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### ACHE VA BCHE INHIBITORLARI SIFATIDA YANGI IZOKSAZOL HOSILALARINING SINTEZI

Аннотация

Ushbu tadqiqot deoksivazitsinon va xinazolinonning izosterik analoglari sifatida trisiklik izoksazol hosilalarini yaratishni taqdim etadi. Yangi yaratilgan birikmalarning tuzilmalari tegishli fizik-kimyoviy va spektral tahlillar orqali tekshirildi. Sintez qilingan birikmalarning atsetilxolinesteraza (AChE) va butirilxolinesteraza (BChE) fermentlariga ingibitiv ta'siri molekulyar doking tadqiqotlari orqali baholandi. Doking tahlili shuni ko'rsatdiki, **5c** va **5d** birikmasi atsetilxolinesteraza uchun eng yuqori bog'lanish yaqinligini, **5e** birikmasi esa butirilxolinesteraza uchun eng muhim bog'lanish potentsialini namoyish etdi.

**Kalit so'zlar:** Izoksazolo-pirimidinon, laktam, sintez, kondensatsiya, atsetilxolinesteraza, butirilxolinesteraza, molekulyar doking.

### СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ ИЗОКСАЗОЛА КАК ВЫСОКОЭФФЕКТИВНЫХ ИНГИБИТОРОВ АСНЕ И ВСНЕ

Аннотация

Данное исследование посвящено получению трициклических производных изоксазола, являющихся изостерическими аналогами дезоксивазацинона и хиназолинона. Структуры синтезированных соединений были подтверждены соответствующими физико-химическими и спектральными методами анализа. Ингибирующее действие синтезированных соединений в отношении ферментов ацетилхолинэстеразы (AChE) и бутирилхолинэстеразы (BChE) было изучено с использованием методов молекулярного докинга. Анализ результатов докинга показал, что соединение **5c** и **5d** проявило наибольшую аффинность связывания с ацетилхолинэстеразой, тогда как соединение **5e** продемонстрировало наибольший потенциал связывания с бутирилхолинэстеразой.

**Ключевые слова:** изоксазол-пиримидинон, лактам, синтез, конденсация, ацетилхолинэстераза, бутирилхолинэстераза, молекулярный докинг.

### SYNTHESIS OF NOVEL ISOXAZOLES AS POTENT ACHE AND BCHE INHIBITORS

Annotation

This research presents the creation of tricyclic isoxazole derivatives as isosteric counterparts of deoxyvasicinone and quinazolinone. The structures of the newly created compounds were verified through relevant physicochemical and spectral analyses. The inhibitory effects of the synthesized compounds on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were assessed through molecular docking studies. Docking analysis indicated that compound **5d** and **5c** exhibited the highest binding affinity for acetylcholinesterase, while compound **5e** displayed the most significant binding potential for butyrylcholinesterase.

**Keywords:** Isoxazolo-pyrimidinone, lactam, synthesis, condensation, acetylcholinesterase, butyrylcholinesterase, molecular docking.

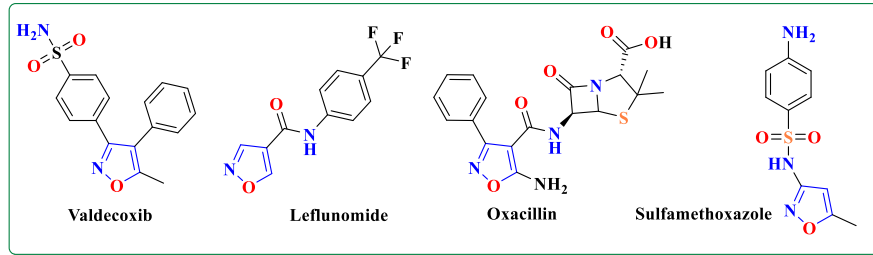
**Kirish.** Altsgeymer kasalligi markaziy asab tizimining surunkali va progressiv kechuvchi neyrodegenerativ xastaligi bo'lib, demensiyaning eng keng tarqalgan shakli hisoblanadi. Ushbu kasallik xotira, tafakkur va nutqning buzilishi hamda kundalik faoliyatni bajarish qobiliyatining pasayishi bilan tavsiflanadi. Aholining umr ko'rish davomiyligi ortib borayotgani sababli u global sog'liqni saqlash tizimi uchun dolzarb muammoga aylanmoqda.

