ALMASHINGAN 1,2,4-TRIAZOLLAR QATORIDA EPILEPSIYAGA QARSHI FAOLLIKGA EGA MODDALAR SINTEZ USULLARI VA ADABIYOTLAR TAHLILI

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Annotation. This work is devoted to the synthesis of substituted 1,2,4-triazole derivatives, confirmation of their structures by physicochemical methods, and investigation of their potential antiepileptic activity. Within the framework of the study, starting from 4-aminobenzoic acid derivatives, 5-(4-aminophenyl)-1,3,4-oxadiazole-2-thiol and its N-acyl derivatives were synthesized. These compounds were converted into the corresponding 1,2,4-triazole-3-thione derivatives through recyclization reactions in the presence of hydrazine hydrate. The synthesis processes were carried out with high yields, and it was established that the reaction efficiency depends on the length of the alkyl chain. The structures of the obtained compounds were confirmed using IR spectroscopy, ^{1}H NMR, and thin-layer chromatography. Comparison with literature data indicates that the synthesized triazole derivatives may exhibit antiepileptic activity.

Keywords. 1,2,4-triazole, 1,3,4-oxadiazole, hydrazine hydrate, epilepsy, heterocyclic compounds, synthesis, IR spectroscopy, ^{1}H NMR, triazole-3-thione.

Аннотация. Данная работа посвящена синтезу замещённых производных 1,2,4-триазола, подтверждению их структуры с использованием физико-химических методов, а также изучению их потенциальной противоэпилептической активности. В рамках исследования, начиная с производных 4-аминобензойной кислоты, были синтезированы 5-(4-аминофенил)-1,3,4-оксадиазол-2-тиол и его N-ацилированные производные.

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Указанные соединения в присутствии гидразингидрата подвергались реакциям рециклизации с образованием соответствующих производных 1,2,4-триазол-3-тиона. Синтетические процессы протекали с высокими выходами, при этом установлена зависимость эффективности реакции от длины алкильной цепи. Строение полученных соединений подтверждено методами ИК-спектроскопии, ^{1}H ЯМР и тонкослойной хроматографии. Сопоставление с литературными данными показало, что синтезированные производные триазола могут обладать противоэпилептической активностью.

Ключевые слова. 1,2,4-триазол, 1,3,4-оксадиазол, гидразингидрат, эпилепсия, гетероциклические соединения, синтез, ИК-спектроскопия, ^{1}H ЯМР, триазол-3-тион.

Annotatsiya. Mazkur ish almashingan 1,2,4-triazol hosilalarini sintez qilish, ularning tuzilishini fizik-kimyoviy usullar yordamida tasdiqlash hamda epilepsiyaga qarshi potensial faolligini o‘rganishga bag‘ishlangan. Tadqiqot doirasida 4-aminobenzoy kislota hosilalaridan boshlab, 5-(4-aminofenil)-1,3,4-oksadiazol-2-tiol va uning N-atsil hosilalari sintez qilindi. Ushbu birikmalar gidrazin gidrat ishtirokida qayta sikllanish reaksiyalari orqali tegishli 1,2,4-triazol-3-tion hosilalariga aylantirildi. Sintez jarayonlari yuqori chiqish bilan olib borildi hamda reaksiyaning unumdorligi alkil zanjir uzunligiga bog‘liqligi aniqlandi. Olingan birikmalarning tuzilishi IQ-spektroskopiya, ^{1}H YaMR va yupqa qatlamli xromatografiya yordamida tasdiqlandi. Adabiyot ma’lumotlari bilan solishtirilganda, sintez qilingan triazol hosilalari epilepsiyaga qarshi faollikka ega bo‘lishi mumkinligi ko‘rsatildi.

Kalit so‘zlar. 1,2,4-triazol, 1,3,4-oksadiazol, gidrazin gidrat, epilepsiya, geterotsiklik birikmalar, sintez, IQ-spektroskopiya, ^{1}H YaMR, triazol-3-tion.

Kirish.

