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Creation of New Local Anesthetics Based on Quinoline Derivatives and Related Heterocycles

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1. Introduction

Pain is a widely spread symptom and one of the most common causes making people seek medical attention. Though at present, different methods of pain control such as general narcosis, acupuncture, hypnosis, electroanaesthesia, homeopathy, etc., are known, nothing is better for safety and reliability than local anaesthesia. More often it is an effective alternative to general narcosis and promotes decreasing and even eliminating the use of narcotic analgesics in surgery. Dentists, dermatologists and other medical professionals apply it in their work. Unfortunately, an "ideal" local anesthetic has not been created yet, and all current medicines of the given pharmacological group have some drawbacks. The most serious disadvantages are high neuro- and cardiotoxicity, as well as tendency to cause allergy. Thus, the search for new, more effective and safe local anesthetics is ongoing and scientists all over the world continue to work on this problem.

Quinolines are the interesting compounds for research in this area. Numerous derivatives of this azaheterocycle are widely distributed in nature. Some of them are well-known to man and used for curative purposes from ancient times. For example, alkaloids cinchonine (**1a**, R = H) and quinine (**1b**, R = OMe, Figure 1) with antimalarial properties are isolated from *Cinchona* L. The utility of the majority of other natural quinolines prospects are to be determined. However, recently there has been a noticeable progress toward a solution of this problem. Natural compounds themselves more often attract the attention of scientists working in different fields of science and engineering. The stimulating motive for their research is the widely spread conviction that the living nature does nothing without purpose and everything it synthesizes is important at all events for life and, therefore, for man (Bochkov & Smith, 1987). This conviction finds the experimental confirmation constantly, as a result, at present the spectrum of biological properties of natural quinolines has expanded significantly (Kartsev, 2007).

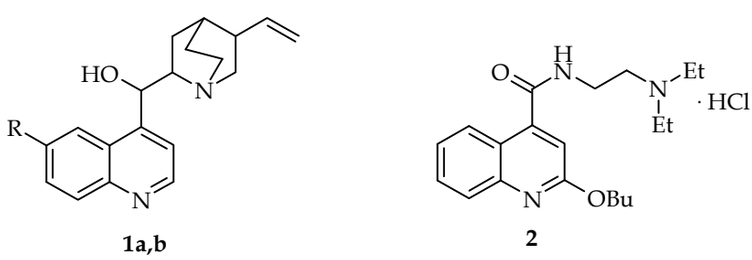


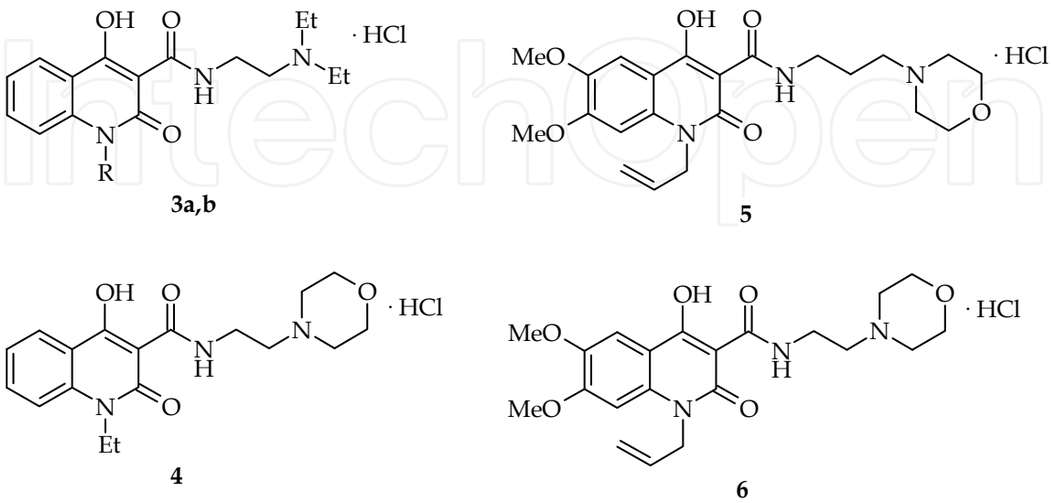
Fig. 1. Natural antimalarial drugs and the first synthetic local anesthetic of the quinoline group

Hence the increased interest in quinolines by synthetic chemists becomes clear. Their belonging to natural metabolites, as well as practically unlimited possibilities for chemical transformations make this molecular system, especially its hydroxyanalogues, rather convenient matrices for fixing various structural elements-pharmacophores on them. It allows making systematic changes into the structure of the finished products and thus to purposefully change their physical and chemical, as well as biological properties. Finally one can succeed in obtaining new substances corresponding to high requirements for medicines. So, in particular, the first local anesthetic of the quinoline group – Cinchocaine (**2**, Figure 1) was synthesized; though it was created 85 ago (Kleemann & Engel, 2001), it has been applied successfully in medical practice nowadays (Tomoda et al., 2009; Kang & Shin, 2010; Douglas et al., 2011).

2. 1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides as a source of new privileged structures with the local anesthetics activity

When systematically studying the biological properties of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides we repeatedly noted the opportunity of creating new potential medicines with various effects on a living organism on their basis, including local anesthetics (Ukrainets, 1992; Ukrainets et al., 1994). After the experimental study of anaesthetic properties of a large group of compounds of this chemical range, our attention was paid to the most active of them. Hydrochlorides of (2-diethylaminoethyl)amides of 1-ethyl- (**3a**, R = Et) and, especially, 1-propyl- (**3b**, R = Pr) substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids (Figure 2), were superior the known local anesthetic Lidocaine by the specific activity possessing at the same time the lower toxicity.

Later (Gorokhova, 1993) in the same range one more compound – hydrochloride of 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (2-morpholin-4-ylethyl)amide (**4**) was found. By the level of infiltration anaesthesia this amide had some more activity than its 1-N-ethyl analogue **3a**, but it was noticeably inferior to 1-N-propyl derivative **3b**. However, after the primary screening it was also included into the list of candidates for profound research as it possessed another important for future medicine property – a relatively low toxicity. By this parameter amide **4** prevailed over its acyclic analogues **3a,b** by a factor of almost 2.



3a,b **5**

4 **6**

Fig. 2. Biologically active 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides

And recently (Davidenko, 2011) a new pharmacological property – the ability to block opioid receptors – has been revealed in 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides. It has also been found that substances closely related in structure can reveal quite opposite biological effects. Hydrochloride of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydro-quinoline-3-carboxylic acid (3-morpholin-4-ylpropyl)amide (**5**) in the dose of 1 mg/kg completely eliminates the analgesic effect of Tramadol and its homologue – (2-morpholin-4-yl-ethyl)amide **6** – prolongs the analgesic effect significantly. This fact requires further research and is doubtless of interest for researchers engaged in searching not only new opioid receptors antagonists, but highly effective pain-killers as well.

3. Chemical modification of Chinoxicaine by its transformation into pro-drugs

All compounds that passed the stage of primary pharmacological screening were subjected to more profound and thorough analysis in pre-clinical trials. To evaluate the local anaesthetic properties a greater number of parameters were taken into account; these parameters characterized the main specific manifestations of the biological effect: potency of local anaesthesia, the rate of its onset and duration. Additionally at this stage some experimental models, such as repeated infiltration and additional conduction anaesthesia, epidural and surface anaesthesia, were involved. The local irritant properties of the compounds, as well as their acute and chronic toxicity were studied.

