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# Thebaine as a Precursor of Opioid Analgesic Agents

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## Abstract

The review is devoted to discussing the world state-of-the-art in the development of selective narcotic analgesic agents of various structural types based on synthetic transformations of thebaine.

**Key words:** thebaine, analgesic agents, opioid receptors, pyrrolidinomorhinanes, sulphothebaine

## INTRODUCTION

Thebaine **1** represents a minor alkaloid of the opium poppy (*Papaver somniferum* L.) whose content in opium amounts to 0.2–1 % [1, 2]. The isolation of thebaine is included into the technological flow chart of opium processing [1]. Characterized as a spasmodic poison [2], thebaine exhibits no independent value for medicine. Nevertheless, with employing its manifold reactivity by chemical researchers, a number of compounds were obtained those have drawn attention of pharmacologists. Already at an early stage of studying the pharmacological properties of these thebaine derivatives they revealed promising agents those have taken root in medical practice within optimum time constraints. The interest in the compounds obtained via synthetic transformations of thebaine is persistent to this very day, too. By the present time a rather impressive library of the compounds synthesized basing on thebaine is accumulated that includes agonists and antagonists of opioid receptors (OR). As a credit side of experimental and clinical pharmacology one could consider both pharmaceutical preparations, and agents used in experimental practice those exhibit a high binding selectivity with respect to various types and subtypes of OR.

Entering into the consideration of the review material, it is appropriate to present some data concerning the opioid system of mammals and the characteristics of OR.

In the nervous system of humans and animals, the responsibility for pain perception and sensation is on so-called antinociceptive system, a complex multilevel formation, whose mechanisms are realized in all the parts of the nervous system, anywhere from the afferent input in a spinal cord to the cerebral cortex [3]. The system mentioned includes presynaptic enkephalin inhibitory receptors, wherewith oligopeptides such as endorphins and enkephalins) as well as others peptides (dynorphins, *etc.*) serve as neurotransmitters (mediators of nervous impulse transmission, which peptides contacting with OR have an analgesic effect [4]. The binding of narcotic analgesic agents with OR is caused by the fact that a certain part of the molecule of all the narcotic analgesic agents exhibits structural and conformational similarity to the tyrosine fragment of endorphin and enkephalin molecules. The endogenous opioid neuropeptides have the conformation structure

of the molecule strictly determined by the quaternary structure of a protein; therefore they influence only those OR which are of conformational similarity with respect to them.

The first concepts concerning OR are referred to 1950ths when the μ receptor whose activation caused morphine-induced analgesia and physiological drug dependence were for the first time classified. In 1960–1970ths pharmacological research *in vivo* resulted in revealing the existence of three more types of OR designated as kappa (κ), sigma (σ) and delta (δ) receptors [5–7]. In 1990th the genes were cloned those encode μ, δ and κ receptors (MOR-1, DOR-1, KOR-1, respectively). On the basis of insignificant pharmacological data several more types of OR were described (ε, ι, λ and ξ) those, however, nowadays are not attached with a particular importance [8]. In 1992 it has been demonstrated that the σ receptor does not belong to the opioid receptors, but it exhibits a greater affinity with respect to glutamate receptors [9].

The physiological effect mediated by the μ receptors is manifested in the form of supraspinal analgesia, euphoria, respiratory depression and physiological drug dependence; the κ receptors are connected with spinal analgesia, miosis and sedative effect; the δ receptors influence the reality perception (it is considered that these receptors play an important role in the pathogenesis of schizophrenia).

Four groups of opiates are distinguished depending on the selectivity of binding with respect to the receptors: full agonists, partial agonists, agonist/antagonists and full antagonists.

Full μ receptor agonists are traditionally used for acute pain therapy as well as within the postoperative period. Agonist/antagonists can cause withdrawal syndrome, as well as they can stop overdose phenomena. The analgesia and a number of other effects with their application are caused by the interaction with κ and δ OR, whereas the necessity to improve pharmaceutical preparations from this group is determined by the requirement for the further analgesia with minimizing serious side effects inherent in μ-agonists: respiratory embarrassment, tolerance with respect to analgesic effect and drug dependence. Full antagonists are employed for stopping the overdose phenomenon.

The problem of searching for novel selectively acting pharmaceutical preparations remains urgent up till now. Solving such problems is carried out with the use of specific standard tests generally accepted in the world pharmacology, both *in vitro* and *in vivo*. In particular, employing the radioligand binding method with the use of standard peptides those represent selective agonists for various OR types (DAMGO – MOR, U69593 – KOR, DPDPE – DOR) one can *in vitro* characterize the selectivity of their action.

Within the framework of *in vivo* experiments researchers are also employing the tests of response thresholds those allow them to estimate the action selectivity for novel substances. They include thermal stimulation such as "tail-flick" (TF) and "hot-plate"» (HP) tests, chemical stimulation such as "acetic writhing" (AW), "acetylcholine writhing" (AchW) and "phenylguanine writhing" (PhW), as well as electric pain stimulation vocalization test. Here the analgesic effect of opioid agents on a particular type of pain stimulation is mediated by the excitation of certain OR types and, hence, correlates with *in vitro* receptor binding. So, in order to inhibit thermal pain reactions it is necessary to involve μ receptors; in the TF test the analgesic effect is caused by agonists of d receptors. With blocking the response to chemical peritoneum stimulation the greatest activity is exhibited by agonists of κ receptors, though the activity can be mediated by all the subtypes of OR (μ, δ and κ) [10]. To all appearance, muscular rigidity such as the Straube syndrome inherent in narcotic analgesic agents is realized *via* μ OR activation [11].

Using a chemical structure principle for the classification of synthetic thebaine derivatives one could distinguish three basic types of the compounds:

– The compounds with conserved morphinane skeleton of the molecule;

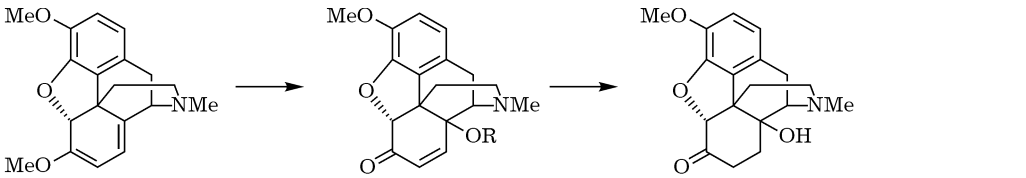
– The compounds containing an additional carbocyclic fragment;

– The compounds with an additional heterocyclic fragment.

**COMPOUNDS WITH CONSERVED MORPHINANE SKELETON**

From the standpoint of the progress in the pharmacology of opioid analgesic agents, one of the most successful thebaine transformations should be considered to consist in the oxidation to produce 14-hydroxycodeinone **2**, for the first time carried out by Robinson [2]. This compound, especially its dihydro derivative such as 14-hydroxydihydrocodeinone **3** have attracted special attention of researchers. This oxyketone **3** that is also known as oxycodone is accepted by the official pharmacopoeia as an anesthetizing remedy. This drug is recommended to use in combination with non-steroid anti-inflammatory remedies such as ibuprophen for pain syndrome elimination [12]. As far as the mode of activity is concerned, oxycodone represents a μ OR antagonist. Synthetic transformations of the oxycodone consist mainly in such procedures as the alkylation of hydroxyl groups, changing the substituent at the nitrogen atom, carbonyl group reactions, and the demethylation of 3-methoxy group. It should be emphasized that the latter operation of demethylation, as a rule, results in the formation of compounds having more valuable (in comparison with 3-methoxy derivatives) pharmacological properties. Of great interest and importance are 14-hydroxycodeine derivatives those represent esters. In particular, cinnamic acid ester **4** exhibits the activity 177 times higher than that of morphine [13].

