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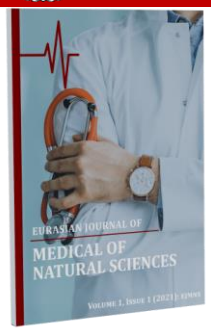

ACUTE TOXICITY AND ANTICONVULSANT ACTIVITY OF 5- (p-AMINOPHENYL) - 4-AMINO-1,2,4-TRIAZOLE-3(2H) – THIONE

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ABSTRACT
In this article, it has been experimentally confirmed that 5-(p-aminophenyl)-4-amino-1,2,4-triazole-3(2H)-thione belongs to the class of low-toxic psychopharmacological activity in doses of 0.1; 0.5; 1.0; 5.0 and 10.0 mg/kg and is not inferior to comparable anticonvulsant drugs carbamazepine and convulex.

ОСТРАЯ ТОКСИЧНОСТЬ И ПРОТИВОСУДОРОЖНАЯ АКТИВНОСТЬ 5 - (п-АМИНОФЕНИЛ) - 4-АМИНО-1,2,4-ТРИАЗОЛ-3 (2H) – ТИОНА

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5-(п-аминофенил)-4-амино-1,2,4-триазол-3(2H)-тион, малотоксичен, психофармакологическая активность, противосудорожная активность, карбамазепин, конвулекс.

ABSTRACT
В этой статье экспериментально подтверждено, что 5-(п-аминофенил)-4-амино-1,2,4-триазол-3(2H)-тион относится к классу малотоксичных, по психофармакологической активности в дозах 0,1; 0,5; 1,0; 5,0 и 10,0 мг/кг и не уступает сопоставимым противосудорожным препаратам карбамазепину и конвулексу.

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5-(p-AMINOFENIL)-4-AMINO-1,2,4-TRIAZOL-3(2H)-TIONNING O‘TKIR ZAHARLILIGI VA TUTQANOQQA QARSHI FAOLLIGI

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ABSTRACT

Ushbu maqolada 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tion kam zaharli sinfga mansub ekanligi, 0.1; 0.5; 1.0; 5.0 va 10.0 mg/kg dozalarda psixofarmakologik faolliklari va tutqanoqqa qarshi solishtirma preparatlar karbamazepin va konvuleksdan qolishmasligi eksperimental tajribalar asosida tasdiqlangan.

Dolzarbligi. Epilepsiya – bu markaziy nerv tizimi neyronlarining faoliyatini buzilishi bilan kechadigan surunkali kasallik hisoblanib, bosh miyaning qo‘zg‘atuvchi va tormozlovchi mediatorlar faoliyatini disbalansi evaziga tutqanoq va es-hushni yoqolishi bilan xarakterlanadi [1, 2]. So‘nggi bir necha o‘n yilliklar davomida 20 dan ortiq yangi antiepileptik dorilar, shu jumladan eslikarbazepin asetat [3], perampanel [4] va ezogabin [5] yaratilgan. Biroq, aholining katta qismi monoterapiya [6] bilan turg‘un antikonvulsant samaraga erisha olmaydi va bemorlarning taxminan 30% refrakter epilepsiyaga ega va davolash kombinatsiyasini talab qiladi [7, 8]. Bundan tashqari, ko‘plab antiepileptik dori preparatlarning jiddiy nojo‘ya ta’siri mavjud [9, 10] va umrbod davolanish kerak. Shuning uchun ko‘proq tanlangan va xavfsizroq antikonvulsant vositalarni izlash alohida qiziqish uyg‘otadi. Shu nuqtai nazardan, turli yondashuvlar bir necha antiepileptik dori [11-13] rivojlantirish uchun o‘rganildi.

