**Design and evaluation of piperidine carboxamide derivatives as potent ALK inhibitors through 3D-QSAR modeling, artificial neural network and computational analysis**

Ya-Kun Zhang a,1, Jian-Bo Tong a\*, Mu-Xuan Luo b,1, Xiao-Yu Xing a, Yu-Lu Yang a, Zhi-Peng Qing a, Ze-Lei Chang a and Yan-Rong Zeng c\*

a *College of Chemistry and Chemical Engineering,* *Shaanxi University of Science and*

*Technology, Xi’an 710021, People’s Republic of China*

b *State Key Laboratory of Advanced Processing and Recycling of Non-ferrous Metals, Lanzhou University of Technology, Lanzhou 730050, People’s Republic of China*

c *School of Chinese Ethnic Medicine, Guizhou Minzu University, Guiyang 550025, People’s Republic of China*

*\* Corresponding authors.*

*E-mail addresses:* jianbotong@aliyun.com (J.B. Tong) and yrong1992@163.com (Y.R. Zeng).

1 Ya-Kun Zhang and Mu-Xuan Luo contributed equally to this work.

1.Data set compounds **1-49**.



**Fig. S1.** Structure of the compounds 1-35



**Fig. S2.** Structure of the compound 36

**Table S1.** Molecular structures of compounds and their actual activity.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| NO | R1 | R2 | IC50 (μm)  | pIC50 |
| 1 |  |  | 0.17 | 6.76 |
| 2 |  |  | 25 | 4.60 |
| 3 |  |  | 2.32 | 5.63 |
| 4 |  |  | 25 | 4.60 |
| 5\* |  |  | 2.01 | 5.70 |
| 6 |  |  | 6.30 | 5.20 |
| 7 |  |  | 1.02 | 5.99 |
| 8\* |  |  | 3.10 | 5.51 |
| 9 |  |  | 0.91 | 6.04 |
| 10 |  |  | 25 | 4.60 |
| 11 |  |  | 1.73 | 5.76 |
| 12\* |  |  | 1.48 | 5.83 |
| 13 |  |  | 0.33 | 6.49 |
| 14\* |  |  | 0.83 | 6.08 |
| 15 |  |  | 0.36 | 6.44 |
| 16\* |  |  | 0.36 | 6.45 |
| 17 |  |  | 2.94 | 5.17 |
| 18\* |  |  | 2.60 | 5.53 |
| 19 |  |  | 2.01 | 5.59 |
| 20 |  |  | 2.01 | 5.70 |
| 21 |  |  | 0.34 | 6.47 |
| 22\* |  |  | 0.08 | 7.08 |
| 23 |  |  | 0.02 | 7.80 |
| 24 |  |  | 0.01 | 8.00 |
| 25\* |  |  | 0.59 | 6.23 |
| 26 |  |  | 0.08 | 7.10 |
| 27 |  |  | 0.10 | 7.02 |
| 28\* |  |  | 0.07 | 7.15 |
| 29 |  |  | 2.93 | 5.53 |
| 30 |  |  | 0.06 | 7.22 |
| 31 |  |  | 1.70 | 5.77 |
| 32 |  |  | 0.02 | 7.72 |
| 33 |  |  | 0.14 | 6.86 |
| 34 |  |  | 0.19 | 6.72 |
| 35 |  |  | 0.03 | 7.51 |
| 36 |  |  | 4.12 | 5.39 |

\* test set.

2. Newly designed compounds **50**-**66**.

**Table S2.** The chemical structures, fragment contribution values and activity prediction results of the newly designed compounds 50-66.

