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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW SULFONAMIDES

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Abstract. A new method for the synthesis of pyrazole- or pyridazole-[1,5-a] pyridines by the reaction of 1-benzenesulfonylimino pyridinium chloride with α- or β-halo-containing sulfamides, chloroacetic acid, 1-chloro-2,3-dihydroxypropane, etc. The optimal conditions for the synchronous reaction of heterocyclization are found. Benzenesulfonyliminopyridinium chloride was found to form pyrazolopyridines with 1,2-polarophiles, and pyridazine pyridines with 1,3-polarophiles. The biochemical properties like anti-Alzheimer's potential was also recorded which reveals strong butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) inhibitory effects. Compound 5 was 1000-fold more active inhibitor of acetylcholinesterase compared to tacrine with a Ki value of 0.05±0.01 μM.

Keywords: *pyrazolpiridines, pyridazole pyridines, dipolarorophiles, antioxidant and anticholinergic.*

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1. Introduction

Sulfonamides containing dual substance in heterocycles are important in reaction of arylsulfonioxamides with heterocyclic amines. It should be noted that the presence of the amine group in the isoxazole has a significant effect on its ability to react. (Tosheva & Antonova, 2005) Hetaryl sulphonamides were obtained with high output by sulfoxoride 5-amino-3,4-dimethylisoxazole (Tamura *et al.*, 2008) and diphenylisoxazole reaction. Sulfonylchlorides also had high yields and selectivity during oxidase (Braje *et al.*, 2008) and pyrazole-like cingulate aminoheterocyclic reaction. However, sulfonylchlorides require a boil to pyridine solution for a long time to react with benzoxazole (Zhong *et al.*, 2007).

The reaction of arylsulphonyl chlorides with oxygen, sulfur, N-pyridine or pyrimidine-containing piperases is very easy. At the same time, the effects of radicals and functional groups in molecules were not observed (Mohammed, 2007; Gan *et al.*, 2011).

Among condensed heterocycles, pyrazolo- or pyridazolopyridines, which have a wide spectrum of biological activity, occupy a special place. Condensed pyridines have a pronounced inhibitory effect of cholinesterase and are widely used in medicine. Among these drugs, pyridostigmine bromide, quinotilin, alloxime and others have found use. Pyrazolo-pyridines are very strong inhibitors of γ-secretase (Ye *et al.*, 2013) and dihydropyrazolopyridinyl sulfamides have an autoimmune property (Herrey *et al.*, 2004). Pyridazonyl sulfamide derivatives exhibit strong antimicrobial activity (Mohammed, 2007).

As can be seen from the examples given above, urea and tiourea fragments contain different application areas. The fact that new compounds that we will synthesize, especially 1-arylsuphonylpyrazole- or pyridazin [1,5-a]-pyridine derivatives, has increased our expectations for their application in the petrochemical industry and has prompted us to accomplish this. New synthesized compounds and active heterocycle rings show that it is necessary to examine their various properties. Moreover, there is no systematic study of the effect of cyclic chains and different functional groups on the chemical properties of the compounds containing the ring in the literature in relation to various side effects with different side effects.

2. Experimental

2.1. General chemistry

The IR spectra were taken on the instrument Nicolet IS-10, and the ^{1}HNMR spectra of the synthesized sulfamides were recorded on a Tesla-467 spectrophotometer with an operating frequency of 90 MHz.

2.1.1. 1-Benzenesulfonamide-2-R-3-Z-1,2-dihydropyrazolo[1,5-a]pyridines (I-III)

0.001 mol of N-benzenesulfonamidepyridinium chloride and 0.001 mol of dipolar (1,2-dichloro-3-benzenesulfamide, chloroacetic acid, β-bromopropionic acid, 1-chloro-2,3-dihydroxypropane) were dissolved in 50 ml of ethanol. To the solution was added dropwise a solution of 0.002 mol NaOH in ethanol. It was boiled until complete precipitation of NaCl or NaBr (5.5 - 6.0 hour). It was cooled, filtered, the filtrate was evaporated to half the volume, cooled and the precipitated crystals were recrystallized from ethanol.

