BIBLID: ISSN 0253-9756 Acta Pharmacologica Sinica 中国药理学报 1997 Mar; 18 (2): 128-132

Interaction models of 3-methylfentanyl derivatives with μ opioid receptors[1]

RONG Suo-Bao, ZHU You-Cheng, JIANG Hua-Liang, WANG Qing-Mi, ZHAO Shan-Rong, CHEN Kai-Xian, JI Ru-Yun
(*Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 200031, China*)

KEY WORDS 3-methylfentanyl; ohmefentanyl; three-dimensional quantitative structure-activity relationship; comparative molecular field analysis; interaction models; mu opioid receptors

AIM: To study the interaction model of 3-methylfentanyl derivatives with μ opioid receptor.. **METHODS:** After a systematic conformational search, a three-dimensional quantitative structure-activity relationship study was carried out with comparative molecular field analysis (CoMFA). **RESULTS:** 1) The 6 CoMFA models had good predictive values and each model corresponded to the minimum-energy conformations of 13 compounds studied; 2) The important geometric parameters of μ pharmacophore d_1(Å), d_2(Å), d_3(Å), d_4(Å), d_5(Å), and d_6(Å) were 5.2, 5.4, 4.9, 10.6, 10.2, and 5.8 in Model A; 5.2, 6.5, 3.6, 10.6, 11.6, and 5.8 in Model B; 5.2, 4.6, 4.9, 11.6, 9.2, and 6.5 in Model C; 5.2, 5.4, 4.9, 10.5, 10.3, and 5.8 in Model D; 3.6, 5.4, 4.9, 5.7, 7.5, and 5.7 in Model E; 5.2, 4.7, 4.9, 11.2, 9.5, and 6.4 in Model F, respectively. **CONCLUSIONS:** The several bioactive conformations of fentanyl analogs possibly existed and did not need to be the absolute minimum-energy conformation, each of which was involved in the interaction with μ opioid receptor.

Fentanyl was a potent analgesic agent[1]. Our laboratory synthesized 4 enantiomers of 3-methylfentanyl (3-MF) and 8 enantiomers of ohmefentanyl (OMF)[2,3], which had tremendous stereo-differences in their analgesic activities.

The analgesic potency of fetanyl derivatives was mainly dependent on binding affinity for opioid receptor[4]. Fentanyl, 3-MF, and OMF were highly potent and selective μ opioid agonists[5,6].

[1] Project supported by the National Natural Science Foundation of China, No 39470805
Received 1995-12-20 Accepted 1996-08-14

Many theoretical studies of fentanyl analogs were made for identifying and characterizing the molecular determinants of μ receptor recognition[7,8]. These results led to a distinct pharmacophore for interaction at μ receptor and 4 key moieties necessary for μ receptor recognition (Fig 1).

The correlations between physicochemical properties and analgesic activities were derived from quantitative structure-activity relationship (QSAR) study, which had good predictive values[9,10]. But the former results could not explain QSAR of fentanyl analogs, the latter results did not consider the pharmacophore and interaction model of 3-MF derivatives with μ opioid receptors.

To investigate both the molecular determinants of μ receptor recognition and the QSAR, we performed a conformational search for the fentanyl derivatives and carried out 3D-QSAR study with comparative molecular field analysis (CoMFA) method[11].

METHODS

The 13 fentanyl derivatives, including fentanyl, 4 enantiomers of 3-MF and 8 enantiomers of OMF, were chosen as the studied compounds. Their 3D structures were constructed, based on the crystal structure of (3R,4S,2'R)-OMF[12], on SGI XZ4000 workstation with molecular modeling software SYBYL 6.1[13].

On account of its highest analgesic activity among the studied compounds, (3R,4S,2'S)-OMF was chosen as the reference molecule of conformational search.