From the experiments, only one compound emerged – hydrochloride of 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (2-diethylaminoethyl)amide (**3b**), which further was studied as a privileged structure under the name of Chinoxicaine and was transferred to the next level of investigations. This amide causes a rapid, deep and long local anaesthesia on all models studied and has a low toxicity. It has been found that prolonged introduction of Chinoxicaine to the experimental animals does not produce any statistically significant changes in the activity of central nervous and cardio-vascular systems and does not cause negative reactions of the liver and gastrointestinal tract. The medicine does not produce nephrotoxic action and, thus, it can be used safely by the patients with renal pathology. While using Chinoxicaine, there were no cases of blood pressure decrease, which is its beneficial advantage over many known anesthetics. Additional advantages of Chinoxicaine are that together with the high specific activity it shows clear antiarrhythmic, antimicrobial, antioxidant, and fungicidal effects.

Simultaneously with the pharmacological studies, diversified synthetic research to find the most available method for obtaining Chinoxicaine substance was carried out. As the result, principally different synthetic schemes providing a high quality of the final product have been suggested (Ukrainets et al., 1998; Ukrayinecz & Bezuhliy, 2002; Romanov & Ukrainets, 2006).

Unfortunately, the "Chinoxicaine" project faced some problems. For example, possessing a unique set of pharmacological properties Chinoxicaine appeared to be surprisingly poorly soluble in water. Its solubility is only 13.85 g in 100 ml of water at 20°C, and this caused great difficulty when preparing a stable medicinal form for injections. We solved this problem rather rapidly, though water had to be replaced by the combined solvent.

At the later stages of introduction of a new local anesthetic into medical practice, namely at the stage of clinical trials, one more serious drawback was revealed. In some patients, Chinoxicaine solution in the site of injection caused a transient feeling of burning. Though this undesirable effect lasted less than one minute, further work with the medicine

practically lost any progress without its removal. Theoretically a rather simple and effective solution of the problem has been found. The irritant action of Chinoxicaine is completely eliminated by addition such substances as adrenaline in insignificant concentrations in its solution.

However, we tried to solve the problem by structure modification well known in the art to modern researchers (Kubinyi, 2006).

For example, on the basis of structural biological regularities previously revealed a quite new analogue of Chinoxicaine with the improved properties can be synthesized. But is should be taken into account that in such case all complex of biological and pharmaceutical trials have to be carried out in a full volume. Besides to achieve the aim is quite unreal as a result of synthesis of only one new substance. Most likely, to solve the task successfully is possible only after the study of the series of new compounds.

Taking this into account we began to improve pharmaceutical properties of Chinoxicaine from the most rational variant – creation of pro-drugs on its basis. Biologically active source in this approach remains the same, that is why both the terms of development and costs for its implementation are greatly reduced.

However, the practical realization of the method is linked with certain difficulties. In particular, to increase the water solubility, as a rule, it is necessary to introduce additional ionizing groups into the structure of the modified compounds, while to eliminate the irritant action the same ionizing groups in the molecule should be masked (Kuznetsov et al., 1991). In other words, theoretically possible methods of elimination of the revealed drawbacks of Chinoxicaine mutually exclude each other.

Most likely the irritant action of Chinoxicaine is related to the presence of 4-OH-group in its structure, which accounts for the marked acid properties in 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (Ukrainets, 1988). However, it has been noted (Gorokhova, 1993) that the potency of the given side effect to a great extent depends on the structure of the amide fragment as well. For example, hydrochloride of 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (2-morpholin-4-ylethyl)amide (**7**, Figure 3) and its 1-N-ethyl analogue **4** mentioned above do not yield to Chinoxicaine in the specific activity, but they do not practically render the irritant action. This fact was the foundation for performing bioreversible chemical modification of Chinoxicaine by the tertiary amino group (Ukrainets et al., 2009).

One of the obvious solutions of the target trasformation of the Chinoxicaine molecule is trasformation into quaternary ammonium salts, which is simple in its performance. It should be noted here that common alkyl halides are not suitable for such transformation since they form with the medicine – tertiary amine – the stable compounds, which are almost not subjected to metabolism and are excreted from the organism unchanged (Kuznetsov et al., 1991). Carboxylic acid haloalkyl esters are more interesting. They allow to transform tertiary amines in quaternary ammonium salts with labile grouping $N^{+}-C-O$, which is capable of relatively easily to be splitted by hydrolysis and release the initial medicine in the form of the corresponding hydrohalide (Kuznetsov et al., 1991; Vinogradova et al., 1980). One of this reagents is commercially available bromomethylacetate, by its interaction with (2-diethylaminoethyl)amide of 4-hydroxy-2-oxo-1-propyl-1,2-dihydro-quinoline-3-carboxylic acid (**8**) in the anhydrous acetonitrile medium the target bromo-acetoxymethylate **9** was obtained (Figure 3).

The biological screening has demonstrated that quaternization conducted eliminated the irritant action of Chinoxicaine almost completely, unlike it bromoacetoxy-methylate **9** in the

form of 2% aqueous solution which causes only insignificant hyperemia of conjunctiva of the rabbit's eye. At the same time in spite of expectations, dissolution in water decreased significantly (up to 8.86 g per 100 ml), but usually it increases sharply in pro-drugs of this type in 1-2 thresholds comparing to hydrohalides (Vinogradova et al., 1980). Significantly there is almost a threefold shortening of the duration of the surface anesthesia by the bromoacetoxymethylate **9** and this is evidently due to the low rate of liberation of the starting tertiary amine.

