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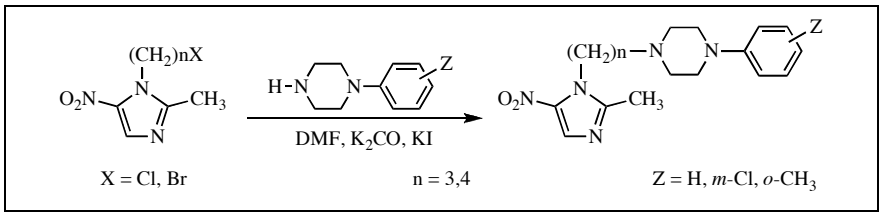

The derivatives of 1-propyl- and 1-butyl- of 2-methyl-5-nitroimidazole containing phenylpiperazine, *m*-chloro- and *o*-methoxyphenylpiperazine attached at the end of alkyl chain were synthesed. For the obtained new compounds, the biological activity was predicted using the computer program PASS.

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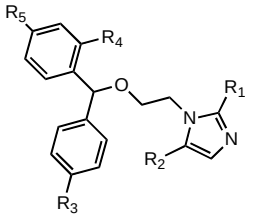
INTRODUCTION

Nitro derivatives of imidazole exhibit broad pharmacological activity [1-5]. Their earliest recognized biological activity was their antiprotozoal action [6]. Nitroimidazoles can act also as photosensitizes, which makes them good candidates for antitumor treatment [7-10]. Moreover, some imidazole derivatives belong to the non-nucleoside reverse transcription inhibitors (NNRIs). The following imidazole derivatives, including some nitro-derivatives, have been evaluated as potential drugs against HIV-1 virus [11]:



Where: R_1 = H, CH_3; R_2 = H, NO_2, R_3 = H, F, Cl, CH_3, *t*-Bu;
R_4 = R_5 = H, Cl

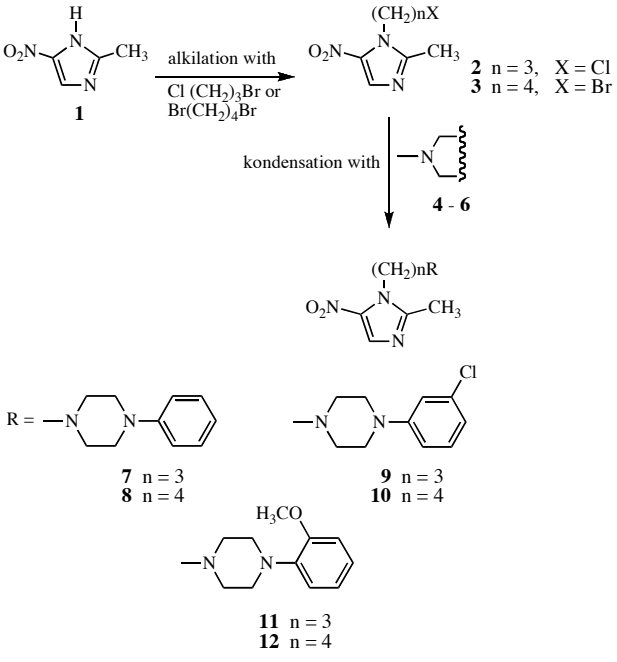
Structure-activity relationships (SARs) suggest that the introduction of nitro group and methyl group into the imidazole ring renders its anti-HIV-1 activity, while the presence of various substituents in the benzhydrol fragment modulates effectiveness and cytotoxicity of the drug. In general, the effect of electron-withdrawing substituents on the anti-HIV-1 activity is stronger than the effect of electron-donating ones.

RESULTS AND DISCUSSION

Upon continuation of our studies on the synthesis of azaheterocyclic compounds with potential biological activity [12], we have obtained the phenylpiperazinyl derivatives **7-12** of 2-methyl-5-nitroimidazole (**1**), shown in Scheme.

