Chapter

Amidoxime Derivatives with Local Anesthetic, Antitubercular, and Antidiabetic Activity

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Abstract

Our task in the field of new derivatives of amidoximes was the elaboration for new medication with increased activity and lower toxicity than medications used in practice. Here are the results of the search for new painkillers and antitubercular and antidiabetic drugs in the class of amidoxime derivatives. Nitrous derivatives of α-chloro-α-isonitrosoacetone, *O*-aroyl-β-aminopropioamidoximes, and 3-[β-(piperidine-1-yl)]ethyl-5-aryl-1,2,4-oxadiazoles were tested for conduction, infiltration, and terminal anesthesia. Among them hit compounds were discovered. The search for new anti-TB drugs is executed in the world. Salts and bases of *O*-aroylation products of β-(thiomorpholin-1-yl) and β-(4-methylpiperazin-1-yl) propioamidoximes during *in vitro* antitubercular screening for DS, DR, and MDR strains of *M. tuberculosis* manifest themselves as highly active competitive compounds. In the series of the derivatives of β-aminopropioamidoximes, a search for new antidiabetic drugs was done. The compounds with pronounced antidiabetic properties were revealed. The obtained data of the most promising samples with a preliminary assessment of their average toxic dose in animals can be used in further *in vivo* testing of infiltration anesthesia conditions, of antidiabetic properties, and at the development of doses and new treatment regimens for TB.

Keywords: nitrous derivatives of α-chloro-α-isonitrosoacetone, bases and salts of *O*-aroyl-β-aminopropioamidoximes, 3-(β-amino)ethyl-5-aryl-1,2,4-oxadiazoles, local anesthetics, *in vitro* antitubercular, antidiabetic screening

1. Introduction

First of all, researchers' interest in amidoximes is due to the possibility of their synthetic modification according to the reaction groups NOH and NH_2. The largest number of derivatives was obtained as a result of acylation reactions at the O-atom of the NOH group and subsequent transformations involving the NH_2 fragment to 1,2,4-oxadiazoles [1]. In most cases, amidoxime derivatives, including heterocyclic radicals, under standard conditions are stable, allowing their structural identification, and withstand storage and biological screening. Arrays of data were obtained on their diverse biological activity: antitubercular, local anesthetic, antidiabetic, antioxidant, etc. [2, 3].

The rational use of drugs is one of the urgent problems of modern medicine. A doctor of any profile most often faces the need to eliminate and prevent pain.

With pain of varying intensities, adequate pain relief reduces the patient's tension and fear, prevents him from forming a negative attitude to medical manipulations, and protects the nervous system of the doctor and patient, providing better medical care. The search for new painkillers with increased activity and lower toxicity than painkillers used in practice is one of the tasks of modern medical chemistry. We developed new β-aminopropioamidoximes and studied their neurotropic properties. Herein we present results from a study of the local anesthetic activities of three chemical groups of new amidoxime derivatives [4].

Tuberculosis (TB) is the leading cause of death and morbidity in more than one third of the world's population. Of the 56.4 million deaths worldwide due to the 10 leading causes in 2016, tuberculosis ranked 10th, from which 1.4 million people died [5].

In May 2014, the World Health Organization (WHO) approved a new global TB control strategy "End TB". This strategy marks a critical shift from tuberculosis control to ending the epidemic by 2035. The "End TB" strategy emphasizes the need for innovation to accelerate progress by optimizing existing ones in the short term and introducing new innovative modes in the long term [6]. In order to reduce the duration of treatment, the rapid development of drug resistance and toxic and side effects of existing anti-TB drugs, and to reduce the cost of extremely expensive treatment of TB (DS, MDR, XDR), the world is searching for new anti-TB drugs. We have synthesized the salts and bases of the *O*-aroylation products of β-(thiomorpholin-1-yl) and β-(4-methylpiperazin-1-yl)propioamidoximes, containing in the β-position pharmacophore fragments of 1-methylpiperazine and thiomorpholine. *In vitro* antitubercular screening of β-aminopropioamidoxime derivatives in the DS, DR, and MDR strains of *M. tuberculosis* revealed highly active competitive compounds which are less toxic than rifampicin and isoniazid with activity significantly exceeding the activity of the reference preparations. It is assumed that these compounds may be the subject of subsequent trials in the development of doses and new treatment regimens for TB [7, 8].