First of all, a systematic conformational search was carried out for (3R,4S,2'S)-OMF with search routine of SYBYL. Fifty-five local minimum-energy conformations of the reference molecule were obtained. The distance map of 4 key moieties (N_{PA}, O_{PA}, pseudoatom A and B; Fig 1) necessary for μ receptor recognition was created, which was selected as the constrainting distances of conformational search for the other studied compounds.

Secondly, based on the constrainting distances of each minimum-energy conformation of the reference molecule, a

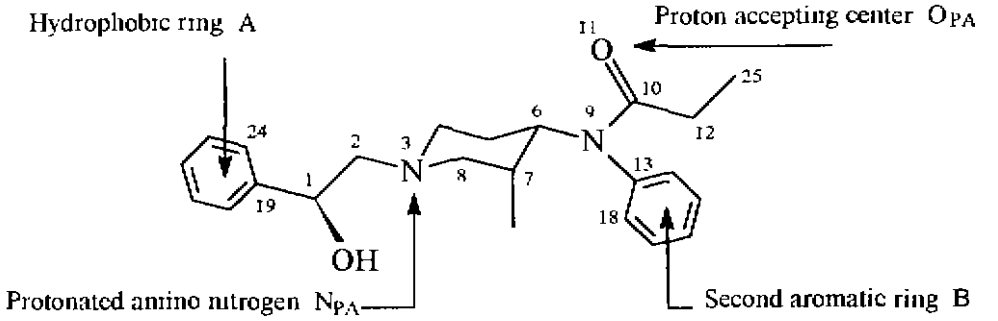


Fig 1. Pharmacophore for μ receptor recognition, shown for (3R,4S,2′S)-OMF, which was used as molecular alignments of CoMFA. Atom ID were used to define the torsion angles in Tab 3.

systematic conformational search was done on the other compounds. The lowest-energy conformation at the condition of constrainting distances was obtained for the other compounds. Thus, 55 series of minimum-energy conformations were formed, each of which contained 13 minimum-energy conformations corresponding to the 13 compounds.

According to the pharmacophore of fentanyl analogs, 4 site points (N_{PA}, O_{PA}, pseudoatom A and B) were used as the alignment rule in CoMFA (Fig 1). For each molecular alignment of 55 series of the minimum-energy conformations, the CoMFA study was made with cross-validation. Consequentially, 6 CoMFA models gave good cross-validated r^2 values, each of which was selected to perform noncross-validated (conventional) analysis.

RESULTS

The 6 CoMFA models, obtained from 55 series of the CoMFA studies, had the same optimal component, 5, and good conventional statistical correlations (Tab 1).

Tab 1. The six CoMFA.

Model	*Cross-validated*		*Conventional*		
	r^2	Optimal component	r^2	s	F
A	0.689	5	1.000	0.034	3 102.5
B	0.711	5	1.000	0.033	3 172.4
C	0.663	5	0.999	0.049	1 434.6
D	0.716	5	0.999	0.052	1 305.1
E	0.677	5	0.998	0.074	630.9
F	0.590	5	0.998	0.073	654.4

Their molecular alignments, predictive activities and residual values are shown in Fig 2 and Tab 2, respectively.