Of particular interest are oxycodone derivatives modified at the nitrogen atom. A wide application in medical practice has been found by N-allyloxycodone, or naloxone **5** exhibiting the properties of competitive type OR antagonist [5]. The naloxone heads a whole series of morphine antagonists, exhibits paramount affinity with respect to μ receptors and κ receptors, with no morphine-like action. These properties of naloxone cause its application for reducing a sharp intoxication due to narcotic analgesic drugs, alcoholic coma and other states [13, 15–17]. Naloxone acetates **6–8** as the antagonists of respiratory depression caused *in vivo* by morphine are identical to the naloxone



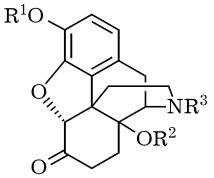
**1**



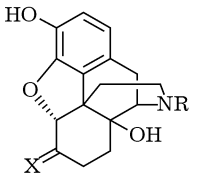
**2** R = H
**4** R = PhCH=CHCO



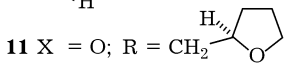
**3**



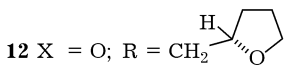
**5** $R^1 = R^2 = H$; $R^3$ = all
**6** $R^1$ = Ac; $R^2 = H$; $R^3$ = all
**7** $R^1 = H$; $R^2$ = Ac; $R^3$ = all
**8** $R^1 = R^2$ = Ac; $R^3$ = all
**9** $R^1 = R^2 = H$; $R^3$ = CPM



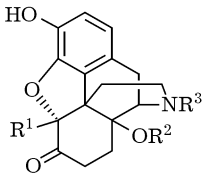
**10** X = OH, H; R = CBM



**11** X = O; R = $CH_2$

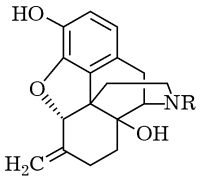


**12** X = O; R = $CH_2$



**13** $R^1 = H$; $R^2$ = Me; $R^3$ = CPM
**14** $R^1 = H$; $R^2$ = Me; $R^3$ = all
**15** $R^1 = H$; $R^2$ = Et; $R^3$ = all
**16** $R^1 = H$; $R^2$ = Et; $R^3$ = CPM
**17** $R^1 = H$; $R^2 = H$; $R^3$ = CBM
**18** $R^1 = H$; $R^2$ = Me; $R^3$ = CBM
**19** $R^1$ = Me; $R^2 = H$; $R^3$ = all
**20** $R^1$ = Me; $R^2 = H$; $R^3$ = CPM
**21** $R^1$ = Me; $R^2$ = Et; $R^3 = (CH_2)_2Ph$

all –allyl
CPM –cyclopropylmethyl
CBM – cyclobutylmethyl



**22** R = all
**23** R = CPM

Scheme 1.

itself, but they demonstrate a much more prolonged action [18].

Naltrexone **9** contains a rather remarkable cyclopropypmethyl substituent at nitrogen atom determining valuable pharmacological properties of the naltrexone and of many its derivatives. Naltrexone represents a pure OR antagonist. Having a higher analgesic activity in comparison with naloxone, the naltrexone can be orally introduced [4], whereas naloxone is active only under parenteral introduction, and the time of its action is shorter as compared to the duration of naltrexone action.

Nalbuphine **10** containing a cyclobutylmethyl substituent is determined as a highly active analgesic agent with a low level of respiratory distress syndrome [19] (Scheme 1).

The dependence of pharmacological properties on the configuration of a substituent at the nitrogen atom has been demonstrated by the example of stereoisomeric agents **11** and **12**. So, *R*-isomer **11** manifests itself as a powerful agonist of opioids surpassing morphine in activity ($ED_{50}$ = 0.02 and 0.5 mg/kg for compound **11** and morphine, respectively), whereas *S*-isomer **12** demonstrated no agonistic properties [20].

The alkylation of 14-hydroxy group in the molecules of nanoxone and naltrexone resulting in the formation of compounds **13–16** has revealed somewhat other properties of these compounds. All these agents *in vivo* (the Straube test for rats) have manifested themselves as pure opioid antagonists [21, 22]. Compound **13** received the name Cyprodime [21] represents a non-peptide specific antagonist width respect to μ receptors that quenches respiratory depression in dogs caused by sufentanyl [14]. Quaternary salts of naloxone and naltrexone **14** and **16** demonstrate themselves as antagonists acting mainly through the peripheral system [23].

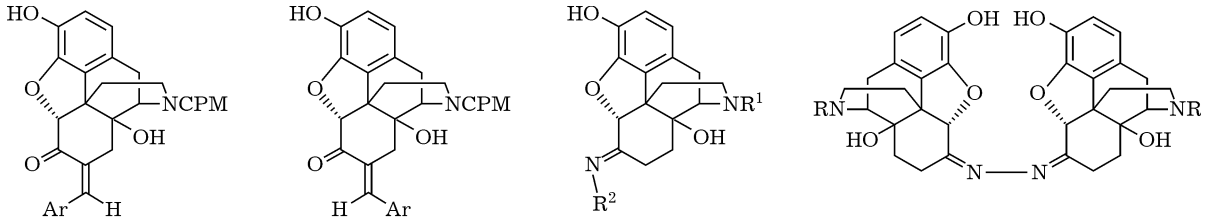
Alkoxymorphinanes with the cyclobutylmethyl group at the nitrogen atom such as **17** and **18** represent partial opioid agonists [21].

The introduction of $C_5$ methyl groups into naloxone and naltrexone molecules has allowed researchers to obtain agents **19** and **20** those exhibited the properties of partial OR agonists. So, the ability of agent **19** for binding with μ receptors is six times less than that parameter for naloxone, at the same time it exhibits an identical (as compared to naloxone) affinity with respect to κ receptors. Agent **20**, being the antagonist of analgesia induced by morphine is characterized by an order of magnitude lower activity in comparison with naltrexone [24]. Compound **21** not only differing in a substituent at the nitrogen atom, but also containing alkyl groups, has exhibited a high affinity with respect to μ and to δ receptors as well as a lowered affinity with respect to κ receptors [25].

Modifying due to the reactions of the carbonyl group allowed researchers to obtain promising agents. So, the methylenation of naloxone and naltrexone has resulted in the obtaining of compounds **22** and **23**; compound **22** demonstrated an identical activity with respect morphine. The second compound known as nalmephene **23** represents a universal opioid antagonist demonstrating the highest affinity with respect to κ receptors [26–28]. The nalmephene acts at oral introduction and it is offered as a remedy for treating the consequences of backbone injury [29–31].

Derivatives of 7-arylidenenaltrexone are described. For example, 7-benzylidenenaltrexone **24** shows itself as an antagonist of $\delta_1$ receptors [32–34]. An influence of geometrical isomerism upon the activity of these compounds has been studied to demonstrate that *Z*-isomers **25** exhibit much higher affinity with respect to δ receptor binding than *E*-isomers **26**.

A number of interesting agents were obtained *via* the introduction of nitrogen-containing groups. For example, the derivative of N-allylhydroxycodeinone oxime **27** has manifested itself as an analgesic agent with a prolonged action [14]. Simple transformation of oxymorphone, naloxone and naltrexone has allowed researchers to obtain rather remarkable agents. So, naloxazone **28** and naltrexazone **29** being pure antagonists, during more than 1 day are quenching the analgesia caused by morphine in the experiments in mice. Naloxazone has been as a reagent for research, since it is capable of binding with μ receptors during 3 days. Oxymorphazone **30** exhibits the properties of a prolonged action agonist in the TF model [35, 36]. Oxybenzoylhydrazone of naloxone **31** is determined as an agonist with respect to all the types of OR, however it demonstrates the



**24** Ar = Ph
**25** Ar = 1-, 2-naphtyl

**26** Ar = 1-, 2-naphtyl

**27** $R^1$ = all; $R^2$ = $OCH_2CO_2H$
**28** $R^1$ = all; $R^2$ = $NH_2$
**29** $R^1$ = CPM; $R^2$ = $NH_2$
**30** $R^1$ = Me; $R^2$ = $NH_2$
**31** $R^1$ = all; $R^2$ = $NHCOC_6H_4OH$

**32** R = all
**33** R = CPM

Scheme 2.

greatest affinity to κ receptors stimulating the binding of guanosine-5′-O(3-[$S^{35}$]-thio)-triphosphate and inhibiting the formation of cyclic adenosine monophosphate. Irreversible OR blockers those 20–40 times surpass the effect of hydrazones **28** and **29** in the experiments *in vitro,* are naloxonazine **32** and naltrexonazine **33** [37] (Scheme 2).

Thus, simple modifications of naloxone allow one to extend the scope of agents influencing upon OR [38].

