

SUPPORTING INFORMATION

SIRT2i_Predictor: A Machine Learning-Based Tool to Facilitate the Discovery of Novel SIRT2 Inhibitors

Nemanja Djokovic ^{1,*}, Minna Rahnasto-Rilla ², Nikolaos Lougiakis ³, Maija Lahtela-Kakkonen ² and Katarina Nikolic ^{1,*}

- ^{1.} Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia
 - ^{2.} School of Pharmacy, University of Eastern Finland, P.O. Box 1627, 70210 Kuopio, Finland
 - ^{3.} Laboratory of Medicinal Chemistry, Section of Pharmaceutical Chemistry, Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Panepistimiopolis-Zografou, 15771 Athens, Greece
- * Correspondence: nemanja.djokovic@pharmacy.bg.ac.rs (N.D.); katarina.nikolic@pharmacy.bg.ac.rs (K.N.)

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Table S1. List of hyperparameters, their values and objectives considered for optimization through Bayesian search.

Model	ML algorithm	Tuned hyperparameters
Regression	RF	{'bootstrap': [True, False], 'max_depth': [5, 20, 35, 50, 65, 80, None], 'max_features': ['log2', 'sqrt'], 'min_samples_leaf': [2, 4, 6], 'min_samples_split': [2, 5, 10], 'n_estimators': [250, 500, 750, 1000, 1250, 1500]}, scoring : (' r2')
	SVR	{'C': [0.01, 0.1, 1, 10, 100, 200, 400, 1000], 'gamma': [100, 10, 1, 1e-1, 1e-2, 1e-3], 'kernel': ['rbf', 'linear']}, scoring : (' r2')
	XGBoost	{'learning_rate': [0.01, 0.1], 'max_depth': [3, 6, 10], 'min_child_weight': [1, 3, 5], 'gamma': [0, 1, 5], 'subsample': [0.6, 0.7, 0.8, 0.9, 1.0], 'colsample_bytree': [0.5, 0.6, 0.7, 0.8, 0.9, 1.0], 'n_estimators': [500, 1500]}, scoring : (' r2')
	KNN	{'n_neighbors': [5, 9, 15, 19, 25, 35, 45, 55, 71], 'weights': ['distance'], 'p': [1, 2], 'metric': ['jaccard', 'dice', 'rogerstanimoto']}, scoring : (' r2')
	DNN	{number of Dense layers: (1-8, activation = 'relu'; None in output layer), number of neurons in each layer: ((100 - 5000), step = (50 - 1000)), added dropouts: ((0 - 0.5), step = 0.1), SGD optimizer learning rate: (1e-4 to 1e-2, sampling = 'log', default = 1e-3), loss_fn : 'MeanSquaredError', batch_size : (32-128, step = 32, default = 64), objective : ('val_mean_squared_error', 'min'), used 30 % of training set as validation set }
Binary	RF	{'bootstrap': [True, False], 'max_depth': [5, 20, 35, 50, 65, 80, None], 'max_features': ['log2', 'sqrt'], 'min_samples_leaf': [2, 4, 6], 'min_samples_split': [2, 5, 10], 'n_estimators': [250, 500, 750, 1000, 1250, 1500]}, scoring : (' balanced_accuracy')
	SVC	{'C': [0.01, 0.1, 1, 10, 100, 200, 400, 1000], 'gamma': [100, 10, 1, 1e-1, 1e-2, 1e-3], 'kernel': ['linear', 'rbf']}, scoring : (' balanced_accuracy')
	XGBoost	{'learning_rate': [0.01, 0.1], 'max_depth': [3, 6, 10], 'min_child_weight': [1, 3, 5], 'gamma': [0, 1, 5], 'subsample': [0.6, 0.7, 0.8, 0.9, 1.0], 'colsample_bytree': [0.5, 0.6, 0.7, 0.8, 0.9, 1.0], 'n_estimators': [500, 1500]}, scoring : (' balanced_accuracy')
	KNN	{'n_neighbors': [5, 9, 15, 19, 25, 35, 45, 55, 71], 'weights': ['distance'], 'p': [1, 2], 'metric': ['jaccard', 'dice', 'rogerstanimoto']}, scoring : (' balanced_accuracy')
	DNN	{number of Dense layers: (1-8, (activation = 'relu'; 'sigmoid' in output layer)), number of neurons in each layer: ((100 - 5000), step = (50 - 1000)), added dropouts: ((0-0.5), step = 0.1), Adam optimizer learning rate: ((1e-4 to 1e-2), sampling = 'log', default = 1e-3), loss_fn : 'BinaryCrossentropy', batch_size : (32-128, step = 32, default = 64), objective : ('val_binary_accuracy', 'max'), used 30 % of training set as validation set }
Multi-class	RF	{'bootstrap': [True, False], 'max_depth': [5, 20, 35, 50, 65, 80, None], 'max_features': ['log2', 'sqrt'], 'min_samples_leaf': [2, 4, 6], 'min_samples_split': [2, 5, 10], 'n_estimators': [250, 500, 750, 1000, 1250, 1500]}, scoring : (' balanced_accuracy')

	SVC	{'C': [0.01, 0.1, 1, 10, 100, 200, 400, 1000], 'gamma': [100,10,1,1e-1,1e-2, 1e-3], 'kernel': ['linear', 'rbf']], scoring : ('balanced_accuracy')
	XGBoost	{'learning_rate': [0.01, 0.1], 'max_depth': [3, 6, 10], 'min_child_weight': [1, 3, 5], 'gamma': [0, 1, 5], 'subsample': [0.6, 0.7, 0.8, 0.9, 1.0], 'colsample_bytree': [0.5, 0.6, 0.7, 0.8, 0.9, 1.0], 'n_estimators': [500, 1500]}, scoring : ('balanced_accuracy')
	KNN	{'n_neighbors': [5,9,15,19,25,35,45,55,71], 'weights': ['distance'],'p': [1,2],'metric': ['jaccard', 'dice', 'rogerstanimoto']}, scoring : ('balanced_accuracy')
	DNN	{number of Dense layers: ((1-8), activation = ('relu'; 'softmax' in outplut layer)), number of neurons in each layer: ((100 - 5000), step = (50 - 1000)), added dropouts: (0 -0.5, step = 0.1), Adam optimizer learning rate: (1e-4 to 1e-2, sampling = ('log', default = 1e-3)), loss_fn : 'SparseCategoricalCrossentropy', batch_size : ((32-128), step = 32, default = 64), objective : ('val_categorical_accuracy','max'), used 30 % of training set as validation set}

Table S2. Optimized hyperparameters for final models included in SIRT2i_Predictor.

