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Original article

QSAR study of 4-phenylpiperidine derivatives as μ opioid agonists by neural network method

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Abstract

A nonlinear QSAR study was conducted on a series of 4-phenylpiperidine derivatives (4PPs) acting as μ opioid agonists by three-layer back-propagation neural network (NN) method. At first a variety of molecular descriptors were calculated and then selected with two-stage least squares combining partial least squares (PLS) method. The selected four molecular descriptors, out of 292 ones, were correlated with the known analgesic activities of 38 4PPs by NN method. The established QSAR model was further validated by five additional 4PPs, as an external testing set. Moreover, a pharmacophore model was hypothesized based on the results, which would be helpful for structural optimization of 4PPs.

Keywords: QSAR; 4-Phenylpiperidine derivatives; PLS; Neural network; μ Opioid agonists

1. Introduction

The 4-phenylpiperidine derivatives (4PPs), discovered in 1930s, have been widely used in clinics as narcotics. The prototype of 4PPs, pethidine (also named meperidine; compound **3** in Table 1), was originally synthesized as an anticholinergic agent but was soon found to be a narcotic. Primary studies postulated that the clinical substitution of pethidine for morphine would circumvent many of the problems inherent to morphine, including respiratory depression, constipation, urinary retention, and the potential to produce chemical dependency [1]. However, subsequent studies demonstrated that pethidine also causes serious side effects, such as serotonergic crisis, norpethidine toxicity and multiple drug interaction, which strongly suggested that a structural modification of pethidine is required. For that purpose, there has been a lot of discussion on the structure–activity relationships (SAR) of 4PPs [2–5]; however, a detailed quantitative SAR (QSAR) study is still lacking. Meanwhile, the biological target of 4PPs—μ opioid receptor, a member of the superfamily G-protein coupled receptors—has not been structurally elucidated yet [6]. Therefore, it would be very helpful to perform QSAR study on a series of 4PPs in order to modify the structure further.

QSAR analysis applies statistical methods to describe the relationships between chemical structures and biological activities of a series of analogs quantitatively. It is usually used for lead optimization and for elucidation of mechanisms of drug action, especially when structural information of the target is unavailable. Many statistical methods have been used for developing QSAR models [7–9]. Among them, neural network (NN) is a robust tool to map nonlinear relationships between molecular descriptors and biological activities [10]. Neural network is a computer-based data-processing system to mimic the structure and function of brain, where a number of nodes—the basic processing unit—are interconnected to form a network. Such a method has been applied in QSAR analysis since 1990 and has proven superior to traditional methods in drug discovery [11–13]. The most widely used NN in QSAR is the

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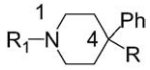
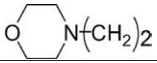
Table 1
Chemical structure of compounds with observed and calculated analgesic activity



