# Drug-induced immune thrombocytopenia toxicity prediction based on machine learning

**SUPPLEMENTARY INFORMATION**

*Binyou Wang [1, †], Xiaoqiu Tan [2,3,4,†], Jianmin Guo [2], Ting Xiao [2], Yan Jiao [5], Junlin Zhao [1], Jianming Wu [6,7,*], Yiwei Wang [2,3,4,*]*

[1]School of Pharmacy, Southwest Medical University, Luzhou, 646000, China.

[2]School of Basic Medical Science, Southwest Medical University, Luzhou, 646000, China.

[3]Key Laboratory of Medical Electrophysiology, Southwest Medical University, Luzhou 646000, China.

[4]Ministry of Education & Medical Electrophysiological Key Laboratory of Sichuan Province, Institute of Cardiovascular Research, Southwest Medical University, Luzhou 646000, China.

[5]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China.

[6]Sichuan Key Medical Laboratory of New Drug Discovery and Druggability Evaluation; School of Pharmacy, Southwest Medical University, Luzhou,646000 China.

[7]Luzhou Key Laboratory of Activity Screening and Druggability Evaluation for Chinese Materia Medica, School of Pharmacy, Southwest Medical University, Luzhou,646000 China.

† These authors contributed equally to this work.

* Corresponding authors: Yiwei Wang, Jianming Wu

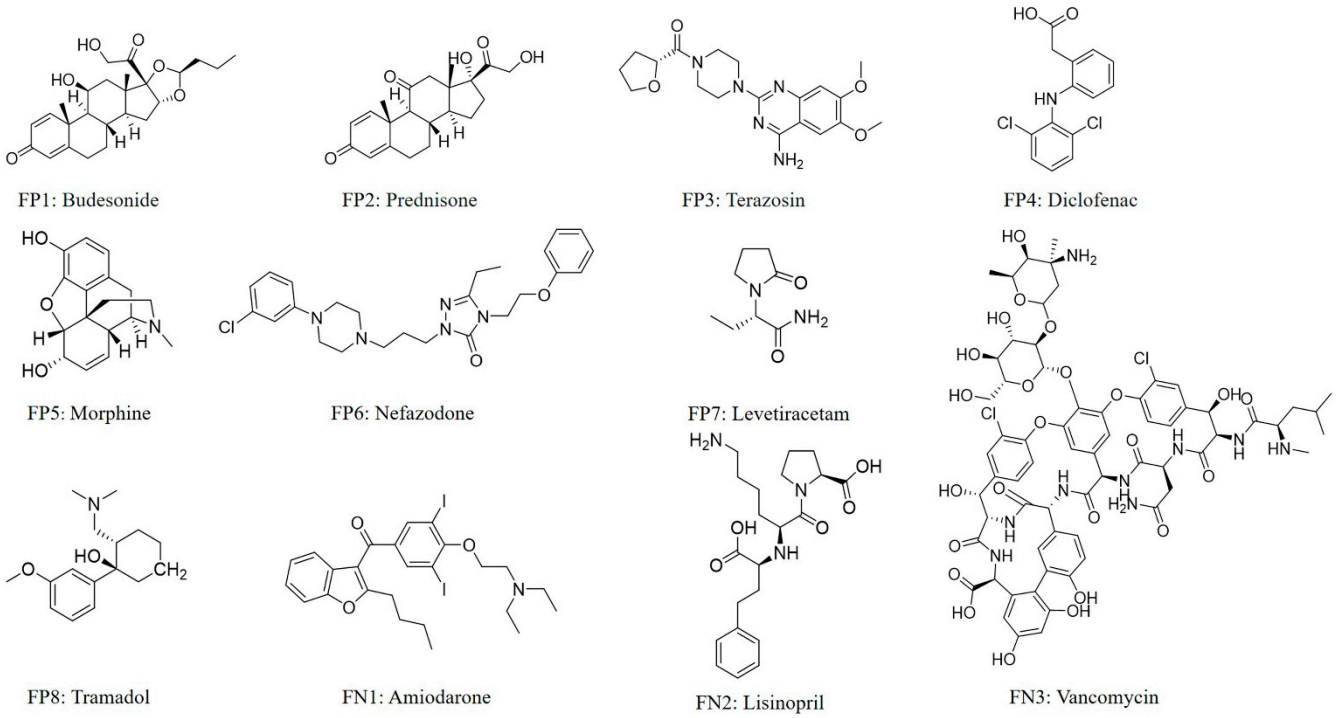



**Figure S1.** Misclassified compounds of the RDMD+PubChem-k-NN model on the external validation set.

**Table S1.** Details of the training set and external validation set compounds.

| **Training set** | | |
|---|---|---|
| **Name** | **Class** | **SMILES** |
| ACETAMINOPHEN | 1 | CC(=O)NC1=CC=C(O)C=C1 |
| ACYCLOVIR | 0 | NC1=NC(=O)C2=C(N1)N(COCCO)C=N2 |
| ALBUTEROL | 0 | CC(C)(C)NCC(O)C1=CC(CO)=C(O)C=C1 |
| ALENDRONATE | 0 | NCCCC(O)(P(O)(O)=O)P(O)(O)=O |
| ALLOPURINOL | 0 | OC1=NC=NC2=C1C=NN2 |
| ALPRAZOLAM | 0 | CC1=NN=C2CN=C(C3=CC=CC=C3)C3=C(C=CC(Cl)=C3)N12 |
| AMITRIPTYLINE | 1 | CN(C)CCC=C1C2=CC=CC=C2CCC2=CC=CC=C12 |
| AMLODIPINE | 0 | CCOC(=O)C1=C(COCCN)NC(C)=C(C1C1=CC=CC=C1Cl)C(=O)OC |
| AMOXICILLIN | 1 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)[C@H](N)C1=CC=C(O)C=C1)C(O)=O |
| AMPHOTERICIN B | 0 | [H][C@]12C[C@@H](O[C@@H]3O[C@H](C)[C@@H](O)[C@H](N)[C@@H]3O)\C=C\C=C\C=C\C=C\C=C\C=C\C=C\[C@H](C)[C@@H](O)[C@@H](C)[C@H](C)OC(=O)C[C@H](O)C[C@H](O)CC[C@@H](O)[C@H](O)C[C@H](O)C[C@](O)(C[C@H](O)[C@H]1C(O)=O)O2 |
| AMPICILLIN | 1 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)[C@H](N)C1=CC=CC=C1)C(O)=O |
| ARGATROBAN | 1 | C[C@@H]1CCN([C@H](C1)C(O)=O)C(=O)[C@H](CCCNC(N)=N)NS(=O)(=O)C1=CC=CC2=C1NCC(C)C2 |
| ASPIRIN | 1 | CC(=O)OC1=CC=CC=C1C(O)=O |
| ATORVASTATIN | 0 | CC(C)C1=C(C(=O)NC2=CC=CC=C2)C(=C(N1CC[C@@H](O)C[C@@H](O)CC(O)=O)C1=CC=C(F)C=C1)C1=CC=CC=C1 |
| AZACITIDINE | 1 | NC1=NC(=O)N(C=N1)[C@@H]1O[C@H](CO)[C@@H](O)[C@H]1O |
| BENZTROPINE | 0 | [H][C@]12CC[C@]([H])(C[C@@]([H])(C1)OC(C1=CC=CC=C1)C1=CC=CC=C1)N2C |
| BIVALIRUDIN | 0 | CC[C@H](C)[C@H](NC(=O)[C@H](CCC(O)=O)NC(=O)[C@H](CCC(O)=O)NC(=O)[C@H](CC1=CC=CC=C1)NC(=O)[C@H](CC(O)=O)NC(=O)CNC(=O)[C@H](CC(N)=O)NC(=O)CNC(=O)CNC(=O)CNC(=O)CNC(=O)[C@@H]1CCCN1C(=O)[C@H](CCCNC(N)=N)NC(=O)[C@@H]1CCCN1C(=O)[C@H](N)CC1=CC=CC=C1)C(=O)N1CCC[C@H]1C(=O)N[C@@H](CCC(O)=O)C(=O)N[C@@H](CCC(O)=O)C(=O)N[C@@H](CC1=CC=C(O)C=C1)C(=O)N[C@@H](CC(C)C)C(O)=O |