Kasallik patogenezida  $\beta$ -amiloid plitalarining to'planishi, tau-oqsilining giperfosforlanishi, oksidlovchi stress va neyroinflammasiya muhim o'rin tutadi. Shuningdek, xolinergik gipotezaga ko'ra, bosh miyada atsetilxolin miqdorining kamayishi kognitiv funksiyalarning buzilishiga olib keladi. Shu sababli atsetilxolinning parchalanishiga mas'ul bo'lgan atsetilxolinesteraza (AChE) va butirilxolinesteraza (BChE) fermentlari muhim terapevtik nishon hisoblanadi.

AChE sinaptik yoriqda atsetilxolinni parchalaydi, BChE esa kasallikning kechki bosqichlarida faolligi ortib, patologik jarayonlarda ishtirok etadi. Mazkur fermentlarni ingibirlovchi moddalar atsetilxolin miqdorini oshirib, kognitiv funksiyalarni yaxshilaydi. Shu bois AChE va BChE ingibitorlarini yaratish zamonaviy farmatsevtika kimyosi va tibbiyotining muhim ilmiy yo'nalishlaridan biri hisoblanadi.

**Adabiyotlar tahlili.** Hozirgi zamon dorivor moddalar kimyosining ustuvor yo'nalishlaridan biri — tabiiy alkaloidlarning bioizosterik analoglarini maqsadli sintez qilish va ularning biologik faollik spektrini o'rganishdan iborat. Tabiatda keng tarqalgan xinazolin-4-on hosilalari o'zining saratonga qarshi[1], mikroblarga[2,3], zamburug'larga qarshi[4], qandli diabetga qarshi[5,6], yallig'lanishga qarshi[7,8], antikonvulsant[9,10], viruslarga qarshi[11,12] va silga qarshi[13,14] yuqori faolligi bilan farmatsevtika sohasida alohida o'rin tutadi. Biroq, ko'plab xinazolinon asosidagi dori vositalarining yuqori toksikligi va past eruvchanligi ularning klinik qo'llanilishida muayyan cheklovlarni yuzaga keltirmoqda. Ushbu tadqiqotda asosiy e'tibor izoksazol yadrosi bilan kondensirlangan yangi trisiklik pirimidinon tizimlarini yaratishga qaratilgan. Izoksazol halqasi o'zining o'ziga xos elektron

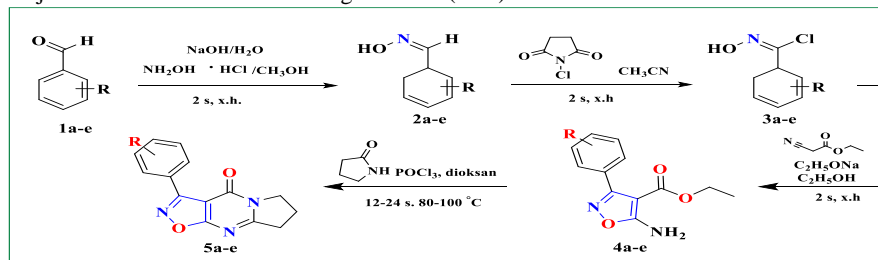
xususiyatlari, vodorod bog'larini hosil qilish qobiliyati va metabolik barqarorligi tufayli ko'plab samarali farmakologik agentlarning (masalan, *valdekoksib*, *leflunomid*, *oksatsillin*, *sulfometoksazol*) tarkibiy qismi hisoblanadi.



