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Synthesis and In Vitro Investigation of Insecticidal Activity of Some Tricyclic Quinazolines and Their Thioanalogues

A.O. Nasrullayev,[1] N.A. Tosheva,[2] B.Zh. Elmuradov,[1] A.A. Eshmuratova,[2] Sh. S. Azimova[2]

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent 100170, Uzbekistan

*corresponding author: b_elmuradov@mail.ru

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Abstract: Hydrochlorides of 2,3-trimethylene-3,4-dihydroquinazoline (deoxypeganine, **3**) and 2,3-trimethylene-3,4-dihydroquinazolin-4-one (deoxyvasicinone, **4**), 2,3-trimethylene-3,4-dihydroquinazolin-4-thione (deoxyvasicinthione, **5**), 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione (mackinazolinthione, **7**), 2,3-pentamethylene-3,4-dihydroquinazolin-4-thione (**9**) were synthesized and their insecticidal activity have been studied. It was found that compounds **3** and **4** have low cytotoxicity, but increasing of quantity of methylene groups in positions 2 and 3 in the series of the thio-analogues **5→7→9** leads to the increasing of cytotoxic activity of them. "Structure-activity" relationship among the tricyclic quinazoline-4-thiones (**5**, **7**, **9**) was revealed. It should be noted that the compounds, consisting reactive thiocarbonyl group are important starting substances for further investigations. The obtained results shows that six-membered and seven-membered quinazolin-4-thiones - **7** and **9** in concentration 1 µg/ml are inhibited cell growth by 59% and 65%, respectively compared with the control, indicating that these compounds can serve as a basis for the development of the new insecticides. Structure of the synthesized compounds was confirmed by the physical methods of research.

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INTRODUCTION

Tricyclic quinazoline alkaloids are widely distributed in nature [Fitzgerald et al., 1966; Mhaske et al., 2001; Cagir et al., 2004; Ma et al., 2004]. In the literature there are many review articles, which covered bi- and tricyclic quinazoline alkaloids [Michael, 1999, 2002, 2005; Mhaske et al., 2004; Nepali et al., 2013; Shakhidoyatov and Elmuradov, 2014].

Many tricyclic quinazoline alkaloids isolated from different plant species. These compounds have multiple reaction centers: the nitrogen atoms in positions 1 and 3, carbonyl (thiocarbonyl) or activated methylene groups, a benzene ring and etc. [Elmuradov et al., 2016]. These centers can react with electrophilic and nucleophilic reagents, resulting in different derivatives of tricyclic quinazoline alkaloids with potential biological activity [Shakhidoyatov et al., 1977, 2010; Richers et al., 2013; Elmuradov et al., 2008, 2010; Abdurazakov, et al., 2009; Nasrullayev et al., 2012].

Quinazolines, quinazolinones, and their analogues are a large class of biologically active compounds that exhibited broad spectrum of biological activities [Shakhidoyatov and Elmuradov, 2014; Levkovich et al., 2016; Khodjaniyazov et al., 2016]. It should be noted cytotoxic activity of many di- and tricyclic quinazolines and quinazolones evaluated as inhibitors of LPS-induced TNF- alpha secretion [Galarce et al., 2008], against TMZ-resistant glioblastoma multiforme (GBM) cells [Elkamhawy et al., 2015], against human leukaemia HL-60 cells [Mikiciuk-Olasik et al., 2004], against breast carcinoma cell line (MCF-7) [Ali Yassen et al., 2014; Jafari et al., 2016; Shi et al., 2014; Prajapati et al., 2014], inhibition on T-cell and B-cell proliferation [Zhang et al., 2012] and etc.

Tricyclic quinazolines (having a methylene group at C-4) and quinazolin-4-ones (having a carbonyl group at C-4) exhibit different properties [Shakdidoyatov and Elmuradov, 2014]; it is often found that several of the quinazoline compounds possess more significant biological activity than the corresponding quinazolin-4-ones. Along with this, the number of methylene groups at C-2 and C-3 have a positive effect on the activity; so increasing of number of the methylene groups (among polymethylene chains of 2,3-tri → 2,3-tetra → 2,3-penta → 2,3-hexamethylene quinazolines) increases the biological activity of the compounds [Tulyaganov N., 1979].