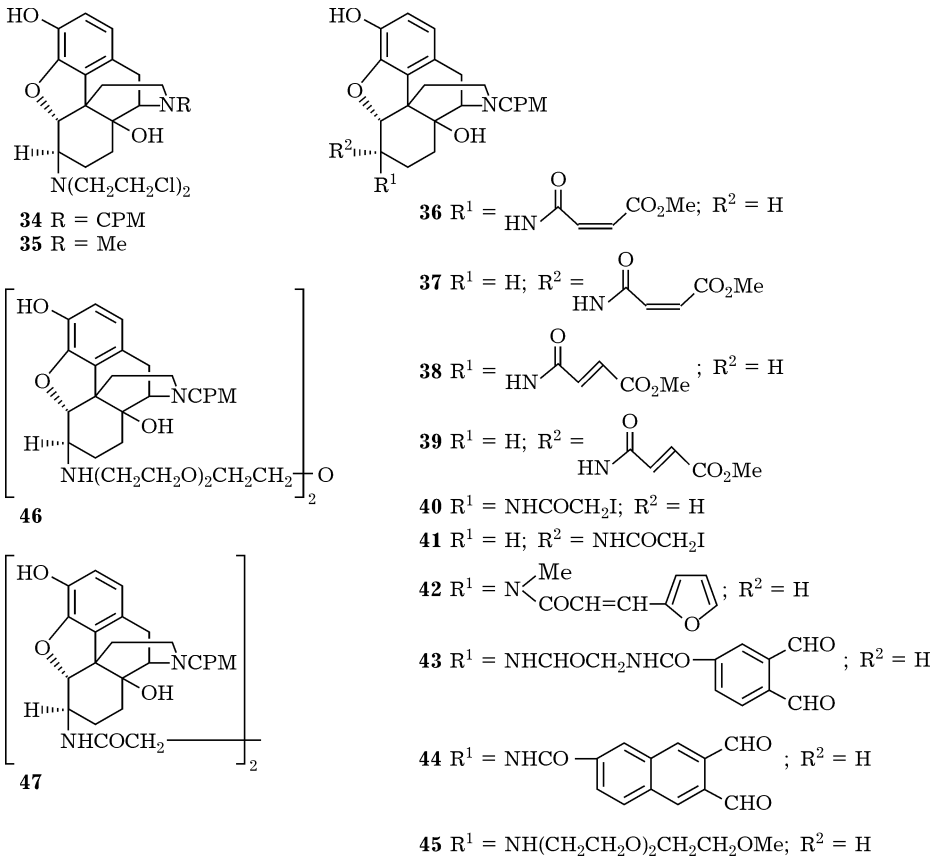
The synthesis of $C_6$ amino derivatives has allowed researchers to obtain a novel group of agents with a high affinity with respect to OR. One of them such as chloronaltrexamine **34** exhibits the properties of an irreversible opioid antagonist, whose prolonged action in the experiments with mice uses to last during 3–6 days [39–41]. This property is caused by the ability of chloronaltrexamine **34** to bind with receptors in a covalent manner due to a high reactivity of such a grouping as "nitrogenous yperite" [42]. The activity of this grouping determines also the fact that chloronaltrexamine is bound not only with μ receptors, but also exhibits the properties of δ and κ antagonists. Another agent such as chloroxymorphine amine **35** acts as an opioid agonist, whereas the presence of dichloroethyl group determines the irreversibility of its binding with receptors [42].

Basing on stereoisomeric naltrexamines researchers have synthesized amides of maleic **36**, **37**, fumaric **38**, **39** and iodoacetic **40**, **41** acids. The nature of substituents determines the ability of all the mentioned agents for the covalent binding with receptors [43, 44]. Agent **38** (funaltrexamine), in binding with phoshatidylinositolglycane (GPI), acts as its powerful reversible agonist, whereas in the experiments *in vitro* with ileum exhibits the properties of an irreversible antagonist with respect to μ receptors. The funaltrexamine is not inclined to binding with κ receptors. It is significant that stereoisomer **39** is passive with respect to μ receptors [45]. In a similar manner as fumarates, the binding of maleates **36** and **37** with receptors depends on their stereochemistry. Iodoacetates **40** and **41** irreversible quench the action of morphine.

As known, analgesic agents with specific action in regard to κ receptors belong to especially promising remedies since they demonstrate minimal physical drug dependence and do not inhibit respiration Amide **42** being under clinical trials in Japan and Europe is attributed to κ receptor agonists [46–48]. There are describe μ receptors binding ligands such as **43** and **44** intended for the use in fluorescent methods [49]. In particular, agent **44** provides an especially high sensitivity in the detection of opioids bound with receptors.

Monovalent ligand **45** and bivalent ligand **46** containing polyester fragments are not morphine antagonists; however, the bivalent ligand **46** is an order of magnitude more active than the former as an antagonist of κ receptors. Among bivalent amides there is a highly active morphine antagonist is presented by succinate **47** [50] (Scheme 3).

The replacement of 14-hydroxo groups by various substituents has allowed researchers to obtain a number of interesting compounds [51–54]. So, 14-β-ethylmorhinone **48** is 117 times more active as compared to morphine [51], the antinociceptive activity of ketone **49** is 10 000 times higher than the antinociceptive activity




Scheme 3.

of morphine, and azide **50** is 5000 times more active than morphine in the TF test [52, 53].

In this group of thebaine modifications of the greatest interest were the derivatives of 14-aminocodeinone. The amides of 4-chlorocinnamic acid **51** and **52**, known as clocinamox and methoclocinamox, respectively, manifest themselves as irreversible antagonists of μ receptors [55, 56]. Agent **52** is considered to be a prospective remedy for the treatment of opiate drug dependence. Relative in structure agents **53** and **54** belong to the same group of selective μ antagonists; the second of them exhibits a greater selectivity with respect to μ receptors [57, 58].

Pharmacological properties of O-alkyl derivatives of clocinamox **55–60** were investigated. In the experiments with rats it has been established that esters **55–57** exhibit a high binding activity with respect to μ receptors similar to the initial agent **51**; the μ affinity of ester **60** five times exceeds the μ affinity of phenol **51**, and for ethers **58** and **59** the affinity with respect to these receptors is very low. To judge the esters as the agonists of δ and κ receptors, the mentioned property is less pronounced by them as compared to phenol **51**. Ester **59** having the lowest μ affinity in this series exhibits the highest κ affinity. A more detailed *in vivo* investigation of esters **57** and **60** has demonstrated that they act first as μ selective agonists, and then they manifest themselves as morphine antagonists [59].

Recent publications are devoted to the studies on the influence of the structure of clocinamox and methoclocinamox derivatives upon their activity [60, 61]. It has been shown that such properties as analgesic action, antagonistic and agonistic activity determined *in vivo*, in many respects depend on the nature and location of substituents in the aromatic ring of amides **61–64** [61]. In the TF test with mice the greatest activity as μ-agonists was demonstrated by compounds **61**, containing substituents 2-$CH_3$, 2-Cl, 4-$NO_2$. Powerful morphine antagonists are presented by compounds **62**

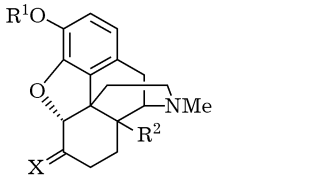
($R^3$ = 4-$CH_3$, 4-Cl, 4-$NO_2$). According to the characteristics of analgesic action compounds **63** ($R^3$ = H, 4-Cl, 2-$CH_3$) and **64** ($R^3$ = 4-$CH_3$) have been chosen as promising agents. Agent **65** (X = $COCH_2$) being a μ agonist exhibits a 10 times higher analgesic effect at a doze of 1 mg/kg in comparison with morphine, its action proceeds during 1 day [60]. Compound **66** is considered to bind with μ receptors due to the interaction with sulphohydryl groups of receptors [62, 63].

Disulphides **67–70** have demonstrated difference in binding with receptors. So, agent **67** is not bound with κ and δ receptors, whereas agent **68** moderately inhibits κ binding and slightly inhibits δ binding. Compounds **69** and **70** inhibit μ, κ and δ binding [64, 65] (Scheme 4).

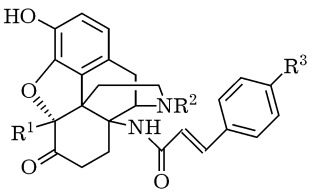
Of interest are oxycodone derivatives containing no keto group, as well as agents with a cleaved oxide ring. In medical practice a wide application has been found by buthorpphanol (moradol) **71** belonging to the group of OR antagonists/agonists. Having a high analgesib activity, moradol acts at smaller dozes than morphine. A remarkable feature of this analgesic agent prescribed to quench severe pain consists in its low narcogenous potential: as compared to other narcotic analgesic agents it causes considerably weaker drug dependence. Among the derivatives with cleaved 4,5-oxide ring, agents **72** and **73** have manifested themselves as an agonist and an antagonist of opioids, respectively. The introduction of the methyl group results in the formation of compound **74** those shows itself as a partial agonist [66].