Final model	Optimized hyperparameters
Regression XGBoost:ECFP4	[('colsample_bytree', 0.5), ('gamma', 0), ('learning_rate', 0.01), ('max_depth', 10), ('min_child_weight', 3), ('n_estimators', 1500), ('subsample', 0.6)]
Binary RF:ECFP4	[('bootstrap', False), ('max_depth', 65), ('max_features', 'sqrt'), ('min_samples_leaf', 2), ('min_samples_split', 5), ('n_estimators', 1000)]
Multiclass SIRT1/2 RF:ECFP4	[('bootstrap', False), ('max_depth', 80), ('max_features', 'sqrt'), ('min_samples_leaf', 2), ('min_samples_split', 5), ('n_estimators', 750)]
Multiclass SIRT2/3 DNN:descriptors model	InputLayer : 'config': {'batch_input_shape': (None, 316), 'units': 4000, 'activation': 'relu'} Dense Layer 1 : 'config': {'name': 'dense_1', 'units': 100, 'activation': 'relu'} Dropout Layer : 'config': {'name': 'dropout', 'rate': 0.0} Dense Layer 2 : 'config': {'name': 'dense_2', 'units': 3, 'activation': 'softmax'} Optimizer: {'name': 'Adam', 'learning_rate': 1e-04, 'decay': 0.0, 'beta_1': 0.9, 'beta_2': 0.999, 'epsilon': 1e-07, 'amsgrad': False} batch_size = 32 Loss function: SparseCategoricalCrossentropy

Table S3. Mordred descriptors selected after feature selection procedure.

Model Type	List of selected Mordred descriptors
Regression models	nAromAtom, ATS0Z, AATS5d, AATS6v, AATS4i, AATS5i, ATSC7dv, ATSC6d, ATSC8d, ATSC7Z, ATSC1v, ATSC2v, ATSC1se, ATSC2i, ATSC4i, ATSC8i, AATSC2dv, AATSC5dv, AATSC0d, AATSC3se, AATSC5se, MATS1p, MATS6p, GATS4dv, GATS6d, GATS4Z, GATS3v, GATS5v, GATS6se, GATS4i, GATS5i, C1SP2, Xc-5d, AXp-1d, NaaS, SaasC, IC2, IC3, PEOE_VSA3, PEOE_VSA8, PEOE_VSA12, SMR_VSA6, SlogP_VSA10, EState_VSA2, VSA_EState1, n10FRing, SLogP, JGI2, JGI6, JGI8, JGI9, TopoShapelIndex
Binary classification models	AATS0dv, AATS1dv, AATS0d, AATS5d, AATS6d, AATS0Z, AATS1Z, AATS5Z, AATS6Z, AATS0v, AATS5v, AATS6v, AATS0se, AATS5se, AATS6se, AATS0i, AATS3i, AATS4i, AATS5i, AATS6i, ATSC1dv, ATSC2dv, ATSC3dv, ATSC4dv, ATSC5dv, ATSC6dv, ATSC7dv, ATSC8dv, ATSC1d, ATSC2d, ATSC3d, ATSC4d, ATSC5d, ATSC6d, ATSC7d, ATSC8d, ATSC1Z, ATSC2Z, ATSC3Z, ATSC4Z, ATSC5Z, ATSC6Z, ATSC7Z, ATSC8Z, ATSC1v, ATSC2v, ATSC3v, ATSC4v, ATSC5v, ATSC6v, ATSC7v, ATSC8v, ATSC0se, ATSC1se, ATSC2se, ATSC3se, ATSC4se, ATSC5se, ATSC6se, ATSC7se, ATSC8se, ATSC1i, ATSC2i, ATSC3i, ATSC4i, ATSC5i, ATSC6i, ATSC7i, ATSC8i, AATSC1dv, AATSC2dv, AATSC4dv, AATSC5dv, AATSC6dv, AATSC0d,