Asosiy ingibirlovchi neyromediator bo‘lgan γ-Amino moy kislota (GAMK) ning rivojlanishi neyrodejenerativ kasalliklar sohasidagi faol tadqiqot sohasidir. GAMK-A retseptorlari barbituratlar, steroidlar, anestetiklar va benzodiazepinlar kabi bir qator terapevtik muhim dorilar uchun [14,15] asosiy nishon hisoblanadi. 1,2,4-triazol hosilalari ko‘plab biologik faolliklarni, jumladan, antikonvulsant [16, 17], zamburug‘ga qarshi [18-20], neyrotrop geterosiklik faollik [21-24], yallig‘lanishga qarshi [25-27] va antibakterial [28-31], namoyon qilishi tajribalarda asoslantirilgan. Savdoda mavjud bo‘lgan antiepileptik dorilarning molekulyar tuzilishi va bioaktivligi fazoviy uzoq gidrofob domenlar (odatda fenil halqalari), vodorod bilan bog‘lanish domenlari va elektron donorlik fragmentlari, bu yuqori antikonvulsant faollik uchun zarur bo‘lgan elementlardir. Boshqa tomondan, qanot va uning hamkasblari loreklezolning (ikkinchi avlod antiepileptik dori) faolligi triazol qismining asparagin amid guruhi (Asn-289) GABA-A retseptorlari 2 subbirliklari bilan o‘zaro ta’siriga bog‘liqligini taklif qilishdi. Bundan tashqari, 1,2,4-triazol qismiga ega bo‘lgan turli xil boshqa

birikmalar epilepsiyaning bir nechta hayvon modellarida antikonvulsant xususiyatlarga ega ekanligi aniqlandi [32-35]. Ushbu topilmalar bizni antikonvulsant faollik bilan ta'minlangan 1,2,4-triazol asosidagi birikmalarni izlashga va olingan hosilalarning GABA-A retseptorlarining allosterik joyida harakat qilishi mumkinligini aniqlashga undadi. Ushbu tadqiqotda biz *in vivo* eksperimental modellar yordamida potentsial antikonvulsant modda sifatida 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning shartli ravishda (D-280) yangi sintez qilingan birikmani, farmakologik baholash bo'yicha tadqiqotlar o'tkazildi.

Tadqiqot maqsadi. 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning o'tkir zaharliligi, harakat faolligiga ta'siri, "ochiq maydon" usulida harakat va qidiruv faolligiga ta'siri va tutqanoqqa qarshi faolliklarini eksperimental baholashdan iborat.

Tadqiqot material va usullari: Tadqiqotlar O'zRFA O'simlik moddalari kimyosi instituti farmakologiya va toksikologiya bo'limi vivariy sharoitida 14 kun davomida karantinda saqlangan tana massasi 17-24 g. bo'lgan oq sichqonlarda olib borildi. Tajribalar xona harorati 20-25^{0}C, havo nisbiy namligi 35-40%, yoritish darajasi 400 lyuks bo'lgan sharoitda olib borildi. Tajribalar institutning Organik sintez bo'limi xodimlari D.S. Ismailova va B.J. Elmuradovlar tomonidan sintezlangan 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozada hamda solishtirma preparatlarda har bir guruhda 8 tadan oq sichqonlarda yuqoridagi faolliklari bo'yicha baholab chiqildi. Tajribalarda D-280 birikmasi 60 daqiqa oldin yuborilib, keyin tutqnoq chaqiradigan analizatorlar yuborilgan. Tadqiqotlar uchun pentilentetrazol, strixninlar Sigma-Aldrich® kompaniyasi maxsulotlari foydalanildi. Birikma suvda erimaganligi sababli, og'iz orqali yuborilganda TVIN-80 moddasida eritilib, 100 mg/kg dozadan 9000 mg/kg dozagacha sinovdan 14 kun davomida o'tkazildi. O'tkir zaharlilik bo'yicha olingan natijalar asosida Kerber usulida hisoblandi. Olingan natijalar statistik tahlili R.B. Strelkov taklif qilgan usullar yordamida ($p \leq 0.05$) tahlil qilindi.

Olingan natijalar. 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning o'tkir zaharliligi dastlab 100-500 mg/kg dozada og'iz orqali yuborilganda hech qanday patologik o'zgarishlar kuzatilmadi. 500-1500 mg/kg dozada esa qisqa muddatda nafas tezlashganligi kuzatildi. 2000 mg/kg dozadan boshlab, umumiy holsizlik va harakat faolligida cheklanishlar kuzatila boshlandi. 4000-9000 mg/kg dozada esa 3-12 soat oralig'ida tremor, tutqanoq holatlari yuzaga kelib, o'lim qayd etildi. O'rtacha o'lim dozasi LD_{50}=4400 mg/kg tashkil etdi.

