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Research Article

Synthesis and Preliminary Antibacterial Activities of novel Schiff bases Derivatives of 3,6-diazahomoadamantane

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Abstract

This work includes synthesis of new Schiff bases derivatives of diazahomoadamntane.

First, 1,3,6,8-tetraazatricyclo[4.4.1.13,8]dodecane **1** was treated with anisyl acetone to produce 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-one **2**. Reaction of ketone compound **2** with aqueous hydrazine yielded 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-hydrazone **3**. Condensation of hydrazone derivative **3** with some benzaldehydes including (4-carboxybenzaldehyde, 3-chlorobenzaldehyde, 3-hydroxybenzaldehyde, 4-nitrobenzaldehyde) under reflux in ethanol afforded imine derivatives of diazahomoadamntane **4a**–**d**. The structures of newly synthesized derivatives have been deduced via FT-IR, ^{1}H NMR, and Mass spectral means. Antibacterial test of new derivatives **4a-d** showed that compounds **4b**, **4c**, and **4d** have activity against *Staphylococcus aurous* more than *Gentamycin* as a reference drug, also compound **4d** pointed higher activity against *Escherichia coli* than the standard drug.

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INTRODUCTION

Adamantane and its derivatives have fascinating structures due to their various physiological, pharmaceutical, and medical activities [1-3]. The biological activity of azaadamantanes and its derivatives has only lately been the subject of systematic research. Analogs of adamantine that are nitrogenous, known as azaadamantanes, have one or more nitrogen atoms in place of carbon atoms. [3-5]. There are a number of reported bioactive compounds with various heteroatoms, including nitrogen, sulfur, and oxygen [6].

Azaadamantanes are derived from tetramethylenediethylenetetramine (1,3,6,8-tetraazatricyclo [4.4.1.13,8] dodecane) and are an important class of heterocyclic compounds.

On the other hand, 1,3,6,8-tetraazatricyclo[4.4.1.13,8]dodecane (tetramethylenediethylenetetramine) has a four nitrogen atoms heterocyclic nucleus. It is a heterocyclic compound is nitrogen atoms inside the ring, and it is a polycyclic compound. Diazaadamantanes are of great importance in both medical and pharmaceutical chemistry. A wide range of biological activities are given by this type of chemical, such as anticonvulsant[7], and sedative [7], antimicrobial [7,8], psychotropic, anti-bacteria, anti-fungal, and anticonvulsant activities [8- 15].

Azaadamantanes have been actively studied as anticancer agents [10,11]. some diazaadamantane compounds were found to be potent sodium channel blockers [12] and to have a high affinity to κ - opioid receptors [13].

The majority of hospital acquired infections are caused by bacteria, which pose a serious risk to patient health and place a heavy strain on healthcare systems. *Escherichia coli*, methicillin-resistant *Staphylococcus aurous* [16], multidrug-resistant tuberculosis, extended-spectrum lactamase-producing Entero bacteriaceae, and other dangerous bacteria have all arisen with various degrees of resistance to current therapeutic treatments [17].

EXPERIMENTAL

Material and Methods

Chemicals and Instruments

Synthetic starting materials, reagents, and solvents were purchased by Sigma-Aldrich, GCC, S.D. Fine, BDH, Scharlau, Fluka, and Merck. The reactions have already been monitored by 0.2 mm, 60 F254, silica TLC plates with an aluminium backing and each pure component displayed a single spot. Cole Paramer MP-200D-120 Stuart Digital Melting Point Measurement Equipment has been used to determine melting points. FT-IR spectral data have been recorded on the SHIMADZU FTIR-8400S Infrared Spectrophotometer. ^{1}H NMR (300 MHz) and spectral data have been measured on a Bruker DPX 300 machine (Bruker AXS Handheld Inc., Kennewick, WA, USA) using $CDCl_3$ as a solvent and TMS as an internal benchmark at Russian Technological, College MRussia the Federation - Moscow. Chemical shifts were recorded as δ (ppm) adjacent to TMS, which was utilized as an internal standard. Coupling constants (*J*) were displayed in Hertz. The mass spectra were measured at the Institute of Organic Chemistry, Russia the Federation, Moscow, using a Finnigan MAT 90 instrument. The parameters were: accelerating voltage of Cathode emission current: 5.0 kV of 100 μA, 70 For eV of ionizing electron energy, and 200°C of ionizing chamber temperature.