Compound	R_1	R_2	$-LogED_{50}$_obs [a]	PLS_cal [b]	NN 4–3–1_cal [c]
Training data set					
1	CH3	COOCH3	3.50	3.340	3.47
2	CH3	$COOC_2H_5$	4.09	3.594	3.61
3	CH3	$OCOCH_3$	4.09	4.187	4.25
4	CH3	$OCOC_2H_5$	4.96	4.392	4.48
5	$PhCH_2$	$COOC_2H_5$	3.56	3.925	3.80
6	$PhCH_2$	$OCOC_2H_5$	4.28	5.012	5.10
7	$PhCH_2CH_2$	$COOCH_3$	3.89	4.589	4.49
8	$PhCH_2CH_2$	$COOC_2H_5$	4.46	4.798	4.87
9	$PhCH_2CH_2$	$OCOCH_3$	5.17	5.413	5.13
10	$PhCH_2CH_2$	$OCOC_2H_5$	5.49	5.624	5.57
11	$PhCH_2CH_2CH_2$	$COOC_2H_5$	5.44	5.066	5.37
12	$PhCH_2CH_2CH_2$	$OCOCH_3$	5.89	5.654	5.66
13	$PhCH_2CH_2CH_2$	$OCOC_2H_5$	6.30	5.943	6.06
14	$PhCH_2CH2CH_2CH_2$	$COOC_2H_5$	4.66	4.997	5.00
15	$PhCH_2CH_2CH_2CH_2$	$OCOCH_3$	5.96	5.938	6.07
16	$PhCH_2CH_2CH_2CH_2$	$OCOC_2H_5$	6.19	6.164	6.48
17	PhCH=CHCH2	$COOCH_3$	4.82	4.649	4.63
18	PhCH=CHCH2	$COOC_2H_5$	5.60	4.847	5.06
19	PhCH=CHCH2	$OCOCH_3$	6.00	5.589	5.30
20	PhCH=CHCH2	$OCOC_2H_5$	6.51	5.805	5.68
21	PhCH=CHCH2CH2	$COOCH_3$	3.98	4.907	4.86
22	PHCH=CHCH2CH2	$COOC_2H_5$	3.76	5.123	5.04
23	PhCH=CHCH2CH2	$OCOCH_3$	5.08	5.995	5.66
24	PhCH=CHCH2CH2	$OCOC_2H_5$	5.22	6.215	6.07
25	$PhCOCH_2$	$COOC_2H_5$	3.55	3.930	3.78
26	$PhCOCH_2CH_2$	$COOCH_3$	5.62	5.100	5.12
27	$PhCOCH_2CH_2$	$COOC_2H_5$	5.96	5.312	5.33
28	$PhCOCH_2CH_2CH_2$	$COOCH_3$	5.20	4.922	4.87
29	$PhCOCH_2CH_2CH_2$	$COOC_2H_5$	5.17	5.723	5.69
30	$PhCH(OH)CH_2$	$COOC_2H_5$	4.51	4.743	4.66
31	$PhCH(OH)CH_2CH_2$	$COOCH_3$	5.31	4.697	4.61
32	$PhCH(OH)CH_2CH_2$	$COOC_2H_5$	6.09	5.007	4.95
33	$PhCH(OH)CH_2CH_2CH_2$	$COOCH_3$	4.60	5.067	5.09
34	$PhCH(OH)CH_2CH_2CH_2$	$COOC_2H_5$	5.09	5.276	5.22
35	$PhCH(OOCCH_3)CH_2CH_2$	$COOC_2H_5$	5.82	5.482	5.49
36	$PhCH(OOCCH_3)CH_2CH_2$	$OCOCH_3$	6.55	6.385	6.32
37	$PhCH(OOCC_2H_5)CH_2CH_2$	$OCOC_2H_5$	7.27	6.791	6.97
38	$PhCH(OOCC_2H_5)CH_2CH_2$	$COOC_2H_5$	6.06	5.710	5.76
Testing data set					
39	$p\text{-}NH_2.C_6H_4.(CH_2)_2$	$COOC_2H_5$	4.87		4.54
40	$p\text{-}NO_2.C_6H_4.(CH_2)_2$	$COOC_2H_5$	4.79		4.59
41	$PhNH(CH_2)_3$	$COOC_2H_5$	5.57		4.85
42	C_6H_{13}	$COOC_2H_5$	4.92		4.65
43		$COOC_2H_5$	4.49		4.30

[a] Negative logarithmic value of experimental activity data.
[b] Calculated activity data by PLS.
[c] Calculated activity data by 4–3–1 network architecture.

three-layer back-propagation network, where the nodes in the hidden layer are connected with any nodes in the input and output layers, adjusted by a weighted value.

A key factor to the success of QSAR study is the selection of molecular descriptors (variables) [14], which express the molecular structure and properties with digital parameters. A wide range of descriptors has been reported in QSAR [15,16], such as physicochemical parameters, molecular connectivity, and quantum chemical indexes, etc. Variables should give the maximum of information in the activity variations and col-

linearity among them must be kept to a minimum. However, how to generate maximal number of variables to sufficiently describe the structural characteristics of compounds and how to effectively select a few most relevant variables from a large number of ones are still problems.