### 1-rasm. Izoksazol hosilalari asosidagi zamonaviy dori vositalarining kimyoviy tuzilishi.

Bugungi kunda izoksazolo[5,4-*d*]pirimidin-4-on yoki uning izomerik tizimlarini o'z ichiga olgan FDA tomonidan tasdiqlangan tayyor dori vositalari xalqaro farmatsevtika bozorida mavjud bo'lmasa-da, ushbu karkas dorivor moddalar dizaynida yuqori istiqbolga ega. Mazkur tizimlar dezoksivazitsinon va makinazolinon kabi tabiiy xinazolinon alkaloidlarining funksional analoglari (biozosterlari) hisoblanib, nazariy jihatdan yuqori terapevtik potentsial va past toksiklik namoyon qilishi kutilmoqda.

**Tajribaviy qism.** Uch halqali izoksazolo[5,4-*d*]pirimidinon hosilalari 4 bosqichda olib borildi. Boshlang'ich modda sifatida turli xil o'rinbosarli aromatik aldegidlardan foydalanildi. Birinchi bosqichda benzaldegid **1a** (uning hosilasi (**1b-e**)) metanolda eritilib, ishqor hamda gidroksilamingidroxloridi bilan xona haroratida reaksiyaga kiritirildi. 2 soat davomida olib borilgan reaksiya natijasida benzaldoksim **2a** va uning hosilalari (**2b-e**) olindi.



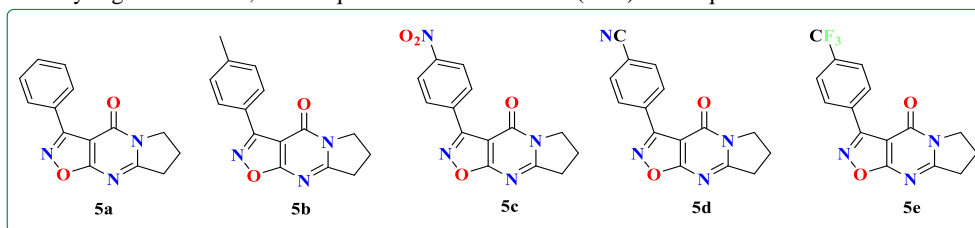
### 1-sxema: 3-aryl-7,8-digidroizoksazolo[5,4-*d*]pirrolo[1,2-*a*]pirimidin-4(6H)-onlar sintezi.

Ushbu birikmalarning (**2a-e**) atsetonitril muhitida *N*-xlorsuksinimid bilan reaksiyasi olib borilib, turli o'rinbosarli benzaldoksimxloridlar (**3a-e**) hosil qilindi. Uchinchi bosqichda etilsiyanoatsetat spirtli muhitda **3a-e** birikmalar bilan intramolekulyar sikllanishga uchrab, turli o'rinbosarli 5-amino-3-aryl-izoksazolo-4-karbon kislota etil efiri (**4a-e**) ni hosil qildi.

#### Reaksiya sharoitlarini muqobillashtirish:

№	Asos	Erituvchi	Harorat	Vaqt	Unum, %
1	TEA	Ksilol	140 °C	2 soat	36
2	TEA	Ksilol	140 °C	4 soat	41
3	TEA	Toluol	120 °C	2 soat	57
4	TEA	Toluol	120 °C	4 soat	43
5	TEA	1,4-dioksan	80 °C	2 soat	92
6	TEA	1,4-dioksan	110 °C	4 soat	56

So'nggi bosqichda **4a-e** birikmalar siklik laktam pirrolidon-2 bilan fosforoksi xlorid yordamida dioksan muhitida kondensatsiya reaksiyasiga kiritirilib, uch halqali izoksazol birikmalari (**5a-e**) sintez qilindi.



### 2-sxema: 5a-e birikmalarining srtuktur tuzilishi.

Har bir bosqich so'ngida reaksiyon aralashma 3 marta dixlormetan bilan ekstraksiya qilindi va organik qism quritildi. Filtrlandi va erituvchi past bosim ostida haydaldi. Yakuniy toza mahsulot olish uchun ustunli xromatografiya usuli qo'llanildi.

1-jadval.

