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NEUROPSYCHOTROPIC ACTIVITY OF 1,2,4-TRIAZOLE DERIVATIVES

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ABOUT ARTICLE

Key words: 1,2,4-triazole derivatives, anticonvulsants, anxiolytics, antidepressants, hypnotics, neurodegenerative diseases and antimigrenous activity

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Abstract: This review article summarizes data from various literature on the various neuropsychotropic activity of 1,2,4-triazole derivatives, which are currently used in medical practice and in recent years are at the stage of preclinical studies. The dependence of their biological activity on the structure and mechanisms of action of various mediators and ion channels is substantiated.

1,2,4-TRIAZOL HOSILALARINING NEYROPSIXOTROP FAOLLIGI

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MAQOLA HAQIDA

Kalit so'zlar: 1,2,4-triazol hosilalari, antikonvulsant, anksiolitik, antidepressant, uyqu chaqiruvchi, neyrodegenerativ kasalliklarga qarshi va migrenga qarshi faolligi

Annotatsiya: Ushbu tahliliy maqolada turli adabiyot ma’lumotlari asosida hozirgi kunda tibbiyot amaliyotida qo‘llanilib kelinayotgan va so‘nggi yillarda klinik oldi tekshiruvlar bosqichidagi 1,2,4-triazol hosilalarining turli xil neyropsixotrop faolliklari haqidagi ma’lumotlar umumlashtirilgan. Biologik faolliklarini ularning strukturaga va ta’sir mexanizmlarini

turli xil mediator hamda ion kanallariga bog‘liqligi asoslantirilgan.

НЕЙРОПСИХОТРОПНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ 1,2,4-ТРИАЗОЛА

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О СТАТЬЕ

Ключевые слова: производные 1,2,4-триазола, противосудорожные, анксиолитические, антидепрессивные, снотворную, нейродегенеративные заболевания и противомигренозная активность

Аннотация: В данной обзорной статье на основе из различной литературы обобщены данные о различной нейропсихотропной активности производных 1,2,4-триазола, которые в настоящее время используются в медицинской практике и в последние годы находятся на стадии доклинических исследований. Обоснована зависимость их биологической активности от структуры и механизмов действия различных медиаторов и ионных каналов.

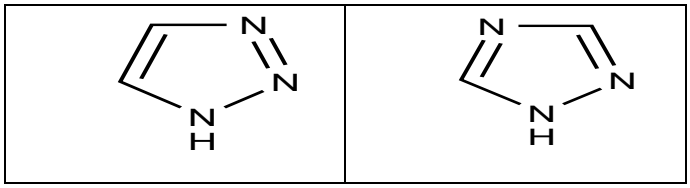
KIRISH

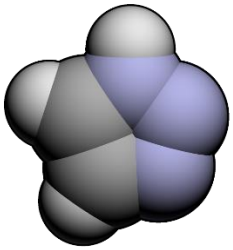
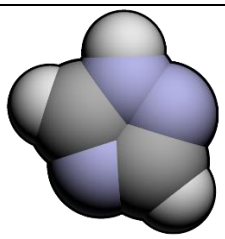
Triazollar birinchi marta 1818 yilda Lui Brugnatelli tomonidan ajratib olingan. Bu guruhga triazol nomi nemis kimyogari, guruhning birinchi sintezini amalga oshirgan J.A. Bladin tomonidan 1855-yilda berilgan [12].

ASOSIY QISM

Triazollar – geterosiklik organik birikmalarning ikkita uglerod va uchta azot tutgan besh a’zoli vakillaridir. Brutto-formulasi $C_2H_3N_3$, molekulyar masssasi 69,06 ni tashkil qiladi. Triazlollarning halqadagi azot atomi holatiga qarab ikki xil izomeri mavjud bo‘lishi mumkin, bular: 1,2,3-triazol (vitsinal triazol) va 1,2,4-triazol (simmetrik triazol) [49] (1-rasm).

