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Synthesis and Antioxidant Properties of Novel Quinazoline Derivatives

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***Abstract* – Quinazoline derivatives have expressed a broad spectrum of biological activities, but there are few examples in literature on an antioxidant activity of different quinazolines. On the basis of literature by Chinese scientists on the effective antioxidant activity of Schiff bases containing 2-oxoquinoline and due to structural similarity of quinoline and quinazoline ring systems, the reactions of 3-aminoquinazolinone with a range of aromatic aldehydes and ethoxymethylene derivatives have been carried out and their radical scavenging activities have been studied.**

***Keywords* – 3-amino-quinazolin-4(3*H*)-one, aldehydes, antioxidant activity, ethoxymethylene compounds, Schiff bases.**

I. Introduction

Quinazoline derivatives have attracted interest over the years because of their various biological activities [1], but there are few examples in literature on antioxidant activity of different quinazolines. Among several quinazolines reported, there are some subtituted quinazolines exhibiting interesting pharmaceutical activities. The antioxidant activity of the molecule may be due to the presence of hydroxyl groups [2] and sulphur atom [3], [4], but no data on systematic studies of quinazoline substituents and antioxidant activity relationships are available.

Recently, Chinese scientists reported [5] an effective antioxidant activity of Schiff bases containing 2-oxoquinoline. Due to the structural similarity of quinoline and quinazolinone ring systems, 4-oxoquinazoline Schiff bases may be viewed as potential antioxidants.

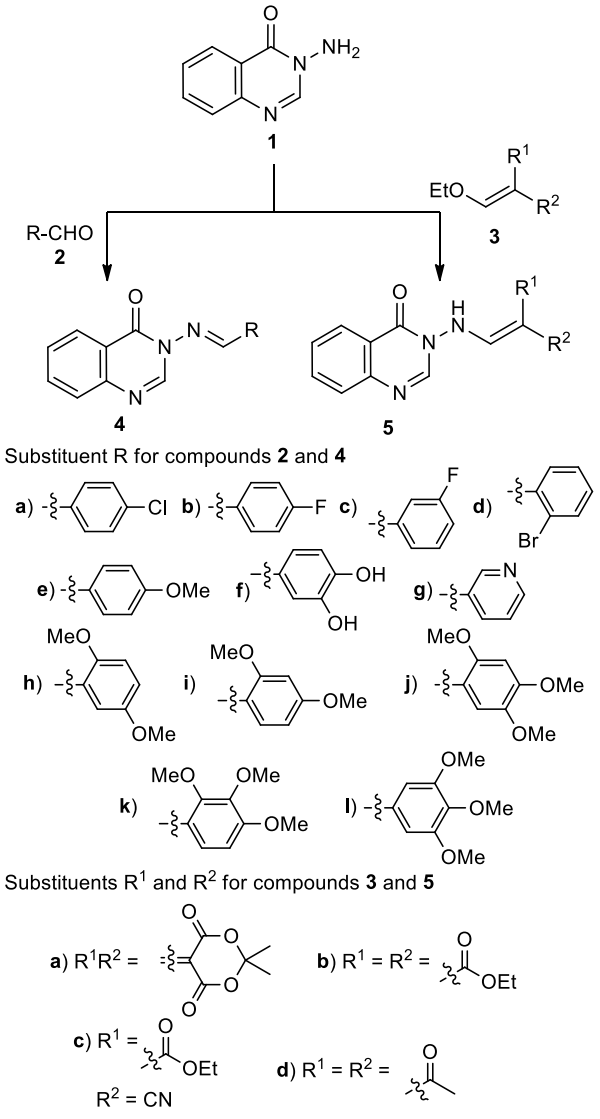
The above-mentioned issue, as well as an increasing necessity and interest in antioxidants as a major defence against damages caused by free radicals, has prompted the synthesis of some derivatives of quinazolin-4(3*H*)-ones and evaluation of their antioxidative activity.

II. Results and Discussion

The starting compound 3-aminoquinazolin-4(3*H*)-one (**1**) was synthesized from anthranilhydrazide and triethyl orthoformate as reported in literature [6].