This work is a continuation of previous work. Therefore, it seems interesting synthesis of thioanalogues of the tricyclic quinazoline alkaloids and study comparative cytotoxicity corresponding quinazolines, quinazolin-4-ones and quinazolin-4-thiones, and to identify the preliminary relationship "structure-biological activity". We investigated the insecticidal activity of the synthesized derivatives on cells HzAMI cotton bollworm. The insecticidal activity was examined by quantitative determination of survival and proliferation by MTT-test. It is based on the reduction of the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) by mitochondrial dehydrogenases of living cells; wherein their color changed to purple crystals of formazan, that are not soluble in an aqueous medium of cells, but soluble in DMSO or isopropanol solutions and have a wavelength at 500-700 nm [Anikina et al., 2014].

MATERIALS AND METHODS

^{1}HNMR spectra was recorded in $CDCl_3$, on Unity 400+ spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxane (HMDSO) was used as internal standard, chemical shift δ of ^{1}H was recorded in ppm. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Barnstead International (USA) and were uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets. The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminum plates using C_6H_6/CH_3OH (5:1) solvent system and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

Cell culture HzAMI from the Culture Collection of Beltslille Agriculture Research Centre (USDA-ARS IBL, USA) is cultivated at 26^{0}C in the medium of Grace (Grace's Insect Cell Culture Medium, «SIGMA», USA) containing 10% heat-inactivated fetal calf serum (Foetal Bovine Serum GIBCO, Invitrogen). Cells were seeded in 96 well plates at 5000 cells per well, then incubated overnight at 26°C. Then the test substance was added in an amount of 100, 10 and 1 μg/ml, incubated for 24 hours at the same temperature and then to each well was added of 20 μl of MTT solution in a concentration of 5 mg/ml («SIGMA», USA). According to the method [Mosmann et al., 1983] plates incubated at the same conditions for 4 hours, further the wells were fused to cells and poured on 100 μl DMSO («SIGMA», USA).

In 10 minutes the readings removed on a spectrophotometer «ELX 808» («BIO-TEK INSTRUMENTS, INS», USA) at a wavelength of 570 nm [Giraudo et al., 2011]. Cells without substances are served as control. As a comparison drug is used known insecticide, containing 20% imidacloprid ("Bagheera", «Agrokim» LTD, Uzbekistan), in the same doses of the tested samples. Investigations were carried out three times in triplicate. Statistical processing was performed using «Excel» program.

Deoxyvasicinone (**2**), **mackinazolinone** (**6**) and **2,3-pentamethylene-3,4-dihydro-quinazolin-4-one** (**8**) have been synthesized according to the literature [Shakhidoyatov, 1983].

Deoxypeganine hydrochloride (**3**) was prepared by method which was described in [Musaeva, 1997].

Deoxyvasicinone hydrochloride (4)

1 g (5 mmol) deoxyvasicinone (**2**) was dissolved in 20 ml dried chloroform, and passed through the reaction solution gaseous HCl during 30 min. The formed crystal was filtered off, washed with chloroform.

Yield: 1.19 g (90%), mp 278-280^{0}C.

Deoxyvasicinthione (5)

10 g (0.054 mol) deoxyvasicinone **2** was dissolved in 50 ml dried pyridine and 11.2 g (0.054 mol) P_2S_5 was added. Reaction mixture was refluxed for 2 h and cooled to room temperature. The formed precipitate was filtered off, washed with 5 ml pyridine and was treated with 200 ml (10%) NaOH. After that the precipitate washed with water till neutral medium and dried. The obtained compound **5** was recrystallized from hexane.

Yield: 9.01 g (83%), mp 138-140^{0}C, R_f=0.8 (C_6H_6/CH_3OH - 5:1).

H^1 NMR (CD_3Cl_3): 8.7 (1H, dd, *J*=1.7, *J*=8.4, H-5), 7.7 (1H, td, *J*=1.7, *J*=8.4, H-7), 7.6 (1H, dd, *J*=1.2, *J*=8.3, H-8), 7.45 (1H, td, *J*=1.2, *J*=8.2, H-6), 4.48 (1H, t, *J*=7.6, γ-CH_2), 3.2 (2H, t, α–CH_2), 2.3 (2H, m, *J*=7.5, β–CH_2). IR (KBr) cm^{-1}: 2976 (ν_{CH2}), 1600 ($\nu_{C=N}$), 1470 (ν_{C-N}), 1290 ($\nu_{C=S}$).