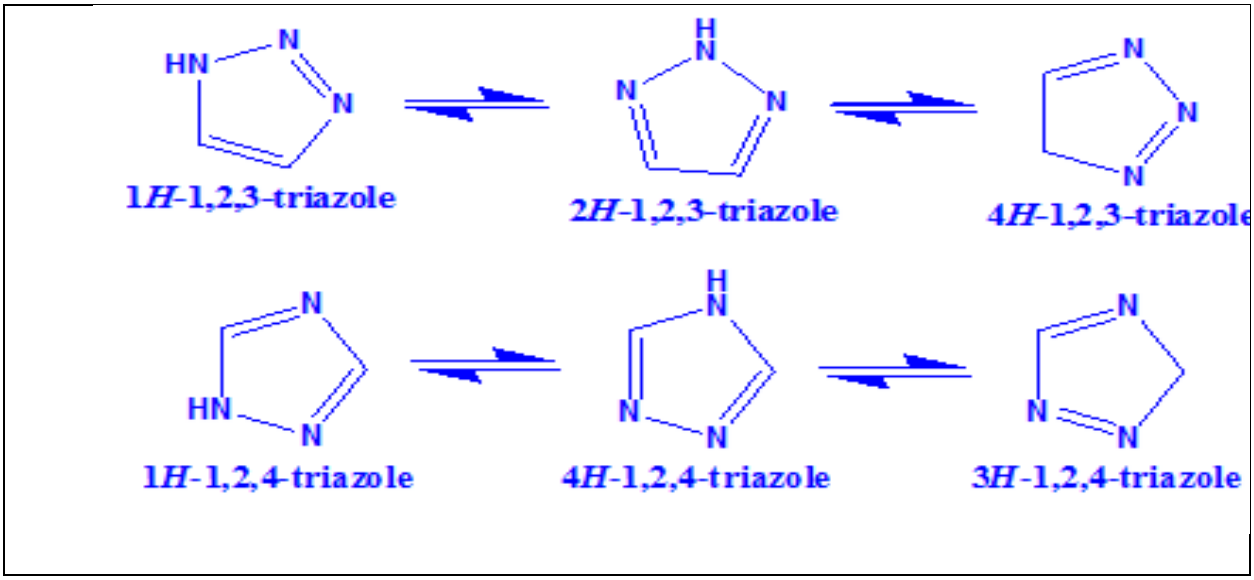
1-rasm. Triazol halqasining izomerlari



	
1,2,3-triazol halqasi	1,2,4-triazol halqasi

Triazollar molekulasi juda mustahkam birikmalar bo‘lib termik ta’sirlarga juda chidamlidir, shuningdek halqa hajmi nisbatan kichik va dipol tabiatga ega. Molekulasi sharoitga qarab uchta tautomer shaklda bo‘lishi mumkin (2-rasm).

2-rasm. Triazol izomerlarining mavjud bo‘lishi mumkin bo‘lgan tautomer shakllari

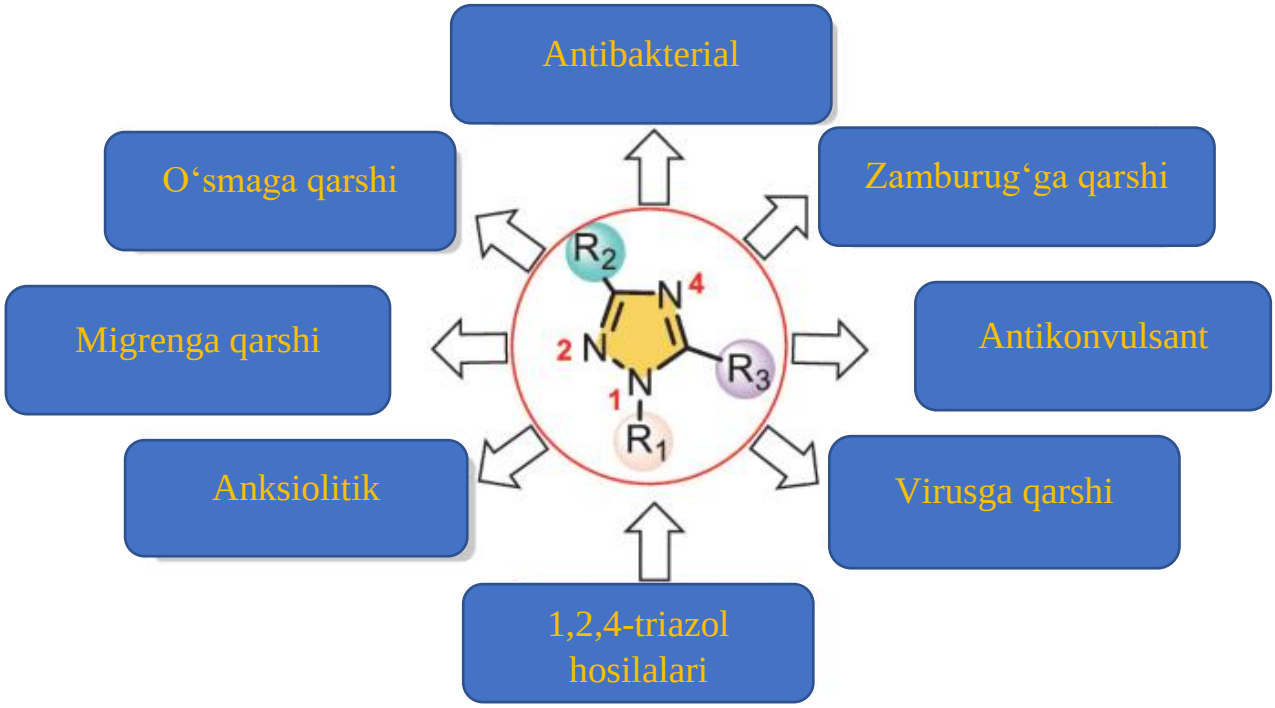


Geterosiklik birikmalar tirik organizmlar hayotida alohida rol o‘ynaydi. Ko‘plab biologik faol birikmalar, jumladan, vitaminlar, gormonlar, antibiotiklar, alkaloidlar, gerbitsidlar, psixotrop dorilar va boshqa ko‘plab birikmalar molekulasida geterosiklik halqa tutuvchi birikmalardir. Geterosikllardagi geteroatomlar hujayralardagi retseptorlar, biologik faol moddalar bilan vodorod bog‘lar orqali ta’sirlashadi va ma’lum bir farmakologik samara chaqiradi. Ayniqsa azot saqlovchi geterosiklik birikmalar tibbiyot amaliyotida va qishloq xo‘jaligida qo‘llaniluvchi yetakchi vositalardir [30].