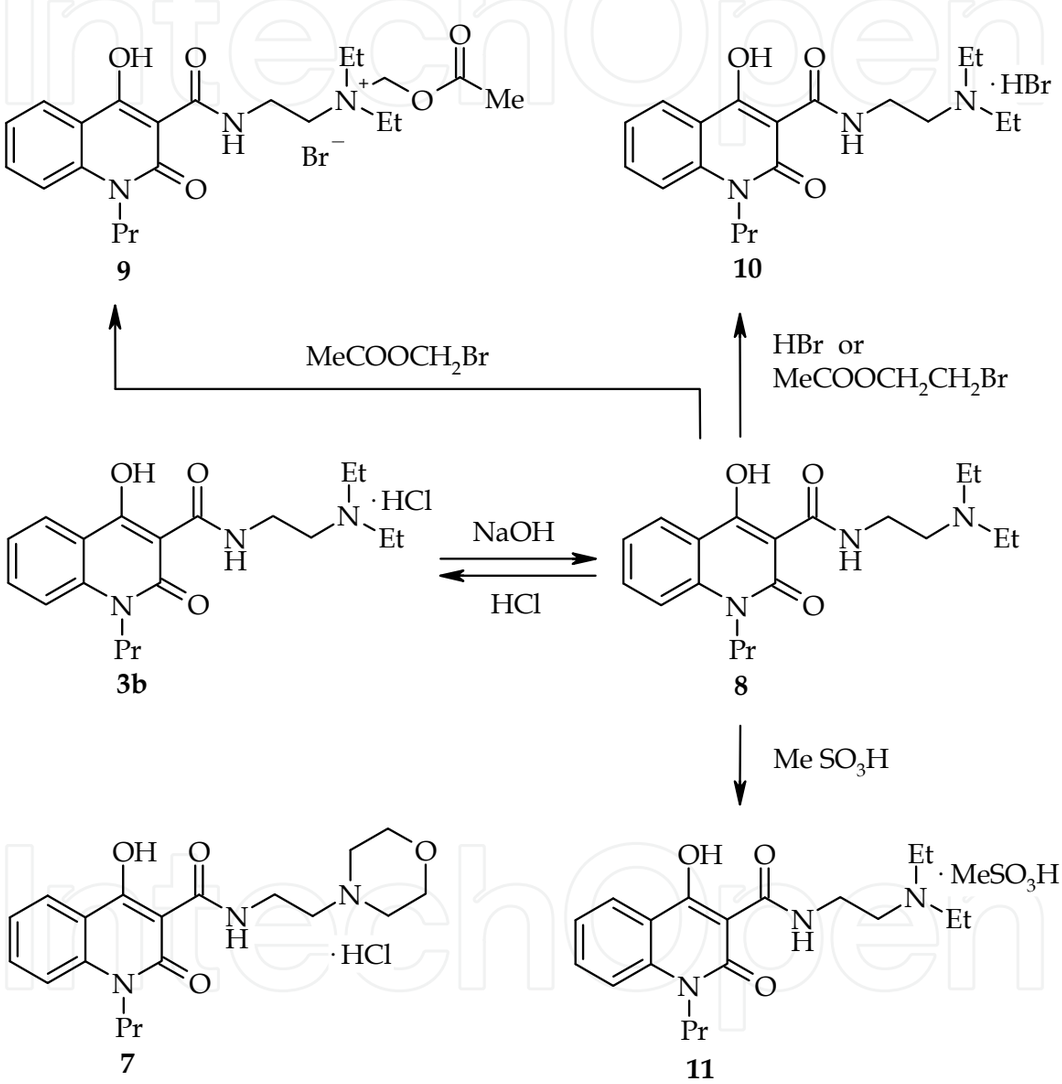


Fig. 3. Modification of Chinoxicaine into pro-drugs

The attempt to optimize the value by substitution of 2-bromomethyl acetate with 2-bromoethyl failed. Under the action of amide **8** the reagent is dehydrobrominated, as a result, instead of bromoacetoxyethylate hydrobromide **10** was isolated, it could be also obtained by neutralization of the tertiary amino group of amide **8** by hydrobromic acid. Though salt formation is not accompanied with the change of number, character and location of covalent bonds, it is widely used as an individual type of chemical modification of medicinal

substances in medical chemistry. Hence, hydrobromide **10** can be considered as an original pro-drug of Chinoxicaine. However, there was no positive results due to transfer of hydrochloride to hydrobromide. Absolutely all the parameters worsened: solubility decreased to 3.40 g in 100 ml of water, the irritant action increased considerably, and the local anaesthetic activity decreased.

The substitution of hydrogen chloride as a salt-forming reagent of methanesulfonic acid, which forms methanesulfonate **11** practically with the quantitative yield reacting with amide **8** in the anhydrous diethyl ester medium, was more successful.

According to the X-ray structural data, in the symmetrically independent part of the unit cell of the methanesulfonate **11** there is a molecule of the 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (2-diethylaminoethyl)amide protonated at atom $N_{(19)}$ and the methanesulfonic acid anion (see Figure 4).

The dihydroquinolone fragment is planar within 0.02 Å. The deviations of atoms $C_{(11)}$ and $C_{(15)}$ from the mean square plane of the dihydropyridine ring are 0.067 and 0.022 Å respectively. A marked deviation of atom $C_{(11)}$ from the ring plane is explained by the presence of a shortened intramolecular contact $H_{(9)}\cdots H_{(11B)}$ of 1.986 Å. The amide fragment is virtually coplanar with the dihydroquinolone (torsional angle $C_{(4)}$–$C_{(3)}$–$C_{(15)}$–$O_{(15)}$ = 4°). Such an orientation is stabilized by two intramolecular hydrogen bonds: $O_{(4)}$–$H_{(4)}\cdots O_{(15)}$ (H···O 1.74 Å, O–H···O 155°) and $N_{(16)}$–$H_{(16)}\cdots O_{(2)}$ (H···N 1.91 Å, N···H–O 140°).

The $O_{(4)}$–$C_{(4)}$ 1.319(3), $N_{(16)}$–$C_{(15)}$ 1.313(3), and $C_{(2)}$–$C_{(3)}$ 1.451(3) Å bonds in the compound studied are shortened (mean values 1.331, 1.334, and 1.464 Å respectively) but the $O_{(15)}$–$C_{(15)}$ 1.264(3) and $C_{(3)}$–$C_{(4)}$ 1.379(3) Å bonds are lengthened (mean values 1.231 and 1.363 Å respectively).

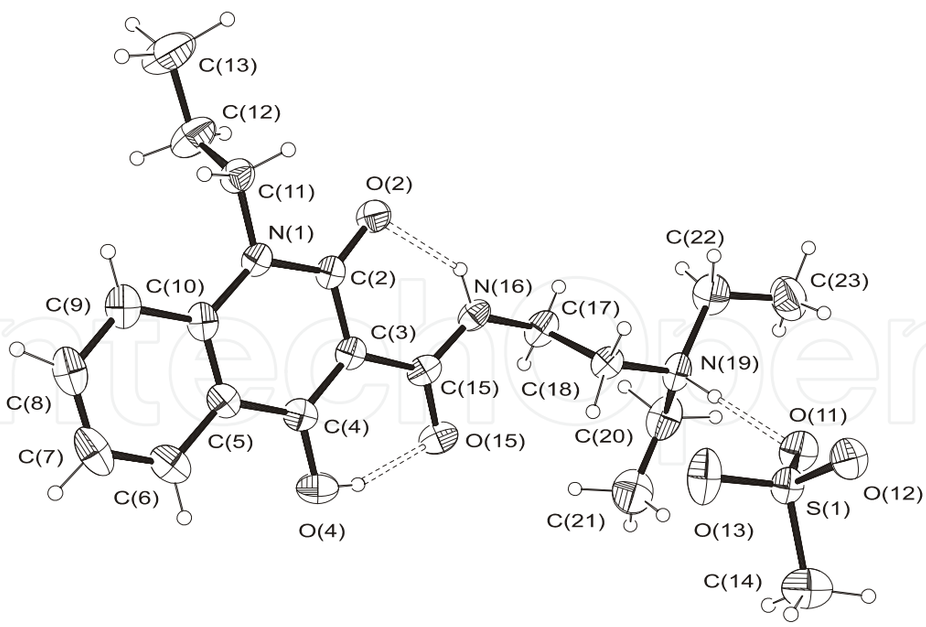


Fig. 4. The structure of the methanesulfonate **11** molecule with atomic numbering. The dotted lines indicate the intra- and intermolecular hydrogen bonds

Atom $N_{(1)}$ has a planar trigonal configuration. The substituents at atoms $N_{(1)}$ and $N_{(16)}$ have an *anti*-periplanar conformation (torsional angles $N_{(1)}$–$C_{(11)}$–$C_{(12)}$–$C_{(13)}$ and $N_{(16)}$–$C_{(17)}$–$C_{(18)}$–

$N_{(19)}$ 176.2 and 176.3° respectively). The plane of the carbon atoms of the propyl group on the $N_{(1)}$ atom is virtually perpendicular to the mean-square plane of the dihydropyridine ring, the angle between them being 89.1°.

In the crystal the molecules of the methanesulfonate **11** form dimers *via* stacking interactions between the dihydroquinolone fragments, the benzene rings being situated over the dihydropyridines. The distance between the ring centroids is 3.54 Å and the mean-square planes of the dihydropyridine and benzene fragments form a dihedral angle of 2.2°.

The cation and anion are mutually bonded by an intermolecular hydrogen bond $N_{(19)}$–$H_{(19)}\cdots O_{(11)}$ (H···O 1.88 Å, N–H···O 176°).

The biological screening has shown that methanesulfonate **11** demonstrates a significant improvement of all pharmaceutical properties comparing to the initial hydrochloride **3b** (Chinoxicaine). In particular, the local irritant action was successfully decreased to the level of bromoacetoxymethylate **9**. Dissolution in water increased in more than six times – up to 85.72 g per 100 ml, and it has eliminated the problem of choosing a solvent for preparation of a stable medicinal form for injections. Finally, there are also some positive aspects of revealing the specific activity: the rate of anaesthesia onset remains the same, but the total duration of the surface anaesthesia and the deep anaesthetization phase increased.

