Pa  | 0,904 | 0,330 | - | 0,237 | 0,252 | 0,335 |
| Pi  | 0,001 | 0,004 | - | 0,009 | 0,035 | 0,132 |
| **4i** | Pa  | 0,882 | 0,298 | 0,267 | 0,265 | 0,214 | 0,261 |
| Pi  | 0,002 | 0,004 | 0,018 | 0,006 | 0,048 | 0,200 |
| **4j** | Pa  | 0,786 | 0,349 | - | 0,128 | 0,193 | 0,395 |
| Pi  | 0,002 | 0,004 | - | 0,038 | 0,059 | 0,098 |
| **4k** | Pa  | 0,881 | 0,310 | 0,095 | 0,169 | 0,258 | 0,255 |
| Pi  | 0,002 | 0,004 | 0,061 | 0,022 | 0,033 | 0,207 |
| **4l** | Pa  | 0,768 | 0,265 | - | 0,082 | 0,176 | - |
| Pi  | 0,002 | 0,004 | - | 0,067 | 0,073 | - |
| **4m** | Pa  | 0,928 | 0,684 | 0,210 | 0,213 | 0,185 | 0,374 |
| Pi  | 0,001 | 0,002 | 0,025 | 0,012 | 0,065 | 0,109 |
| **4n** | Pa | 0,464 | 0,369 | 0,274 | 0,351 | 0,247 | 0,193 |
| Pi | 0,003 | 0,003 | 0,041 | 0,005 | 0,037 | 0,093 |
| **7a** | Pa | 0,322 | 0,438 | 0,154 | 0,232 | 0,156 | 0,368 |
| Pi | 0,004 | 0,003 | 0,091 | 0,021 | 0,096 | 0,112 |
| **7b** | Pa | 0,361 | 0,312 | 0,198 | 0,174 | 0,452 | 0,154 |
| Pi | 0,004 | 0,004 | 0,031 | 0,119 | 0,072 | 0,027 |
| **7c** | Pa | 0,408 | 0,299 | 0,205 | 0,190 | 0,170 | 0,416 |
| Pi | 0,003 | 0,004 | 0,064 | 0,034 | 0,079 | 0,088 |
| **7d** | Pa | 0,346 | 0,345 | 0,229 | 0,196 | 0,245 | 0,168 |
| Pi | 0,004 | 0,004 | 0,055 | 0,032 | 0,038 | 0,129 |
| **7e** | Pa | 0,354 | 0,276 | 0,269 | 0,357 | 0,254 | 0,182 |
| Pi  | 0.003 | 0.004 | 0.056 | 0.041 | 0.032 | 0.059 |
| **7f** | Pa  | 0,925 | 0,781 | - | 0,195 | 0,317 | 0,529 |
| Pi  | 0,001 | 0,002 | - | 0,015 | 0,020 | 0,048 |
| **7g** | Pa | 0,277 | 0,279 | 0,216 | 0,166 | 0,290 | 0,470 |
| Pi | 0,005 | 0,004 | 0,024 | 0,023 | 0,025 | 0,066 |
| **7h** | Pa | 0.504 | 0.391 | 0.440 | 0.327 | 0.263 | 0.367 |
| Pi | 0.003 | 0.003 | 0.007 | 0.004 | 0.032 | 0.113 |
| **7i** | Pa | 0,527 | 0,346 | 0,341 | 0,293 | 0,176 | 0,288 |
| Pi | 0,003 | 0,004 | 0,011 | 0,005 | 0,073 | 0,172 |
| **7j** | Pa | 0,229 | 0,155 | 0,298 | - | - | - |
| Pi | 0,005 | 0,009 | 0,005 |  |  |  |
| **7k** | Pa | 0,336 | 0,367 | 0,153 | 0,230 | 0,348 | 0,177 |
| Pi | 0,004 | 0,003 | 0,091 | 0,021 | 0,124 | 0,020 |
| **7l** | Pa | 0,395 | 0,280 | 0,189 | 0,217 | 0,183 | - |
| Pi | 0.003 | 0.004 | 0.047 | 0.031 | 0.098 | - |
| **7m** | Pa | 0,273 | 0,237 | 0,102 | 0,122 | - | - |
| Pi | 0,005 | 0,005 | 0,056 | 0,041 | - | - |
| Galantamin | - | - | - | - | - | 0,173 | - |
| - | - | - | - | - | 0,076 | - |
| Donepezil | - | - | - | - | - | - | 0,211  |
| - | - | - | - | - | - | 0,172 |