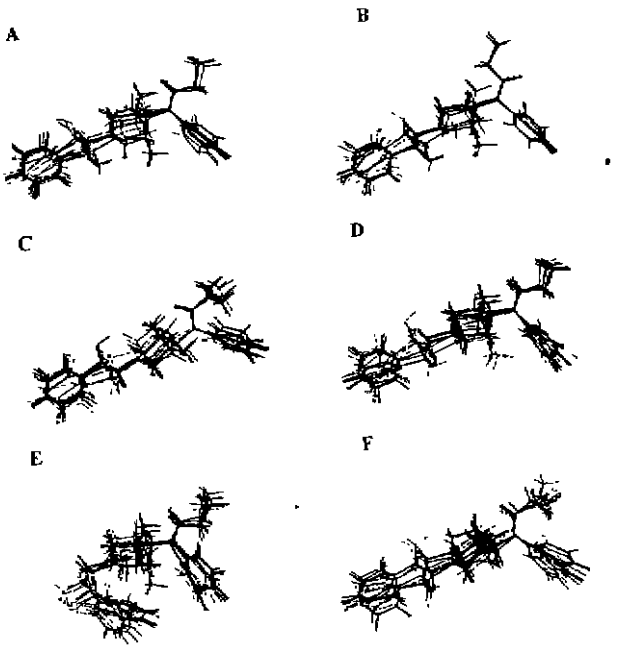


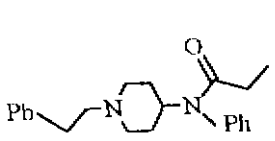
Fig 2. The molecular alignments of the six CoMFA models.

The torsion angles of the rotatable bonds were calculated for all minimum-energy conformations of each model (Tab 3).

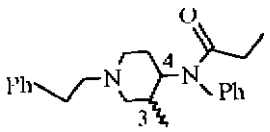
The geometric parameters of μ pharmacophore were calculated for the 6 CoMFA models (Tab 4).

On the basis of μ pharmacophore of fentanyl analogs, we could infer the complementary μ receptor sites. RP1 was located 3 Å from the piperidine nitrogen in the direction of its proton; RP2 was located 3 Å from proton accepting oxygen

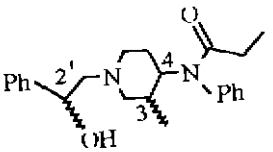
Tab 2. Experimental activities and predictive activities with 6 CoMFA models.



Fentanyl



3-Methylfentanyl



Ohmefentanyl

Compounds	EA[a]	Model A PA[b]	Model A δ[c]	Model B PA[b]	Model B δ[c]	Model C PA[b]	Model C δ[c]	Model D PA[b]	Model D δ[c]	Model E PA[b]	Model E δ[c]	Model F PA[b]	Model F δ[c]
Fentanyl	6.78	6.81	−0.03	6.80	−0.02	6.79	−0.01	6.75	0.03	6.77	0.01	6.69	0.09
(3R,4R)-3-MF	6.42	6.41	0.01	6.45	−0.03	6.45	−0.03	6.35	0.07	6.44	−0.02	6.50	−0.08
(3R,4S)-3-MF	7.76	7.73	0.03	7.70	0.06	7.76	0.00	7.78	−0.02	7.66	0.10	7.71	0.05
(3S,4R)-3-MF	5.69	5.66	0.03	5.70	−0.01	5.75	−0.06	5.77	−0.08	5.65	0.04	5.73	−0.04
(3S,4S)-3-MF	7.01	7.01	0.00	7.03	−0.02	6.94	0.07	7.07	−0.06	7.10	−0.09	7.03	−0.02
(3R,4R,2′R)-OMF	6.71	6.68	0.03	6.72	−0.01	6.71	0.00	6.72	−0.01	6.65	0.06	6.63	0.08
(3R,4S,2′R)-OMF	7.90	7.92	−0.02	7.89	0.01	7.90	0.00	7.89	0.01	7.91	−0.01	7.95	−0.05
(3S,4R,2′R)-OMF	4.57	4.56	0.01	4.55	0.02	4.57	0.00	4.56	0.01	4.52	0.05	4.54	0.03
(3S,4S,2′R)-OMF	6.69	6.68	0.01	6.71	−0.02	6.75	−0.06	6.65	0.04	6.72	−0.03	6.75	−0.06
(3R,4R,2′S)-OMF	7.58	7.57	0.01	7.56	0.02	7.58	0.00	7.56	0.02	7.59	−0.01	7.56	0.02
(3R,4S,2′S)-OMF	8.54	8.56	−0.02	8.57	−0.03	8.52	0.02	8.55	−0.01	8.58	−0.04	8.57	−0.03
(3S,4R,2′S)-OMF	4.57	4.62	−0.05	4.56	0.01	4.52	0.05	4.57	0.00	4.66	−0.09	4.60	−0.03
(3S,4S,2′S)-OMF	7.41	7.43	−0.02	7.40	0.01	7.40	0.01	7.43	−0.02	7.38	0.03	7.38	0.03

a) Experimental activity $\lg 1/ED_{50}(mol \cdot kg^{-1})$ in hot plate test on mice; b) Predictive activity; c) Residual.

