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UDC 547.799 : 615.244 : 615.281

SYNTHESIS AND EVALUATION OF THE ANTIOXIDANT ACTIVITY OF {[1-ARYL-4-CHLORO-1H-IMIDAZOLE-5-YL) METHYL]THIO}ALKANE CARBOXYLIC ACIDS

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Key words: synthesis; imidazole; [(1-aryl-5-formyl-1H-imidazol-4-yl)thio]acetic acids; {[1-aryl-4-chloro-1H-imidazole-5-yl)methyl]thio}alkanecarboxylic acids; antioxidant activity

This study is devoted to development of the optimal conditions for synthesis and the study of some "structure – antioxidant activity" regularities of [(1-aryl)imidazole-5-yl)methylthio]alkane carboxylic acids, which structural analogues have found an application as medicinal products with a wide range of biological activities. The methodology of interaction between 4-chloro-5-chloromethylimidazoles with thioglycolic and thiopropionic acids has been used to obtain these compounds. Selection of the optimal reaction conditions has allowed to obtain target compounds in a dry dimethylformamide in the presence of potash at 50°C with yields of 75-82%. The compounds synthesized are high-melting crystalline substances that dissolve well in polar organic solvents and aqueous alkaline solutions. Their composition and structure have been confirmed by the results of elemental analysis and measurement data of IR-, ¹H NMR- and chromatography mass-spectra. The study of the compounds synthesized has been conducted in vitro on biological samples. The antioxidant activity has been determined by the inhibition value of the ascorbate-dependent endogenous lipid peroxidation rate in rats' liver found by the concentration of one of the final products of free-radical lipid oxidation processes – malonaldehyde in the test sample. The results of the biological activity screening of the compounds synthesized show that all imidazole derivatives studied in the final concentration ranges of 10⁻³-10⁻¹ M exhibit a high antioxidant action in the system in vitro. It has been found that the value of the antioxidant activity is influenced by the nature and position of the substituent in position 1 of imidazole. In particular, the presence of electron-acceptor substituents in the aryl fragment decreases the molecule activity in comparison with electron-donor substituents, wherein increase of the methylene groups quantity in the carboxyalkylthiol fragment does not significantly impact the antioxidant effect of the compounds synthesized.

The process of free-radical lipid oxidation (FRLO) plays a significant role in development of the most diseases of the liver, cardiovascular, respiratory and nervous systems [1, 16]. Antioxidants are widely used to normalize the basic organism functions as a part of complex therapy of such diseases [7]. It should be noted that at present there is insufficient amount of medicines with the antioxidant mechanism of action offered for clinical use, and those that are in use have many adverse effects and high toxicity [4]. Taking this into account, the search of compounds that are able to inhibit the FRLO processes effectively is of high interest nowadays.

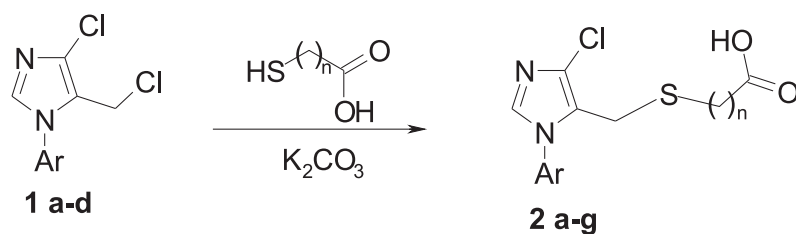
Design and synthesis of new compounds with antioxidant properties is a subject of many studies as they are of high interest in prophylactics and therapy of many diseases that have FRLO in their pathogenesis [3, 9]. From this aspect the derivatives of imidazole are not left aside too; according to the literature data they are characterized by a wide spectrum of pharmacological properties, among which the antioxidant effect is particularly noteworthy [10, 11, 15].