	AATSC1d, AATSC2d, AATSC5d, AATSC6d, AATSC5Z, AATSC6Z, AATSC0v, AATSC1v, AATSC6v, AATSC0se, AATSC2se, AATSC3se, AATSC4se, AATSC6se, AATSC1pe, AATSC0i, MATS5Z, MATS1p, MATS4p, MATS6p, GATS1dv, GATS2dv, GATS3dv, GATS5dv, GATS1d, GATS2d, GATS4d, GATS5d, GATS6d, GATS5Z, GATS6Z, GATS2v, GATS6v, GATS1se, GATS2se, GATS4se, GATS5se, GATS6se, GATS1p, GATS2p, GATS3p, GATS6i, BalabanJ, Xc-6dv, Xpc-4d, Xpc-4dv, AXp-1d, AXp-0dv, AXp-1dv, NsCH3, NdCH2, NtCH, NdsCH, NaaCH, NsssCH, NdssC, NaasC, NaaaC, NssssC, NsNH2, NdNH, NssNH, NaaNH, NdsN, NaaN, NsssN, NddsN, NaasN, NsOH, NssO, NaaO, NsSH, NdS, NssS, NaaS, NddssS, NdSe, SssCH2, SsssCH, SdssC, SaasC, SssssC, ECIndex, fragCpx, fMF, nHBAcc, nHBDOn, IC0, IC1, IC2, IC3, SIC0, SIC1, SIC2, SIC3, MIC0, MIC1, ZMIC1, Lipinski, GhoseFilter, FilterItLogS, PEOE_VSA2, PEOE_VSA3, PEOE_VSA4, PEOE_VSA5, PEOE_VSA6, PEOE_VSA7, PEOE_VSA8, PEOE_VSA9, PEOE_VSA10, PEOE_VSA11, PEOE_VSA12, PEOE_VSA13, SMR_VSA2, SMR_VSA3, SMR_VSA4, SMR_VSA6, SMR_VSA9, SlogP_VSA3, SlogP_VSA4, SlogP_VSA8, SlogP_VSA10, EState_VSA2, EState_VSA3, EState_VSA4, EState_VSA5, EState_VSA6, EState_VSA7, EState_VSA8, EState_VSA9, VSA_EState1, VSA_EState2, VSA_EState3, VSA_EState5, VSA_EState8, VSA_EState9, MDEC-23, MDEC-33, nRing, n7Ring, nG12Ring, nFRing, n8FRing, n9FRing, nFHRing, nG12FaRing, nFaHRing, n9FARing, n10FARing, SLogP, JGI1, JGI2, JGI3, JGI4, JGI5, JGI6, JGI7, JGI8
Multiclass Classification Models SIRT1/2	nAromAtom, nSpiro, nBridgehead, nHetero, nN, nO, nS, nP, nF, nCl, nBr, nI, nX, ATS0Z, AATS0dv, AATS0d, AATS5d, AATS6d, AATS0Z, AATS1Z, AATS5Z, AATS6Z, AATS4v, AATS5v, AATS6v, AATS0se, AATS5se, AATS6se, AATS0p, AATS0i, AATS3i, AATS4i, AATS5i, AATS6i, ATSC1dv, ATSC2dv, ATSC3dv, ATSC4dv, ATSC5dv, ATSC6dv, ATSC7dv, ATSC8dv, ATSC1d, ATSC2d, ATSC3d, ATSC4d, ATSC5d, ATSC6d, ATSC7d, ATSC8d, ATSC1Z, ATSC2Z, ATSC3Z, ATSC4Z, ATSC5Z, ATSC6Z, ATSC7Z, ATSC8Z, ATSC1v, ATSC2v, ATSC3v, ATSC4v, ATSC5v, ATSC6v, ATSC7v, ATSC8v, ATSC1se, ATSC2se, ATSC3se, ATSC4se, ATSC5se, ATSC6se, ATSC7se, ATSC8se, ATSC1p, ATSC3p, ATSC4p, ATSC5p, ATSC6p, ATSC7p, ATSC8p, ATSC1i, ATSC2i, ATSC3i, ATSC4i, ATSC5i, ATSC6i, ATSC7i, ATSC8i, AATSC0dv, AATSC1dv, AATSC2dv, AATSC3dv, AATSC4dv, AATSC5dv, AATSC6dv, AATSC0d, AATSC1d, AATSC2d, AATSC5d, AATSC6d, AATSC5Z, AATSC6Z, AATSC0v, AATSC1v, AATSC2v, AATSC6v, AATSC1se, AATSC2se, AATSC3se, AATSC4se, AATSC5se, AATSC6se, AATSC0p, AATSC2p, AATSC6p, AATSC2i, MATS4Z, GATS1dv, GATS4dv, GATS3d, GATS4Z, GATS5Z, GATS2v, GATS6v, GATS1se, GATS2se, GATS3se, GATS4se, GATS5se, GATS1p, GATS2p, GATS4p, GATS5p, GATS6i, Xch-6d, Xch-5dv, Xc-3d, Xc-4d, Xc-5d, Xc-6d, Xc-3dv, Xc-4dv, Xc-5dv, Xc-6dv, Xpc-4d, Xpc-4dv, AXp-1d, AXp-0dv, AXp-1dv, NsCH3, NdCH2, NtCH, NdsCH, NaaCH, NsssCH, NaasC, NaaaC, NssssC, NsNH2, NdNH, NssNH, NaaNH, NdsN, NaaN, NsssN, NddsN, NaasN, NsOH, NssO, NaaO, NsSH, NdS, NssS, NaaS, NddssS, NdSe, SssCH2, SdssC, SaasC, SssssC, ECIndex, fragCpx, fMF, nHBDOn, IC0, IC1, IC2, IC3, SIC0, SIC1, SIC2, SIC3, MIC0, MIC1, Lipinski, GhoseFilter, FilterItLogS, PEOE_VSA2, PEOE_VSA3, PEOE_VSA4, PEOE_VSA5,

	PEOE_VSA6, PEOE_VSA7, PEOE_VSA8, PEOE_VSA9, PEOE_VSA10, PEOE_VSA11, PEOE_VSA12, PEOE_VSA13, SMR_VSA2, SMR_VSA3, SMR_VSA4, SMR_VSA6, SMR_VSA9, SlogP_VSA3, SlogP_VSA4, SlogP_VSA8, SlogP_VSA10, SlogP_VSA11, EState_VSA2, EState_VSA3, EState_VSA4, EState_VSA6, EState_VSA7, EState_VSA8, EState_VSA9, VSA_EState1, VSA_EState3, VSA_EState5, VSA_EState7, VSA_EState8, VSA_EState9, MDEC-23, MDEC-33, piPC3, nRing, n7Ring, n8Ring, nG12Ring, nHRing, naHRing, n6aHRing, nARing, nAHRing, n6AHRing, nFRing, n9FRing, nG12FRing, nFHRing, n10FHRing, nFaRing, n9FaRing, n10FaRing, nG12FaRing, nFARing, n9FARing, n10FARing, nFAHRing, n9FAHRing, n10FAHRing, RotRatio, SLogP, JGI1, JGI2, JGI3, JGI4, JGI5, JGI6, JGI7
Multiclass Classification Models SIRT2/3	AATS0dv, AATS5d, AATS6d, AATS0Z, AATS1Z, AATS6Z, AATS5v, AATS6v, AATS0se, AATS5se, AATS6se, AATS0p, AATS4p, AATS5p, AATS6p, AATS0i, AATS1i, AATS3i, AATS4i, AATS5i, AATS6i, ATSC2c, ATSC3c, ATSC5c, ATSC6c, ATSC7c, ATSC8c, ATSC1dv, ATSC2dv, ATSC3dv, ATSC4dv, ATSC5dv, ATSC6dv, ATSC7dv, ATSC8dv, ATSC1d, ATSC2d, ATSC3d, ATSC4d, ATSC5d, ATSC6d, ATSC7d, ATSC8d, ATSC1Z, ATSC2Z, ATSC3Z, ATSC4Z, ATSC5Z, ATSC6Z, ATSC7Z, ATSC8Z, ATSC1v, ATSC2v, ATSC3v, ATSC4v, ATSC5v, ATSC6v, ATSC7v, ATSC8v, ATSC1se, ATSC2se, ATSC3se, ATSC4se, ATSC5se, ATSC6se, ATSC7se, ATSC8se, ATSC1pe, ATSC1p, ATSC3p, ATSC4p, ATSC5p, ATSC6p, ATSC7p, ATSC8p, ATSC1i, ATSC2i, ATSC3i, ATSC4i, ATSC5i, ATSC6i, ATSC7i, ATSC8i, AATSC0c, AATSC1c, AATSC2c, AATSC3c, AATSC4c, AATSC5c, AATSC6c, AATSC1dv, AATSC2dv, AATSC3dv, AATSC4dv, AATSC5dv, AATSC6dv, AATSC0d, AATSC1d, AATSC2d, AATSC4d, AATSC5d, AATSC6d, AATSC3Z, AATSC5Z, AATSC6Z, AATSC0v, AATSC1v, AATSC2v, AATSC6v, AATSC1se, AATSC2se, AATSC3se, AATSC4se, AATSC5se, AATSC6se, AATSC1pe, AATSC0p, AATSC1p, AATSC6p, AATSC2i, AATSC6i, MATS1c, MATS3Z, MATS4Z, MATS5Z, MATS6Z, MATS2se, GATS2c, GATS3c, GATS4c, GATS5c, GATS6c, GATS1dv, GATS2dv, GATS3dv, GATS4dv, GATS5dv, GATS6dv, GATS1d, GATS2d, GATS3d, GATS4d, GATS5d, GATS6d, GATS1Z, GATS2Z, GATS3Z, GATS4Z, GATS5Z, GATS6Z, GATS2v, GATS6v, GATS1se, GATS2se, GATS3se, GATS4se, GATS5se, GATS6se, GATS1p, GATS2p, GATS4p, GATS6p, GATS1i, GATS3i, GATS4i, GATS6i, BalabanJ, nBondsD, nBondsT, nBondsKD, RNCG, RPCG, C1SP1, C2SP1, C1SP2, C2SP2, C3SP2, C1SP3, C3SP3, C4SP3, Xch-3d, Xch-4d, Xch-5d, Xch-6d, Xch-6dv, Xc-3d, Xc-4d, Xc-5d, Xc-6d, Xc-3dv, Xc-4dv, Xc-5dv, Xc-6dv, AXp-1d, AXp-0dv, NsCH3, NtCH, NdsCH, NaaCH, NaasC, NaaaC, NssssC, NsNH2, NdNH, NaaNH, NdsN, NaaN, NssssN, NddsN, NaasN, NsOH, NssO, NaaO, NsSH, NdS, NssS, NaaS, NddssS, SssCH2, SaasC, SssssC, ECIndex, fragCpx, fMF, IC0, IC1, IC2, IC3, SIC0, SIC1, SIC3, MIC0, MIC1, Lipinski, GhoseFilter, FilterItLogS, PEOE_VSA2, PEOE_VSA3, PEOE_VSA4, PEOE_VSA5, PEOE_VSA6, PEOE_VSA7, PEOE_VSA8, PEOE_VSA9, PEOE_VSA10, PEOE_VSA11, PEOE_VSA13, SMR_VSA2, SMR_VSA4, SMR_VSA6, SMR_VSA9, SlogP_VSA3, SlogP_VSA4, SlogP_VSA8, SlogP_VSA10, SlogP_VSA11, EState_VSA2, EState_VSA3, EState_VSA4, EState_VSA5, EState_VSA6, EState_VSA7, EState_VSA8, EState_VSA9,

