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SYNTHESIS, PHYSICOCHEMICAL PROPERTIES, ANTIMICROBIAL AND FREE-RADICAL SCAVENGING ACTIVITY OF SUBSTITUTED BENZO[4,5]IMIDAZO[1,2-*c*]QUINAZOLINE-6(5*H*)-ONES (-THIONES)

Dmytro V. Kravtsov, Dmytro Yu. Skoryna, Inna S. Nosulenko, Oleksii Yu. Voskoboinik*, Serhii I. Kovalenko

Zaporizhzhia State Medical University, Mayakovskyi, Ave., 26, 69035, Zaporizhzhia, Ukraine

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Abstract

This study describes the elaboration of synthetic procedures for 6-*S*-subtituted and 5-*N*-substituted benzo[4,5]imidazo[1,2-*c*]quinazolines, as well as their antiradical and antimicrobial activity screening results. It has been showed that target substances can be prepared by alkylation of initial potassium benzo[4,5]imidazo[1,2-c]quinazolin-6-thiolate and benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one with substituted 2-chloracetamides in appropriate conditions. The features of synthesized compounds' NMR spectra have been investigated and discussed. It has been found out that 2-(6-oxobenzo[4,5]imidazo[1,2-*c*]quinazoline-5(6*H*)-yl)acetamides do not reveal antiradical activity, while most of 6-S-substituted benzo[4,5]imidazo[1,2-*c*]quinazolines are active free radical scavenging agents. The conducted study of synthesized compound`s antibacterial and antifungal activity revealed their low or moderate activity against *E. coli, S. aureus* and *P. aeruginosa* strains. An opportunistic pathogenic yeast *C. albicans* has been identified as the most susceptible to synthesized compounds strain. The reliable correlation between the nature of substituent at acetamide Nitrogen and antimicrobial activity has not been found. It has been substantiated that studied classes of compound are promising objects for the search of chemotherapeutic agents.

Keywords: benzo[4,5]imidazo[1,2-c]quinazoline; antimicrobial activity; free-radical scavenging activity

СИНТЕЗ ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ, АНТИМІКРОБНА ТА АНТИРАДИКАЛЬНА АКТИВНІСТЬ ЗАМІЩЕНИХ БЕНЗО[4,5]ІМІДАЗО[1,2-*c*]ХІНАЗОЛІН-6(5*H*)-ОНІВ (-ТИОНІВ)

Дмитро В. Кравцов, Дмитро Ю. Скорина, Інна С. Носуленко, Олексій Ю. Воскобойнік, Сергій І. Коваленко

Запорізький державний медичний університет, пр. Маяковського 26, 69035, Запоріжжя, Україна

Анотація

В представленій роботі описано методи синтезу ряду 6-S-заміщенних та 5-N-заміщенних бензо[4,5]імідазо[1,2-*c*]хіназолінів, а також результати дослідження їх антирадикальної та протимікробної активностей. Було показано, що цільові сполуки можуть бути одержані алкілуванням вихідних калій бензо[4,5]імідазо[1,2-*c*]хіназолін-6-тіолату та бензо[4,5]імідазо[1,2-*c*]хіназолін-6(5*H*)-ону заміщеними 2-хлорацетамідами у відповідних умовах. Особливості спектрів ЯМР синтезованих сполук були встановлені та обговорені. Виявлено, що 2-(6-оксобензо[4,5]імідазо[1,2-*c*]хіназолін-5(6*H*)-іл)ацетаміди не проявляють антирадикальну дію, в той самий час як більшість 6-S-заміщених бензо[4,5]імідазо[1,2-*c*]хіназолінів є активними радикал-зв'язуючими агентами. Проведене дослідження антибактеріальної та протигрибкової дії синтезованих сполук дозволило встановити їх низьку або помірну дію проти таких штамів як *E. coli*, *S. Aureus* та *P. aeruginosa*. Умовно-патогенний штам грибів *C. albicans* було ідентифіковано як найбільш чутливий до дії синтезованих сполук. Достовірної кореляції між природою замісника при атомі Нітрогену ацетамідного залишку та антимікробною активністю виявлено не було. Обґрунтовано перспективність дослідженого класу сполук як об'єктів досліджень спрямованих на пошук нових хіміотерапевтичних агентів.

Ключові слова: бензо[4,5]імідазо[1,2-*c*]хіназоліни; антимікробна активність; антирадикальна активність.

**Corresponding author: e-mail: a.yu.voskoboynik@gmail.com*

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СИНТЕЗ ФИЗИКО-ХИМИЧЕСКИЕ СВОЙСТВА, АНТИМИКРОБНАЯ И АНТИРАДИКАЛЬНАЯ АКТИВНОСТЬ ЗАМЕЩЕННЫХ БЕНЗО[4,5]ИМИДАЗО[1,2-*c*]ХИНАЗОЛИН-6(5*H*)-ОНОВ (-ТИОНОВ)

Дмитрий В. Кравцов, Дмитрий Ю. Скорина, Инна С. Носуленко, Алексей Ю. Воскобойник, Сергей И. Коваленко

Запорожский государственный медицинский университет, пр. Маяковского 26, 69035, Запорожье, Украина.

Аннотация

В представленной работе описаны методы синтеза ряда 6-S-замещенных и 5-N-замещенных бензо[4,5]имидазо[1,2-c]хиназолинов, а также результаты исследования их антирадикальной и противомикробной активностей. Было показано, что целевые соединения могут быть получены алкилированием исходных калий бензо[4,5]имидазо[1,2-*c*]хиназолин-6-тиолата и бензо[4,5]имидазо[1,2-*c*]хиназолин-6(5*H*)-она замещенными 2-хлорацетамидами в соответствующих условиях. Особенности ЯМР-спектров синтезированных соединений были установлены и обсуждены. Установлено, что 2-(6-оксобензо[4,5]имидазо[1,2-*c*]хиназолин-5(6*H*)-ил)ацетамиды не проявляют антирадикального действия, в то самое время как большинство 6-S-замещенных бензо[4,5]имидазо[1,2-*c*]хиназолинов являются активными радикал-связывающими агентами. Проведённое исследование антибактериального и противогрибкового действия синтезированных соединений позволило установить их низкое или умеренное действие по отношению к таким штаммам как *E. coli*, *S. Aureus* и *P. aeruginosa*. Условно-патогенный штамм грибов *C. albicans* был идентифицирован как наиболее чувствительный к действию синтезированных веществ. Достоверная корреляция между природой заместителя при атоме азота ацетамидного остатка и антимикробной активностью установлена не была. Обоснована перспективность исследуемого класса соединений как объектов исследований направленных на поиск новых химиотерапевтических агентов.

Ключевые слова: бензо[4,5]имидазо[1,2-*c*]хиназолины; антимикробная активность; антирадикальная активность.

