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A Most Prominent Structural Characteristic in Opioid Receptor Agonist Analgesics*

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***Abstract*—The molecular structures of tramadol and 20 other opioid receptor agonist analgesics were optimized by chemical software MM2. Some essential structure parameters such as molecular refractivity (CMR), calculated n-octanol/water partition coefficients (ClogP) as well as D_{NC} (the distance from a nitrogen atom to the farthest carbon atom in the nearest phenyl group) were calculated when the stereo structures of agonist molecules have a minimized energy. An Artificial Neural Networks was set up while the molecular parameters of 21 agonist compounds were net inputs and the opioid receptor combine affinities were net outputs. Randomly input 10^5 structure parameters as net input values to the trained ANNs and calculate the peak inputted values frequency of CMR, ClogP as well as D_{NC} while the outputs of affinity are less than 0.1nM. The results reveal that it will be maximum possibility to have a powerful affinity if the D_{NC} in candidate molecules is about 6 angstroms. This finding will be useful to the molecular design of agonist analgesics.**

Keywords—Opioid Receptor Agonist; ANNs; QSAR

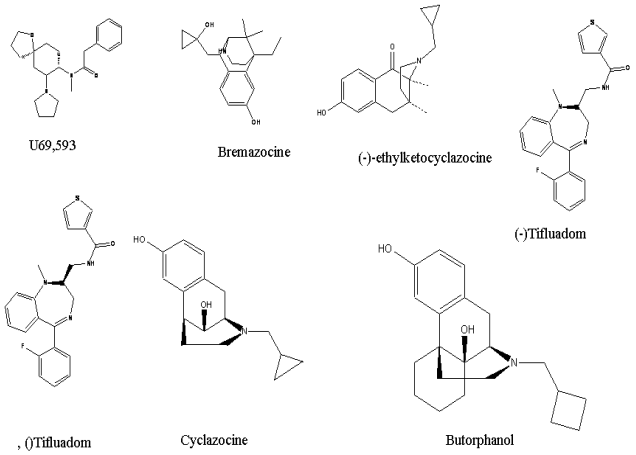
I. INTRODUCTION

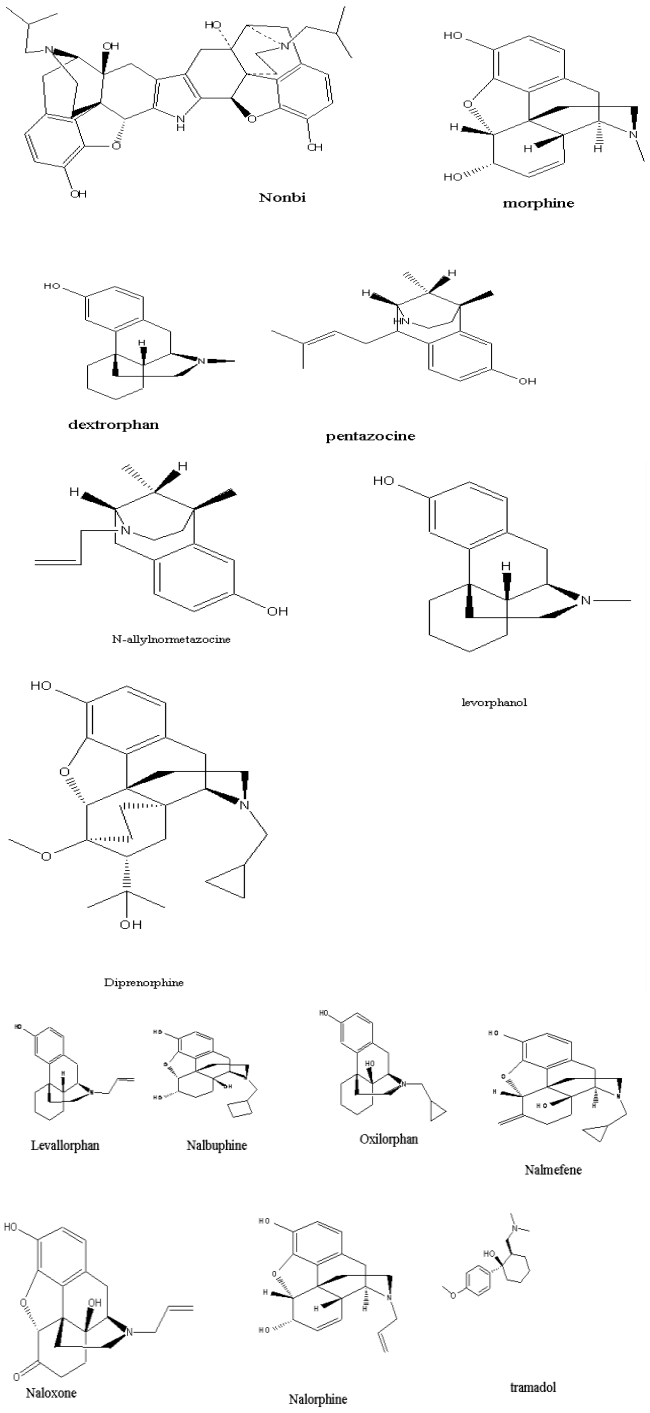
Anodynes are generally classified as mu, kappa, delta and sigma opioid receptor agonists that act on different opioid receptors to relieve pain, but they have a common molecular characteristic that nearly all opioid receptor agonists contain at least one nitrogen atom and one phenyl group in the molecules. A lot of researches [1-12] have focused on the structure and activity relationship about opioid receptor agonist analgesics; Articles try to solve these fundamental questions: what is the paramount structural character that leads the candidate has high activity to opioid receptor? Given a molecular structure of candidate, without experimental data and just by a simple and quick calculation, whether a researcher immediately predicts its opioid receptor activity? Following a basic rule, can we design a series leading molecules which have high opioid receptor activity? But so far, these questions remain unanswered. In this article, the artificial neural networks (ANNs) and molecule software MM2 are employed to reveal the key factor of QSAR in opioid receptor agonists. The higher predictive ability of ANNs that is generally more accurate than some classical models arises from their flexibility and their ability to model nonlinear relationships. A variety of neural networks are available depending on the characteristic of the problem being studied and some interesting results have been showed from the models with combination of QSAR and ANNs. The finding of general rules will be useful tools for investigating the pharmacological properties of the opioid receptor agonist.