| | | |
|---|---|---|
| BUPROPION | 1 | CC(NC(C)(C)C)C(=O)C1=CC(Cl)=CC=C1 |
| BUSPIRONE | 0 | O=C1CC2(CCCC2)CC(=O)N1CCCCN1CCN(CC1)C1=NC=CC=N1 |
| CAPTOPRIL | 0 | C[C@H](CS)C(=O)N1CCC[C@H]1C(O)=O |
| CARBAMAZEPINE | 1 | NC(=O)N1C2=CC=CC=C2C=CC2=CC=CC=C12 |
| CARBIDOPA | 0 | C[C@@](CC1=CC(O)=C(O)C=C1)(NN)C(O)=O |
| CARVEDILOL | 0 | COC1=CC=CC=C1OCCNCC(O)COC1=CC=CC2=C1C1=CC=CC=C1N2 |
| CASPOFUNGIN | 0 | [H][C@@]12C[C@@H](O)CN1C(=O)[C@@H](NC(=O)[C@]([H])(C[C@@H](O)[C@@H](NCCN)NC(=O)[C@@H]1[C@@H](O)CCN1C(=O)[C@@H](NC(=O)[C@@H](NC2=O)[C@H](O)[C@@H](O)C1=CC=C(O)C=C1)[C@H](O)CCN)NC(=O)CCCCCCCC[C@@H](C)C[C@@H](C)CC)[C@@H](C)O |
| CEFADROXIL | 1 | [H][C@]12SCC(C)=C(N1C(=O)[C@H]2NC(=O)[C@H](N)C1=CC=C(O)C=C1)C(O)=O |
| CEFEPIME | 1 | C[N+]1(CCCC1)CC2=C(N3[C@@H]([C@@H](C3=O)NC(=O)/C(=N\OC)/C4=CSC(=N4)N)SC2)C(=O)[O-] |
| CEFPODOXIME | 1 | [H][C@]12SCC(COC)=C(N1C(=O)[C@H]2NC(=O)C(=N/OC)\C1=CSC(N)=N1)C(O)=O |
| CEFTIZOXIME | 1 | CO/N=C(\C(=O)N[C@@H]1C(=O)N2C(C(=O)O)=C(CSc3nc(=O)c(O)nn3C)CS[C@H]12)c1csc(N)n1 |
| CEFTRIAXONE | 1 | [H][C@]12SCC(CSC3=NC(=O)C(=O)NN3C)=C(N1C(=O)[C@H]2NC(=O)C(=N/OC)\C1=CSC(N)=N1)C(O)=O |
| CEFUROXIME | 0 | [H][C@]12SCC(COC(N)=O)=C(N1C(=O)[C@H]2NC(=O)C(=N/OC)\C1=CC=CO1)C(O)=O |
| CELECOXIB | 1 | CC1=CC=C(C=C1)C1=CC(=NN1C1=CC=C(C=C1)S(N)(=O)=O)C(F)(F)F |
| CEPHALEXIN | 1 | [H][C@]12SCC(C)=C(N1C(=O)[C@H]2NC(=O)[C@H](N)C1=CC=CC=C1)C(O)=O |
| CHLORPROMAZINE | 0 | CN(C)CCCN1C2=CC=CC=C2SC2=C1C=C(Cl)C=C2 |
| CIMETIDINE | 0 | CN\C(NCCSCC1=C(C)NC=N1)=N\C#N |
| CIPROFLOXACIN | 1 | OC(=O)C1=CN(C2CC2)C2=CC(N3CCNCC3)=C(F)C=C2C1=O |
| CITALOPRAM | 0 | CN(C)CCCC1(OCC2=C1C=CC(=C2)C#N)C1=CC=C(F)C=C1 |
| CLARITHROMYCIN | 0 | [H][C@@]1(C[C@@](C)(OC)[C@@H](O)[C@H](C)O1)O[C@H]1[C@H](C)[C@@H](O[C@]2([H])O[C@H](C)C[C@@H]([C@H]2O)N(C)C)[C@@](C)(C[C@@H](C)C(=O)[C@H](C)[C@@H](O)[C@](C)(O)[C@@H](CC)OC(=O)[C@@H]1C)OC |
| CLAVULANATE POTASSIUM | 0 | O=C([C@@H](/C(O[C@]1([H])C2)=C/CO)N1C2=O)O[K] |

| | | |
|---|---|---|
| CLINDAMYCIN | 1 | [H][C@@](NC(=O)[C@@H]1C[C@@H](CCC)CN1C)([C@H](C)Cl)[C@@]1([H])O[C@H](SC)[C@H](O)[C@@H](O)[C@H]1O |
| CLONIDINE | 0 | ClC1=CC=CC(Cl)=C1NC1=NCCN1 |
| CLOPIDOGREL | 0 | [H][C@@](N1CCC2=C(C1)C=CS2)(C(=O)OC)C1=CC=CC=C1Cl |
| COLCHICINE | 0 | COC1=CC2=C(C(OC)=C1OC)C1=CC=C(OC)C(=O)C=C1C(CC2)NC(C)=O |
| CYCLOSPORINE | 1 | CC[C@@H]1NC(=O)[C@H]([C@H](O)[C@H](C)C\C=C\C)N(C)C(=O)[C@H](C(C)C)N(C)C(=O)[C@H](CC(C)C)N(C)C(=O)[C@H](CC(C)C)N(C)C(=O)[C@@H](C)NC(=O)[C@H](C)NC(=O)[C@H](CC(C)C)N(C)C(=O)[C@@H](NC(=O)[C@H](CC(C)C)N(C)C(=O)CN(C)C1=O)C(C)C |
| DAPSONE | 0 | NC1=CC=C(C=C1)S(=O)(=O)C1=CC=C(N)C=C1 |
| DAPTOMYCIN | 1 | CCCCCCCCCC(=O)N[C@@H](CC1=CNC2=C1C=CC=C2)C(=O)N[C@H](CC(N)=O)C(=O)N[C@@H](CC(O)=O)C(=O)N[C@H]1[C@@H](C)OC(=O)[C@H](CC(=O)C2=CC=CC=C2N)NC(=O)[C@@H](NC(=O)[C@@H](CO)NC(=O)CNC(=O)[C@H](CC(O)=O)NC(=O)[C@@H](C)NC(=O)[C@H](CC(O)=O)NC(=O)[C@H](CCCN)NC(=O)CNC1=O)[C@H](C)CC(O)=O |
| DEXAMETHASONE | 1 | [H][C@@]12C[C@@H](C)[C@](O)(C(=O)CO)[C@@]1(C)C[C@H](O)[C@@]1(F)[C@@]2([H])CCC2=CC(=O)C=C[C@]12C |
| DIAZEPAM | 0 | CN1C2=C(C=C(Cl)C=C2)C(=NCC1=O)C1=CC=CC=C1 |
| DIGOXIN | 0 | [H][C@]12CC[C@]3([H])[C@]([H])(C[C@@H](O)[C@]4(C)[C@H](CC[C@]34O)C3=CC(=O)OC3)[C@@]1(C)CC[C@@H](C2)O[C@H]1C[C@H](O)[C@H](O[C@H]2C[C@H](O)[C@H](O[C@H]3C[C@H](O)[C@H](O)[C@@H](C)O3)[C@@H](C)O2)[C@@H](C)O1 |
| DILTIAZEM | 0 | COC1=CC=C(C=C1)[C@@H]1SC2=C(C=CC=C2)N(CCN(C)C)C(=O)[C@@H]1OC(C)=O |
| DIPHENHYDRAMINE | 1 | CN(C)CCOC(C1=CC=CC=C1)C1=CC=CC=C1 |
| DOBUTAMINE | 1 | CC(CCC1=CC=C(O)C=C1)NCCC1=CC(O)=C(O)C=C1 |
| DOCUSATE | 0 | CCCCC(CC)COC(=O)CC(C(=O)OCC(CC)CCCC)S(O)(=O)=O |
| DONEPEZIL | 0 | COC1=C(OC)C=C2C(=O)C(CC3CCN(CC4=CC=CC=C4)CC3)CC2=C1 |
| DOPAMINE | 0 | NCCC1=CC(O)=C(O)C=C1 |
| DOXAZOSIN | 0 | COC1=C(OC)C=C2C(N)=NC(=NC2=C1)N1CCN(CC1)C(=O)C1COC2=CC=CC=C2O1 |
| DOXYCYCLINE | 1 | [H][C@@]12[C@@H](C)C3=CC=CC(O)=C3C(=O)C1=C(O)[C@]1(O)C(=O)C(C(N)=O)=C(O)[C@@H](N(C)C)[C@]1([H])[C@H]2O |
| ENALAPRIL | 0 | CCOC(=O)[C@H](CCC1=CC=CC=C1)N[C@@H](C)C(=O)N1CCC[C@H]1C(O)=O |
| ESCITALOPRAM | 0 | CN(C)CCC[C@]1(OCC2=C1C=CC(=C2)C#N)C1=CC=C(F)C=C1 |

| | | |
|---|---|---|
| ESOMEPRAZOLE | 1 | COC1=CC2=C(NC(=N2)[S@@](=O)CC2=NC=C(C)C(OC)=C2C)C=C1 |
| ETHAMBUTOL | 1 | CC[C@@H](CO)NCCN[C@@H](CC)CO |
| ETHOXISUXIMIDE | 1 | O=C(C(C)(CC)C1)NC1=O |
| EZETIMIBE | 0 | [H][C@]1(CC[C@H](O)C2=CC=C(F)C=C2)C(=O)N(C2=CC=C(F)C=C2)[C@]1([H])C1=CC=C(O)C=C1 |
| FAMOTIDINE | 0 | NC(N)=NC1=NC(CSCCC(N)=NS(N)(=O)=O)=CS1 |
| FELBAMATE | 1 | NC(=O)OCC(COC(N)=O)C1=CC=CC=C1 |
| FELODIPINE | 1 | CCOC(=O)C1=C(C)NC(C)=C(C1C1=C(Cl)C(Cl)=CC=C1)C(=O)OC |
| FENOFIBRATE | 0 | CC(C)OC(=O)C(C)(C)OC1=CC=C(C=C1)C(=O)C1=CC=C(Cl)C=C1 |
| FENTANYL | 1 | CCC(=O)N(C1CCN(CCC2=CC=CC=C2)CC1)C1=CC=CC=C1 |
| FEXOFENADINE | 1 | CC(C)(C(O)=O)C1=CC=C(C=C1)C(O)CCCN1CCC(CC1)C(O)(C1=CC=CC=C1)C1=CC=CC=C1 |
| FLUCONAZOLE | 0 | OC(CN1C=NC=N1)(CN1C=NC=N1)C1=C(F)C=C(F)C=C1 |
| FLUOROURACIL | 0 | FC1=CNC(=O)NC1=O |
| FLUOXETINE | 0 | CNCCC(OC1=CC=C(C=C1)C(F)(F)F)C1=CC=CC=C1 |
| FOSINOPRIL | 0 | CCC(=O)O[C@@H](OP(=O)(CCCCC1=CC=CC=C1)CC(=O)N1C[C@@H](C[C@H]1C(O)=O)C1CCCCC1)C(C)C |
| FUROSEMIDE | 1 | NS(=O)(=O)C1=C(Cl)C=C(NCC2=CC=CO2)C(=C1)C(O)=O |
| GABAPENTIN | 0 | NCC1(CC(O)=O)CCCCC1 |
| GLIMEPIRIDE | 0 | CCC1=C(C)CN(C(=O)NCCC2=CC=C(C=C2)S(=O)(=O)NC(=O)N[C@H]2CC[C@H](C)CC2)C1=O |
| GLYBURIDE | 0 | COC1=C(C=C(Cl)C=C1)C(=O)NCCC1=CC=C(C=C1)S(=O)(=O)NC(=O)NC1CCCCC1 |
| HYDRALAZINE | 0 | NNC1=NN=CC2=CC=CC=C12 |
| HYDROCHLOROTHIAZIDE | 0 | NS(=O)(=O)C1=C(Cl)C=C2NCNS(=O)(=O)C2=C1 |
| HYDROCORTISONE | 0 | [H][C@@]12CC[C@](O)(C(=O)CO)[C@@]1(C)C[C@H](O)[C@@]1([H])[C@@]2([H])CCC2=CC(=O)CC[C@]12C |
| HYDROXYCHLOROQUINE | 1 | CCN(CCO)CCCC(C)NC1=C2C=CC(Cl)=CC2=NC=C1 |