Introduction

Condensed quinazolines currently are of considerable interest due to their wide spectrum of biological activity and ability for chemical modification [1]. Benzo[4,5]imidazo[1,2-*c*]quinazolines are among promising, but insufficiently studied fused derivatives of aforementioned heterocyclic system. Despite synthetic availability of the aforementioned derivatives, they are infrequently considered as perspective biologically active agents partly in consequence of rigidity of their structure. However, compounds with anti-tumor [2] and antimicrobial [3-7] activities were described. Moreover, dialkylaminoalkylbenzoimidazo[1,2-*c*]quinazolines could be considered as promising antiviral drugs thanks to their DNA affinity [8]. It should be mentioned here that 6-aryl-, 6-alkyl- and 6-alkylamino benzo[4,5]imidazo[1,2-*c*]quinazoline derivatives are constantly described as those which have got some type of biological activity [9]. Simultaneously, biological potential of 6-*S*-subtituted and 5-*N*-substituted benzo[4,5]imidazo[1,2-*c*]quinazolines is poorly examined. Thus, it has been decided to elaborate synthetic approaches for construction of aforementioned compounds' combinatorial library and estimate their antiradical and antimicrobial properties.

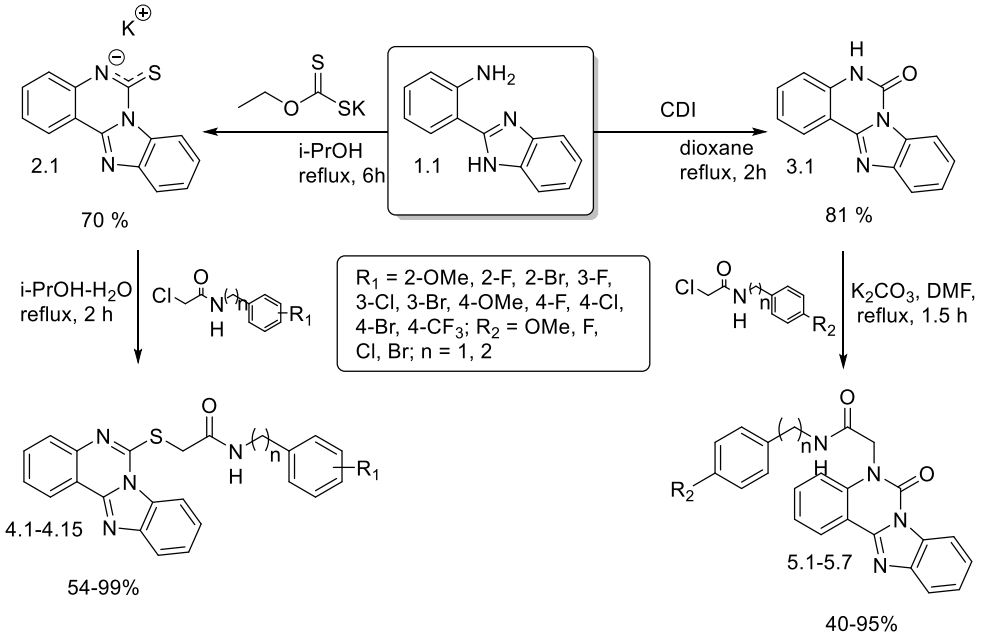
Results and discussion

The chemical modification of initial 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**1.1**) [7,8] was conducted by its conversion into potassium benzo[4,5]imidazo[1,2-*c*]quinazolin-6-thiolate (**2.1**) and benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**3.1**). Salt **2.1** was prepared by condensation of 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**1.1**) with potassium xanthate in propan-2-ol (i-PrOH) (Scheme 1) (5*H*-benzimidazo[1,2-*c*]quinazoline-6-thione was previously obtained by a similar synthetic method [10]). Benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one **(3.1**) was obtained *via* reaction between aniline (**1.1**) and 1,1`-carbonyldiimidazole (CDI) (Scheme 1). It should be noted, that products **2.1** and **3.1** might be considered as efficient substrates for chemical modification aimed at forming a combinatorial library of promising bioactive molecules.

Thus, compounds **4.1-4.15** were obtained by alkylation of benzo[4,5]imidazo[1,2-*c*]quinazolin-6-thiolate **(2.1)** with substituted 2-chloracetamides (Scheme 1). The above-mentioned transformation was fast and resulted in high yields and purity of the products. The development of benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**3.1**) alkylation method required the selection of certain base to improve the initial compound reactivity. It was shown that the alkylation of compound **3.1** with substituted 2-chloracetamides was successful when K_2CO_3 was used as basic agents and dimethylformamide (DMF) as solvent. Substances **5.1-5.7** were prepared using the elaborated procedure (Scheme 1).

The structure of synthesized compounds was proven by complex of physicochemical methods

including LC/MS, ^{1}H and ^{13}C NMR-spectrometry and elementary analysis. The molecular ion signals in LC-MS-spectrum of obtained compounds were observed with the *m/z* values corresponding to the proposed structures.



Scheme 1. Synthesis and alkylation of potassium benzo[4,5]imidazo[1,2-*c*]quinazolin-6-thiolate (2.1) and benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (3.1)

The ^{1}H NMR spectra of amides **4.1–4.15**, **5.1–5.7** are additionally characterized by the NH-protons signals that are observed as singlets at the 10.76–9.69 ppm for arylamides or triplets at 8.82-8.44 ppm for substituted benzylamides. Also, the signals associated with aryl fragment of acetamide moiety are observed in aromatic part of the ^{1}H NMR spectra of compounds **4.1–4.15** and **5.1-5.7**. These signals are split in accordance with the nature and position of substituents at benzene moiety [11].

The series of signals that correspond to the protons of benzo[4,5]imidazo[1,2-*c*]quinazoline system are observed in aromatic part of ^{1}H NMR spectra of all obtained compounds.

The ^{13}C NMR-spectra of compounds **4.2**, **4.7**, **4.9**, **4.15**, **5.3**, **5.4**, **5.7** additionally verified the proposed structures. The position of the signal of methylene-group Carbons (35.4–36.7 ppm) in ^{13}C NMR-spectra of compound **4.2**, **4.7**, **4.9**, **4.15** proved that alkylation occurs on Sulfur atom. In ^{13}C NMR spectra of compounds **5.3, 5.4, 5.7** the signal of 5-NCH_2-moiety is observed at the 45.1 and 47.7 ppm correspondingly. Listed signals allowed to identify compounds **5** as products of *N*-alkylation.

Radical scavenging properties of synthetic and native compounds may be associated with various types of biological effects including antifungal activity [12–15]. Thus, antiradical activity of synthesized compounds was studied using 1,1-diphenyl-2-picrylhydrazyl radical (DPPH) scavenging model [16; 17] (Table 1). As it was expected, most of 6-*S*-substituted benzo[4,5]imidazo[1,2-*c*]quinazolines revealed free radical scavenging activity due to the presence of Sulfur atom, while the alkylation products of compound **3.1** were of low activity.