II. METHODS

A. Molecular parameters analysis

For this investigation, 21 opioid receptor agonist analgesics were collected from the literatures and the chiral structures of the molecules are listed in Scheme 1. Optimization of molecular geometries and determination of ClogP, CMR are all set up by using MM2 method, a semi-empirical quantum mechanical method as implemented in ChemBio 3D. The parameters of D_{nc}, the distance from a nitrogen atom to the farthest carbon atom in the nearest phenyl group, were measured when the conformational structures of agonist molecules have a minimized energy.





Scheme.1.Chiral structures of opioid receptor agonist analgesics.

B. ANNs Data set

The affinity values toward opioid receptor, expressed as K_i (nM), are collected from scattered papers. Calculations were performed to transform the original K_i into affinity, as in (1), and the results were showed in table 1.

$$\text{Affinity}=-\log(1+K_i) \quad (1)$$

Using affinity as response variable, with transformation, the distribution of the activities is almost uniformed. Without high leverage points, as observed in the case of histogram, and in any case affinity is better than that obtained by using the transformation of $-\log K_i$ (pK_i), which is very commonly employed in QSAR studies.

Majority of pharmaceutical agents must cross a biological membrane to reach their site of action and to be available in a cellular environment. Lipophilicity of the medicine's molecule has a major impact upon its distribution and biological action. Quantitative measures of lipophilicity are very important in the development of medicine's molecules. Partition coefficient of a molecule is the ratio of its solubility in n-octanol to its solubility in water. Logarithm of this quantity, ClogP, is a well-established measure of a compound's lipophilicity which often based on complex molecular representations. On the other hand, CMR, which reflect to the molecule's volume, was selected here as an important variable to set out the QSAR model.

TABLE 1. CHEMICAL STRUCTURE PARAMETERS AND AFFINITY WITH OPIOID RECEPTOR IN AGONIST ANALGESICS

NO	Name	ClogP	CMR	Dnc (Å)	Affinity (nM)
1	Tramadol	3.1	7.82	6.25	180
2	tramadol N-oxide	3.2288	7.9772	6.178	4
3	U69593	2.7627	10.5034	6.581	6
4	(-)Tifluadom	3.3941	11.2574	7.435	5.9
5	(+)Tifluadom	3.3941	11.2574	5.997	0.18
6	Cyclazocine	3.938	8.2008	5.679	0.71
7	Nalorphine	1.1757	8.6196	5.806	6.5
8	Butorphanol	3.7263	9.5279	5.645	0.88
9	Levallorphan	4.133	8.5162	5.552	0.43
10	Nalbuphine	1.3905	9.5737	5.502	2.4
11	Oxilorphan	2.17745	8.9267	5.799	0.33
12	Nalmefene	2.636	9.4352	5.659	0.39
13	Naloxone	0.1595	8.6807	5.84	7.6
14	NorBNI	4.126	18.643	5.79	0.22
15	morphine	0.5717	7.7174	5.799	0.3
16	pentazocine	4.71	8.7766	5.399	5.7
17	Allylnormeta-zocine	3.739	7.849	5.646	0.9
18	diprenorphine	2.6621	11.6723	5.849	0.2
19	levorphanol	3.529	7.69	5.601	0.5
20	codeine	0.9775	8.1812	5.879	0.5
21	imipramine	5.037	9.0064	6.46	58