| | | |
|---|---|---|
| IBRUTINIB | 1 | NC1=NC=NC2=C1C(=NN2[C@@H]1CCCN(C1)C(=O)C=C)C1=CC=C(OC2=CC=CC=C2)C=C1 |
| IRBESARTAN | 0 | CCCCC1=NC2(CCCC2)C(=O)N1CC1=CC=C(C=C1)C1=CC=CC=C1C1=NNN=N1 |
| IRINOTECAN | 1 | CCC1=C2CN3C(=CC4=C(COC(=O)[C@]4(O)CC)C3=O)C2=NC2=CC=C(OC(=O)N3CCC(CC3)N3CCCCC3)C=C12 |
| ISONIAZID | 0 | NNC(=O)C1=CC=NC=C1 |
| ISOSORBIDE | 0 | [H][C@]1(O)CO[C@]2([H])[C@]([H])(O)CO[C@]12[H] |
| ISOTRETINOIN | 0 | C\C(\C=C\C1=C(C)CCCC1(C)C)=C/C=C/C(/C)=C\C(O)=O |
| LABETALOL | 0 | CC(CCC1=CC=CC=C1)NCC(O)C1=CC(C(N)=O)=C(O)C=C1 |
| LAMOTRIGINE | 1 | NC1=NC(N)=C(N=N1)C1=C(Cl)C(Cl)=CC=C1 |
| LANSOPRAZOLE | 1 | CC1=C(OCC(F)(F)F)C=CN=C1CS(=O)C1=NC2=CC=CC=C2N1 |
| LEUCOVORIN | 1 | [H]C(=O)N1C(CNC2=CC=C(C=C2)C(=O)N[C@@H](CCC(O)=O)C(O)=O)CNC2=C1C(=O)NC(N)=N2 |
| LEVOFLOXACIN | 1 | C[C@H]1COC2=C3N1C=C(C(O)=O)C(=O)C3=CC(F)=C2N1CCN(C)CC1 |
| LEVOTHYROXINE | 0 | N[C@@H](CC1=CC(I)=C(OC2=CC(I)=C(O)C(I)=C2)C(I)=C1)C(O)=O |
| LIDOCAINE | 0 | CCN(CC)CC(=O)NC1=C(C)C=CC=C1C |
| LINEZOLID | 0 | CC(=O)NC[C@H]1CN(C(=O)O1)C1=CC(F)=C(C=C1)N1CCOCC1 |
| LOPERAMIDE | 0 | CN(C)C(=O)C(CCN1CCC(O)(CC1)C1=CC=C(Cl)C=C1)(C1=CC=CC=C1)C1=CC=CC=C1 |
| LORATADINE | 0 | CCOC(=O)N1CCC(CC1)=C1C2=C(CCC3=C1N=CC=C3)C=C(Cl)C=C2 |
| LORAZEPAM | 1 | OC1N=C(C2=CC=CC=C2Cl)C2=C(NC1=O)C=CC(Cl)=C2 |
| LOSARTAN | 1 | CCCCC1=NC(Cl)=C(CO)N1CC1=CC=C(C=C1)C1=CC=CC=C1C1=NNN=N1 |
| LOVASTATIN | 0 | [H][C@]12[C@H](C[C@@H](C)C=C1C=C[C@H](C)[C@@H]2CC[C@@H]1C[C@@H](O)CC(=O)O1)OC(=O)[C@@H](C)CC |
| MEFLOQUINE | 0 | OC(C1CCCCN1)C1=CC(=NC2=C1C=CC=C2C(F)(F)F)C(F)(F)F |
| MEROPENEM | 0 | [H][C@]1([C@@H](C)O)C(=O)N2C(C(O)=O)=C(S[C@@H]3CN[C@@H](C3)C(=O)N(C)C)[C@H](C)[C@]12[H] |
| METFORMIN | 0 | CN(C)C(=N)NC(N)=N |
| METHOTREXATE | 0 | [H][C@@](CCC(O)=O)(NC(=O)C1=CC=C(C=C1)N(C)CC1=NC2=C(N)NC(=N)N=C2N=C1)C(O)=O |

| | | |
|---|---|---|
| METHYLPHENIDATE | 0 | COC(=O)C(C1CCCCN1)C1=CC=CC=C1 |
| METOCLOPRAMIDE | 0 | CCN(CC)CCNC(=O)C1=CC(Cl)=C(N)C=C1OC |
| METOPROLOL | 0 | COCCC1=CC=C(OCC(O)CNC(C)C)C=C1 |
| METRONIDAZOLE | 1 | CC1=NC=C(N1CCO)[N+]([O-])=O |
| MIDAZOLAM | 0 | CC1=NC=C2CN=C(C3=CC=CC=C3F)C3=C(C=CC(Cl)=C3)N12 |
| MILRINONE | 0 | CC1=C(C=C(C#N)C(=O)N1)C1=CC=NC=C1 |
| MINOCYCLINE | 0 | [H][C@@]12CC3=C(C(O)=CC=C3N(C)C)C(=O)C1=C(O)[C@]1(O)C(=O)C(C(N)=O)=C(O)[C@@H](N(C)C)[C@]1([H])C2 |
| MINOXIDIL | 0 | NC1=CC(=NC(N)=[N+]1[O-])N1CCCCC1 |
| MIRTAZAPINE | 0 | CN1CCN2C(C1)C1=CC=CC=C1CC1=C2N=CC=C1 |
| MONTELUKAST | 0 | OC(=O)CC1(CC1)CS[C@H](CCC1=CC=CC=C1C(O)(C)C)C1=CC=CC(\C=C\C2=NC3=C(C=CC(Cl)=C3)C=C2)=C1 |
| MOXIFLOXACIN | 0 | [H][C@]12CN(C[C@@]1([H])NCCC2)C1=C(F)C=C2C(=O)C(=CN(C3CC3)C2=C1OC)C(O)=O |
| MYCOPHENOLATE | 0 | COC1=C(C\C=C(/C)CCC(O)=O)C(O)=C2C(=O)OCC2=C1C |
| NAFCILLIN | 1 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)C1=C(OCC)C=CC2=CC=CC=C12)C(O)=O |
| NAPROXEN | 1 | COC1=CC2=C(C=C1)C=C(C=C2)[C@H](C)C(O)=O |
| NIFEDIPINE | 0 | COC(=O)C1=C(C)NC(C)=C(C1C1=CC=CC=C1[N+]([O-])=O)C(=O)OC |
| NITROFURANTOIN | 1 | C1C(=O)NC(=O)N1/N=C/C2=CC=C(O2)[N+](=O)[O-] |
| NITROGLYCERIN | 0 | [O-][N+](=O)OCC(CO[N+]([O-])=O)O[N+]([O-])=O |
| NIZATIDINE | 1 | CNC(NCCSCC1=CSC(CN(C)C)=N1)=C[N+]([O-])=O |
| NOREPINEPHRINE | 0 | NC[C@H](O)C1=CC(O)=C(O)C=C1 |
| NYSTATIN | 0 | C[C@H]1/C=C/C=C/CC/C=C/C=C/C=C/C=C/C(CC2C(C(C[C@](O2)(CC(C(CCC(CC(CC(CC(=O)O[C@H]([C@@H]([C@@H]1O)C)C)O)O)O)O)O)O)O)C(=O)O)O[C@@H]3[C@H]([C@H]([C@@H]([C@H](O3)C)O)N)O |
| OLANZAPINE | 1 | CN1CCN(CC1)C1=NC2=CC=CC=C2NC2=C1C=C(C)S2 |
| OLMESARTAN | 1 | CCCC1=NC(=C(N1CC1=CC=C(C=C1)C1=C(C=CC=C1)C1=NN=NN1)C(O)=O)C(C)(C)O |
| OMEPRAZOLE | 0 | COC1=CC2=C(C=C1)N=C(N2)S(=O)CC1=NC=C(C)C(OC)=C1C |