	VSA_EState1, VSA_EState3, VSA_EState7, VSA_EState8, MDEC-22, MDEC-23, MDEC-33, piPC3, nRing, n4Ring, n6Ring, n7Ring, nG12Ring, nHRing, n6HRing, naHRing, n6aHRing, nARing, n5ARing, n6ARing, nAHRing, n5AHRing, n6AHRing, nFRing, n8FRing, n9FRing, n10FRing, nG12FRing, nFHRing, n10FHRing, n9FaRing, n10FaRing, n10FaHRing, nFARing, n9FARing, n10FARing, nFAHRing, n9FAHRing, n10FAHRing, RotRatio, SLogP, JGI1, JGI2, JGI3, JGI4, JGI5, JGI6, JGI7, JGI8, JGI9, JGI10, TopoShapeIndex
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Table S4. Results of internal (train set (int) and cross validation (CV)) and external (ext) validation for regression models.

ML algorithm	Molecular feature	R^2_{int}	RMSE_{int}	Q^2	RMSE_{cv}	R^2_{ext}	RMSE_{ext}	r^2_m	\bar{r}^2_m	Δr^2_m	Q^2_{F1}	Q^2_{F2}	Q^2_{F3}	CCC	Criteria 1 ^a	Criteria 2 ^b	Criteria 3 ^c	k (or k') ^d
RF	descriptors	0.99	0.11	0.7 +/- 0.02	0.55 +/- 0.01	0.7	0.55	0.7	0.52	0.27	0.7	0.7	0.7	0.81	0.008	0.300	0.206	1.000 (0.990)
	ECFP4	0.9	0.31	0.74 +/- 0.03	0.5 +/- 0.03	0.75	0.5	0.75	0.6	0.23	0.75	0.75	0.75	0.85	0.004	0.170	0.125	1.001 (0.991)
	MACCS	0.86	0.37	0.68 +/- 0.03	0.56 +/- 0.03	0.71	0.53	0.71	0.55	0.26	0.71	0.71	0.71	0.82	0.005	0.243	0.171	1.001 (0.991)
	ECFP6	0.93	0.26	0.75 +/- 0.03	0.49 +/- 0.03	0.77	0.48	0.77	0.62	0.21	0.77	0.77	0.76	0.86	0.003	0.139	0.104	1.001 (0.992)
SVM	descriptors	0.99	0.11	0.63 +/- 0.03	0.6 +/- 0.03	0.62	0.61	0.63	0.44	0.31	0.62	0.62	0.62	0.77	0.004	0.074	0.052	1.003 (0.989)
	ECFP4	0.98	0.15	0.74 +/- 0.03	0.51 +/- 0.03	0.74	0.51	0.74	0.63	0.13	0.74	0.74	0.73	0.84	0.004	0.476	0.296	0.997 (0.992)
	MACCS	0.96	0.21	0.66 +/- 0.05	0.57 +/- 0.04	0.68	0.57	0.68	0.55	0.21	0.68	0.68	0.68	0.81	0.001	0.173	0.116	1.002 (0.988)
	ECFP6	0.99	0.11	0.75 +/- 0.03	0.5 +/- 0.03	0.74	0.51	0.74	0.63	0.18	0.74	0.74	0.74	0.86	0.001	0.098	0.072	0.997 (0.995)
XGBoost	descriptors	0.99	0.09	0.7 +/- 0.02	0.55 +/- 0.01	0.67	0.58	0.66	0.53	0.25	0.68	0.68	0.68	0.82	0.001	0.089	0.065	0.999 (0.993)
	ECFP4 [*]	0.97	0.17	0.74 +/- 0.02	0.5 +/- 0.02	0.79	0.46	0.79	0.7	0.17	0.74	0.74	0.74	0.86	9.06E-05	0.064	0.050	1.005 (0.998)
	MACCS	0.87	0.35	0.69 +/- 0.04	0.55 +/- 0.03	0.71	0.53	0.71	0.58	0.24	0.7	0.7	0.7	0.82	0.000	0.176	0.124	1.001 (0.990)
	ECFP6	0.99	0.1	0.73 +/- 0.02	0.52 +/- 0.02	0.73	0.52	0.73	0.62	0.2	0.73	0.73	0.73	0.87	0.000	0.115	0.084	0.993 (0.999)
KNN	descriptors	1	0.05	0.65 +/- 0.06	0.59 +/- 0.06	0.68	0.56	0.68	0.56	0.23	0.68	0.68	0.68	0.86	0.004	0.068	0.048	0.995 (0.997)
	ECFP4	1	0.07	0.7 +/- 0.04	0.54 +/- 0.04	0.74	0.51	0.75	0.64	0.13	0.74	0.74	0.74	0.87	0.000	0.180	0.123	0.986 (1.004)
	MACCS	0.97	0.17	0.6 +/- 0.07	0.63 +/- 0.05	0.6	0.63	0.6	0.47	0.16	0.6	0.6	0.6	0.79	0.014	0.216	0.123	0.991 (0.996)
	ECFP6	1	0.06	0.72 +/- 0.04	0.53 +/- 0.04	0.76	0.49	0.76	0.66	0.12	0.76	0.76	0.76	0.87	0.003	0.057	0.041	0.999 (0.993)
DNN	descriptors	0.98	0.16	0.79 +/- 0.07	0.45 +/- 0.06	0.66	0.58	0.68	0.57	0.03	0.66	0.66	0.66	0.81	0.032	0.053	0.015	1.005 (0.985)
	ECFP4	0.99	0.09	0.85 +/- 0.07	0.37 +/- 0.07	0.74	0.51	0.74	0.63	0.18	0.73	0.73	0.73	0.84	0.000	0.108	0.079	1.002 (0.989)
	MACCS	0.93	0.27	0.64 +/- 0.07	0.59 +/- 0.05	0.68	0.56	0.69	0.56	0.16	0.68	0.68	0.67	0.80	0.007	0.123	0.079	1.004 (0.985)
	ECFP6	0.96	0.19	0.82 +/- 0.05	0.41 +/- 0.07	0.73	0.52	0.74	0.63	0.17	0.73	0.73	0.73	0.81	0.048	0.571	0.380	1.170 (0.832)