Tab 3. Torsion angles (degree) of rotatable bonds of minimum-energy conformations (Atom ID shown in Fig 1).

Model	ξ_1 (3-2-1-19)	ξ_2 (11-2-3-8)	ξ_3 (7-6-9-13)	ξ_4 (6-9-10-12)	ξ_5 (9-10-12-25)	ξ_6 (6-9-13-18)	ξ_7 (12-1-19-24)
A	155~183	−173~−89, 62~72	0~103	179~181	177~182	87~93	84~111
B	156~189	−173~−130, 67~72	28~84	−3~5	173~187	59~112	55~116
C	159~203	−173~−59, 69	−151~−85	175~185	−89~−74, 74~87	68~111	59~124
D	163~192	−165~−97, 58~62	1~101	179~181	177~183	88~94	60~118
E	−60~56	−146~−81	2~125	179~181	176~184	89~92	45~119
F	−179~−168, 168~179	−138~−87, 60~77	125~277	175~182	−178~−74, 76~77	75~111	61~119

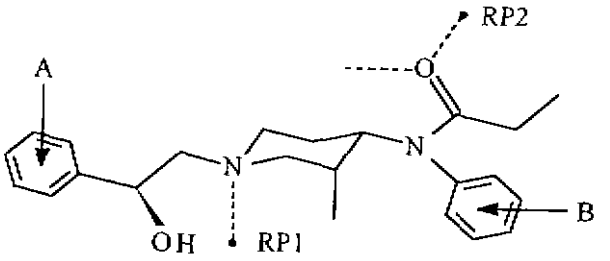
Tab 4. Geometric parameters of μ pharmacophore (Related atoms shown in Fig 1).

Model	d_1^a	s^i	d_2^b	s^i	d_3^c	s^i	d_4^d	s^i	d_5^e	s^i	d_6^f	s^i	θ_1^g	s^i	θ_2^h	s^i
A	5.17	0.01	5.35	0.11	4.88	0.01	10.61	0.21	10.20	0.17	5.80	0 12	152 4	5.8	68.9	3.2
B	5.17	0.02	6.48	0.02	3.61	0.02	10.58	0.10	11.56	0.03	5.77	0.13	165.8	2.1	62 2	3.0
C	5.16	0.01	4.56	0.06	4.89	0.01	11.58	0 12	9.22	0 14	6.53	0.06	143.6	6 6	87.3	2.0
D	5.16	0.01	5.37	0 08	4.88	0.01	10 48	0.11	10.31	0.26	5.78	0 15	157.8	7.5	68.8	3.1
E	3 63	0.05	5 38	0.07	4.88	0.01	5.65	0 08	7.53	0.11	5.70	0.13	112.6	5.4	67.4	3.4
F	5.17	0.02	4 66	0.04	4 89	0.01	11.24	0 31	9.54	0 25	6.40	0.09	153.8	6 3	84.5	4.6

a) distance between A and N_{PA}(Å); b) distance between N_{PA} and O_{PA}(Å); c) distance between O_{PA} and B (Å); d) distance between A and B (Å); e) distance between A and O_{PA}(Å); f) distance between N_{PA} and B (Å); g) angle between A, N_{PA} and O_{PA}(degree); h) angle between N_{PA}, O_{PA} and B (degree); i) standard derivation of the parameters of 13 minimum-energy conformations in each model.

(sp_2 hybridization) in one of the 2 directions of possible protonations, which was far away from piperidine. The geometric parameters of complementary μ receptor sites were also calculated for Models A, B and E, which are shown in Tab 5.

Tab 5. Geometric parameters of complementary μ receptor sites.



