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SYNTHESIS, STRUCTURE AND PASS PREDICTED BIOLOGICAL ACTIVITY OF 4-PHENYLNAPHTHOXYBUTYNYLPIPERAZINES

Abstract. New potentially biologically active 4-phenylnaphthoxybutynylpiperazines were synthesized. The structure of the synthesized compounds was established based on the IR and NMR (^{1}H and ^{13}C) spectroscopic data. A predicted biological activity of 4-phenylnaphthoxybutynylpiperazines was studied using the PASS program.

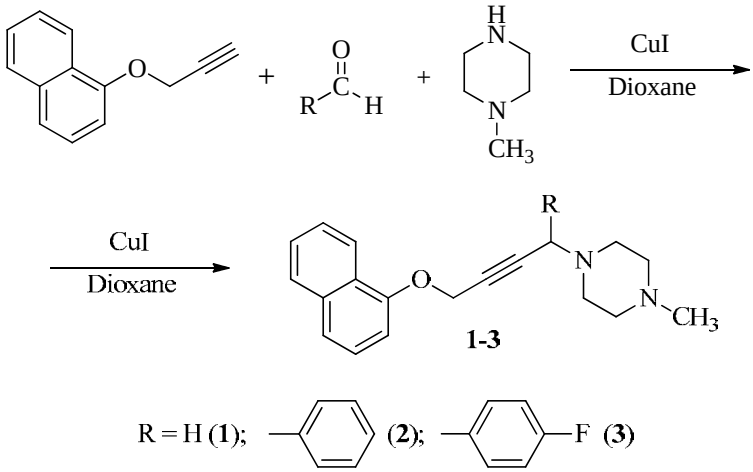
Keywords: 1-(prop-2-ynyloxy)naphthalene, aminomethylation, benzaldehydes, 1-methylpiperazine, ^{1}H and ^{13}C NMR, PASS prediction.

Piperazine and its derivatives are used as antihelminthic drugs, as well as initial reagents in the synthesis of pharmaceutically active compounds, such as antibacterial drugs (ciproflaxin) [1], quinolone antibiotics, some tranquilizers (baspirone and jepiron) (CINNARIZIN) [2]. A number of piperazine derivatives are metabolites of some drugs. In addition, piperazinecontaining preparations with a wide spectrum of biological activity are described: anticonvulsant [3], antibacterial against gram-positive (S. aureus, B. subtilis) and gram-negative strains (E. coli, P. aeruginosa) [4], anti-tuberculosis [5] and antitumor activity [6, 7].

As a task of this study, the design of potentially biologically active new piperazine derivatives with a naphthyloxypropargyl fragment was determined as a continuance of the development of aminomethylation of 1,5-di(prop-2-ynyloxy)naphthalene with secondary amines and aldehydes under catalysis of CuCl or CuI [8].

2-(Prop-2-ynyloxy)naphthalene was determined as the object of aminomethylation, 1-methylpiperazine is the amine compound and as the aldehyde is formaldehyde and two aromatic aldehydes (benzaldehyde and p-fluorobenzaldehyde). The choice of fluorinated aldehyde was dictated by the well-known fact that the introduction of fluorine into the quinolone drug molecule leads to increased activity [9].

The aminomethylation reaction of 1-(prop-2-ynyloxy)naphthalene was carried out in absolute dioxane in the presence of catalytic amounts of copper (I) iodide at the temperature 35−40 °C for 2 h.



As a result of separation from the reaction mixtures, 4-phenylnaphthoxybutynylpiperazines **1–3** were obtained in the following yields: 1-methyl-4-(4-(naphthalen-1-yloxy)but-2-ynyl)piperazine (**1**) (71%), 1-methyl-4-(4-(naphthalen-1-yloxy)-1-phenylbut-2-ynyl)piperazine (**2**) (82%), 1-(1-(4-fluorophenyl)-4-(naphthalen-1-yloxy)but-2-ynyl)-4-methylpiperazine (**3**) (73%). It was established that 1-(prop-2-ynyloxy)naphthalene easily reacts with formaldehyde and aromatic aldehydes in the presence of copper (I) iodide.

