ORIGINAL ARTICLE

Synthesis and biological activity evaluation Of 3-[2-(1h-imidazol-2-Yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4 (1h) -one derivatives

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Abstract

Aims: Detection of general patterns of the synthesis of quinazoline derivatives contains a fragment of 2-aminoalkylimidazole and studying their antimicrobial activity. **Materials and Methods:** Methods of organic synthesis; physical and physicochemical methods of analysis of organic compounds ^{1}Hydrogen nuclear magnetic resonance spectroscopy and elemental analysis were used. **Results:** To construct a focused library of compounds with potential antimicrobial and antifungal properties, we have chosen a strategy of combining quinazoline fragments with an imidazole residue in one molecule. The possibility of using 2-aminoalkylimidazoles as an amine component in the heterocyclization reaction with o-isothiocyanato esters was considered. 3-Substituted 2-thioxoquinazoline-4-ones were synthesized by the interaction of methyl esters of 4,5-substituted 2-isothiocyanatobenzoic acids with 2-(α,β,ω-aminoalkyl)imidazoles. Experimental study of antimicrobial activity was performed for the obtained substances, which according to the results of virtual screening showed the best results. **Conclusions:** A virtual library design with structural fragments of quinazoline and imidazole was made. The systematic series of 6,7-substituted 3-[2-(1H-imidazol-2-yl)-alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-one were synthesized. According to the results of the study of the biological effects of the new derivatives of 3-N-(alkylimidazolyl-2) pyrimidine, a number of patterns of connection "chemical structure - antibacterial action" were established and the main directions of the purposeful modification of the structure for the search of new antimicrobial and antifungal agents were determined.

Key words: 2-(α,β,ω-aminoalkyl)imidazole, 2-isothiocyanatobenzoate, 3-[2-(1*H*-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one, antibacterial activity, antifungal activity

INTRODUCTION

Recently compounds, which combine several heterocyclic fragments in their structures, attract particular interest in the development of innovative drug substances. The combination of various pharmacophores, especially heterocyclic fragments, in the same molecule, can lead both to the synergy of known effects and the emergence of new kinds of pharmacological activity. The choice of pharmacophore fragments for modeling of new structures is based on many factors, among which the most important is the analysis of the evidence-based medicine data about pharmacological action of substances containing the fragment. In this aspect, derivatives of imidazole and quinazoline are promising compounds, because these fragments are part of the structure of known antimicrobial drugs[1-3] and substances, which demonstrated antitubercular[4] and antimicrobial[5-10] activity

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during preclinical trials. However, it should be noted that there is almost no information about the synthesis and properties of quinazolines containing 2-aminoalkylimidazole moiety. Hence, revealing general pattern about the synthesis of quinazolines, combined by alkyl chain with 2-aminoalkylimidazole moiety and examination of their pharmacological potential is actual and represent the subject of the present study.

MATERIALS AND METHODS

A number of virtual screening methods have been applied to estimate potential biologic activity. Computer modeling of a virtual library of quinazoline derivatives, which contains 2-aminoalkylimidazole moiety, has been carried out by Project Library software. For the design of virtual library of 3-[2-(1*H*-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones 4 randomization points (length of the alkyl chain, substituents in imidazole, alkyl chain, 6 or 7 position of quinazoline moiety) was chosen based on availability of starting 2-aminobenzoates and in attempts to achieve chemical diversity in imidazole moiety and alkyl chain. Evaluation of potential biologic activity has been conducted by PASS Professional, version 2010.[11] This determined the path of synthesis and the most promising compounds were synthesized. Analysis of the computer prediction results for a virtual library of 3-[2-(1*H*-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(*1H*)-ones showed high level of probability of antimicrobial and antifungal activity and allowed to generate the library of the most perspective compounds 4{1-30} for further biological investigations [Table 1].

Table 1: Structure and analytical data of 3-[2-(1H-imidazol-2-yl) alkyl]-2-thioxo-2,3-dihydroquinazolin-4 (1H)-ones 4{1-30} library