Epilepsiya markaziy asab tizimining surunkali kasalliklaridan biri bo‘lib, u takrorlanuvchi tutqanoqlar bilan namoyon bo‘ladi. Jahon sog‘liqni saqlash tashkiloti ma’lumotlariga ko‘ra, dunyo bo‘yicha 50 milliondan ortiq inson epilepsiya bilan kasallangan. Mavjud antiepileptik preparatlarning (fenitoin, karbamazepin, valproat va boshqalar) qator nojo‘ya ta’sirlari, toksikligi hamda ayrim bemorlarda rezistentlik kuzatilishi yangi, samarali va xavfsiz dorilar yaratishni dolzarb masalaga aylantiradi.

So‘nggi yillarda azot qatori geterotsiklik birikmalar, xususan 1,2,4-triazollar farmatsevtik kimyoda katta qiziqish uyg‘otmoqda. Ushbu sinf birikmalari yuqori biologik faollik, past toksiklik va sintezning nisbatan qulayligi bilan ajralib turadi. Adabiyotlar tahlili. 1,2,4-triazol birikmalarining umumiy tavsifi.

1,2,4-triazol besh a’zoli geterotsiklik sistema bo‘lib, uchta azot atomini o‘z ichiga oladi. Ushbu yadroning mavjudligi molekulaga:

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elektron donor-akseptor xususiyat,
vodorod bog‘lari hosil qilish qobiliyati,

Almashingan 1,2,4-triazollar deganda triazol yadrosining 3-, 4- yoki 5-pozitsiyalarida turli radikallar (alkil, aril, geteril) bilan almashgan hosilalari tushuniladi. Tadqiqotlar shuni ko‘rsatadiki, aril va geteriaril guruhlar epilepsiyaga qarshi faollikni sezilarli oshiradi [1].

Eng ko‘p qo‘llaniladigan usullardan biri — karboksil kislota gidrazidlari **va** nitrillar asosida triazol halqasini hosil qilishdir. Ushbu usul yuqori chiqish (60–85 %) bilan ajralib turadi [2]. Bu usulda gidrazin hosilalari va ortoefirlar reaksiyaga kiritilib, 1,2,4-triazol yadrosi shakllantiriladi. Afzalligi:
yumshoq sharoit, kam bosqichli jarayon.
Zamonaviy sintez yondashuvlari
So‘nggi yillarda:
mikroto‘lqinli sintez, ultratovushli aktivatsiya, yashil kimyo usullari keng joriy etilmoqda. Bu usullar energiya tejamkorligi va ekologik xavfsizligi bilan ajralib turadi [3].

Farmakologik xususiyatlari. 1,2,4-triazol hosilalari quyidagi faolliklarni namoyon etadi:

antimikrob, antifungal, yallig‘lanishga qarshi, antidepressant, antikonvulsant.

Epilepsiyaga qarshi faollikka ega 1,2,4-triazol hosilalari [4]. Tadqiqotlar shuni ko‘rsatadiki:
lipofillikning oshishi (qon-miya to‘sig‘i)dan o‘tishni yaxshilaydi,
galogenli substituentlar faollikni kuchaytiradi,
aromatik halqalarning mavjudligi antikonvulsant ta’sirni oshiradi.

Ko‘plab 1,2,4-triazol hosilalari faollik testida fenitoindan kam bo‘lmagan faollik ko‘rsatgan.

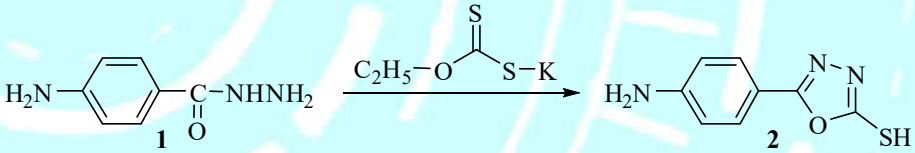
Modda olish texnologiyasi. Laboratoriya miqyosidan sanoat miqyosiga o‘tishda quyidagilar muhim: reaksiya chiqishini oshirish, erituvchilarni qayta ishlatish, kristallanish jarayonini optimallashtirish.
Dori shakllari. 1,2,4-triazol hosilalari:
tabletka,
kapsula,
suspenziya ko‘rinishida ishlab chiqilishi mumkin. Ularning barqarorligi va biofoydalanish ko‘rsatkichi yuqori ekanligi aniqlangan. 5-(p-aminofenil)- 4-amino-1,2,4-Triazol-3(2H)-tion sintez qilish usullar bosqichlari keltirib o’tildi [5].