Earlier we found the antioxidant activity in the series of [(1-phenyl-5-formyl-1H-imidazole-4-yl)thio]acetic acids and their derivatives [5, 6, 8, 13]. It was to

be expected that the change in the position of the thio-alkanecarboxylic acid fragment in the structure of the imidazole cycle would allow a much bigger quantity of potentially active compounds with the antioxidant action, and also give an opportunity to approach to the solution of the topical problem of pharmaceutical chemistry – establishing of the structure – activity relationship. With this purpose we have synthesized [(1-aryl-imidazole-5-yl)methylthio]alkanecarboxylic acids (**2a-g**) and carried out the screening of their antioxidant properties.

The reaction of easily available 4-chloro-5-chloromethylimidazoles (**1a-d**) [12] with thioglycolic and thiopropionic acids, which occurs selectively at 50°C in a dry DMFA in the presence of potash, has been used to obtain compounds of such kind. The reaction gives the target compounds (**2a-g**) with yields of 75-82%.

The compounds (**2a-g**) synthesized (Tab. 1, 2) are light-yellow, high-melting crystalline compounds, readily soluble in polar organic solvents and aqueous alkaline solutions. Their composition and structure were confirmed by elemental analysis and by the results of IR-, ¹H NMR and chromatography mass-spectra measurements. IR-spectra, in particular, are characterized



I, Ar = Ph (a), 4-FC₆H₄ (b), 4-ClC₆H₄ (c), 4-MeC₆H₄ (d); II, n=1, Ar = 4-FC₆H₄ (a), 4-ClC₆H₄ (b), 4-MeC₆H₄ (c); n=2, Ar = Ph (d), 4-FC₆H₄ (e), 4-ClC₆H₄ (f), 4-MeC₆H₄ (g)

Scheme

Table 1

Physical and chemical characteristics, data of the elemental analysis and chromatography mass spectra of [(1-aryl-4-chloro-1H-imidazole-5-yl)methyl]thio}alkanecarboxylic acids (2a-g)

Compound	Ar	Yield, %	T melt., °C	Empiric formula	Found, %			Calculated, %			[M+1] ⁺	M
					C	H	N	C	H	N		
2a	4-FC ₆ H ₄	75	139-140	C ₁₂ H ₁₀ ClFN ₂ O ₂ S	47.82	3.28	9.14	47.93	3.35	9.31	301	300.74
2b	4-ClC ₆ H ₄	81	86-87	C ₁₂ H ₁₀ Cl ₂ N ₂ O ₂ S	45.64	3.28	9.01	45.44	3.18	8.83	318	317.20
2c	4-MeC ₆ H ₄	76	111-113	C ₁₃ H ₁₃ ClN ₂ O ₂ S	52.42	4.33	9.30	52.61	4.42	9.44	297	296.78
2d	Ph	82	105-107	C ₁₃ H ₁₃ ClN ₂ O ₂ S	52.34	4.33	9.42	52.61	4.42	9.44	297	296.78
2e	4-FC ₆ H ₄	75	132-134	C ₁₃ H ₁₂ ClFN ₂ O ₂ S	49.34	3.79	8.77	49.61	3.84	8.90	315	314.77
2f	4-ClC ₆ H ₄	79	100-102	C ₁₃ H ₁₂ Cl ₂ N ₂ O ₂ S	47.07	3.62	8.33	47.14	3.65	8.46	332	331.22
2g	4-MeC ₆ H ₄	75	142-144	C ₁₄ H ₁₅ ClN ₂ O ₂ S	53.88	4.75	8.87	54.10	4.86	9.01	311	310.80

by intensive absorption bands of carbonyl groups at 1675-1685 cm⁻¹ and by a wide absorption range (2430-2850 cm⁻¹) of carboxyl groups, and it indicates a dimeric character of the acids obtained in their solid state. In ¹H NMR spectra of all compounds the most illustrative are H² proton singlets of the imidazole cycle at 7.83-7.95 ppm and the singlets of methylene groups bound with the imidazole cycle at 3.72-3.85 ppm. In their turn,

the methylene protons of thioacetic acid fragments are visible as singlets at 3.17 ppm, and those of thiopropionic acid – as triplets in the range of 2.30-2.35 and 2.49-2.54 ppm.