The activity of 14-methoxy derivatives **75–77** is 10 to 20 times higher than the activity of morphine [67]. Agent **75** with oral introduction is 10 times more active than morphine, introduced subcutaneously. Changing the structure of a substituent at the nitrogen atom results in obtaining full agonists **78** and **79** or partial agonists **80** and **81** [68]. Agent cyprodime **76** represents a pure and selective antagonist of μ OR differing from naloxone in a more favourable κ/μ and δ/μ ratio for binding selectivity [68, 69].

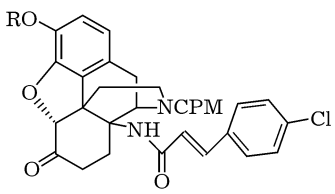
Among the derivatives of 3-hydroxycyprodime there are agents **82** and **83** distinguished with the selectivity ratio δ/μ > 400, as well as agent **84** with the value of κ/μ = 80 [70]. In a similar manner as cyprodime, O-benzyl derivatives **85** and **86** are characterized by a high δ/μ selectivity ratio [14]. The introduction of phenylethoxy group into $C_{14}$ position of cyprodime



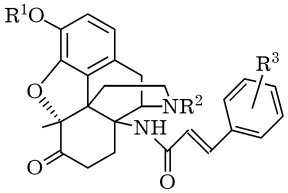
**48** $R^1$ = H; $R^2$ = Et; X = O
**49** $R^1$ = $R^2$ = Me; X = O
**50** $R^1$ = Me; $R^2$ = Et; X = 



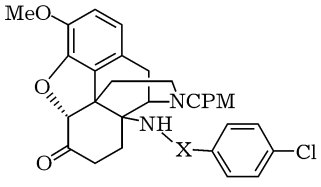
**51** $R^1$ = H; $R^2$ = CPM; $R^3$ = Cl
**52** $R^1$ = H; $R^2$ = Me; $R^3$ = Cl
**53** $R^1$ = Me; $R^2$ = CPM; $R^3$ = $NO_2$
**54** $R^1$ = $R^2$ = Me; $R^3$ = $NO_2$



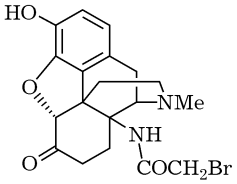
**55** R = all
**56** R = $CH_2CN$
**57** R = $CH_2CHMe_2$
**58** R = Pr
**59** R = *i*-Pr
**60** R = $H_2C$–C≡CH



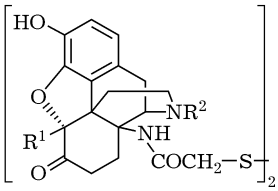
**61** $R^1$ = Me; $R^2$ = CPN
**62** $R^1$ = H; $R^2$ = CPM
**63** $R^1$ = $R^2$ = Me
**64** $R^1$ = H; $R^2$ = Me;
$R^3$ = Me, Cl, $NO_2$



**65** X = $COCH_2$, $CO(CH_2)_2$, $COCH_2CH$=CH

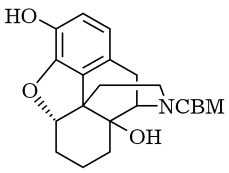


**66**

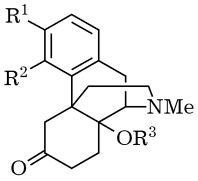


**67** $R^1$ = H; $R^2$ = Me
**68** $R^1$ = H; $R^2$ = CPM
**69** $R^1$ = $R^2$ = Me
**70** $R^1$ = Me; $R^2$ = CPM

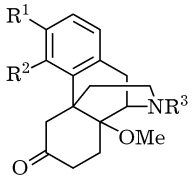
Scheme 4.



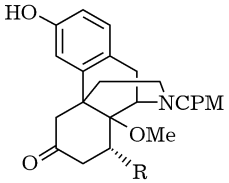
**71**



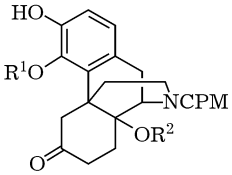
**72** $R^1$ = OMe; $R^2$ = H; $R^3$ = Me
**75** $R^1$ = $R^2$ = OMe; $R^3$ = Me
**76** $R^1$ = H; $R^2$ = OMe; $R^3$ = Me
**77** $R^1$ = $R^2$ = H; $R^3$ = Me



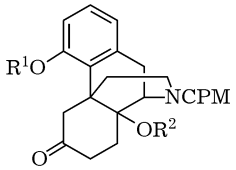
**78** $R^1$ = $R^2$ = H; $R^3$ = CBM
**79** $R^1$ = OMe; $R^2$ =H; $R^3$ = CBM
**81** $R^1$ = $R^2$ = OMe; $R^3$ = CBM
**80** $R^1$ = H; $R^2$ = OMe; $R^3$ = CPM



**73** R = H
**74** R = Me



**82** $R^1$ = Bn; $R^2$ = Me
**83** $R^1$ = $R^2$ = Me
**84** $R^1$ = Me; $R^2$ = Et
**85** $R^1$ = Me; $R^2$ = Bn



**86** $R^1$ = Me; $R^2$ = Bn
**87** $R^1$ = H; $R^2$ = $Ph(CH_2)_2$
**88** $R^1$ = Me; $R^2$ = $Ph(CH_2)_2$

Scheme 5.

has resulted in the formation of derivatives **87** and **88** those manifest themselves as an antagonist and an agonist with respect to κ receptors, respectively [71]. The activity of compound **87** as an analgesic agent is 21 times higher than the activity of morphine in the HP test, 38 times higher in the TF test and in 300 times higher in the phenylquinone chemical stimulation test (Scheme 5).

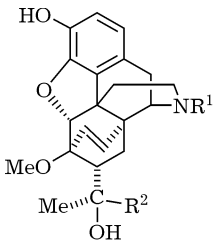
## COMPOUNDS CONTAINING AN ADDITIONAL CARBOCYCLIC FRAGMENT

Diene synthesis with the participation thebaine and dienophiles with different structure has become a basis for obtaining extensive series of compounds containing the structural fragment of bicyclo[2,2,2]-octane. Pioneering works by K. Bently in this direction stimulated the revealing of agents with outstanding pharmacological properties as well as the development of practically important analgesic agents [72, 73].

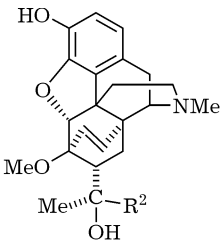
A series of the tertiary alcohols **89** differing in the structure of substituents at the nitrogen atom of and in the lateral chain should be considered as agents of special value. One of them such as ethorphine **90** has an extremely high activity as agonist 8600 times exceeding morphine in analgesic action. However its application in medicine appeared impossible since, having a very low therapeutic index, this substance severely inhibits respiration and stimulates narcotic drug dependence [74]. The ethorphine is used in veterinary science, in particular in order to narcotize large animals in reserves for moving them.

The influence of the structure of a substituent in the lateral chain and the configuration can be judged from analgesic activity of agents **91–94**. So, the action of compounds **91–93** 4–10 times exceeds the effect of morphine. Stereoisomer **94** is 187 times more active than morphine [75]. Tertiary alcohols of such a structure as **95** and **96** appeared less active ($ED_{50}$ for these compounds in the TF test amounts to 0.35 and 0.0028 mg/kg, respectively) [76]. Non-substituted derivative **97** manifests itself as an opioid agonist which has 40 times higher analgesic activity than morphine, whereas its N-cyclopropyl derivative **98** is pure OR antagonist [77].

