**Probability-driven 3D pharmacophore mapping of antimycobacterial potential of hybrid molecules combining phenylcarbamoyloxy and *N*-arylpiperazine fragments**

A. Baka\*, V. Kozika, I. Malikb, J. Jampilekb and A. Smolinskic

SUPPLEMENTARY MATERIALS

**Table S1**. The SMILES code notation for currently analyzed phenylcarbamic acid derivatives containing an *N*-arylpiperazine moiety.

|  |  |
| --- | --- |
| **No.** | **SMILES code** |
| **Ia** | c1c(cccc1OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1C)O |
| **Ib** | c1c(cccc1OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1C)O |
| **Ic** | c1c(ccc(c1)OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1C)O |
| **Id** | c1c(ccc(c1)OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1C)O |
| **IIa** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1F)O)OC |
| **IIb** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1F)O)OCC |
| **IIc** | c1c(cccc1OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1F)O |
| **IId** | c1c(cccc1OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccccc1F)O |
| **IIIa** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O)OC |
| **IIIb** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O)OCC |
| **IIIc** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O)OCCC |
| **IIId** | c1c(cccc1OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIe** | c1c(cccc1OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIf** | c1c(cccc1OCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIg** | c1c(ccc(c1)OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIh** | c1c(ccc(c1)OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIi** | c1c(ccc(c1)OCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IIIj** | c1c(ccc(c1)OCCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ccc(cc1)F)O |
| **IVa** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O)OC |
| **IVb** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O)OCC |
| **IVc** | c1c(cccc1OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVd** | c1c(cccc1OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVe** | c1c(cccc1OCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVf** | c1c(ccc(c1)OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVg** | c1c(ccc(c1)OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVh** | c1c(ccc(c1)OCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **IVi** | c1c(ccc(c1)OCCCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1cccc(c1)C(F)(F)F)O |
| **Va** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ncccn1)O)OC |
| **Vb** | c1(c(cccc1)NC(=O)OCC(C[NH+]1CCN(CC1)c1ncccn1)O)OCC |
| **Vc** | c1c(cccc1OC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ncccn1)O |
| **Vd** | c1c(cccc1OCC)NC(=O)OCC(C[NH+]1CCN(CC1)c1ncccn1)O |

**Table S2**. The comparison of three CoMSA models for the training/test series of the phenylcarbamic acid analogues for pMICd14 (*q2cv*>0.7 and *q2test >*0.50) and pMICd21 (*q2cv*>0.9 and *q2test >*0.50) activities with Golbraikh-Tropsha and Roy validation parameters, respectively [46,50].

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Model | *q*2cv (onc)b | *q*2test | *k* | *k*’ | *R*2 | *R*o2 | *R*o2’ | *MAE90%* | *MAE90%+3σ90%* | *MAE100%* | *MAE100%+3σ100%* |
| **1.** | CoMSAa | 0.71(4) | 0.52 | 0.85 | 1.13 | 0.67 | 0.64 | 0.84 | 0.26 | 1.22 | 0.33 | 1.66 |
| **2.** | CoMSAa | 0.71(3) | 0.53 | 0.88 | 1.10 | 0.64 | 0.68 | 0.89 | 0.22 | 1.16 | 0.30 | 1.62 |
| **3.** | CoMSAa | 0.71(3) | 0.53 | 0.87 | 1.11 | 0.65 | 0.70 | 0.88 | 0.22 | 1.16 | 0.30 | 1.62 |
| **4.** | CoMSAb | 0.92(6) | 0.53 | 0.89 | 1.07 | 0.61 | 0.75 | 0.93 | 0.30 | 1.38 | 0.35 | 1.67 |
| **5.** | CoMSAb | 0.92(9) | 0.52 | 0.91 | 1.05 | 0.57 | 0.86 | 0.97 | 0.32 | 1.43 | 0.37 | 1.70 |
| **6.** | CoMSAb | 0.92(9) | 0.52 | 0.91 | 1.05 | 0.58 | 0.86 | 0.97 | 0.32 | 1.43 | 0.37 | 1.69 |

(onc) - optimal number of components

a 14 days of incubation

b 21 days of incubation

c model: training/test set ratio (21/10)

e map size 20×20, md=0.4, compound IIIj was used as reference compound R

**Table S3**. Hotelling’s T-squared matric for Dragon-based data of analyzed phenylcarbamic acid derivatives containing an *N*-arylpiperazine moiety.

|  |  |
| --- | --- |
| **No.** | **T-squared metric** |
| **Ia** | 28.14 |
| **Ib** | 27.09 |
| **Ic** | 27.91 |
| **Id** | 26.34 |
| **IIa** | 27.55 |
| **IIb** | 28.88 |
| **IIc** | 28.10 |
| **IId** | 28.76 |
| **IIIa** | 27.83 |
| **IIIb** | 28.92 |
| **IIIc** | 28.70 |
| **IIId** | 28.29 |
| **IIIe** | 28.62 |
| **IIIf** | 27.48 |
| **IIIg** | 28.35 |
| **IIIh** | 28.36 |
| **IIIi** | 27.05 |
| **IIIj** | 24.03 |
| **IVa** | 24.66 |
| **IVb** | 25.86 |
| **IVc** | 25.94 |
| **IVd** | 26.90 |
| **IVe** | 26.09 |
| **IVf** | 26.37 |
| **IVg** | 27.11 |
| **IVh** | 25.99 |
| **IVi** | 23.24 |
| **Va** | 25.38 |
| **Vb** | 27.80 |
| **Vc** | 26.24 |
| **Vd** | 27.96 |