In this study, a total of 43 4PPs, which changed at both C-4 and N positions, were collected from literatures to build a reliable QSAR model with three-layer back-propagation neural network method. Two-stage least squares (2SLS) and partial least squares (PLS) methods were used for the selection of molecular descriptors in a combining mode.

2. Materials and methods

A series of 43 4PPs were collected from literature [3,17]; 38 molecules were used to build the QSAR model, and the rest five ones were served as an external testing set. Their molecular structures and analgesic activities (experimental $-\log ED_{50}$ values ranging from 3.5 to 7.27) are summarized in Table 1. The activity data were determined in vivo with hot plate method.

2.1. Generation and selection of molecular descriptors

All the 43 molecules were drawn in 2D structures with MDL software ISIS/Draw [18], and subsequently converted into 3D structures with software CORINA [19]. After a short energy minimization, the conformation was used in descriptor calculation for each molecule. Most of the descriptors were calculated online with software E-Dragon 1.0 [20]. The physicochemical parameters such as hydrophobicity, surface area, and molecular refractivity were generated with freeware Hyperchem [21] and Chemsketch 3.5 [22]. The quantum chemical indexes were also calculated with B3LYP (6-31G) method in a freeware CADPAC [23], from which atomic charges and interatomic distances were obtained.

The structural minimization and model validation were carried out on a R14000 SGI Fuel workstation using molecular modeling software package SYBYL v6.9 [24].

Selection of molecular descriptors was performed in a two-step variable screening process, at first with 2SLS method followed by PLS method.

2.2. Construction and validation of QSAR model

Thirty-eight compounds were used to establish the QSAR model with three-layer back-propagation neural network method embodied in software SNNS V4.2 [25]. Default parameters were used unless otherwise indicated. The sigmoid function was used as the transformation function and a standard back-propagation algorithm was implemented. All input values were normalized to [0.1–0.9] interval by the following equation:

$$X = 0.1 + 0.8(X\mathrm{max} - X_\mathrm{i})/(X\mathrm{max} - X\mathrm{min})$$

where X and X_i are the transformed and original input data, Xmax and Xmin are the maximal and minimal data in that series.

The number of hidden layer nodes was decided by root mean squares of deviations (RMSD) and mean square error (MSE) values [26].

Leave-one-out (LOO) cross-validation procedure was applied to estimate the predictive capability of the QSAR model [27,28]. In LOO process, for any single compound removed from the data set, all the rest compounds were served as a training set to build the QSAR model, which was then used to predict the activity of the removed compound. This procedure was repeated until each of the compounds in the data set was predicted once. After trained, the predicted activities of the entire data set were obtained. The cross-validated coefficient q^2 was calculated with the following equation:

$$q2 = 1.0 - \frac{\sum_\gamma (\gamma_\mathrm{pred} - \gamma_\mathrm{actual})^2}{\sum_\gamma (\gamma_\mathrm{actual} - \gamma_\mathrm{mean})^2}$$

where γ_pred, γ_actual and γ_mean are predicted, actual, and mean values of the target property, respectively. And $\mathrm{PRESS} = \sum_\gamma (\gamma_\mathrm{pred} - \gamma_\mathrm{actual})^2$ is the sum of predictive sum of squares.

The five additional compounds were used to validate the established QSAR model.

2.3. Conformational analysis

Two 4PPs, i.e. compounds **8** and **9**, together with another potent μ opioid agonist fentanyl, were selected for further conformational analysis. The crystal structure of fentanyl was used as a starting point. The energy-minimized conformations were used for structural comparison.