Experimental Part (Chemistry)

IR-spectra of the compounds synthesized were recorded on a UR-20 spectrophotometer in KBr tablets. ¹H NMR spectra were recorded on a Varian-Mercu-

Table 2

IR and ¹H NMR spectra of [(1-aryl-4-chloro-1H-imidazole-5-yl)methyl]thio}alkanecarboxylic acids

Compound	IR-spectrum, cm ⁻¹		¹ H NMR, δ, ppm
	C=O	COOH	
2a	1685	2430-2850	3.17 s (2H, CH ₂), 3.82 s (2H, CH ₂), 7.36-7.43 m (2H _{arom.}), 7.60-7.65 m (2H _{arom.}), 7.87 c (1H, H ² _{imidazole}), 12.55 br.s. (1H, COOH)
2b	1680	2450-2840	3.17 s (2H, CH ₂), 3.85 s (2H, CH ₂), 7.57-7.63 m (4H _{arom.}), 7.90 s (1H, H ² _{imidazole}), 12.60 br.s. (1H, COOH)
2c	1680	2450-2820	2.38 s (3H, CH ₃), 3.17 s (2H, CH ₂), 3.82 s (2H, CH ₂), 7.36 d (2H _{apom.} , J 8.0 Hz), 7.41 d (2H _{arom.} , J 8.0 Hz), 7.83 s (1H, H ² _{imidazole}), 12.54 br.s. (1H, COOH)
2d	1675	2435-2830	2.34 t (2H, CH ₂ , J 6.8 Hz), 2.54 t (2H, CH ₂ , J 6.8 Hz), 3.75 s (2H, CH ₂), 7.49-7.55 m (5H _{arom.}), 7.87 s (1H, H ² _{imidazole}), 12.24 s. (1H, COOH)
2e	1680	2440-2835	2.32 t (2H, CH ₂ , J 6.8 Hz), 2.50 t (2H, CH ₂ , J 6.8 Hz), 3.77 s (2H, CH ₂), 7.40-7.48 m (2H _{arom.}), 7.62-7.69 m (2H _{arom.}), 7.90 s (1H, H ² _{imidazole}), 12.28 br.s. (1H, COOH)
2f	1680	2435-2850	2.35 t (2H, CH ₂ , J 6.8 Hz), 2.49 t (2H, CH ₂ , J 6.8 Hz), 3.76 s (2H, CH ₂), 7.56 d (2H _{arom.} , J 8.0 Hz), 7.64 d (2H _{arom.} , J 8.0 Hz), 7.94 s (1H, H ² _{imidazole}), 12.20 br.s. (1H, COOH)
2g	1685	2445-2840	2.30 t (2H, CH ₂ , J 6.8 Hz), 2.38 s (3H, CH ₃), 2.53 t (2H, CH ₂ , J 6.8 Hz), 3.72 s (2H, CH ₂), 7.36 d (2H _{arom.} , J 7.0 Hz), 7.42 d (2H _{arom.} , J 7.0 Hz), 7.95 s (1H, H ² _{imidazole}), 12.40 br.s. (1H, COOH)

Table 3

The antioxidant activity of $\{[(1\text{-aryl-4-chloro-1H-imidazole-5-yl)methyl}]thio\}$ alkanecarboxylic acids *in vitro*