**Table S4**. The calculated values of chosen Sybyl descriptors for presently analyzed phenylcarbamic acid derivatives containing an *N*-arylpiperazine moiety.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | Molecularweight | Volume | Surface area | Polar surface area | Atom count | Bond count | Acceptor count | Donor count | Rotatable bond count | Hydrophobe count | ClogP | Lipinski violations |
| **Ia** | 400.4913 | 1221.444 | 729.534 | 108.640 | 59 | 61 | 7 | 3 | 8 | 2 | 3.7261 | 0 |
| **Ib** | 414.5179 | 1264.332 | 766.274 | 101.007 | 62 | 64 | 7 | 3 | 9 | 2 | 4.2551 | 0 |
| **Ic** | 400.4913 | 1240.118 | 729.288 | 108.235 | 59 | 61 | 7 | 3 | 8 | 2 | 3.7261 | 0 |
| **Id** | 414.5179 | 1312.656 | 765.941 | 100.716 | 62 | 64 | 7 | 3 | 9 | 2 | 4.2551 | 0 |
| **IIa** | 404.4552 | 1234.188 | 715.957 | 99.855 | 56 | 58 | 7 | 3 | 8 | 2 | 3.5409 | 0 |
| **IIb** | 418.4818 | 1298.698 | 751.084 | 94.003 | 59 | 61 | 7 | 3 | 9 | 2 | 4.0699 | 0 |
| **IIc** | 404.4552 | 1190.444 | 718.241 | 108.588 | 56 | 58 | 7 | 3 | 8 | 2 | 3.5409 | 0 |
| **IId** | 418.4818 | 1238.213 | 754.839 | 101.075 | 59 | 61 | 7 | 3 | 9 | 2 | 4.0699 | 0 |
| **IIIa** | 404.4552 | 1244.996 | 721.352 | 99.972 | 56 | 58 | 7 | 3 | 8 | 2 | 3.5409 | 0 |
| **IIIb** | 418.4818 | 1297.521 | 756.457 | 93.981 | 59 | 61 | 7 | 3 | 9 | 2 | 4.0699 | 0 |
| **IIIc** | 432.5083 | 1372.409 | 788.856 | 93.814 | 62 | 64 | 7 | 3 | 10 | 3 | 4.5989 | 0 |
| **IIId** | 404.4552 | 1193.176 | 723.869 | 108.589 | 56 | 58 | 7 | 3 | 8 | 2 | 3.5409 | 0 |
| **IIIe** | 418.4818 | 1245.928 | 760.508 | 101.056 | 59 | 61 | 7 | 3 | 9 | 2 | 4.0699 | 0 |
| **IIIf** | 432.5083 | 1296.684 | 793.093 | 100.966 | 62 | 64 | 7 | 3 | 10 | 3 | 4.5989 | 0 |
| **IIIg** | 404.4552 | 1216.953 | 723.563 | 108.269 | 56 | 58 | 7 | 3 | 8 | 2 | 3.5409 | 0 |
| **IIIh** | 418.4818 | 1268.558 | 760.338 | 100.935 | 59 | 61 | 7 | 3 | 9 | 2 | 4.0699 | 0 |
| **IIIi** | 432.5083 | 1319.276 | 792.580 | 100.723 | 62 | 64 | 7 | 3 | 10 | 3 | 4.5989 | 0 |
| **IIIj** | 446.5349 | 1380.513 | 825.015 | 100.668 | 65 | 67 | 7 | 3 | 11 | 3 | 5.1279 | 1 |
| **IVa** | 454.4627 | 1321.086 | 766.228 | 99.793 | 59 | 61 | 7 | 3 | 8 | 3 | 4.4090 | 0 |
| **IVb** | 468.4893 | 1387.111 | 801.297 | 93.947 | 62 | 64 | 7 | 3 | 9 | 3 | 4.9380 | 0 |
| **IVc** | 454.4627 | 1268.440 | 768.749 | 108.457 | 59 | 61 | 7 | 3 | 8 | 3 | 4.4090 | 0 |
| **IVd** | 468.4893 | 1333.249 | 805.468 | 101.157 | 62 | 64 | 7 | 3 | 9 | 3 | 4.9380 | 0 |
| **IVe** | 482.5158 | 1376.143 | 838.150 | 100.855 | 65 | 67 | 7 | 3 | 10 | 4 | 5.4670 | 1 |
| **IVf** | 454.4627 | 1298.473 | 768.340 | 108.260 | 59 | 61 | 7 | 3 | 8 | 3 | 4.4090 | 0 |
| **IVg** | 468.4893 | 1349.673 | 805.345 | 100.902 | 62 | 64 | 7 | 3 | 9 | 3 | 4.9380 | 0 |
| **IVh** | 482.5158 | 1417.146 | 837.411 | 100.695 | 65 | 67 | 7 | 3 | 10 | 4 | 5.4670 | 1 |
| **IVi** | 496.5424 | 1479.086 | 869.907 | 100.753 | 68 | 70 | 7 | 3 | 11 | 4 | 5.9960 | 1 |
| **Va** | 388.4408 | 1206.049 | 703.998 | 115.082 | 54 | 56 | 9 | 3 | 8 | 2 | 1.5142 | 0 |
| **Vb** | 402.4674 | 1265.510 | 739.397 | 109.283 | 57 | 59 | 9 | 3 | 9 | 2 | 2.0433 | 0 |
| **Vc** | 388.4408 | 1159.528 | 706.658 | 123.914 | 54 | 56 | 9 | 3 | 8 | 2 | 1.5142 | 0 |
| **Vd** | 402.4674 | 1221.828 | 743.228 | 116.405 | 57 | 59 | 9 | 3 | 9 | 2 | 2.0433 | 0 |