3. Results and discussion

3.1. Generation and selection of molecular descriptors

With different software, a total of 292 descriptors were calculated for each compound, including five different sets: constitutional descriptors, topological descriptors, connectivity indices, geometrical descriptors and physicochemical parameters, summarized in Table 2.

How to efficiently mine the most correlated variables from a large data set is still a problem in QSAR study. Here, a two-step variable screening process was developed. First, a two-stage least-squares method [29] was applied to exam the correlation of descriptors and to detect the linearly independent variables. The two-stage least-squares technique uses instrumental variables to produce regressors that are not contemporaneously correlated with the disturbance. With this method, the number of descriptors was dramatically reduced from 292 to 33.

Then, the extracted 33 variables were analyzed by the PLS method [30], using LOO cross-validation q^2 as the screening criterion. At first one-by-one analysis of each descriptor was

performed. Next, combinatorial analysis of the most correlated variables was processed. A few suitable models were then obtained. Finally, four indices showing high accordance with analgesic activity were selected out and the activities of 38 compounds were fitted.

The four indices included the net charge of the atom N (CN), the torsional angle around carbonyl oxygen, C-4, C-3 and N atom bond sequence ($T_{O-4-3-N}$), distance between the two atoms N and O (DNO), and the Kier flexibility index (PHI) [15] (Table 3). With PLS method, the conventional R^2 value was 0.647 and the cross-validated q^2 value was 0.577. The calculated activities are listed in Table 1. The regression equation is shown in the following:

$$-\log ED_{50} = 20.637 - 48.722*CN + 0.585*DNO + 0.004*T_{O-4-3-N} + 0.373*PHI$$
$$N = 38, S = 0.598, R^2 = 0.647, q^2 = 0.577$$

3.2. Construction and validation of QSAR model

Three-layer back-propagation neural network method was used to construct the QSAR model based on 38 4PPs whose activities were determined under the same conditions.

One major problem in neural network is how to determine the number of nodes in the hidden layer. Though there is no rigorous rule to rely on [31], a practical way is to use a ratio, ρ, to determine the number of hidden units [32]. ρ is defined as following:

$$\rho = \frac{\text{Number of compounds presented to the network}}{\text{Number of connections in the network}}$$

The reasonable value of ρ should be between 1.0 and 3.0. If $\rho < 1.0$, the network simply memorizes the data, whereas if $\rho > 3.0$, the network is not able to generalize [31]. In our study, the

Table 2
Brief description of type of descriptors used in the study

Descriptor	Molecular descriptors	Number of descriptors
Constitutional descriptor	Molecular weight, number of atoms, number of non-H atoms, number of heteroatoms, number of multiple bonds, number of aromatic bonds, number of functional groups, number of rings, number of H-bond donors, etc.	48
Topological descriptors	Zagreb index, Quadratic index, Narumi simple topological index, Pogliani index, polarity number, Wiener W index, Balaban-type index, Kier symmetry index, Kier flexibility index, Randic shape index, etc.	119
Connectivity indices	Average valence connectivity index, salvation connectivity index, modified Randic connectivity index, reciprocal distance Randic-type index, etc.	33
Geometrical descriptors	3D-Wiener index, 3D-Harary index, average geometric distance, gravitational index, HOMA total, aromaticity index, etc.	74
Chemical parameters	ClogP, molecular refractivity, polarizability, hydration energy, atomic charge, interatomic distance, etc.	18