Table 1

Antiradical activity (ARA) of synthesized compounds

Compound	ARA ($1*10^{-3}$M)	ARA ($1*10^{-4}$M)	Compound	ARA ($1*10^{-3}$M)	ARA ($1*10^{-4}$M)
Ascorbic acid	91.17	84.33	4.11	40.70	7.90
4.1	23.95	n/a	4.12	24.8	n/a
4.2	35.74	5.54	4.13	23.83	8.22
4.3	34.73	7.89	4.14	20.97	6.54

Continuation of the table 1

4.4	40.27	6.04	4.15	53.86	11.91
4.5	51.34	7.38	5.1	n/a	n/a
4.6	n/a*	n/a	5.2	n/a	n/a
4.7	53.49	5.12	5.3	n/a	n/a
4.8	43.96	14.77	5.4	n/a	n/a
4.9	16.61	15.44	5.5	n/a	n/a
4.10	40.05	n/a	5.7	n/a	n/a

*n/a – non-active

Subsequently the antibacterial and antifungal activity of synthesized compounds were studied [18] (Table 2). It was shown that *E. coli* strain was not sensitive to the action of synthesized compounds. The minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC) values were at the level of 100 μg/ml and 200 μg/ml correspondingly for the majority of the obtained compounds. Compounds **4.4** and **4.12** were the exceptions and reveal moderate antibacterial activity against *E. coli* (MIC = 50 μg/ml, MBC = 100 μg/ml). Compounds **3.1**, **4.2**, **4.3**, **4.6**, **4.10**, **4.15** revealed moderate activity against *S. aureus* (MIC = 50 μg/ml, MBC = 100 μg/ml). *P. aeruginosa* strain was sensitive to the activity of the compounds **3.1, 4.1, 4.4**, **4.7**-**4.9**, **4.10**-**4.12**, **4.15**, **5.1**, **5.3**-**5.6**. *C. albicans* was identified as most sensitive to the synthesized compounds strain. Thus, about half of the compounds obtained at the concentration 50 μg/ml revealed both fungistatic and fungicidal activity.

Structure-activity relationships (SAR) analysis showed that 6-*S*-substituted derivatives **4** revealed higher antibacterial activity against *S. aureus* comparing to compounds **5**. The reliable correlation between the nature of substituent at acetamide Nitrogen and antimicrobial activity was not found. Despite the moderate level of antibacterial and antifungal activity studied classes of compound can be found as promising objects for the search of chemotherapeutic agents owing to the wide possibilities of their structural modification and consequently pharmacophore fragments introduction.

Table 2.

Antimicrobial activity of synthesized compounds

Compound	E. coli		S. aureus		P. aeruginosa		C. albicans	
	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MBC, μg/ml	MIC, μg/ml	MFC, μg/ml
3.1	100	>200	50	100	50	100	50	100
4.1	100	200	100	200	50	100	50	50
4.2	100	200	50	100	100	200	50	50
4.3	100	200	50	100	100	200	50	50
4.4	50	100	100	200	50	100	100	200
4.5	100	200	100	200	100	200	50	50
4.6	100	200	50	100	100	200	50	50
4.7	100	200	100	200	50	100	100	100
4.8	100	100	100	>200	50	100	50	50
4.9	100	200	100	200	50	100	50	100
4.10	100	200	50	100	100	200	50	50
4.11	100	200	100	200	50	100	50	50
4.12	50	100	100	200	50	100	100	100
4.13	100	200	100	200	50	100	50	100
4.14	100	200	100	200	100	200	100	200
4.15	100	200	50	100	100	200	50	50
5.1	100	200	100	200	50	100	50	50
5.2	100	200	100	200	100	200	50	50
5.3	100	100	100	200	50	100	50	50
5.4	100	200	100	200	50	100	100	200
5.5	100	200	100	200	50	100	100	100
5.6	100	200	100	200	50	100	50	100
5.7	100	200	100	200	100	200	100	100
Fluconazole	–	–	–	–	–	–	15.6	62.5
Pipemidic acid	25.0	–	6.25	–	12.5	–	–	–

Conclusion

Potassium benzo[4,5]imidazo[1,2-*c*]quinazolin-6-thiolate (**2.1**) and benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**3.1**) that could be obtained by chemical modification of 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline are efficient initial compounds for formation of combinatorial library of perspective bioactive agents. Alkylation of benzo[4,5]imidazo[1,2-*c*]quinazolin-6-thiolate (**2.1**) and benzo[4,5]imidazo[1,2-*c*]quinazolin-6(5*H*)-one (**3.1**) occurs on Sulfur and Nitrogen atom correspondingly. 6-*S*-substituted benzo[4,5]imidazo[1,2-*c*]quinazolines revealed antiradical activity in DPPH-scavenging test. Some of the obtained compounds at the concentration of 50 μg/ml revealed both fungistatic and fungicidal activity against *C. albicans*. Studied substances are interesting in scope of novel antibacterial and antifungal drug elaboration.

Experimental part

Melting points were determined in open capillary tubes by a Stuart SMP30 (Cole Parmer, Staffordshire, UK) apparatus and were uncorrected. The elemental analyses (C, H, and N) were performed using the ELEMENTAR vario EL Cube analyzer (Elementar Analysensysteme GmbH, Langenselbold, Germany). ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on Varian Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometers with tetramethyl silane (TMS) as internal standard and deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated trifluoroacetic acid (TFA-d_4) as a solvent. LC-MS data were acquired with an Agilent 1100 Series (Agilent, Palo Alto, CA, USA) equipped with diode matrix and mass-selective detector Agilent LC/MSD SL (atmospheric pressure chemical ionization).

Compound **1.1** was synthesized according to the described synthetic protocols. [7, 8] The other starting reagents and solvents were purchased from commercially available sources and were used without purification.

Synthesis of potassium benzo[4,5]imidazo[1,2-c]quinazoline-6-thiolate (**2.1**). A total of 3.2 g (20 mmol) of potassium ethyl xanthogenate was added to the suspension of 4.18 g (20 mmol) of 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**1.1**) in 30 ml of *i*-PrOH. The formed mixture was refluxed for 6 h and cooled. The formed precipitate was filtered off, washed with *i*-PrOH and dried at 60°C.

Potassium benzo[4,5]imidazo[1,2-c]quinazoline-6-thiolate (**2.1**). Yield: 69.6% as a beige solid; m.p. >300°C, ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.11, 148.64, 145.3, 144.4, 132.5, 131.2, 124.7, 124.2, 123.8, 122.4, 120.3, 118.8, 118.1, 115.7. Calculated for: $C_{14}H_8KN_3S$: C, 58.10; H, 2.79; N, 14.52; S, 11.08; Found: C, 58.06; H, 2.72; N, 14.46; S, 11.02 (Please, see the link for more spectral data [10]).