Tubi yumaloq 2 l kolbaga 512 gr benzokain $C_9H_{11}O_2N$ va 800 ml 64% li gidrazingidrat N_2H_4 :H_2O solib 115^0C da 6 soat davomida reaksiya olib borildi. Reaksiya tugagach sovitilganda reaksiya maxsuloti oq kristal bo’lib cho’kmaga

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tushadi, maxlsulot filtrlab dis suv bilan yuvib quritib olinadi. Maxsulot 4-aminobenzogidrazin (450 gr) 93,7% unum bilan olindi.

Tubi yumaloq 4 l kolbaga 423,2 gr 4-aminobenzogidrazin, 448 gr etilksantaginatkaliy C_2H_5OCSSK (1:1 nisbatda 2,8 mol), 2,5 l etil spirt va 600 ml suv solib 78^0C da 8 soat reaksiya olib borildi. So'ngra etil spirit haydab olinib reaksiya sovitildi. Sovugan reaksiya maxsulotiga 500 ml suv qo'shildi va 14%li HCl bilan och sariq rangli 5-(4-aminofenil)-1,3,4-oksadiazol-2-tiol cho'ktirib olindi keyin filtrlab dis suvda yuvib quritib olindi. 478 gar maxsulot 88,5% unum bilan olindi. Benzol:metanol (5:1) sistemasida R_f=0,6. Suyuqlanish temperaturasi 235^0C.

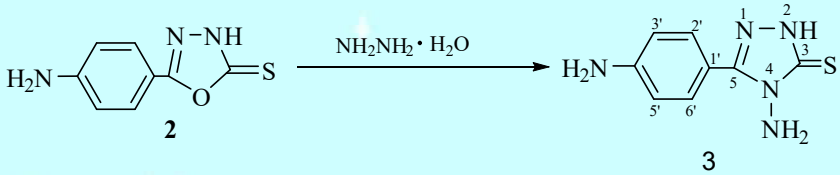


(2) 5-(4-aminofenil)-1,3,4-oksadiazol-2-tiol

ИК-spektr, ν, см –1: 3350 (NH2); 3063 (NH), 1348 (C=S), 1170 (C-O-C). UF spektr, λmax, нм. 261, 318 [6].

5-(p-aminofenil)- 4-amino-1,2,4-Triazol-3(2H)-tion sintezi

Ikki og'izli tubi yumaloq kolbaga 5-(p-aminofenil)-1,3,4-oksadiazol-2-tion va 80% li gidrazingidrat ($NH_2NH_2 \cdot H_2O$) solib moy hammomida qizdirilib reaksiya mexanik meshalkada aralashtirib turgan holatda olib borildi. Reaksiya tugagandan so'ng sovitilib, muz solingan stakanga solinib ustiga $HCl_{(suyultitilgan)}$ tomchilatib qo'shilib aralashtirib turgan holatda p^H neytralga keltiriladi. 225 ml HCl sraflandi. Neytrallash jarayonida oq cho'kma tushishni boshlaydi. Neytrallanganda to'liq 5-(p-aminofenil)- 4-amino-1,2,4-Triazol-3(2H)-tion hosil bo'ladi. Cho'kma filtrlab olinib dis suvda yuvib quritiladi. Hosil bo'lgan maxsulot yupqa qatlamli xromatografiyada xloroform:metanol (10:1) sistemasida tekshirilganda R_f=0,67 da hosil bo'ldi. Suyuqlanish harorati $241\text{-}242^0$C.



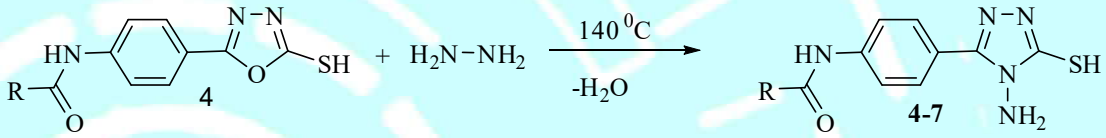
IK-spektr, ν, sm–1; 3351 (NH2-Ar), 3268 (N-NH2). UF-spektr, λmax, 292 нм.

Triazol xosilalari sintezi. *p*-aminobenzoy kislota gidrazidini kaliy etilksantogenat bilan reaksiyasi olib borilib 5-(4-aminfenil)-1,3,4-oksadiazol-2-tiol sintezi amalga oshirilgan. Sitez qilingan 5-(4-aminfenil)-1,3,4-oksadiazol-2-tiolni karbon kislota angidridlari bilan reaksiyasi natijasida hosilalar olingan [7,8].