Table 3
Four descriptors selected by PLS

	CN [a]	DNO [b]	$T_{O-4-3-N}$ [c]	PHI [d]		CN [a]	DNO [b]	$T_{O-4-3-N}$ [c]	PHI [d]
1	–0.414	3.732	69.788	3.603	23	–0.428	4.890	134.740	6.379
2	–0.415	3.732	69.927	4.152	24	–0.428	4.890	134.172	6.975
3	–0.412	4.891	136.302	3.603	25	–0.408	3.734	68.832	5.976
4	–0.412	4.891	136.447	4.152	26	–0.432	3.732	69.200	5.976
5	–0.412	3.732	68.586	5.444	27	–0.432	3.732	69.026	6.547
6	–0.415	4.89	134.402	5.444	28	–0.424	3.732	68.820	6.547
7	–0.423	3.735	100.345	5.444	29	–0.436	3.732	67.975	7.136
8	–0.423	3.735	99.671	6.011	30	–0.423	3.733	68.127	6.205
9	–0.426	4.900	99.304	5.444	31	–0.422	3.732	68.821	6.205
10	–0.426	4.900	99.117	6.011	32	–0.424	3.732	68.072	6.785
11	–0.424	3.736	99.674	6.597	33	–0.425	3.733	70.658	6.785
12	–0.427	4.900	94.627	6.011	34	–0.425	3.733	67.246	7.382
13	–0.428	4.900	99.909	6.597	35	–0.425	3.733	68.151	7.923
14	–0.425	3.738	70.050	6.597	36	–0.429	4.891	131.918	7.324
15	–0.428	4.900	98.651	6.597	37	–0.428	4.89	132.539	8.537
16	–0.428	4.900	98.850	7.201	38	–0.425	3.733	68.082	8.537
17	–0.421	3.736	106.068	5.801	39	–0.425	4.287	77.412	4.111
18	–0.421	3.736	101.672	6.379	40	–0.426	4.273	76.903	4.730
19	–0.424	4.889	135.937	5.801	41	–0.425	4.281	77.333	5.041
20	–0.424	4.889	136.077	6.379	42	–0.425	4.289	77.625	4.652
21	–0.425	3.733	68.585	6.379	43	–0.430	4.286	108.586	4.478
22	–0.425	3.733	66.909	6.975					

[a] Atomic charge of atom N.
[b] Interatomic distance between atom N and carbonyl oxygen at C-4.
[c] Torsional angle around carbonyl oxygen, C-4, C-3 and atom N bond sequence.
[d] Kier flexible index.

Table 4
Observing errors of different neural network architecture

	RMSD [a]	MSE [b]
4–3–1	0.1620	0.6688
4–4–1	0.1953	0.6705
4–5–1	0.2544	0.6990
4–6–1	0.7030	0.6717

[a] Root mean squares of deviations.
[b] Mean square error.

four selected variables were used as input and the analgesic activity was used as output, so a 4-*x*-1 network was constructed and the suitable value of *x* could be defined from 3 to 6 (ρ was located between 1.0 and 3.0). The optimum number 3 was determined after a training process by comparing the RMSD and MSE values as shown in Table 4. The value of MSE was also used to determine the learning parameter that specifies the step length of the gradient descent method. From Fig. 1, the optimal value was determined as 0.002 where the curve would achieve balance appropriately after 20,000 cycles.

In order to confirm the QSAR model, LOO cross-validation procedure was used. The predictive coefficient q^2 value for training set by PLS and NN (4–3–1) was respectively 0.577 and 0.658 (Table 5). Meanwhile, additional five compounds were used as an external testing set to validate the QSAR model. Since predictive results in testing set were in good accordance with the experimental data, we came to the conclusion that the 4–3–1 NN architecture simultaneously showed high correlation and predictive power that would be well adopted to relate the analgesic activity of 4PPs to their molecular descriptors, so it was applied in the subsequent analyses.

The conventional calculated activities from NN are listed in Table 1, too. The quality of fitting is estimated by the standard error of calculation (S) and the correlation coefficient (R^2). It is easy to notice that the results of neural network would generate a better QSAR model than traditional method PLS.