Synthesis of benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3.1**). A total of 3.24 g (20 mmol) of carbonyldiimidazole was added to the suspension of 4.18 g (20 mmol) of 2-(1*H*-benzo[*d*]imidazol-2-yl)aniline (**1.1**) in 50 ml of dioxane. The formed mixture was refluxed for 2 h. Then, reaction mixture was cooled, poured into 100 ml of water, and acidified by conc. hydrochloric acid. The formed precipitate was filtered off, washed with water, and dried at 60°C. Obtained compound was additionally purified by crystallization from DMF-H_2O.

Benzo[4,5]imidazo[1,2-c]quinazolin-6(5H)-one (**3.1**). Yield: 81 % as a white solid; m.p. >300°C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.32 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.04, 146.8, 143.9, 137.5, 132.6, 131.0, 125.4, 124.8, 124.0, 123.7, 119.5, 116.3, 115.2, 112.2; LC-MS, *m/z* =236; Calculated for: $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86; Found: C, 71.51; H, 3.78; N, 17.89.

General method of 2-(benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)acetamides synthesis (**4.1-4.17**). 3 mmol of corresponding *N*-substituted 2-chloroacetamide was added to the suspension of 0.87 g (3 mmol) of potassium benzo[4,5]imidazo[1,2-*c*]quinazoline-6-thiolate (**2.1**) in the mixture of 20 ml propanol-2 and 0.5 ml of water. The formed mixture was refluxed for 6 h and cooled. The formed precipitate was filtered off, washed by propanol-2 and dried at 60°C.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(2-fluorobenzyl)acetamide (**4.1**). Yield: 58 %; grey crystalline powder; m.p. 218-219°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (t, 1H, CONH), 8.55 (d, *J* = 7.9 Hz, 1H, H-8), 8.50 (d, *J* = 8.1 Hz, 1H, H-11), 7.92 (d, *J* = 8.0 Hz, 1H, H-1), 7.80 – 7.71 (m, 2H, H-4, 10), 7.66 – 7.59 (m, 1H, H-9), 7.56 (t, 1H, H-3), 7.50 (t, 1H, H-2), 7.32 (t, *J* = 7.3 Hz, 1H, Bn H-5), 7.20 (q, 1H, Bn H-3), 7.02 (t, 1H, Bn H-4), 6.93 (t, *J* = 7.3 Hz, 1H, Bn H-6), 4.40 (d, *J* = 5.3 Hz, 2H, $ArCH_2$), 4.33 (s, 2H, SCH_2); LC-MS, *m/z* =417; Calculated for: $C_{23}H_{17}FN_4OS$: C, 66.33; H, 4.11; N, 13.45; S, 7.70; Found: C, 66.27; H, 4.06; N, 13.40; S, 7.65.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-fluorobenzyl)acetamide (**4.2**). Yield: 96 %; pale pink crystalline powder; m.p. 216°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (t, 1H, CONH), 8.52 (dd, *J* = 17.0, 7.7 Hz, 2H, H-8, 11), 7.91 (d, *J* = 7.9 Hz, 1H, H-1), 7.78 – 7.68 (m, 2H, H-4, 10), 7.65 – 7.42 (m, 3H, H-2, 3, 9), 7.19 (q, 1H, Bn H-5), 7.15 – 6.98 (m, 2H, Bn H-2, 4), 6.96 – 6.84 (m, 1H, Bn H-6), 4.38 (d, *J* = 5.4 Hz, 2H, $ArCH_2$), 4.32 (s, 2H, SCH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 163.6, 149.8, 147.2, 143.0 (d, J = 237.2 Hz), 142.8, 142.7 (d, J = 7.3 Hz), 132.5, 130.5 (d, J = 8.1 Hz), 129.0, 127.6, 126.9, 126.1, 124.3, 123.7, 123.5 (d, J = 2.4 Hz), 120.1, 117.0, 115.3, 114.2 (d, J = 21.4 Hz), 113.9 (d, J = 20.8 Hz), 42.6, 35.4; LC-MS, *m/z* = 417; Calculated for: $C_{23}H_{17}FN_4OS$: C, 66.33; H, 4.11; N, 13.45; S, 7.70; Found: C, 66.38; H, 4.18; N, 13.49; S, 7.78.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(4-fluorobenzyl)acetamide (**4.3**). Yield: 76 %; pale pink crystalline powder; m.p. 243°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H, CONH), 8.55 (d, *J* = 7.7 Hz, 1H, H-8), 8.50 (d, *J* = 8.0 Hz, 1H, H-11), 7.91 (d, *J* = 8.0 Hz, 1H, H-1), 7.79 – 7.67 (m, 2H, H-4, 10), 7.66 – 7.41 (m, 3H, H-2, 3, 9), 7.27 (q, 2H, Bn H-3, 5), 6.90 (t, *J* = 8.6 Hz, 2H, Bn H-2, 6), 4.34 (d, *J* = 5.3 Hz, 2H, $ArCH_2$), 4.30 (s, 2H, SCH_2); LC-MS, *m/z* =417; Calculated for: $C_{23}H_{17}FN_4OS$: C, 66.33; H, 4.11; N, 13.45; S, 7.70; Found: C, 66.38; H, 4.18; N, 13.49; S, 7.76.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-chlorobenzyl)acetamide (**4.4**). Yield: 96 %; grey crystalline powder; m.p. 208-211°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (t, 1H, CONH), 8.53 (d, *J* = 7.8 Hz, 1H, H-8), 8.49 (d, *J* = 8.1 Hz, 1H, H-11), 7.91 (d, *J* = 7.8 Hz, 1H, H-1), 7.72 (d, 2H, H-4, 10), 7.60 (t, 1H, H-9), 7.55 (t, 1H, H-3), 7.49 (t, *J* = 7.7 Hz, 1H, H-2), 7.28 (s, 1H, Bn H-2), 7.23 – 7.11 (m, 3H, Bn H-4, 5, 6), 4.36 (d, *J* = 5.7 Hz, 2H, $ArCH_2$), 4.32 (s, 2H, SCH_2); LC-MS, *m/z* =; Calculated for: $C_{23}H_{17}ClN_4OS$: C, 63.81; H, 3.96; N, 12.94; S, 7.41; Found: C, 63.85; H, 3.98; N, 12.97; S, 7.39.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-bromobenzyl)acetamide (**4.5**). Yield: 57 %; pale pink crystalline powder; m.p. 224-225°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H, CONH), 8.55 (d, *J* = 7.8 Hz, 1H, H-8), 8.50 (d, *J* = 8.0 Hz, 1H, H-11), 7.91 (d, *J* = 7.9 Hz, 1H, H-1), 7.78 – 7.66 (m, 2H, H-4, 10), 7.62 (t, *J* = 10.7, 4.0 Hz, 1H, H-9), 7.56 (t, 1H, H-3), 7.50 (t, 1H, H-2), 7.30 (d, *J* = 8.2 Hz, 2H, Bn H-3, 5), 7.19 (d, *J* = 8.1 Hz, 2H, Bn H-2, 6), 4.32 (d, *J* = 5.7 Hz, 2H, $ArCH_2$), 4.29 (s, 2H, SCH_2); LC-MS, *m/z* =429; Calculated for: $C_{23}H_{17}BrN_4OS$: C, 57.87; H, 3.59; N, 11.74; S, 6.72; Found: C, 57.93; H, 3.64; N, 11.79; S, 6.76.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-methoxybenzyl)acetamide (**4.6**). Yield: 54 %; pale pink crystalline powder; m.p. 217-219°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 – 8.44 (m, 3H, CONH, H-8, 11), 7.91 (d, *J* = 7.9 Hz, 1H, H-1), 7.79 – 7.71 (m, 2H, H-4, 10), 7.67 – 7.43 (m, 3H, H-2, 3, 9), 7.19 (d, *J* = 7.0 Hz, 1H, Bn H-6), 7.14 (t, *J* = 7.7 Hz, 1H, Bn H-4), 6.83 (d, *J* = 8.0 Hz, 1H, Bn H-5), 6.70 (t, *J* = 7.2 Hz, 1H, Bn H-3), 4.44 – 4.21 (m, 4H, $ArCH_2$, SCH_2), 3.78 (s, 3H, OCH_3); LC-MS, *m/z* = 428; Calculated for: $C_{24}H_{20}N_4O_2S$: C, 67.27; H, 4.70; N, 13.08; S, 7.48; Found: C, 67.32; H, 4.77; N, 13.14; S, 7.51.

