Communications to the Editor

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AGONIST-ANTAGONIST PROPERTIES OF 5,7-ETHANO-4,5,5a,6,7,11b-HEXAHYDRO-2,6,7-TRIMETHYL-1H-BENZO[g]HOMOQUINOLIN-9-OL AND 4,6-ETHANO-3,4,4a,5,6,10b-HEXAHYDRO-2,5,6-TRIMETHYLBENZO[f]QUINOLIN-8-OL

Mikio Hori,*,[a] Tadashi Kataoka,[a] Hiroshi Shimizu,[a] Eiji Imai,[a] Yoshinari Suzuki,[a] Norihiro Kawamura,[a] Hajime Fujimura,[b] Masakatsu Nozaki,[b] and Masayuki Niwa [b]

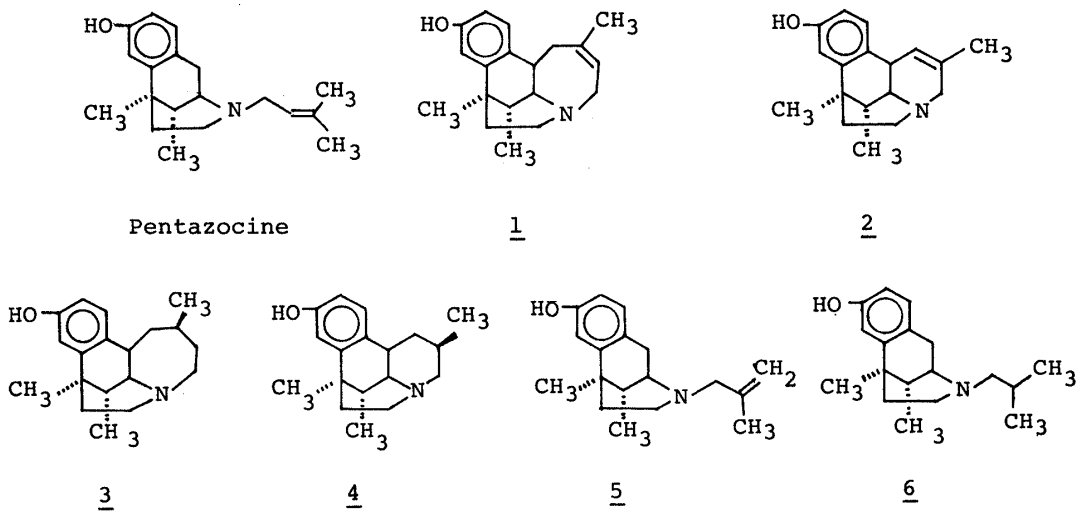
Gifu College of Pharmacy,[a] 6-1 Mitahora-higashi 5-chome, Gifu 502, Japan and Department of Pharmacology, Gifu University School of Medicine,[b] 40 Tsukasa, Gifu 500, Japan

Agonistic and antagonistic properties of novel tetracyclic benzomorphans (1-4) were evaluated in vivo and in vitro opioid receptor interaction tests. Seven-membered derivatives (1,3) showed synergism with morphine analgesia. Six-membered derivatives (2,4) demonstrated antagonist opioid characters.

KEYWORDS —— tetracyclic benzomorphan ; analgesic activity ; opioid antagonist ; opioid receptor binding ; N-lone electron pair direction ; unsaturated bond ; stracture activity relationship

The studies of the interaction mechanism between the receptor and opioid ligands are main topic in the fields of opioid research after the direct demonstration of opioid receptors. However, the differences in the receptor binding of agonist and antagonist are still obscure regardless of extensive research efforts. We previously reported that there might be discriminating systems of agonist and/or antagonist character in opioid receptor binding sites.[1] The most decisive structure in opioids has been considered to be the direction of N-lone electron pairs, on which there are two conflicting theories. Snyder reported a lone pair-equatorial model for opioid agonists.[2] On the contrary, Kolb emphasized axial direction of N-lone electron pairs.[3] In order to define structural features of agonists and antagonists as well as to elucidate the discriminating system of the receptor binding site(s), we synthesized novel tetracyclic benzomorphans, 5,7-ethano-4,5,5a,6,7,11b-hexahydro-2,6,7-trimethyl-1H-benzo[g]homoquinolin-9-ol (1), 4,6-ethano-3,4,4a,5,6,11b-hexahydro-2,5,6-trimethylbenzo[f]quinolin-8-ol (2) and corresponding dihydrogenated derivatives 3 and 4, and also ring-opened derivatives 5 and 6.[4] Compound 1 is considered tetracyclic pentazocine. These tetracyclic derivatives have rigid stereostructures; piperidine rings are chair form and N-lone electron pairs are in axial directions.