2.1.2. 6,6-Dimethyl-4-oxycyclohexane-2,3-pyrazolo-1-phenylsulfamido [1,5-a] pyridine (IV)

4.2 g (0.03 mol) of dimedone and 8.12 g (0.03 mol) of pyridinimine were dissolved in 20 ml of ethanol. With stirring, a 7% alkali solution (1.5 g of NaOH in 40 ml of ethanol) was added dropwise. Then the mixture was heated for 5-6 hours, half the volume of the alcohol was distilled off, cooled, 20 ml of water was added and the crystals obtained were filtered. Then they were recrystallized in ethanol.

2.1.3. 1-Benzenesulfamido-2-R1-4-R2-pyridazo[1,6-a]pyridines (V-X)

The method of obtaining is similar to the method of synthesis of compounds. However, 0.15 mmol of morpholine is taken, instead of alkali.

2.2. Cholinesterase inhibition

For this part, horse serum were and electric eel used as sources of BChE and AChE enzymes, respectively. The Ellman's assay was used to record the BChE and AChE inhibitory activity. The reaction mixture consisted of 100 μL of buffer at pH 8, 50 μL of the test molecule, 20 μL enzyme butyrylcholine or acetylcholinesterase and 50 μL DTNB. Also, 1 mM of 10 μL of substrate butyrylthiocholine iodide for BChE and acetylcholine iodide for AChE were added. The amount of product formed was measured by using spectrophotometer at 412 nm.

3. Results and discussion

3.1. Chemistry

The reaction of 1,3-dipolar addition of pyridine-N-imines to polarophiles is the only method for the synthesis of pyrazolo-, pyridazolo-, triazolopyridines. For this purpose, methods have been developed for the preparation of pyridine-N-imines by the reaction of pyridine with hydrazine sulfonate (Omietanski & Sisler, 1956) and aminosulfonic acid (Killer *et al.*, 1946). The reaction of the dipolar with these imine is difficult, and the yields of heterocycles are low. When treating mesityl-o-sulfonate with amberlite, very reactive pyridine-N-imines were obtained (Tamura *et al.*, 1972).

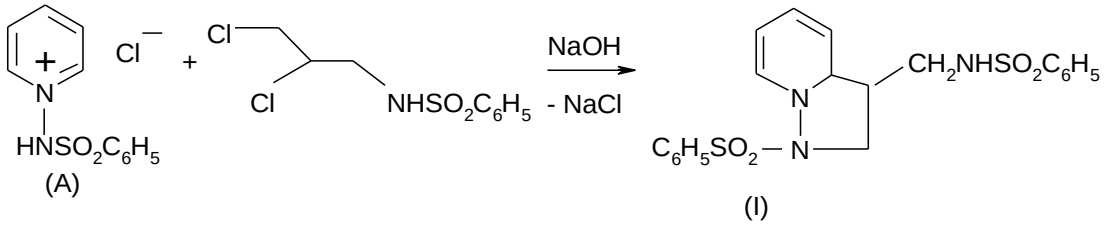
The reaction of heterocyclization of pyridine-N-imine with derivatives of alkynes and alkenes (Anderson *et al.*, 1981; Tamura *et al.*, 1975) with the preparation of pyrazolopyridines was studied. Given the low yield of this class of compounds, they are obtained using catalysts (Miki *et al.*, 1988).

1,3-dipolar compounds containing N-arylsulfone fragments have been studied not enough. They are obtained either with great difficulty (Ashay *et al.*, 1947) or indirectly (Herrey *et al.*, 2004).

Condensed pyrimidines containing sulfamide fragments were obtained indirectly by the reaction of triazolopyrimidines with sulfochlorides (Chernyshev *et al.*, 2008). The yields of the resulting 2-sulfonylamino-1,2,4-triazolo [1,5-a] pyrimidines are very high.

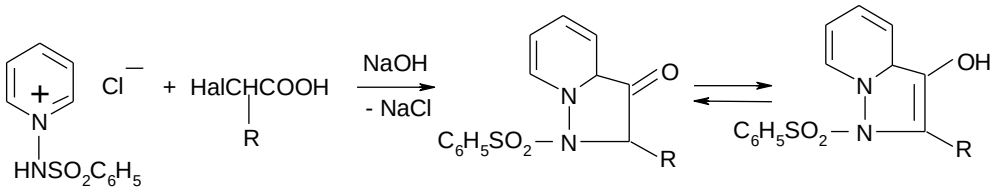
N-[(1,2,4)-triazolo]pyridines were synthesized by a similar method. Aminotriazolopyrimidines and aryl sulphochlorides were taken for this reaction (Hamilton, 2008).