Compounds	*n*	R	Molecular formula, m. m.	Yield, %	*n*, % calc. exp.
4{1}	*n*=0	R_1=H, R_2=H, R_3=H, R_4=H	$C_{12}H_{10}N_4OS$ 258.30	82	21.69 (21.72)
4{2}	*n*=1	R_1=H, R_2=H, R_3=H, R_4=H	$C_{13}H_{12}N_4OS$ 272.33	85	20.57 (20.59)
4{3}	*n*=2	R_1=H, R_2=H, R_3=H, R_4=H	$C_{14}H_{14}N_4OS$ 286.36	88	19.57 (19.60)
4{4}	*n*=3	R_1=H, R_2=H, R_3=H, R_4=H	$C_{15}H_{16}N_4OS$ 300.38	81	18.65 (18.69)
4{5}	*n*=0	R_1=H, R_2=H, R_3=CH_3, R_4=H	$C_{13}H_{12}N_4OS$ 272.33	84	20.57 (20.61)
4{6}	*n*=0	R_1=H, R_2=H, R_3=$CH(CH_3)_2$, R_4=H	$C_{15}H_{16}N_4OS$ 300.38	83	18.65 (18.700
4{7}	*n*=0	R_1=H, R_2=H, R_3=$CH_2CH(CH_3)_2$, R_4=H	$C_{16}H_{18}N_4OS$ 314.41	87	17.8 (17.86)
4{8}	*n*=0	R_1=H, R_2=H, R_3=$CH(CH_3)CH_5$, R_4=H	$C_{16}H_{18}N_4OS$ 314.41	82	17.82 (17.87)
4{9}	*n*=0	R_1=H, R_2=H, R_3=Bn, R_4=H	$C_{19}H_{16}N_4OS$ 348.43	84	16.08 (16.11)
4{10}	*n*=1	R_1=H, R_2=H, R_3=H, R_4=Bn	$C_{20}H_{18}N_4OS$ 362.46	83	15.46 (15.48)
4{11}	*n*=0	R_1= CH3, R_2=H, R_3=H, R_4=H	$C_{13}H_{12}N_4OS$ 272.33	90	20.57 (20.60)
4{12}	*n*=1	R_1= CH_3, R_2=H, R_3=H, R_4=H	$C_{14}H_{14}N_4OS$ 286.36	87	19.57 (19.60)
4{13}	*n*=2	R_1= CH_3, R_2=H, R_3=H, R_4=H	$C_{15}H_{16}N_4OS$ 300.38	85	18.65 (18.68)
4{14}	*n*=3	R_1= CH_3, R_2=H, R_3=H, R_4=H	$C_{16}H_{18}N_4OS$ 314.41	88	17.82 (17.84)
4{15}	*n*=0	R_1=CH_3, R_2=H, R_3=CH3, R_4=H	$C_{16}H_{18}N_4OS$ 314.41	86	17.82 (17.84)
4{16}	*n*=0	R_1= CH_3, R_2=H, R_3=$CH(CH_3)_2$, R_4=H	$C_{14}H_{14}N_4OS$ 286.36	81	19.57 (19.60)
4{17}	*n*=0	R_1= CH_3, R_2=H, R_3=$CH_2CH(CH_3)_2$, R_4=H	$C_{17}H_{20}N_4OS$ 328.44	80	17.06 17.10)
4{18}	*n*=0	R_1= CH_3, R_2=H, R_3=$CH(CH_3)C_2H_5$, R_4=H	$C_{17}H_{20}N_4OS$ 328.44	82	17.0 (17.10)
4{19}	*n*=0	R_1=CH_3, R_2=H, R_3=Bn, R_4=H	$C_{20}H_{18}N_4OS$ 362.46	91	15.46 (15.46)
4{20}	*n*=1	R_1=CH_3, R_2=H, R_3=H, R_4=Bn	$C_{21}H_{20}N_4OS$ 376.48	92	14.88 (14.88)
4{21}	*n*=1	R_1=F, R_2=H, R_3=H, R_4=H	$C_{13}H_{11}FN_4O$ 290.32	90	19.30 (19.35)
4{22}	*n*=2	R_1=F, R_2=H, R_3=H, R_4=H	$C_{14}H_{13}FN_4OS$ 304.35	86	18.41 (18.45)
4{23}	*n*=3	R_1=F, R_2=H, R_3=H, R_4=H	$C_{15}H_{15}FN_4OS$ 318.38	92	17.60 (17.64)
4{24}	*n*=1	R_1=F, R_2=H, R_3=H, R_4=Bn	$C_{20}H_{17}FN_4OS$ 380.45	93	14.73 (14.79)
4{25}	*n*=1	R_1=Cl, R_2=H, R_3=H, R_4=H	$C_{13}H_{11}ClN_4OS$ 306.78	87	18.26 (18.30)
4{26}	*n*=2	R_1=Cl, R_2=H, R_3=H, R_4=H	$C_{14}H_{13}ClN4OS$ 320.80	88	17.46 (17.48)
4{27}	*n*=3	R_1=Cl, R_2=H, R_3=H, R_4=H	$C_{15}H_{15}ClN_4OS$ 334.83	86	16.73 (16.75)
4{28}	*n*=1	R_1=H, R_2=Cl, R_3=H, R_4=Bn	$C_{20}H_{17}ClN_4OS$ 396.90	96	14.12 (14.15)
4{29}	*n*=1	R_1=H, R_2=$COOCH_3$, R_3=H, R_4=H	$C_{15}H_{14}N_4O_3S$ 330.37	85	16.96 (16.98)
4{30}	*n*=2	R_1=H, R_2=$COOCH_3$, R_3=H, R_4=H	$C_{16}H_{16}N_4O_3S$ 344.39	84	16.27 (16.30)