The structure of the synthesized compounds **1−3** was established based on the data of elemental analysis and on the analysis of IR, ^{1}H and ^{13}C NMR spectroscopic data (tables 1, 2).

A absorption band $\nu_{C\equiv CH}$ of the starting 2-(prop-2-ynyloxy)naphthalene at ν 3309 cm^{-1} does not present in the IR spectra of 4-phenylnaphthoxybutynylpiperazines **1−3**. A weak band of disubstituted C≡C bond at ν 2120 cm^{-1} confirms the formation of the aminomethylation products.

Table 1 – ^{1}H NMR (δ, ppm) spectral data
for 4-phenylnaphoxybutynylpiperazines **1–3**

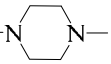
Comp.		OCH_2	CH_2N (CHN)	Ph		CH_3
1	6,91–8,34	4,86	3,34	–	2,57; 2,34	2,30
2	6,93–8,35	4,87	(5,03)	7,29–7,32; 7,49–7,53; 7,59–7,62	2,58; 2,46	2,30
3	6,91–8,32	4,86	(5,02)	7,13–7,17; 7,47–7,51	2,57;2,62	2,30

Table 2 – ^{13}C NMR (δ, ppm) spectral data
for 4-phenylnaphoxybutynylpiperazines **1–3**

Comp.	O–<u>C</u>H$_2$	–<u>C</u>≡C–	–C≡<u>C</u>–	≡C–<u>C</u>H$_2$	—N N—	CH$_3$	Ph
1	56,20	80,27	78,79	47,26	52,08; 55,03	46,10	–
2	56,22	83,17	78,80	61,62	55,24; 56,56	46,05	128,31; 129,12; 129,86
3	56,19	83,43	78,79	60,54	55,25; 56,67	46,13	116,29; 132,25; 160,13

Comp.	Carbon atoms of the naphthalene ring									
	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8	C^9	C^{10}
1	153,43	105,58	125,48	121,10	126,15	125,74	122,17	121,33	127,62	134,67
2	153,44	105,61	125,57	121,32	126,68	125,76	122,18	121,51	127,63	134,58
3	153,43	104,58	125,55	121,30	126,66	125,74	122,17	122,08	127,62	134,67

In the ^{1}H NMR spectra of 4-phenylnaphthoxybutynylpiperazines **1–3** are found the signals of the aminomethylene and aminomethine groups protons at δ 3,34 ppm and 5,03–5,02 ppm. Chemical shift at δ 2,30 ppm was assigned to the methyl group protons standing at the nitrogen atom of the piperazine cycle. The signals of the piperazinemethylene groups protons are found at δ 2,57 and 2,62 ppm. Chemical shifts in the region δ 4,86−4,87 ppm were assigned to the protons of the O-methylene group. The signals of the naphthalene nucleus protons are found at δ 6,91−8,32 ppm. The protons of the benzene nucleus resonate in the region δ 7,13–7,17 and 7,47–7,51 ppm.

^{13}C NMR spectra of 4-phenylnaptoxybutynylpiperazines **1−3** have carbon atoms signals of the aminomethylene and aminomethine groups at δ 47,26, 61,32 and 60,54 ppm. The carbon atoms of the triple C≡C bond resonate in the regions δ 78,79−78,80 and 80,27–83,43 ppm. Signals in the region δ 56,19−56,22 ppm were assigned to the oxymethylene carbon. Weak field signals at δ 104,58−153,44 ppm were assigned to the carbon atoms of the naphthalene ring. Signals of the CH_3-N group are found in the region δ 46,05−46,13 ppm. The carbon atoms of the piperazine cycle resonate in the region δ 52,08−56,67 ppm.