The compounds **7**-**12** were synthesized in two steps. In the first step, 1-(3-chloropropyl)-2-methyl-5-nitro-imidazole (**2**) and its 1-(4-bromobutyl)- analog (**3**) were obtained by alkylation of the N1 nitrogen in **1** with 1-bromo-3-chloropropane and 1,4-dibromobutane, respectively. Next, the compounds **2** and **3** were reacted with the phenylpiperazines **4**-**6**. The reactions were carried out in dimethylformamide (DMF), in the presence of anhydrous potassium carbonate, at room temperature, for 30 h.

Scheme



Structure of the phenylpiperazinyl derivatives **7**-**12** of 2-methyl-5-nitroimidazole (**1**) have been confirmed by ^{1}H nmr, ir and ms spectral methods, and elemental analysis (Table 1 and 2).

Table 1

Characterization Data of Compounds **7-12**

Compound	Melting point (°C)	Yield (%)	Molecular Formula	MW	Ms m/z ($M^{+\cdot}$ %)	Analysis Calcd./ Found C	H	N
7	133 – 135 isopropyl alcohol	60	$C_{17}H_{23}N_5O_2$	329.40	329 (30)	61.99 61.72	7.04 7.12	21.26 21.21
8	88 – 90 cyclohexane	62	$C_{18}H_{25}N_5O_2$	343.43	343 (47)	62.95 62.74	7.34 7.40	20.39 20.20
9	136 – 137 isopropyl alcohol	41	$C_{17}H_{22}N_5O_2Cl$	363.84	-	56.12 55.93	6.09 6.17	19.25 19.03
10	89 – 90 isopropyl alcohol	41	$C_{18}H_{24}N_5O_2Cl$	377.87	-	57.21 56.88	6.40 6.52	18.53 18.50
11	101 – 103 cyclohexane	64	$C_{18}H_{25}N_5O_3$	359.43	359 (66)	60.15 59.91	7.01 6.98	19.48 19.31
12	88 – 91 methyl alcohol	42	$C_{19}H_{27}N_5O_3$ x H_2O	391.47	373 (11)	58.30 58.29	7.47 7.52	17.89 17.86

Mass spectra of the compounds **7**, **8**, **11** and **12** show well-defined signals of parent molecular ions, which decompose by subsequent detachment of the fragments with molecular weights of 17 ($M^{+\cdot}$-OH), 17 and 15 ($M^{+\cdot}$-CH_3). No fragment ions characteristic for decomposition of typical nitro compounds ($M^{+\cdot}$-NO or $M^{+\cdot}$-NO_2) and no cleavage of HCN from the parent ions are observed in the mass spectra.

In order to confirm the identity of the compounds **7**-**12** by infrared spectroscopy, several characteristic absorption bands have been identified. Stretching vibrations of C-H bonds in CH_3 and CH_2 groups occur at 2344-2937 cm^{-1} (asymmetric vibrations) and 2822-2821 cm^{-1} (symmetric vibrations). For all of the compounds studied, asymmetric scissors-type bending of the CH_3 and CH_2 groups show up in the range 1471-1362 cm^{-1}. Two strong bands characteristic for NO_2 group are observed at 1500-1494 cm^{-1} (asymmetric stretching vibrations) and 1291-1293 cm^{-1} (the corresponding symmetric ones). Moreover, in IR spectra of the compounds **11** and **12**, characteristic stretching vibrations of C_R-O-C_{Ar} bonds appear at 1242-1239 cm^{-1} and 1027-1025 cm^{-1}, respectively. Additionally, in the spectrum of **12**, a broad absorption band within the range 3500-3260 cm^{-1} indicates that this compound formed a hydrate.

The ^{1}H nmr spectra of compounds **7**-**12** revealed (from high to low field) signals consistent with alkyl protons of propyl and butyl chain and of the piperazine ring, the signals of methyl groups of the imidazole ring (singlet), additionally in case of **11** and **12** signals of methoxy groups (singlet), and the signals of the aromatic protons of phenyl and imidazole ring. The exact number of protons was given by integration (see Table 2).