In continuation of investigations conducting at the National University of Pharmacy, which lead to suitable synthetic methods, providing high yields and purity of 3-substituted condensed 2-thioxopyrimidin-4-ones,[12-15] we examined the possibility of use 2-(α,β,ω-aminoalkyl) imidazoles as amine components due to presence of primary amino group in the heterocyclization reaction with ortho-isothiocyanato esters. Synthesis of intermediate methyl 2-isothiocyanatobenzoates 2{1-6} was carried out by treatment of substituted methyl 2-aminobenzoates 1{1-6} with thiophosgene in a two-phase system of chloroform - water at room temperature [Figure 1].

Starting 2-(α,β,ω-aminoalkyl)imidazoles 3{1-10} was obtained according to previously developed methods.[16-17] 3-Subsituted 2-thioxoquinazolin-4-ones 4{1-30} was synthesized by reaction of methyl 2-isothiocyanato benzoates 2{1-6} with 2-(α,β,ω-aminoalkyl)imidazoles 3{1-10} in propan-2-ol solution with KOH as basic catalyst [Figure 2]. Formation of reaction products was controlled by TLC.

Screening of first time synthesized compounds for microbiological activity has been conducted *in vitro* by a generally accepted method of double serial dilution both in liquid and solid nutrient media. As biological target, the set of clinical and reference strains of 4 bacteria: *Escherichia coli* ATCC 25922 (F-50), *Staphylococcus aureus* ATCC 25923 (F-49), *Bacillus anthracoides* ATCC 1312, *Pseudomonas aeruginosa* ATCC 27853, and 1 fungi *Candida albicans* ATCC 885-653 have been used. Fluoroquinolone antibiotic Pipemidic acid was used as positive control for bacteria. Fluconazole was used as a positive fungal inhibitor standard for *C. albicans*.

RESULTS AND DISCUSSION

The structures of obtained compounds have been proved by analytical data [Table 1] and by hydrogen nuclear magnetic resonance (^{1}H NMR) spectroscopy data [Table 2]. Formation of the 2-thioxoquinazolin-4-one condensed system is confirmed by signals of NHCS protons at 13.20−12.78 ppm, while signals of NH protons of imidazole ring appear as a broad singlet at 14.83–13.54 ppm. Signals of CH=CH protons of imidazole ring show at 7.10−7.22 ppm and 6.80−6.92 ppm. Position and multiplicity of signals of other protons are complied with the proposed structure of compounds.

Results of microbiological screening of 3-[2-(1H-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-one derivatives 4{1-30} are showed in Tables 3 and 4. The substances 4{21} –4{28} demonstrated the highest activity against *S. aureus* ATCC 25923 and *C. albicans* ATCC 885-653. Considering the structure-activity relations can be noted the following regularities:

- Elongation of carbon chain between 2-thioxoquinazolin-4-one and imidazole moieties up to 3 carbon atoms led to increasing of antimicrobial and antifungal action.
- The combination of 2-thioxoquinazolin-4-one and imidazole fragments in the molecules promotes the enhancement of activity against *S. aureus*.

EXPERIMENTAL PART

^{1}H NMR-spectra were recorded on Varian WXR-400 (200 MHz) spectrometer in Dimethyl sulfoxide (DMSO)-d_6