Compound	Concentration, mole/l									
	10^{-1}		5×10^{-2}		10^{-2}		5×10^{-3}		10^{-3}	
	MA, $\mu\text{mole/g}$ of the tissue	AOA, %	MA, $\mu\text{mole/g}$ of the tissue	AOA, %	MA, $\mu\text{mole/g}$ of the tissue	AOA, %	MA, $\mu\text{mole/g}$ of the tissue	AOA, %	MA, $\mu\text{mole/g}$ of the tissue	AOA, %
2a	45.68±0.19*	60.8	46.32±0.12*	60.2	44.39±0.12*	61.9	46.19±0.07*	60.3	45.16±0.12*	61.2
2b	66.26±0.25*	43.1	53.14±0.19*	54.4	44.78±0.32*	61.5	43.36±0.19*	62.8	50.31±0.31*	56.8
2c	50.44±0.19*	56.7	53.01±0.07*	54.5	44.39±0.12*	61.9	49.79±0.21*	57.2	45.42±0.19*	61.0
Control 1	100.36±0.37	–	100.36±0.37	–	100.36±0.37	–	100.36±0.37	–	100.36±0.37	–
2d	24.19±0.07*	59.0	16.73±0.07*	71.6	14.02±0.07*	76.2	13.90±0.12*	76.4	16.60±0.12*	71.9
2e	28.95±0.12*	50.9	20.07±0.12*	66.0	16.98±0.32*	71.2	29.34±0.12*	50.3	20.46±0.12*	65.3
2f	23.93±0.12*	59.4	24.58±0.19*	58.3	20.84±0.24*	64.7	35.13±0.12*	40.5	35.13±0.12*	40.5
2g	17.37±0.12*	70.5	19.56±0.07*	66.8	23.03±0.14*	61.0	26.25±0.12*	55.5	24.70±0.12*	58.1
Control 2	59.06±0.12	–	59.06±0.12	–	59.06±0.12	–	59.06±0.12	–	59.06±0.12	–
Thiotriazoline	70.64±0.56*	38.5	73.98±0.19*	35.6	77.33±0.25*	32.7	76.43±0.24*	33.5	79.13±0.12*	31.2
Control 4	115.03±0.24	–	115.03±0.24	–	115.03±0.24	–	115.03±0.24	–	115.03±0.24	–

* – valid in relation to control ($p \leq 0.05$)

ry-400 spectrophotometer (400 MHz) in the solution of DMSO- d_6 , the inner standard – tetramethylsilane. Chromatography mass-spectra were recorded by a PE SCXAPI 150 EX device, UV (250 nm) and ELSOJ detectors.

$\{[(1\text{-Aryl-4-chloro-1H-imidazole-5-yl)methyl}]thio\}$ acetic (propionic) acids (2 a-g). To the solution of 2 mmoles of 5-chloromethylimidazole (**1a-d**) in 20 ml of a dry DMFA 0.55 g (4 mmoles) of potash and 0.19 g (2 mmoles) of thioglycolic acid (in cases of **2a-c**) or 0.21 g (2 mmoles) of thiopropionic acid (in cases of **2d-g**) were added; the mixture was stirred at 50°C for 2 hours. After that the reaction mixture was poured into 20 ml of water, and acidified with diluted hydrochloric acid to pH 4-5. The precipitate formed was filtered, washed with water, dried and crystallized from 70% aqueous solution of ethanol.

Experimental Part (Biology)

The research of the antioxidant activity of the compounds (**2a-g**) synthesized was performed *in vitro* [14] and determined by the inhibition value of the ascorbate-dependent endogenous lipid peroxidation rate in rats' liver found by the concentration of one of the final products of free-radical lipid oxidation processes – malonaldehyde (MA) in the test sample. The content of MA was determined by the reaction with thiobarbituric acid (TBA) and was calculated in $\mu\text{moles/g}$ of the tissue. Statistical analysis of the results obtained was performed using the parametric Student's t-test [2]. The value of ascorbate-induced FRLO inhibition was calculated in percents, with MA concentration in the control samples being equal to 100%.