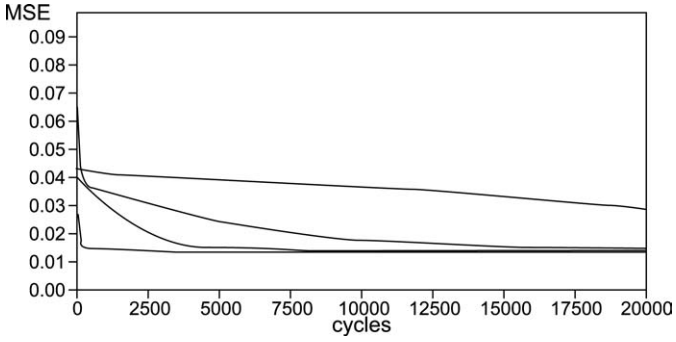


Fig. 1. Observing mean square error within 20,000 cycles (the curves from top to underside represent the studying process when learning rate is 0.001, 0.002, 0.01, 0.2, representatively).

Table 5
Statistical results and predictive ability of training and testing data set

	NN (4–3–1)	PLS	Testing set
R^2	0.683	0.647	0.889
S	0.542	0.598	0.152
q^2	0.658	0.577	0.457
S	0.553	0.585	0.343

Due to high correlation coefficients, we can confidently say that the analgesic activity is significantly correlated with the four variables adopted in our work. Based on the above learning pattern, the relationship between each descriptor and activity was investigated (shown in Fig. 2). The plot of Fig. 2 was obtained using the technique proposed by So and Richards [33] and Andrea and Kalayeh [32], changing the value of one descriptor while keeping the other inputs constant. It is easy to detect some structural features represented by the four variables. At first, the charge of atom N is crucial to the analgesic activity, which is reasonable because atom N should be protonated in physiological environment and form an electrostatic interaction with a counter-charged residue of the receptor [2]. Secondly, the values of both interatomic distance and torsional angle, which define the position of atom O, suggest an important interaction related to the carbonyl oxygen. Finally, the structural flexibility of the 4PPs is mainly rooted in the N-substitution, and the biological activity is enhanced by increasing the hydrophobility of N-substitution. So the last Kier flexibility index PHI should indicate a lipophilic cavity on the receptor.

3.3. Implication for drug discovery

From the structural point of view, the 43 compounds could be divided into two clusters based on the R_2 substitution (see Table 1), and an activity elevation is always produced when the R_2 substitution is changed from ester group to acyloxy group regardless of the nature of N-substitution (as illustrated by compounds **8** and **9**). The interrelated information that emerged from the forenamed result of QSAR study, while two of the four selected molecular descriptors likewise direct to the effect of the carbonyl oxygen. Additionally, according to the conformational analysis of compounds **8** and **9** (shown in Fig. 3A), the carbonyl oxygen, which is likely in an opposite position, should constitute interactions with distinct residues on the receptor. Bearing on these, we could propose that a hydrogen bond exists between receptor and the carbonyl oxygen, which would contribute to the varying activity of the two compound clusters through different binding site.

According to Ref. [3], the phenolic analogues in both 4-acyloxy substituted 4PPs and fentanyl series, not 4-ester substituted 4PPs, exhibit little or no narcotic agonist activity. Such a phenomenon indicates a uniform role of the aromatic group. Interestingly, the results of this study are quite similar to the previous work of Tang et al. [34] on QSAR study of fentanyl analogs. We performed a structure overlap of compound **9** with fentanyl (Fig. 3B), it is surprising that the carbonyl oxygen in the two molecules were located in almost the same position, though some difference could be found on 4-substitution. Based on the induced fit theory, the two flexible skeletons may alter to share the same subsite in bioactive conformation. Therefore, we could hypothesize that 4-acyloxy-substituted phenylpiperidine derivatives might have a similar receptor-binding model with fentanyl analogs, which have been confirmed to be quite different from that of morphine [35].