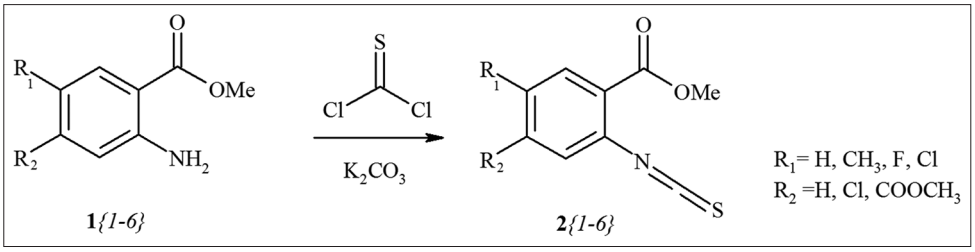

Figure 1: The scheme of methyl 2-isothiocyanato benzoates synthesis

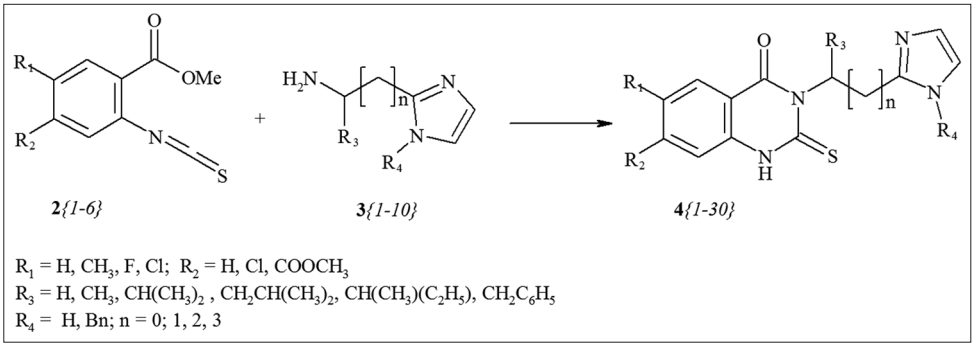

Figure 2: The scheme of 3-subsituted 2-thioxoquinazolin-4-ones synthesis

Table 2: ^{1}H NMR spectra of 3-[2-(1H-imidazol-2-yl) alkyl]-2-thioxo-2,3-dihydroquinazolin-4 (1H)-ones 4{1-30}