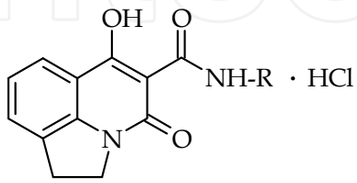
4. Synthesis of conformation stable forms of quinolones as an attempt to improve pharmaceutical properties of Chinoxicaine

In modern medical chemistry several standard methods are successfully applied for improving the privileged structures chosen according to the results of preliminary pharmacological trials. Recently with accumulation of information about the spatial structure of active binding sites for many types of receptors a greater attention has been paid to methodology of conformation restrictions (Chen et al., 2010; Watanabe et al., 2010; Nirogia et al., 2011). In general, this method of the structural transformation of a molecule suggests the preservation of all functional groups contacting with a biological target in their original form and at the same time it is directed to fixing of some of them in "active" conformation.

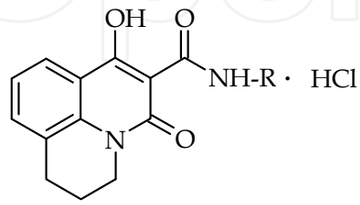
One of the most wide-spread ways of practical realization of the method is cyclization, which allows transformation of the open side chains of the initial molecule in endo- or exo-cyclic fragments, making possible the change of the pharmaceutical and (or) pharmacokinetic properties. Taking into account the given data it is quite logical to study N-R-amides of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo- (**12a-m**) and 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido- (**13a-m**) [3,2,1-*ij*]quinoline-2-carboxylic acids as potential local anesthetics (Figure 5).

The interest of these compounds is caused by the fact that they are very similar to Chinoxicaine (**3b**) and its 1-N-ethyl analogue **3a** by their structure. At the same time amides **12-13a-m** have a principally important structural difference: though their 1-N-alkyl substituents contain the same two-three carbon atoms, they are situated not in the open alkyl chains, but are included in the composition of pyrrole or tetrahydropyridine cycles annelation with the quinolone nucleus. Such modification is known to lead to the essential spatial trasformation of the molecule. In particular, in 1-propylsubstituted 4-hydroxy-quinolones-2 the ethyl fragment is placed perpendicular the plane of the quinolone nucleus, as a result the terminal methyl group is far from the bicycle more than 3 Å (Ukrainets et al., 2009). And on the contrary, the tricyclic pyrido[3,2,1-*ij*]quinoline

system is much compact – in spite of the *sofa* conformation of the tetrahydropyridine ring, $C_{(6)}$ atom deviates from its relative plane only in 0.56 Å (Ukrainets et al., 2008). Unlike 1-N-ethylsubstituted 4-hydroxyquinolones-2, in which the methyl group of ethyl substituent is never located in the quinolone cycle plane (Baumer et al., 2004; Ukrainets et al., 2007), tricyclic pyrrolo[3,2,1-*ij*]- quinoline system is practically flat (Ukrainets et al., 2006a). It is clear that transfer from 1-N-ethyl- and 1-N-propylsubtituted **3a,b** to conformation limited pyrrolo- and pyridoquinolines **12-13** should be obligatory reflected to the biological properties. The answer to the question about this influence has been found in one of the recent investigations (Kravtsova, 2011).



12a-m



13a-m

12-13: **a** R = 2-aminoethyl; **b** R = 3-aminopropyl; **c** R = 4-aminobutyl; **d** R = 6-aminohexyl; **e** R = 2-ethylaminoethyl; **f** R = 2-(2-hydroxyethylamino)ethyl; **g** R = 2-dimetylaminoethyl; **h** R = 2-diethylaminoethyl; **i** R = 3-dimethylaminopropyl; **j** R = 3-diethylaminopropyl; **k** R = 2-piperazin-1-ylethyl; **l** R = 2-morpholin-4-ylethyl; **m** R = 3-morpholin-4-ylpropyl

Fig. 5. Tricyclic analogues of Chinoxicaine

Testing of the samples synthesized has been carried out on the infiltration anaesthesia model by Buelbring-Yueid method (Table 1).

Analysis of the experimental data obtained demonstrates that compounds with the primary amino groups, i.e. amides **12-13a-d**, do not practically show the anesthetic properties. The weak activity (the anaesthesia lasts for not more 5 min, and the phase of complete sensitivity loss has not come) has appeared in monoalkylaminoalkylamides **12-13e,f**. And only when the second alkyl residue is introduced into the terminal amino group (amides **12-13g-m**), the local anaesthetic action increases noticeably, but though in this case its duration remains rather short. For example, for the most active diethylaminoethyl derivative **13h** this index is approximately 40 min, though the infiltration anaesthesia index reaches the maximum possible value. As compared, Chinoxicaine in the similar conditions causes total anaesthesia lasting for approximately 75 min (with the general duration of anaesthesia of 4 hours), and its 1-N-ethyl analogue **3a** – approximately 60 min (with the general duration of anaesthesia of 2 hours).

It is interesting to note that the irritant action of 2% aqueous solutions of tricyclic amides **12-13,** determined by the rabbit's eye cornea according to the simplified modification of Setnikar method, is absent in most examples at all or decreases significantly comparing to its bicyclic prototypes **3a,b**. And it is in spite of the fact that acidity of enolic OH-groups in 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid and its 1-N-ethyl analogue is practically the same, and in 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]-quinoline-2-carboxylic acid is similar with its 1-N-propyl analogue (pKa^{OH} = 13,44-13,48).

In general, based on the biological trials conducted, it can be stated that the structural transformation of the molecule, which accompanies the transfer from 1-alkylsubstitued 4-hydroxyquinolin-2-ones to conformation limited tricyclic pyrrolo- or tetrahydropyrido-quinolones, allows to decrease the irritant action of compounds of this class, but at the same time it has a strong negative effect on the local anesthetic properties and that is why it can be considered as unperspective.

Compound	Infiltration anaesthesia			Irritative effect, points
	The start of anaesthesia, min	Index	Duration of total anaesthesia, min	
12a	4.32 ± 0.28	1.1	Undetermined	0
12b	3.81 ± 0.21	2.7	Undetermined	0
12c	4.60 ± 0.33	2.0	Undetermined	0
12d	4.93 ± 0.39	1.2	Undetermined	0
12e	3.27 ± 0.30	5.1	Undetermined	0
12f	3.66 ± 0.27	3.5	Undetermined	0
12g	2.82 ± 0.31	12.2	10.64 ± 1.20	2
12h	2.05 ± 0.17	36.0	39.82 ± 2.37	1
12i	3.09 ± 0.28	9.8	9.27 ± 1.33	2
12j	2.91 ± 0.32	14.2	15.92 ± 1.24	1
12k	3.87 ± 0.45	6.4	5.30 ± 1.45	1
12l	2.24 ± 0.26	27.0	25.56 ± 1.62	0
12m	3.04 ± 0.34	16.2	14.75 ± 1.18	0
13a	5.26 ± 0.44	2.8	Undetermined	0
13b	4.32 ± 0.35	3.9	Undetermined	0
13c	4.63 ± 0.41	4.2	Undetermined	0
13d	5.65 ± 0.48	2.3	Undetermined	0
13e	3.72 ± 0.33	7.6	Undetermined	0
13f	4.08 ± 0.29	5.4	Undetermined	0
13g	3.26 ± 0.30	16.7	13.51 ± 1.81	1
13h	2.23 ± 0.23	36.0	40.24 ± 3.06	1
13i	3.92 ± 0.22	14.1	8.83 ± 1.26	1
13j	3.10 ± 0.25	17.3	11.48 ± 2.55	1
13k	4.05 ± 0.36	9.7	6.63 ± 1.14	0
13l	2.64 ± 0.23	21.4	28.96 ± 3.73	0
13m	3.22 ± 0.31	15.8	15.37 ± 2.02	0
3a	1.84 ± 0.10	36.0	58.92 ± 4.11	2
Chinoxicaine	1.61 ± 0.13	36.0	74.79 ± 4.71	2