* Final model statistics

^a $(R^2 - R_0^2) / R^2 < 0.1$

^b $(R^2 - R_0'^2) / R^2 < 0.1$

^c $|R^2 - R_0'^2| < 0.3$

^d $0.85 \leq k \text{ (or } k') \leq 1.15$

Table S5. Results of internal (train set (int) and cross validation (CV)) validation for binary classification models.

ML algorithm	Molecular feature	BA _{int}	MCC _{int}	ROC_AUC _{int}	BA _{cv}	MCC _{cv}	ROC_AUC _{cv}
RF	ECFP4	0.95	0.89	0.99	0.80 +/- 0.04	0.60 +/- 0.04	0.90 +/- 0.02
	MACCS2	0.93	0.84	0.98	0.79 +/- 0.03	0.60 +/- 0.03	0.88 +/- 0.02
	descriptors	1	1	1	0.81 +/- 0.02	0.63 +/- 0.02	0.90 +/- 0.02
	ECFP6	0.97	0.93	1	0.80 +/- 0.04	0.62 +/- 0.04	0.90 +/- 0.02
SVC	ECFP4	1	0.99	1	0.78 +/- 0.04	0.59 +/- 0.04	0.87 +/- 0.03
	MACCS2	0.96	0.91	0.98	0.77 +/- 0.02	0.56 +/- 0.02	0.84 +/- 0.02
	descriptors	1	1	1	0.80 +/- 0.03	0.61 +/- 0.03	0.87 +/- 0.02
	ECFP6	1	1	1	0.67 +/- 0.03	0.44 +/- 0.03	0.87 +/- 0.02
XGBoost	ECFP4	0.99	0.99	1	0.77 +/- 0.03	0.55 +/- 0.03	0.88 +/- 0.02
	MACCS2	0.93	0.84	0.98	0.77 +/- 0.02	0.56 +/- 0.02	0.87 +/- 0.01
	descriptors	1	1	1	0.80 +/- 0.02	0.61 +/- 0.02	0.89 +/- 0.01
	ECFP6	1	1	1	0.79 +/- 0.03	0.58 +/- 0.03	0.88 +/- 0.02
KNN	ECFP4	1	0.99	1	0.79 +/- 0.03	0.59 +/- 0.03	0.87 +/- 0.03
	MACCS2	0.96	0.92	1	0.77 +/- 0.02	0.55 +/- 0.02	0.84 +/- 0.01
	descriptors	1	1	1	0.64 +/- 0.03	0.34 +/- 0.03	0.82 +/- 0.03
	ECFP6	1	1	1	0.80 +/- 0.03	0.61 +/- 0.03	0.88 +/- 0.03
DNN	ECFP4	1	0.99	1	0.8 +/- 0.05	0.61 +/- 0.05	0.89 +/- 0.02
	MACCS2	0.96	0.9	1	0.81 +/- 0.03	0.63 +/- 0.03	0.9 +/- 0.01
	descriptors	1	1	1	0.84 +/- 0.01	0.69 +/- 0.01	0.91 +/- 0.01
	ECFP6	0.98	0.96	1	0.82 +/- 0.02	0.64 +/- 0.02	0.91 +/- 0.02

Table S6. Results of internal (train set (int) and cross validation (CV)) validation for multiclass classification models.