Compounds	^{1}H NMR, δ, p.p.m
4{1}	14.74–14.80 (br. s, 1H, NH), 12.78 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.45 (d, 1H, H-8), 7.20–7.24 (m, 2H, H-6+CH), 6.84 (s, 1H, CH), 4.28–4.32 (t, 2H, CH_2)
4{2}	14.80–14.83 (br. s, 1H, NH), 12.80 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.66 (t, 1H, H-7), 7.47 (d, 1H, H-8), 7.22–7.25 (m, 2H, H-6+CH), 6.82 (s, 1H, CH), 3.90–3.94 (t, 2H, NCH_2), 2.06–2.10 (t, 2H, CH_2)
4{3}	13.80–13.83 (br. s, 1H, NH), 13.10 (s, 1H, NH), 7.88 (d, 1H, H-5), 7.68 (t, 1H, H-7), 7.46 (d, 1H, H-8), 7.28–7.33 (m, 2H, H-6+CH), 6.82 (s, 1H, CH), 3.63 (t, 2H, NCH_2), 2.18 (t, 2H, CH_2), 1.78–1.82 (m, 2H, CH_2)
4{4}	13.54–13.58 (br. s, 1H, NH), 12.82 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.68 (t, 1H, H-7), 7.47 (d, 1H, H-8), 7.28–7.33 (m, 2H, H-6+CH), 6.82 (s, 1H, CH), 3.60 (t, 2H, NCH_2), 2.21 (t, 2H, CH_2), 1.30–1.35 (m, 4H, $2CH_2$)
4{5}	14.20–14.25 (br. s, 1H, NH), 12.83 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.66 (t, 1H, H-7), 7.42 (d, 1H, H-8), 7.24–7.27 (m, 2H, H-6+CH), 6.92 (s, 1H, CH), 4.83–4.85 (m, 1H, CH), 1.52 (s, 3H, CH_3)
4{6}	14.00–14.02 (br. s, 1H, NH), 12.83 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.67 (t, 1H, H-7), 7.44 (d, 1H, H-8), 7.20–7.25 (m, 2H, H-6+CH), 6.92 (s, 1H, CH), 4.43–4.47 (m, 1H, CH), 2.50–2.54 (m, 1H, CH), 0.80 (s, 6H, $2CH_3$)
4{7}	13.85–13.92 (br. s, 1H, NH), 12.93 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.70 (t, 1H, H-7), 7.44 (d, 1H, H-8), 7.20–7.25 (m, 2H, H-6+CH), 6.96 (s, 1H, CH), 4.74–4.77 (m, 1H, CH), 2.16–2.20 (m, 2H, CH_2), 1.79–1.82 (m, 1H, CH), 0.90 (s, 3H, CH_3), 0.80 (s, 3H, CH_3)
4{8}	13.88–13.94 (s, 1H, NH), 13.03 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.70 (t, 1H, H-7), 7.42 (d, 1H, H-8), 7.18–7.23 (m, 2H, H-6+CH), 6.92 (s, 1H, CH), 4.48–4.51 (m, 1H, NCH), 1.43–1.46 (m, H, CH), 1.38–1.40 (m, 2H, CH_2), 0.98 (s, 3H, CH_3), 0.80 (s, 3H, CH_3)
4{9}	13.90–14.02 (br. s, H, NH), 12.97 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.74 (t, 1H, H-7), 7.46 (d, 1H, H-8), 7.18–7.25 (m, 7H, H-6+CH+Ar-H), 6.94 (s, 1H, CH), 5.02–5.10 (m, 1H, CH), 3.58–3.63 (m, 2H, CH_2)
4{10}	13.02 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.74 (t, 1H, H-7), 7.46 (d, 1H, H-8), 7.18–7.25 (m, 7H, H-6+CH+Ar-H), 6.94 (s, 1H, CH), 5.18 (s, 2H, NCH_2), 3.75–3.70 (t, 2H, NCH_2), 2.82–2.85 (t, 2H, CH_2)
4{11}	14.74–14.80 (br. s, 1H, NH), 12.78 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.45 (d, 1H, H-8), 7.10 (s, 1H, CH), 6.84 (s, 1H, CH), 4.28–4.32 (t, 2H, CH_2), 2.35 (s, 3H, CH_3-Ar)
4{12}	14.56–14.60 (br. s, 1H, NH), 12.78 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.45 (d, 1H, H-8), 7.10 (s, 1H,CH), 6.84 (s, 1H, CH), 3.90–3.94 (t, 2H, NCH_2), 2.06–2.10 (t, 2H, CH_2), 2.35 (s, 3H, CH_3-Ar)
4{13}	14.56–14.60 (br. s, 1H, NH), 12.78 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.47 (d, 1H, H-8), 7.10 (s, 1H,CH), 6.84 (s, 1H, CH), 3.90–3.94 (t, 2H, NCH_2), 2.08–2.12 (t, 2H, CH_2), 2.37 (s, 3H, CH_3-Ar)
4{14}	14.50–14.56 (br. s, 1H, NH), 12.80 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.45 (d, 1H, H-8), 7.10 (s, 1H, CH), 6.84 (s, 1H, CH), 3.63 (t, 2H, NCH_2), 2.35 (s, 3H, CH_3-Ar), 2.18 (t, 2H, CH_2), 1.78–1.82 (m, 2H, CH_2)
4{15}	13.78–13.82 (br. s, 1H, NH), 12.78 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.47 (d, 1H, H-8), 7.10 (s, 1H, CH), 6.86 (s, 1H, CH), 4.42–4.45 (m, 1H, CH), 2.53–2.56 (m, 1H, CH), 2.37 (s, 3H, CH_3-Ar), 0.82 (s, 6H, $2CH_3$)
4{16}	13.80–13.84 (br. s, 1H, NH), 12.74 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.62 (t, 1H, H-7), 7.45 (d, 1H, H-8), 7.10 (s, 1H, CH), 6.82 (s, 1H, CH), 4.80–4.85 (m, 1H, CH), 2.35 (s, 3H, CH_3-Ar), 1.52 (s, 6H, $2CH_3$)
4{17}	13.88–13.92 (br. s, 1H, NH), 12.80 (s, 1H, NH), 8.04 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.47 (d, 1H, H-8), 7.10 (s, 1H,CH), 6.88 (s, 1H, CH), 5.42–5.45 (m, 1H, CH), 2.37 (s, 3H, CH_3-Ar), 2.16–2.20 (m, 2H, CH_2), 1.76–1.80 (m, 1H, CH), 0.88 (s, 6H, $2CH_3$)
4{18}	13.88–13.92 (br. s, 1H, NH), 12.76 (s, 1H, NH), 8.04 (d, 1H, H-5), 7.64 (t, 1H, H-7), 7.48 (d, 1H, H-8), 7.12 (s, 1H, CH), 6.88 (s, 1H, CH), 4.48–4.51 (m, 1H, NCH), 2.33 (s, 3H, CH_3-Ar), 1.40–1.46 (m, 3H, CH+CH_2), 0.98 (s, 3H, CH_3), 0.80 (s, 3H, CH_3)
4{19}	13.90–14.02 (br. s, H, NH), 12.85 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.74 (t, 1H, H-7), 7.48 (d, 1H, H-8), 7.20–7.26 (m, 6H,CH+Ar-H), 6.94 (s, 1H, CH), 5.04–5.08 (m, 1H, CH), 3.60 (m, 2H, CH_2), 2.37 (s, 3H, CH_3-Ar)
4{20}	13.00 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.74 (t, 1H, H-7), 7.46 (d, 1H, H-8), 7.18–7.25 (m, 6H, CH+Ar-H), 6.94 (s, 1H, CH), 5.18 (s, 2H, NCH_2), 3.72–3.78 (t, 2H, NCH_2), 2.82–2.85 (t, 2H, CH_2), 2.34 (s, 3H, CH3-Ar)
4{21}	14.00–14.04 (br. s, H, NH), 12.93 (s, 1H, NH), 7.60–7.80 (m, 2H, H-5, 7), 7.12 (s, 1H, CH), 7.33 (qr, 1H, H-8), 6.88 (s, 1H, CH), 3.88 (t, 2H, CH_2), 2.10 (t, 2H, CH_2)

(Contd...)