Synthesis of 1-(4-methoxybenzyl-3,6-diazahomoadamantan-9-one [2]

A mixture of 14.30g (85mmol) of tetramethylenediethylenetetramine **1,** 14.10g (95mmol) of 4-(4-methoxy phenyl)-2-butanone **2** and 130 ml of 2-propanol and 15.30g (260 mmol) of acetic acid were heated around 60 and 70 ^{0}C for 30 minutes. After that, the reaction mixture was concentrated under reduced pressure, hot heptane (4 x 50 ml) was used to treat the viscous residue an anhydrous aluminum oxide bed. (10g) activity level II laid a glass frit filter was used to filter the heated extract in order to remove impurities. Distillation was used to remove the solvent, and the residue from heptane was crystallized again., White crystals with a yield of 7.00 g (32%). melting point: 106-107 ^{0}C Lit. : 106–107 ^{0}C [18]. IR spectrum, ν, cm^{-1}: 1698 (C=O), 1607 (Ph), 1258, 1174 (OCH_3). ^{1}H

NMR ($CDCl_3$)spectrum, δ,ppm: ^{1}H NMR ($CDCl_3$): 1.26 (s, 1 H, CH); 2.67 (s, 2 H, CH_2Ar); 2.76-3.60 (m, 8 H, 4 NCH_2C), 3.15 (m, 4 H,NCH_2CH_2N); 3.80 (s, OCH_3); 6.81, 6.95 (both d, 4 H, Ar, *J* = 8.9 Hz). Mass spectrum, *m/z* (*I*rel, %*)*: 286 [*M*]+ (90), 243 (73), 202 (10), 159 (08), 121 (55), 83 (18), 101 (50), 91 (05),72 (90), 57 (29), 43 (57). Found, %: C, 71.12; H, 7.77; N, 9.80. $C_{17}H_{22}N_2O_2$. Calculated, %: C, 71.30; H, 7.74; N, 9.78. *M* 286.37.

Synthesis of 1--(4-methoxybenzyl)-3,6-diazahomoadamantan-9-hydrazone [3]

A mixture of 1.30 g (4.8 mmol) of ketone and hydrazine hydrates was heated to a boil for 3 hrs. The solvent was evaporated, and the residue from toluene was recrystallized. The reaction was followed up by TLC (Chloroform: 1 percent in 10 mL of an 80% methanol, 5:1). Produce 1.19 g (84%), crystals of white m.p. 194-195 ^{0}C Lit.: m.p. 194-195^{0}C) [19]. IR spectrum, ν, cm^{-1}: 3359,3321 (NH_2),1637 (C=N), 1503 (Ph), 1259, 1173(OCH_3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.09 (s, 1H, CH), 3.15 (s, 2 H, CH_2Ar);, 3.27-337 m (4H, NCH_2C), 3.48 d (2H,NCH_2C, *J* 14.0 Hz), 3.34 m (4H, NCH_2CH_2N), 3.48 d(2H, NCH_2C, *J* 14.0 Hz), 3.70 d (2H, NCH_2C, *J*14.0 Hz), 3.80 s (3H, OCH_3), 5.01 br.s (2H, NH_2), 6.87d (2HAr, *J* 8.8 Hz), 7.21 d (2HAr, *J* 8.8 Hz). Mass spectrum, *m/z* (*I*rel, %): 300 [*M*]+ (73), 284 (73), 242 (72), 242 (10), 200 (22), 172 (17), 121 (42), 91 (20), 72(80), 57 (19), 42 (53). Found, %: C, 67.84; H, 8.16; N, 18.54. $C_{17}H_{24}N_4O$. Percentage calculated: C = 67.97; H = 8.05; N = 18.65; *M* 300.40.

Synthesis of imines of diazahhmoadamantane [4a-d]

Condensation of 1 mmol of hydrazone **3** and (1 mmol) the corresponding aldehyde derivatives in 50 mL of pure ethanol. The reaction's mixture was refluxed for six hours. The evaporator was distilled off, the reaction was followed up by TLC (Chloroform: methanol, 5:1) and the formed precipitate was filtered off and recrystallized from ethanol.