Jumladan, 1,2,4-triazol hosilalari turli retseptorlar, enzimlar va protein komplekslarga affinitet namoyon qiladi. Molekulasidagi kichik o‘zgarishlar ham ularning biologik faolliklarida jiddiy o‘zgarishlarga olib keladi. Bu holat ularning keng biologik faollikka egaligini tushinishda yordam beradi. Bugungi kunda 1,2,4-triazol hosilalari juda muhim fundamental polisiklik sistema

bo‘lib, keng farmakologik ta’sirli antifungal, antibakterial, antivirus, anksiolitik, antioksidant, antikonvulsant va boshqa guruh vositalarni ishlab chiqish uchun manbalardir (3-rasm) [12].

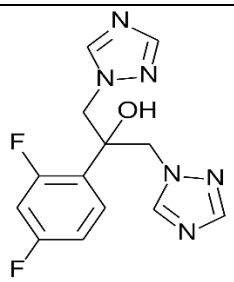
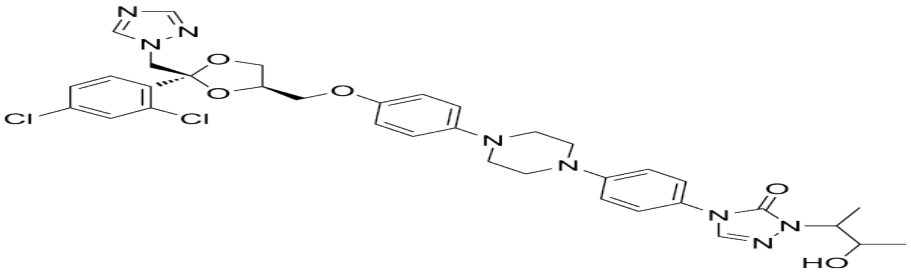
3-rasm. 1,2,4-triazol hosilalarining farmakologik ta’sir spektri (S. Kumar, S. Lal Khokra 2021)



1,2,4-triazol hosilalari tibbiy va farmatsevtik nuqtai nazardan juda ahamiyatlidir. 1,2,4-triazol hosilalari o‘zining keng spektrli biologik faolliklari antibakterial, fungitsid [1, 9], silga qarshi [19], antikonvulsant [2, 11], viruslarga qarshi [32], yallig‘lanishga qarshi [20, 29], antioksidant [1, 28], ureaza ingibitori [5], lipaza ingibitori, o‘smaga qarshi [3, 4, 10, 31], kislota ishqor indikatori [6] kabi maqsadlarda ishlatiladi.

1,2,3- va 1,2,4-triazol halqalari allaqachon muhim farmakofor fragmentlar sifatida keng ko‘lamli ilmiy tadqiqot ishlarining asosiy ob’yektlari bo‘lib ulgurdi. 1,2,4-triazol hosilalarining biologik faolliklari haqidagi ilk ma’lumotlar 1905-yilda italyan olimlari G. Pellizzari va A. Soldining ishlarida keltirilgan. Aynan shu olimlar xizmatlari evaziga triazol hosilalarini qishloq xo‘jaligi uchun potensial antifungal birikmalar sifatida o‘rganish boshlangan [21]. Keyinchalik 1960-1970-yillarda W.C. von Meyer va S.A. Greenfield kabi olimlar 1,2,4-triazollarni tibbiyot amaliyotida zamburug‘li kasalliklarga qarshi vositalar sifatida ishlatish bo‘yicha izlanishlar boshlangan. Olingan natijalar ilmiy jamoatchilikda 1,2,4-triazollarni o‘rganishga qiziqishni orttirib yubordi. Shu yo‘nalishdagi ishlar natijasi o‘laroq 1981 yilda Pfizer kompaniyasi tomonidan 2 - (2,4-difluoropenil) - 1,3 – bis (1H-1,2,4-triazol-1-il) propan – 2 - ol (flukonazol nomi bilan patentlangan) amaliyotga joriy etilgan. Biroz keyinroq 1992 yilda guruhning yana bir vakili Intrakonazol kashf qilinib amaliyotga tadbiq etilgan (4-rasm).