We studied the reactions of 1,3-dipolar cycloaddition of 1-(arylsulfonyl)-aminopyridinium to dipolarophiles (chloroacetonitrile, benzoin, diketones, and to unsaturated ketones) and synthesized 1-(arylsulfonyl)-pyrazolo-[1,5-a] pyridines. When comparing the reactivity of dipolarophiles, it was found that with increasing tension and in the presence of electron-withdrawing substituents their reactivity increases. For the synthesis of such compounds, the reaction of sulphonic acid chloramides (chloramine-B or -T) with pyridine was used (Mamedov *et al.*, 2007). The resulting 1-(arylsulfonyl) iminopyridinium chloride, interacting with dipolarophiles, for example, with arylidenemaldonodinitriles, with a high degree of stereospecificity, forms 1-(arylsulfonyl)-pyrazolo-[1,5-a] pyridines (Farzaliev *et al.*, 2010). It was clarified that due to the high reactivity of the compound, the electronegativity and the spatial loading of the dipolarophile does not affect the reaction of 1,3-dipolar heterocyclization. Our further research has shown that the reaction of heterocyclization of a dipolarophile with 1-(arylsulfonyl)iminopyridine (comp. A), the nature and content of the electron-withdrawing group in their composition have little effect. For example, the reaction of compound (A) with 1,2-dichloro-3-benzenesulfonamide produces 1-benzenesulfanilamido-3-benzenesulfamidomethyl-pyrazolo [1,5-a] pyridine:



Probably, in the presence of alkali, nucleophilic substitution of hydrogen of sulfamide nitrogen by chlorine in secondary carbon occurs, followed by substitution of pyridine hydrogen and closure of the heterocycle. An attempt to obtain an intermediate of N-alkyl sulfonamide nitrogen from sulfonylpyridine-N-imine was unsuccessful.

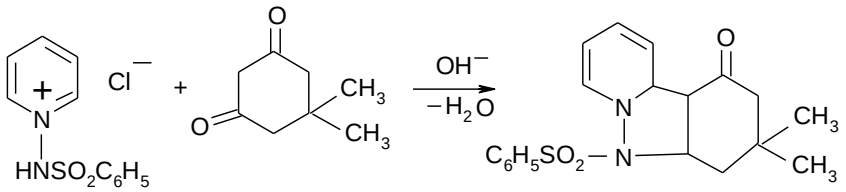
In the interaction of sulfonyliminopyridinium with chloroacetic and α-bromopropionic acid, 1-(benzenesulfonyl)pyrazolo [1,5-a] pyridinones are formed:



R = H (II); CH_3 (III)

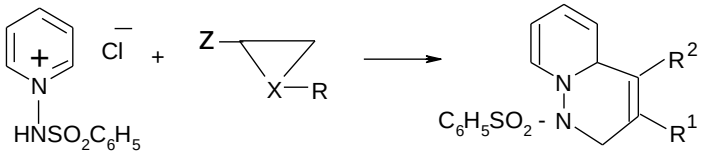
Compounds (II) and (III) dissolve in 15-20% alkali, which proves the presence of keto-enol tautomerism. In addition, in the PMR spectrum recorded in a solution of a highly ionizing solvent, dimethyl sulfoxide, there is a band in the region of 5.2 ppm, corresponding to the OH group.