Model		A		B		C	
d_1^a	s^h	6.10	0.24	6.16	0.23	1.79	0.07
d_2^b	s^h	9.26	0.30	9.67	0.21	9.03	0.23
d_3^c	s^h	7.16	0.01	6.37	0.02	7.17	0.02
d_4^d	s^h	12.66	0.21	13.84	0.06	10.26	0.27
d_5^e	s^h	5.00	0.21	4.81	0.17	4.56	0.13
θ_1^f	s^h	109.8	6.1	120.0	5.0	132.9	8.1
θ_2^g	s^h	32.3	4.2	25.9	3.9	29.9	2.4

a) distance between A and RP1 (Å); b) distance between RP1 and RP2 (Å); c) distance between RP2 and B (Å); d) distance between A and RP2 (Å); e) distance between RP1 and B (Å); f) angle between A, RP1 and RP2 (degree); g) angle between RP1, RP2 and B (degree); h) standard derivation of the parameters of 13 minimum-energy conformations in each model.

DISCUSSION

The CoMFA models and the bioactive conformations of the studied compounds It can be seen from Tab 1 and Tab 2 that, the 6 resultant CoMFA models had fair predictive ability. Such highly predictive ability implies that the conformations of the studied compounds in the CoMFA models could be their bioactive conformations. It means that the studied compounds probably have several bioactive conformations involved in interacting with μ opioid receptor, which did not need to be the absolute minimum-energy conformation.

From Tab 3, the bioactive conformations in each model were different. Moreover, in each model, some rotatable bonds were almost fixed (underlined data in Tab 3), others were more variable. Our derived bioactive conformations were consistent with the results of Dr Wang [14], in which ξ_6 was about 90°, but ξ_4 and ξ_5 are absent.

On the basis of above facts, the bioactive conformations of the studied compounds in each model may be reasonable. In each model, the nearly fixed rotatable bonds were mainly the requirements of molecular characteristics, whereas the more variable rotatable bonds were principally the stereo-requirements of recognition for μ opioid receptor.

The interaction models of the studied compounds with μ opioid receptor The geometric parameters of μ pharmacophore of Models A, B and E are accordant with some results of Ref 7. For example, d_1, d_2, d_3, d_4, d_5, d_6, θ_1, and θ_2 of fentanyl in Ref 7 were 5.1 Å, 5.2 Å, 4.9 Å, absent, 9.9 Å, 5.7 Å, 150°, and 73°, respectively, which are consistent with those of Model A (Tab 4). These facts show again that, the bioactive conformations of the studied compounds in the CoMFA models could be meaningful.

Models A and D, as well as Models C and F, had the very similar geometric parameters of μ pharmacophore, respectively (Tab 4). The possible bioactive conformations in Models A, C, D and F were also very similar (Fig 2). Therefore, Models A, C, D and F may be considered to the much similar, even same, interaction model with μ opioid receptor.

Comparatively, Models B and E, especially Model E, had the strange geometric parameters of μ pharmacophore (underlined data in Tab 4). In Model B, the carbonyl oxygen of 4-phenylpropanamide directs far away from piperidine (Fig 2); whereas this carbonyl oxygen close to piperidine in the other Models. In Model E, the benzene ring of *N*-phenylethyl bents close to 4-phenylpropanamide (Fig 2); but this benzene ring is extended in the other Models.

The complementary sites of μ opioid receptor Models A, B and E had very different geometric parameters of complementary μ receptor sites (Tab 5). For example, d_1 (1.79 Å) in Model E is extremely shorter, whereas d_4 (13.84 Å) in Model

B is much longer.

On the basis of the complementarity between ligand and receptor, the geometric parameters in Tab 5 indicate the possible steric-arrangement of binding sites of μ opioid receptor, which are benefit for us to build up the 3D structure model of μ opioid receptor and further design novel analgesic agents using structure-based drug design method.

REFERENCES

1 Janssen PAJ A review of the chemical features associated with strong morphine-like activity. Br J Anaesth 1962; **34**: 260 - 8.