***N*-4-carboxy benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.1^{3,8}] undec-9-ylidene] hydrazine (4a):**

Yield (71%), pale yellow crystals, m.p 286-278°C. FT-IR spectrum, ν, cm-1: 3423 (OH), 1704 (C=O), 1611 (C=N), 1510 (Ph), 1244, 1105 (OCH_3). ^{1}H NMR (CDCl3) δ, ppm: 1.89s (1H, CH), 2.85 (s, 2 H, CH_2Ar);, 2.82-3.69 m (8H, NCH_2C), 3.03 m (4H, NCH_2CH_2N), 3.81 s (3H, OCH_3), 6.88 -7.53 m (8H, Ph), 9.03 s (1H, CH=N). 12.04 br. (1H, COOH). Mass spectrum (m/z). (*I*rel, %): 432 [*M*]+ (33), 366 (02), 301 (40), 272 (50), 258 (60), 179 (33), 135 (75), 107(30), 79(48), 43 (55). Found, %: C, 69.96; H, 6.68; N, 12.74;. $C_{25}H_{28}N_4O_3$. Calculated, %: C, 69.42; H, 6.53; N, 12.95; *M* 432.51.

***N*-3-Chloro benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.13,8] undec-9-ylidene] hydrazine (4b)**

Yield (74%), white crystals, m.p 188-190°C. IR (cm-1): IR spectrum, ν, cm^{-1}: 1607 (C=N), 1514 (Ph), 1258, 1174 (OCH_3). ^{1}H NMR spectra ($CDCl_3$), δ, ppm: 2.78`s (1H, CH), 2.83 (s, 2 H, CH_2Ar), 2.94-3.30 m (8H, NCH_2C), 3.04 m (4H, NCH_2CH_2N), , 3.81 s (3H, OCH_3), 7.09 -7.73 m (8H, Ph), 9.38 s (1H, CH=N). Mass spectrum, *m/z* (*I*rel, %*)*: 422 [*M*]+ (05), 328 (25),270 (30), 227 (15), 200 (05), 159 (11), 135 (30), 93 (100), 66 (38), 42 (33). Found, %: C, 69.96; H, 6.68; N, 12.74;. $C_{25}H_{28}N_4O_3$. Calculated, %: C, 69.42; H, 6.53; N, 12.95; *M* 432.51.

***N*-3-Hydroxy benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.13,8] undec-9-ylidene] hydrazine (4c)**

Yield (76%), crystals, m.p 229-231°C. IR (cm^{-1}): 3249 (O-H),1640 (C=N), 1604 (Ph), 1211, 1168 (OCH_3). ^{1}H NMR spectra ($CDCl_3$), δ, ppm: 2.37 (s, 2 H, CH_2Ar), 2.74`s (1H, CH), 3.19-3.82 m (8H, NCH_2C), 3.29 m (4H, NCH_2CH_2N), , 3.84 s (3H, OCH_3), 5.73 br. s (1H, OH), 6.79 -7.27 m (8H, Ph), 8.98 s (1H, CH=N). Mass spectrum, *m/z* (*I*rel, %*)*: 404 [*M*]+ (11), 328 (25), 270 (75), 227 (19), 186 (15), 159 (12), 101 (50), 91 (72), 72 (61),

42 (100). Found, %: C, 68.04; H, 6.54; N, 13.42. $C_{24}H_{27}ClN_4O$. Calculated, %: C, 68.15; H, 6.43; N, 13.25. *M* 422.95.