|  |  |  |  |
| --- | --- | --- | --- |
| NO | Structures | Fragment contribution | pIC50 |
| R1 | R2 | Pred  |
| N1 |  | 2.32 | 1.52 | 8.17 |
| N2 |  | 2.32 | 1.67 | 8.32 |
| N3 |  | 2.32 | 2.38 | 9.02 |
| N4 |  | 2.32 | 2.23 | 8.87 |
| N5 |  | 2.32 | 2.20 | 8.84 |
| N6 |  | 2.32 | 1.66 | 8.31 |
| N7 |  | 2.20 | 1.74 | 8.27 |
| N8 |  | 2.32 | 1.90 | 8.54 |
| N9 |  | 2.32 | 1.66 | 8.31 |
| N10 |  | 2.32 | 1.81 | 8.46 |
| N11 |  | 2.32 | 1.38 | 8.03 |
| N12 |  | 2.32 | 1.87 | 8.52 |
| N13 |  | 2.06 | 1.52 | 7.91 |
| N14 |  | 2.06 | 1.67 | 8.07 |
| N15 |  | 2.06 | 2.38 | 8.77 |
| N16 |  | 2.06 | 2.23 | 8.62 |
| N17 |  | 2.06 | 2.20 | 8.59 |
| N18 |  | 2.06 | 1.66 | 8.05 |
| N19 |  | 2.06 | 1.74 | 8.14 |
| N20 |  | 2.06 | 1.90 | 8.29 |
| N21 |  | 2.06 | 1.66 | 8.06 |
| N22 |  | 2.06 | 1.81 | 8.20 |
| N23 |  | 2.06 | 1.38 | 7.78 |
| N24 |  | 2.06 | 1.87 | 8.27 |
| N25 |  | 1.91 | 1.52 | 7.76 |
| N26 |  | 1.91 | 1.67 | 7.91 |
| N27 |  | 1.91 | 2.38 | 8.61 |
| N28 |  | 1.91 | 2.23 | 8.47 |
| N29 |  | 1.91 | 2.20 | 8.44 |
| N30 |  | 1.91 | 1.66 | 7.90 |
| N31 |  | 1.91 | 1.74 | 7.98 |
| N32 |  | 1.91 | 1.90 | 8.13 |
| N33 |  | 1.91 | 1.66 | 7.90 |
| N34 |  | 1.91 | 1.81 | 8.05 |
| N35 |  | 1.91 | 1.38 | 7.62 |
| N36 |  | 1.91 | 1.87 | 8.11 |
| N37 |  | 1.78 | 1.52 | 7.63 |
| N38 |  | 1.78 | 1.67 | 7.78 |
| N39 |  | 1.78 | 2.38 | 8.49 |
| N40 |  | 1.78 | 2.23 | 8.34 |
| N41 |  | 1.78 | 2.20 | 8.31 |
| N42 |  | 1.78 | 1.66 | 7.77 |
| N43 |  | 1.78 | 1.74 | 7.85 |
| N44 |  | 1.78 | 1.90 | 8.01 |
| N45 |  | 1.78 | 1.66 | 7.77 |
| N46 |  | 1.78 | 1.81 | 7.92 |
| N47 |  | 1.78 | 1.38 | 7.49 |
| N48 |  | 1.78 | 1.87 | 7.98 |
| N49 |  | 2.06 | 1.52 | 7.91 |
| N50 |  | 2.06 | 1.67 | 8.07 |
| N51 |  | 2.06 | 2.38 | 8.77 |
| N52 |  | 2.06 | 2.23 | 8.62 |
| N53 |  | 2.06 | 2.20 | 8.59 |
| N54 |  | 2.06 | 1.66 | 8.05 |
| N55 |  | 2.06 | 1.74 | 8.14 |
| N56 |  | 2.06 | 1.90 | 8.29 |
| N57 |  | 2.06 | 1.66 | 8.06 |
| N58 |  | 2.06 | 1.81 | 8.20 |
| N59 |  | 2.06 | 1.38 | 7.77 |
| N60 |  | 2.06 | 1.87 | 8.27 |

3. Artificial neural network

Regardless of core code:

1.%%Partitioning of data sets

% Training set

P\_train= data(1:end-1,1:ceil(size(data,2)\*0.75));

T\_train = data(end,1:ceil(size(data,2)\*0.75));

% Set of tests

P\_test = data(1:end-1,1+ceil(size(data,2)\*0.75):end);

T\_test = data(end,1+ceil(size(data,2)\*0.75):end);

%% Forecasting

t\_sim=[];

RMSE=[];

RMSE\_average=[];

aa=size(T\_test,1);

bb=size(T\_test,2);

for i=1:15

for j=1:35

net0=newff(p\_train,t\_train,j,{'tansig','purelin'},'trainlm');

net0.trainParam.epochs=1000;

net0.trainParam.lr=0.1;

net0.trainParam.goal=0;

net0.trainParam.show=25;

net0.trainParam.mc=0.01;

net0.trainParam.min\_grad=1e-6;

net0.trainParam.max\_fail=6;

net0=train(net0,p\_train,t\_train);

T\_sim=sim(net0,p\_test);

t\_sim(aa\*(i-1)+1:aa\*i,bb\*(j-1)+1:bb\*j)=mapminmax('reverse',T\_sim,ps\_output);

t\_Sim=t\_sim(aa\*(i-1)+1:aa\*i,bb\*(j-1)+1:bb\*j);

RMSE(i,j)=[(mean((t\_Sim-T\_test).^2)).^0.5];

RMSE\_average(j)=mean(RMSE(:,j));

end

end

2.%% Find the most hidden element

[R,location]=sort(RMSE\_average,'descend');

b=find (RMSE (:,location(end))==min(RMSE(:,location(end))));

T\_sim\_use=t\_sim(aa\*(b-1)+1:aa\*b,bb\*(location(end)-1)+1:bb\*location(end));

MAPE=mean(abs(T\_test-T\_sim\_use)./T\_test)\*100;

MAE=mean(abs(T\_test-T\_sim\_use));

3. %% Relative prediction error

figure

subplot(2,1,1)

plot(T\_test-T\_sim\_use,'-dc','LineWidth',0.2,'MarkerSize',4,'MarkerFaceColor','c')

xlabel('\fontname{Time New Roman} Sample ')

ylabel('\fontname{ Time New Roman } Error of relative ')

set(gca,'FontName','Times New Roman','linewidth',1)

set(gca,'fontsize',16);

set(gca,'LooseInset',get(gca,'TightInset'))

grid on

set(gca,'GridLineStyle',':','GridColor','k','GridAlpha',1);

subplot(2,1,2)

plot(abs(T\_test-T\_sim\_use),'-dc','LineWidth',0.2,'MarkerSize',4,'MarkerFaceColor','c')

xlabel('\fontname{ Time New Roman } Sample ')

ylabel('\fontname{ Time New Roman } absolute error ')

set(gca,'FontName','Times New Roman','linewidth',1)

set(gca,'fontsize',16);

set(gca,'LooseInset',get(gca,'TightInset'))

grid on

set(gca,'GridLineStyle',':','GridColor','k','GridAlpha',1);