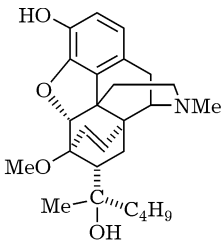
As seen by the example of agent **99,** the saturation with oxygen-containing groups results in an increase in toxicity. As far as the toxicity is concerned, base **99** and its hydrochloride **99** · HCl are comparable with fentanyl ($LD_{50}$ = 60 mg/kg). The base exhibits an especially high activity in the models of chemical (AW) and thermal (HP) stimulation, whereas



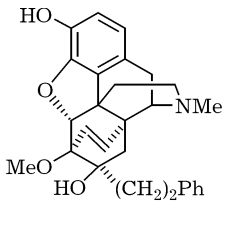
**89** $R^1$ = alk, all, CPM, $CH_2CH{=}CMe_2$, $H_2C{\equiv}C{-}CH$, $R^2$ = alk, Ph, Bn, $Ph(CH_2)_2$



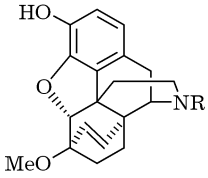
**90** R = Pr
**91** R = Me
**92** R = $CH_2OH$
**94** R = *n*-Bu
**96** R = $(CH_2)_2Ph$



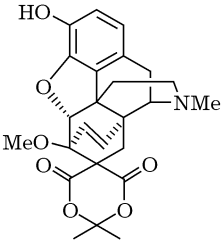
**93**



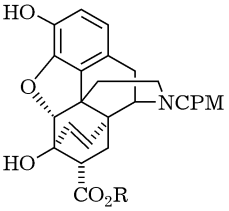
**95**



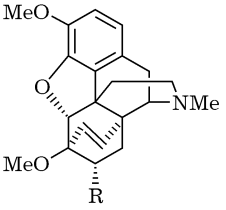
**97** R = Me
**98** R = CPM



**99**



**100** R = Et
**101** R = *n*-Bu



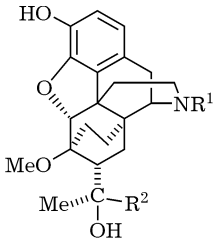
**102** R = $NR'_2$
**103** R = $CH_2NR'_2$
**104** R = $NHCOCH{=}CHCO_2Me$

Scheme 3.

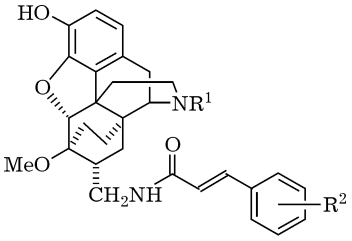
in the model of electric pain stimulation it is characterized by the therapeutic index value identical to fentanyl. In TF model describing selective binding with δ receptors, a high level of activity has been demonstrated by hydrochloride, whereas in the AW test its therapeutic index appeared five times higher than the therapeutic index value for fentanyl. Agent **99** does not eliminate the action of morphine upon locomotor activity; therefore it can be reliably attributed to the group of μ receptor agonists. Hydrochloride **99** · HCl belongs to this series, too [78, 79].

Noteworthy is the dependence of pharmacological properties on an insignificant, at first sight, changing in the structure. So, ethyl ether **100** is an antagonist, whereas butyl ether **101** is powerful opioid agonist [80]. Amine derivatives **102** and **103** are yielding to tertiary alcohols in analgesic activity [81, 82]. Fumaramide **104** has manifested itself to be an irreversible inhibitor of δ receptors [83] (Scheme 6).

*Via* hydrogenation of the double bond in the endo-ethene bridge a novel group of highly active analgesic agents has been obtained. Dihydroethorphine **105** belongs to a series of μ receptor activators [84–86]. A powerful antagonist of opioids is presented by diprenorphine **106** which is used in experiments *in vivo* (in-



**105** $R^1$ = Me; $R^2$ = Pr
**106** $R^1$ = CPM; $R^2$ = Me
**107** $R^1$ = CPM; $R^2$ = *t*-Bu



**108** $R^1$ = Me; $R^2$ = 2-Me, 2-Cl, 4-Me, 4-Cl, 4-$NO_2$
**109** $R^1$ = CPM; $R^2$ = H, 4-Me, 4-Cl, 4-$NO_2$

Scheme 7.

cluding primates) with the application of radioligand compounds [87]. Potentialities have been demonstrated concerning its use for the diagnostics of diseases in humans [88] (Scheme 7).

To all appearance, the most important achievement in the thebaine modification direction under discussion could be considered to consist in the development of the preparation such as buprenorphine **107**, whose analgesic

action is much higher as compared to morphine effect. The duration of buprenorphine action in sublingual introduction amounts to 8 to 12 h. The scope consists in acute pain elimination within postoperative period, connected with traumas, oncological diseases as well as other pain syndromes [13]. The buprenorphine has been qualified as a partial μ agonist and antagonist with respect to κ and δ receptors [89, 90].

In the two types of experimental models within the framework of *in vitro* and *in vivo* experiments, amides of cinnamic acid **108** have manifested themselves as μ receptor antagonists capable of binding with κ receptors. Their activity is comparable to the activity of naltrexone [91]. Analogues **109** also belong to analgesic agents of prolonged action, which has been demonstrated in the TF model [92, 93].

The derivatives of endo-ethenothebaine with a more complicated structure were obtained *via* diene synthesis with the participation of 1,4-benzoquinones. The first data concerning the analgesic activity of these compounds are referred to 1956, when it has been established that agent **110** exhibits as much as 1/7 of the activity of morphine [94, 95]. It is significant that the activity of agent **111**, whose structure differs from **112** in the absence of the keto groups and double bond in an additional cycle, is 1000 times higher than the activity of morphine [96, 97].

The agents of this group studied in the series of works [78, 79, 97–101] could be conventionally divided into three structural types. Compounds **113–118** belong to the first type, and first of them due to the oxidizing potentialities of an organism *in vivo* can be conversed into hydroquinone **114** containing the quaternized nitrogen atom occurring rather seldom among the derivatives of thebaine. The second type includes compounds with cleaved oxide ring such as **119–124.** The third type is presented by the products of the flavothebaone rearrangement **125–127** and their hydrochlorides. The special place is occupied by polycyclic compound **128**, whose testing has demonstrated a possibility of complicating the structure of opioid with the preservation of a target kind of activity.

All the compounds belong to moderately toxic substances ($LD_{50}$ = 570–3200 mg/kg). With passing from bases to hydrochlorides a decrease in toxicity is observed, except for compound **117**, whose hydrochloride **117** · HCl is three times more toxic than corresponding base. The reduction of toxicity is also observed with the quarternization of nitrogen atom (compound **114**). A triple increase in toxicity is observed in passing from sulphide species to sulphone species (compounds **113** and **115**).

In the studies on analgesic activity in the AW visceral pain model, such agents as **118**, **125**, **126**, **133** were distinguished among those the first three ones completely quenched painful reactions. In the HP model the effect of compounds **113**, **114**, **116**, **117** · HCl, **119**, **124**, **125** · HCl and **128** is the most noteworthy, which effect appeared on the average twice higher than the reference value. In the TF test a high activity was demonstrated by agents **115**, **118**, **123**, **125** · HCl, **126** · HCl and **127** · HCl.

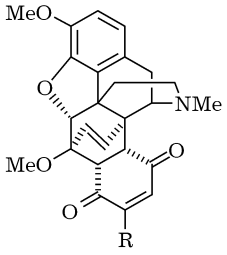
Agent **118** demonstrated a high analgesic activity in all the four models (*i.e.* in the electrical pain stimulation, HP, TF and AW tests) has been determined to be the most promising. The similar universality of action represents a phenomenon rather scarcely occurring among narcotic analgesic agents. Due to the ability to eliminate pain of all types (both physical and visceral) and a low toxicity ($LD_{50}$ = 3200 mg/kg) this substance is much more preferable as compared to morphine ($LD_{50}$ =1645 mg/kg). The latter, being the agonist of μ receptors, uses to eliminate pain caused by thermal (the HP test) and chemical (the AW test) stimulation. The ability of compound **118** to inhibit both thermal and chemical pain reactions allows one to assume its binding with μ, δ and κ receptor subtypes. The range of the agent **118** action is 18 times greater than this parameter for morphine in the model of electric pain stimulation and six times greater than that for the AW model testing. As opposed to morphine this agent insignificantly changes the rhythm of cardiac beat and does not influence the bronchial tonus in cats and the respiratory amplitude in rabbits. Basing experimental data including the results of neurotropic action investigation, the agent **118** is considered to belong to morphine agonists.

A high activity in the three models was exhibited by compound **119**, **122** and **126** · HCl,

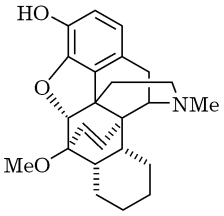
in this case the first and third of them quench the physical pain, and the second eliminates the thermal and chemical influence upon animals. Samples **115**, **125** · HCl, **126** and **128** have appeared active in two models, and sample **126** eliminates both physical and visceral pain manifesting itself as an agonist of μ receptors. Among the agents those have demonstrated a high activity in one model, one can note compounds **125** eliminating the visceral pain (which is inherent in κ receptors), and **127** · HCl that exhibits an activity as the agonist of δ receptors only in the TF test.