2-(benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(4-(trifluoromethyl)phenyl)acetamide (**4.7**). Yield: 90 %; pale pink crystalline powder; m.p. 246-247°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.76 (s, 1H, CONH), 8.52 (dd, *J* = 9.5 Hz, 2H, H-8, 11), 7.92 (d, *J* = 8.0 Hz, 1H, H-1), 7.88 – 7.82 (m, 2H, H-4, 10), 7.78 – 7.68 (m, 2H, H-3, 9), 7.63 – 7.46 (m, 5H, H-2, Ar H-2, 3, 5, 6), 4.50 (s, 2H, SCH_2). ^{13}C NMR (100 MHz, TFA) δ 170.2, 149.5, 145.9, 144.7, 139.3, 138.4, 131.1, 130.9, 128.4, 128.2, 127.3, 127.2 (q), 124.5, 122.1, 116.9, 116.5, 114.8, 110.5, 36.6; LC-MS, *m/z* = 453; Calculated for: $C_{23}H_{15}F_3N_4OS$: C, 61.06; H, 3.34; N, 12.38; S, 7.09; Found: C, 61.01; H, 3.30; N, 12.32; S, 7.03.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-fluorophenyl)acetamide (**4.8**). Yield: 68 %; white crystalline powder; m.p. 239°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H, CONH), 8.53 (dd, *J* = 11.9, 8.3 Hz, 2H, H-8, 11), 7.92 (d, *J* = 7.9 Hz, 1H, H-1), 7.81 – 7.68 (m, 2H, H-4, 10), 7.64 – 7.47 (m, 4H, H-2, 3, 9, Ar H-2), 7.37 (d, *J* = 7.9 Hz, 1H, Ar H-6), 7.28 (q, *J* = 7.5 Hz, 1H, Ar H-4), 6.77 (t, *J* = 7.1 Hz, 1H, Ar H-5), 4.47 (s, 2H, SCH_2); LC-MS, *m/z* =403; Calculated for: $C_{22}H_{15}FN_4OS$: C, 65.66; H, 3.76; N, 13.92; S, 7.97; Found: C, 65.71; H, 3.79; N, 13.97; S, 8.02.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(4-fluorophenyl)acetamide (**4.9**). Yield: 76 %; grey crystalline powder; m.p. 252°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H, CONH), 8.53 (dd, 2H, H-8, 11), 7.92 (d, *J* = 7.8 Hz, 1H, H-1), 7.82 – 7.70 (m, 2H, H-4, 10), 7.69 – 7.48 (m, 5H, H-2, 3, 9, Ar H-2, 6), 7.02 (t, *J* = 8.7 Hz, 2H, Ar H-3, 5), 4.46 (s, 2H, SCH_2); ^{13}C NMR (100 MHz, TFA) δ 170.7, 149.5, 145.3 (d, J = 189.7 Hz), 138.4, 131.2, 130.9 (d, *J* = 3.3 Hz), 128.3 (d, *J* = 19.5 Hz), 127.4, 125.3 (d, *J* = 8.4 Hz), 124.6 , 116.9, 116.9, 116.8, 116.5, 115.8, 114.8, 114.6, 113.9, 110.5, 36.3; LC-MS, *m/z* =403; Calculated for: $C_{22}H_{15}FN_4OS$: C,