Diabetes is on the rise across the globe. Presently every 7 seconds someone is estimated to die from diabetes or its complications. This is against the background of a global diabetes prevalence of 8.8% of the world population in 2017. The prevalence is expected to further increase to 9.9% by the year 2045. In total numbers, this reflects a population of 424.9 million people with diabetes worldwide in 2017 with an estimate of a 48% increase to 628.6 million people for the year 2045 [9]. Due to the urgency of the problem of diabetes in the world, a search is underway for new antidiabetic drugs. The antidiabetic activity of amidoxime derivatives is known [10, 11]. We conducted *in vitro* testing of derivatives of β-aminopropioamidoximes: bases and pharmacologically acceptable salts of *O*-aroyl-β-(morpholin-1-yl) propioamidoxime and 5-aryl-3-β-(piperidin-1-yl and morpholin-1-yl)ethyl-1,2,4-oxadiazoles with respect to their ability to inhibit the activity of α-amylase and α-glucosidase enzymes. Identified compounds with pronounced antidiabetic properties must be noted; a series of 3,5-disubstituted 1,2,4-oxadiazoles is more active than a series of *O*-aroyl-β-aminopropioamidoximes [12].

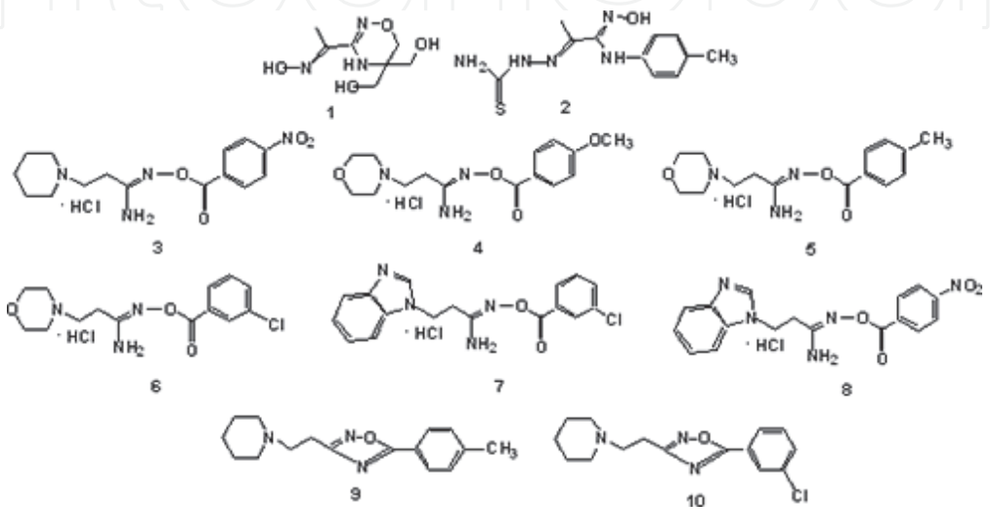
The data obtained can be used in further *in vivo* testing of the antidiabetic properties of the most promising samples with a preliminary assessment of their average toxic dose in animals.

2. Local anesthetic activity of new amidoxime derivatives

Herein we present results from a study of the local anesthetic activities of three chemical groups of new amidoxime derivatives (**1–10**) [4].

The first group includes derivatives of α-chloro-α-isonitrosoacetone such as 3-acetyl-5,5-bis(hydroxymethyl)-5,6-dihydro-4*H*-1,2,4-oxadiazine (**1**) and the *anti*-isomer of *N*-(4-methylphenyl)acetylformamidoxime thiosemicarbazone (**2**). The second group includes the hydrochlorides of *O*-aroyl-β-aminopropioamidoximes with piperidine (**3**), morpholine (**4–6**), and benzimidazole (**7** and **8**) in the β-position. The third group consists of 3-[β-(piperidin-1-yl)]ethyl-5-*p*-tolyl-1,2,4-oxadiazole (**9**) and 3-[β-(piperidin-1-yl)]ethyl-5-*m*-chlorophenyl-1,2,4-oxadiazole (**10**).