Table 1. Biological properties of tricyclic compounds **12-13**

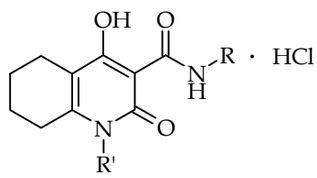
5. Application of the bioisosteric replacements methodology for optimization of the Chinoxicaine molecule

The term „isosters“ was introduced by Irwing Langmuir at the beginning of the 20th century. By his definition, isosters are molecules or ions containing the same number of

atoms, as well as the same number and arrangement of electrons. Therefore, "isosteric replacements" in the created drugs are replacement of an atom or the group to the similar one by size or valency. If the physiological activity remains at the same time, then such replacement is called "bioisosteric". After a while the term "bioisoster" has been referred to compounds obtained by replacement of quite "unsimilar" groupings, but with preserving their biological properties (King, 2002). As a result, the concept of bioisosteric replacements at present has become one of the most powerful means for creating effective and safe medicines (Devereux & Popelier, 2010; Wassermann & Bajorath, 2011; Large et al., 2011). Its application allows not only to optimise the known biologically active substances, but to reveal new structures with the similar or related properties and, thus, to increase the patent protection of a future medicine.

5.1 Hydrochlorides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acids N-R-amides

The first attempt to optimize the Chinoxicaine molecule by the method of bioisosteric replacements was replacement of its 1,2-dihydroquinoline nucleus by 1,2,5,6,7,8-hexahydroquinoline. We did it expecting that such transformation may appear to be bioisosteric. With this aim a large group of hydrochlorides of 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acids N-R-amides **14a-y** has been synthesized by the method developed earlier (Kolisnyk, 2009) (Figure 6).



14a-y

14: R' = H: **a** R = 2-aminoethyl; **b** R = 3-aminopropyl; **c** R = 4-aminobutyl; **d** R = 6-aminohexyl; **e** R = 2-ethylaminoethyl; **f** R = 2-(2-hydroxyethylamino)ethyl; **g** R = 2-dimetylaminoethyl; **h** R = 2-diethylaminoethyl; **i** R = 3-dimethylaminopropyl; **j** R = 3-diethylaminopropyl; **k** R = 1-ethylpyrrolidin-2-ylmethyl; **l** R = 2-morpholin-4-ylethyl; **m** R = 3-morpholin-4-ylpropyl; **o** R = 3-piperidin-1-ylpropyl; **p** R = 3-(4-methylpiperazin-1-yl)propyl; **q** R = 4-diethylamino-1-methylbutyl
R' = Pr: **r** R = 2-diethylaminoethyl; **s** R = 3-diethylaminopropyl
R' = *cyclo*-Pr: **t** R = 2-ethylaminoethyl; **u** R = 2-(2-hydroxyethylamino)ethyl; **v** R = 2-dimetylaminoethyl; **w** R = 2-diethylaminoethyl; **x** R = 3-dimethylaminopropyl; **y** R = 3-diethylaminopropyl

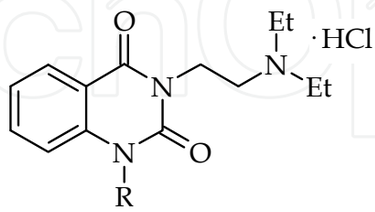
Fig. 6. Hydrogenated analogues of Chinoxicaine

The biological screening conducted allow to state that reduction of the benzene part of the quinolone ring, unfortunately, leads to practically complete loss of local anaesthetic properties and that is why such modification should be considered unsuccessful. In other words, there is no reason to declare 4-hydroxy-2-oxo-1,2-dihydroquinoline and 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydroquinoline molecular systems to be bioisosteric (at least, in relation to local anaesthesia).

5.2 1-R-3-(2-Diethylaminoethyl)-1H-quinazoline-2,4-diones hydrochlorides

All ways of modification of Chinoxicaine molecule considered by us previously could not remove the local irritant action completely, therefore, it can be assumed that this drawback

had been stipulated mainly by the presence of 4-OH-group. Thus, the next step of potentially bioisosteric transformation of Chinoxicaine was the synthesis of compounds known to be without groupings with acid properties. One of the examples of such substances were 1-R-3-(2-diethylaminoethyl)-1H-quinazoline-2,4-diones hydrochlorides **15a-f** (Figure 7). We considered various variants of obtaining compounds of this class allowing to choose the most suitable of them depending on the structure of the target product (Ukrainets et al., 2010)



15: a R = H; **b** R = Me; **c** R = Et; **d** R = Pr; **e** R = Bu; **f** R = *i*-Bu

Fig. 7. Derivatives of 1H-quinazoline-2,4-dione

The study of the local irritant action of 1-R-3-(2-diethylaminoethyl)-1H-quinazoline-2,4-diones hydrochlorides **15** conducted in rabbits by the method of Lebo and Camage, has shown that the substances under research in the form of aqueous solutions with 2% concentration do not cause any reactive changes on the surface of the skin of the experimental animals. It should be worth mentioning that in similar conditions Chinoxicaine also does not reveal the irritating effect. That is why other, more sensitive, models should be involved in further research.

The ability of 2% aqueous solutions of the compounds synthesized to cause infiltration anaesthesia of the skin and subcutaneous cellulose has been studied in guinea pigs (Buelbring-Yueid method). Simultaneously several parameters characterizing the basic specific manifestations of the pharmacological effect such as the rate of anaesthesia onset, its depth (potency) and duration were taken into account. The data given in Table 2 shows that all 1-R-3-(2-diethylaminoethyl)-1H-quinazoline-2,4-diones hydrochlorides **15**, without exception, possess the local anaesthetic properties in some degree. In most cases anaesthesia occurs rather quickly and in some minutes after injection, the phase of deep anaesthesia begins. However, in spite of high values of the infiltration anaesthesia index, sometimes reaching the duration of the total anaesthesia caused by quinazolones **15** remains comparatively short and they yield to Chinoxicaine and Lidocaine greatly by this parameter. However, unlike the reference drugs the most active of the compounds synthesized – hydrochlorides **15a,e,f** – reveal a number of new properties, which can be considered as useful in the complex of the short, but powerful local anaesthetic action. They are sedation as well as movement disorder or motor block on the site of introduction of the substance examined. The motor block was estimated on the "peak" of the local anesthesia by 5 point scale: 0 points - the tail root tone preserved, movements preserved in full; 1 point - weakening of the tail root tone; 2 points - the weak tail root tone, sluggish movement, the animal sitting more; 3 points - lowering of the tail root tone and possible slight movement of the animal during stimulation of the skin section not occurring in the anesthetized zone, slight inhibition of the animal; 4 points - general atonia of the tail root, appearance of some inhibition of movement in response to stimulation, overall inhibition of the animal; 5 points

- the state of general atonia of the tail root without movement upon pain or electrical stimulation of the skin outside the area of anesthesia, the animal lying on side.

Compound	Infiltration anaesthesia			Motor block, points	Sedative effect, points
	The start of anaesthesia, min	Index	Duration of total anaesthesia, min		
15a	1.14 ± 0.16	36.0	32.35 ± 1.38	4	1
15b	1.53 ± 0.19	35.8	30.19 ± 0.75	0	0
15c	4.46 ± 0.29	18.5	15.74 ± 1.05	0	1
15d	2.97 ± 0.32	35.7	29.82 ± 0.59	0	0
15e	2.82 ± 0.43	36.0	36.46 ± 2.53	5	1
15f	1.59 ± 0.25	34.2	29.20 ± 1.43	5	3
Chinoxicaine	1.50 ± 0.04	36.0	75.61 ± 4.54	0	0
Lidocaine	2.12 ± 0.19	36.0	52.80 ± 3.76	0	0

Table 2. Biological properties of the quinazoline-2,4-diones hydrochlorides **15**

The sedative effect was estimated in the following way: 0 points - absent, the animal moving independently in cage; 1 point - the animal calm, sitting more, moving around the cage only when disturbed by the researcher; 2 points - the animal slowed down, sitting in the corner of the cage, anxiety with the researcher significantly set aside and again sitting, often closing eyelids, sleep onset; 3 points - the animal sleeping, lying on side, not responsive to stimulation by the researcher or to needle stick.