65.66; H, 3.79; N, 13.99; S, 7.97; Found: C, 65.64; H, 3.75; N, 13.94; S, 7.95.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-chlorophenyl)acetamide (**4.10**). Yield: 99 %; pale pink crystalline powder; m.p. 241°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H, CONH), 8.54 (d, *J* = 8.0 Hz, 1H, H-8), 8.51 (d, *J* = 8.1 Hz, 1H, H-11), 7.92 (d, *J* = 7.8 Hz, 1H, H-1), 7.84 – 7.68 (m, 3H, H-4, 9, 10), 7.62 – 7.45 (m, 4H, H-2, 3, Ar H-2, 6), 7.27 (t, *J* = 8.0 Hz, 1H, Ar H-5), 7.02 (d, *J* = 7.9 Hz, 1H, Ar H-4), 4.47 (s, 2H, SCH_2); LC-MS, *m/z* = 419; Calculated for: $C_{22}H_{15}ClN_4OS$: C, 63.08; H, 3.61; N, 13.38; S, 7.65; Found: C, 63.04; H, 3.59; N, 13.34; S, 7.61.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(4-chlorophenyl)acetamide (**4.11**). Yield: 85 %; white crystalline powder; m.p. 254°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H, CONH), 8.52 (dd, *J* = 12.2, 8.1 Hz, 2H, H-8, 11), 7.92 (d, *J* = 8.0 Hz, 1H, H-1), 7.80 – 7.70 (m, 2H, H-4, 10), 7.66 (d, *J* = 8.7 Hz, 2H, Ar H-2, 6), 7.63 – 7.45 (m, 3H, H-2, 3, 9), 7.26 (d, *J* = 8.4 Hz, 2H, Ar H-3, 5), 4.46 (s, 2H, SCH_2); LC-MS, *m/z* =419; Calculated for: $C_{22}H_{15}ClN_4OS$: C, 63.08; H, 3.61; N, 13.38; S, 7.65; Found: C, 63.02; H, 3.58; N, 13.42; S, 7.67.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(2-bromophenyl)acetamide (**4.12**). Yield: 79 %; pale pink crystalline powder; m.p. 242°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H, CONH), 8.56 (d, *J* = 7.7 Hz, 1H, H-8), 8.51 (d, *J* = 8.0 Hz, 1H, H-11), 7.93 (d, *J* = 8.1 Hz, 1H, H-1), 7.90 – 7.80 (m, 2H, H-4, 10), 7.76 (t, *J* = 7.3 Hz, 1H, H-9), 7.68 – 7.45 (m, 4H, H-2, 3, Ar H-3, 6), 7.31 (t, *J* = 7.3 Hz, 1H, Ar H-4), 7.06 (t, *J* = 7.1 Hz, 1H, Ar H-5), 4.55 (s, 2H, SCH_2); LC-MS, *m/z* = 463; Calculated for: $C_{22}H_{15}BrN_4OS$: C, 57.03; H, 3.26; N, 12.09; S, 6.92; Found: C, 57.01; H, 3.29; N, 12.15; S, 6.89.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-bromophenyl)acetamide (**4.13**). Yield: 83 %; pale pink crystalline powder; m.p. 247°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H, CONH), 8.52 (dd, *J* = 13.5, 8.0 Hz, 2H, H-8, 11), 8.00 – 7.86 (m, 2H, H-1, 10), 7.81 – 7.68 (m, 2H, H-4, 9), 7.65 – 7.45 (m, 4H, H-2, 3, Ar H-2, 6), 7.20 (m, 2H, Ar H-4, 5), 4.47 (s, 2H, SCH_2); LC-MS, *m/z* =463; Calculated for: $C_{22}H_{15}BrN_4OS$: C, 57.03; H, 3.26; N, 12.09; S, 6.92; Found: C, 57.08; H, 3.24; N, 12.07; S, 6.88.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(4-bromophenyl)acetamide (**4.14**). Yield: 89 %; white crystalline powder; m.p. 258°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H, CONH), 8.53 (dd, *J* = 11.5, 8.0 Hz, 2H, H-8, 11), 7.92 (d, *J* = 7.9 Hz, 1H, H-1), 7.84 – 7.69 (m, 2H, H-4, 10), 7.66 – 7.46 (m, 5H, H-2, 3, 9, Ar H-2, 6), 7.40 (d, *J* = 8.3 Hz, 2H, Ar H-3, 5), 4.46 (s, 2H, SCH_2); LC-MS, *m/z* =463; Calculated for: $C_{22}H_{15}BrN_4OS$: C, 57.03; H, 3.26; N, 12.09; S, 6.92; Found: C, 57.09; H, 3.20; N, 12.10; S, 6.97.

2-(Benzo[4,5]imidazo[1,2-c]quinazolin-6-ylthio)-N-(3-methoxyphenyl)acetamide (**4.15**). Yield: 88 %; pale pink crystalline powder; m.p. 243°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.21 (s, 1H, CONH), 8.53 (dd, *J* = 9.2 Hz, 2H, H-8, 11), 7.92 (d, *J* = 7.8 Hz, 1H, H-1), 7.80 (d, *J* = 8.2 Hz, 1H, H-4), 7.74 (t, *J* = 7.5 Hz, 1H, H-10), 7.66 – 7.44 (m, 5H, H-2, 3, 9, Ar H-2, 6), 6.81 (d, *J* = 8.9 Hz, 2H, Ar H-3, 5), 4.44 (s, 2H, SCH_2), 3.76 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.35 (CS), 155.85 (CONH), 149.89 (ArCN(N)), 147.15, 143.99, 142.12, 132.66, 132.59, 128.98, 127.61, 126.76, 126.11, 124.33, 123.72, 121.29, 120.15, 117.06, 115.23, 114.39 (16-C, C-Ar), 55.64 (CH_3), 36.74 (CH_2); LC-MS, *m/z* =415; Calculated for: $C_{23}H_{18}N_4O_2S$: C, 66.65; H, 4.38; N, 13.52; S, 7.73; Found: C, 66.62; H, 4.41; N, 13.54; S, 7.68.

General method for synthesis of 2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazoline-5(6H)-yl)acetamides (**5.1-5.7**). 0.21 g (1,5 mmol) of potassium carbonate was added to the suspension of 0.71 g (3 mmol) in 15 ml of anhydrous DMF. The formed mixture was heated at 80°C for 1.5 h. Then 3 mmol of corresponding *N*-substituted chloracetamide was added to the formed potassium salt and reaction mixture was refluxed for 3 h. After completion of the reaction, the mixture was cooled and poured into 100 ml water. The formed precipitate was filtered off, washed by water, and dried. For additional purification, the product was re-crystallized from DMF-water mixture.

N-(4-Fluorobenzyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)acetamide (**5.1**). Yield: 79 %; pale pink crystalline powder; m.p. 282-284°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H, NH), 8.47 (d, *J* = 7.5 Hz, 1H, H-8), 8.40 (d, *J* = 7.6 Hz, 1H, H-11), 7.82 (d, *J* = 7.4 Hz, 1H, H-4), 7.68 (t, *J* = 7.5 Hz, 1H, H-10), 7.54 – 7.38 (m, 3H, H-2, 3, 9), 7.32 (d, *J* = 8.3 Hz, 1H, H-1), 7.21 (t, 2H, Bn H-2, 6), 7.01 (t, *J* = 7.0 Hz, 2H, Bn H-3, 5), 4.99 (s, 2H, CH_2), 4.30 (s, 2H, $ArCH_2$); LC-MS, *m/z* = 401; Calculated for: $C_{23}H_{17}FN_4O_2$: C, 68.99; H, 4.28; N, 13.99; Found: C, 68.94; H, 4.31; N, 14.02.

N-(4-Bromobenzyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazoline-5(6H)-yl)-acetamid (**5.2**). Yield: 72%; white crystalline powder; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H, NH), 8.47 (d, *J* = 7.1 Hz, 1H, H-8), 8.40 (d, *J* =

7.9 Hz, 1H, H-11), 7.82 (d, *J* = 8.3 Hz, 1H, H-4), 7.69 (t, *J* = 7.5 Hz, 1H, H-10), 7.55 – 7.36 (m, 4H, H-1, 2, 3, 9), 7.33 (d, *J* = 8.4 Hz, 2H, Bn H-2, 6), 7.13 (d, *J* = 8.1 Hz, 2H, Bn H-3, 5), 5.00 (s, 2H, CH_2), 4.29 (s, 2H, $ArCH_2$); LC-MS, *m/z* = 461; Calculated for: $C_{23}H_{17}Br\,N_4O_2$: C, 59.88; H, 3.71; N, 12.15; Found: C, 59.94; H, 3.68; N, 12.18.