C. ANNs arithmetic

Artificial neural networks (ANNs) are biologically inspired computer programs designed to simulate the way in which the human brain processes information. As the neurons are differently interconnected in brain, it can be distinguished 3 types of layer in our ANNs model, an input, a hidden and an output layer. In the input layer, the ANNs take 3 input variables, included ClogP, CMR and D_{NC}, and distribute them to the following layers. Hidden layer does calculations and the output layer serves the calculated results. The ANN_S output layer only consists one variable of Affinity. Showed as Fig. 1, ANN_S structures in this article is a feed forward multilayer network in which Back Propagation Network (BPN) algorithm is used for

training. In BPN the signal flow will be in feed forward direction, but the error is back propagated and weights are updated to reduce error. The modification of the weights is according to the gradient of the error curve, which points in the direction to the local minimum and makes it much reliable in prediction. In BPN, weights are initialized randomly at the beginning of training. During forward pass of the signal, according to the initial weights and activation function used, the network gives an output. That output is compared with desired output. If both are not same, an error occurs. During reverse pass, the error is back-propagated and weights of hidden and output layer are adjusted. The whole process then continues to cycle until the sum squared errors of 21 outputs is less than 10^{-6}.

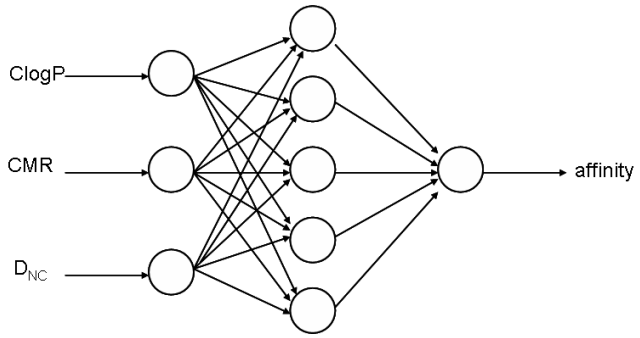


Figure.1.Artificial neural networks sketch map about QSAR of opioid receptor agonist analgesics.

III. RESULTS AND DISCUSSION

Conformational geometries of 21 molecules have been optimized in the state of the minimum molecular energies by MM2 in ChemBio 3D, V11.0. Choose "minimize energy" as the job type then click on "display every iteration" and leave the minimum RMS gradient at 0.100. The total steric energy of the molecule is much less after geometry optimization. The molecule properties of ClogP, CMR and D_{NC} were determined and given as table 1.

To Train the artificial neural networks by putting molecular parameters of 21 compounds as net input and letting opioid receptor combine affinity as net output, the model of QSAR about opioid receptor agonist analgesics was set up.

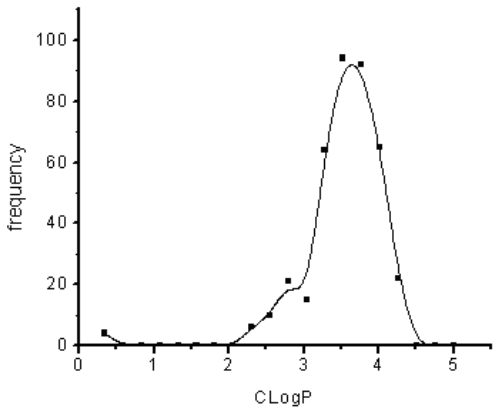


Figure.2.The frequency distribution of net input of variable ClogP while the affinity outputs of trained ANNs are less than 0.1 nM.