**Table S4: Prediction of** **toxicity of coumarin hybrids by OSIRIS**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **Mutagenic** | **Tumorigenic** | **Irritant** | **Reproductive effective** | **Solubility** | **Drug likeness** | **Drug-Score** |
| **4a** | Green | Green | Green | Red | -3.45 | -16.09 | 0.23 |
| **4b** | Green | Green | Green | Red | -2.93 | -17.17 | 0.24 |
| **4c** | Green | Green | Green | Red | -4.17 | -16.16 | 0.22 |
| **4d** | Green | Green | Green | Red | -4.49 | -14.54 | 0.21 |
| **4e** | Green | Green | Green | Red | -386 | -15.9 | 0.24 |
| **4f** | Green | Green | Green | Red | -3.47 | -15.47 | 0.22 |
| **4g** | Green | Green | Green | Red | -3.57 | -16.33 | 0.24 |
| **4h** | Green | Green | Green | Red | -3.28 | -15.68 | 0.25 |
| **4i** | Green | Green | Green | Red | -3.76 | -14.48 | 0.22 |
| **4j** | Green | Green | Green | Red | -4.44 | -15.37 | 0.2 |
| **4k** | Green | Green | Green | Red | -3.27 | -14.76 | 0.22 |
| **4l** | Green | Green | Green | Red | -4.75 | -15.11 | 0.17 |
| **4m** | Green | Green | Green | Red | -4.01 | -15.08 | 0.22 |
| **4n** | Green | Green | Green | Red | -5.16 | -15.38 | 0.19 |
| **7a** | Green | Green | Green | Green | -3.07 | 3.06 | 0.8 |
| **7b** | Green | Green | Green | Green | -2.55 | 1.87 | 0.8 |
| **7c** | Green | Green | Green | Green | -3.79 | 2.94 | 0.78 |
| **7d** | Green | Green | Green | Green | -4.1 | 4.49 | 0.75 |
| **7e** | Green | Green | Green | Green | -3.48 | 3.27 | 0.82 |
| **7f** | Green | Green | Green | Green | -3.08 | 3.7 | 0.78 |
| **7g** | Green | Green | Green | Green | -3.18 | 2.76 | 0.82 |
| **7h** | Green | Green | Green | Green | -3.38 | 3.9 | 0.75 |
| **7i** | Green | Green | Green | Green | -3.38 | 4.6 | 0.77 |
| **7j** | Green | Green | Green | Green | -4.05 | 2.6 | 0.71 |
| **7k** | Green | Green | Green | Green | -2.88 | 4.22 | 0.79 |
| **7l** | Green | Green | Green | Red | -4.73 | 2.85 | 0.38 |
| **7m** | Green | Green | Green | Green | -3.63 | 2.82 | 0.77 |
| **Donepezil** | Green | Green | Green | Green | -4.35 | 7.29 | 0.63 |
| **Galantamine** | Green | Green | Green | Green | -2.67 | 6.2 | 0.91 |

**Table S5: Prediction of Pharmacokinetic profile of coumarin hybrids by ADMETsar**

Absorption :

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Compound** | **BBB+** | **HIA+** | **Caco2-** | **P-glycoprotein Substrate****(Non-substrate)** |
| **4a** | 0.6584 | 0.9944 | 0.5188 | 0.6406 |
| **4b** | 0.8442 | 0.9945 | 0.5870 | 0.6744 |
| **4c** | 0.5590 | 0.9966 | 0.5376 | 0.6883 |
| **4d** | 0.8027 | 1.0000 | 0.5118 | 0.7173 |
| **4e** | 0.7096 | 0.9941 | 0.6931 | 0.5773 |
| **7g** | 0.5812 | 0.9947 | 0.7373 | 0.6493 |
| **7i** | 0.8690 | 1.0000 | 0.5219 | 0.7258 |
| **7l** | 0.9007 | 1.0000 | 0.5242 | 0.7731 |
| **7m** | 0.8805 | 1.0000 | 0.5236 | 0.7630 |