Sintez qilingan N-atsil birikmalarni gidrazin gidrat ishtirokida reaksiyalari ilgari o'rganilmagan. Ushbu ishda olingan N-atsil hosilalar gidrazin gidrat

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ishtirokida reaksiyasi olib borildi va tegishli 1,2,4-triazol (**4-7**) hosilalari sintez qilindi.



R= CH_3 (**5**), CH_2CH_3 (**6**), $CH_2CH_2CH_3$ (**7**)

Raksiya dastlab N-(4-(5-merkapto-1,3,4-oksadiazol-2-il)fenil)asetamid (**1**) bilan gidrazin gidrat ishtrokida 140 °C haroratda olib borilganda 85% unum bilan N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-yl)fenyl)atsetamid (**4**) olingan, metilen guruhi soni oshib borishi bilan mos ravishda N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-yl)fenyl)propionamid (**5**) 74,3 % unum bilan olingan, N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-yl)fenyl)butiramid (**6**) 55,8 % unumni tashkil qilgan. Ta'kidlash joizki usbu reaksiylar 1,3,4-oksadiazol molekulasida metilen guruhi soni oshib borishi (atsetamid, propionamid, butiramid) bilan reaksiya unumi kamayib borgan (1-jadval), olingan natijalar adabiyot ma'lumotlariga mos keladi. va **4**-moddalarning unumini oshirish mumkin, buning uchun albatta reaksiyani olib borish sharoiti o'zgartirishni talab qiladi. Olingan (**4-7)** moddalarning tuzilishi IQ va ^{1}H YaMR spektr usullari yordamida tasdiqlandi [9,10].

N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-il)fenyl)atsetamid (5) sintezi: Kolbaga 0,1 g N-(4-(5-merkapto-1,3,4-oksadiazol-2-il)fenil)asetamid va 2 ml 80% li gidrazin gidrat solindi. Reaksiya 140 °C haroratda 8 soat davomida olib borildi. Reaksiya tugagach 12 soat xona haroratida qoldirildi. Shundan so'ng 0 °C da sekinlik bilan sirka kislotasi qo'shildi. Natijada oq rangli cho'kma tushdi 85% unum bilan (**1)** modda olindi. ^{1}H NMR (600 MHz, DMSO-d_6+CCl_4, δ, ppm, *J*/Hz): 2.16 (3H, *s*, CH_3-15), 5.67 (2H, *s*, NH_2-17), 7.63 (1H, *t, J*=1.8, H-3), 7.65 (1H, *t, J*=1.8, H-5), 8.01 (1H, *t, J*=1.8, H-2), 8.02 (1H, *t, J*=1.8, H-6), 9.16 (1H, *s*, NH-12). IK N–H 3300–3500 cm^{-1}, O–C=O 1640–1690 cm^{-1}, Aromatik C–H: 3030 cm^{-1}, Aromatik C=C: 1500–1600 cm^{-1}, C–N 1200–1350 cm^{-1}, S–H: 2550–2600 cm^{-1}, C–S: 650–750 cm^{-1} [11,12].

N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-il)fenyl)propionamid (6): sintezi: 0,1 g N-(4-(5-merkapto-1,3,4-oksadiazol-2-il)fenil)propianamid va 2 ml 80% li gidrazin gidrat solindi. Reaksiya 140 °C haroratda 8 soat davomida olib borildi. Reaksiya tugagach 12 soat xona haroratida qoldirildi. Shundan so'ng 0 °C da sekinlik bilan sirka kislotasi qo'shildi. Natijada oq rangli cho'kma hosil bo'lib, 74,3% unum bilan triazol (**3**) olinadi. ^{1}H NMR (600 MHz, DMSO-d_6+CCl_4, δ, ppm, *J*/Hz): 1.46 (3H, *t*, *J*=8.4, CH_3-18), 2.4 (2H, *q*, *J*=9, CH_2-15), 5.67 (2H, *s*, NH_2-17), 7.61 (1H, *t, J*=1.8, H-3), 7.63 (1H, *t, J*=1.8, H-5), 8.01 (1H, *t, J*=1.8, H-2), 8.01 (1H, *s*, NH-12), 8.02 (1H, *t, J*=1.8, H-6). IK 3300–3500 cm^{-1} N–H Triazolga