Table 2: *(Continued)*

Compounds	^{1}H NMR, δ, p.p.m
4{22}	13.78–13.81 (br. s, 1H, NH), 12.95 (s, 1H, NH), 7.62–7.78 (m, 2H, H-5, 7), 7.14 (s, 1H, CH), 7.33 (qr, 1H, H-8), 6.88 (s, 1H, CH), 3.65 (t, 2H, CH_2), 2.16 (t, 2H, CH_2), 1.80–1.84 (m, 2H, CH_2)
4{23}	13.52–13.56 (br. s, 1H, NH), 12.90 (s, 1H, NH), 7.60–7.76 (m, 2H, H-5, 7), 7.12 (s, 1H, CH), 7.33 (qr, 1H, H-8), 6.88 (s, 1H, CH), 3.60 (t, 2H, CH_2), 2.22–2.26 (t, 2H, CH_2), 1.30–1.34 (m, 4H, $2CH_2$)
4{24}	13.00 (s, 1H, NH), 8.02 (d, 1H, H-5), 7.74 (t, 1H, H-7), 7.46 (d, 1H, H-8), 7.18–7.25 (m, 6H, CH+Ar-H), 6.94 (s, 1H, CH), 5.18 (s, 2H, NCH_2), 3.72-3.78 (t, 2H, NCH_2), 2.82–2.85 (t, 2H, CH_2)
4{25}	14.82 (s, 1H, NH), 12.95 (s, 1H, NH), 7.87 (s, 1H, H-5), 7.75 (d, 1H, H-7), 7.20 (s, H, CH), 7.38 (d, 1H, H-8), 6.86 (s, H, CH), 3.94 (t, 2H, CH_2), 2.12 (t, 2H, CH_2)
4{26}	13.78–13.82 (br. s, 1H, NH), 12.97 (s, 1H, NH), 7.89 (s, 1H, H-5), 7.75 (d, 1H, H-7), 7.22 (s, H, CH), 7.38 (d, 1H, H-8), 6.86 (s, H,CH), 3.64 (t, 2H, CH_2), 2.18 (t, 2H, CH_2), 1.78–1.80 (m, 2H, CH_2)
4{27}	13.56– 13.60 (br. s, 1H, NH), 12.90 (s, 1H, NH), 7.95 (d, 1H, H-5), 7.24–7.32 (m, 2H, H-6, 8), 7.18 (s, H, CH), 6.90 (s, H, CH), 3.04 (t, 2H, CH_2), 2.22 (t, 2H, CH_2), 1.32–1.36 (m, 4H, $2CH_2$)
4{28}	13.00 (s, 1H, NH), 7.98 (d, 1H, H-5), 7.26–7.35 (m, 2H, H-6, 8), 7.18–7.22 (m, 6H, CH+Ar-H), 6.94 (s, 1H, CH), 5.16 (s, 2H, NCH_2), 3.72–3.75 (t, 2H, NCH_2), 2.80–2.83 (t, 2H, CH_2)
4{29}	14.81 (s, 1H, NH), 13.20 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.78 (s, 1H, H-8), 7.66 (d, 1H, H-6), 7.18 (s, H, CH), 7.38 (d, 1H, H-8), 6.84 (s, H, CH), 3.96 (t, 2H, CH_2), 3.90 (s, 3H, OCH_3), 2.12 (t, 2H, CH_2)
4{30}	13.80–13.85 (br. s, 1H, NH), 13.20 (s, 1H, NH), 8.00 (d, 1H, H-5), 7.78 (s, 1H, H-8), 7.66 (d, 1H, H-6), 7.18 (s, H, CH), 7.38 (d, 1H, H-8), 6.84 (s, H, CH), 3.90 (s, 3H, OCH_3), 3.64 (t, 2H, CH_2), 2.18 (t, 2H, CH_2), 1.74–1.78 (m, 2H, CH_2)

H NMR: Hydrogen nuclear magnetic resonance

using TMS as an internal standard (chemical shifts are reported in ppm). Elemental analysis was performed on Euro EA-3000 apparatus. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. Thin-layer chromatography was performed on Silufol UV 254 aluminum plates precoated with silica gel. Ethyl acetate was used as eluent.

Chemicals and solvents were of analytical grade. Methyl 2-aminobenzoate 99% purity (CAS Number 134-20-3), methyl 2-amino-5-chlorobenzoate 95% purity (CAS Number 5202-89-1), dimethyl 2-aminoterephtalate 97% purity (CAS Number 5372-81-6), thiophosgene 97% purity (CAS Number 463-71-8), and solvents were purchased from Sigma-Aldrich, methyl 2-amino-5-methylbenzoate 98% purity (CAS Number 18595-16-9), methyl 2-amino-5-fluorobenzoate 98% purity (CAS Number 319-24-4), and methyl 2-amino-4-chlorobenzoate 98% purity (CAS Number 5900-58-3) were purchased from Enamine, Kyiv, Ukraine.