The local anesthetic activity of **1–10** was studied in three types of anesthesia, i.e., infiltration, conduction, and terminal. The reference drugs were trimecaine, lidocaine, novocaine, and kazcaine [hydrochloride of 1-(2-ethoxyethyl)-4-ethynyl-4-benzoyloxypiperidine] (**Tables 1–3**).



Compound	Anesthesia index (M ± m)	Duration of complete anesthesia (M ± m), min	Total duration of anesthesia (M ± m), min
1	22.6 ± 1.4*	10.0 ± 2.5**	40.0 ± 2.7*
2	28.0 ± 2.2**	14.4 ± 0.4***	29.1 ± 2.2**
3	28.8 ± 3.7****	15.0 ± 0.0*	28.0 ± 4.9***
4	31.4 ± 1.4**	18.3 ± 7.7	55.0 ± 1.8****
5	30.6 ± 1.3*	20.8 ± 2.4****	55.8 ± 2.1**
6	21.0 ± 2.4*	8.3 ± 2.7	34.1 ± 0.8*
7	31.0 ± 1.2****	20.0 ± 2.8*	45.8 ± 2.5****
8	34.0 ± 1.15*	25.0 ± 2.8**	55.8 ± 2.1**
9	34.1 ± 0.7**	25.0 ± 0.3*	58.3 ± 2.7*
10	36.0 ± 0.0*	85.0 ± 0.8****	125.0 ± 1.8**
Trimecaine	34.1 ± 0.5	30.0 ± 1.7	44.1 ± 1.7
Lidocaine	32.3 ± 2.3	25.8 ± 0.8	54.5 ± 2.3
Novocaine	30.0 ± 0.2	10.0 ± 0.0	22.0 ± 0.1
Kazkain	31.1 ± 1.2	25.0 ± 2.5	75.0 ± 0.7

**Compared to trimecaine.*
***Compared with lidocaine.*
****In comparison with novocaine.*
*****Compared to cascaine.*

Table 1.
*Activity and duration of action of compounds **1–10** (0.5% concentration) for infiltration anesthesia.*

Compound	Anesthesia index (M ± m)	Duration of complete anesthesia (M ± m), min	Total duration of anesthesia (M ± m), min
1	329.0 ± 20.0*	10.0 ± 0.0***	64.0 ± 1.5*
2	301.0 ± 5.3**	15.0 ± 0.0*	72.0 ± 4.0*
3	319.7 ± 5.6***	45.0 ± 0.0**	69.3 ± 3.0**
4	427.0 ± 44.0*	48.0 ± 0.0****	80.6 ± 2.0***
5	310.0 ± 43.7*	20.0 ± 0.0*	65.0 ± 3.1*
6	242.9 ± 4.7**	10.0 ± 0.8*	61.2 ± 1.2*
7	425.7 ± 15.6*	84.0 ± 2.6**	144.0 ± 3.5****
8	534.0 ± 12.0****	88.0 ± 0.0***	118.0 ± 3.1*
9	591.0 ± 34.0*	90.0 ± 2.4*	105.0 ± 5.9*
10	600.0 ± 0.0*	70.4 ± 1.1***	90.0 ± 3.1**
Trimecaine	324.0 ± 14.0	20.0 ± 0.0	63.0 ± 1.3
Lidocaine	366.8 ± 94.8	10.0 ± 0.0	68.0 ± 2.8
Novocaine	310.0 ± 43.7	10.0 ± 0.0	60.0 ± 0.0
Kazkain	600.0 ± 0.0	208.9 ± 7.3	280.0 ± 0.0

*Compared to trimecaine.
**Compared with lidocaine.
***In comparison with novocaine.
****Compared to cascaine.