Sulfonyliminopyridine with cyclic diketones (Dimedone) in the presence of a base also easily reacts to heterocyclization:



(A) (IV)

It was established that the reaction of sulfonyliminopyridine with chloromethyl- or nitrilaziridine sulfamides and with epichlorohydrin produces 1-(benzenesulfonyl)pyridazino- [1,6-a] pyridines:



(A)

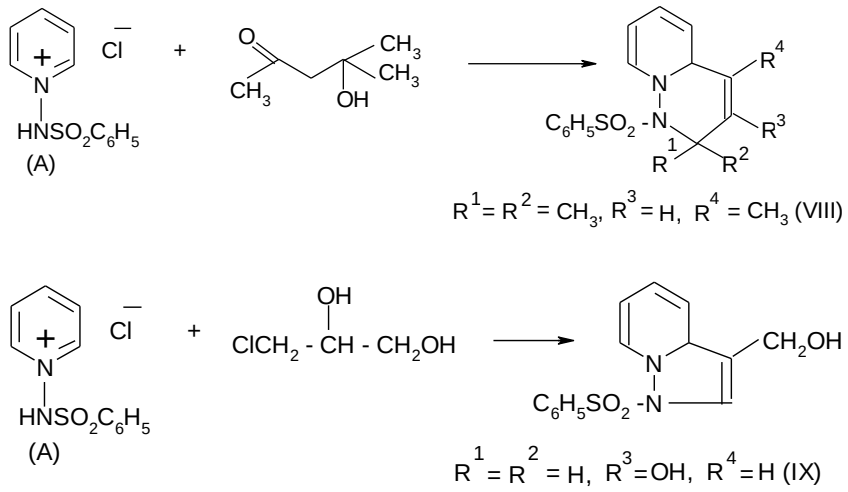
Z = $ClCH_2$, X=N, R=$SO_2C_6H_5$ (a): R^1 = $NHSO_2C_6H_5$, R^2 = H (V)

Z = CN, X = N, R = $SO_2C_6H_5$ (b): R^1 = $NHSO_2C_6H_5$, R^2 = NH_2 (VI)

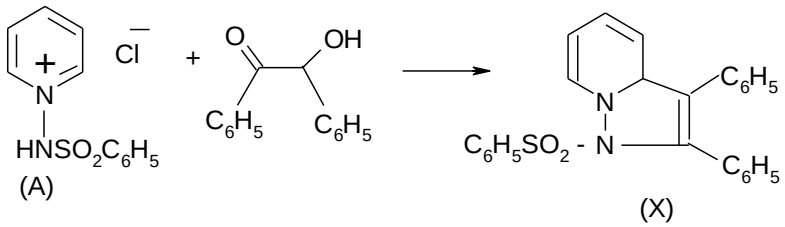
Z = $ClCH_2$, X , R = O (c) : R^1 = OH, R^2 = H (VII)

The outputs of compound (VII) are lower than those of compounds (V) - (VI). This can be explained by the fact that when using 2-chloroxyrane, the opening of the epoxy group is difficult.

Sulfamidopyridinimine in the presence of alkali enters easily into a heterocyclization reaction with diacetone alcohol and with 1-chloro-2,3-hydroxypropane :



The yields of compounds (VIII) and (IX) are lower than those of other pyridazine pyridines (60 - 65%). Heterocyclization with benzoin takes place with brief heating. The yield in this reaction reaches 85%:



In the PMR spectrum (Fig. 1) of compound III, methyl protons appear in the region of 1.7 ppm. (triplet) The proton of the OH groups as a doublet is in the region of 5.2 ppm, the protons of the aromatic ring are in the region of 7.0 ppm, and the pyridine fragment is in the region of 7.6 ppm. Integral intensity corresponds to the number of protons in the product.