The starting aminoquinazolinone **1** was modified at N(3) to yield compounds with C=C and C=N bonds by reactions of this derivative **1** with aromatic and heterocyclic aldehydes **2** and ethoxymethylene compounds **3** (scheme 1).

The reaction of aminoquinazolinone **1** with isopropylidene ethoxymethylenemalonate (**3a**) proceeds readily even at room temperature. To carry out the reactions with aromatic **2a-f** and heteroaromatic **2g** aldehydes it is necessary to reflux the components **1** and **2a-g** for 3 – 6 hours, while to prepare the desired compounds **5b-d** the heating of aminoquinazolinone **1** with ethoxymethylene derivatives **3b-d** in toluene at reflux for long time (~ 15 h) is required.



Scheme 1. Synthesis of the derivatives of quinazoline **4** and **5**.

The structure of synthesized compounds was confirmed by the results from elemental analyses (Table 1) and ^{1}H NMR spectra (Table 2) in which signals for the protons of all the structural units were observed in their characteristic ranges. The newly prepared compounds **3a-g, 5a-d** as well as previously synthesized compounds **3h-l** [7] were evaluated for their antioxidant activities.

TABLE 1

CHARACTERISTIC OF THE SYNTHESIZED COMPOUNDS **4a-g** AND **5a-d**

Compound	Empirical formula	Found, % / Calculated, %			M. p., ºC (recrystallization solvent)	Yield, %
		C	H	N		
4a	$C_{15}H_{10}ClN_3O$	63.36 63.50	3.51 3.55	14.74 14.81	165-168 (ethanol)	75.0
4b	$C_{15}H_{10}FN_3O$	67.14 67.41	3.67 3.77	15.68 15.72	160-161 (ethanol)	98.0
4c	$C_{15}H_{10}FN_3O$	67.26 67.41	3.61 3.77	15.66 15.72	147-148 (methanol)	51.5
4d	$C_{15}H_{10}BrN_3O$	54.76 54.90	3.14 3.07	12.67 12.80	165-167 (ethanol)	79.0
4e	$C_{16}H_{13}N_3O_2$	68.47 68.81	4.70 4.69	15.03 15.05	134-135 (ethanol)	82.0
4f	$C_{15}H_{11}N_3O_3$	64.10 64.05	3.90 3.94	15.01 14.94	140-142 (ethyl acetate)	71.0
4g	$C_{14}H_{10}N_4O$	67.21 67.19	4.07 4.03	22.43 22.39	> 250	71.0
5a	$C_{15}H_{13}N_3O_5$	57.11 57.33	3.93 3.85	13.40 13.37	208-210 (ethanol)	78.0
5b	$C_{16}H_{17}N_3O_5$	58.03 58.00	5.01 5.17	12.72 12.68	131-132 ethanol/water, 1:1	72.0
5c	$C_{14}H_{12}N_4O_3$	59.04 59.15	4.22 4.25	19.97 19.71	187-190 (ethanol)	72.0
5d	$C_{14}H_{13}N_3O_3$	62.03 61.99	4.90 4.83	15.61 15.49	238-239 (ethanol)	74.0