4-rasm. Flukonazol va intrakonazol preparatlari ta’sir etuvchi moddasining kimyoviy tuzilishi

	
2 - (2,4-difluoropenil) - 1,3 – bis (1H-1,2,4-triazol-1-il) propan – 2 – ol birikmasi (flukonazol)	4-[4-[4-[4-[[Cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[[cis-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl]-2,4-dihydro-3H-1,2,4-triazol-3-one

Triazol hosilalarining tutqanoqqa qarshi faolligi

Adabiyotlar tahlili ko‘rsatishicha, 1,2,4-triazol halqasi yuqori antiepileptik potensial namoyon qiladi [18]. *T. Plech* boshchiligidagi tadqiqotchilar guruhi 4-alkil-1,2,4-triazol-3-tion hosilalarining sintezini amalga oshirgan. Olingan vakillar tutqanoqning maksimal elektro-shok (MESH) modelida tajriba hayvonlaridagi tonik-klonik tutqanoq hurujlarini yaxshi bartaraf etgan [23]. Shu qatorga mansub boshqa birikmalardan 4-alkil-5-aril-1,2,4-triazol-3-tion hosilalar MESH usulida chaqirilgan tonik-klonik tutqanoq hurujlarida juda yaxshi samaradorlik namoyon qilgan. Ta’sir mexanizimini o‘rganishga qaratilgan ishlar ko‘rsatishicha, bu qator triazol hosilalar boshqa guruhdoshlaridan farqli o‘laroq, GAMKergik retseptorlarga emas, balki potensialga bog‘liq Na^+ - kanallariga ta’siri ustunroqligini ko‘rsatdi. Shuningdek mualliflar tomonidan bu qator triazollar molekulasi 4-holatidagi alkil guruhi antikonvulsiv ta’sirini yuzaga chiqaruvchi asosiy farmakofor vazifasini o‘tashi aniqlandi. Bunda alkil guruhning tarmoqlanmagan hamda 4 tadan 7 tagacha uglerod tutgan bo‘lishi hal qiluvchi omildir [15]. Uglerod zanjirining uzayishi bilan samara kuchaya boradi va 7 ta uglerodli zanirda maksimal qiymatga yetishi, keyin pasaya borishi ma’lum bo‘ldi [16]. Molekuladagi 1,2,4-triazol-3-tion va 5-holatdagi aril qismlarni o‘zaro bog‘lashda qisqa alifatik zanjirdan foydalanish farmakologik samaradorlikning oshishiga olib kelgani qayd qilingan [24]. Potensialga bog‘liq Na^+ - kanallarining blokatorlari molekulasida tarmoqlanmagan alkil zanjir bo‘lishi asosiy omillardan biri ekanligi valproy kislota (2-propil-pentan kislota) va uning tuzlari misolida ham yaqqol o‘z isbotini topadi [35]. Ushbu guruh preparatlari kardiologik va nevrologik amaliyotdagi bir qancha fatal kasalliklarni davolashda tanlov preparatlari hisoblanadi. Hozirgi kunda potensialga bog‘liq Na^+ - kanallarining 9 xil tipi aniqlangan bo‘lib

organizmda joylashuvi to‘qima turiga bog‘liq. Biroq asosiy tuzilish markazi aminokislotalar ketma-ketligi o‘xshashligi sababli Na^+ - blokatorlar yuqori selektivlik namoyon qilmaydi [36].