Table 2.
Activity and duration of action of compounds ***1–10*** *(1% concentration) for conduction anesthesia.*

Compound	Regnier index (M ± m)	Duration of complete anesthesia (M ± m), min	Total duration of anesthesia (M ± m), min
1	85.6 ± 5.0	0.0	14.4 ± 1.5
2	242.5 ± 16.4	0.0	33.1 ± 1.6
3	186.3 ± 9.7	0.0	28.0 ± 2.4
4	150.6 ± 16.2	0.0	27.5 ± 1.9
5	281.6 ± 18.5	0.0	38.0 ± 1.9
6	13.0 ± 0.0	0.0	0.0
7	103.0 ± 10.5	0.0	22.0 ± 0.9
8	373.4 ± 37.3	0.0	43.1 ± 4.0
9	601.5 ± 32.7	0.0	62.0 ± 2.3
10	430.0 ± 14.4	0.0	48.75 ± 2.1
Dikain	1300.0 ± 0.0	65.0 ± 0.0	120.0 ± 0.0

Table 3.
Activity and duration of action of compounds ***1–10*** *(1% concentration) for terminal anesthesia.*

The experimental results indicated that all compounds **1–10** were effective to different degrees in infiltration anesthesia (**Table 1**). The most active compound was **10**, which induced the maximum deep anesthesia (anesthesia index 36.0) and exceeded statistically that of the reference drugs with the exception of lidocaine.

This compound also turned out to be more active than the other tested compounds. The anesthesia indices of **8** and **9** were almost the same as that for trimecaine and were slightly greater than those for lidocaine, novocaine, and kazcaine. The strength of the anesthesia induced by **4** and **7** was greater than that of novocaine, equal to that of kazcaine, and less than that of trimecaine and lidocaine. The anesthesia indices of **1**–**3** and **4** were less than those of the reference drugs. Compound **10** had a longer duration of conduction anesthesia than the other tested compounds (including the reference drugs).

Compounds **5** and **7**–**9** had longer durations of action than novocaine, shorter than trimecaine, and essentially the same as lidocaine and kazcaine. The duration of total anesthesia of **4** was longer than that of novocaine and slightly shorter than that of the other reference drugs. The durations of total anesthesia for **1** and **4** (10.0 and 8.3 min) were comparable with that of novocaine.

Table 2 presents results from a study of conduction anesthesia by **1**–**10**.

Like in the preceding series of tests, **10** had the highest activity. Its anesthesia index was greater than those of trimecaine, lidocaine, and novocaine and equal to that of kazcaine. Compounds **1**–**5** and **7**–**9** were rather active. Their anesthesia indices were greater than those of trimecaine, novocaine, and lidocaine. However, they were less than that of kazcaine. Compound **6** was less active than the reference drugs. Like in the preceding series of tests, the durations of total anesthesia of the studied compounds were compared. **Table 2** shows that all compounds **1**–**10** had total anesthesia duration indices that were shorter than that of kazcaine although **3**, **4**, and **7**–**10** had durations of action longer than those of novocaine, lidocaine, and trimecaine.

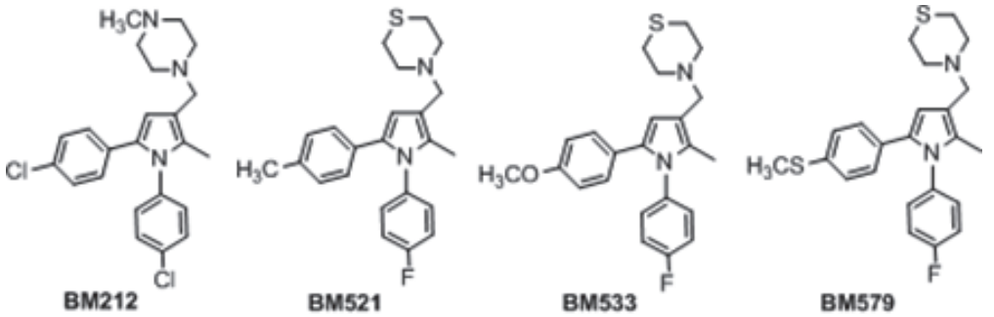
Compounds **1**–**10** in terminal anesthesia were weaker and shorter acting than dicaine (**Table 3**). However, not one of these compounds exhibited an irritating effect.