Mackinazolinthione (7)

The mixture of 7.2 g (0.036 mol) mackinazolinone (**6**) and 8.3 g (0.037 mol) phosphorus pentasulfide in 50 ml m-xylene was refluxed for 3-4 h. After cooling till room temperature, the formed precipitate was filtered and was treated with 80 ml (10%) NaOH and mixture was left for 1 h. The precipitate was washed with distilled water till pH=7 and dried. The reaction product **7** was recrystallized from hexane.

Yield: 5.5. g (70%), mp 118-120^{0}C, R_f=0.85 (C_6H_6/CH_3OH - 5:1).

H^1 NMR (CD_3Cl_3): 8.73 (1H, dd, J=8.2, J=1.6, H-5), 7.7 (1H, t, J=8.2, H-7), 7.5 (1H, d, J=8.2, H-8), 7.4 (1H, t, J=8.2, H-6), 4.55 (2H, t, J=6.2, δ–CH_2), 3.0 (2H, t, J=6.9, α–CH_2), 2.0 (2H, m, γ–CH_2),

1.92 (2H, m, β–CH_2). IR (KBr) cm^{-1}: 2992 (ν_{CH2}), 1585 ($\nu_{C=N}$), 1470 (ν_{C-N}), 1275 ($\nu_{C=S}$).

2,3-Pentamethylene-3,4-dihydroquinazolin-4-thione (9)

Reaction carried out according to the synthesis method of compound **7**. From 8 g (0.0374 mol) 2,3-pentamethylene-3,4-dihydroquinazolin-4-one (**8**) and 8.3 g (0.0374 mol) P_2S_5 in 80 ml m-xylene the targeted compound **9** has been synthesized in good yield.

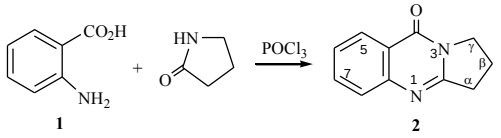
Yield: 7.0. g (81%), mp 104-105^{0}C, R_f=0.83 (C_6H_6/CH_3OH - 5:1).

H^1 NMR (CD_3Cl_3): 8.68 (1H, dd, J=8.2, J=1.5, H-5), 7.65 (1H, td, J=8.2, J=1.5, H-7), 7.54 (1H, dd, J=8.2, J=1.3, H-8), 7.4 (1H, td, J=8.2, J=1.3, H-6), 5.01 (2H, t, J=5.2, ε–CH_2), 3.14 (2H, t, J=5.2, α–CH_2), 1.83 (6H, m, β,γ,δ–CH_2). IR (KBr) cm^{-1}: 2995 (ν_{CH2}), 1590 ($\nu_{C=N}$), 1460 (ν_{C-N}), 1277 ($\nu_{C=S}$).

RESULTS AND DISCUSSION

Hydrochlorides of deoxypeganine (**3**) and deoxyvasicinone (**4**), deoxyvasicinthione (**5**), mackinazolinthione (**7**), 2,3-pentamethylene-3,4-dihydroquinazolin-4-thione (**9**) are objects of the our investigations.

Alkaloid deoxyvasicinone (**2**) is starting compound for the synthesis of corresponding hydrochlorides **3,4**. Therefor we synthesized compound **2** according to the literature method [Shakhidoyatov, 1983] (scheme 1):

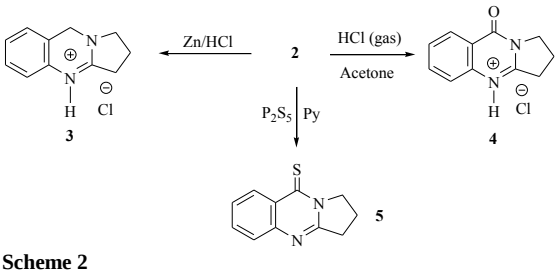


1 **2**

Scheme 1

Deoxyvasicinone can be synthesized by various methods. One effective method among them is the condensation of anthranilic acid (**1**) with a lactam in the presence of condensing agents (for example: phosphorus oxychloride, thionyl chloride); wherein deoxyvasicinone is formed in good yields (70-85%).