One of the possibilities of a comprehensive study of the biological activity of compounds is computer prediction and further evaluation of the likely types of activity of new substances with subsequent testing in accordance with the results of the forecast. In order to determine the types of potential biological effects of the synthesized compounds, a predictive assessment of the probable biological activity was carried out using the PASS (Prediction of Activity Spectra for Substance) program [10]. This program PASS - Pharma Expert allows the selection of substances that are likely to have a certain type of activity.

The results of the forecast with an indication of the predicted type of activity and a calculated estimate of its probability, which ranges from 0 to 100% are presented in the table 3.

Analysis of the forecast shows that 4-phenylnaptoxybutynylpiperazines **1**−**3** are substrates of the Cytochrome CYP2C12 families with the probability above 70% and they are responsible for the metabolism of endogenous steroids in a body. An antispasmodic activity similar to the drug papaverine for the piperazines **1**−**3** was forecast with the probability 16% to 39%, whereas anti-neurotic activity was predicted with the probability of 51−73%.

It should be noted that introduction of the aromatic substituents [phenyl- (**2**) and p-fluorophenyl- (**3**)] into the molecule imparts a high probability of neotropic activity, which is capable of stimulate mental activity, activating cognitive functions, improving memory and increasing the ability to learn.

The compound 1-methyl-4-(4-(naphthalen-1-yloxy)but-2-ynyl)piperazine (**1**) has a high probability of the activity for the treatment of phobic disorders (neuroses) (64%) and anti-neurotic action (71%).

Also, the obtained compounds can be preparations for urticariatreatment (23-52%), phobicdisorders treatment (64%), as well as vasoprotector (37−50%) and Musclerelaxant (31−38%).

Table 3 – Predicted biological activity of 4-phenylnaphthoxybutynylpiperazines **1–3**

Chemical compounds	Probability of occurrence of predicted activity, %									
	CYP2C12 substrate	Antineurotic	Urticariatreatment	Spasmolytic,Papaverin-like	Vasoprotector	Anthelmintic	Musclerelaxant	Platelet aggregation stimulant	Phobic disorder streatment	Nootropic
1	71	73	52	37	50	33	36	57	64	52
2	63	51	31	39	35		31	49		66
3	28	64	23	16	37		38			71

Thus new 4-phenylnaphthoxybutynylpiperazines with potential biological activity were synthesized. It was established that 4-phenylnaphthoxybutynylpiperazines with high probability can be the agents for the treatment of various neuropathic and phobic disorders, also they could promote the metabolism of endogenous steroids organism.

EXPERIMENTAL PART

The course of the reactions and the purity of the products were monitored by the TLC analysis on "Silufol UV-254" plates with the appearance of substances spots with iodine vapor. The eluent for TLC was a mixture acetone–hexane (2:1).

Elemental analysis was performed on the CE 440 elemental analyzer. The IR spectra were recorded on a Nicolet 5700 spectrometer in KBr tablets. The ^{1}H and ^{13}C NMR spectra of the samples were recorded on a JNM-ECA 400 (Jeol) spectrometer with operating frequencies 400 (^{1}H), 100 MHz (^{13}C) in deuterated chloroform $CDCl_3$.

1-Methyl-4-(4-(naphthalen-1-yloxy)but-2-ynyl)piperazine (1). A solution of 1-methylpiperazine 0,82 g (0,0082 mol) in 10 ml of dioxane was added dropwise with stirring at 40 °C to the mixture of 1,5 g (0,0082 mol) 1-(prop-2-ynyloxy)naphthalene, 0,24 g (0,0082 mol) paraform, 0,15 g (0,00078 mol) copper (I) iodide in 20 ml of dioxane. After completion of the reaction, dioxane was distilled off, the residue was treated with an aqueous solution of ammonia and was extracted with benzene. The benzene extract was dried with potash, then the solvent was evaporated. The residue was separated by column chromatography on silica gel. The eluent was benzene. Chromatographically homogeneous fractions were combined, benzene was distilled off under reduced pressure. 1-Methyl-4-(4-(naphthalen-1-yloxy)but-2-ynyl)piperazine (**1)** was obtained in the form of an oil in 1,7 g (71%) yield, R_f = 0,78. Found (%): C 77,52; H 7,53; N 9,52. $C_{19}H_{22}N_2O$. Calculated (%): C 77,92; H 7,03; N 9,25.