Selective reagents with respect to δ receptors are, in particular, spirane type ketones. So, agent **129** is qualified as the first non-peptide agonist of $\delta_1$ receptors which acts only in the TF test, seven times being higher in the antinociceptive activity than the activity of the standard enkephaline DPDPE. Naltrexone derivative **130** represents a powerful and selective δ antagonist [103, 104].

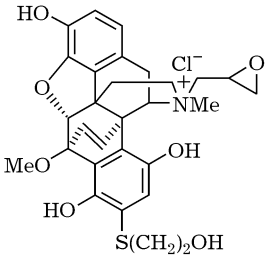
Antagonists of $\delta_1$ OR have been in particular presented by agents **131** and **132**, and agent **132** at intravenous introduction to animals acts at a doze of 10 nmol [105]. Homospirane agents **133** and **134** have demonstrated such a combination of properties, as high affinity with respect to δ receptors and antagonism with respect to μ receptors [106] (Scheme 8).



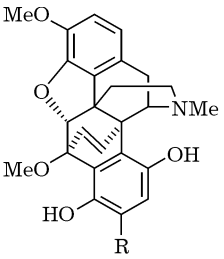
**110** R = H
**112** R = $S(CH_2)_2OH$



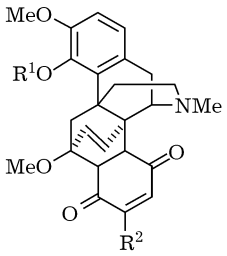
**111**



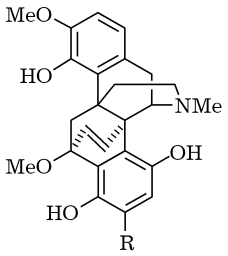
**114**



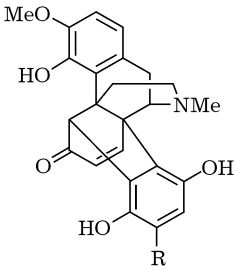
**113** R = $S(CH_2)_2OH$
**115** R = $SO_2(CH_2)_2OH$
**116** R = $SCH_2CO_2H$
**117** R = $SCH_2CH(NH_2)CO_2H$
**118** R = NHCOMe



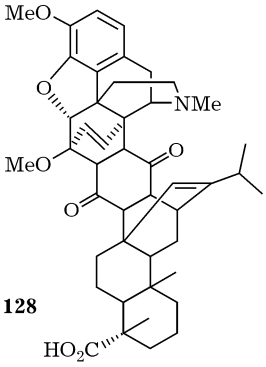
**119** $R^1$ = H; $R^2$ = NHCOMe
**120** $R^1$ = Ph; $R^2$ = NHCOMe
**121** $R^1$ = H; $R^2$ = $S(CH_2)_2OH$
**122** $R^1$ = H; $R^2$ = $SCH_2CO_2H$



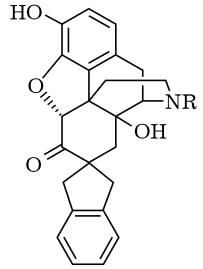
**123** R = $SO_2(CH_2)_2OH$
**124** R = $SO_2CH_2CO_2H$



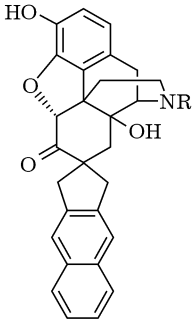
**125** R = NHCOMe
**126** R = $S(CH_2)_2OH$
**127** R = $SCH_2CO_2H$



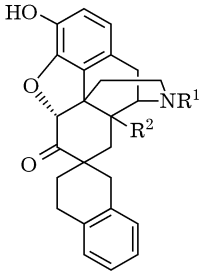
**128**



**129** R = Me
**130** R = CPM



**131** R = CPM
**132** R = Me



**133** $R^1$ = Me; $R^2$ = H
**134** $R^1$ = CPM; $R^2$ = OH

Scheme 8.

**COMPOUNDS WITH AN ADDITIONAL HETEROCYCLIC FRAGMENT**

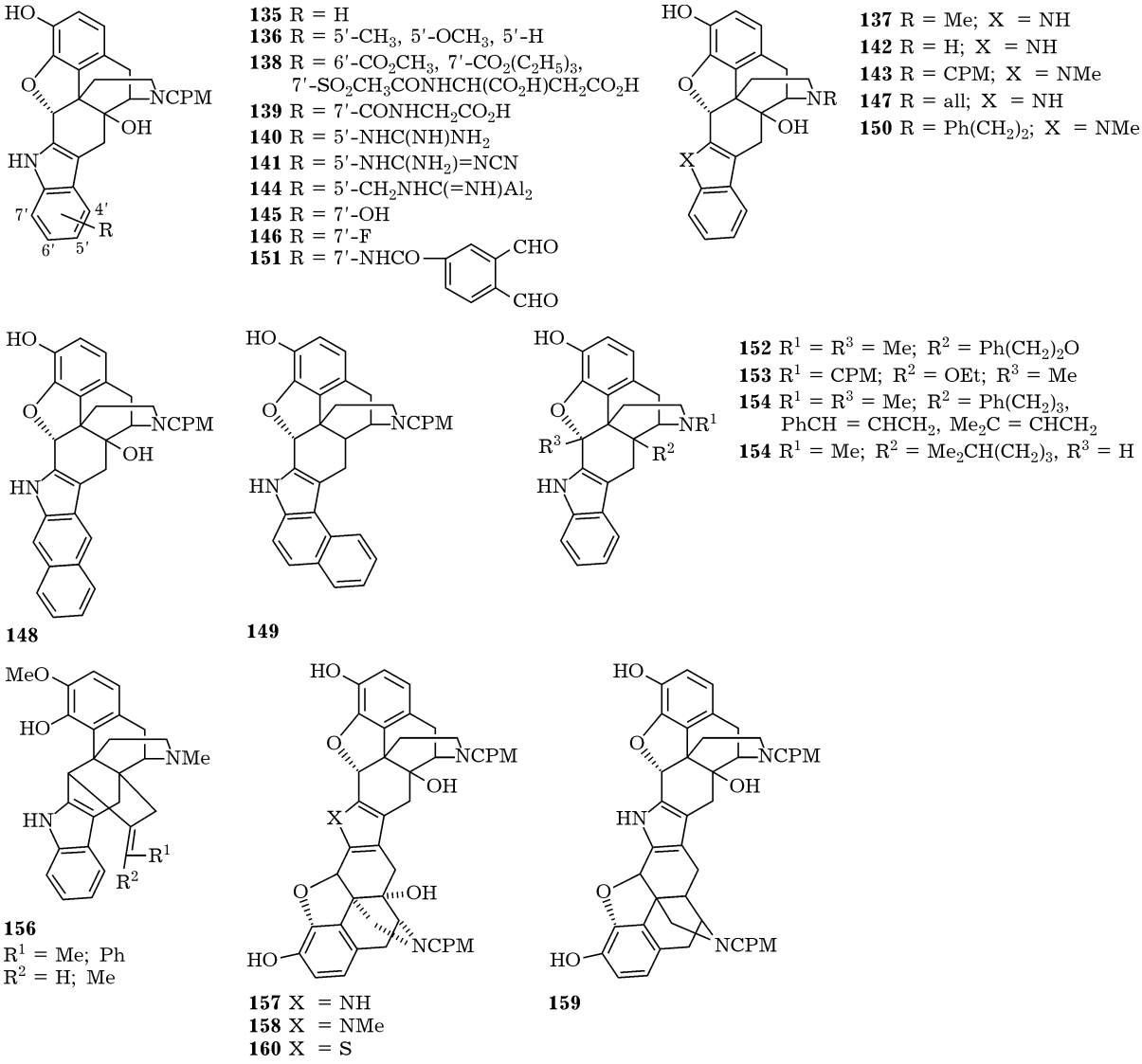
Thebaine derivatives containing additional heterocyclic fragments may be divided into two basic groups according to the principle of their synthesis. The first group includes the compounds obtained *via* heterocyclization of oxycodone and its analogues. The second group is presented by the derivatives of endoethene series, the products of thebaine diene synthesis with hetrodienophils.