Finding a correlation between a compound structure and its biological activity is very difficult, because of complexity of biological systems. However, application of special computer techniques makes some predictions possible. Using PASS program [13], developed in the

Table 2

^{1}H nmr spectra of compounds **7**-**12**

Comp.	σ (ppm) in $CDCl_3$
7	2.03 (quintet, 2H, $CH_2CH_2CH_2$), 2.37 (t, 2H, CH_2N-piperazine), 2.47 (s, 3H, CH_3), 4.09 (t, 2H, CH_2N- imidazole), 2.60 and 3.22 (t, 4H and t, 4H, piperazine), 6.78-7.03 (m, 3H, Ph 2,4,6-H), 7.31 (t, 2H, Ph 3,5-H) 7.73 (s, 1H, imidazole)
8	1.38-2.00 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.37- (2H, CH_2N-piperazine signal overlap), 2.45 (s, 3H, CH_3), 2.62 and 3.22 (t, 4H and t, 4H, piperazine), 4.00 (t, 2H, CH_2N-imidazole), 6.78-7.03 (m, 3H, Ph 2,4,6-H), 7.31 (t, 2H, Ph 3,5-H), 7.71 (s, 1H, imidazole)
9	2.03 (quintet, 2H, $CH_2CH_2CH_2$), 2.38 (t, 2H, CH_2N-piperazine), 2.47 (s, 3H, CH_3), 2.56 and 3.27 (t, 4H and t, 4H, piperazine), 4.05 (t, 2H, CH_2N-imidazole), 6.67-6.92 (m, 3H, Ph 2,4,6-H), 7.17 (t, 1H, Ph 5-H), 7.73 (s, 1H, imidazole)
10	1.42- 2.08 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.36- (2H, CH_2N-piperazine signal overlap), 2.45 (s, 3H, CH_3) 2.57 and 3.20 (t, 4H and t, 4H, piperazine), 3.96 (t, 2H, CH_2N-imidazole), 6.69-6.90 (m, 3H, 2,4,6-H Ph), 7.17 (t, 1H, 5-H Ph), 7.71 (s, 1H, imidazole)
11	2.02 (quintet, 2H, $CH_2CH_2CH_2$), 2.38 (t, 2H, CH_2N- piperazine), 2.48 (s, 3H, CH_3), 2.65 and 3.16 (t, 4H and t, 4H, piperazine), 3.87 (s, 3H, OCH_3), 4.06 (t, 2H, CH_2N-imidazole, 6.94 (pseudo s, 4H, Ph), 7.74 (s, 1H, imidazole)
12	1.47-2.00 (m, 4H, $CH_2CH_2CH_2CH_2$), 2.34 (t, 2H, CH_2N-piperazine), 2.45 (s, 3H, CH_3), 2.63 and 3.12 (t, 4H and t, 4H, piperazine), 3.86 (s, 3H, OCH_3), 3.96 (t, 2H, CH_2N-imidazole), 7.02 (pseudo s, 4H, Ph), 7.71 (s, 1H, imidazole)

nstitute of Biomedical Chemistry at Russian Academy of Medical Sciences, we have determined probability of pharmacological activity (Pa) and probability of the lack of such activity (Pi) for the compounds **7**-**12**. The biological activities with highest probability of appearance in the compounds studied are collected in Table 3.

Table 3

Probabilities of biological activity (Pa) of the compounds **7**-**12**

Activity Type	Compound					
	7	**8**	**9**	**10**	**11**	**12**
Antiprotozoal	0.880	0.873	0.846	0.839	0.831	0.802
Convulsant	0.879	0.880	0.868	0.868	0.835	0.836
Dopaminne D4 agonist	0.857	0.857	0.807	0.807	0.755	0.755
Antialcoholic	0.826	0.831	0.803	0.808	0.777	0.783
Antiprotozoal (Trichomonas)	0.799	0.809	0.703	0.709	0.672	0.678
Antiprotozoal (Amoeba)	0.703	0.703	0.676	0.676	0.665	0.665
Oxidizing agent	0.687	0.696	0.634	0.657	0.629	0.638
Radiosensitizer	0.689	0.694	0.648	0.643	0.654	0.662
Cardioprotectant	0.588	0.651	0.572	0.633	0.721	0.752
Urologic disorders treatment	0.619	0.527	0.623	0.549	0.711	0.643