Model	ML algorithm	Molecular feature	BA _{int}	MCC _{int}	ROC_AUC _{int}	BA _{cv}	MCC _{cv}	ROC_AUC _{cv}
SIRT1/2	RF	ECFP4	0.93	0.89	0.99	0.74 +/- 0.02	0.63 +/- 0.02	0.9 +/- 0.01
		MACCS2	0.9	0.85	0.99	0.73 +/- 0.03	0.62 +/- 0.03	0.89 +/- 0.01
		descriptors	1	1	1	0.75 +/- 0.03	0.63 +/- 0.03	0.9 +/- 0.01
		ECFP6	0.94	0.91	1	0.75 +/- 0.02	0.64 +/- 0.02	0.9 +/- 0.01
	SVC	ECFP4	0.97	0.95	1	0.75 +/- 0.03	0.64 +/- 0.03	0.89 +/- 0.01
		MACCS2	0.97	0.94	0.99	0.72 +/- 0.03	0.6 +/- 0.03	0.86 +/- 0.01
		descriptors	1	0.99	1	0.73 +/- 0.05	0.61 +/- 0.05	0.88 +/- 0.02
		ECFP6	1	1	1	0.75 +/- 0.03	0.64 +/- 0.03	0.89 +/- 0.01
	XGBoost	ECFP4	0.99	0.99	1	0.75 +/- 0.02	0.64 +/- 0.02	0.9 +/- 0.01
		MACCS2	0.92	0.88	0.99	0.74 +/- 0.01	0.63 +/- 0.01	0.9 +/- 0.01
		descriptors	1	1	1	0.75 +/- 0.02	0.64 +/- 0.02	0.89 +/- 0.01
		ECFP6	0.9	0.84	0.98	0.74 +/- 0.01	0.63 +/- 0.01	0.9 +/- 0.01
	KNN	ECFP4	1	1	1	0.72 +/- 0.01	0.59 +/- 0.01	0.88 +/- 0.01
		MACCS2	0.97	0.95	1	0.69 +/- 0.03	0.56 +/- 0.03	0.86 +/- 0.02
		descriptors	0.85	0.76	0.96	0.67 +/- 0.03	0.54 +/- 0.03	0.86 +/- 0.01
		ECFP6	1	1	1	0.71 +/- 0.02	0.58 +/- 0.02	0.89 +/- 0.01
	DNN	ECFP4	1	1	1	0.75 +/- 0.03	0.63 +/- 0.02	0.9 +/- 0.02
		MACCS2	0.95	0.92	1	0.74 +/- 0.01	0.61 +/- 0.05	0.89 +/- 0.01
		descriptors	0.99	0.99	1	0.75 +/- 0.03	0.64 +/- 0.02	0.9 +/- 0.01
		ECFP6	0.98	0.99	1	0.75 +/- 0.03	0.63 +/- 0.01	0.9 +/- 0.01
SIRT2/3	RF	ECFP4	0.94	0.9	1	0.8 +/- 0.03	0.74 +/- 0.03	0.95 +/- 0.02
		MACCS2	0.94	0.89	0.99	0.78 +/- 0.01	0.72 +/- 0.01	0.93 +/- 0.02
		descriptors	1	1	1	0.8 +/- 0.03	0.74 +/- 0.03	0.94 +/- 0.02
		ECFP6	0.96	0.93	1	0.81 +/- 0.03	0.76 +/- 0.03	0.95 +/- 0.02
	SVC	ECFP4	1	1	1	0.71 +/- 0.03	0.65 +/- 0.03	0.94 +/- 0.03
		MACCS2	0.98	0.95	0.99	0.8 +/- 0.02	0.72 +/- 0.02	0.91 +/- 0.02
		descriptors	1	0.99	1	0.73 +/- 0.05	0.61 +/- 0.05	0.88 +/- 0.02
		ECFP6	1	1	1	0.78 +/- 0.03	0.7 +/- 0.03	0.94 +/- 0.02
	XGBoost	ECFP4	1	1	1	0.76 +/- 0.05	0.69 +/- 0.05	0.94 +/- 0.02

		MACCS2	0.98	0.95	1	0.78 +/- 0.04	0.7 +/- 0.04	0.92 +/- 0.02
		descriptors	1	1	1	0.79 +/- 0.01	0.72 +/- 0.01	0.94 +/- 0.01
		ECFP6	1	1	1	0.79 +/- 0.04	0.72 +/- 0.04	0.94 +/- 0.02
	KNN	ECFP4	1	1	1	0.77 +/- 0.05	0.7 +/- 0.05	0.92 +/- 0.03
		MACCS2	0.98	0.96	1	0.73 +/- 0.03	0.65 +/- 0.03	0.9 +/- 0.02
		descriptors	0.85	0.76	0.96	0.67 +/- 0.03	0.54 +/- 0.03	0.86 +/- 0.01
		ECFP6	1	1	1	0.77 +/- 0.04	0.69 +/- 0.04	0.92 +/- 0.03
	DNN	ECFP4	1	1	1	0.8 +/- 0.03	0.74 +/- 0.03	0.94 +/- 0.03
		MACCS2	1	1	1	0.78 +/- 0.03	0.74 +/- 0.03	0.94 +/- 0.02
		descriptors	1	1	1	0.8 +/- 0.03	0.76 +/- 0.03	0.95 +/- 0.02
		ECFP6	0.99	0.99	1	0.78 +/- 0.03	0.65 +/- 0.03	0.93 +/- 0.02

Table S7. External (test set) validation parameters of the multiclass SIRT1/2 models.

ML algorithm	Molecular feature	BA	MCC	ROC_AUC ^a	Precision ^a	Recall ^a	F1 ^a
RF	descriptors	0.85	0.77	0.96	0.84	0.85	0.84
	ECFP4	0.84	0.74	0.96	0.81	0.84	0.82
	MACCS2	0.82	0.72	0.95	0.81	0.82	0.81
	ECFP6	0.83	0.74	0.96	0.81	0.83	0.82
SVC	descriptors	0.86	0.79	0.96	0.85	0.86	0.86
	ECFP4	0.83	0.73	0.95	0.81	0.83	0.82
	MACCS2	0.82	0.72	0.94	0.8	0.82	0.81
	ECFP6	0.8	0.7	0.95	0.8	0.8	0.8
XGBoost	descriptors	0.84	0.76	0.95	0.83	0.84	0.84
	ECFP4	0.84	0.74	0.96	0.82	0.84	0.83
	MACCS2	0.83	0.73	0.95	0.81	0.83	0.82
	ECFP6	0.81	0.71	0.95	0.79	0.82	0.8
KNN	descriptors	0.8	0.69	0.93	0.78	0.8	0.79
	ECFP4	0.84	0.73	0.94	0.82	0.84	0.82
	MACCS2	0.84	0.75	0.94	0.82	0.84	0.83
	ECFP6	0.83	0.71	0.93	0.81	0.83	0.81
DNN	descriptors	0.84	0.77	0.93	0.84	0.84	0.84
	ECFP4	0.82	0.77	0.94	0.84	0.82	0.83
	MACCS2	0.82	0.73	0.92	0.81	0.82	0.81
	ECFP6	0.84	0.74	0.95	0.82	0.84	0.82
^a Values are calculated using macro averages and one-vs-rest approach.							