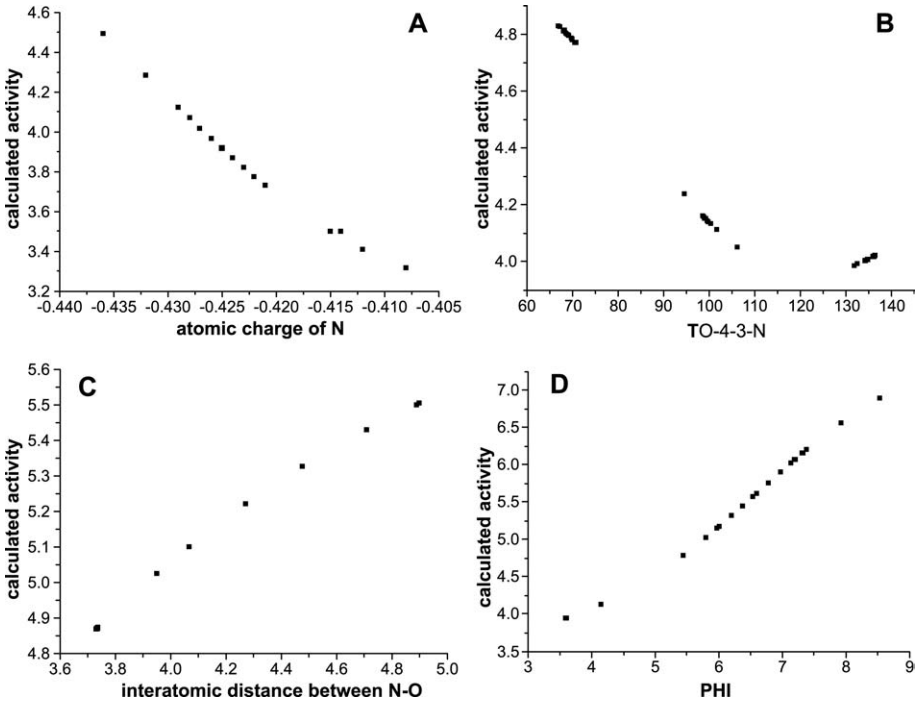


Fig. 2. (A) Calculated activity versus charge of atom N. (B) Calculated activity versus torsional angle $T_{O-4-3-N}$. (C) Calculated activity versus ineratomic distance between N and O. (D) Calculated activity versus PHI.

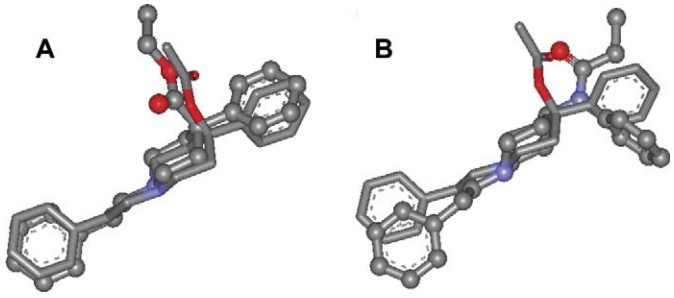


Fig. 3. (A) Skeletal superposition of compound **8** (ball and stick) and compound **9** (stick); (B) Superposition of fentanyl (ball and stick) and compound **9** (stick).

4. Conclusion

In this paper, we applied the neural network method to analyze the nonlinear QSAR of 4-phenylpiperidines as μ opioid agonist. Our study demonstrated that the three-layer back-propagation NN provided us a promising QSAR model for 4PPs. We also developed a rapid descriptor mining method, and the selected four descriptors matched well with the structural requirements of 4PPs binding to the receptor. Based on the results, we hypothesized a pharmacophore model for these compounds, in which the protonated N should interact with an anionic residue, a hydrogen bonding formed between the carbonyl oxygen and the residues on receptor with a specified location. Besides, on the N-substitution, the addition of phenyl group with flexible alkyl chain would engender a hydrophobic bonding with a lipophilic cavity. Thus, the results provide us new insight so as to investigate the role of aromatic group in 4PPs and to design new derivatives to understand the structural basis of μ opioid agonists.

Acknowledgements

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