TABLE 2

^{1}H NMR SPECTRA OF THE SYNTHESIZED COMPOUNDS **4a-g** AND **5a-d**

Compound	^{1}H NMR SPECTRA
4a	7.49-7.93 (4H, m, arom.); 8.18 (1H, t, *J*=5.8, arom.); 8.25 (1H, d, *J*=7.6, arom.); 8.36-8.41 (2H, m, arom.); 8.60 (1H, s, =CH); 9.89 (1H, s, =CH)
4b	7.41 (2H, t, *J*=8.8, arom.); 7.61 (1H, t, *J*=7.0, arom.); 7.76 (1H, d, *J*=8.1, arom.); 7.87 (1H, t, *J*=8.8, arom.); 8.02 (2H, t, *J*=8.8, arom.); 8.57 (1H, s, =CH); 8.82 (1H, d, *J*=7.0, arom.); 9.31 (1H, s, =CH)
4c	7.47 (1H, t, *J*=7.0, arom.); 7.58-7.79 (3H, m, arom.); 7.86 (1H, t, *J*=7.0, arom.); 7.99 (2H, t, *J*=7.0, arom.); 8.24 (1H, d, *J*=7.9, arom.); 8.65 (1H, s, =CH); 9.42 (1H, s, =CH)
4d	7.51-7.65 (3H, m, arom.); 7.76 (1H, d, *J*=8.1, arom.); 7.80-7.84 (1H, m, arom.); 7.90 (1H, t, *J*=8.1, arom.); 8.16-8.20 (1H, m, arom.); 8.26 (1H, d, *J*=8.1, arom.); 8.60 (1H, s, =CH); 9.88 (1H, s, =CH)
4e	3.86 (3H, s, CH_3); 7.12 (2H, d, *J*=8.7, arom.); 7.61 (1H, t, *J*=7.5, arom.); 7.75 (1H, d, *J*=7.5, arom.); 7.83-7.94 (3H, m, arom.); 8.22 (1H, d, *J*=7.5, arom.); 8.54 (1H, s, =CH); 9.13 (1H, s, =CH)
4f	5.88 (2H, s, 2OH); 7.56 (1H, t, *J*=7.4, arom.); 7.67-7.74 (1H, m, arom.); 7.80-7.88 (2H, m, arom.); 8.05 (1H, t, *J*=7.7, arom.); 8.18 (1H, d, *J*=7.7, arom.); 8.26 (1H, d, *J*=8.1, arom.); 8.36 (1H, s, =CH); 8.66 (1H, s, =CH)
4g	7.56 (1H, t, *J*=7.9, arom.); 7.67-7.74 (2H, m, arom.); 7.79 (2H, m, arom.); 8.00 (1H, t, *J*=7.9, arom.); 8.18 (1H, d, *J*=7.9, arom.); 8.26 (1H, d, *J*=8.1, arom.); 8.34 (1H, s, =CH); 8.66 (1H, s, =CH)
5a	1.69 (6H, s, $2CH_3$); 7.63 (1H, t, *J*=8.0, arom.); 7.74 (1H, d, *J*=8.1, arom.); 7.91 (1H, t, *J*=7.1, arom.); 8.20 (1H, d, *J*=7.1, arom.); 8.47 (1H, br. S, =CH); 8.62 (1H, br. S, =CH); 11.76 (1H, s, NH)
5b	1.26 (3H, t, *J*=6.5, CH_3); 1.37 (3H, t, *J*=6.5, CH_3); 4.21 (2H, q, *J*=6.9, CH_2); 4.33 (2H, q, *J*=6.9, CH_2); 7.56 (1H, t, *J*=7.3, arom.); 7.72-7.86 (2H, m, arom.); 7.94 (1H, d, *J*=11.3, =CH); 8.16 (1H, s, NH); 8.30 (1H, d, *J*=7.7, arom.); 10.61 (1H, d, *J*=11.3, =CH)
5c	1.21 (3H, t, *J*=6.8, CH_3); 4.17 (2H, q, *J*=7.2, CH_2); 7.52-7.94 (3H, m, arom.); 8.19 (1H, t, *J*=6.4, arom.); 8.37 (1H, br. S, *J*=7.7, =CH); 8.47 (1H, br. S, NH.); 11.18 (1H, br. S, =CH)
5d	2.19 (3H, s, CH_3); 2.40 (3H, s, CH_3); 7.62 (1H, t, *J*=8.1, arom.); 7.75 (1H, d, *J*=7.7, arom.); 7.90 (1H, d, *J*=8.1, arom.); 8.19 (1H, t, *J*=7.7, arom.); 8.31 (1H, d, *J*=10,5, =CH); 8.43 (1H, s, NH); 11.92 (1H, d, *J*=10,5, =CH)