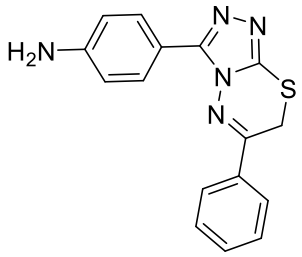
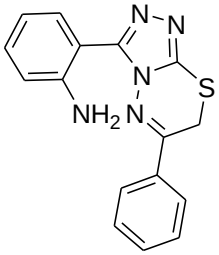
A. Ayati va boshqa mualliflar tomonidan e’lon qilingan tahliliy maqolada bir qancha triazollarning antikonvulsiv faolligi bo‘yicha ma’lumotlar berilgan. Aynan ushbu ishlarda triazol tutgan geterosiklik birikmalar antikonvulsiv faollikka ega bo‘lishi mumkinligi chuqur tahlil qilib berilgan [3]. Boshqa bir manbalarda 4-(4-alkoksilfenil)-3-etil-4H-1,2,4-triazolning MESH modelida yuqori antikonvulsiv faolligi haqida ma’lumotlar keltirilgan [37]. Armanistonlik olimlar guruhi 6-(4-propoksifenil) triazolo[3,2-b]-[1,2,4]triazolning tutqanoqqa qarshi faolligini turli xil tajriba modellarida karbamazepin bilan solishtirib o‘rgangan, tajriba natijalari ko‘rsatishicha o‘rganilayotgan hosila yuqori tutqanoqqa qarshi faollik namoyon qilgan [39]. Xarkov Milliy farmatsevtika universiteti laboratoriyasida 1,2,4-triazollar va 1,3,4-oksadiazollarning yangi sintezlangan 46 ta vakilining tutqanoqning bir necha xil: korazolli, pikrotoksinli, strixninli modellarida tutqanoqqa qarshi faolliklari bo‘yicha o‘rganishlar olib borilgan. Oligan natijalardan ma’lum bo‘lishicha 3-xlor-4-metoksianilid 1-(2'-ftorfenil)-5-metil-1,2,3-triazol(1H)-4-karbon kislota birikmasi 100 mg/kg dozada korazolli modelda juda yuqori faollik namoyon qilgan. Klonik tutqanoq xurujlari soni bo‘yicha solishtirma preparat valproy kislotadan ikki barobar faol bo‘lgan. Ma’lumki korazolning tutqanoq chaqirish mexanizmi xlor ionlarining hujayraga kirishini ta’minlovchi $GAMK_A$ – retseptor saytni bloklashi bilan bog‘liq. [45]. Organizmda aniqlangan GAMK-retseptori juda katta kompleks bo‘lib unda $GAMK_A$, $GAMK_B$ va $GAMK_C$ tarzida belgilanuvchi maxsus saytlar bo‘ladi. $GAMK_A$ – sayt bikukulinga, $GAMK_B$ – baklofenga, $GAMK_C$ – sayt pikrotoksinga sezgirlik namoyon qiladi. A va C tip ionotrop retseptorlar bo‘lib xlor kanallari bilan bog‘langan, B tip metabotrop retseptorlar sinfiga mansub. 1,2,4-triazollarning xinolonlar bilan birikishidan olingan hosilalarning sezilarli antikonvulsiv faollikka egaligi qayd qilingan [8]. Tiazol va 1,2,4-triazol halqalari kondensatsiyasidan olingan 6-(4-propoksifenil) tiazolo[3,2-*b*]-[1,2,4]triazol tipik tutqanoqqa qarshi preparat karbamazepindan ko‘ra yuqoriroq faollik namoyon qilishi haqida ma’lumotlar bor [39]. Molekuladagi aril, piridin, fenil, triazol, anilin va boshqa siklik halqalarga aminoguruh, alkilaminoguruh, amid guruh va atsetamid guruh birikishidan molekulada turli xil intensivlikdagi antikonvulsiv faollik paydo bo‘lishi qayd etilgan va shu prinsip asosida sintezlangan 4-benzoilpiridin oksimi - (oksalat O-(2-morfolinoetil) oksim-4-benzoilpiridinda yaqqol tutqanoqqa qarshi faollik borligi aniqlangan [35].

Shunga o‘xshash tuzilishga ega (Z)-3-(4-bromfenil)-N, N-dimetil-3-(piradin-3-il) prop-2-en-1-amin va (RS)-N-metil-3-fenil-3-[4-(triftormetil) fenoksi] propan-1-amin birikmasining antidepressant faolligi bilan birga antikonvulsiv va tremorga qarshi ta’sirlari isbotlangan [22, 26]. Monokarbon va dikarbon kislotalarning alkil-, sikloalkil-, aril- va triazolil- almashgan amidlari va gidrazidlari orasidan tekshirilgan 800 ta birikmadan 318 tasi (40%) da, alifatik monokarbon

kislotalarning amidlari va gidrazidlari orasidan tekshirilgan 336 ta birikmadan 153 tasi (45%) da, N-ftalimidoalkilkarbon kislota halqasi tutgan amidlardan 26 ta birikma tekshirilganda 14 tasi (54%) da antikonvulsiv faollik borligi aniqlangan [42]. Valproy kislotaning molekulasiga amid halqasi birikishidan hosil bo`lgan (N-(5-etil-1,3,4-tiadiazol-2-il)-2-propilpentanamid) birikmasida antikonvulsiv faollik oshgani qayd etilgan [43]. Bugungi kunda molekulasida 1,2,4-triazol halqasi tutgan birikmalarning antikonvulsiv, sedativ va miorelaksant faolliklari bo‘yicha jadal o‘rganishlar olib borilmoqda. Ushbu guruhga kiruvchi yuqori samarador 1-[(Z)-2-chloro-2-(2,4-dichlorophennyl) vinyl]-1H-1,2,4-triazol birikmasi (Loreklezol) allaqachon klinik amaliyotda muafaqiyatli qo‘llanilmoqda. 1,2,4- triazol halqasi tutgan shartli ravishda D-286 va D-389 deb nomlangan 4-(6-fenil-7H-[1,2,4] triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilin va 2-(6-fenil-7H-[1,2,4] triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilinning tutqanoqqa qarshi faolligi to‘g‘risida ma’lumotlar bor (5-rasm). Bunda triazol halqasiga birikkan anilindagi aminoguruhning orto- va meta- holatlarga qaraganda para-holatda joylashuvi antikonvulsiv faollikning yaqqolroq namoyon bo‘lishiga olib kelgan [27].