Thus, it was shown that amidoxime derivatives **1**–**10** exhibited anesthetic effects that were greater than those of the reference drugs in conduction and infiltration anesthesia. The 1,2,4-oxadiazoles **9** and **10** and to a lesser extent *O*-aroylaminopropioamidoximes with a β-benzimidazole substituent **7** and **8** had longer durations of action than the reference drugs.

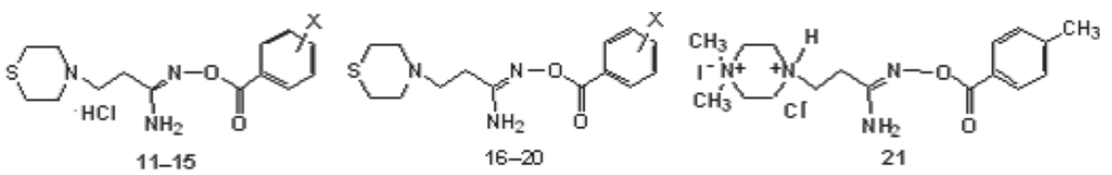
3. Search for new antitubercular drugs among the salts and bases of *O*-aroylation products of β-(thiomorfolin-1-yl)- and β-(4-methylpiperazin-1-yl)propioamidoximes

A search for qualitatively new antitubercular drugs with the requirements of reducing the duration of treatment, eliminating of the rapid drug resistance development and toxic side effects of the existing antitubercular drugs, and reducing the cost of extremely expensive treatment of TB (DS, MDR, XDR) is being conducted in the world.

1,5-Diphenylpyrroles have been identified as a class of compounds with high *in vitro* antitubercular activity. Replacing of the methylpiperazine substituent for thiomorpholine and replacing the chlorine atom in position 4 of the N-phenyl moiety with the fluorine atom, as well as varying the aromatic substituents at the C-2 atom of the pyrrole ring during the transition from *p*-CH_3 (BM221) to *p*-CH_3O (BM233) and to *p*-CH_3S (BM579) in 1,5-(4-chlorophenyl)-2-methyl-3-(4-methylpiperazin-1-yl)methyl-1H-pyrrole (BM212), leads to an increase in *in vitro* antitubercular activity on *M. tuberculosis* H37Rv strains [13, 14].



Taking into account the above examples, we synthesized compounds of the β-aminopropioamidoxime series containing in the β-position fragments of 1-methylpiperazine and thiomorpholine (**11**–**21**).



X = *p*-CH_3O (11, 16), *p*-CH_3 (12, 17), H (13, 18), *p*-Br (14, 19), *m*-Cl (15, 20)

In vitro antitubercular screening of a series of *O*-aroyl-β-aminopropioamidoximes (**11**–**21**) on DS museum H37Rv and wild* I MTB strains and two wild DR and MDR strains of MTB II and III on Shkolnikova liquid medium found that compounds **11**–**21** in varying degrees have antitubercular activity from >100 to 0.01 μg/ml (**Table 4**).

Thus, on the DS strains of MTB *O*-benzoyl-β-(thiomorpholin-1-yl) propioamidoxime (**18**) and hydrochloride, iodomethylate of *O*-*p*-toluoyl-β-(1-methylpiperazin-1-yl)propioamidoxime (**21**) showed the highest activity at 0.01 μg/ml; compound **19** had an average antitubercular activity with MBC >20 μg/ml; the remaining compounds **11**–**17** and **20** had MBC from 100 to >100 μg/ml.

The highest activity in 0.1 μg/ml on DR and MDR strains of MTB II and III was shown by hydrochloride, iodomethylate of *O*-*p*-toluoyl-β-(1-methylpiperazin-1-yl) propioamidoxime (**21**) (**Table 4**).

The acute toxic effect of rifampicin, isoniazid, and compounds **18** and **21** (LD_{50}) was determined on white mice of both sexes weighing 17–23 g when administered subcutaneously. The toxicity of rifampicin SV is 267.6 ± 7.2 mg/kg; of isoniazid 62.5 ± 12.8 mg/kg; and of compounds **18** and **21**, respectively, 325.0 ± 17.8 and 1750.0 ± 35.6 mg/kg.