| | | |
|---|---|---|
| ONDANSETRON | 1 | CN1C2=C(C3=CC=CC=C13)C(=O)C(CN1C=CN=C1C)CC2 |
| OXACILLIN | 0 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)C1=C(C)ON=C1C1=CC=CC=C1)C(O)=O |
| OXALIPLATIN | 1 | C1CC[C@H]([C@@H](C1)[NH-])[NH-].C(=O)(C(=O)[O-])[O-].[Pt+4] |
| OXAPROZIN | 1 | OC(=O)CCC1=NC(=C(O1)C1=CC=CC=C1)C1=CC=CC=C1 |
| OXYCODONE | 0 | COC1=C2O[C@H]3C(=O)CC[C@@]4(O)[C@H]5CC(C=C1)=C2[C@@]34CCN5C |
| PAPAVERINE | 1 | COC1=C(OC)C=C(CC2=NC=CC3=CC(OC)=C(OC)C=C23)C=C1 |
| PAROXETINE | 1 | FC1=CC=C(C=C1)[C@@H]1CCNC[C@H]1COC1=CC2=C(OCO2)C=C1 |
| PENICILLIN | 0 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)CC1=CC=CC=C1)C(O)=O |
| PHENOBARBITAL | 1 | CCC1(C(=O)NC(=O)NC1=O)C1=CC=CC=C1 |
| PIOGLITAZONE | 0 | CCC1=CN=C(CCOC2=CC=C(CC3SC(=O)NC3=O)C=C2)C=C1 |
| PIPERACILLIN | 1 | [H][C@]12SC(C)(C)[C@@H](N1C(=O)[C@H]2NC(=O)[C@H](NC(=O)N1CCN(CC)C(=O)C1=O)C1=CC=CC=C1)C(O)=O |
| PREGABALIN | 0 | CC(C)C[C@H](CN)CC(O)=O |
| PROPRANOLOL | 1 | CC(C)NCC(O)COC1=CC=CC2=C1C=CC=C2 |
| PROPYLTHIOURACIL | 1 | CCCC1=CC(=O)NC(=S)N1 |
| QUETIAPINE | 1 | OCCOCCN1CCN(CC1)C1=NC2=CC=CC=C2SC2=CC=CC=C12 |
| QUINAPRIL | 0 | CCOC(=O)[C@H](CCC1=CC=CC=C1)N[C@@H](C)C(=O)N1CC2=CC=CC=C2C[C@H]1C(O)=O |
| QUININE | 1 | [H][C@]1(C[C@@H]2CC[N@]1C[C@@H]2C=C)[C@H](O)C1=CC=NC2=CC=C(OC)C=C12 |
| RABEPRAZOLE | 0 | COCCCOC1=C(C)C(CS(=O)C2=NC3=CC=CC=C3N2)=NC=C1 |
| RALOXIFENE | 0 | OC1=CC=C(C=C1)C1=C(C(=O)C2=CC=C(OCCN3CCCCC3)C=C2)C2=C(S1)C=C(O)C=C2 |
| RAMIPRIL | 0 | [H][C@@]12CCC[C@]1([H])N([C@@H](C2)C(O)=O)C(=O)[C@H](C)N[C@@H](CCC1=CC=CC=C1)C(=O)OCC |
| RANITIDINE | 1 | CNC(NCCSCC1=CC=C(CN(C)C)O1)=C[N+]([O-])=O |
| RIFABUTIN | 0 | CO[C@H]1\C=C\O[C@@]2(C)OC3=C(C2=O)C2=C(C(O)=C3C)C(=O)C(NC(=O)\C(C)=C/C=C/[C@H](C)[C@H](O)[C@@H](C)[C@@H](O)[C@@H](C)[C@H](OC(C)=O)[C@@H]1C)=C1NC3(CCN(CC3)CC(C)C)N=C21 |

| | | |
|---|---|---|
| RIFAMPIN | 1 | C[C@H]1/C=C/C=C(\C(=O)NC2=C(C(=C3C(=C2O)C(=C(C4=C3C(=O)[C@](O4)(O/C=C/[C@@H]([C@H]([C@H]([C@@H]([C@@H]([C@@H]([C@H]1O)C)O)C)OC(=O)C)C)OC)C)C)O)O)/C=N/N5CCN(CC5)C)/C |
| RIFAXIM | 1 | O=C1C2=C(O[C@@]1(O/C=C/[C@@H]([C@H]([C@H]([C@@H]([C@@H]([C@@H]([C@@H](O)[C@@H](C)/C=C/C=C(C)\C3=O)C)O)C)OC(C)=O)C)OC)C)C(C)=C(O)C4=C2C5=C(C(N3)=C4O)N6C(C=C(C)C=C6)=N5 |
| RISPERIDONE | 0 | CC1=C(CCN2CCC(CC2)C2=NOC3=C2C=CC(F)=C3)C(=O)N2CCCCC2=N1 |
| ROSUVASTATIN | 0 | CC(C)C1=NC(=NC(C2=CC=C(F)C=C2)=C1\C=C\[C@@H](O)C[C@@H](O)CC(=O)O)N(C)S(C)(=O)=O |
| SERTRALINE | 1 | CN[C@H]1CC[C@@H](C2=CC(Cl)=C(Cl)C=C2)C2=CC=CC=C12 |
| SILDENAFIL | 0 | CCCC1=NN(C)C2=C1N=C(NC2=O)C1=CC(=CC=C1OCC)S(=O)(=O)N1CCN(C)CC1 |
| SIMVASTATIN | 1 | [H][C@]12[C@H](C[C@@H](C)C=C1C=C[C@H](C)[C@@H]2CC[C@@H]1C[C@@H](O)CC(=O)O1)OC(=O)C(C)(C)CC |
| SOTALOL | 0 | CC(C)NCC(O)C1=CC=C(NS(C)(=O)=O)C=C1 |
| SPIRONOLACTONE | 1 | [H][C@@]12CC[C@@]3(CCC(=O)O3)[C@@]1(C)CC[C@@]1([H])[C@@]2([H])[C@@]([H])(CC2=CC(=O)CC[C@]12C)SC(C)=O |
| SUCRALFATE | 0 | O.O[Al](O)O.O[Al](O)OS(=O)(=O)OC[C@H]1O[C@@](COS(=O)(=O)O[Al](O)O)(O[C@H]2O[C@H](COS(=O)(=O)O[Al](O)O)[C@@H](OS(=O)(=O)O[Al](O)O)[C@H](OS(=O)(=O)O[Al](O)O)[C@H]2OS(=O)(=O)O[Al](O)O)[C@@H](OS(=O)(=O)O[Al](O)O)[C@@H]1OS(=O)(=O)O[Al](O)O |
| SULFISOXAZOLE | 1 | CC1=NOC(NS(=O)(=O)C2=CC=C(N)C=C2)=C1C |
| SURAMIN | 1 | CC1=C(NC(=O)C2=CC(NC(=O)NC3=CC=CC(=C3)C(=O)NC3=C(C)C=CC(=C3)C(=O)NC3=C4C(C=C(C=C4S(O)(=O)=O)S(O)(=O)=O)=C(C=C3)S(O)(=O)=O)=CC=C2)C=C(C=C1)C(=O)NC1=C2C(C=C(C=C2S(O)(=O)=O)S(O)(=O)=O)=C(C=C1)S(O)(=O)=O |
| TACROLIMUS | 1 | CO[C@@H]1C[C@@H](CC[C@H]1O)\C=C(/C)[C@H]1OC(=O)[C@@H]2CCCCN2C(=O)C(=O)[C@]2(O)O[C@@H]([C@H](C[C@H]2C)OC)[C@H](C[C@@H](C)C\C(C)=C\[C@@H](CC=C)C(=O)C[C@H](O)[C@H]1C)OC |
| TAMOXIFEN | 0 | CC\C(=C(/C1=CC=CC=C1)C1=CC=C(OCCN(C)C)C=C1)C1=CC=CC=C1 |
| TAMSULOSIN | 0 | CCOC1=CC=CC=C1OCCN[C@H](C)CC1=CC(=C(OC)C=C1)S(N)(=O)=O |

| | | |
|---|---|---|
| TETRACYCLINE | 0 | [H][C@@]12C[C@@]3([H])C(=C(O)[C@]1(O)C(=O)C(C(N)=O)=C(O)[C@H]2N(C)C)C(=O)C1=C(O)C=CC=C1[C@@]3(C)O |
| TIROFIBAN | 1 | CCCCS(=O)(=O)N[C@@H](CC1=CC=C(OCCCCC2CCNCC2)C=C1)C(O)=O |
| TOBRAMYCIN | 0 | NC[C@H]1O[C@H](O[C@@H]2[C@@H](N)C[C@@H](N)[C@H](O[C@H]3O[C@H](CO)[C@@H](O)[C@H](N)[C@H]3O)[C@H]2O)[C@H](N)C[C@@H]1O |
| TOLTERODINE | 0 | CC(C)N(CC[C@H](C1=CC=CC=C1)C1=C(O)C=CC(C)=C1)C(C)C |
| TOPIRAMATE | 0 | [H][C@@]12CO[C@@]3(COS(N)(=O)=O)OC(C)(C)O[C@@]3([H])[C@]1([H])OC(C)(C)O2 |
| TRAZODONE | 1 | ClC1=CC=CC(=C1)N1CCN(CCCN2N=C3C=CC=CN3C2=O)CC1 |
| TRIAMTERENE | 0 | NC1=NC(N)=C2N=C(C(N)=NC2=N1)C1=CC=CC=C1 |
| TRIAZOLAM | 0 | CC1=NN=C2CN=C(C3=CC=CC=C3Cl)C3=C(C=CC(Cl)=C3)N12 |
| TRIMETHOPRIM | 1 | COC1=CC(CC2=CN=C(N)N=C2N)=CC(OC)=C1OC |
| URSODIOL | 0 | C[C@H](CCC(O)=O)[C@H]1CC[C@@]2([H])[C@]3([H])[C@@H](O)C[C@]4([H])C[C@H](O)CC[C@]4(C)[C@@]3([H])CC[C@]12C |
| VALACYCLOVIR | 0 | CC(C)[C@H](N)C(=O)OCCOCN1C=NC2=C1NC(N)=NC2=O |
| VALGANCICLOVIR | 0 | CC(C)[C@H](N)C(=O)OCC(CO)OCN1C=NC2=C1NC(N)=NC2=O |
| VALPROIC ACID | 1 | CCCC(CCC)C(O)=O |
| VERAPAMIL | 1 | COC1=C(OC)C=C(CCN(C)CCCC(C#N)(C(C)C)C2=CC(OC)=C(OC)C=C2)C=C1 |
| VORICONAZOLE | 1 | C[C@@H](C1=NC=NC=C1F)[C@](O)(CN1C=NC=N1)C1=C(F)C=C(F)C=C1 |
| WARFARIN | 0 | CC(=O)CC(C1=CC=CC=C1)C1=C(O)C2=C(OC1=O)C=CC=C2 |
| ZOLMITRIPTAN | 1 | CN(C)CCC1=CNC2=CC=C(C[C@H]3COC(=O)N3)C=C12 |