The range of concentrations of the compounds synthesized was chosen within the limits of concentrations already researched for their structural analogue, thiotriazoline (**T**), (the manufacturer is "Arterium" corporation, Ukraine, solution for injections, 25 mg/ml), which has the proven antioxidant activity [7].

Results and Discussion

The results of the antioxidant activity screening of the compounds synthesized *in vitro* (Tab. 3) show that all compounds are able to inhibit Fe^{2+} -ascorbate initiated FRLO in these conditions in the final concentration ranges of 10^{-3} - 10^{-1} M studied. Thus, the degree of Fe^{2+} -ascorbate initiated FRLO inhibition *in vitro* of all original compounds synthesized was higher than the antioxidant activity of thiotriazoline in the same final concentrations. The antioxidant activity of thiotriazoline in the specified range of final concentrations *in vitro* varied between 31.32% and 38.59% and was the highest with the final drug concentration of 10^{-1} M. With the same final concentration the highest inhibiting effect on the initiated FRLO was shown by compound **2g** (the degree of FRLO inhibition was 70.59%). Most compounds (**2a**, **2c**, **2e**, **2f**) have shown the highest antioxidant activity *in vitro* in the concentrations of 10^{-2} M. The highest antioxidant effect *in vitro* was recorded for compound **2d** in the range of the final concentrations of $5 \cdot 10^{-3}$ - 10^{-2} M: the degree of FRLO inhibition was 76.47-76.25%. On average, it is 43% higher than the results shown by thiotriazoline in the same range of the final concentrations, and 37% higher than the maximum effect of thiotriazoline recorded *in vitro*.

Analysis of the data obtained shows that the value of the antioxidant activity is influenced by the nature and position of the substituent in position 1 of imidazole. In particular, the presence of electron-acceptor substituents in the aryl fragment decreases the molecule activity in comparison with electron-donor substituents, wherein increase of the methylene groups quantity in the carboxyalkylthiol fragment does not significantly impact the antioxidant effect of the compounds synthesized.

CONCLUSIONS

1. By interaction of 5-chloromethylimidazoles with thioglycolic and thiopropionic acids new $\{[(1\text{-Aryl-4-}$

chloro-1*H*-imidazole-5-yl)methyl]thio}alkanecarboxylic acids have been synthesized.

2. All derivatives of imidazole studied in the range of concentrations of 10^{-3} - 10^{-1} M show a high antioxidant activity in the system *in vitro*. The highest activity was

recorded for compound **2d** in the final concentration of $5 \cdot 10^{-3}$ M.

3. Increase of the methylene groups quantity in the carboxyalkylthiol fragment does not significantly affect the antioxidant effect of the compounds synthesized.

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СИНТЕЗ ТА ОЦІНКА АНТИОКСИДАНТНОЇ АКТИВНОСТІ {{{1-АРИЛ-4-ХЛОРО-1Н-ІМІДАЗОЛ-5-ІЛ)МЕТИЛ]ТІО}АЛКАНКАРБОНОВИХ КИСЛОТ

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Ключові слова: синтез; імідазол; [(1-арил-5-форміл-1*H*-імідазол-4-іл)тіо]оцтові кислоти; [(1-арил-4-хлоро-1*H*-імідазол-5-іл)метил]тіо}алканкарбонові кислоти; антиоксидантна активність