Thus, hydrochloride, iodomethylate of *O*-*p*-toluoyl-β-(4-methylpiperazin-1-yl) propioamidoxime, is by 100 times more active against DS strains than rifampicin SV and by 10 times more active than isoniazid; it is by 20 times more active against DR strains than rifampicin SV and by 10 times more active than isoniazid. Hydrochloride, iodomethyl *O*-*p*-toluoyl-β-(4-methylpiperazin-1-yl)propioamidoxime, is less toxic than rifampicin SV by 6.5 times and by 28 times less toxic than isoniazid.

O-Benzoyl-β-(thiomorpholin-1-yl)propioamidoxime is by 100 times more active against DS strains than rifampicin SV and by 10 times more than isoniazid; it is less toxic than rifampicin SV by 1.2 times and by 5.2 times less toxic than isoniazid. These data are protected by the patents of the Republic of Kazakhstan [7, 8].

№ comp.	MBC on the *M. tuberculosis* strains, μg/ml				
	H37Rv	I	II	III	LD_{50}, mg/kg
11	>100	>100	100	100	—
12	100	100	100	100	—
13	100	100	100	100	—
14	>100	>100	100	100	—
15	100	100	100	100	—
16	100	100	100	100	—
17	>100	>100	>100	>100	—
18	0.01	0.01	100	100	325.0 ± 17.8
19	>20	>20	100	100	—
20	100	100	100	100	—
21	0.01	0.01	0.1	0.1	1750.0 ± 35.6
Rifampicin	1	1	2	2	267.6 ± 7.2
Isoniazid	0.1	0.1	1	1	62.5 ± 12.8

[*] Wild strains of M. tuberculosis I, II, and III were isolated from the patients and typed in the RSE "National Scientific Center for Phthisiopulmonology of the Republic of Kazakhstan" of the Ministry of Health of the Republic of Kazakhstan: I, DS (drug-sensitive) to anti-TB drugs; II, DR (drug-resistant) to rifampicin; III, MDR (multidrug-resistant) to rifampicin, isoniazid, and ethambutol.

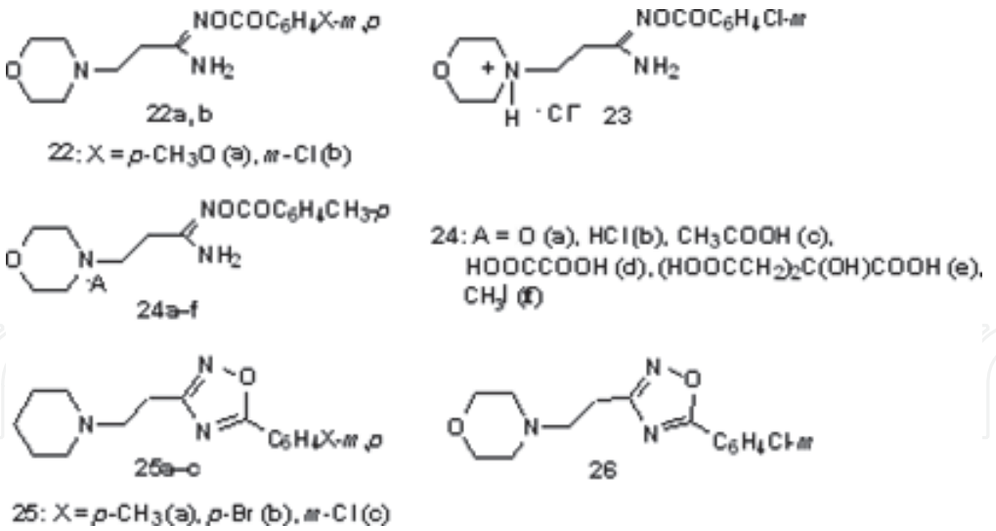
Table 4.
*Bactericidal activity and average subcutaneous toxicity of O-aroyl-β-(thiomorpholin-1-yl)propioamidoximes (**11–20**) and double salt of O-p-toluoyl-(4-methylpiperazin-1-yl)propioamidoxime (**21**) on DS and DR strains of M. tuberculosis.*

Based on the high priority requirements of increasing the effectiveness and safety of treatment in the development of new antitubercular drugs, it can be argued that *O*-benzoyl-β-(thiomorpholin-1-yl)propioamidoxime and hydrochloride, iodomethylate of *O*-*p*-toluoyl-β-(4-methylpiperazine-1-yl)propioamidoxime, are competitive because they are less toxic and more active than the basic tuberculostatics used in practice: isoniazid and rifampicin.