Distribution:

|  |  |
| --- | --- |
| **Compound** | **Subcellular localization** |
| **Mitochondria** | **Plasma membrane** |
| **4a** | 0.5455 | - |
| **4b** | 0.6249 | - |
| **4c** | 0.6451 | - |
| **4d** | 0.7042 | - |
| **4e** | 0.6413 | - |
| **7g** | - | 0.5092 |
| **7i** | - | 0.4687 |
| **7l** | 0.5848 | - |
| **7m** | 0.7150 | - |

Metabolism:

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **CYP450 2C9 Substrate** | **CYP450 2D6 Substrate** | **CYP450 3A4 Substrate** | **CYP450 1A2 Inhibitor** | **CYP450 2C9 Inhibitor** | **CYP450 2D6 Inhibitor** | **CYP450 2C19 Inhibitor** | **CYP450 3A4 Inhibitor** |
| **4a** | 0.8007 | 0.8146 | 0.6792 | 0.5240 | 0.5554 | 0.9389 | 0.5931 | 0.5894 |
| **4b** | 0.8022 | 0.7744 | 0.6165 | 0.6276 | 0.5294 | 0.9242 | 0.5172 | 0.7235 |
| **4c** | 0.8192 | 0.8168 | 0.6826 | 0.5288 | 0.7462 | 0.9404 | 0.7285 | 0.6543 |
| **4d** | 0.8356 | 0.8004 | 0.7374 | 0.5291 | 0.8610 | 0.9623 | 0.8475 | 0.7854 |
| **4e** | 0.8059 | 0.8142 | 0.6139 | 0.6325 | 0.5363 | 0.9306 | 0.5000 | 0.5809 |
| **7g** | 0.7649 | 0.8341 | 0.5000 | 0.8552 | 0.5547 | 0.9154 | 0.5329 | 0.6083 |
| **7i** | 0.8034 | 0.8254 | 0.6571 | 0.5747 | 0.7436 | 0.9639 | 0.7924 | 0.7948 |
| **7l** | 0.8149 | 0.8342 | 0.5972 | 0.8158 | 0.7320 | 0.9012 | 0.7263 | 0.8216 |
| **7m** | 0.8335 | 0.8144 | 0.6538 | 0.7636 | 0.7482 | 0.8785 | 0.7525 | 0.8244\* |

Toxicity:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **AMES Toxicity** **(AMES toxic)** | **Fish Toxicity****(High FHMT)** | **Honeybee Toxicity****(Low HBT)** | **Acute Oral Toxicity****(III)** | **Rat Acute Toxicity**LD50, mol/kg | **Fish Toxicity** pLC50, mg/L |
|
| 4a | 0.6019 | 0.9525 | 0.6034 | 0.6943 | 2.3541  | 0.5725  |
| 4b | 0.5673 | 0.9117 | 0.6653 | 0.7113 | 2.2308  | 0.9060  |
| 4c | 0.5657 | 0.9302 | 0.6916 | 0.6409 | 2.4794  | 0.6641  |
| 4d | 0.5000 | 0.9507 | 0.6384 | 0.6054 | 2.4388  | 0.5311  |
| 4e | 0.5607 | 0.9835 | 0.7464 | 0.6643 | 2.2861 | 0.8434  |
| 7g | 0.7328 | 0.9904 | 0.7306 | 0.5254 | 2.3758  | 1.1506  |
| 7i | 0.5891 | 0.9962 | 0.5393 | 0.5214 | 2.6020  | 0.5057  |
| 7l | 0.6282 | 0.9920 | 0.6688 | 0.6436 | 2.3775  | 0.7214  |
| 7m | 0.5656 | 0.9529 | 0.7430 | 0.6673 | 2.2556  | 0.8438 |

**Figure S1: NMR and MS Spectra of 4l**

****

****

****

**Figure S2: NMR and MS Spectra of 4m **

****

****