Nowadays a lot of attention is devoted to the study of antiradical activity of various Schiff bases, e.g., thymol and carvacrol based imines [8] and 4-aminoantipyrine derivatives [9]. We were interested in finding out the possible antiradical activity of imines containing quinozolinone moiety. Antiradical activity for the synthesized compounds was detected with 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. Unfortunately, most of the synthesized compounds **4** and **5** did not demonstrate any antiradical activity against DPPH. Only compounds **4e** and **4f** exhibited a weak scavenging activity against DPPH; unfortunately, the antiradical activity of imine containing substituents exact as for protocatechuic aldehyde **4f** was surprisingly low in comparison with other compounds containing moiety of 3,4-dihydroxybenzaldehyde, e.g., caffeic acid esters or their hydrogenated derivatives are well-known antioxidants [10], [11]. Also compounds **5c** and **5d** demonstrated a slight antiradical activity; their antiradical activity is nearly 50 % of the antiradical activity demonstrated by widely used antioxidant butylated hydroxytoluene (nearly 38 % [12]). It seems that Schiff bases **4** and **5** containing quinolinone moiety are not promising antiradical agents.

TABLE 3

DPPH SCAVENGING ACTIVITY FOR THE QUINAZOLINONES **4** AND **5** AGAINST FREE RADICAL DPPH [a]

Compound	Inhibition of DPPH, %	Standard deviation
4a	-0.8	0.3
4b	0.2	0.2
4c	-0.9	0.2
4d	0.1	0.2
4e	9.5	1.1
4f	8.0	0.5
4g	0.7	0.1
4h	-0.5	0.3
4i	-0.4	0.4
4j	0.0	0.1
4k	2.9	0.4
4l	-0.5	0.0
5a	4.1	0.4
5b	4.9	0.1
5c	19.5	1.4
5d	14.9	0.4

[a]The molar ratio of DPPH and quinazoline derivative **4** or **5** was 1:1.

III. EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained on Bruker 300 spectrometer in DMSO-d_6. The progress of the chemical reactions and the purity of products were monitored by TLC on silica gel plates (Merck 60 F_{254}), using $CHCl_3$-CH_3OH-CH_3COOH (9:1:1) as eluent. The characteristics and ^{1}H NMR spectra of the compounds **4a-g** and **5a-d** are cited in Table 1 and Table 2. The absorption of the solutions (for DPPH test) was measured with Camspec M501 Single Beam Scanning UV/Visible spectrophotometer. The DPPH test was carried out as described previously [12]. The results are presented as the mean of two independent measurements ± standard deviation. Each experiment was repeated three times for various concentrations of the solutions of Schiff base **4** or **5**.

2,2-Dimethyl-5-[(2-(4-oxoquinazolin-3(4*H*)-ylamino)-methylene]-1,3-dioxane-4,6-dione (**5a**), diethyl-2-(4-oxoquinazolin-3(4*H*)-ylamino)methylene malonate (**5b**), ethyl-2-cyanocarbonyl-(4-oxoquinazolin-3(4*H*)-ylamino) acrylate (**5c**), 3-[(4-oxoquinazolin-3(4*H*)-ylamino) methylene]pentane-2,4-dione (**5d**).

3-Aminoquinazolin-4(3*H*)-one (**1**) (0.001 mol) and ethoxymethylene derivative **3a-d** (0.001 mol) were stirred in ethanol (5 ml) at room temperature for 3 h (for compound **3a**) or refluxed in toluene (5 ml) for 15 h (for compounds **3b-d**). Compound **5a** was filtered off and recrystallized. The reaction mixtures containing compounds **5b-d** were cooled, the precipitate filtered and recrystallized.

(*Z*)-3-(Arylideneamino)quinazolin-4(3*H*)-one (**4a-f**), (*Z*)-3-(pyridin-3-ylmethyleneamino)quinazolin-4(3*H*)-one (**4g**).

A mixture of 3-aminoquinazolin-4(3*H*)-one (**1**) (0.001 mol) and aldehyde **2a-g** (0.001 mol) was heated to reflux in ethanol (5 ml) for 3 h (for compounds **2a**,**b**,**d**,**e**) or 6 h (for compound **2c**) or in toluene (5 ml) for 3 h (for compound **2f**) or 8 h (for compound **2g**), then cooled, kept for 16 h in a refrigerator and filtered.