It should be emphasized that deoxypeganine hydrochloride (**3**) which is anticholinesterase drug [Yunusov et al., 1978], can be prepared by reduction of deoxyvasicinone (**2**) or by "multicomponent one-step" synthesis of anthranilic acid (**1**) [Musayeva et al., 1997] (scheme 2).

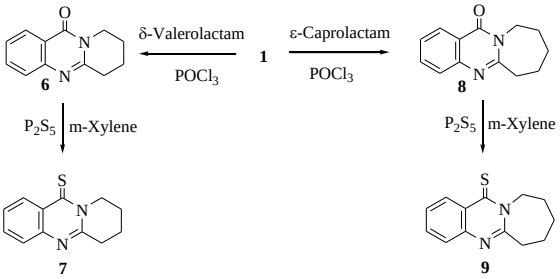


3 **4** **5**

Scheme 2

With purpose synthesis of first thioanaloge – deoxyvasicinthione (**5**) we carried out interaction of alkaloid deoxyvasicinone **2** with P_2S_5 in dried pyridine by reflux for 2 h and targeted compound **5** was obtained in 83% yield.

Continuing our researches, we synthesized mackinazolinthione (**7**) and 2,3-pentamethylene-3,4-dihydroquinazolin-4-thione (**9**) by reactions of mackinazolinone (**6**) and 2,3-pentamethylene-3,4-dihydroquinazolin-4-one (**8**) and phosphorus pentasulphide. Starting compounds **6** and **8** were synthesized by cyclization of anthranilic acid (**1**) with δ–valerolactam and ε–caprolactam (scheme 3):



Scheme 3

The structure of the synthesized compounds (**2-9**) was confirmed by IR- and ^{1}H NMR-spectroscopy.

The synthesized compounds were tested for in vitro insecticidal activity. During the investigation of the insecticidal activity of compounds was not observed the pronounced concentration dependence of the tested compounds. However, under the action of the compounds **3, 4, 5** practically no inhibiting of the cotton bollworm cells, but under the action of samples **7** and **9** is inhibited cell growth by 59% and 65%, respectively compared with the control - imidacloprid, indicating that these compounds can serve as a basis for the development of the new insecticides (Table 1).

Table 1. Insecticidal activity of the synthesized compounds (%).

Concentration / Compounds	100 μg/ml	10 μg/ml	1 μg/ml
3	21±1,8	8±0,6	0
4	19±0,8	5±0,1	0
5	18±0,8	17±0,1	19±0,4
7	35±0,9	36±0,9	30±0,2
9	75±1,7	37±0,6	33±0,9
Imidacloprid (control)	97±0,5	70±1,1	51±0,6

The cytotoxic effect of the investigated compounds could be observed also at the morphological analysis (see Fig.1). Thus, in Fig. 1 (**A**) shows those cells without affecting of substances form a dense monolayer. At the same time, under the

action of imidacloprid cell density significantly reduced (Fig.1, **D**), which is confirmed by MTT data (Table 1). Under the influence of the substance **3** monolayer density does not decrease, therefore the action of the substances does not affect to the state of the cells (Fig. 1, **C**). However, the analysis confirms the toxicity of the compound **9** is expressed in the depletion of the cell monolayer, loss of the sphericity of the cells (Fig. 1, **B**).

CONCLUSION

Hydrochlorides of 2,3-trimethylene-3,4-dihydro quinazoline (**3**) and 2,3-trimethylene-3,4-dihydroquinazolin-4-one (**4**), 2,3-trimethylene-3,4-dihydroquinazolin-4-thione (**5**), 2,3-tetramethylene-3,4-dihydroquinazolin-4-thione (**7**), 2,3-pentamethylene-3,4-dihydroquinazolin-4-thione (**9**) were synthesized and their cytotoxic activity have been studied.

It was found that compounds **3** and **4** have low cytotoxicity, but increasing of quantity of methylene groups in positions 2 and 3 in the series of the thio-analogues **5→7→9** leads to the increasing of cytotoxic activity of them. Preliminary "structure-activity" relationship among the tricyclic quinazoline-4-thiones (**5**, **7**, **9**) was revealed.

It should be noted that the compounds, consisting reactive thiocarbonyl group are important starting substances for further investigations. It was showed that compounds **7** and **9** in concentration 1 µg/ml are inhibited cell growth by 59% and 65%, respectively compared with the control, indicating that these compounds can serve as a basis for the development of the new insecticides. Research in this area continues.