5-rasm

1,2,4- triazol halqasi tutgan shartli ravishda D-286 va D-389 deb nomlangan birikmalar

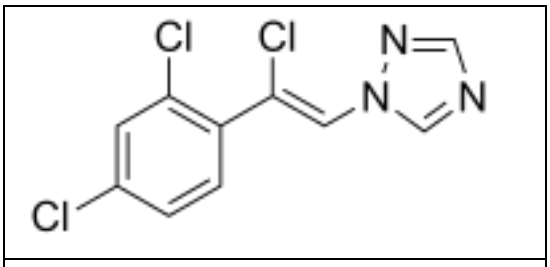
	
4-(6-fenil-7H-[1,2,4] triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilin birikmasi	2-(6-fenil-7H-[1,2,4] triazolo[3,4-b][1,3,4]tiadiazin-3-il)-anilin birikmasi

Oxirgi yillarda 1,3-tiazol va 1,2,4-triazol halqalari kondensatsiyalanishidan olingan birikmalar ham yuqori neyropsixofarmakologik faolligi bilan katta qiziqishga sabab bo‘lmoqda. Jumladan 6-(4-propoksifenil)tiazolo[3,2-*b*]-[1,2,4]triazol tutqanoqning turli tajriba modellarida karbamazepinga nisbatan yuqori faollik namoyon qilgan [39].

Guruhning tibbiyot amaliyotida qo‘llanuvchi tutqanoqqa qarshi vakillaridan loreklezol alohida ahamiyatga egadir (6-rasm). Loreklezol $GAMK_A$ – retseptorlarining allosterik modulyatori hisoblanadi. Sedativ va antikonvulsiv faollikka ega. Loreklezol hayvonlarda o‘tkazilgan pentilentetrazol bilan antagonizm modelida antikonvulsiv faollik namoyon qiladi, biroq maksimal elektroshok modelida samaradorligi past (Rogawski M. 1996). Preparat kam zahar hamda absanslarda yuqori samaradordir. Surunkali qabul qilinganda preparatga tolerantlik rivojlanmaydi. Terapevtik profili jihatidan benzodiazepinlarga o‘xshash. *In vitro* sharoitida kalamushlarning nativ

$GAMK_A$ – retseptorlariga ta’sir etib xlor anionlarining hujayra ichiga oqimini sezilarli darajada oshirgan.

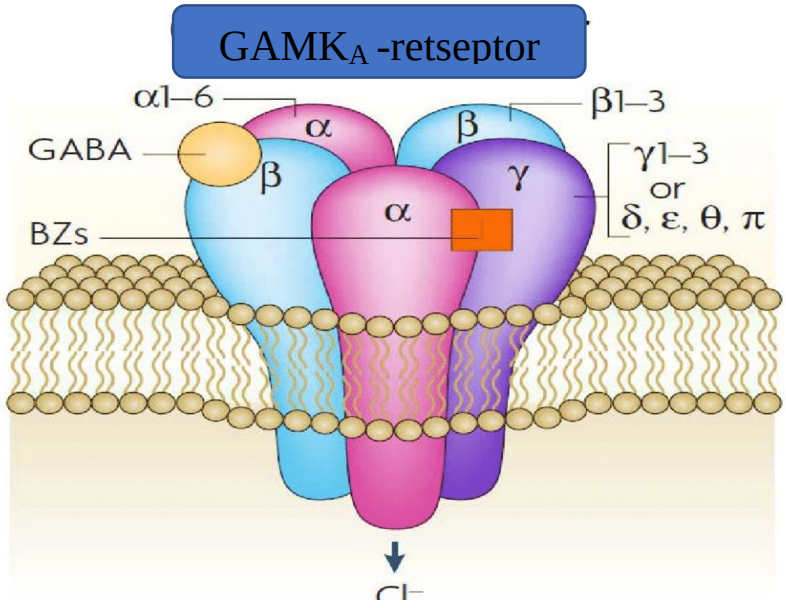
6-rasm. Tibbiyot amaliyotida anksiolitik va tutqanoqqa qarshi vosita sifatida qo’llanuvchi loreklezol preparati kimyoviy tuzilishi



- 1-[(*Z*)-2-xloro-2-(2,4-dixlorfenil) vinil]-1*H*-1,2,4-triazol

Biroq benzodiazepinlar antogonisti flumazenil loreklezolning tutqanoqqa qarshi faolligiga ta’sir qilmaydi, bundan kelib chiqadiki preparatning ta’siri $GAMK_A$ – retseptorlarining benzodiazepin sayti bilan bog‘liq emas (7-rasm). Oxirgi o‘rganishlar ko‘rsatishicha loreklezol $GAMK_A$ – retseptor kompleksining β_2 va/yoki β_3 – saytining allosterik modulyatoridir (Wingrove P.B. va b. 1994).