REFERENCES

[1] **Rakhi, R., Abhinav, P. M.** A Review on Biological Activity of Quinazolinones. *International Journal of Pharmacy and Pharmaceutical Sciences*, 2012, vol. 4, N 2, pp. 66-70.

[2] **Panneer Selvam, T., Nijayaraj Kumar, P., Siva Kumar, A.** Synthesis and Anti-oxidant Activity of Novel 6,7,8,9-tetrahydro-5H-5-(2'-hydroxy phenyl)-2-(4'-substituted benzylidene)-3-(4-nitrophenylamino)triazolo quinazoline Derivatives. *Research in Biotechnology*, 2010, N 1, pp. 38-48.

[3] **Mohana Roopan, S., Nawaz Khan, F.** Free Radical Scavenging Activity of Nitrogen Heterocyclics-quinazolinones and Tetrahydrocarbazolones. *Indian Journal of Heterocyclic Chemistry*, 2008, vol. 18, N 2, pp. 183-184.

[4] **Kovalenko, S., Belenichev, I., Galitsa, V., Krivoshey, O.** Synthesis of 2-(3,4-dihydro-3-oxo-2H-[1,2,4]triazino[4,3-c]quinazolin-4-yl)acetic Acid Derivatives as Potential Antioxidants in Nitrosative Stress Model. *Farmacia*, 2010, vol. 58, N 2, pp. 145-157.

[5] **Zhang, Y., Fang, Y., Liang, H., et. al.** Synthesis and Antioxidant Activities of 2-oxo-quinoline-3-carbaldehyde Schiff-base *Derivatives. Bioorganic and Medicinal Chemistry Letters*, 2013, vol. 23, N 1, pp. 107-111. http://dx.doi.org/10.1016/j.bmcl.2012.11.006

[6] **Shemchuk, L. A., Chernykh, V. P., Arzumanov, P. S. et al.** Synthesis of *N*-(4-oxo-3,4-dihydroquinazolin-3-yl)succinimide and *N*-(4-oxoquinazolin-3-yl)succinamic Acid Derivatives Based Thereon. *Russian Journal of Organic Chemistry*, 2007, vol. 43, pp. 615-618. http://dx.doi.org/10.1134/S1070428007040215

[7] **Rāviņa, I., Tetere, Z., Zicāne, D.** Metoksibenzolidēnamino-3, 4-dihidrohinazolinonu sintēze. *Latvijas Ķīmijas žurnāls,* 2009, Nr. 3, 231.-235.lpp.

[8] **Deepak Kumar, B., Rawat, D. S.** Synthesis and Antioxidant Activity of Thymol and Carvacrol Based Schiff Bases. *Bioorganic and Medicinal Chemistry Letters*, 2013, vol. 23, N 3, pp. 641-645. http://dx.doi.org/10.1016/j.bmcl.2012.12.001

[9] **Sayed Alam, M., Choi, J.-H., Lee, D.-U.** Synthesis of Novel Schiff Base Analogues of 4-Amino-1,5-dimethyl-2-phenylpyrazol-3-one and Their Evaluation for Antioxidant and Anti-inflammatory Activity. *Bioorganic and Medicinal Chemistry*, 2012, vol. 20, N 13, pp. 4103-4108. http://dx.doi.org/10.1016/j.bmc.2012.04.058

[10] **LeBlanc, L. M., Paré, A. F., Jean-François, J., et al.** Synthesis and Antiradical/Antioxidant Activities of Caffeic Acid Phenethyl Ester and Its Related Propionic, Acetic, and Benzoic Acid Analogues. *Molecules*, 2012, vol. 17, pp. 14637-14650.

http://dx.doi.org/10.3390/molecules171214637

[11] **Gülçin, I.** Antioxidant Activity of Caffeic acid (3,4-dihydroxycinnamic acid). *Toxicology*, 2006, vol. 217, N 2-3, pp. 213-220. http://dx.doi.org/10.1016/j.tox.2005.09.011

[12] **Mieriņa, I., Tetere, Z., Zicāne, D. et al.** Synthesis and Antioxidant Activity of New Analogs of Quin-C1. *Chemistry of Heterocyclic Compounds*, 2013, vol. 48, pp. 1824-1831. http://dx.doi.org/10.1007/s10593-013-1215-3