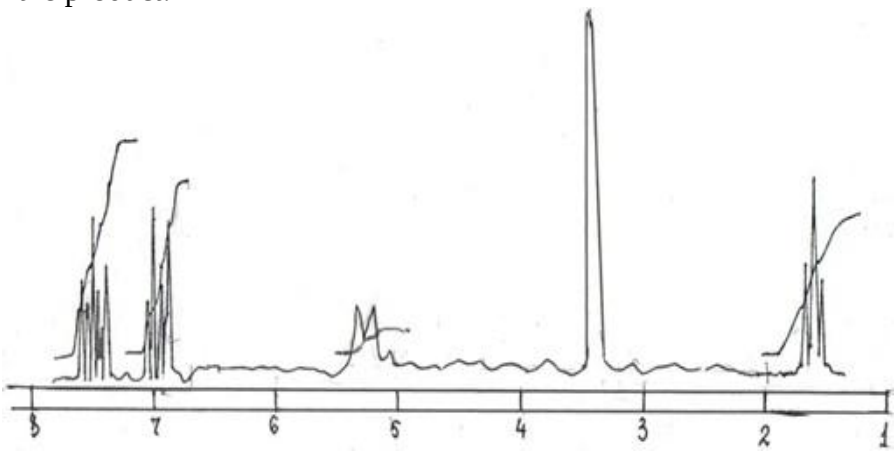


Figure 1. PMR spectrum of 1-benzenesulfamido-2-methyl-3-hydroxypyrazolo-[1,5-a]-pyridine (III)

In the PMR spectrum (Fig. 2) of compound VI, the protons of the 2H-pyridazole fragment appear as a singlet in the 7.2 ppm region. The region of manifestation of 5H-aromatics is 7.3 - 7.7 ppm. The protons of 4H-pyridine lie in the range of 7.9 - 8.2 ppm.

The hydrogen atoms of the amino groups appear as a doublet in the region of 5.7. ppm, and hydrogen of sulfamide nitrogen in the area of 6.3. ppm.

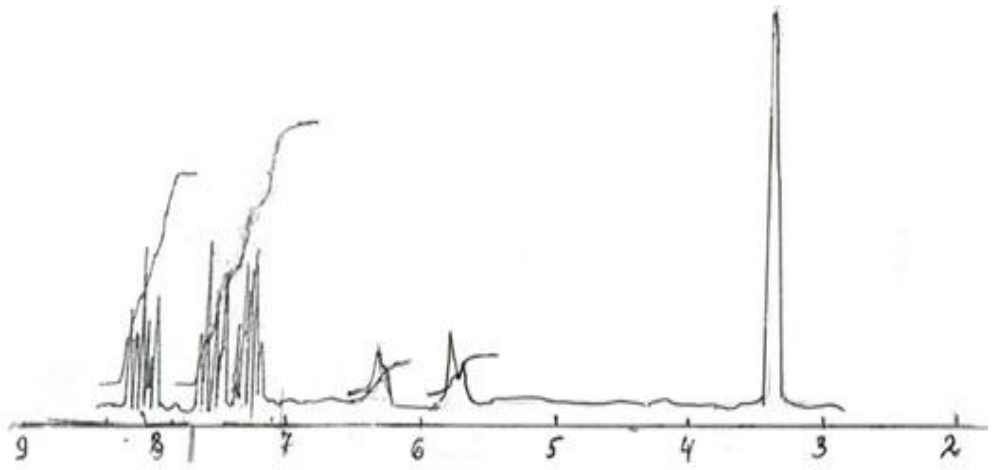


Figure 2. PMR spectrum of 1,3-diphenylsulfamido-3-amino-pyridazo-[1,6-a]-pyridine (VI)

In the PMR spectrum (Fig. 3) of compound VIII, the protons of the two methyl groups appear together in the 2.1–2.4 ppm region. The protons of another methyl group (4-position of pyridazine) in the form of a triplet are in the region of 2.6 ppm. Pyridazine protons appear at 6.8 ppm. The protons of the aromatic fragment are in the region of 7.0 - 7.2 ppm, and pyridine in the region of 7.8 - 8.0 ppm.

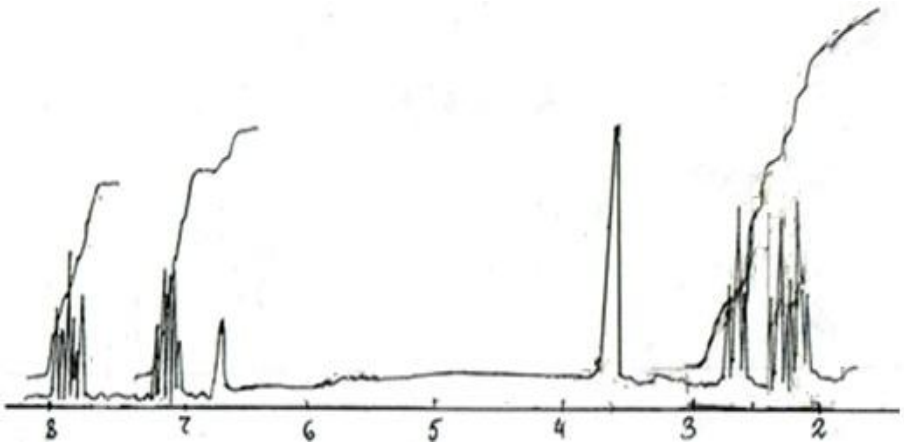


Figure 3. PMR spectrum of 1-benzenesulfonamide-2,2,4-trimethyldihydropyridazo-[1,5-a]-pyridine (VIII)