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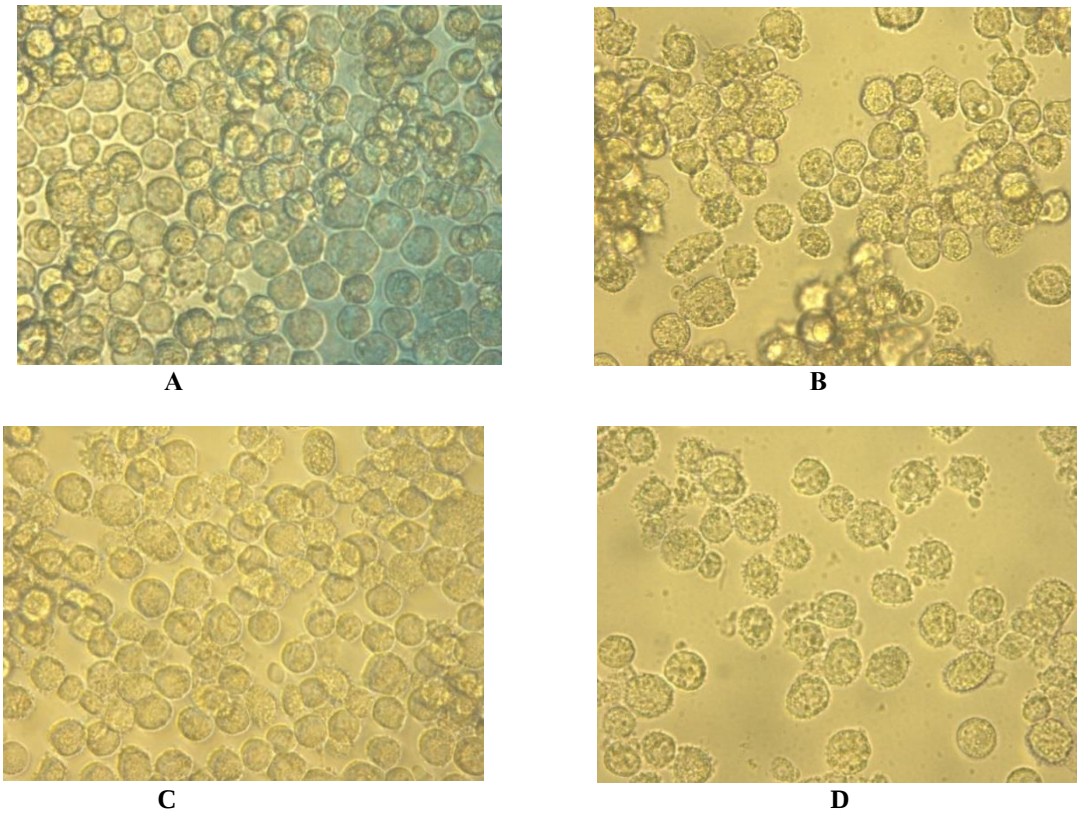

Figure 1. Cell Culture HzAMI. **A**- control cells, which are not exposed by substances; **B**- cell culture after exposure of the substance **9** in concentration of 1µg/ml; **C**- cell culture after exposure of the compound **3** in concentration of 1µg/ml; **D**- cell culture after exposure of the imidacloprid in concentration 1µg/ml; (Microscope «LeicaDMIL», USA, 40 fold increase).

REFERENCES

Abdurazakov A.S., Elmuradov B.Z., Turdibaev Z.E., Shakhidoyatov K.M. (2009). Reaction of 2,3-tetramethylene-3,4-dihydroquinazol-4-one and its derivatives with aromatic aldehydes and furfurol, *Chem. Nat. Compd.*, *45*, 402-408.

Ali Yassen A.S., Abd Elhamed H.E., Elshihawy A., Amin Said M.M., Mohamed Abouzid K.A. (2014). Molecular Modelling and

Synthesis of Quinazoline-Based Compounds as Potential Antiproliferative Agents. *Chem. Pharm. Bull.*, Vol. 62, №5, 454-466.

Anikina L.V., Pukhov S.A., Dubrovskaya E.S., Afanaseva S.V., Klochkov S.G. (2014). Comparative definition of cell viability by MTT and Resazurin. *Fundamental research.* №12, 1423-1427. (in Russian).