_N_-4-Nitro benzyliden [(9)-1-(4-methoxybenzyl)-3,6-diazatricyclo [4.3.1.13,8] undec-9-ylidene] hydrazine (4d)

Yield (70%), yellow crystals, m.p 199-201°C. IR (cm^{-1}): IR spectrum, ν, cm^{-1}: 1616 (C=N), 1512, 1342 (NO_2), 1446 (Ph), 1246, 1188 (OCH_3). ^1H NMR spectrum (CDCl3), δ, ppm: 2.80 (s, 2 H, CH_2Ar), 2.91s (1H, CH), 3.02-3.12 m (4H, NCH_2C), 3.07 m (4H, NCH_2CH_2N), 3.12 d (2H, NCH_2C, *J* 14.0 Hz), 3.26 d(2H, NCH_2C, *J* 14.0 Hz), 3.81 s (3H, OCH_3), 6.83 -7.82 m (8H, Ph), 9.00 s (1H, CH=N). Mass spectrum, *m/z* (*I*rel, %): 433 [*M*]+ (30), 342 (15), 384 (42), 241 (10), 212 (05), 172 (05), 135 (40), 93 (100), 77 (30), 43 (20). Found, %: 71.13; H, 7.10; N, 13.37. $C_{24}H_{28}N_4O_2$. Calculated, %: 71.26; H, 6.98; N, 13.85., 13.25. *M* 404.50.

Results and discussion

The synthesis of some new imines of diazatricyclo [4.3.1.1^{3,8}] undecan-9-one was carried out at the nodal atom C1 with substituents provided by the reaction of tetramethylenediethylenetetramine using methyl ketones and their subsequent conversions to 3,6-diazatricyclo [4.3.1.1^{3,8}] undecane and its derivatives [20-27]. In this study, new compounds of 3,6-diazahomoadamantane were synthesized. 1-(4-methoxybenzyl) -3,6- diazatricyclo [4.3.1.1^{3,8}] undecan -9- one 2 by the reaction of 4- Anisy l ketone with tetramethylenediethylenetetramine 1 (Scheme 1).

IR spectrum of compound **2** pointed peak of carbonyl group stretching vibration at1698 cm^{-1}, phenyl groups (1607 cm^{-1}), and methoxy groups (1258, 1174) are alo detected. The ^1H NMR spectrum includes the set of signals typical of the diazatricyclo [4.3.1.1^{3,8}] undecane scaffold N including two proton AB systems CH_2C, the ethylene bridge's proton multiplet, NCH_2CH_2N and the expanded singlet at 1.26 ppm from the proton in the location of the node. The 4-methoxybenzyl group signal manifests as two doublets of the benzene group protons in the range of 6.80–6.97 ppm, a singlet of the methylene at 2.67 ppm, and methoxy group protons at 3.80 ppm. Molecular ion peak ([M]+ 286) in the mass spectrum is mostly fragmented as a result of skeleton degradation and cation production at m/z 72 and 57.