Among the compounds of the first group a particular attention is attracted by indoles. Interesting results were obtained in the studies on natrindole **135** and its derivatives referred to so-called competitive antagonists [107–114]. The introduction of various substituents into the aromatic ring of the indol fragment of natrindole has allowed the researchers to vary activity of these compounds within a wide range. Natrindol differs from naloxone in the ratio between receptor binding selectivity values [115]. So, the μ/δ and κ/δ ratio values for natrindole are equal to 152 and 231, respectively, whereas for naloxone these parameters amount to 0.06 and 0.4, respectively. Natrindol has exhibited a high antitussive action upon experimental animals. Natrindol itself and its derivatives **136** are determined as high-power selective δ OR antagonists. It is significant that N-methyl natrindole analogue **137** is manifested as δ agonist [108]. In the *in vitro* experiments 6- and 7-substituted natrindole derivatives **138** have exhibited higher antagonism with respect to δ receptors. The introduction of amide substituents at C7' has resulted in the formation of the δ antagonists poorly influencing upon the central nervous system [116]. A high selectivity with respect to δ receptors was demonstrated by agent **139**. Noteworthy is an effect observed due to the introduction of guanidine type substituents at C5' atom (agents **140**, **141,** and **144**) [117]. Provided agent **140** is close to natrindole according to κ/μ and κ/δ binding selectivity ratio values (208 and 199 respectively), then for agent **141** these ratio values amount to 5 and 3, respectively. An abrupt reduction of κ/μ and κ/δ ratio values as compared to natrindole was noted for nor- (**142**) and N-methyl-(**143**) derivatives [108, 112]. The same series of agents with moderate of κ/μ and κ/δ ratio values (10–24 and 62–93, respectively) includes 5'-guanidyl natrindoles **144** [112]. High κ/μ and κ/δ ratios (264 and 595, respectively) are inherent in 7'-oxynatrindole **145** and agents **146** (κ/δ = 951) and **157** (κ/μ = 655). Passing to the structures with a modified indole fragment has resulted in obtaining agents such as **148** and **149** with a distinctly lowered binding selectivity ratio [109]. Agent with phenylethyl substituent at the nitrogen atom such as **150** shows itself as a selective antagonist of δ receptors with a minimal analgesic effect [110].

A lot of modified indole agents are described in [118, 119, 116]. Among them dialdehyde **151** is noteworthy that has been obtained with the purpose of studying the receptor binding by means of fluorescent methods [118]. Alkoxy derivatives **152** use to act as selective δ antagonists, whereas compounds **153** represent partial δ agonists [119]. For 14-alkyl derivatives the authors have presented the relationship between the action and the substituent at $C_5$. So, for derivatives **154** the binding ratio κ/δ varies within the range of 2.7–8.6, whereas the μ/δ binding ratio ranges within 0.21–4.9. For compound **155** these ratio values demonstrate an increase up to 101 and 88, respectively [119]. Indole-based derivatives **156** exhibit the action of κ selective ligands [116].

The authors of [105, 120–124] described the synthesis and pharmacological properties of bivalent ligands **157** and **158** those have been determined as selective antagonists of κ receptors. In particular, it has been demonstrated that for agent **157** κ/μ = 400, κ/δ = 250. The replacement of a substituent at the nitrogen atom by the allyl group, as well as the oxy group acetylation has resulted in the formation of agents such as **159** with the activity being equal or slightly higher as compared to the activity of compound **157 [**121**]**. The introduction of other substituents does not result in any improvement of the properties [105]. The parameters of thiophene analogue **160** are close to the parameters of pyrrole derivatives **157** [122] (Scheme 9).

The derivatives of benzofuran **161** belong to the antagonists of δ receptors, and 6'-methoxy substituted derivative **162** differs in high selectivity. Agent **163** is notorious by active




Scheme 9.

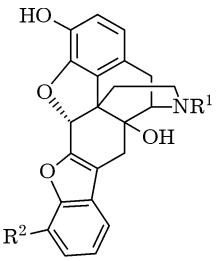
binding with all the three kinds of receptors [101, 111, 125, 126].

Among pyrrolomorphinanes described one can distinguish pyrrolonaltrexon **164**, that represents a μ selective ligand with a lowered antagonism with respect to δ OR [110, 121] characterized by a low selectivity ratio for receptor binding ($\delta/\mu = 0.03$, $\delta/\kappa = 0.17$) [127]. Low selectivity ratio values (0.2–1.0) are also inherent in another substituted pyrrole derivative such as agent **165**. Compound **166** is determined as a selective δ antagonist which inhibits the convulsive effect induced by δ antagonists [128].

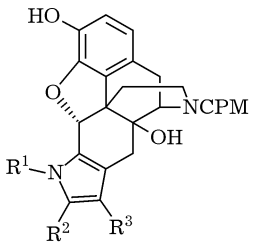
Synthesis and pharmacological properties of pyridomorphinanes were described in [32, 129]. It has been demonstrated that a low selectivity ratio $\mu/\delta$ (1.2–1.9) is exhibited by agent **167**. Among the derivatives of phenylpyridine the authors have emphasized agent **168** that demonstrated antinociceptive activity causing no analgesic tolerance under repeated application [32].

The derivatives of pyrimidinomorhinane **169** are characterized by a low selectivity ratio for receptor binding ($\mu/\delta = 0.31.5$, $\kappa_1/\delta = 0.7–1.7$) [125, 129].

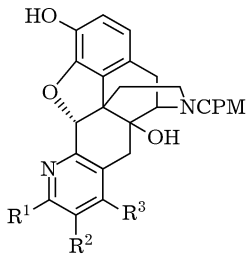
Compounds combining two structural types (**170**, **171** and **172**, **173**), the derivatives of furanobuprenorphine [59] were obtained. It has been established that agents **170** and **171** ex-



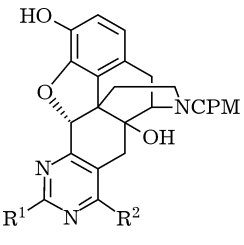
**161** $R^1$ = Me, CPM; $R^2$ = H
**162** $R^1$ = CPM; $R^2$ = OMe
**163** $R^1$ = CPM; $R^2$ = OH



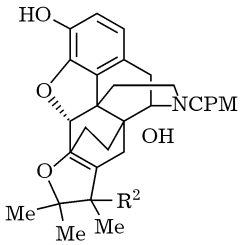
**164** $R^1 = R^2 = R^3$ = H
**165** $R^1$ = H; $R^2$ = CPM; $R^3$ = Ph
**166** $R^1$ = Bn; $R^2$ = H; $R^3$ = Ph



**167** $R^1 = R^2 = R^3$ = H
$R^1$ = Me; $R^2$ = H; $R^3$ = Ph
**168** $R^1 = R^3$ = H; $R^2$ = 4-Cl-$C_6H_4$



**169** $R^1 = R^2$ = H
$R^1$ = Me; $R^2$ = H
$R^1$ = Ph; $R^2$ = H
$R^1$ = Me; $R^2$ = Ph



**170** $R^1 = R^2$ = Me
**171** $R^1$ = Me; $R^2$ = H
**172** $R^1$ = CPM; $R^2$ = H
**173** $R^1$ = CPM; $R^2$ = Me

Scheme 10.

hibit μ selectivity, whereas agents **172** and **173** demonstrate the affinity with respect to κ and is shown δ receptors (Scheme 10).

The analgesic agents deserving attention were revealed among the derivatives of 6,14-*endo*-etheno-7,8-pyrrolidinemorphinane **174–196** [130–132]. These agents divided into three groups according to a chemical structure principle have allowed the researchers to reveal a number of the features connecting the analgesic activity with the structure.

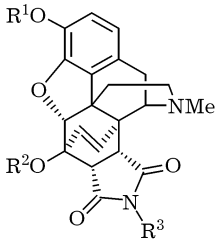
The first group of compounds is presented by the derivatives N-substituted 6,14-endo-etheno-7,8-pyrrolidinedione. The basic agent of this group **174** in all the three tests (such as AW, HP, and TF) not only demonstrated no activity, but also caused an effect of hyperalgesia in the HP test. To all appearance, this agent is of no interest as an analgesic one, but it is worthy of notice as the agent causing the sensitization of nociceptive afferents (an increase in excitability) with respect to injuring mechanical and thermal stimuli [133].