N-(4-Methoxybenzyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)-acetamide (**5.3**). Yield: 93 %; pale pink crystalline powder; m.p. 282-284°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 – 8.61 (m, 1H, NH), 8.47 (d, *J* = 7.7 Hz, 1H, H-8), 8.40 (d, *J* = 7.7 Hz, 1H, H-11), 7.82 (d, *J* = 7.7 Hz, 1H, H-4), 7.68 (t, *J* = 7.6 Hz, 1H, H-10), 7.53 – 7.39 (m, 3H, H-2, 3, 9), 7.32 (d, *J* = 8.3 Hz, 1H, H-1), 7.10 (d, *J* = 8.1 Hz, 2H, Bn H-2, 6), 6.79 (d, *J* = 8.2 Hz, 2H, Bn H-3, 5), 4.98 (s, 2H, CH_2), 4.25 (d, *J* = 5.2 Hz, 2H, $ArCH_2$), 3.75 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9 (CONH), 158.7 (NCON), 147.3 (ArCN(N)), 147.3, 143.9, 138.1, 133.0, 131.4, 131.4, 128.9, 125.8, 125.3, 124.4, 124.3, 119.7, 115.7, 115.3, 114.1, 113.4 (16-C, C-Ar), 55.6 (OCH_3), 46.6 (NCH_2), 42.1 (CH_2Ar); LC-MS, *m/z* = 413; Calculated for: $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58; Found: C, 69.86; H, 4.82; N, 13.63.

N-(4-Fluorophenyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)-acetamide (**5.4**). Yield: 40%; pale pink crystalline powder; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H, NH), 8.49 (d, *J* = 7.9 Hz, 1H, H-8), 8.40 (d, *J* = 7.7 Hz, 1H, H-11), 7.83 (d, *J* = 7.7 Hz, 1H, H-4), 7.69 (t, *J* = 7.7 Hz, 1H, H-10), 7.62 – 7.55 (m, 2H, H-2, 9), 7.51 – 7.39 (m, 4H, H-1, 3, FArH-2, 6), 7.03 (t, *J* = 8.4 Hz, 2H, FArH-3, 5), 5.16 (s, 2H, $COCH_2$); ^{13}C NMR (100 MHz, TFA) δ 168.08 , 162.40 (d, J = 246.6 Hz), 146.46 , 146.26 , 140.06 , 139.26 , 131.53 , 130.95 , 130.74 , 129.47 , 128.88 , 127.48 , 126.77 , 125.05 (d, J = 8.1 Hz), 117.65 , 116.76 (d, J = 23.4 Hz), 116.54 , 114.67 , 106.54 , 47.73; LC-MS, *m/z* = 387; Calculated for: $C_{22}H_{15}FN_4O_2$: C, 68.39; H, 3.91; N, 14.50; Found: C, 68.43; H, 3.88; N, 14.57.

N-(4-Chlorophenyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)-acetamide (**5.5**). Yield: 89 %; pale pink crystalline powder; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, NH), 8.49 (d, *J* = 7.4 Hz, 1H, H-8), 8.40 (d, *J* = 7.5 Hz, 1H, H-11), 7.83 (d, *J* = 7.8 Hz, 1H, H-4), 7.69 (t, *J* = 7.6 Hz, 1H, H-10), 7.60 (d, *J* = 8.4 Hz, 2H, ClArH-2, 6), 7.54 – 7.36 (m, 4H, H-1, 2, 3, 9), 7.27 (d, *J* = 8.3 Hz, 2H, ClArH-3, 5), 5.17 (s, 2H, $COCH_2$); LC-MS, *m/z* = 403; Calculated for: $C_{22}H_{15}ClN_4O_2$: C, 65.60; H, 3.75; N, 13.91; Found: C, 65.62; H, 3.71; N, 13.96.

N-(4-Bromophenyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)-acetamide (**5.6**). Yield: 95 %; pale pink crystalline powder; m.p. >300°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H, NH), 8.49 (d, *J* = 7.1 Hz, 1H, H-8), 8.40 (d, *J* = 7.8 Hz, 1H, H-11), 7.83 (d, *J* = 7.4 Hz, 1H, H-4), 7.69 (t, *J* = 7.8 Hz, 1H, H-10), 7.55 (d, *J* = 8.4 Hz, 2H, BrArH-2, 6), 7.51 – 7.36 (m, 6H, H-1, 2, 3, 9, BrArH-3, 5), 5.17 (s, 2H, $COCH_2$); LC-MS, *m/z* = 447; Calculated for: $C_{22}H_{15}Br\,N_4O_2$: C, 59.08; H, 3.38; N, 12.53; Found: C, 59.01; H, 3.42; N, 12.55.

N-(4-Methoxyphenyl)-2-(6-oxobenzo[4,5]imidazo[1,2-c]quinazolin-5(6H)-yl)-acetamide (**5.7**). Yield: 86 %; pale pink crystalline powder; m.p. 281-283°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H, NH), 8.49 (d, *J* = 8.0 Hz, 1H, H-8), 8.41 (d, *J* = 7.9 Hz, 1H, H-11), 7.83 (d, *J* = 7.9 Hz, 1H, H-4), 7.70 (t, *J* = 7.7 Hz, 1H, H-10), 7.58 – 7.37 (m, 6H, H-1, 2, 3, 9, MeOArH-2, 6), 6.81 (d, *J* = 8.1 Hz, 2H, MeOArH-3, 5), 5.13 (s, 2H, $COCH_2$), 3.74 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, TFA) δ 168.14 , 157.77 , 146.42 , 146.23 , 140.04 , 139.25 , 130.92 , 130.72 , 130.04 , 129.45 , 129.03 , 128.85 , 127.45 , 126.70 , 125.09 , 117.63 , 116.53 , 116.02 , 106.50 , 56.43 , 47.66; LC-MS, *m/z* = 399; Calculated for: $C_{23}H_{18}N_4O_3$: C, 69.34; H, 4.55; N, 14.06; Found: C, 69.38; H, 4.57; N, 14.09.

Radical scavenging activity. The compounds were dissolved in dimethyl sulfoxide (DMSO) to obtain 1 mM solution. Then, 2 mL of this solution was mixed with 2 mL of 0.1 mM DPPH methanol (MeOH) solution, and it was incubated for 30 min at the temperature of 25°C. Then optical density (OD_{sample}) was measured.[17] The optical density of 2 mL of 0.1 mM DPPH solution with additional 2 mL of dimethyl sulfoxide (OD_{DPPH}) was determined simultaneously. Anti-radical activity (ARA) was calculated by the next formula: ARA % = $((OD_{DPPH} - OD_{sample})/OD_{DPPH})\times100\%$. In the case of a negative meaning, ARA was estimated as 0%. The reagents and synthesized compounds were weighed on electronic scales ANG200C (Axis, Gdansk, Poland), and the optical density was measured by a spectrophotometer ULAB 108UV (Ulab, Shanghai, China).