In general, the combination of analgesic, sedative and immobile extremities effects rendering by hydrochlorides **15a,e,f** can be used in creating medicines on their basis that are available for practical application in tiny surgical interventions, for example, in veterinary medicine. Thus, it can be stated confidently that 1-R-quinazoline-2,4-dionic cycle is bioisoster of 4-hydroxy-2-oxo-1,2-dihydroquinoline nucleus.

5.3 The irreversible chemical modification of Chinoxicaine at position 4 of the quinolone nucleus

The complex research described by us above has shown convincingly that 4-OH-group is the main cause of the local irritant properties of Chinoxicaine. Therefore, after its blocking one can expect the elimination of the undesired side effect. Meanwhile, we have not even considered alkylation or acylation of 4-OH-group as the most obvious variant of another bioreversible modification of Chinoxicaine. The reason is quite simple. Within a rather limited choice of pharmacologically available protective groups, neither 4-O-alkyl, nor 4-O-acyl derivatives of 4-hydroxyquinolin-2-ones have a high chemical stability. It is the tendency to hydrolysis that is a serious obstacle when synthesizing such compounds, as well as when further preparing sterile solutions for injections on their basis.

Taking it into account we tried to modify 4-OH-group of Chinoxicaine not by means of forming pro-drugs, but by using the same method of bioisosteric replacements, i.e. by its irreversible replacement with the groupings similar not by sizes or volume, but having the same physical and chemical properties and that is why inducing the similar pharmacological effect (King, 2002).

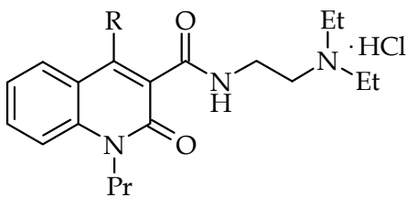
The first example of such transformation was 4-chloro-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (2-diethylaminoethyl)amide hydrochloride **16** (Figure 8).

A high reactivity of the chlorine atom in 1-R-4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines in relation to nucleophilic reagents allows to transform them easily into 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, one being the basis for synthesis of one more bioisoster of Chinoxicaine – 4-methyl substituted analogue **17**.

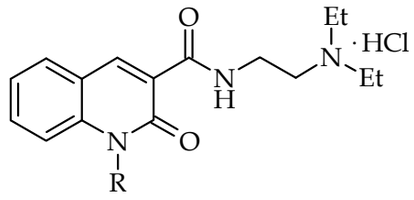
N-R-Amides of 2-oxo-1,2-dihydroquinoline-3-carboxylic acid with a primary amino group in position 4 of the quinolone ring exist in the 2-hydroxy-4-imino form rapidly hydrolyzed by mineral acids to 4-hydroxy-2-quinolones (Ukrainets et al., 2006b). Proceeding from it as the next object for pharmacological screening we deliberately obtained hydrochloride of 4-diethylamino-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (2-diethylaminoethyl)-amide **18** as chemically more stable product. Amides **19a-d** containing no substituents at position 4 are of particular interest, in spite of the fact that due to the absence of these substituents they cannot be considered to be classical bioisosters of Chinoxicaine.

The study of local irritant action of the compounds synthesized, the ability to cause infiltration anaesthesia of the skin and subcutaneous cellulose, as well as the evaluation of the motor block and the sedative effect were carried out by standard methods previously described in detail by us (Ukrainets et al., 2010). It has been determined that all substances tested in the form of aqueous solutions with 2% concentration do not cause any reactive changes on the skin surface of the experimental animals.

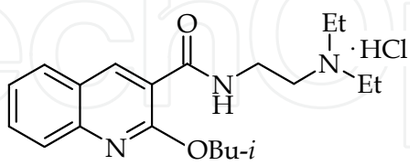
From the data presented in Table 3 it follows that bioisosteric replacement of 4-OH-group to the chlorine atom – amide **16** – leads to significant decrease of all pharmacological indexes and, therefore, it is unsuccessful.



16 R = Cl
17 R = Me
18 R = $N(Et)_2$



19: a R = Et; **b** R = Pr; **c** R = Bu; **d** R = *i*-Bu



20

Fig. 8. Modification of 4-OH-group of Chinoxicaine

More interesting was the replacement of the hydroxyl group to the methyl one. From all substances of the last series 4-methyl-substituted amide **17** possesses the most rapid development of the biological effect (less than 2 min after injection). The infiltration anaesthesia index reaches the maximum possible value, and the total anaesthesia or the time of absence of pain and all types of sensitivity (tactile, temperature, etc.), during which the surgical intervention can be made (the section of tissues, wound suture, etc.), last

approximately 55 min. These data prove the sufficient high activity of amide **17**, which are comparable to the reference drugs - Chinoxicaine and Lidocaine. However, amide **17** yields them significantly in the total duration of anaesthesia, i.e. time when the sensitivity increases gradually and then restores completely.

Compound	Infiltration anaesthesia				Motor block, points	Sedative effect, points
	The start of anaesthesia, min	Index	The total anaesthesia, min	The general duration of anaesthesia, min		
16	3.96 ± 0.42	26.3	14.25 ± 1.11	24.72 ± 2.18	0	0
17	1.94 ± 0.21	36.0	55.33 ± 2.74	68.38 ± 2.68	0	0
18	2.28 ± 0.31	36.0	37.51 ± 2.83	67.85 ± 2.37	0	0
19a	4.52 ± 0.32	19.3	13.20 ± 1.00	21.01 ± 1.67	0	0
19b	4.50 ± 0.36	35.5	27.89 ± 1.89	32.34 ± 2.92	0	0
19c	3.03 ± 0.28	36.0	39.04 ± 2.12	58.26 ± 2.81	5	2
19d	2.71 ± 0.37	36.0	53.77 ± 1.93	83.28 ± 2.05	5	3
20	2.82 ± 0.44	35.6	47.56 ± 1.74	85.48 ± 2.33	5	3
Chinoxicaine	1.62 ± 0.13	36.0	74.74 ± 4.71	236.89 ± 9.34	0	0
Lidocaine	2.34 ± 0.20	36.0	51.26 ± 3.45	140.27 ± 6.20	0	0

Table 3. Biological properties of 4-OH-modified derivatives of Chinoxicaine

A special attention should be paid to 4-diethylamine derivative **18**, not only for its high anaesthetic properties, but for the perspective to perform further modifications of such type easily and practically in unlimited quantity as well and to reach the result required.

From the series of non-substituted amides **19** at position 4 it is worth mentioning only compounds with butyl and *iso*-butyl substituents at the cyclic nitrogen atom (amides **19c** and **19d** respectively). Both are characterized by a rather rapid onset of action and high values of infiltration anaesthesia indexes. The distinctive feature of the first one is the signs of drowsiness, inertia in animals in 10-15 min after the injection and complete sleepiness can occur at 15-20 min. The motor block with the strength of 5 points lasts for approximately 20 min on the site of introduction of the substance examined. In the case of amide **19d** already by 7-10 min after injection the animals had the state of deep sleep: they slept on their side without the reaction to the active stimulation by the needle (tactile, pain and temperature sensitivity is absent). In 15-20 min the animals awoke, but they were drowsy and motionless for approximately 20 min and then began to move their paws. Therefore, one can speak about the deep and prolonged motor block and the marked sedative effect, which can be very useful properties of local anesthetic while conducting a number of short-termed surgical interventions, especially when rendering aid to patients with the increased excitability and possible fear before any surgical manipulations.