#### Olingan birikmalarning ba'zi fizik kimyoviy kattaliklari

Moddalar	Brutto formulasi	R	Unum, %	T <sub>Suy3</sub> , °C	Mahsulot rangi
5a	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub>	H	18	210-211	oq
5b	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub>	4-Me	13	184-185	oq
5f	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> O <sub>4</sub>	4-NO <sub>2</sub>	7	265-266	sarg'ish
5g	C <sub>15</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub>	4-CN	8	197-198	oq
5h	C <sub>15</sub> H <sub>10</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub>	4-CF <sub>3</sub>	14	212-213	oq

**Natijalar va ularning muhokamasi.** Olingan ma'lumotlarga ko'ra, barcha sintez qilingan birikmalar ikkala fermentning faol markazlari bilan barqaror komplekslar hosil qilishi aniqlandi. Xususan, atsetilxolinesteraza fermentiga nisbatan eng yuqori yaqinlik **4a** moddasida kuzatildi (-7.478 kkal/mol).

#### 1-jadval.

Sintez qilingan birikma(5a-e)larning doking tadqiqot natijalari:

#	Modda	5a	5b	5c	5d	5e
Bog'lanish potentsiali, $\Delta$ kkal/mol	AChE	-6.785	-6.827	-7.022	-7.478	-6.860
	BChE	-5.641	-4.446	-5.850	-4.833	-7.944

Bu ko'rsatkich ushbu molekulaning fermentning katalitik va periferik bog'lanish joylari bilan kuchli vodorod bog'lari va  $\pi$ - $\pi$  tutashish ta'sirlashuvlariga kirishishidan dalolat beradi.

Boshqa tomondan, butirilxolinesteraza fermenti bilan bog'lanish energiyasini tahlil qilganda, **5a** birikmasi rekord darajadagi eng past energiya qiymatini (-7.944 kkal/mol) ko'rsatdi. Bu natija **5a** moddasining butirilxolinesteraza fermenti uchun yuqori selektivlikka ega ekanligini va uni Alsgeymer kasalligi kabi neyrodegenerativ holatlarni davolashda potentsial ingibitor sifatida qarash mumkinligini tasdiqlaydi. Shuningdek, **3a** moddasi ikkala ferment uchun ham bir xil darajadagi o'rtacha faollikni (-7.022 va -5.850 kkal/mol) namoyon qilishi bilan ajralib turadi. Umuman olganda, izoksazol yadrosining pirimidinon tizimi bilan kondensirlanishi molekulaning fermentativ nishonlar bilan komplementarligini sezilarli darajada oshirgan.

**Xulosa.** Yangi yaratilgan birikmalarning tuzilmalari tegishli fizik-kimyoviy va spektral tahlillar orqali tekshirildi. Sintez qilingan birikmalarning atsetilxolinesteraza (AChE) va butirilxolinesteraza (BChE) fermentlariga ingibitiv ta'siri molekulyar doking tadqiqotlari orqali baholandi. Doking tahlili shuni ko'rsatdiki, **5c** va **5d** birikmalari atsetilxolinesteraza uchun eng yuqori bog'lanish yaqinligini, **5e** birikmasi esa butirilxolinesteraza uchun eng muhim bog'lanish potentsialini namoyish etdi. Ushbu tadqiqotda olingan natijalar, izoksazol saqlagan yangi trisiklik tizimlar asosida samaradorligi yuqori va nojo'ya ta'siri kam bo'lgan yangi avlod dori vositalarini yaratish uchun ilmiy poydevor bo'lib xizmat qilishi mumkin.