Cagir A., Jones S. H., Eisenhauer B. M., Gao R., Hecht S.M. (2004). Synthesis and biological properties of E-ring modified luotonin A derivatives, *Bioorg. Med. Chem. Lett.*, 14, 2051-2054.

Elmuradov B. Z., Abdurazakov A. S., Shakhidoyatov K. M. (2008). Synthesis and bactericidal activity of 6-H(nitro)-9-arylidendeoxyvasicinone and their perchlorates, *Chem. Nat. Compd.*, 44, 475-479.

Elmuradov B. Z., Abdurazakov A. S., Shakhidoyatov K. M. (2010). Directions of reactions of 6-amino-, -acetylamino-, and –benzoylaminodeoxyvasicinones with aldehydes, *Chem. Nat. Compd.*, 46, 262-267.

Elmuradov, B. Z., Shakhidoyatov, Kh. M., Dräger, G., Butenschön, H. (2016). Tricyclic quinazoline alkaloids conjugated to ferrocene. Synthesis, structure, and redox behavior of ferrocenylmethylene substituted 7H-deoxyvasicinones. *Eur. J. Org. Chem.*, 483–492.

Elkamhawy A., Nath A., Viswanath I., Pae A. N., Kim H.Y., Heo J.-Ch., Park W.-K., Lee Ch.-O., Yang H., Kim K. H., Nam D.-H., Seol H. J., Cho H.. Downloads/Literature (Cytotoxicity)/Discovery of potent and selective cytotoxic activity of new quinazoline-ureas against TMZ-resistant glioblastoma multiforme (GBM).html - cor2, Roh E. J. (2015). Discovery of potent and selective cytotoxic activity of new quinazoline-ureas against TMZ-resistant glioblastoma multiforme (GBM). *Eur. J. Med. Chem.*, Vol. 103, 210–222.

Fitzgerald J.S., Johns S.R., Lamberton J.A., Redcliffe A.H. (1966). 6,7,8,9-Tetrahydropyrido-quinazolines, a new class of alkaloids from *Mackinlaya species* (*Araliaceae*), *Aust. J. Chem.*, 19, 151-155.

Galarce G.D., Foncea R.E., Edwards A.M., Pessoa-Mahana H., Pessoa-Mahana C.D., Ebensperger R.A. (2008). Biological evaluation of novel 6-arylbenzimidazo [1,2-c] quinazoline derivatives as inhibitors of LPS-induced TNF- alpha secretion. *Biol. Res.*, 41, 43-50.

Giraudo M., Califano J., Hilliou F., Tran T., Taquet N., Feyereisen R., Le Goff G. (2011). Effect of Hormone Agonists on Sf9 Cells, Proliferation and Cell Cycle Arrest. *PLoS ONE* 6(10): e25708. doi:10.1371/journal.pone.0025708.

Jafari E., Khajouei M. R., Khodarahmi G.A. (2016). Quinazolinone and quinazoline derivatives: recent structures with potent antimicrobial and cytotoxic activities. *Res. Pharm. Sci..*, Vol.11, Issue 1, 1–14.

Khodjaniyazov Kh.U., Makhmudov U.S., Kutlimuratov N.M. (2016). Synthesis and X-ray crystal structure of (E)-9-(N,N-Dimethylaminomethylidene)-8,9-dihydropyrido[2,3-d]pyrrolo[1,2-a]pyrimidin-5(7H)-one. *J. basic appl. Res.* 2(3): 382-385.

Levkovich M. G., Elmuradov B. Zh., Shakhidoyatov Kh. M., Abdullaev N. D. (2016). Deuterium Exchange of the α-Methylene Group Protons in the Quinazolones. III. Environment Influence on the Exchange Rate. *J. basic appl. Res.* 2(2): 202-204.

Ma Z.-Z., Hano Y., Nomura T., Chen Y.-J. (2004). Novel quinazoline-quinoline alkaloids with cytotoxic and DNA topoisomerase II inhibitory activities, *Bioorg. Med. Chem. Lett.*, 14, 1193-1196.

Mhaske S. B. and Argade N. P. (2001). Concise and efficient synthesis of bioactive natural products pegamine, deoxyvasicinone, and (-)-vasicinone. *J. Org. Chem.*, Vol.66, №26, 9038-9040.