**External validation set**

| Name | Class | SMILES |
|---|---|---|
| AMIODARONE | 1 | CCCCC1=C(C(=O)C2=CC(I)=C(OCCN(CC)CC)C(I)=C2)C2=C(O1)C=CC=C2 |
| ATENOLOL | 1 | CC(C)NCC(O)COC1=CC=C(CC(N)=O)C=C1 |
| ATOVAQUONE | 0 | OC1=C([C@H]2CC[C@@H](CC2)C2=CC=C(Cl)C=C2)C(=O)C2=CC=CC=C2C1=O |
| AZITHROMYCIN | 0 | CC[C@H]1OC(=O)[C@H](C)[C@@H](O[C@H]2C[C@@](C)(OC)[C@@H](O)[C@H](C)O2)[C@H](C)[C@@H](O[C@@H]2O[C@H](C)C[C@@H]([C@H]2O)N(C)C)[C@](C)(O)C[C@@H](C)CN(C)[C@H](C)[C@@H](O)[C@]1(C)O |

| | | |
|---|---|---|
| AZTREONAM | 1 | C[C@H]1[C@H](NC(=O)C(=N/OC(C)(C)C(=O)O)\C2=CSC([NH3+])=N2)C(=O)N1S([O-])(=O)=O |
| BENAZEPRIL | 0 | [H][C@@]1(CCC2=CC=CC=C2N(CC(O)=O)C1=O)N[C@@H](CCC1=CC=CC=C1)C(=O)OCC |
| BUDESONIDE | 0 | [H][C@@]12C[C@H]3OC(CCC)O[C@@]3(C(=O)CO)[C@@]1(C)C[C@H](O)[C@@]1([H])[C@@]2([H])CCC2=CC(=O)C=C[C@]12C |
| BUMETANIDE | 1 | CCCCNC1=C(OC2=CC=CC=C2)C(=CC(=C1)C(O)=O)S(N)(=O)=O |
| CEFAZOLIN | 1 | [H][C@]12SCC(CSC3=NN=C(C)S3)=C(N1C(=O)[C@H]2NC(=O)CN1C=NN=N1)C(O)=O |
| CEFTAZIDIME | 1 | [O-]C(=O)C1=C(CS[C@]2([H])[C@H](NC(=O)C(=N/OC(C)(C)C(O)=O)\C3=CSC(N)=N3)C(=O)N12)C[N+]1=CC=CC=C1 |
| CILASTATIN | 0 | CC1(C)C[C@@H]1C(=O)N\C(=C/CCCCSC[C@H](N)C(O)=O)C(O)=O |
| CLONAZEPAM | 0 | [O-][N+](=O)C1=CC2=C(NC(=O)CN=C2C2=CC=CC=C2Cl)C=C1 |
| DICLOFENAC | 0 | OC(=O)CC1=CC=CC=C1NC1=C(Cl)C=CC=C1Cl |
| FINASTERIDE | 0 | [H][C@@]12CC[C@H](C(=O)NC(C)(C)C)[C@@]1(C)CC[C@@]1([H])[C@@]2([H])CC[C@@]2([H])NC(=O)C=C[C@]12C |
| FLUVASTATIN | 0 | CC(C)N1C(\C=C\[C@H](O)C[C@H](O)CC(O)=O)=C(C2=CC=C(F)C=C2)C2=CC=CC=C12 |
| GENTAMICIN | 0 | CNC(C)C1CCC(N)C(OC2C(N)CC(N)C(OC3OCC(C)(O)C(NC)C3O)C2O)O1 |
| GLIPIZIDE | 0 | CC1=NC=C(N=C1)C(=O)NCCC1=CC=C(C=C1)S(=O)(=O)NC(=O)NC1CCCCC1 |
| HALOPERIDOL | 1 | OC1(CCN(CCCC(=O)C2=CC=C(F)C=C2)CC1)C1=CC=C(Cl)C=C1 |
| HYDROMORPHONE | 0 | [H][C@@]12OC3=C(O)C=CC4=C3[C@@]11CCN(C)[C@]([H])(C4)[C@]1([H])CCC2=O |
| IBUPROFEN | 1 | CC(C)CC1=CC=C(C=C1)C(C)C(O)=O |
| IPRATROPIUM | 0 | [H][C@]12CC[C@]([H])(C[C@@H](C1)OC(=O)C(CO)C1=CC=CC=C1)[N+]2(C)C(C)C |
| LEVETIRACETAM | 0 | CC[C@H](N1CCCC1=O)C(N)=O |
| LISINOPRIL | 1 | NCCCC[C@H](N[C@@H](CCC1=CC=CC=C1)C(O)=O)C(=O)N1CCC[C@H]1C(O)=O |
| LORACARBEF | 1 | N[C@@H](C(=O)N[C@H]1[C@H]2CCC(Cl)=C(N2C1=O)C(O)=O)C1=CC=CC=C1 |
| MELOXICAM | 0 | CN1C(C(=O)NC2=NC=C(C)S2)=C(O)C2=C(C=CC=C2)S1(=O)=O |
| METHYLDOPA | 0 | C[C@](N)(CC1=CC=C(O)C(O)=C1)C(O)=O |
| METHYLPREDNISOLONE | 1 | [H][C@@]12CC[C@](O)(C(=O)CO)[C@@]1(C)C[C@H](O)[C@@]1([H])[C@@]2([H])C[C@H](C)C2=CC(=O)C=C[C@]12C |

| | | |
|---|---|---|
| METOLAZONE | 0 | CC1NC2=CC(Cl)=C(C=C2C(=O)N1C1=CC=CC=C1C)S(N)(=O)=O |
| MORPHINE | 0 | [H][C@@]12OC3=C(O)C=CC4=C3[C@@]11CCN(C)[C@]([H])(C4)[C@]1([H])C=C[C@@H]2O |
| NEFAZODONE | 0 | CCC1=NN(CCCN2CCN(CC2)C2=CC(Cl)=CC=C2)C(=O)N1CCOC1=CC=CC=C1 |
| OXCARBAZEPINE | 1 | NC(=O)N1C2=CC=CC=C2CC(=O)C2=C1C=CC=C2 |
| PANTOPRAZOLE | 1 | COC1=C(OC)C(CS(=O)C2=NC3=C(N2)C=C(OC(F)F)C=C3)=NC=C1 |
| PHENYTOIN | 1 | O=C1NC(=O)C(N1)(C1=CC=CC=C1)C1=CC=CC=C1 |
| PRAVASTATIN | 0 | [H][C@]12[C@H](C[C@H](O)C=C1C=C[C@H](C)[C@@H]2CC[C@@H](O)C[C@@H](O)CC(O)=O)OC(=O)[C@@H](C)CC |
| PREDNISONE | 0 | [H][C@@]12CC[C@](O)(C(=O)CO)[C@@]1(C)CC(=O)[C@@]1([H])[C@@]2([H])CCC2=CC(=O)C=C[C@]12C |
| PROCAINAMIDE | 1 | CCN(CC)CCNC(=O)C1=CC=C(N)C=C1 |
| PROPOXYPHENE | 1 | CCC(=O)O[C@@](CC1=CC=CC=C1)([C@H](C)CN(C)C)C1=CC=CC=C1 |
| QUINIDINE | 1 | [H][C@@]12CCN(C[C@@H]1C=C)[C@]([H])(C2)[C@@H](O)C1=C2C=C(OC)C=CC2=NC=C1 |
| RISEDRONIC ACID | 0 | OC(CC1=CN=CC=C1)(P(O)(O)=O)P(O)(O)=O |
| TERAZOSIN | 0 | COC1=C(OC)C=C2C(N)=NC(=NC2=C1)N1CCN(CC1)C(=O)C1CCCO1 |
| TRAMADOL | 0 | COC1=CC=CC(=C1)[C@@]1(O)CCCC[C@@H]1CN(C)C |
| VALSARTAN | 0 | CCCCC(=O)N(CC1=CC=C(C=C1)C1=CC=CC=C1C1=NNN=N1)[C@@H](C(C)C)C(O)=O |
| VANCOMYCIN | 1 | CN[C@H](CC(C)C)C(=O)N[C@@H]1[C@H](O)C2=CC=C(OC3=C(O[C@@H]4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O[C@H]4C[C@](C)(N)[C@H](O)[C@H](C)O4)C4=CC(=C3)[C@@H](NC(=O)[C@H](CC(N)=O)NC1=O)C(=O)N[C@@H]1C3=CC(=C(O)C=C3)C3=C(O)C=C(O)C=C3[C@H](NC(=O)[C@@H](NC1=O)[C@H](O)C1=CC(Cl)=C(O4)C=C1)C(O)=O)C(Cl)=C2 |
| VENLAFAXINE | 0 | COC1=CC=C(C=C1)C(CN(C)C)C1(O)CCCCC1 |
| ZOLPIDEM | 0 | CN(C)C(=O)CC1=C(N=C2C=CC(C)=CN12)C1=CC=C(C)C=C1 |

**Table S2.** Summary of the six types of molecular fingerprints used.

| Fingerprints type | Abbreviation | Pattern type | Bit size |
|---|---|---|---|
| MACCS | MACCS | Structural features | 166 |
| Atom Pairs 2D | AP2D | Structural features | 780 |
| PubChem | PubChem | Structural features | 881 |
| Klekota-Roth | KRFP | Structural features | 4860 |
| CDK | CDK | Hash fingerprints | 1024 |
| CDK Extended | ExtFP | Hash fingerprints | 1024 |