Дослідження присвячене розробці оптимальних умов синтезу та вивченню деяких закономірностей «структура-антиоксидантна активність» [(1-арилімідазол-5-іл)метилтіо]алканкарбонових кислот, структурні аналоги яких знайшли застосування в ролі лікарських засобів із широким спектром біологічної дії. Для отримання зазначених сполук було використано методологію, що полягає у взаємодії 4-хлоро-5-хлорометилімідазолів з тіогліколевою та тіопропановою кислотами. Підбір оптимальних умов перебігу реакції дозволив отримати цільові сполуки в сухому ДМФА в присутності поташу при 50°C з виходами 75-82%. Синтезовані сполуки – високоплавкі кристалічні речовини, що добре розчиняються в полярних органічних розчинниках та водних розчинах лугів. Їх склад та структура підтверджені результатами елементного аналізу і даними вимірювань ІЧ-, ЯМР ¹H- та хроматомас-спектрів. Дослідження синтезованих сполук проводили *in vitro* на біологічних зразках. Антиоксидантну активність визначали за величиною інгібування швидкості аскорбатзалежного пероксидного окиснення ендогенних ліпідів у печінці щурів, яку встановлювали за концентрацією одного з кінцевих продуктів процесів ВРОЛ – малонового альдегіду у досліджуваному зразку. Результати скринінгу біологічної активності синтезованих сполук свідчать про те, що всі досліджені похідні імідазолу в діапазоні кінцевих концентрацій 10^{-3} - 10^{-1} M проявляють високу антиоксидантну дію в системі *in vitro*. Встановлено, що на величину антиоксидантної активності впливає характер та положення замісника в положенні 1 імідазолу. Зокрема, присутність в арильному фрагменті електроноакцепторних замісників знижує активність порівняно з електронодонорними. При цьому збільшення кількості метиленових груп в карбоксилкітільному фрагменті суттєво не впливає на антиоксидантний ефект синтезованих сполук.

СИНТЕЗ И ОЦЕНКА АНТИОКСИДАНТНОЙ АКТИВНОСТИ {[1-АРИЛ-4-ХЛОР-1Н-ИМИДАЗОЛ-5-ИЛ)МЕТИЛ]ТИО}АЛКАНКАРБОНОВЫХ КИСЛОТ**А.Н.Грозаев, А.А.Паламар, В.А.Чорноус, И.Н.Яремий, М.В.Возк****Ключевые слова:** синтез; имидазол; [(1-арил-5-формил-1Н-имидазол-4-ил)тио]уксусные кислоты; {[1-арил-4-хлоро-1Н-имидазол-5-ил)метил]тио}алканкарбоновые кислоты; антиоксидантная активность

Исследование посвящено разработке оптимальных условий синтеза и изучению некоторых закономерностей «структура-антиоксидантная активность» [(1-арилимидазол-5-ил)метил]алканкарбоновых кислот, структурные аналоги которых нашли применение в качестве лекарственных средств с широким спектром биологического действия. Для получения указанных соединений использована методология, которая заключается во взаимодействии 4-хлор-5-хлорметилимидазолов с тиогликолевой и тиопропановой кислотами. Подбор оптимальных условий протекания реакции позволил получить целевые соединения в сухом ДМФА в присутствии поташа при 50°C с выходами 75-82%. Синтезированные соединения – высокоплавкие кристаллические вещества, хорошо растворимые в полярных органических растворителях и водных растворах щелочей. Их состав и структура подтверждены результатами элементного анализа и данными измерений ИК-, ЯМР ¹H- и хроматомасс-спектров. Исследование синтезированных соединений проводили *in vitro* на биологических образцах. Антиоксидантную активность определяли по величине ингибирования скорости аскорбат-зависимого перекисного окисления эндогенных липидов в печени крыс, которую устанавливали по концентрации одного из конечных продуктов процессов СРОЛ – малонового альдегида в исследуемом образце. Результаты скрининга биологической активности синтезированных соединений свидетельствуют о том, что все исследованные производные имидазола в диапазоне конечных концентраций 10⁻³-10⁻¹ М проявляют высокое антиоксидантное действие в системе *in vitro*. Установлено, что на величину антиоксидантной активности влияет характер и положение заместителя в положении 1 имидазола. В частности, присутствие в арильном фрагменте электроноакцепторных заместителей снижает активность по сравнению с электронодонорными. При этом увеличение количества метиленовых групп в карбоксиалкилтиольном фрагменте существенно не влияет на антиоксидантный эффект синтезированных соединений.