1-Methyl-4-(4-(naphthalen-1-yloxy)-1-phenylbut-2-ynyl)piperazine (2) was synthesized similarly from 1,5 g (0,0082 mol) 1-(prop-2-ynyloxy)naphthalene, 0,87 g (0,0082 mol) benzaldehyde and 0,82 g (0,0082 mol) 1-methylpiperazine in the presence of 0,15 g (0,00078 mol) copper iodide (I) in dioxane at 40 °C. 1-Methyl-4-(4-(naphthalen-1-yloxy)-1-phenylbut-2-ynyl)piperazine (**2**) was obtained in the form of oil in 2,5 g (82%) yield, R_f = 0,8. Found (%): C 81,05; H 7,07; N 7,56. $C_{25}H_{26}N_2O$. Calculated (%): C 81,61; H 6,78; N 6,79.

1-[1-(4-Fluorophenyl)-4-(naphthalen-1-yloxy)but-2-ynyl]-4-methylpiperazine (3) was synthesized similarly from 1,5 g (0,0082 mol) 1-(prop-2-ynyloxy)naphthalene, 1,02 g (0,0082 mol) p-fluorobenzaldehyde and 0,82 g (0,0082 mol) 1-methylpiperazine in the presence of 0,15 g (0,00078 mol) copper (I) iodide in dioxane at 40 °C. 1-[1-(4-Fluorophenyl)-4-(naphthalen-1-yloxy)but-2-ynyl]-4-methylpiperazine was obtained as an oil in 2,36 g (73%) yield, R_f = 0,93. Found (%): C 77,29; H 6,49; F 4,89; N 7,21. $C_{25}H_{26}FN_2O$. Calculated (%): C 77,71; H 6,02; N 6,97.

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Резюме

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4-ФЕНИЛНАФТОКСИБУТИНИЛПИПЕРАЗИНДЕРДІҢ СИНТЕЗІ, ҚҰРЫЛЫСЫ ЖӘНЕ PASS БОЛЖАМДЫ БИОЛОГИЯЛЫҚ АКТИВТІЛІГІ

Жаңа потенциалды биологиялық активті 4-фенилнафтоксибутинилпиперазиндер синтезделінді. Синтезделген қосылыстардың құрылысы ИК-спектроскопиялық, ЯМР ^{1}Н және ^{13}С спектроскопиялық мәліметтер негізінде дәлелденді. PASS бағдарламасының көмегімен 4-фенилнафтоксибутинилпиперазиндердің болжамды биологиялық активтіліктері анықталынды.

Түйін сөздер: 1-(проп-2-инилокси)нафталин, аминометилдеу, бензальдегидтер, 1-метилпиперазин, ЯМР ^{1}Н және^{13}С, PASS болжау.

Резюме

Е. С. Сычева, М. С. Муканова, В. К. Ю, К. Н. Иманкулова, Т. М. Сейлханов

СИНТЕЗ, СТРУКТУРА И ПРОГНОЗИРУЕМАЯ PASS БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ 4-ФЕНИЛНАФТОКСИБУТИНИЛПИПЕРАЗИНОВ

Синтезированы новые потенциально биологически активные 4-фенилнафтоксибутинилпиперазины. Строение синтезированных соединений установлено на основании данных ИК-спектроскопии и спектроскопии ЯМР ^{1}Н и ^{13}С. С помощью программы PASS изучена прогнозируемая биологическая активность 4-фенилнафтоксибутинилпиперазинов.

Ключевые слова: 1-(проп-2-инилокси)нафталин, аминометилирование, бензальдегиды, 1-метилпиперазин, ЯМР ^{1}Н и ^{13}С, PASS прогнозирование.