Physico-chemical characteristics of the compounds (I-X) are given in Table 1.

3.2. Biochemical Results

3.2.1. Biological activity

Our previous studies have shown that compounds containing a sulfamide fragment have high bactericidal properties.

In order to expand the understanding of the dependence of biological activity on the chemical structure, we studied the biologicial properties of some synthesized sulfamide derivatives. To this end, a study was conducted on the effect of the concentration of hetarylsulfamides in mol/l $\bullet 10^{-3}$ for a certain period of time. These data are shown in the diagram (Fig. 4).

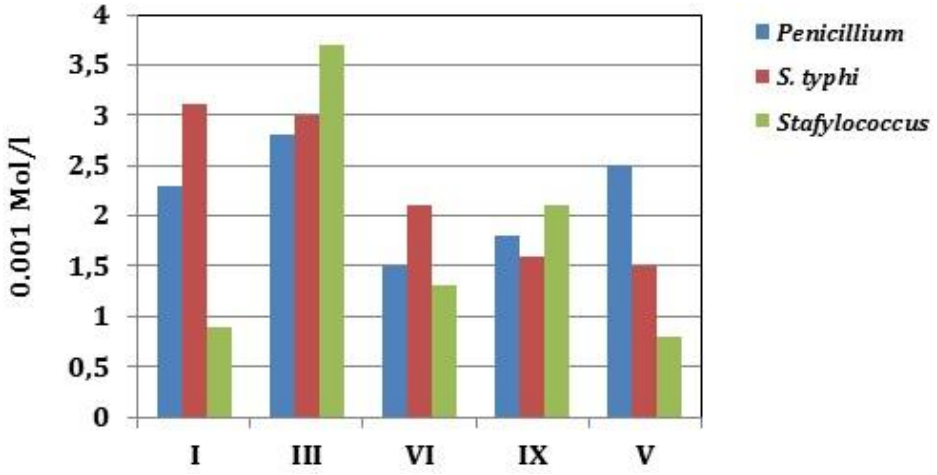


Figure 4. Antimicrobial properties of sulfamides

Table1. Physical and chemical characteristics and data of IR spectra of pyrazolo- and pyridazolopyridines

№ comp.	Yield, %	$T_{melt.}$, ^0C	Gross formula	Elemental analysis, Found % Calculated		Data ofIR spectroscopy, cm^{-1}
				N	S	
I	71.6	188 – 190	$C_{20}H_{20}N_3O_4S_2$	9.40 9.74	15.21 14.85	NH – 3370, SO_2N – 1140, 1440
II	76.3	186 – 188	$C_{13}H_{12}N_2O_3S$	10.02 10.15	11.78 11.59	O – 1690, OH – 3410, SO_2N – 1130, 1420
III	69.5	189 – 191	$C_{14}H_{14}N_2O_3S$	9.69 9.55	11.26 11.03	O – 1685, OH – 3410, SO_2N – 1160, 1450
IV	69.8	193 – 195	$C_{19}H_{22}N_2O_3S$	7.61 7.82	9.28 8.94	O – 1705, SO_2N – 1155, 1460
V	69.9	178 – 180	$C_{20}H_{19}N_3O_4S_2$	9.63 9.79	14.98 14.92	SO_2N – 1145, 1150, 1438, 1445
VI	68.9	189 – 191	$C_{20}H_{22}N_4O_4S_2$	12.39 12.61	14.72 14.41	NH_2 – 3380, SO_2N – 1140, 1460
VII	67.9	171 – 173	$C_{14}H_{16}N_2O_3S$	9.39 9.62	11.32 10.99	OH – 3410, SO_2N – 1140, 1450
VIII	62.2	187 – 189	$C_{17}H_{20}N_2O_2S$	8.09 8.86	9.82 10.14	SO_2N – 1140, 1450
IX	68.7	171 – 173	$C_{14}H_{16}N_2O_3S$	9.28 9.63	10.76 10.96	OH – 3390, SO_2N – 1135, 1425
X	84.9	185 – 186	$C_{25}H_{20}N_2O_2S$	7.15 6.80	7.49 7.77	–