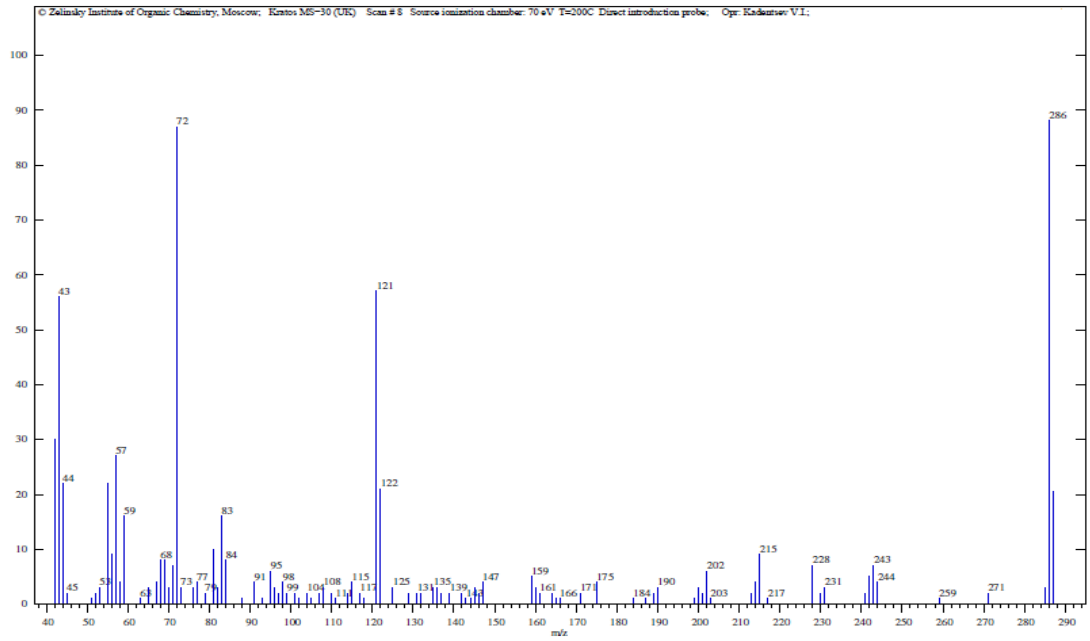
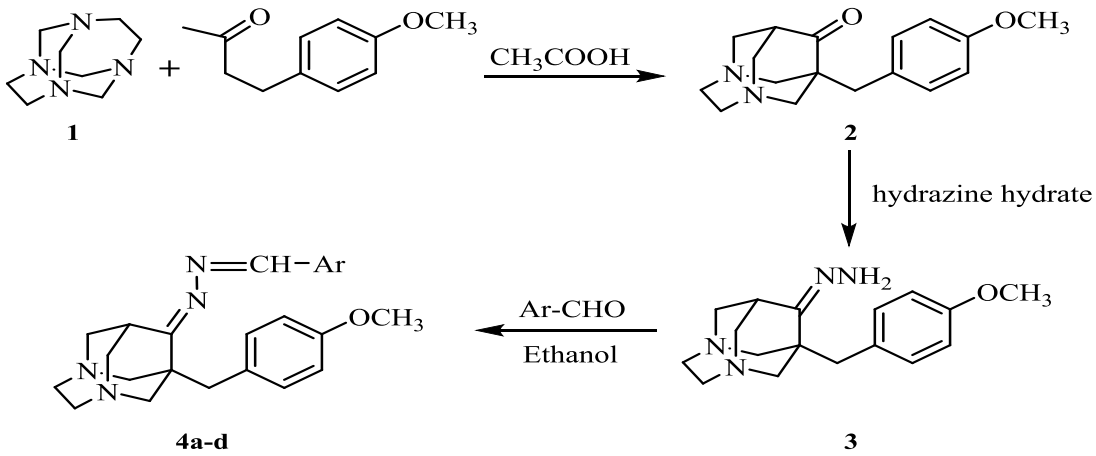


Fig. 1: Mass spectrum of compound 2

The reaction of 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-one **2** with hydrazine hydrate produced 1-(4-methoxybenzyl)-3,6-diazahomoadamantan-9-hydrazone. Hydrazone derivative **3** has been treated with aldehyde derivatives (4-carboxybenzaldehyde, 3-chlorobenzaldehyde, 3-hydroxybenzaldehyde, 4-nitrobenzaldehyde) on reflux in ethyl alcohol to give four imines of 3,6-diazahomoadamantan **4a–d,** respectively **(Scheme 1)**.



Ar= 4-HOOCPh- (a), 3-ClPh- (b), 3-HOPh- (c), 4-NO_2Ph- (d)

Scheme 1: Synthesis of imines 3,6- diazahomoadamntane

IR spectrum of hydrazone derivative **3** showed disappearance of peak of carbonyl group stretching vibration at1698 cm^{-1}, and appearance peaks around 3359,3321 cm^{-1} for amino group, also presence peak at 1637 cm^{-1} for (C=N) group stretching. In the ^{1}H NMR spectrum two protons of the amino group appeared as a broad at 5.01 ppm, the protons of the ethylene fragment NCH_2CH_2N, as a multiplet at 3.34 ppm. multi at 3.27, 3.48, 3.70, and 3.75 ppm correspond to the protons of four methylene groups NCH_2C. The protons of the methylene group CCH_2C are observed as a singlet at 3.15 ppm. and methoxy group protons at 3.80 ppm, two doublets of the phenyl group protons in the region 6.87-7.21 ppm. Mass spectrum pointed the molecular ion peak at ([*M*]+300).

IR spectra of imine derivatives of 3,6-diazahomoadamantane **4a-d** indicated absence of amino group peaks at 3359,3321 cm^{-1} and appearance of peak around 1611, 1607, 1604, and 1616 cm^{-1}, respectively assigned to (C=N) groups stretching. ^{1}H NMR means (300 MHz, $CDCl_3$) that appeared new signal around δ 8.50-9.67 ppm assigned to the (CH=N) proton of azomethine group. The phenyl protons (Ar-H) appeared multiple signals at the range δ 6.60-8.15 ppm. The structures of all products obtained were identified by using Mass measure, Nuclear magnetic resonance (NMR) spectra, (FTIR) spectra. The microanalysis of (CHNS) as certained accepted agreement to the calculated percentage.