**Table S3.** Hyperparameters of the machine learning-based models.

| **Method** | **Hyperparameter** | **Value** |
|---|---|---|
| SVM | penalty parameter *C* | {0.5, 0.6, 0.7, 0.8, 0.9, 1} |
| RF | number of estimators | {10, 50, 100} |
| | max features | {auto, sqrt, log2, 0.5} |
| k-NN | number of neighbors | {2–10} |
| ANN | hidden layer size | {10, 50, 100} |
| Adaboost | number of estimators | {10, 50, 100} |
| XGboost | maximum tree depth | {3, 5, 8, 10} |
| | minimum sum of instance weights in child | {1, 3, 5} |

**Table S4.** Prediction results of the optimal classification models on training set by using the five-fold cross-validation.

| Methods | Molecular features | SE | SP | ACC | MCC | AUC |
|---|---|---|---|---|---|---|
| SVM | RDKit+MACCS | 0.537±0.034 | 0.646±0.026 | 0.580±0.013 | 0.185±0.028 | 0.591±0.014 |
| | RDKit+CDK | 0.550±0.023 | 0.649±0.023 | 0.590±0.014 | 0.205±0.026 | 0.599±0.012 |
| | RDKit+PubChem | 0.515±0.025 | 0.584±0.035 | 0.537±0.011 | 0.101±0.029 | 0.549±0.014 |
| | RDKit+KRFP | 0.690±0.027 | 0.508±0.025 | 0.590±0.016 | 0.205±0.029 | 0.599±0.014 |
| | RDKit+AP2D | 0.530±0.026 | 0.607±0.031 | 0.558±0.014 | 0.139±0.021 | 0.569±0.010 |
| | RDKit+ExtFP | 0.577±0.022 | 0.629±0.036 | 0.590±0.022 | 0.210±0.028 | 0.603±0.014 |
| | 10md+MACCS | 0.571±0.020 | 0.512±0.033 | 0.527±0.019 | 0.085±0.037 | 0.541±0.018 |
| | 10md+CDK | 0.539±0.035 | 0.659±0.024 | 0.587±0.014 | 0.206±0.026 | 0.599±0.0120 |
| | 10md+PubChem | 0.564±0.032 | 0.575±0.032 | 0.559±0.014 | 0.141±0.021 | 0.569±0.011 |
| | 10md+KRFP | 0.572±0.019 | 0.636±0.021 | 0.589±0.010 | 0.212±0.023 | 0.604±0.010 |
| | 10md+AP2D | 0.571±0.045 | 0.533±0.042 | 0.532±0.021 | 0.110±0.038 | 0.552±0.019 |
| | 10md+ExtFP | 0.579±0.028 | 0.629±0.036 | 0.588±0.018 | 0.215±0.030 | 0.604±0.015 |
| | CC+MACCS | 0.544±0.032 | 0.654±0.033 | 0.590±0.015 | 0.199±0.030 | 0.599±0.015 |
| | CC+CDK | 0.514±0.023 | 0.697±0.034 | 0.591±0.018 | 0.222±0.022 | 0.605±0.010 |
| | CC+PubChem | 0.561±0.030 | 0.596±0.032 | 0.568±0.020 | 0.162±0.030 | 0.578±0.014 |
| | CC+KRFP | 0.582±0.036 | 0.625±0.044 | 0.589±0.014 | 0.210±0.026 | 0.603±0.013 |
| | CC+AP2D | 0.440±0.017 | 0.692±0.019 | 0.555±0.020 | 0.137±0.034 | 0.566±0.016 |
| | CC+ExtFP | 0.550±0.029 | 0.664±0.026 | 0.602±0.017 | 0.218±0.029 | 0.607±0.015 |
| k-NN | RDKit+MACCS | 0.464±0.020 | 0.731±0.025 | 0.592±0.015 | 0.206±0.031 | 0.597±0.015 |
| | RDKit+CDK | 0.485±0.023 | 0.711±0.017 | 0.594±0.014 | 0.203±0.028 | 0.598±0.014 |
| | RDKit+PubChem | 0.690±0.023 | 0.566±0.021 | 0.627±0.010 | 0.261±0.022 | 0.628±0.011 |
| | RDKit+KRFP | 0.651±0.022 | 0.474±0.039 | 0.557±0.021 | 0.128±0.038 | 0.563±0.018 |
| | RDKit+AP2D | 0.634±0.044 | 0.539±0.031 | 0.585±0.019 | 0.175±0.040 | 0.586±0.019 |
| | RDKit+ExtFP | 0.487±0.021 | 0.692±0.009 | 0.583±0.017 | 0.183±0.027 | 0.590±0.012 |
| | 10md+MACCS | 0.435± 0.023 | 0.749±0.029 | 0.584±0.011 | 0.195±0.025 | 0.592±0.011 |
| | 10md+CDK | 0.481±0.015 | 0.718±0.031 | 0.596±0.008 | 0.207±0.021 | 0.600±0.010 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10md+PubChem | 0.669±0.020 | 0.572±0.024 | 0.618±0.017 | 0.243±0.031 | 0.621±0.016 |
| | 10md+KRFP | 0.646±0.026 | 0.509±0.044 | 0.574±0.013 | 0.158±0.028 | 0.578±0.015 |
| | 10md+AP2D | 0.435±0.023 | 0.763±0.021 | 0.597±0.015 | 0.213±0.032 | 0.599±0.015 |
| | 10md+ExtFP | 0.500±0.027 | 0.696±0.027 | 0.597±0.015 | 0.199±0.035 | 0.598±0.016 |
| | CC+MACCS | 0.626±0.032 | 0.571±0.028 | 0.599±0.016 | 0.198±0.037 | 0.598±0.019 |
| | CC+CDK | 0.481±0.027 | 0.706±0.027 | 0.592±0.018 | 0.192±0.041 | 0.593±0.020 |
| | CC+PubChem | 0.655±0.020 | 0.565±0.024 | 0.608±0.014 | 0.222±0.027 | 0.610±0.013 |
| | CC+KRFP | 0.466±0.021 | 0.737±0.011 | 0.598±0.008 | 0.215±0.021 | 0.601±0.009 |
| | CC+AP2D | 0.646±0.023 | 0.564±0.020 | 0.603±0.012 | 0.211±0.024 | 0.605±0.013 |
| | CC+ExtFP | 0.489±0.025 | 0.711±0.023 | 0.593±0.017 | 0.207±0.024 | 0.600±0.013 |
| NB | RDKit+MACCS | 0.506±0.022 | 0.610±0.047 | 0.558±0.020 | 0.117±0.039 | 0.558±0.019 |
| | RDKit+CDK | 0.520±0.016 | 0.624±0.024 | 0.566±0.014 | 0.145±0.026 | 0.572±0.013 |
| | RDKit+PubChem | 0.541±0.037 | 0.505±0.035 | 0.523±0.013 | 0.047±0.024 | 0.523±0.012 |
| | RDKit+KRFP | 0.604±0.030 | 0.567±0.026 | 0.571±0.021 | 0.174±0.027 | 0.585±0.014 |
| | RDKit+AP2D | 0.544±0.031 | 0.475±0.041 | 0.505±0.018 | 0.018±0.031 | 0.509±0.015 |
| | RDKit+ExtFP | 0.521±0.042 | 0.587±0.023 | 0.551±0.021 | 0.109±0.040 | 0.554±0.020 |
| | 10md+MACCS | 0.477±0.023 | 0.565±0.030 | 0.519±0.013 | 0.042±0.022 | 0.521± 0.011 |
| | 10md+CDK | 0.526± 0.028 | 0.592±0.020 | 0.558±0.008 | 0.118±0.018 | 0.559± 0.009 |
| | 10md+PubChem | 0.559±0.033 | 0.493±0.024 | 0.524±0.017 | 0.053±0.031 | 0.526±0.015 |
| | 10md+KRFP | 0.565±0.031 | 0.635±0.017 | 0.589±0.014 | 0.204±0.019 | 0.600±0.009 |
| | 10md+AP2D | 0.613±0.030 | 0.421±0.035 | 0.499±0.015 | 0.037±0.036 | 0.517±0.017 |
| | 10md+ExtFP | 0.487±0.021 | 0.593±0.024 | 0.537±0.018 | 0.081±0.025 | 0.540±0.012 |
| | CC+MACCS | 0.434±0.017 | 0.588±0.028 | 0.504±0.014 | 0.021±0.038 | 0.511±0.018 |
| | CC+CDK | 0.526±0.029 | 0.577±0.028 | 0.550±0.016 | 0.103±0.038 | 0.551±0.019 |
| | CC+PubChem | 0.558±0.032 | 0.525±0.020 | 0.535±0.020 | 0.083±0.020 | 0.541±0.010 |
| | CC+KRFP | 0.557±0.028 | 0.627±0.029 | 0.583±0.008 | 0.188±0.032 | 0.592±0.015 |
| | CC+AP2D | 0.494±0.018 | 0.593±0.014 | 0.537±0.008 | 0.088±0.017 | 0.543±0.008 |
| | CC+ExtFP | 0.493±0.030 | 0.596±0.026 | 0.545±0.011 | 0.090±0.030 | 0.545±0.014 |