#### ADABIYOTLAR

- M.K. Krapf, J. Gallus, M. Wiese, Synthesis and biological investigation of 2, 4- substituted quinazolines as highly potent inhibitors of breast cancer resistance protein (ABCG2), *Eur. J. Med. Chem.* 139 (2017) 587–611
- Qureshi SI, Chaudhari HK. Design, synthesis, in-silico studies and biological screening of quinazolinone analogues as potential antibacterial agents against MRSA. *Bioorg. Med. Chem.* 2019,15;27(12):2676–88.
- Ankireddy AR, Syed R, Gundla R, Manasa KL, Reddy CV, Yatam S, Paidikondala K. Kumada cross coupling reaction for the synthesis of quinazoline derivatives, evaluation of their antibacterial activity and docking studies. *Russ. J. Gen. Chem.* 2019 Dec;89:2544–57.
- Abuelizz HA, Bakheit AH, Al-Agamy MH, Rashid H, Mostafa GA, Al-Salahi R. Benzo [g] quinazolines as antifungal against candidiasis: screening, molecular docking, and QSAR investigations. *Saudi Pharm.* 2023,1;31(6):815–23.
- Safapoor S, Halimi M, Ghomi MK, Noori M, Dastyafteh N, Javanshir S, Hosseini S, Mojtavavi S, Faramarzi MA, Nasli-Esfahani E, Larijani B. Synthesis, ADMT prediction, and in vitro and in silico  $\alpha$ -glucosidase inhibition evaluations of new quinoline–quinazolinone–thioacetamides. *RSC Adv.* 2023;13(28):19243–56.
- Metwally K, Pratsinis H, Kletsas D, Quattrini L, Coviello V, Motta CL, El-Rashedy AA, Soliman ME. Novel quinazolinone-based 2, 4-thiazolidinedione-3-acetic acid derivatives as potent aldose reductase inhibitors. *Future Med. Chem.* 2017, 1;9 (18):2147-66.
- Bonacorso HG, Rosa WC, Oliveira SM, Brusco I, Dalla Pozza CC, Nogara PA, Wiethan CW, Rodrigues MB, Frizzo CP, Zanatta N. Synthesis and antinociceptive activity of new 2-substituted 4-(trifluoromethyl)-5, 6-dihydrobenzo [h] quinazolines. *Bioorg. Med. Chem. Lett.* 2016, 1;26(19):4808-14.
- Smith GF, Altman MD, Andresen B, Baker J, Brubaker JD, Chen H, Chen Y, Childers M, Donofrio A, Ferguson H, Fischer C. Identification of quinazoline based inhibitors of IRAK4 for the treatment of inflammation. *Bioorg. Med. Chem. Lett.* 2017, 15;27(12):2721-6.
- Guerrini G, Ciciani G, Crocetti L, Daniele S, Ghelardini C, Giovannoni MP, Iacovone A, Di Cesare Mannelli L, Martini C, Vergelli C. Identification of a new pyrazolo [1, 5-a] quinazoline ligand highly affine to  $\gamma$ -aminobutyric type A (GABAA) receptor subtype with anxiolytic-like and antihyperalgesic activity. *J. Med. Chem.* 2017, 14;60(23):9691-702.
- Mohamed T, Rao PP. 2, 4-Disubstituted quinazolines as amyloid- $\beta$  aggregation inhibitors with dual cholinesterase inhibition and antioxidant properties: Development and structure-activity relationship (SAR) studies. *Eur. J. Med. Chem.* 2017, 27;126:823–43.
- Held FE, Guryev AA, Frohlich T, Hampel F, Kahnt A, Hutterer C, Steingruber M, Bahsi H, von Bojnićić-Kninski C, Mattes DS, Foertsch TC. Facile access to potent antiviral quinazoline heterocycles with fluorescence properties via merging metal-free domino reactions. *Nat. Commun.* 2017, 2;8(1):15071
- Zhao J, Zhang Y, Wang M, Liu Q, Lei X, Wu M, Guo S, Yi D, Li Q, Ma L, Liu Z. Quinoline and quinazoline derivatives inhibit viral RNA synthesis by SARS-CoV-2 RdRp. *ACS infectious diseases.* 2021, 26;7(6):1535-44.
- Laleu B, Akao Y, Ochida A, Duffy S, Lucantoni L, Shackelford DM, Chen G, Katneni K, Chiu FC, White KL, Chen X. Discovery and structure–activity relationships of quinazolinone-2-carboxamide derivatives as novel orally efficacious antimalarials. *J. Med. Chem.* 2021, 26;64(17):12582-602.
- Dutta A, Sarma D. Recent advances in the synthesis of Quinazoline analogues as anti-TB agents. *Tuberculosis* 2020, 1;124:101986.