5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozada og'iz orqali yuborilib, 60 daqiqadan so'ng harakat faolligi (HF) va vertikalizatsiya ko'rsatkichlari baholandi. 0.1 va 10 mg/kg dozalarda harakat faolligini kamaytirib, 0.5; 1.0 va 5.0 mg/kg dozalarda HF oshirganligini, vertikalizatsiya bo'yicha esa 0.1; 0.5; 1.0 va 5.0 mg/kg dozada nazorat guruhiga nisbatan yuqori faollik namoyon etgan. Olingan natijalar 1-rasmda ko'rsatilgan.

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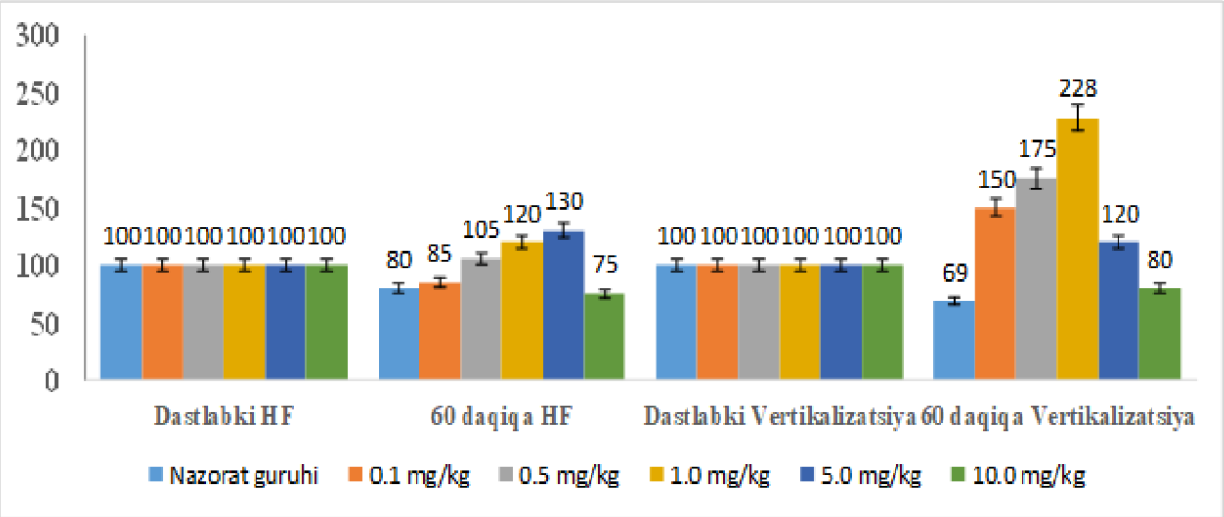

1-rasm. D-280 birikmasini turli dozalarda oq sichqonlarda bir marotaba yuborilganda harakat faolligiga ta'siri

D-280 birikmasini "ochiq maydon" usulida harakat va qidiruv faolligiga ta'sirini baholash. 5-(p-aminofenil)-4-amino-1,2,4-triazol-3(2H)-tionning 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozada og'iz orqali yuborilib, 60 daqiqadan so'ng harakat faolligi kvadratlar kesishmasidagi o'tishlar soniga qarab va qidiruv faolligi esa tuynuklardan mo'ralashiga qarab baho beriladi. Olingan natijalar 1-jadvalda ko'rsatilgan.

1-jadval. D-280 birikmasini "ochiq maydon" usulida harakat va qidiruv faolligiga ta'sirini baholash

Dozalar mg/kg / Ko'rsatkishlar	Nazorat guruhi	0.1	0.5	1.0	5.0	10.0
Harakat faolligi	12.2±1.24	13.4±0.93*	14.2±0.62*	15.4±2.17*	14.8±1.24*	15.2±0.93*
Qidiruv faolligi	10.0±0.62	13.8±1.24*	15.2±2.17*	16.8±1.24*	15.8±0.93*	16.4±2.17*

Eslatma. P≤0.05 nazorat guruhiga nisbatan

Olingan natijalarga asoslanib, D-280 birikmasi barcha dozalarda harakat va qidiruv faolligini oshirganligini ko'rishimiz mumkin.