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ulangan –NH_2, 2550–2600 cm^{-1} S–H, 2970–2880 cm^{-1} Alifatik C–H (CH_2-CH_3), 3030 cm^{-1}, Ar C–H, 1640–1680 cm^{-1} C=O, 1500–1600 cm^{-1} Ar C=C, 1450–1550 cm^{-1} N–N, C=N, 1300–1350 cm^{-1} C–N, 1200–1250 cm^{-1} Ar–N va N–N, 650–750 cm^{-1} — C–S, 750–870 cm^{-1} — Ar C–H [13-16].

N-(4-(4-amino-5-merkapto-4H-1,2,4-triazol-3-il)fenyl)butiramid sintezi (7) sintezi: 3. 0,1 g N-(4-(5-merkapto-1,3,4-oksadiazol-2-il)fenil)butilamid va 2 ml 80% li gidrazin gidrat solindi. Reaksiya 140 °C haroratda 8 soat davomida olib borildi. Reaksiya tugagach 12 soat xona haroratida qoldirildi. Shundan so‘ng 0 °C da sekinlik bilan sirka kislotasi qo‘shildi. Natijada oq rangli cho‘kma hosil bo‘lib, 55,8% unum bilan triazol olinadi. Agar 80 % dan past konsentratsiyadagi gidrazin gidrat ishlatilsa, reaksiya unumining kamayishi kuzatiladi. ^{1}H NMR (600 MHz, DMSO-d_6+CCl_4, δ, ppm, J/Hz): 0.96 (3H, t, J=9, CH_3-19), 2.02 (2H, m, CH_2-18), 2.24 (2H, t, J=7.8, CH_2-15), 5.67 (2H, s, NH_2-17), 7.61 (1H, t, J=1.8, H-3), 7.63 (1H, t, J=1.8, H-5), 8.01 (1H, t, J=1.8, H-2), 8.02 (1H, t, J=1.8, H-6), 8.42 (1H, s, NH-12). IK spektrida funksional guruhlarga xos bo‘lgan quyidagi asosiy yutilish chiziqlari kuzatildi. 3300–3500 sm^{-1} N–H, 2550–2600 sm^{-1} (S–H). 2970–2860 sm^{-1} C–H , 1640–1680 sm^{-1}(C=O), Ar C=C 1500–1600 sm^{-1}, Triazol halqasidagi C=N, N–N 1450–1550 sm^{-1}, 1200–1300 sm^{-1} , C–N 1280–1350 sm^{-1}, C–S 650–750 sm^{-1}, . Ar C–H 750–870 sm^{-1}[17-19] .

Olingan triazol moddasining texnalogiyasi ham ishlab chiqildi. Keyingi ishlarimiz maqolalarida texnalogiyasini batafsil yoritamiz.

Xulosa. Ushbu tadqiqotda almashingan 1,2,4-triazol hosilalarini sintez qilishning samarali usullari ishlab chiqildi va ularning kimyoviy tuzilishi zamonaviy fizik-kimyoviy tahlil usullari yordamida ishonchli tarzda tasdiqlandi. 5-(4-aminofenil)-1,3,4-oksadiazol-2-tiol asosida olingan N-atsil hosilalarning gidrazin gidrat bilan qayta sikllanishi natijasida bir qator yangi 1,2,4-triazol-3-tion hosilalari sintez qilindi. Reaksiya unumining alkil zanjiri uzunligi ortishi bilan kamayishi aniqlanib, bu holat adabiyot ma’lumotlari bilan mos kelishi ko‘rsatildi. Sintez qilingan birikmalarning fizik-kimyoviy xossalari ularning biologik faol moddalar sifatida istiqbolli ekanligini tasdiqlaydi. Adabiyot tahlili asosida ushbu triazol hosilalarining epilepsiyaga qarshi faollik namoyon etish ehtimoli yuqori ekanligi aniqlanib, kelgusida ularni farmakologik sinovlardan o‘tkazish maqsadga muvofiq deb topildi. Olingan natijalar yangi avlod antiepileptik preparatlarini yaratishda muhim ilmiy-amaliy ahamiyatga ega.

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