The study of hydrochloride of 2-isobutoxyquinoline-3-carboxylic acid (2-diethylamino-ethyl)amide **20** is of particular interest. This compound has been specially synthesized by us as an aromatic analogue of the most active of 1,2-dihydro derivatives, i.e. amide **19d**. A comparative analysis of biological properties of these isomers demonstrates that with transfer to the aromatic structure some parameters decrease, and others, vice versa, intensify. For example, amide **20** differs with the later start of anaesthesia, decrease of the

index and reduction of duration of the deep anaesthesia phase. At the same time the general duration of anaesthesia increases a little, as well as duration of the sedative effect. Unfortunately, transfer of the isobutyl substituent from the nitrogen atom to the oxygen atom is accompanied by appearance of undesirable properties – unlike amide **19d** its aromatic isomer **20** has been found to have the irritant action, though a transient one.

6. Conclusion

The research carried out by us gives reason to suppose that 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids are of great interest as a base in creating new effective medicines to eliminate pain. Such medicines can be not only local anesthetics possessing the unique complex of pharmacological properties, but, as it has been found quite recently, non-narcotic analgesics with high activity and low toxicity as well. The rich arsenal of structural and biological regularities accumulated, as well as practically unlimited synthetic potential of 4-hydroxyquinolin-2-ones allow to change the character of impact of such compounds on a living organism easily and in the required direction, and thus, to provide their direct practical value and a great perspective.

7. Acknowledgment

We appreciate the assistance of professor V.I. Mamchur (Dnepropetrovsk State Medical Academy, Ukraine) in studying biological properties of the compounds synthesized and useful comments while discussing the results obtained.

8. References

Bochkov, A.F. & Smit, V.A. (1987). *Organic Synthesis. Purposes, Methods, Tactics, Strategy* [in Russian], Nauka, Moscow, Russia

Kartsev, V.G. (Ed.). (2007). *Selected Methods for Synthesis and Modification of Heterocycles. Vol. 6. Quinolines: Chemistry and Biological Activity* [in Russian], International charitable foundation "Scientific Partnership Foundation" (ICSPF), ISBN 978-5-903078-10-3, Moscow, Russia

Kleemann, A. & Engel J. (2001). *Pharmaceutical Substances: Syntheses, Patents, Applications,* Thieme Medical Publishers, ISBN 1588900312, Stuttgart, Germany

Tomoda, K.; Asahiyama, M.; Ohtsuki, E.; Nakajima, T.; Terada, H.; Kanebako, M.; Inagi, T. & Makino, K. (2009). Preparation and Properties of Carrageenan Microspheres Containing Allopurinol and Local Anesthetic Agents for the Treatment of Oral Mucositis. *Colloids and Surfaces. B, Biointerfaces,* Vol.71, No.1, pp. 27-35, ISSN 0927-7765

Kang, C. & Shin, S.C. (2010). Preparation and Evaluation of Bioadhesive Dibucaine Gels for Enhanced Local Anesthetic Action. *Archives of Pharmacal Research,* Vol.33, No.8, pp. 1277-1283, ISSN 0253-6269

Douglas, H.A.; Callaway, J.K.; Sword, J.; Kirov, S.A. & Andrew, R.D. (2011). Potent Inhibition of Anoxic Depolarization by the Sodium Channel Blocker Dibucaine. *Journal of Neurophysiology,* Vol.105, No.4, pp. 1482-1494, ISSN 0022-3077

Ukrainets, I.V. (1992). Synthesis, Chemical Transformation and Biological Properties of Alkyl(aryl)amides of Malonic Acid Derivatives [in Russian]. *Thesis for Doctor Degree*

in Chemistry in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy, Manuscript, Kharkov, Ukraine

Ukrainets, I.V.; Gorokhova, O.V.; Taran, S.G.; Bezugly, P.A.; Filimonova, N.I. & Turov, A.V. (1994). 4-Hydroxy-2-Quinolones. 24. Improved Synthesis and Biological Properties of 1-Alkyl-4-Hydroxy-2-Quinoline-3-Carboxylic Acid β-Dialkylaminoalkylamide Hydrochlorides. *Chemistry of Heterocyclic Compounds,* Vol.30, No.10, pp. 1214-1219, ISSN 0009-3122

Gorokhova, O.V. (1993). Synthesis, Chemical and Biological Properties of Alkyl- and Arylamides of Malonic Acid Derivatives [in Russian]. *Thesis for Candidate Degree in Chemistry in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy,* Manuscript, Kharkov, Ukraine

Davidenko, O.O. (2011). Synthesis, Physical, Chemical Properties and Biological Activity of Substituted 4-Hydroxy-2-Oxo-1,2-Dihydroquinoline-3-Carboxylic Acids and Their Derivatives [in Ukrainian]. *Thesis for Candidate Degree in Pharmacy in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy,* Manuscript, Kharkov, Ukraine

Ukrainets, I.V.; Bezugly, P.A.; Gorokhova, O.V.; Taran, S.G. & Treskach, V.I. (1998). Method for Preparing 1-Propyl-2-Oxo-4-Hydroxyquinoline-3-Carboxylic Acid Diethylaminoethylamide Hydrochloride (Chinoxycaine). *Patent Ukraine 24967*, Available from http://base.ukrpatent.org/searchINV/

Ukrayinecz, I.V. & Bezuhliy, P.A. (2002). Injectable Anesthetic. *Patent USA 6340692*, Available from http://worldwide.espacenet.com/searchResults?NUM=US6340692&DB=EPODOC&locale=en_EP&ST=number&compact=false

Romanov, I.V. & Ukrainets, I.V. (2006). Method for Preparing 1-Propyl-2-Oxo-4-Hydroxyquinoline-3-Carboxylic Acid Diethylaminoethylamide Hydrochloride (Chinoxycaine). *Patent Russia 2285692*, Available from http://worldwide.espacenet.com/searchResults?NUM=RU2285692&DB=EPODOC&locale=en_EP&ST=number&compact=false

Kubinyi, H. (2006). In Looking ups of the New Compounds-leaders for Creation of Drugs [in Russian]. *Russian Chemical Journal*, Vol.L, No.2, pp. 5-17, ISSN 0373-0247, Available from http://www.chem.msu.su/rus/journals/jvho/2006-2/5.pdf

Kuznetsov, S.G.; Chigareva, S.M. & Ramsh, S.M. (1991). Pro-drugs. Chemical Aspect. *Summaries in Science and Technology. Organic Chemistry* [in Russian], VINITI, ISSN 0137-0251, Moscow, Russia

Ukrainets, I.V. (1988). Synthesis and Research of New Biological Active Derivatives of Malonic Acid 2-Carboxyphenylamide [in Russian]. *Thesis for Candidate Degree in Pharmacy in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy,* Manuscript, Kharkov, Ukraine

Ukrainets, I.V.; Kravtzova, V.V.; Tkach, A.A. & Rybakov, V.B. (2009). 4-Hydroxy-2-Quinolones. 155. Bioreversible Chemical Modification of Chinoxycaine at the Tertiary Amino Group as a Method of Improving its Pharmaceutical Activity. *Chemistry of Heterocyclic Compounds,* Vol.45, No.6, pp. 698-704, ISSN 0009-3122

Vinogradova, N.D.; Kuznetsov, S.G. & Chigareva, S.M. (1980). Quaternary Ammonium Salts with Labile N+-C Bonds as Drug Precursors. *Pharmaceutical Chemistry Journal*, Vol.14, No.9, pp. 604-609, ISSN 0091-150X