7-rasm. $GAMK_A$ -retseptor kompleksi tuzilishi (manba: Jacob va b. 2008)



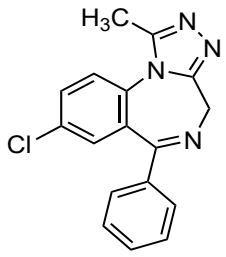
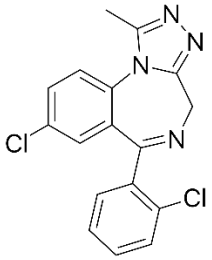
Triazol hosilalarining anksiolitik va uyqu chaqiruvchi faolligi

Benzodiazepin hosilalariga triazol halqasi kiritish orqali olingan birikmalarni o‘rganish 1960 yillar oxirida AQSHning Upjohn farmasevtik kompaniyasi olimlari tomonidan boshlab berilgan. Biroq birinchi triazolobenzodiazepin qatori anksiolitigi 8-xloro-1-metil-6-fenil-4*H*-

[1,2,4]triazolo[4,3-a] [1,4]benzodiazepin (Alprazolam) ning klinik amaliyotga kirishi 1981 yildagina amalga oshirilgan [47].

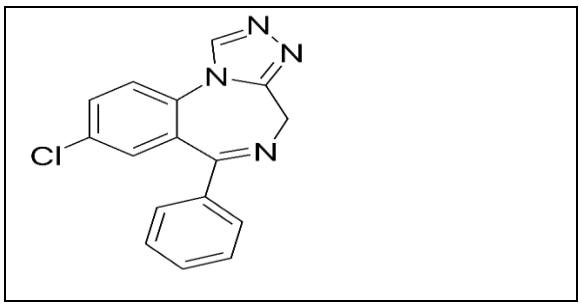
Preparat tezda klinik amaliyotda o‘z o‘rnini topgan va bugungi kunda uyqu buzilishlari, panik buzilishlar, essensial tremor, qo‘rquv va xavotirli holatlarni davolashda muaffaqiyatli qo‘llanilmoqda. Triazolobenzodiazepinlar benzodiazepin hosilalariga nisbatan kamroq o‘rganib qolish chaqiradi, bekor qilish sindromi nisbatan kam ifodalangan, shuningdek vegetativ sferaga ta’siri ham nisbatan kamroq [40]. 1987 yilda boshqa bir triazolobenzodiazepin 8-xloro - 6 - (2-xlorofenil) - 1 - metil - 4*H* - [1,2,4] triazolo [4,3-*a*][1,4] benzodiazepin (Triazolam) amaliyotga tadbiq etildi (8-rasm). Triazolam yengil anksiolitik ta’siri bilan ajralib turadi, asosan tinchlantiruvchi va uyquni yaxshilovchi vosita sifatida ishlatilmoqda. Triazolamda boshqa benzodiazepinlarga nisbatan tutqanoqqa qarshi va miorelaksant ta’sir kuchliroq ifodalangan [25].

8-rasm. Alprazolam va triazolam preparatlari ta’sir etuvchi birikmasining kimyoviy tuzilishi

	
8-xloro-1-metil-6-fenil-4*H*-[1,2,4]triazolo[4,3-a] [1,4]benzodiazepin birikmasi (Alprazolam)	8-xloro - 6 - (2-xlorofenil) - 1 - metil - 4*H* - [1,2,4] triazolo [4,3-*a*][1,4] benzodiazepin birikmasi (Triazolam)

Uyqu buzilishlarida ishlatiluvchi vakillaridan 8-xlor-6-fenil-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin (Estazolam) ni qayd qilish lozim (9-rasm). Tinchlantiruvchi va uyqu chaqiruvchi faolliklari bosh miya stvoli retikulyar formatsiyasi, po‘stloq osti markazlar hamda limbik sistemani faolligini kamaytirishi bilan bog‘liq. Uyquga ketish vaqtini qisqartirib tungi uyg‘onishlar sonini kamaytiradi, uyqu davomiyligini uzaytiradi. Boshqa benzodiazepinlarga qaraganda uyqu fazalariga kam ta’sir etadi [13].

9-rasm. Estazolam preparatlari ta’sir etuvchi birikmasining kimyoviy tuzilishi



8-xlor-6-fenil-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin birikmasi (Estazolam)

Triazol hosilalarning antidepressant faolligi

Klinik amaliyotda ishlatiluvchi turli tuman ta’sir mexanizimiga ega antidepressiv birikmalar mavjud. Molekulasida triazol halqasi tutgan piridin hosilasi 2-(3-[4-(3-xlorfenil)piperazin-1-il]propil)-[1,2,4]triazoloo[4,3-*a*]piridin-3(2*H*)-on (Trazodon) antidepressant ta’sir anksiolitik ta’sir bilan uyg‘un namoyon bo‘luvchi antidepressantlarning noyob vakilidir [7]. Ta’sir mexanizimi to‘liq o‘rganilmagan, biroq serotoninning qayta neyronal so‘rilishini qamal qiluvchi va 5–HT_2 retseptorlarining antogonisti deb taxmin qilinadi. Yuqorida aytilganidek, o‘zining ikki tomonlama ta’siri tufayli qo‘rquv epizodlari bilan kechuvchi depressiyalarni davolashda tanlov vositasidir.

2-(3-brom-1,2,4-triozolil-5-tio) sirka kislotasining past molekulyar spirtlar bilan hosil qilgan efirlari yaqqol ifodalangan antidepressiv faollik namoyon qilganligi haqida ma’lumotlar bor [41].