2 Wang ZX, Zhu YC, Chen XJ, Ji RY. Stereoisomers of 3-methylfentanyl: Synthesis, absolute conformation and analgesic activity. Acta Pharm Sin 1993; **28**: 905 - 10.

3 Wang ZX, Zhu YC, Chen XJ, Ji RY Enantiomers of ohmefentanyl: Synthesis and analgesic activity Chin Sci Bull 1994; **39**: 1432 - 34

4 Jin WQ, Xu H, Zhu YC, Fang SN, Xia XL, Huang ZM, *et al*. Studies on synthesis and relationship between analgesic activities and receptor affinity for 3-methylfentanyl derivatives Sci Sin 1981; **24**: 710 - 20.

5 Goldstein A, Naidu A. Multiple opioid receptors: Ligand selectivity profile and binding site signatures. Mol Pharmacol 1989; **36**: 265 - 72.

6 Xu H, Chen J, Chi ZQ. Ohmefentanyl — a new agonist for μ-opiate receptor. Sci Sin 1985; **28**: 504 - 11.

7 Cometta-Morini C, Maguire PA, Loew GH. Molecular determinants of μ receptor recognition for the fentanyl class of compounds. Mol Pharmacol 1992; **41**: 185 - 96.

8 Cometta-Morini C, Loew GH. Structural and electronic requirements for binding at the Mu-opioid receptor. Int J Quantum Chem 1992; **44**: 235 - 50

9 Zhu YC, Wu JA, Xu XR. Studies on quantitative structure-activity relationship (QSAR) of 3-methylfentanyl derivatives. Acta Pharm Sin 1985; **20**: 267 - 76.

10 Wang HW, Tang Y, Chen KX, Ji RY. QSAR study on 3-methylfentanyl derivatives using the PLS method. Chin J Med Chem 1994; **4**: 269 - 73

11 Gramer RD Ⅲ, Patterson DE, Bunce JD. Comparative molecular field analysis (CoMFA). 1. Effect of shape on binding of steroids to carried proteins J Am Chem Soc 1988; **110**: 5959 - 67.

12 Wang ZX, Zhu YC, Ji RY, Lu Y, Tian ZY, Zheng QT. Crystal structures of ohmefentanyl stereoisomers. Acta Pharm Sin 1994; **29**: 433 - 37.

13 SYBYL [computer program]. Version 6.1. St Louis (MO): Tripos Associates, 1994.

14 Wang HW, Chen KX, Ji RY A systematic conformation search for ohmefentanyl a high-potency analgesic agent. Chin J Med Chem 1994; **4**: 121 - 7.

3-甲基芬太尼衍生物与μ阿片受体的作用模型

戎锁宝，朱友成，蒋华良，王沁泌，赵善荣，陈凯先，稽汝运

（中国科学院上海药物研究所，上海 200031，中国）

关键词 3-甲基芬太尼；羟甲基芬太尼；三维定量构效关系；比较分子力场分析；相互作用模型；μ阿片受体

目的：研究3-甲基芬太尼衍生物与μ阿片受体的作用模型. **方法**：经过系统构象搜寻，用比较分子力场分析法(CoMFA)研究三维定量构效关系. **结果**：① 6种CoMFA模型具有良好的预测活性，且每种模型均对应于13个被研究化合物的低能构象；② μ药效基团的几何参数 d_1(Å)，d_2(Å)，d_3(Å)，d_4(Å)，d_5(Å)和 d_6(Å)分别为模型A：5.2，5.4，4.9，10.6，10.2和5.8；模型B：5.2，6.5，3.6，10.6，11.6和5.8；模型C：5.2，4.6，4.9，11.6，9.2和6.5；模型D：5.2，5.4，4.9，10.5，10.3和5.8；模型E：3.6，5.4，4.9，5.7，7.5和5.7；模型F：5.2，4.7，4.9，11.2，9.5和6.4. **结论**：可能存在几种活性构象与μ受体相互作用，并且不一定是最低能量构象.