Table S8. The predictive performance parameters of the multiclass SIRT1/2 models on the decoys dataset.

ML algorithm	Molecular feature	BA	MCC	ROC_AUC _a	Precision _a	Recall _a	F1 ^a
RF	descriptors	0.72	0.09	0.91	0.35	0.72	0.24
	ECFP4	0.82 (0.88) *	0.2 (0.73) *	0.92 (0.95)*	0.37 (0.72)*	0.82 (0.89)*	0.37 (0.79) *
	MACCS2	0.71	0.09	0.89	0.35	0.71	0.25
	ECFP6	0.8	0.16	0.91	0.36	0.8	0.34
SVC	descriptors	0.68	0.08	0.92	0.35	0.68	0.19
	ECFP4	0.7	0.09	0.9	0.35	0.7	0.23
	MACCS2	0.72	0.1	0.9	0.35	0.72	0.26
	ECFP6	0.69	0.08	0.91	0.35	0.69	0.22
XGBoost	descriptors	0.71	0.09	0.89	0.34	0.71	0.22
	ECFP4	0.75	0.12	0.93	0.35	0.75	0.28
	MACCS2	0.7	0.09	0.89	0.34	0.7	0.24
	ECFP6	0.73	0.11	0.91	0.35	0.73	0.28
KNN	descriptors	0.62	0.06	0.7	0.34	0.62	0.17
	ECFP4	0.69	0.08	0.81	0.34	0.69	0.22
	MACCS2	0.65	0.07	0.76	0.34	0.65	0.17
	ECFP6	0.67	0.08	0.81	0.34	0.67	0.21
DNN	descriptors	0.7	0.09	0.71	0.35	0.7	0.22
	ECFP4	0.67	0.08	0.87	0.34	0.67	0.22
	MACCS2	0.67	0.08	0.74	0.34	0.67	0.21
	ECFP6	0.68	0.08	0.87	0.34	0.68	0.21
^a Values are calculated using macro averages and one-vs-rest approach.							
* Values in brackets are obtained after applicability domain corrections.							

Table S9. External (test set) validation parameters of the multiclass SIRT2/3 models.

ML algorithm	Molecular feature	BA	MCC	ROC_AUC ^a	Precision ^a	Recall ^a	F1 ^a
RF	descriptors	0.9	0.83	0.97	0.87	0.9	0.88
	ECFP4	0.83	0.73	0.96	0.8	0.83	0.81
	MACCS2	0.85	0.75	0.95	0.82	0.85	0.84
	ECFP6	0.83	0.74	0.95	0.8	0.83	0.81
SVC	descriptors	0.94	0.88	0.98	0.91	0.94	0.92
	ECFP4	0.77	0.71	0.97	0.83	0.78	0.8
	MACCS2	0.85	0.74	0.95	0.81	0.85	0.83
	ECFP6	0.82	0.74	0.95	0.82	0.82	0.82
XGBoost	descriptors	0.88	0.81	0.97	0.86	0.88	0.87
	ECFP4	0.84	0.73	0.96	0.81	0.85	0.82
	MACCS2	0.87	0.77	0.95	0.84	0.87	0.85
	ECFP6	0.8	0.71	0.96	0.79	0.81	0.8
KNN	descriptors	0.85	0.73	0.96	0.8	0.85	0.82
	ECFP4	0.85	0.74	0.93	0.8	0.85	0.82
	MACCS2	0.85	0.73	0.93	0.8	0.85	0.82
	ECFP6	0.85	0.73	0.93	0.79	0.85	0.82
DNN	descriptors	0.94	0.89	0.97	0.92	0.94	0.93
	ECFP4	0.84	0.75	0.95	0.81	0.84	0.83
	MACCS2	0.87	0.78	0.95	0.83	0.87	0.85
	ECFP6	0.88	0.81	0.97	0.85	0.88	0.86
^a Values are calculated using macro averages and one-vs-rest approach.							

Table S10. The predictive performance parameters of the multiclass SIRT2/3 models on the decoys dataset.

ML algorithm	Molecular feature	BA	MCC	ROC_AUC _a	Precision _a	Recall _a	F1 ^a
RF	descriptors	0.66 (0.59) *	0.06 (0.12) *	0.93 (0.88)*	0.34 (0.47)*	0.66 (0.59)*	0.14 (0.34) *
	ECFP4	0.59	0.08	0.91	0.34	0.59	0.27
	MACCS2	0.65	0.06	0.92	0.34	0.65	0.17
	ECFP6	0.62	0.08	0.92	0.34	0.62	0.25
SVC	descriptors	0.62	0.06	0.95	0.34	0.62	0.02
	ECFP4	0.54	0.04	0.92	0.32	0.54	0.06
	MACCS2	0.58	0.05	0.93	0.34	0.58	0.08
	ECFP6	0.62	0.05	0.92	0.34	0.62	0.11
XGBoost	descriptors	0.7	0.07	0.92	0.34	0.7	0.19
	ECFP4	0.61	0.07	0.91	0.35	0.61	0.17
	MACCS2	0.69	0.07	0.92	0.34	0.69	0.21
	ECFP6	0.63	0.07	0.92	0.35	0.63	0.17
KNN	descriptors	0.64	0.05	0.71	0.34	0.64	0.15
	ECFP4	0.66	0.06	0.74	0.34	0.66	0.17
	MACCS2	0.61	0.04	0.66	0.34	0.61	0.12
	ECFP6	0.65	0.06	0.73	0.34	0.65	0.16
DNN	descriptors	0.72 (0.72) *	0.07 (0.1)*	0.87 (0.87)*	0.34 (0.34)*	0.72 (0.75)*	0.18 (0.2)*
	ECFP4	0.65	0.06	0.87	0.34	0.65	0.16
	MACCS2	0.67	0.06	0.87	0.34	0.67	0.18
	ECFP6	0.63	0.06	0.8	0.34	0.63	0.1
^a Values are calculated using macro averages and one-vs-rest approach.							
* Values in brackets are obtained after applicability domain corrections.							

Table S11. Utility SIRT2i_Predictor for the processing of the previously published structure-based virtual screening results[20].