Mhaske S. B. and Argade N. P. (2004). Ficile zeolite induced Fisher-indole synthesis: A new approach to bioactive natural product rutaecarpine, *Tetrahedron*, 60, 3417-3420.

Michael J. P. (1999). Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, Vol.16, Issue 6, 697-709.

Michael J. P. (2002). Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, Vol.19, Issue 6, 742-760.

Michael J. P. (2005). Quinoline, quinazoline and acridone alkaloids, *Nat. Prod. Rep.*, Vol.22, Issue 5, 627-646.

Mikiciuk-Olasik E., Baszczak-Świątkiewiz K., Żurek E., Krajewska U., Różalski M., Kruszyński R., Bartczak T. J. (2004). New Derivatives of Quinazoline and 1,2-Dihydro-quinazoline N^3-Oxide with Expected Antitumor Activity. *Arch. Pharm*. Vol. 337, Issue 5, 239–246.

Mosmann, T.R. (1983). Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *J. Immunil. Methods*, Vol. 65, Issues 1–2, 55-63.

Musayeva G.V. (1997). *Technology of 2,3-polymethylene-3,4-dihydroquinazolines*. Candidate Dissertation, Tashkent.

Nasrullaev A.O., Turdibaev Z. E., Elmuradov B. Z., Yili A., Aisa H.A., Shakhidoyatov K. M.

(2012). Chemical transformations of mackinazolinone and its derivatives, *Chem. Nat. Compd.,* Vol. 48, Issue 4, 638-642.

Nepali K., Sharma S., Ojha R., Dhar K.L. (2013). Vasicine and structurally related quinazolines. *Med. Chem. Res.*, Vol. 22, Issue 1, 1-15.

Prajapati B., Panchal I. (2014). Synthesis and preliminary in-vitro cytotoxic activity of morpholino propoxy quinazoline derivatives. *Int. J. ChemTech Research.*, Vol.6, Issue 1, 547-555.

Richers M. T., Zhao C., Seidel D. (2013). Selective copper (II) acetate and potassium iodide catalyzed oxidation of aminals to dihydroquinazoline and quinazolinone alkaloids, *Beilstein J. Org. Chem.*, 9, 1194-1201.

Shakhidoyatov K. M., Yamankulov M. Y., Kadyrov C. S. (1977). Quinazolines. XI. Condensation of deoxyvasicinone with aldehydes. *Chem. Nat. Compd.,* 13, 461-463.

Shakhidoyatov K. M. (1983). *Synthesis and chemical modification of quinazoline derivatives*. Diss. Doctor of Sciences, Moscow, 334 p.

Shakhidoyatov K. M., Ibragimov T. F., Mukhamedov N. S. (2010). Reaction of deoxyvasicinone with organolithium compounds, *Chem. Nat. Compd.,* Vol.46, Issue 4, 598-599.

Shakhidoyatov, Kh. M., Elmuradov, B. Zh. (2014). Tricyclic quinazoline alkaloids: isolation, synthesis, chemical modification and biological activity. *Chem. Nat. Compd.*, Vol.50, №5, 781-800.

Shi B., Zhang J., Cao Sh., Gao M., Ding P., Li Zh., Liao J., Xu X. (2014). Synthesis and cytotoxic evaluation of hybrids of indolin-2-one and quinazoline-4(3H)-one linked via carbon-carbon double bond**.** *J. Chinese Pharm. Sci.*, Vol. 23, Issue 11, 765-771.

Tulyaganov N. (1979). Pharmacological investigations of alkaloids of the Peganum harmala L. of quinazoline and quinazolone structure and their derivatives. *Pharm. Nat. Compd.*, Tashkent: Fan, 71-80 (in Russian).

Yunusov S.Yu., Tulyaganov N., Telezhenetskaya M. V., Sadritdinov F., Khashimov Kh. (1978). USSR Pat. No. 605,614, Byull. Izobret., No. 17.

Zhang L., Gao Zh., Peng Ch., Bin Zh.-Y., Zhao D., Wu J., Xu Q., Li J.-X. (2012). Ultrasound-promoted synthesis and immunosuppressive activity of novel quinazoline derivatives. *Molec. Diver.,* Vol.16, Issue 3, 579-590.