The Synthesis of methyl 2-isothiocyanato benzoates 2{1-6}. To stirred mixture of 100 ml of chloroform and 50 ml of water 0.1 mol of corresponding substituted methyl 2-aminobenzoates 1{1-6} was added. Then, the solution of 12.65 g (0.11 mol) of thiophosgene in 50 ml of chloroform was added dropwise with effective stirring in such a way that temperature does not exceed 25°C. The reaction mixture was stirred at room temperature for 2–3 h and solution of 34.5 g (0.25 mol) of K_2CO_3 in 50 ml of water was added. Lower organic layer was separated, washed 3 times of 100 ml of water and dried with $MgSO_4$. Chloroform was evaporated under lowered pressure. Obtained methyl 2-isothiocyanato benzoates 2{1-6} was used for next stage of synthesis without additional purification.

- Methyl 2-isothiocyanato benzoate 2{1}: Yield 86%, m.p. 97°C, m.p. 98°C [24].
- Methyl 2-isothiocyanato-5-methylbenzoate 2{2}: Yield 93%, m.p. 96°C.
- Methyl 2-isothiocyanato-5-fluorobenzoate 2{3}: Yield 83%, m.p. 102°C.
- Methyl 2-isothiocyanato-5-chlorobenzoate 2{4}: Yield 79%, m.p. 81°C.
- Methyl 2-isothiocyanato-4-chlorobenzoate 2{5}: Yield 86%, m.p. 91°C.
- Dimethyl 2-isothiocyanato terephthalate 2{6}: Yield 88%, m.p. 109°C.

The synthesis of 3-[2-(1H-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1H)-ones 4{1-30}. Corresponding methyl 2-isothiocyanatobenzoate 2*{1-6}* (0.05 mol) was dissolved in 40 ml of propanol-2. Then, corresponding 2-(α,β,ω-aminoalkyl)imidazole 3*{1-10}* (0.055 mol) was added slowly and 6 ml of 50% water solution of KOH was added dropwise. The reaction mixture was refluxed for 30 minutes, cooled to room temperature, poured into 100 ml of water and neutralized by acetic acid to pH = 7. Formed precipitate was filtered and crystallized from a mixture of DMF and propanol-2 (1:1). Yields of obtained compounds 4*{1-30}* are given in Table 1.

Experimental Biological Part

Samples of each compound were dissolved in DMSO that gave 1 mg/ml solution just before screening. Hottinger broth

Table 3: Results of microbiological screening of 3-[2-(1*H*-imidazol-2-yl) alkyl]-2-thioxo-2,3-dihydroquinazolin-4 (1*H*)-ones 4*{1-30}* to *S. aureus. E. coli, P. aeruginosa*

Compounds	*S. aureus* ATCC 25923		*Escherichia coli* ATCC 25922		*P. aeruginosa* ATCC 27853	
	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml
Pipemidic acid	6.25		25.00		12.50	
4{1}	50.0	100.0	50.0	200.0	50.0	100.0
4{2}	25.0	100.0	100.0	200.0	50.0	200.0
4{3}	50.0	100.0	25.0	50.0	50.0	100.0
4{4}	50.0	100.0	50.0	25.0	50.0	25.0
4{5}	50.0	100.0	50.0	100.0	50.0	100.0
4{6}	50.0	100.0	50.0	200.0	50.0	100.0
4{7}	25.0	100.0	100.0	200.0	50.0	200.0
4{8}	50.0	100.0	50.0	200.0	100.0	200.0
4{9}	50.0	100.0	50.0	100.0	50.0	100.0
4{10}	50.0	100.0	50.0	100.0	50.0	100.0
4{11}	50.0	100.0	50.0	200.0	50.0	100.0
4{12}	50.0	100.0	100.0	200.0	50.0	200.0
4{13}	50.0	100.0	50.0	200.0	50.0	100.0
4{14}	50.0	100.0	25.0	50.0	50.0	100.0
4{15}	50.0	100.0	50.0	200.0	50.0	100.0
4{16}	25.0	50.0	100.0	200.0	50.0	200.0
4{17}	50.0	100.0	50.0	200.0	100.0	200.0
4{18}	50.0	100.0	50.0	100.0	50.0	100.0
4{19}	50.0	100.0	50.0	100.0	50.0	200.0
4{20}	50.0	100.0	50.0	200.0	50.0	100.0
4{21}	25.0	50.0	50.0	100.0	50.0	100.0
4{22}	25.0	50.0	25.0	100.0	50.0	100.0
4{23}	25.0	50.0	50.0	100.0	50.0	100.0
4{24}	25.0	50.0	25.0	50.0	50.0	100.0
4{25}	25.0	50.0	50.0	100.0	50.0	100.0
4{26}	25.0	50.0	50.0	100.0	50.0	100.0
4{27}	25.0	50.0	25.0	50.0	50.0	25.0
4{28}	50.0	100.0	50.0	100.0	50.0	100.0
4{29}	50.0	200.0	50.0	100.0	50.0	100.0
4{30}	50.0	100.0	50.0	100.0	50.0	100.0