ID	SMILES	Activity (Inh% or IC50 (μM)) ^a	SIRT2 activity according to criteria of this work	Binary model predictions ^b	Predicted probability (binary model) ^c
NDJ134*	<chem>CCN1C(=O)c2cccc3c(S(=O)(=O)NCCc4cccc4)cc1c23</chem>	70.2%*	Twilight zone	Outside AD	0.455224
NDJ18	<chem>O=C(CCC1CCCC1)Nc1ccc(Cc2ccncc2)cc1</chem>	58.7 μM	Twilight zone	No	0.354493
NDJ85	<chem>Cc1cccc1C(=O)NC(=S)NCc1ccc(-c2nn3c(C)nnc3s2)cc1</chem>	85.9 μM	Twilight zone	Outside AD	0.555415
NDJ11	<chem>Cc1cccc1OCC(=O)Nc1ccc(Oc2ccc3c(c2)C(=O)NC3=O)cc1</chem>	55.6%	Twilight zone	No	0.383697
NDJ57	<chem>Cc1nnc2sc(-c3ccc(CNC(=O)c4ccc(-c5ccc(Cl)cc5)o4)cc3)nn12</chem>	47.2%	Twilight zone	Outside AD	0.415945
NDJ20	<chem>O=C(NCCc1cccc1)c1ccc(NC(=O)c2cc(-n3cnnc3)ccc2Cl)cc1</chem>	45.1%	Twilight zone	No	0.335031
NDJ10	<chem>Cc1ccc(C)c(SCCc2nn3c(Cc4cccc4F)nnc3s2)c1</chem>	40.5%	Twilight zone	Outside AD	0.549759
NDJ4	<chem>Cc1cc(=O)oc2cc(OC[C@H](O)Cn3c(C)nc4cccc43)ccc12</chem>	31.8%	Inactive	Outside AD	0.518789
NDJ26	<chem>O=C1Nc2ccc(S(=O)(=O)N3CCN(c4cccc4)CC3)c3cccc1c23</chem>	30.0%	Inactive	No	0.391046

^a Inh% assays were performed at compounds concentration of 200 μM.

^b No – not predicted to be active SIRT2 inhibitor; Yes – Predicted to be active SIRT2 inhibitor. For definition of “active” class see the Manuscript.

^c The predicted probability for “active” class prediction could be between 0 and 1. If between 0.4 – 0.6, it is considered outside applicability domain (AD).

* Compound interfered with the fluorescent assay.

Table S12. Results of *in vitro* evaluation of the in-house compounds.

ID	SMILES	Activity (Inh% ^a)	SIRT2 activity according to criteria of this work	Binary model predictions ^b	Predicted probability (binary model) ^c
316	<chem>COc1ccc([C@H]2Cc3cc(OC4O[C@H](CO)[C@@H](O)[C@H](O)[C@H]4O)cc(O)c3C(=O)O2)cc1</chem>	28.2%	Inactive	Outside AD	0.473878
1024*	/†	48.7% *	Twilight zone	No	0.294624
1558 ³	<chem>COc1ccc(Cn2cnc3c(Cl)nccc32)cc1</chem>	51.1%	Twilight zone	No	0.34941
1657 ⁴	<chem>COc1ccc(CN2NC([N+](=O)[O-])c3ccnc(NC4CCCC4)c32)cc1</chem>	59.7%	Twilight zone	Outside AD	0.427429
Ex-527	<chem>NC(=O)C1CCCc2c1[nH]c1ccc(Cl)cc21</chem>	89.6%	Active	Yes	0.830218

^a Inh% assays were performed at compounds concentration of 200 μM.
^b No – not predicted to be active SIRT2 inhibitor; Yes – Predicted to be active SIRT2 inhibitor. For definition of “active” class see the Manuscript.
^c The predicted probability for “active” class prediction could be between 0 and 1. If between 0.4 – 0.6, it is considered outside applicability domain (AD).
* Compound tested at 100 μM due to assay interference.
† The compound structure is available upon request since synthesis is yet to be published.

Supplementary Note S1 – Internal validation parameters

Following formula were used for calculation of internal validation parameters:

$$R_{int}^2 = 1 - \frac{\sum_{i=1}^{n_{int}} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n_{int}} (y_i - \bar{y})^2} \quad (1)$$

$$RMSE_{int} = \sqrt{\frac{\sum_{i=1}^{n_{int}} (y_i - \hat{y}_i)^2}{n_{int}}} \quad (2)$$

$$Q^2 = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_{i/i})^2}{\sum_{i=1}^n (y_i - \bar{y})^2} \quad (3)$$

$$RMSE_{CV} = \sqrt{\frac{\sum_{i=1}^n (y_i - \hat{y}_{i/i})^2}{n}} \quad (4)$$

Where y_i represents experimental data values; \hat{y}_i represents predicted data values; $\hat{y}_{i/i}$ response of the i-th object estimated by using a model obtained without using the i-th; n - number of objects.

For binary classification models, Matthews correlation coefficient (MCC) was calculated according to the equation (5):

$$MCC = \frac{(TP \times TN) - (FP \times FN)}{\sqrt{(TP+FP) \times (TP+FN) \times (TN+FP) \times (TN+FN)}} \quad (5)$$

Where TP stands for number of true positive predictions, TN stands for number of true negative predictions, FP stands for number of false positive predictions and FN stands for number of false negative predictions.

Supplementary Note S2 - Supplementary methods

In vitro enzymatic assays for SIRT2. Deacetylation activities of SIRT2 in presence of in-house compounds were determined using previously described protocol for Fluor de Lys fluorometric assays (Enzo Life Sciences, Ann Arbor, MI, USA)[68]. Briefly, the reaction was started by incubating the enzyme (SIRT2) with the reaction mixture of acetylated peptide substrate BioMol KI179 for SIRT2 (0.7 Km: 198 μ M for SIRT2), NAD^+ (0.9 Km: 547 μ M for SIRT2), and 5% dimethyl sulfoxide (DMSO) or compounds in 5% final DMSO concentration. Incubation was done at 37 °C, for 1 hour. The developer and nicotinamide (2 mM in histone deacetylase (HDAC) assay buffer in total volume of 50 μ l) were added and the incubation was continued for 45 min at 37 °C. The fluorescence was measured using EnVision 2104 Multilabel Reader (PerkinElmer, Waltham, MA, USA) with excitation and emission wavelengths of 370 nm and 460 nm, respectively. All

experiments were performed in triplicates. Compounds were screened on SIRT2 inhibitory activity at 200 μ M to obtain percent of inhibition.