Antibacterial activity

Using the agar diffusion technique [28], *Staphylococcus aureus*, *Streptococcus mutants* (Gram-positive) and *Escherichia coli*, *Pseudomonas aeruginosa* (Gram-negative) bacteria were employed to evaluate the antibacterial effect of the target 3,6-diazahomoadamantane derivatives **(4a-d)**. In 1 mL of DMSO, 20 mg of each tested compound were resolved. The inhibition zone

findings were compared to the reference antibiotic (Gentamycin) as a control drug. Table 1 show the inhibition zone of each tested compound.

Table 1a-The antibacterial activity of 3,6-diazahomoadamantane derivatives 1,2,3-4a-d

Bacteria Type	*Staphylococcus Aurous* (G+)	*Escherichia Coli* (G-)
Compound No.	*Inhibitory zone (diameter) (mm)*	
1	5	07
2	6	5
3	8	6
4a	7	8
4b	13	8
4c	12	9
4d	14	12
Gentamycin	9	7

Table 1b-The antibacterial activity of 3,6-diazahomoadamantane derivatives 1,2,3-4a-d

Bacteria Type	*Streptococcus mutants*	*Pseudomonas aeruginosa*
Compound No.	*Inhibitory zone (diameter) (mm)*	
1	5	06
2	4	5
3	8	7
4a	7	6
4b	14	10
4c	15	9
4d	14	12
Gentamycin	7	9

Conclusions

The preliminary antibacterial action of the target 3,6-diazahomoadamantane derivatives **(4a-d)**. showed promising antibacterial results against both types of bacteria. Most compounds appeared activity better than that of standard antibiotic. The prepared 3,6-diazahomoadamantane derivatives **(4a-d)** have good solubility in water due to presence of some polar substituents like hydroxyl, methoxy, carboxyl groups in addition of presence number of nitrogen atoms.

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REFERENCES

1. Štimac, A., Šekutor, M., Mlinarić-Majerski, K., Frkanec, L., and Frkanec, R., 2017, , *Molecules*, 22 (2), 297.
2. Savel'eva, S.A., Leonova, M.V., Baimuratov, M.R., and Klimochkin, Y.N., 2018, *Russ. J. Org. Chem.*, 54 (7), 996–1002.
3. . Ivleva, E.A., Tkachenko, I.M., and Klimochkin, Y.N.,2017, *Russ. J. Org. Chem.*, 52 (11), 1558–1564.
4. Suslov, E., Zarubaev, V.V., Slita, A.V., Ponomarev, K., Korchagina, D., Ayine-Tora, D.M., Reynisson, J., Volcho, K., and Salakhutdinov, N., 2017, , *Bioorg. Med. Chem. Lett.*, 27 (19), 4531–4535.
5. Hickmott, P.W., Wood, S., and Murray-Rust, P., 1985*J. Chem. Soc., Perkin Trans. 1*, 0, 2033–2038.
6. A. K. Jain, A. Vaidya, V. Ravichandran, S. K. Kashaw, and R. K. Agrawal, *Bioorganic and Medicinal Chemistry*, vol. 20, no. 11, pp. 3378-3395, 2012.
7. G. L. Arutyunyan, R. V. Paronikyan, G. S. Saakayan, A. D.Arutyunyan, K. A. Gevorkyan, *Pharm. Chem. J.* (*Engl. Transl.*),2008, 42, 18 [*Khim._Farm. Zh.*, 2008, 42, 20].
8. G. L. Arutyunyan, K. A. Gevorkyan, A. D. Arutyunyan, R. V.Paronikyan, G. M. Stepanyan, G. A. Panosyan, *Russ. J. Org.Chem.* (*Engl. Transl.*), 2014, 50, 1480 [*Zh. Org. Khim.*, 2014.50, 1494].
9. G. L. Arutyunyan, I. A. Dzhagatspanyan, I. M. Nazaryan, A. G.Akopyan, A. D. Arutyunyan, *Pharm. Chem. J.* (*Engl. Transl.*),2007, 41, 591 [*Khim._Farm. Zh.*, 2007, 41, 25].
10. Y. Sharabi_Ronen, S. Levinger, M. Ben_Dahan Lellouche,A. Albeck, *Med. Chem.*, 2014, 10, 27.