Antimicrobial activity. The studied strains susceptibility to the synthesized compounds was evaluated according to the described methods [18]. The assay was performed on Mueller–Hinton agar by twofold serial dilution of the compound in 1 mL of DMSO. After that, 0.1 mL of microbial seeding (10^{-6} cells/mL) was added. Minimal inhibit concentration of the compound was determined by the absence of visual growth in the test tube with a minimal concentration of the substance; minimal bactericide or fungicide

concentration was determined by the absence of growth on agar medium after inoculation of the microorganism from the transparent test tubes. DMSO was used as a solvent; the initial solution concentration was 1 mg/mL. For the preliminary screening, the following mentioned ahead standard test cultures were used: *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *C. albicans* ATCC 885-653. All test strains were received from bacteriological laboratory, Zaporizhzhia Regional Laboratory Center of State Sanitary and Epidemiological Service of Ukraine. Fluconazole and pipemidic acid were used as reference compounds with proved antifungal or antibacterial activity.

Referens

[1] Demeunynck, M., Baussanne, I. (2013). Survey of Recent Literature Related to the Biologically Active 4(3*H*)-Quinazolinones Containing Fused Heterocycles. *Current Medicinal Chemistry*, *20*(6), 794–814. https://doi.org/10.2174/092986713805076711

[2] Lamazzi, C., Léonce, S., Pfeiffer, B., Renard, P., Guillaumet, G., Rees, C. W., & Besson, T. (2000). Expeditious synthesis and cytotoxic activity of new cyanoindolo[3,2-c]quinolines and benzimidazo[1,2-c]quinazolines. *Bioorganic & Medicinal Chemistry Letters*, 10(19), 2183–2185. https://doi.org/10.1016/S0960-894X(00)00427-3

[3] Kuarm, B. S., Reddy, Y. T., Madhav, J. V., Crooks, P. A., & Rajitha, B. (2011). 3-[Benzimidazo- and 3-[benzothiadiazoleimidazo-(1,2-c)quinazolin-5-yl]-2H-chromene-2-ones as potent antimicrobial agents. *Bioorganic & Medicinal Chemistry Letters*, 21(1), 524–527. https://doi.org/10.1016/j.bmcl.2010.10.082

[4] Habib, O. M. O., Hassan, H. M., & El-Mekabaty, A. (2012). Novel quinazolinone derivatives: synthesis and antimicrobial activity. *Medicinal Chemistry Research*, 22(2), 507–519. https://doi.org/10.1007/s00044-012-0079-x

[5] El-Sayed, R., Wasfy, A. A. F., & Aly, A. A. (2005). Synthesis of novel heterocycles with antimicrobial and surface activity. *Journal of Heterocyclic Chemistry*, 42(1), 125–130. https://doi.org/10.1002/jhet.5570420119

[6] Rohini, R., Shanker, K., Reddy, P. M., Ho, Y.-P., & Ravinder, V. (2009). Mono and bis-6-arylbenzimidazo[1,2-c]quinazolines: A new class of antimicrobial agents. *European Journal of Medicinal Chemistry*, 44(8), 3330–3339. https://doi.org/10.1016/j.ejmech.2009.03.022

[7] Rohini, R., Shanker, K., Reddy, P. M., & Ravinder, V. (2010). Synthesis and antimicrobial activities of a new class of 6-arylbenzimidazo[1,2-c]quinazolines. *Journal of the Brazilian Chemical Society*, 21(1), 49–57. https://doi.org/10.1590/s0103-50532010000100009

[8] Lyakhova, E. A., Gusyeva, Y. A., Nekhoroshkova, J. V., Shafran, L. M., & Lyakhov, S. A. (2009). Synthesis and affinity to DNA of phenylbenzoimidazoles and benzoimidazo[1,2-c]quinazolines. *European Journal of Medicinal Chemistry*, 44(8), 3305–3312. https://doi.org/10.1016/j.ejmech.2009.03.004

[9] Vostrova, L. N., Voronina, T. A., Karaseva, T. L., Gernega, S. A., Ivanov, E. I., Kirichenko, A. M., & Totrova, M. Y. (1986). Synthesis and anticonvulsant activity of benzimidazo[1, 2-c]quinazolines. Pharmaceutical Chemistry Journal, *20*(6), 404–406. https://doi.org/10.1007/bf00758335

[10] Esparza-Ruiz, A., Peña-Hueso, A., Ramos-García, I., Flores-Parra, A., & Contreras, R. (2008). Heptacoordinated diphenyllead; hexa- and pentacoordinated triphenyllead and tin compounds derived from 5H-benzimidazo[1,2-c]quinazoline-6-thione. Journal of Organometallic Chemistry, *693*(16), 2739–2747. https://doi.org/10.1016/j.jorganchem.2008.05.022

[11] Breitmaier, E. (2002). Structure Elucidation By NMR In Organic Chemistry: A Practical Guide, John Wiley &Sons, Ltd.

[12] Kovacic, P., Abadjian, M.-C. Z. (2017) Mechanism of antifungal triazoles and related drugs: electron transfer, reactive oxygen species and oxidative stress. *SOJ Microbiology & Infectious Diseases,* 5 (5), 1-9. https://doi.org/10.15226/sojmid/5/5/00182

[13] Sharma, M., Manoharlal, R., Puri, N., & Prasad, R. (2010). Antifungal curcumin induces reactive oxygen species and triggers an early apoptosis but prevents hyphae development by targeting the global repressorTUP1inCandida albicans. *Bioscience Reports*, 30(6), 391–404. https://doi.org/10.1042/BSR20090151

[14] Morales, J., Mendoza, L., Cotoras, M. (2017). Alteration of oxidative phosphorylation as a possible mechanism of the antifungal action of p -coumaric acid against Botrytis cinerea. *Journal of Applied Microbiology*, 123(4), 969–976. https://doi.org/10.1111/jam.13540

[15] Ansari, M. A., Anurag, A., Fatima, Z., Hameed, S. (2013) Natural phenolic compounds: a potential antifungal agent. *Microbial pathogens and strategies for combating them: science, technology and education*, 1189-1195.

[16] Kedare, S. B., & Singh, R. P. (2011). Genesis and development of DPPH method of antioxidant assay. *Journal of Food Science and Technology*, 48(4), 412–422. https://doi.org/10.1007/s13197-011-0251-1

[17] Szabo, M., Idiţoiu, C., Chambre, D., & Lupea, A. (2007). Improved DPPH determination for antioxidant activity spectrophotometric assay. *Chemical Papers*, 61(3). https://doi.org/10.2478/s11696-007-0022-7

[18] Balouiri, M., Sadiki, M., & Ibnsouda, S. K. (2016). Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis*, 6(2), 71–79. https://doi.org/10.1016/j.jpha.2015.11.005