MIC: Minimum inhibitor concentration, *S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa*

(pH 7.2–7.4), which was used as a nutrition medium for bacteria, was poured at 2 ml into 10 sterile test tubes. Then, 2 ml of the solution of the tested compound was added into first test tube. The mixture was thoroughly stirred, and 2 ml of obtained solution was added into the next test tube. The procedure was repeated until penultimate tube, from which 2 ml of the resulted mixture was poured out. The last tube with 2 ml of nutrition medium was used as the control. Thus, consecutive dilutions of the solution of tested compound at concentrations ranging from 400 to 2 µg/ml were obtained. Then, tested microbial cultures of 2×10^5 CFU/ml were added, and test tubes were incubated at 37°C for 18–24 h. Fungi strains were cultured in Sabouraud medium with microbial density 2×10^5 CFU/ml; the test tubes were incubated at 30°C for 48 h. Minimum inhibitory concentration (MIC) was determined by the absence of apparent growth of microorganisms in a liquid nutrient medium. The medium remained transparent in those test tubes, where the concentration of the tested compound was sufficient to completely suppress the growth of the test microorganism. The turbidity of the samples indicates that the concentration of the substance in them is less than the MIC for this test culture. Minimum bactericidal concentration

Table 4: Results of microbiological screening of 3-[2-(1*H*-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones 4*{1-30}* to *P. vulgaris, B. anthracoides, C. albicans*

Compounds	*P. vulgaris* ATCC 4636		*B. anthracoides* ATCC 1312		*C. albicans* ATCC 885-653	
	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml	MIC µg/ml	MBC µg/ml
Pipemidic acid	12.5		12.5			
Fluconazole					15.6	62.5
4{1}	50.0	200.0	50.0	100.0	100.0	200.0
4{2}	100.0	200.0	50.0	200.0	50.0	100.0
4{3}	25.0	50.0	25.0	50.0	25.0	50.0
4{4}	50.0	50.0	50.0	25.0	50.0	25.0
4{5}	50.0	200.0	50.0	100.0	50.0	100.0
4{6}	50.0	200.0	50.0	200.0	100.0	200.0
4{7}	50.0	100.0	50.0	200.0	50.0	100.0
4{8}	50.0	200.0	50.0	100.0	50.0	200.0
4{9}	50.0	200.0	50.0	100.0	50.0	100.0
4{10}	50.0	200.0	50.0	200.0	50.0	100.0
4{11}	50.0	200.0	50.0	100.0	100.0	200.0
4{12}	50.0	100.0	50.0	200.0	100.0	200.0
4{13}	50.0	200.0	50.0	100.0	100.0	200.0
4{14}	50.0	100.0	25.0	50.0	25.0	50.0
4{15}	50.0	200.0	50.0	100.0	100.0	200.0
4{16}	50.0	100.0	50.0	200.0	50.0	100.0
4{17}	50.0	200.0	50.0	100.0	50.0	50.0
4{18}	50.0	200.0	50.0	100.0	50.0	100.0
4{19}	50.0	200.0	50.0	100.0	50.0	100.0
4{20}	50.0	200.0	50.0	100.0	100.0	200.0
4{21}	25.0	100.0	50.0	100.0	25.0	50.0
4{22}	50.0	100.0	50.0	100.0	25.0	50.0
4{23}	25.0	50.0	50.0	100.0	25.0	50.0
4{24}	50.0	100.0	50.0	100.0	25.0	50.0
4{25}	25.0	50.0	50.0	100.0	50.0	100.0
4{26}	50.0	100.0	50.0	100.0	50.0	100.0
4{27}	25.0	50.0	25.0	50.0	25.0	50.0
4{28}	50.0	100.0	50.0	100.0	100.0	200.0
4{29}	50.0	200.0	50.0	100.0	50.0	100.0
4{30}	50.0	200.0	50.0	100.0	50.0	100.0

MIC: Minimum inhibitor concentration, MBC: Minimum bactericidal concentration, *P. vulgaris: Proteus vulgaris, B. anthracoidesm: Bacillus anthracoidesm, C. albicans: Candida albicans*

(MBC) was determined by seeding microorganisms from samples on a solid nutrient medium.

CONCLUSIONS

The series of novel 6,7-substituted 3-[2-(1*H*-imidazol-2-yl) alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-ones, which contain 2-thioxoquinazolin-4-one and imidazole moieties connected by carbon chain have been synthesized.

Antibacterial and antifungal activity of novel 6,7-substituted 3-[2-(1*H*-imidazol-2-yl)alkyl]-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one derivatives has been studied by the method of double serial dilution with the standard set of microbial strains as a biological target.

Elongation of carbon chain between 2-thioxoquinazolin-4-one and imidazole moieties up to three carbon atoms led to increasing of antimicrobial and antifungal action.

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