Analgesic activities were evaluated by acetic acid writhing inhibition test in mice. Antagonist activities against morphine analgesia were obtained by the tail pinch test in mice, and ED_{50} values of morphine analgesia with each test compound were calculated. Opioid receptor binding assays (ORB) were presented as relative affinities of tested compounds for the stereospecific binding of tritiated opioid



Pentazocine 1 2

3 4 5 6

Fig. Structures of Novel Tetracyclic Benzomorphans

Table 1. Analgesic and Antagonist Activities of Tetracyclic Benzomorphans

	AcOH Writhing inhibition test ED_{50} (95% C.L.) mg/kg s.c.	Antagonism to morphine analgesia* (Tail pinch test) ED_{50} (95% C.L.)	Ratio $\left(\frac{+\text{compound}}{-\text{compound}}\right)$
Morphine	0.5 (0.18-0.95)	7.1 (5.07-9.94)	1.0
Pentazocine	1.7 (1.13-2.55)	9.6 (6.81-13.5)	1.4
1	6.3 (4.23-9.39)	5.6 (3.27-9.58)	0.8
2	20 mg : 25%	11.5 (8.52-15.5)	1.6
3	3.8 (2.79-5.17)	4.3 (2.90-6.84)	0.6
4	10 mg : 20%	9.4 (6.91-12.8)	1.3
5	20 mg : 40%	28.5 (21.4-37.9)	4.0
6	1.1 (0.86-1.41)	35.0 (25.5-48.0)	4.8

* Test compound was injected simultaneously after injection of morphine(1mg/kg).

Table 2. ORB and GPI of Tetracyclic Benzomorphans

	ORB			GPI
	IC_{50} (^{3}H-NLX)		IC_{50} (^{3}H-DHM) nM	IC_{50} nM
	Na^+ free nM	Na Index		
Pentazocine	15	8.0	110	150
1	3	9.0	15	130
2	33	3.2	130	1000 : 46%
3	6	2.7	1	350
4	48	3.4	175	1000 : 40%
5	15	3.3	24	18
6	10	1.2	4	8

ligands in rat brain homogenate : ^{3}H-naloxone (^{3}H-NLX) and ^{3}H-dihydromorphine (^{3}H-DHM) were used. The receptor affinities of the test compounds were also measured by inhibition of electrically evoked longitudinal contractions of guinea-pig ileum (GPI). These results of the receptor affinities were demonstrated as IC_{50} values (concentration of compound required to inhibit the receptor binding or the contraction by 50%). The results of pharmacological activities are summarized in Table 1. The ORB and GPI are shown in Table 2.

Action profiles between 7-membered (1,3) and 6-membered ring compounds (2,4) which have the same N-lone pair direction were greatly different. Analgesic activities of 1 and 3 were less potent than that of pentazocine. In the case of 2 and 4, the activities almost disappeared. Although 2 and 4 showed antagonist activity, 1 and 3 potentiated morphine analgesia. It is interesting that ring opened derivatives (5,6) showed strong antagonistic activities. No difference in pharmacological activities between saturated (3,4) and unsaturated tetracyclic benzomorphans (1,2) was observed.

In ORB experiment the receptor affinities of 1 and 3 were more potent than that of pentazocine. On the contrary, 6-membered compounds (2,4) showed smaller affinities than pentazocine to the binding sites of both DHM and NLX. Saturation of double bonds in 7-membered derivative markedly affected the receptor binding. Compound 3 bound to the DHM binding site; 1 bound to the NLX binding site with higher affinity. The results of GPI test were consistent with those of ORB using ^{3}H-DHM as the ligand.

The significance of N-lone electron pair orientation for analgesic activities has been reported in morphinan derivatives.[5] Our present study demonstrates that the directions are not crucial for the discrimination between agonist and antagonist at the receptor binding sites. Similar observations were reported by Shiotani et al.[6] From X-ray[7,8] and NMR studies,[9] benzomorphans possess considerably rigid chair conformations of piperidine rings and axial directions of N-lone electron pairs. We may conclude that both Snyder's and Kolb's conceptions do not explain satisfactorily the characters of opioid agonists and antagonists. It can be assumed that conformational changes of the receptor binding sites are significant and thereby good fit to opioid molecules is achieved. Susceptive binding portions in opioid receptor might play discriminative roles on agonist or antagonist properties.[10] These tetracyclic benzomorphans with definite spatial stereochemistry might be useful pharmacological tools for the investigation of a true discriminating system of opioid receptor. Further studies are now in progress.

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