Triazol hosilalarining neyrodegenerativ kasalliklarga qarshi faolligi

Ma’lumki neyronlarda sitoskelet tarkibiga kiruvchi hamda mitoz, sitokinez va vezikulyar transport jarayonlarida ishtirok etuvchi maxsus mikrotrubkachalar mavjud. Ushbu mikrotrubkachalarni o‘zaro bog‘lanishida va stabilizatsiyasida muhim o‘rin tutuvchi maxsus tau oqsili (Microtubule-associated protein tau - MAPT) va shunga o‘xshash boshqa oqsillar (Microtubule-associated protein-MAP) guruhi mavjud. Ma’lum bo‘lishicha serin/treonin kinaza (cdk5) va uning kofaktori (p25, shuningdek boshqa bir kofaktori p35) tau oqsilining giperfosforilizatsiyasiga olib keladi. Bu jarayonlar natijasida neyronlarda atipik juft spiral neyrofibrillyar to‘plam hosil bo‘lib sitoplazmada to‘plana boshlaydi va sitotoksik ta’sir ko‘rsatadi [33]. Aynan shu jarayonlar Altsgeymer kasalligi, Parkinson kasalligi, Gentington kasalligi kabi bir qator neyrodegenerativ kasalliklar negizida yotadi deb qaraladi [17]. Shiradkar M. va uning guruhi tomonidan olib borilgan ilmiy izlanishlar natijasida yangi triazolil tiofen qatori birikmalari cdk5/p25 kompleksining potensial ingibitorlari ekanligi ko‘rsatib berildi [34]. Shuni ta’kidlash kerakki bu ishlar hali boshlang‘ich bosqichda bo’lib ilmiy izlanishlar davom etmoqda. Neyrodegenerativ kasalliklarni davolashda patogenetik yondashuv istiqboli biroz munozarali bo‘lib bu borada haligacha samarador preparatlar amaliyotga tadbiq etilmagan. Ushbu kasalliklarni davolashda asosiy yo‘nalish hozirgi kunda ham simptomatik va o‘rin bosuvchi terapiyadir [44].

Triazol hosilalarining migrenga qarshi faolligi

Migren neyrotomir patologiyalariga mansub etiopatogenezi yaxshi o‘rganilmagan bosh miyaning surunkali kasalligidir. Kasallikning asosiy belgisi sifatida boshning bir tomonlama kuchli og‘riqlari, ko‘ngil aynish, bosh aylanishi, fotofobiya va fonofobiyalarni ko‘rsatish mumkin. Migren patogenezida bir nechta messenjer-molekulalar: azot oksidi (NO), serotonin (5-HT) va migrendagi og‘riq transmissiyasida asosiy mediator bo‘lgan CGRP (calcitonin gene-related peptide) ishtrok etadi [14]. CGRP retseptori antogonistlari olsegepant va telkagepant kutilgan natijani olib kelmadi va bu yo‘nalishdagi ishlarni olib borayotgan Merck kompaniyasi tadqiqotlarni to‘xtatdi [38]. Boshqa vakillari urbogepant va rimedgepantlar samaradorligi yuqori emas. Shu o‘rinda migrenni davolashning zamonaviy yondashuvida markaziy 5-HT_{1F} serotoninergik retseptorlarning agonistlari lasmiditan va 5-$HT_{1B/D}$ serotoninergik retseptorlarning agonistlari sumatriptan va rizatriptanlar alohida o‘rin tutadi [46]. Triazol hosilalaridan bo‘lmish Rizatriptan preparati nevrologik amaliyotda o‘zining mustahkam o‘rnini topa olgan. Ta’sir mexanizimi bo‘yicha markaziy 5-$HT_{1B/1D}$ serotonin retseptorlari anogisti deb qaraladi. Rizatriptan ta’siri uch asosiy klinik samara bilan ifodalanadi, bular: meningeal tomirlarni toraytirish, neyrogen yallig‘lanishni bostirish va og‘riq impulslari o‘tishini kamaytirish. Rizatriptan referens preparat sumatriptanga ko‘ra yaxshiroq o‘zlashtiriladi hamda klinik samarasi deyarli bir xil [48].

XULOSA

Xulosa. Ilmiy manbalardan olingan ma’lumotlar shuni ko‘rsatadiki, 1,2,4-triazol hosilalari zamonaviy farmakologiyaning asosiy o‘rganish ob’yektlaridan biridir. Bunga sabab triazol halqasining keng spektrli faramkofor hususiyati, kam zaharliligi, termik bardoshliligi, maqbul farmakokinetik xususiyatlaridir. Ko‘plab triazol hosilalari vakillari klinik amaliyotda o‘zining mustahkam o‘rnini topgan, ko‘plab yangi vakillari antibakterial, zamburug‘ga qarshi, o‘smalarga qarshi, antidepressant, anksiolitik, tutqanoqqa qarshi va boshqa guruh vositalarini izlash uchun manba bo‘lib xizmat qilmoqda.

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