The introduction of bromine atom into the phenyl substituent has resulted in an acute increase in the analgesic activity of agent **175** in the AW test up to a level exceeding the activity of morphine. The presence of two methylene groups between the nitrogen atom and the phenyl fragment of agent **190** has resulted in the activity reduction in the AW test, however, as opposed to agent **175**, a tendency has outlined towards amplifying the activity in the HP and TF tests. The introduction of the 4'-hydroxy group (agent **192)** has resulted in the amplification of hyperalgesic effect in the thermal stimulation (HP and TF) tests. Shortening the carbon chain between the nitrogen atom and the phenyl ring with simultaneous introducing the 4'-methoxy group (agent **179**) allowed the researchers to achieve only a 50 % activity of agent **175** in the AW test. In addition, the excitability of nocireceptors with respect to thermal stimulus in the HP and TF tests decreased. The compound **183** characterized by the presence of the oxymethyl group in the substituent at the nitrogen atom, has appeared to be an active promotor causing the excitability of nociceptive afferents to be increased in the AW test. To all appearance, the novel structural fragment plays a key role determining the interaction with receptors.

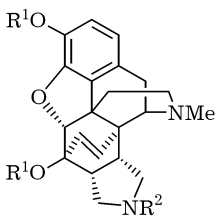
The substitution of the methoxyl groups by hydroxyl ones at $C_3$ и $C_6$ has resulted in a 3.5-fold reduction of the analgesic activity in the AW test for the pair of debrominated ana-

logues **174** and **176**. The presence of the bromine atom in the pair of **175** and **178** has allowed one to save the activity of agent **178** though the latter activity appeared twice lower than the activity of its dimethoxy analogue **175**. Compound **181**, the derivative of compound **180**, has the same structural feature as the oxy group at $C_6$. Together with the carbonyl group of the pyrrolidine fragment this oxy group could promote a selective binding with the receptors, which is exhibited by a 2.3-fold increase in the activity in the AW test. Compound **184** containing three hydroxyl groups, has demonstrated a high activity in the visceral pain model. Thus, estimating as a whole the compounds of the first group as visceral pain blockers, one could indicate agents **175** and **186** exhibited the analgesic activity surpassing the effect of morphine.

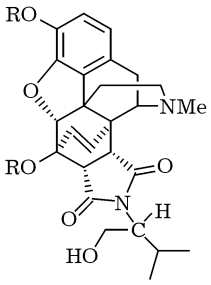
The second group of the compounds is presented by the derivatives of N-substituted 6,14-*endo*-etheno-7,8-pyrrolidine. The basic agent of this group **186** completely quenches the development of visceral pain in AW test and demonstrates insignificant analgesic activity in HP test. As the result of bromine atom introduction into the phenyl substituent **187** researchers found out only a certain tendency towards hyperalgesia occurrence in the TF test. Lengthening the carbon chain in the substituent at the nitrogen atom **190** has resulted in a certain activity decrease in the AW test (20 %). Agent **188** having $C_3$-oxy group, has exhibited a high activity in all the three models, exceeding the activity of morphine. Its 4'-bromo derivative **189** was demonstrated to be an analgesic agent acting selectively only in AW test. An interesting change in the structure was resulted from the reduction of one of the carbonyl groups of the pyrrolidinedione fragment. So, agent **185,** whose structure contains two hydroxyl groups, demonstrated the selectivity of action in HP test, which could be usually connected with the influence upon d receptors [10]. Thus, among the compounds of the second group, the most efficient and prospective substances for the further studying are presented by agents **188** and **189.**



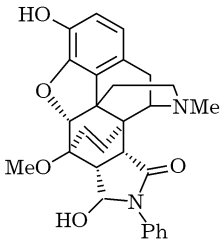
**174** $R^1 = R^2 = Me$; $R^3 = Ph$
**175** $R^1 = R^2 = Me$; $R^3 = 4\text{-BrPh}$
**176** $R^1 = R^2 = H$; $R^3 = Ph$
**177** $R^1 = H$; $R^2 = Me$; $R^3 = Ph$
**178** $R^1 = R^2 = H$; $R^3 = 4\text{-BrPh}$
**179** $R^1 = R^2 = Me$; $R^3 = 4\text{-MeOC}_6H_4CH_2$
**180** $R^1 = R^2 = Me$; $R^3 = Ph(CH_2)_2$
**181** $R^1 = Me$; $R^2 = H$; $R^3 = Ph(CH_2)_2$
**182** $R^1 = R^2 = Me$; $R^3 = 4\text{-HOC}_6H_4(CH_2)_2$



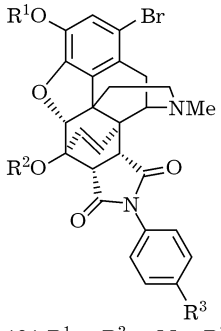
**186** $R^1 = Me$; $R^2 = Ph$
**187** $R^1 = Me$; $R^2 = 4\text{-BrPh}$
**188** $R^1 = H$; $R^2 = Ph$
**189** $R^1 = H$; $R^2 = 4\text{-BrPh}$
**190** $R^1 = Me$; $R^2 = 4\text{-HOC}_6H_4(CH_2)_2$



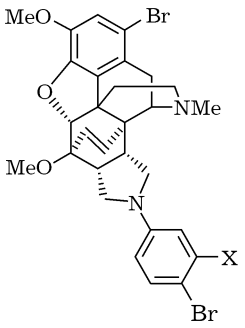
**183** R = Me
**184** R = H



**185**



**191** $R^1 = R^2 = Me$; $R^3 = H$
**192** $R^1 = R^2 = Me$; $R^3 = Br$
**193** $R^1 = R^2 = R^3 = H$
**194** $R^1 = R^2 = H$; $R^3 = Br$



**195** X = Br; R = 4-BrPh
**196** X = Br; R = 3, 4-$BrC_6H_3$
**197** X = H; R = $COCH{=}CHC_6H_4Me$

Scheme 11.

The comparative analysis of the activity of the agents belonging to both groups, *i. e.* pyrrolidinedione and pyrrolidine derivatives differing in the structure of the heterocyclic fragment allows one to draw the following conclusions. The reduction of the carbonyl groups results either in an essential increase in the analgesic effect in AW test and the disappearance of hyperalgesic effect in HP test (the pairs of agents **174** and **186**, **175** and **187**), or in the amplification of the analgesic effect in AW test and a decrease in the excitability of nociceptive afferents in HP and TF tests (a pair of compounds **182** and **190**).

The compounds of the third group (agents **191–196**) contain bromine atom in the base skeleton of the molecule. As a whole, such chemical modification as bromine atom introduction into morphinane carbon skeleton results in the reduction of the analgesic activity of agents [132]. It was demonstrated that amides of 2- and 4-methylcinnamic acid **197** with respect to μ and κ receptors binding are close to antagonist naltrexone [91] (Scheme 11).

Opioid agonists with a high affinity were obtained basing on morphinane imines and pyrrolidines. So, imine **198** acts as a μ selective agent which exhibits the following selectivity ratio values: $\mu/\delta = 10$, $\mu/\kappa_1 = 70$, $\mu/\kappa_2 = 1300$. As compared to compound **198** agent **199** exhibits a lower affinity [59].

Analgesic agents of new structural type include the derivatives of *endo*-etheno-7,8-sulpholanomorphinane **200–210** [78, 134–136]. In this series of the greatest interest is compound **200** that in a similar manner as morphine eliminates both physical pain and visceral pain. As opposed to morphine, this sulpholanomorphinane does not influence the respiration rate and amplitude and does not change bronchial tonus and cardiac beat frequency in animals. It is interesting to note that hydrochloride **200** · HCl results only in the elimination of physical pain with the amplification of visceral pain, causing hyperalgesia.

The reduction of the keto group (agent **201**) has resulted in the reduction of the analgesic activity and increase in the toxicity. The introduction of the benzylidene fragment (agent **202**) results in the effect of thermal pain elimination only. Compound **203** containing 4-methoxybebzylidene substituent causes hyperalgesia in the AW model.

Comparing the properties of agents **205** and **206** it has been established that the occurrence of phenolic hydroxyl results in the activity reduction in the models of electrical and thermal stimulation as well as in the analgesic effect increase in the AW test. The quaternization of the nitrogen atom has resulted in the amplification of the agent **207** anesthetizing effect in the model of chemical stimulation. The oxide ring cleavage (agents **208–210**) promotes the reduction of activity in all the models as compared both to morphine, and to the compounds with conserved ring (Scheme 12).

## CONCLUSION

From the data presented in this review one can see that the interest in research concerning pharmacological properties of novel synthetic thebaine derivatives is not only far from subsiding, but also is given with a new impetus for development. Searching for highly efficient antagonists of opioid analgesic agents, as well as analgesic remedies without toxic effects inherent in opioids remains an especially important line of investigation.

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