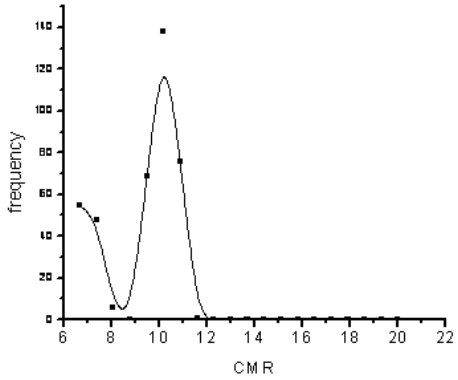


Figure.3.The frequency distribution of net input of variable CMR while the affinity of trained ANNs outputs are less than 0.1 nM.

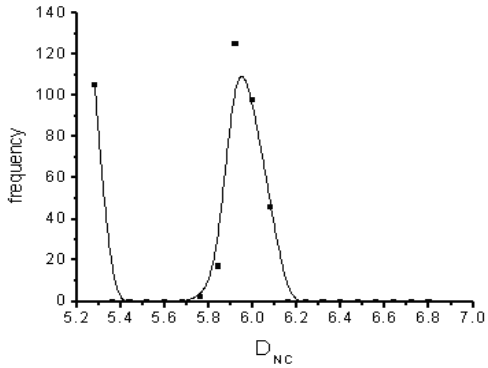


Figure.4.The frequency distribution of net input of variable D_{NC} when the affinity outputs are less than 0.1 nM.

In the all chemical structure parameter's interzone, from 0.1 to 5 for ClogP, from 6 to 20 for CMR and from 5 to 7 for D_{NC}, using Monte Carlo method, randomly input 10^5 structure parameters as net input data to the trained ANNs. When the outputs of affinity are less than 0.1nM, count the frequency of net input about variable ClogP, CMR and D_{NC}, The frequency distribution figures show there is high possibility to attain an high activity opioid receptor agonist when the ClogP, CMR and D_{NC} near the peak of the curves(figure 2-4). The output results demonstrated that chemical structure parameters of opioid receptor agonist analgesics which have the highest possible of low affinity are 3.914 for ClogP, 9.836 for CMR and about 6 angstroms for D_{NC} respectively. Comparison of the structural characteristics of (+)Tifluadom and (-)Tifluadom (Figure 5A and 5B) can obviously find this phenomenon. (+)Tifluadom and (-)Tifluadom have the same structural parameters in ClogP and CMR but in D_{NC}. The D_{NC} for the former is 5.997 and the affinity is 0.18nM while for the latter is 7.435 and the affinity is 5.9 nM, which leads to a difference in affinity to opioid receptor.

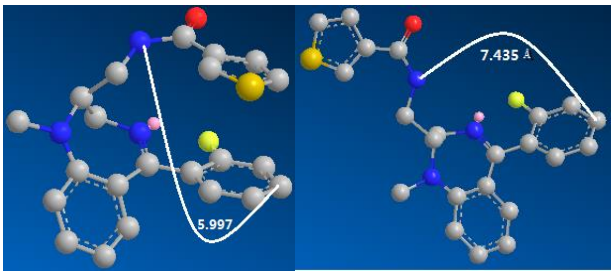


Figure.5.(+)Tifluadom (A) and (-)Tifluadom (B) have the same structural parameters in ClogP and CMR but different in D_{NC}. The difference in chemical structure leads to a difference in affinity to opioid receptor.

An agonist is a chemical that binds to some receptor of a cell and triggers a response by that cell. Agonists often mimic the action of a naturally occurring substance. Of the three major classes of opioid receptors, mu (μ), delta (δ), and kappa (κ), the μ opioid receipts has proven to be the major target of opiate analgesics. The opioid receptors belong to the family of G protein-coupled receptors (GPCRs), and like most GPCRs, they can be regulated by multiple mechanisms including receptor desensitization, internalization, resensitization and down regulation. Based on the "lock and key" model, receptor and agonist must be selective bonding each other while nitrogen atoms with positive charge and the phenol with big Pi band are binding to the particularly parts of opioid receptor respectively. The three major classes of opioid receptors have same resemble protein structures which can bind to the nitrogen atom and phenol ring but they provide evidence for the existence of one or more intermediate conformational states linking the inactive receptor to the fully active receptor.

IV. CONCLUSION

Chemical structure parameters of receptor agonist analgesics which have more possibility of high activity are ClogP 3.914, CMR 9.836 and D_{NC} about 6 angstroms respectively. The affinity of opioid receptor analgesics is impressible to the distance of D_{NC} (the distance between the nitrogen atom and the farthest carbon atom in the nearest phenyl group while the stereo molecular structure has a minimization energy), thus, the 6 angstroms rule of opioid receptor agonist analgesics will be a simple and efficacious rule for the novel opioid receptor agonist discovery.

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