Chen, H.; Gong, Y.; Gries, R.M. & Plettner, E. (2010). Synthesis and Biological Activity of Conformationally Restricted Gypsy Moth Pheromone Mimics. Bioorganic and Medicinal Chemistry, Vol.18, No.8, pp. 2920-2929, ISSN 0968-0896

Watanabe, M.; Hirokawa, T.; Kobayashi, T.; Yoshida, A.; Ito, Y.; Yamada, S.; Orimoto, N.; Yamasaki, Y.; Arisawa, M. & Shuto, S. (2010). Investigation of the Bioactive Conformation of Histamine H3 Receptor Antagonists by the Cyclopropylic Strain-based Conformational Restriction Strategy. Journal of Medicinal Chemistry, Vol.53, No.9, pp. 3585-93, ISSN 0022-2623

Nirogia, R.V.; Kambhampati, R.; Daulatabad, A.V.; Gudla, P.; Shaikh, M.; Achanta, P.K.; Shinde, A.K. & Dubey, P.K. (2011). Design, Synthesis and Pharmacological Evaluation of Conformationally Restricted N-Arylsulfonyl-3-Aminoalkoxy Indoles as a Potential 5-HT(6) Receptor Ligands. *Journal of Enzyme Inhibition and Medicinal Chemistry,* Vol.26, No.3, pp. 341-349, ISSN 1475-6366

Ukrainets, I.V.; Tkach, A.A. & Grinevich, L.A. (2008). 4-Hydroxy-2-Quinolones. 148. Synthesis and Anti-tubercular Activity of 1-Hydroxy-3-Oxo-6,7-Dihydro-3H,5H-Pyrido-[3,2,1-*ij*]quinoline-2-Carboxylic Acid N-R-Amides. *Chemistry of Heterocyclic Compounds,* Vol.44, No.8, pp. 956-966, ISSN 0009-3122

Baumer, V.N.; Shishkin, O.V.; Ukrainets, I.V.; Sidorenko, L.V. & El Kayal, S.A. (2004). 1-Ethyl-4-Hydroxyquinolin-2(1H)-one. *Acta Crystallographica Section E,* Vol.60, No.12, pp. o2356-o2358, ISSN 1600-5368

Ukrainets, I.V.; Gorokhova, O.V.; Sidorenko, L.V. & Bereznyakova, N.L. (2007). 4-Hydroxy-2-Quinolones. 111. Simple Synthesis of 1-Substituted 4-Methyl-2-Oxo-1,2-Dihydroquino-line-3-Carboxylic Acids. *Chemistry of Heterocyclic Compounds,* Vol.43, No.1, pp. 58-62, ISSN 0009-3122

Ukrainets, I.V.; Sidorenko, L.V.; Gorokhova, O.V.; Mospanova, E.V. & Shishkin, O.V. (2006a). 4-Hydroxy-2-Quinolones. 94. Improved Synthesis and Structure of 1-Hydroxy-3-Oxo-5,6-Dihydro-3H-Pyrrolo[3,2,1-*i,j*]quinoline-2-Carboxylic Acid Ethyl Ester. *Chemistry of Heterocyclic Compounds,* Vol.42, No.5, pp. 631-635, ISSN 0009-3122

Kravtsova, V.V. (2011). The Search of New Local Anesthetics in the Range of Amide Derivatives of Oxoquinoline-3-Carboxylic Acids [in Ukrainian]. *Thesis for Candidate Degree in Pharmacy in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy,* Manuscript, Kharkov, Ukraine

King, F.D. (Ed.). (2002). *Medicinal Chemistry: Principles and Practice,* Royal Society of Chemistry, ISBN 0854046313, Cambridge, UK

Devereux, M. & Popelier, P.L. (2010). In Silico Techniques for the Identification of Bioisosteric Replacements for Drug Design. *Current Topics in Medicinal Chemistry,* Vol.10, No.6, pp. 657-668, ISSN 1568-0266

Wassermann, A.M. & Bajorath, J. (2011). Large-scale Exploration of Bioisosteric Replacements on the Basis of Matched Molecular Pairs. *Future Medicinal Chemistry*, Vol.3, No.4, pp. 425-36, ISSN 1756-8919

Large, J.M.; Torr, J.E.; Raynaud, F.I.; Clarke, P.A.; Hayes, A.; Stefano, F.; Urban, F.; Shuttleworth, S.J.; Saghir, N.; Sheldrake, P.; Workman, P. & McDonald, E. (2011). Preparation and Evaluation of Trisubstituted Pyrimidines as Phosphatidylinositol 3-Kinase Inhibitors. 3-Hydroxyphenol Analogues and Bioisosteric Replacements. Bioorganic and Medicinal Chemistry, Vol.19, No.2, pp. 836-851, ISSN 0968-0896

Kolisnyk, O.V. (2009). Synthesis, Physical, Chemical and Biological Properties of 4-Hydroxy-2-Oxo-1,2,5,6,7,8-Hexahydroquinoline-3-Carboxylic Acids Amidation Derivatives. [in Ukrainian]. *Thesis for Candidate Degree in Pharmacy in speciality 15.00.02 – Pharmaceutical Chemistry and Pharmacognosy,* Manuscript, Kharkov, Ukraine

Ukrainets, I.V., Kravtsova, V.V., Tkach, A.A., Mamchur, V.I. & Kovalenko, E.Yu. (2010). 4-Hydroxy-2-Quinolones. 173. 1-R-3-(2-Diethylaminoethyl)-1H-Quinazoline-2,4-Dione Hydrochlorides as Potential Local Anesthetic Agents. *Chemistry of Heterocyclic Compounds,* Vol.46, No.1, pp. 96-105, ISSN 0009-3122

Ukrainets, I.V.; Sidorenko, L.V.; Gorokhova, O.V. & Jaradat, N.A. (2006b). 4-Hydroxy-2-Quinolones. 93. Synthesis and Biological Properties of 2-Hydroxy-4-Imino-1,4-Dihydroquinoline-3-Carboxylic Acid N-R-Amides. *Chemistry of Heterocyclic Compounds,* Vol.42, No.4, pp. 475-487, ISSN 0009-3122

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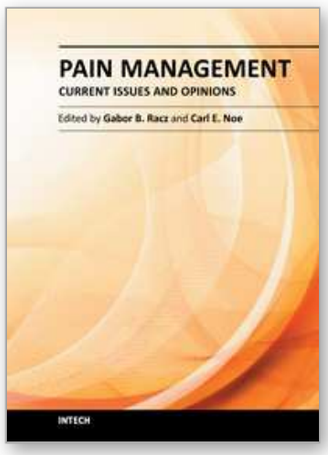

Pain Management - Current Issues and Opinions
Edited by Dr. Gabor Racz

ISBN 978-953-307-813-7
Hard cover, 554 pages
Publisher InTech
Published online 18, January, 2012
Published in print edition January, 2012

Pain Management - Current Issues and Opinions is written by international experts who cover a number of topics about current pain management problems, and gives the reader a glimpse into the future of pain treatment. Several chapters report original research, while others summarize clinical information with specific treatment options. The international mix of authors reflects the "casting of a broad net" to recruit authors on the cutting edge of their area of interest. Pain Management - Current Issues and Opinions is a must read for the up-to-date pain clinician.

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Igor Ukrainets (2012). Creation of New Local Anesthetics Based on Quinoline Derivatives and Related Heterocycles, Pain Management - Current Issues and Opinions, Dr. Gabor Racz (Ed.), ISBN: 978-953-307-813-7, InTech, Available from: http://www.intechopen.com/books/pain-management-current-issues-and-opinions/creation-of-new-local-anesthetics-based-on-quinoline-derivatives-and-related-heterocycles

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