| | | | | | | |
|---|---|---|---|---|---|---|
| AdaBoost | RDKit+MACCS | 0.611±0.044 | 0.529±0.047 | 0.566±0.012 | 0.144±0.034 | 0.570±0.016 |
| | RDKit+CDK | 0.594±0.039 | 0.593±0.035 | 0.590±0.014 | 0.189±0.025 | 0.594±0.013 |
| | RDKit+PubChem | 0.539±0.042 | 0.614±0.046 | 0.570±0.009 | 0.156±0.020 | 0.576±0.010 |
| | RDKit+KRFP | 0.541±0.031 | 0.654±0.031 | 0.593±0.013 | 0.197±0.026 | 0.598±0.013 |
| | RDKit+AP2D | 0.572±0.030 | 0.576±0.024 | 0.568±0.015 | 0.148±0.023 | 0.574±0.010 |
| | RDKit+ExtFP | 0.557±0.031 | 0.619±0.031 | 0.580±0.015 | 0.180±0.029 | 0.588±0.014 |
| | 10md+MACCS | 0.559±0.014 | 0.568±0.025 | 0.559±0.015 | 0.127±0.024 | 0.563±0.012 |
| | 10md+CDK | 0.602±0.027 | 0.588±0.025 | 0.588±0.014 | 0.190±0.039 | 0.595±0.019 |
| | 10md+PubChem | 0.586±0.027 | 0.558±0.028 | 0.566±0.011 | 0.145±0.019 | 0.572±0.009 |
| | 10md+KRFP | 0.574±0.042 | 0.628±0.029 | 0.599±0.014 | 0.206±0.023 | 0.601±0.012 |
| | 10md+AP2D | 0.601±0.033 | 0.601±0.043 | 0.594±0.008 | 0.205±0.025 | 0.601±0.013 |
| | 10md+ExtFP | 0.624±0.031 | 0.566±0.027 | 0.587±0.019 | 0.193±0.041 | 0.595±0.021 |
| | CC+MACCS | 0.607±0.043 | 0.587±0.029 | 0.592±0.018 | 0.194±0.032 | 0.597±0.016 |
| | CC+CDK | 0.596±0.025 | 0.603±0.026 | 0.596±0.014 | 0.199±0.027 | 0.599±0.013 |
| | CC+PubChem | 0.615±0.024 | 0.558±0.034 | 0.577±0.015 | 0.173±0.039 | 0.587±0.020 |
| | CC+KRFP | 0.600±0.025 | 0.602±0.035 | 0.598±0.009 | 0.203±0.022 | 0.601±0.011 |
| | CC+AP2D | 0.580±0.046 | 0.572±0.046 | 0.570±0.010 | 0.152±0.023 | 0.576±0.011 |
| | CC+ExtFP | 0.604±0.029 | 0.587±0.023 | 0.589±0.009 | 0.192±0.020 | 0.595±0.009 |
| RF | RDKit+MACCS | 0.544±0.019 | 0.639±0.028 | 0.583±0.015 | 0.186±0.030 | 0.591±0.015 |
| | RDKit+CDK | 0.565±0.024 | 0.632±0.032 | 0.593±0.018 | 0.199±0.030 | 0.599±0.015 |
| | RDKit+PubChem | 0.530±0.019 | 0.635±0.032 | 0.576±0.021 | 0.168±0.043 | 0.583±0.020 |
| | RDKit+KRFP | 0.565±0.044 | 0.628±0.045 | 0.587±0.025 | 0.196±0.044 | 0.596±0.022 |
| | RDKit+AP2D | 0.565±0.025 | 0.613±0.029 | 0.579±0.018 | 0.180±0.018 | 0.589±0.017 |
| | RDKit+ExtFP | 0.536±0.043 | 0.648±0.031 | 0.583±0.015 | 0.188±0.031 | 0.592±0.015 |
| | 10md+MACCS | 0.567±0.019 | 0.596±0.033 | 0.576±0.025 | 0.164±0.043 | 0.582±0.021 |
| | 10md+CDK | 0.522±0.037 | 0.686±0.031 | 0.591±0.015 | 0.213±0.032 | 0.604±0.016 |
| | 10md+PubChem | 0.537±0.035 | 0.604±0.035 | 0.563±0.017 | 0.143±0.038 | 0.570±0.019 |
| | 10md+KRFP | 0.609±0.022 | 0.588±0.024 | 0.592±0.014 | 0.198±0.025 | 0.598±0.012 |
| | 10md+AP2D | 0.585±0.038 | 0.618±0.044 | 0.594±0.013 | 0.203±0.023 | 0.601±0.011 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 10md+ExtFP | 0.545±0.029 | 0.656±0.036 | 0.590±0.018 | 0.204±0.028 | 0.600±0.013 |
| | CC+MACCS | 0.611±0.018 | 0.592±0.036 | 0.601±0.019 | 0.206±0.034 | 0.601±0.017 |
| | CC+CDK | 0.554±0.033 | 0.655±0.028 | 0.596±0.009 | 0.210±0.015 | 0.604±0.007 |
| | CC+PubChem | 0.650±0.019 | 0.557±0.028 | 0.598±0.015 | 0.210±0.032 | 0.603±0.016 |
| | CC+KRFP | 0.558±0.038 | 0.642±0.029 | 0.584±0.018 | 0.210±0.022 | 0.601±0.011 |
| | CC+AP2D | 0.599±0.032 | 0.602±0.030 | 0.597±0.011 | 0.204±0.025 | 0.601±0.013 |
| | CC+ExtFP | 0.585±0.029 | 0.621±0.046 | 0.594±0.021 | 0.208±0.040 | 0.603±0.020 |
| XGBoost | RDKit+MACCS | 0.586±0.022 | 0.603±0.044 | 0.590±0.023 | 0.189±0.038 | 0.595±0.019 |
| | RDKit+CDK | 0.588±0.017 | 0.609±0.028 | 0.593±0.017 | 0.199±0.036 | 0.598±0.018 |
| | RDKit+PubChem | 0.597±0.031 | 0.600±0.026 | 0.592±0.009 | 0.196±0.021 | 0.598±0.011 |
| | RDKit+KRFP | 0.606±0.036 | 0.574±0.037 | 0.588±0.013 | 0.181±0.026 | 0.590±0.013 |
| | RDKit+AP2D | 0.585±0.037 | 0.597±0.029 | 0.588±0.014 | 0.182±0.024 | 0.591±0.013 |
| | RDKit+ExtFP | 0.562±0.018 | 0.600±0.020 | 0.579±0.012 | 0.163±0.025 | 0.581±0.012 |
| | 10md+MACCS | 0.562±0.021 | 0.628±0.021 | 0.587±0.020 | 0.192±0.034 | 0.595±0.017 |
| | 10md+CDK | 0.602±0.034 | 0.605±0.038 | 0.598±0.021 | 0.206±0.045 | 0.603±0.022 |
| | 10md+PubChem | 0.580±0.032 | 0.609±0.025 | 0.590±0.010 | 0.191±0.021 | 0.595±0.011 |
| | 10md+KRFP | 0.593±0.036 | 0.600±0.037 | 0.592±0.020 | 0.193±0.031 | 0.596±0.014 |
| | 10md+AP2D | 0.581±0.041 | 0.623±0.033 | 0.593±0.021 | 0.206±0.035 | 0.602±0.018 |
| | 10md+ExtFP | 0.546±0.023 | 0.618±0.043 | 0.576±0.021 | 0.166±0.042 | 0.582±0.021 |
| | CC+MACCS | 0.642±0.027 | 0.583±0.021 | 0.607±0.008 | 0.226±0.023 | 0.613±0.011 |
| | CC+CDK | 0.594±0.024 | 0.609±0.024 | 0.603±0.014 | 0.204±0.027 | 0.602±0.013 |
| | CC+PubChem | 0.610±0.011 | 0.615±0.021 | 0.608±0.009 | 0.226±0.021 | 0.612±0.010 |
| | CC+KRFP | 0.619±0.027 | 0.614±0.033 | 0.611±0.012 | 0.233±0.025 | 0.617±0.010 |
| | CC+AP2D | 0.603±0.026 | 0.603±0.027 | 0.600±0.011 | 0.207±0.020 | 0.603±0.010 |
| | CC+ExtFP | 0.594±0.039 | 0.608±0.034 | 0.596±0.021 | 0.203±0.046 | 0.601±0.021 |
| ANN | RDKit+MACCS | 0.550±0.038 | 0.553±0.029 | 0.540±0.013 | 0.105±0.027 | 0.551±0.013 |
| | RDKit+CDK | 0.621±0.027 | 0.569±0.023 | 0.589±0.021 | 0.192±0.038 | 0.595±0.018 |
| | RDKit+PubChem | 0.577±0.037 | 0.518±0.024 | 0.545±0.008 | 0.096±0.020 | 0.548±0.010 |
| | RDKit+KRFP | 0.584±0.019 | 0.539±0.037 | 0.553±0.019 | 0.125±0.036 | 0.562±0.018 |

| | | | | | |
|---|---|---|---|---|---|
| RDKit+AP2D | 0.566±0.048 | 0.551±0.032 | 0.549±0.020 | 0.120±0.039 | 0.559±0.019 |
| RDKit+ExtFP | 0.654±0.028 | 0.539±0.017 | 0.591±0.022 | 0.195±0.038 | 0.597±0.019 |
| 10md+MACCS | 0.557±0.045 | 0.477±0.046 | 0.506±0.032 | 0.035±0.029 | 0.517±0.014 |
| 10md+CDK | 0.625±0.036 | 0.554±0.045 | 0.579±0.012 | 0.179±0.023 | 0.589±0.012 |
| 10md+PubChem | 0.572±0.042 | 0.540±0.016 | 0.549±0.023 | 0.113±0.046 | 0.556±0.022 |
| 10md+KRFP | 0.552±0.032 | 0.608±0.038 | 0.569±0.009 | 0.163±0.022 | 0.580±0.010 |
| 10md+AP2D | 0.565±0.038 | 0.505±0.024 | 0.523±0.028 | 0.072±0.032 | 0.535±0.017 |
| 10md+ExtFP | 0.622±0.045 | 0.567±0.048 | 0.589±0.011 | 0.190±0.026 | 0.595±0.013 |
| CC+MACCS | 0.546±0.026 | 0.541±0.040 | 0.533±0.022 | 0.087±0.043 | 0.543±0.021 |
| CC+CDK | 0.634±0.015 | 0.552±0.018 | 0.590±0.008 | 0.187±0.012 | 0.593±0.006 |
| CC+PubChem | 0.537±0.042 | 0.570±0.024 | 0.542±0.017 | 0.107±0.032 | 0.553±0.016 |
| CC+KRFP | 0.585±0.031 | 0.595±0.021 | 0.577±0.022 | 0.182±0.028 | 0.590±0.013 |
| CC+AP2D | 0.520±0.022 | 0.580±0.038 | 0.534±0.022 | 0.101±0.040 | 0.550±0.020 |
| CC+ExtFP | 0.633±0.031 | 0.551±0.042 | 0.585±0.020 | 0.185±0.034 | 0.592±0.017 |