The compounds **7**-**12** exhibit high probability of appearance of convulsant activity (83-88 %), while the probability that such activity will not appear is low (about 1.3 %). High (*i.e.*, 80-88 %) is also the probability that these compounds will show general antiprotozoal action. Moreover, the probability of antialcoholic activity is relatively high (78-83 %), while the highest values are obtained for the derivatives, where the phenyl ring of the phenylpiperazinyl residue is not substituted. The presence of *ortho*-methoxy substituent in the phenyl ring of **11** and **12** enhances their potential cardioprotectant properties in comparison to the other compounds studied (increase by 7 to18% - penultimate line of Table 3).

Similar trend is observed in the case of urologic disorder treatment, where the probability is highest for the compound **11** having trimethylene link between the imidazole and the piperazine rings. There is also high probability that the compounds obtained will be effective Dopamine D4 agonists (80 % probability) and radiosensitizers (60 % probability). The aliphatic chain length within the structure of the compounds **7**-**12** does not have significant effect on their pharmacological properties. On the other hand, the probability that the predicted biological activities will not appear is very low for all of the compounds studied.

Concluding, these results shows, that the new 2-methyl-5-nitroimidazole derivatives **7-12** synthesized by us, can be considered as candidates for testing them, especially, as the agents with potential Antiprotozoal`s and Convulsive effect.

EXPERIMENTAL

Melting points (uncorrected) were determined on a Boetius melting point apparatus. The ^{1}H nmr spectra were recorded on Tesla BS-587A (80 MHz) spectrometer in $CDCl_3$ solution, using TMS as internal standard; the chemical shifts (δ) are expressed in parts per million (ppm). The infrared spectra were recorded on Bio-Rad FTS-175C spectrometer (in potassium bromide pellets). The mass spectra (EI) were recorded with Varian- MAT 112 spectrometer at 70 eV. Elemental analyse was performed on a Perkin-Elmer 2400 analyzer. Starting materials, solvents and reagents were purchased from commercial sources (Aldrich and Merck) and were used without further purification, except of DMF, which was purified by distillation shortly before use.

Synthesis of Alkylation Reagents, 2 and 3. 1-(3-Chloropropyl)-2-methyl-5-nitroimidazole (2) was prepared according to described procedure [12]. 1-(4-Bromobutyl)-2-methyl-5-nitroimidazole (**3**) was obtained likewise as compound **2** in reaction with 2-methyl-5-nitroimidazole (**1**) using of 1,4-dibromobutane instead of 1-bromo-3-chloropropane. Recrystalization from water gives compound **3** in shape of colourless crystals with mp 80-82°C, yield 85 %.

General Procedure for Synthesis of compounds 7-12. The mixture of 6.4 mmoles halogeno derivatives of 2-methyl-5-nitroimidazole **2** or **3**, 6.4 mmoles of phenylpiperazine (**4**), *m*-chloro- (**5**) and *o*-methoxyphenylpiperazine (**6**), 19.1 mmoles anhydrous potassium carbonate and few crystals (~0.01g) potassium iodide in 15-20 mL of fresh distillated DMF were placed into an Erlenmeyer flask. All was stirred with magnetic stirrer at room temperature for 30 hours. Next, the reaction mixture was poured into 100-150 mL of water and the precipitate was collected by filtration, dried and recrystallizated with appropriate solvents. When an oil was obtained, it was extracted with chloroform, which was dried over magnesium sulphate, evaporated and residue recrystallized. In case of compound **11** unreacted *o*-methoxyphenylpiperazine (**6**) separated on chromatography column, before crystallization. The compounds **8**-**12** were obtained in shape of colourless needles and compound **7** as plates.

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