4. Inhibition of α-amylase and α-glucosidase by new β-aminopropioamidoxime derivatives

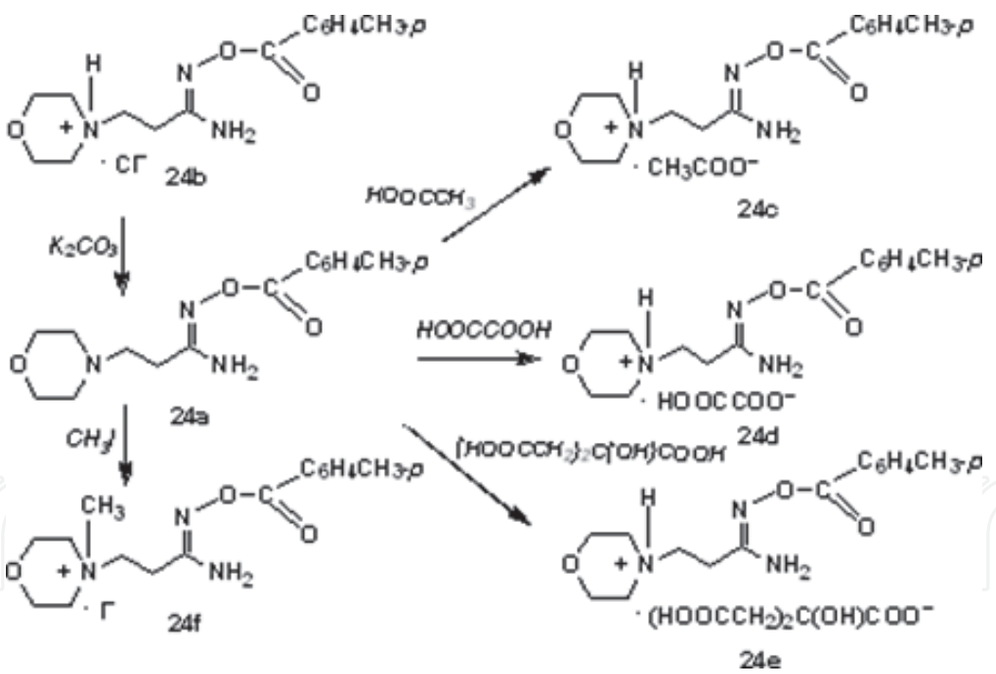
The urgency of discovering effective medicines to treat diabetes and information about the antidiabetic activity of amidoxime derivatives [9–11] prompted us to test β-aminopropionamidoxime bases and pharmacologically acceptable salts of *O*-aroyl-β-(morpholin-1-yl)propionamidoximes and 5-aryl-3-β-(piperidin-1-yl- and morpholin-1-yl)ethyl-1,2,4-oxadiazoles for *in vitro* inhibitory activity against the enzymes α-amylase and α-glucosidase, which determine the supply level of glucose from the gastrointestinal tract into the blood pool.

Herein, results from *in vitro* screening of new β-aminopropionamidoximes (**22–26**) for antidiabetic activity are now reported. The series of β-aminopropionamidoximes included bases and pharmacologically acceptable salts (hydrochloride, acetate, oxalate, citrate, and methyl iodide) of *O*-aroyl-β-(morpholin-1-yl) propionamidoximes **22–24** and 5-(*p*-, *m*-substituted phenyl)-3-(β-piperidin-1-yl- and morpholin-1-yl)-1,2,4-oxadiazoles **25** and **26**.



Compounds **22**–**24a** and **b**, **25**, and **26** were described [12, 15, 16].