11. R. S. Dothager, K. S. Putt, B. J. Allen, B. J. Leslie, V. Nesteren_ko, P. J. Hergenrother, *J. Am. Chem. Soc*., 2005, 127, 8686.
12. I. Yamawaki, S. W. Bukovac, A. Sunami, *Chem. Pharm. Bull.*,1994, 42, 2365.
13. W. Brandt, S. Drosihn, M. Haurand, U. Holzgrabe, C. Nacht_sheim, *Arch. Pharm.*, 1996, 329, 311.
14. J. M. Barosa_Filho, J. R. Guedes da Silva Almeida, V. C. deOliveira Costa, E. V. da_Cunha, M. S. da Silva, R. Braz_Filho,*J. Asian Natural Prod. Res.*, 2004, 6, 11.
15. A. V. Ivachtchenko, A. Khvat, S. E. Tkachenko, Y. B. Sandu_lenko, V. Y. Vvedensky, *Tetrahedron Lett.*, 2004, 45, 6733.
16. A. Hassoun, P. K. Linden, and B. Friedman, *ritical Care,* vol. 21, no. 1, pp. 1-10, 2017.
17. A. Cheddie, S. A. Shintre, A. Bantho, C. Mocktar, and N. A. Koorbanally, , *Journal of Heterocyclic Chemistry*, vol. 57, no. 1, pp. 299-307, 2020.
18. A. I. Kuznetsov, R. T. Alasadi, I. M. Senan, T. M. Serova, *Russ. Chem. Bull.* (*Int. Ed.*), 2015, 64, 962.
19. RT Alasadi, VV Burmistrov, DA Pitushkin, AI Kuznetsov, GM Butov *Russ. J. Org. Chem.*, 2020, vol. 56, p. 749.
20. A. I. Kuznetsov, R. T. Alasadi, T. M. Serova T.M., *Russ. J. Org. Chem.*, 2015, vol. 51,p. 1593.
21. R. T. Alasadi, and Z. H. Abood, in *The 8th International Conference on Applied Science and Technology (ICAST 2019)*, Karbala, Iraq, . *AIP Conf. Proc.* 2144, 020006 (2019).
22. Kuznetsov, A.I., Senan, I.M., Shukkur, A.Kh., Azzheurova,I.A., and Serova, T.M., *Russ. J. Org. Chem.*, 2012, vol. 48,p. 119.
23. . Kuznetsov, A.I., Mazhed, G.M., and Serova, T.M., *Russ. J. Org. Chem.*,2010, vol. 46, p. 380.
24. Kuznetsov, A.I., Vladimirova, I.A., and Serova, T.M.,Moskovkin, A.S., *Khim. Geterotsikl. Soedin.*, 1992, p. 653.
25. Kuznetsov, A.I., Vladimirova, I.A., and Serova, T.M.,Moskovkin, A.S., *Khim. Geterotsikl. Soedin.*, 1992, p. 643.5. Kuznetsov, A.I., Barri, U., Mazhed, G., and Vladimirova,I.A., *Khim. Geterotsikl. Soedin.*, 1992, p. 1257.6. Kuznetsov, A.I., Barri, U., and Serova, T.M., *Khim. Geterotsikl. Soedin.*, 1993, p. 1405.
26. . Kuznetsov, A.I., Mazhed, G.M., and Serova, T.M., *Russ. J. Org. Chem.*,2016, vol. 52, p. 740.
27. R. T. Alasadi, I. O. Razenko V. V. Burakov, A. N. Proshin, T. M. Serova, and A. I. Kuznetsov *Russ. J. Org. Chem.*, 2016, vol. 52, p. 740.
28. R. Finn, "Theory of agar diffusion methods for bioassay", *Analytical Chemistry*, vol. 31, no. 6, pp. 975-977, 1959.