Among the studied compounds, the most effective against Staphylococcus aureus are comp. (I) and (V). The optimal concentration to suppress Staphylococcus aureus for comp. (I) is 0.54 mol/l $\bullet 10^{-3}$, and for comp. (V) - 0.56 mol/l $\bullet 10^{-3}$. Both of these compounds contain two sulfamide groups in their molecule, which may be the reason for their high efficacy against staphylococcus. A slight difference in efficiency can be

explained by the presence of pyrazole fragment in comp. (I) in contrast to the pyridazine fragment in comp. (V). Compounds containing a hydroxyl group have little effect not only on staphylococcus, but also on strains of typhoid fever and penicillium. However, in the presence of amino groups (compound VI), their antimicrobial effect is enhanced. This compound, due to the presence of two sulfamide fragments and the amino group, inhibits the development of staphylococcus at a concentration of 1.3 mol/l $\bullet 10^{-3}$, typhoid fever - at 2.0 mol/l $\bullet 10^{-3}$, penicillium - at 1.4 mol/l $\bullet 10^{-3}$.

Compound IX, containing a sulfamide group, as well as pyrazole and hydroxymethyl fragments, is highly effective against all tested microbial strains.

3.2.2. Enzyme inhibition results

Alzheimer's disease (AD) is a chronic brain disturbance which is determined by cognitive impairments. AD has emerged as the third leading cause of death between old humans, and also defined as a major public health difficulty global. However, the exact reason of AD remains unclear, cholinergic deficits in the central neural mechanism is associated closely with the intensity of cognitive impairments and available as a main neuropathological factor in AD. Indeed, AChE inhibitor compounds, which raise the concentration of ACh and compensate cholinergic deficiency, are used to therapy of AD. Among biological activity (I-X), V molecule, was investigated for the assessment of its antineurodegenerative potential using cholinesterase (AChE & BChE) enzymes. Tacrine was used as standard inhibitor. The data presented in Table 2 demonstrated the remarkable potential of these compounds as anticholinesterase inhibitors.

Table 2. Inhibition effects of new sulfoamides (I-X) on cholinesterase enzymes

Compounds	AChE Ki values (μM)	BChE Ki values (μM)
I	23.76±3.55	16.73±1.42
II	0.95±0.13	2.84±0.24
III	8.05±1.14	5.62±1.12
IV	46.85±5.10	18.45±2.63
V	0.05±0.01	0.97±0.18
VI	6.85±0.94	3.73±0.31
VII	25.66±4.92	9.94±0.91
VIII	1.95±0.13	4.84±1.14
IX	7.05±1.14	5.42±1.02
XI	4.85±0.74	3.53±0.21
Tacrine	50.73±4.83	37.84±4.88

The inhibition efficacy was several folds higher compared to the standard drugs. These novel derivatives were effective inhibitor compounds of the AChE and BChE enzymes with K i values in the range of 0.05±0.01-46.85±5.10 μM for AChE, 0.97±0.18-18.45±2.63 μM for BChE, respectively.

4. Conclusions

Thus, the effectiveness of the antimicrobial action of the synthesized compounds depends not only on the composition of the functional groups, but also on the nature of the heterocycle and the location of the functional groups.

Each of the studied drugs has a relatively long latent period of action. This is probably due to the difficulty of transporting the toxophore molecules through the cell walls of microorganisms to the vital centers they suppress.

Anti-Alzheimer's potential was also assessed by evaluating the inhibitory efficacy of compound V against acetyland butyryl-cholinesterase enzymes. The results were remarkably intriguing with several folds stronger inhibition compared to standard drugs.

Conflicts of interests

The authors declare that no conflicts of interests.

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