Compounds **24b**–**f** were derived from the base of *O*-*p*-toluoyl-β-(morpholin-1-yl)propionamidoxime **24a** and were prepared in one step by adding of equivalent amounts of organic acids (acetic, oxalic, citric) and methyl iodide in various solvents. Acetate **24c** was prepared by reacting **24a** with a twofold excess of glacial AcOH in refluxing in EtOH.



The *in vitro* activity of **22**–**26** for inhibition of α-amylase and α-glucosidase was tested using two series of experiments. **Table 5** presents the screening results using acarbose as the standard in both instances.

The greatest inhibitory activities (~50%) for α-amylase were found for O-*m*-chlorobenzoyl-β-(morpholin-1-yl)propionamidoxime (**22b**, 48%); 5-(*p*-bromophenyl)-3-[(β-piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**25b**, 51%); and 5-(*m*-chlorophenyl)-3-[(β-morpholin-1-yl)ethyl]-1,2,4-oxadiazole (**26**, 48%). Moderate activity for α-amylase (from 27 to 43%) was found for O-*m*-chlorobenzoyl-β-(morpholin-1-yl)propionamidoxime hydrochloride (**23**, 35%); base *O*-*p*-toluoyl-β-(morpholin-1-yl)propionamidoxime (**24a**, 32.5%); citrate of *O*-*p*-toluoyl-β-

Compound		22a	22b	23	24a	24b	24c	24d	Acarbose
Inhibition, %	α-Amylase	—	48.0 ± 5.8	35.0 ± 0.6	32.5 ± 0.22	27.0 ± 5.5	25.6 ± 0.26	—	71.0 ± 2.7
	α-Glucosidase	78.7 ± 0.91**	23.0 ± 0.84	45.1 ± 1.99	22.8 ± 0.09	34.7 ± 1.36	27.4 ± 0.15	—	75.0 ± 1.32

Compound		24e	24f	25a	25b	25c	26	Acarbose
Inhibition, %	α-Amylase	37.0 ± 3.4	—	43.0 ± 3.0	51.0 ± 9.1	—	48.0 ± 5.9	71.0 ± 2.7
	α-Glucosidase	—	78.1 ± 4.41**	67.2 ± 0.82	68.7 ± 1.81	67.2 ± 1.79	61.7 ± 2.26	75.0 ± 1.32

**Activity absent (—).*
***$p > 0.05$ vs. acarbose.*

Table 5.
Inhibitory activity of **22–26** *for α-amylase and α-glucosidase, %*.*

(morpholin-1-yl)propionamidoxime (**24e**, 37%); and 5-(*p*-toluoyl)-3-[(β-piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**25a**, 43%).

The highest inhibitory activities against α-glucosidase were exhibited by O-*p*-anisoyl-β-(morpholin-1-yl)propionamidoxime (**22a**, 78.7%); iodine methylate of O-*p*-toluoyl-β-(morpholin-1-yl)propionamidoxime (**24f**, 78.1%); and 5-(*m*-chlorophenyl)-3-[(β-morpholin-1-yl)ethyl]-1,2,4-oxadiazole (**26**, 61.7%).

Moderate inhibitory activity for α-glucosidase was manifested by O-*m*-chlorobenzoyl-β-(morpholin-1-yl)propionamidoxime (**22b**, 23%) and its hydrochloride (**23**, 45.1%).

The reference compound acarbose exhibited the standard inhibitory activity against α-amylase and α-glucosidase of 71.0 and 75.5%, respectively.

In conclusion, it is noteworthy that bases and pharmacologically acceptable salts of *O*-aroyl-β-aminopropionamidoximes and 5-substituted phenyl-3-β-(piperidin-1-yl and morpholin-1-yl)ethyl-1,2,4-oxadiazoles (**22–26**) showed more pronounced inhibitory activity for α-glucosidase than for α-amylase. Both **22a** and **24f** had α-glucosidase activity comparable with that of the standard acarbose.

A structure–activity relationship for two series of screening experiments found that, as a rule, 3,5-disubstituted 1,2,4-oxadiazoles exhibited greater inhibition of α-amylase and α-glucosidase than their chemical precursors, i.e., bases and pharmacologically acceptable salts of *O*-aroyl-β-aminopropionamidoximes.

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