**Table S5.** Prediction results of RDMD+PubChem-k-NN and CCMD+KPFP-XGBoost models for external validation dataset.

| Name | True label | Model prediction | |
|---|---|---|---|
| | | RDMD+PubChem-k-NN | CCMD+KPFP-XGBoost |
| AMIODARONE | 1 | 0 | 0 |
| ATENOLOL | 1 | 1 | 0 |
| ATOVAQUONE | 0 | 0 | 0 |
| AZITHROMYCIN | 0 | 0 | 0 |
| AZTREONAM | 1 | 1 | 1 |
| BENAZEPRIL | 0 | 0 | 0 |
| BUDESONIDE | 0 | 1 | 1 |
| BUMETANIDE | 1 | 1 | 1 |
| CEFAZOLIN | 1 | 1 | 1 |
| CEFTAZIDIME | 1 | 1 | 1 |
| CILASTATIN | 0 | 0 | 0 |
| CLONAZEPAM | 0 | 0 | 0 |
| DICLOFENAC | 0 | 1 | 1 |
| FINASTERIDE | 0 | 0 | 0 |
| FLUVASTATIN | 0 | 0 | 0 |
| GENTAMICIN | 0 | 0 | 0 |
| GLIPIZIDE | 0 | 0 | 0 |
| HALOPERIDOL | 1 | 1 | 0 |
| HYDROMORPHONE | 0 | 0 | 0 |
| IBUPROFEN | 1 | 1 | 0 |
| IPRATROPIUM | 0 | 0 | 0 |
| LEVETIRACETAM | 0 | 1 | 0 |
| LISINOPRIL | 1 | 0 | 0 |
| LORACARBEF | 1 | 1 | 1 |
| MELOXICAM | 0 | 0 | 0 |
| METHYLDOPA | 0 | 0 | 0 |

| | | | |
|---|---|---|---|
| METHYLPREDNISOLONE | 1 | 1 | 1 |
| METOLAZONE | 0 | 0 | 1 |
| MORPHINE | 0 | 1 | 0 |
| NEFAZODONE | 0 | 1 | 0 |
| OXCARBAZEPINE | 1 | 1 | 1 |
| PANTOPRAZOLE | 1 | 1 | 0 |
| PHENYTOIN | 1 | 1 | 1 |
| PRAVASTATIN | 0 | 0 | 0 |
| PREDNISONE | 0 | 1 | 1 |
| PROCAINAMIDE | 1 | 1 | 1 |
| PROPOXYPHENE | 1 | 1 | 1 |
| QUINIDINE | 1 | 1 | 1 |
| RISEDRONIC ACID | 0 | 0 | 0 |
| TERAZOSIN | 0 | 1 | 0 |
| TRAMADOL | 0 | 1 | 0 |
| VALSARTAN | 0 | 0 | 0 |
| VANCOMYCIN | 1 | 0 | 1 |
| VENLAFAXINE | 0 | 0 | 0 |
| ZOLPIDEM | 0 | 0 | 0 |

**Table S6.** The comparison results of the PubChem fingerprint between Levetiracetam and its corresponding tautomeric form.

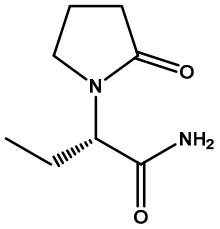
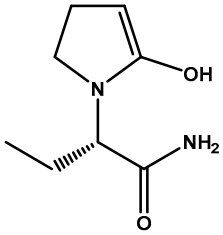
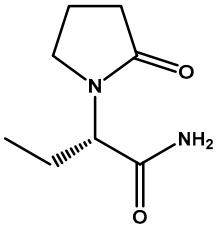
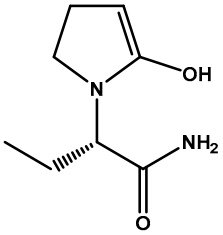
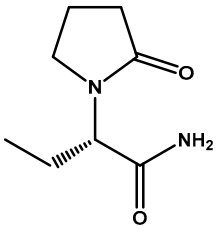
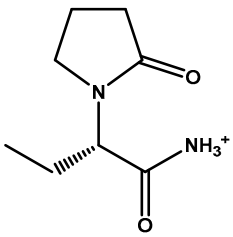
| **Structures** / **Bits** |  |  **(Tautomeric form)** |
|---|---|---|
| 145 | 1 | 0 |
| 146 | 1 | 0 |
| 148 | 0 | 1 |
| 149 | 0 | 1 |
| 308 | 0 | 1 |
| 406 | 0 | 1 |
| 415 | 0 | 1 |
| 434 | 0 | 1 |
| 441 | 0 | 1 |
| 446 | 0 | 1 |
| 449 | 0 | 1 |
| 490 | 0 | 1 |
| 498 | 0 | 1 |
| 502 | 0 | 1 |
| 556 | 0 | 1 |
| 645 | 1 | 0 |
| 646 | 1 | 0 |
| 685 | 1 | 0 |

**Table S7.** The comparison results of the RDKit descriptors between Levetiracetam and its corresponding tautomeric form and protonation state.

| **Structures** / **Descriptors** |  |  **(Tautomeric form)** |
|---|---|---|
| MaxEStateIndex | 11.197 | 10.905 |
| MinEStateIndex | -0.396 | -0.376 |
| MinAbsEStateIndex | 0.056 | 0.181 |
| qed | 0.641 | 0.642 |
| FpDensityMorgan1 | 1.750 | 1.917 |
| FpDensityMorgan3 | 2.750 | 2.917 |
| BalabanJ | 2.647 | 2.664 |
| BertzCT | 203.235 | 213.103 |
| Chi1n | 4.253 | 4.115 |
| Chi3v | 2.201 | 2.083 |
| Chi4n | 1.574 | 1.455 |
| HallKierAlpha | -1.060 | -1.190 |
| Kappa3 | 1.571 | 1.519 |
| PEOE_VSA1 | 10.634 | 15.740 |
| PEOE_VSA11 | 0.000 | 5.883 |
| PEOE_VSA12 | 11.814 | 5.907 |
| PEOE_VSA2 | 9.589 | 4.795 |
| PEOE_VSA7 | 12.842 | 18.918 |
| PEOE_VSA8 | 12.966 | 6.545 |
| SMR_VSA1 | 9.589 | 9.901 |
| SMR_VSA10 | 11.814 | 5.907 |
| SMR_VSA5 | 32.228 | 25.807 |

| | | |
|---|---|---|
| SMR_VSA7 | 0.000 | 11.959 |
| SlogP_VSA2 | 29.301 | 28.500 |
| SlogP_VSA3 | 9.589 | 4.795 |
| SlogP_VSA5 | 26.186 | 19.765 |
| TPSA | 63.400 | 66.560 |
| EState_VSA1 | 5.907 | 0.000 |
| EState_VSA2 | 11.949 | 17.832 |
| EState_VSA3 | 19.386 | 12.966 |
| EState_VSA6 | 4.900 | 10.976 |
| VSA_EState9 | 32.667 | 32.167 |
| FractionCSP3 | 0.750 | 0.625 |
| NHOHCount | 2 | 3 |
| NumHAcceptors | 2 | 3 |
| NumSaturatedHeterocycles | 1 | 0 |
| NumSaturatedRings | 1 | 0 |
| MolLogP | -0.127 | 0.355 |
| fr_C_O | 2 | 1 |
| fr_Ndealkylation2 | 1 | 0 |
| fr_amide | 2 | 1 |
| **Structures** / **Descriptors** |  |  **(Protonation state)** |
| MaxEStateIndex | 11.197 | 11.225 |
| MinEStateIndex | -0.396 | -0.278 |
| MinAbsEStateIndex | 0.056 | 0.096 |
| qed | 0.641 | 0.601 |
| MolWt | 170.212 | 171.220 |

| | | |
|---|---|---|
| Chi1n | 4.253 | 4.317 |
| Chi3v | 2.201 | 2.245 |
| Chi4n | 1.574 | 1.620 |
| HallKierAlpha | -1.060 | -0.900 |
| Kappa3 | 1.571 | 1.637 |
| PEOE_VSA1 | 10.634 | 4.900 |
| PEOE_VSA12 | 11.814 | 5.907 |
| PEOE_VSA14 | 0.000 | 5.907 |
| PEOE_VSA2 | 9.589 | 10.528 |
| PEOE_VSA3 | 0.000 | 4.795 |
| SMR_VSA1 | 9.589 | 15.323 |
| SMR_VSA4 | 5.734 | 0.000 |
| TPSA | 63.400 | 65.020 |
| EState_VSA1 | 5.907 | 0.000 |
| EState_VSA2 | 11.949 | 17.856 |
| EState_VSA3 | 19.386 | 12.842 |
| EState_VSA4 | 6.421 | 12.966 |
| EState_VSA8 | 0.000 | 5.734 |
| EState_VSA9 | 5.734 | 0.000 |
| VSA_EState9 | 32.667 | 31.667 |
| NHOHCount | 2 | 3 |
| MolLogP | -0.127 | -0.844 |
| fr_priamide | 1 | 0 |
| fr_quatN | 0 | 1 |