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Zenta Tetere, Daina Zicāne, Irisa Rāviņa, Inese Mieriņa, Inese Rijkure. Jaunu hinazolinonu atvasinājumu sintēze un to antioksidatīvās īpašības

Hinazolīna ciklu saturošie savienojumi literatūrā ir ļoti plaši pētīti, jo tiem piemīt visdažādākā bioloģiskā aktivitāte, taču ziņu par hinazolīna atvasinājumu antioksidatīvām īpašībām literatūrā nav daudz. Publicēti atsevišķi ziņojumi par hidroksilgrupas un sēra atoma klātbūtnes veicinošu ietekmi uz hinazolīna antioksidatīvo īpašību paaugstināšanu, tomēr publikācijā nav aprakstīti sistemātiskie pētījumi par hinazolīna cikla aizvietotāju un antioksidatīvās aktivitātes rādītāju savstarpējām likumsakarībām. Literatūrā publicēti dati par hinolīna rindas Šiffa bāzu augstiem antioksidatīvās aktivitātes rādītājiem. Hinolīna un hinazolīna ciklu strukturālā līdzība ļauj uzskatīt arī hinazolīna rindas Šiffa bāzes par potenciāliem antioksidantiem. Minētie fakti, kā arī antioksidantu nozīmes pieaugums brīvo radikāļu izraisīto procesu stabilizācijā rosināja darba autorus veikt dažu hinazolīn-4(3*H*)-onu atvasinājumu sintēzi un antioksidatīvās aktivitātes pētījumus. Par izejvielu eksperimentos izmantots 3-aminohinazolīn-4(3*H*)-ons, kas iegūts no antranilskābes hidrazīda un ortoskudrskābes trietilestera. 3-Aminohinazolīn-4(3*H*)-ons modificēts pie N(3) atoma ar aldehīdiem un etoksimetilēnatvasinājumiem, iegūstot C=C un C=N saiti saturošus savienojumus. Sintezēto savienojumu struktūras noteiktas ar ^{1}H KMR spektru palīdzību un pamatotas ar elementanalīzes datiem. Pārbaudīta publikācijā aprakstīto savienojumu, kā arī piecu agrāk sintezēto hinazolīna Šiffa bāzu antioksidatīvā aktivitāte.

Зента Тетере, Дайна Зицане, Ириса Равиня, Инесе Миериня, Инесе Рийкуре. Синтез новых производных хиназолинона и их антиоксидантные свойства

Соединения с хиназолиновым циклом очень широко исследованы, поскольку они обладают самой различной биологической активностью, в то же время сведений об их антиоксидантной активности в литературе крайне мало. Имеются сообщения авторов некоторых статьей о заместителях хиназолинового цикла, которые, по их мнению, придают молекуле антиоксидантную активность, например, гидроксильные группы и присутствие атома серы, но систематический анализ возможной закономерности структура-активность практически отсутствует. В литературе имеются данные о высокой антиоксидантной активности оснований Шиффа в ряду 2-оксохинолина. Структурное сходство циклов хинолина и хиназолина позволяет основания Шиффа 4-оксохиназолина также представлять потенциальными антиоксидантами. Всё вышеизложенное, а также рост значения и необходимость применять к антиоксидантам, стабилизирующие процессы, вызванные свободными радикалами, было стимулом для синтеза и изучения нами антиоксидантной активности некоторых производных хиназолин-4(3*H*)-онов. В качестве исходного вещества выбрали 3-аминохиназолин-4(3*H*)-он, синтезированный из гидразида антраниловой кислоты и триэтилового эфира ортомуравьиной кислоты по литературной методике. Исходный аминохиназолон модифицировали при N(3) с образованием соединений с C=C и C=N связями в его реакциях с альдегидами и этоксиметиленсоединениями. Структуры синтезированных соединений определены с помощью спектров ЯМР ^{1}H и подтверждены с данными элементного анализа. Проверена антиоксидативная активность в публикации описанных соединений и пять ранее синтезированных Шиффовых оснований хиназолина.