D-280 birikmasini turli dozalarda strixnin ta'sirida chaqirilgan tutqanoqqa qarshi ta'sirini o'rganish. Bu test odamlarda birlamchi-tarqalgan tutqanoqqa o'xshash holatlarni yuzaga chiqaradi. Ushbu modeldagi birikmalarning antikonvulsant faolligi glitsinga sezgir retseptorlarning bevosita faollashishi va glitsin va GAMK-ergik faollikning birgalikda kuchayishi bilan bog'liq bo'lishi mumkin. Strixnin yuborilgandan so'ng, nazorat hayvonlarining 100% tonik-klonik tutqanoqlar rivojlandi. Tajribalar oq sichqonlarda 1.5 mg/kg strixnin teri ostiga yuborib o'rganildi. O'rganiluvchi modda 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozada og'iz orqali yuborilganda tutqanoqning latent davrini nazorat va solishtirma preparatga yaqin ta'sir etganligi, tutqanoqlar sonini oshirganligi hamda o'lim yuzaga kelish vaqti bo'yicha deyarli bir xil faollik namoyon qildi. Olingan natijalar 2-jadvalda ko'rsatilgan.

2-jadval. D-280 birikmasini strixnin yordamida chaqirilgan tutqanoqqa ta'sirini baholash (n=8)

O‘rganilgan modda	Doza, mg/kg	Tutqanoq boshlanish vaqti (daqiqa)	Tutqanoqlar soni	O‘lim vaqti (daqiqa)	O‘lgan soni
Nazorat (strixnin t/o)	1.5	7.00±0.00	1.00±0.00	7.00±0.00	8
D-280	10.0	5.75±0.62*	1.00±0.00	6.50±0.31	8
	5.0	6.75±1.55	1.25±0.31*	7.25±1.24*	8
	1.0	5.25±0.62*	3.50±1.24*	7.00±2.17	8
	0.5	7.00±0.93	1.25±0.31*	7.75±0.93*	8
	0.1	5.75±0.31*	2.75±0.93*	7.50±0.93*	8
Konvuleks	200.0	7.25±1.24	1.00±0.00	8.25±0.31*	8
	100.0	6.00±0.62	1.25±0.31	6.25±0.31	8
	50.0	7.00±1.24	1.25±0.31	7.00±1.24	8
Karbamazepin	20.0	8.00±0.31*	1.25±0.31*	9.25±0.93*	7*
	50.0	7.00±0.62	1.00±0.00*	7.00±1.24	7*

Eslatma.*P≤0.05 nazorat guruhiga nisbatan

Shunday qilib, sintetik birikma tutqanoq ko‘rsatkichlari bo‘yicha: tutqanoqlarning boshlanishi, soni va hayvonlarning yashovchanligi bo‘yicha nazorat guruhiga hamda Karbamazepin va Konvuleksga yaqin faollik namoyon qilganligi kuzatildi. Sintetik birikma bilan davolangan hayvonlarda strixninni teri ostiga yuborish natijasida kelib chiqadigan tutqanoqlarning yashirin davri davomiyligining statistik jihatdan ahamiyatli o‘zgarmasligi o‘rganilayotgan birikmaning glitsinergik sistemaga ta’sir ko‘rsatishini bildiradi.

D-280 birikmasini pentilentetrazol (korazol) ta’sirida chaqirilgan tutqanoqqa qarshi ta’sirini o‘rganish.

Ushbu test epilepsiyaga qarshi faolligi mavjud birikmalarning klinik oldi sinovlarini o‘tkazish uchun eng zarur usullardan biri hisoblanadi. Pentilentetrazol $GAMK_A$ antagonisti hisoblanib, qorin bo‘shlig‘iga yuborilganda katta (*grand mal*) va kichik (*petit mal*) tutqanoq xurujlarini keltirib chiqarsa, teri ostiga yuborilganda esa kichik tutqanoq xurujlarini “*petit mal*” hamda tutqanoqning asosiy komponenti klonik tutqanoqlarni yuzaga keltiradi. Bosh miya yarim sharlarining harakat zonasini qo‘zg‘alishi tufayli tutqanoqni yuzaga keltiradigan pentilentetrazol 90 mg/kg dozada teri ostiga yuborildi hamda o‘rganiluvchi modda 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozada og‘iz orqali yuborib o‘rganildi. Ushbu testda nazorat guruhiga nisbatan latent davrni 1,5-3.0 barobar uzaytirganligi va o‘lim yuzaga kelishini kamaytirganligini ko‘rish mumkin (3-jadval).

3-jadval. D-280 birikmasini pentilentetrazol yordamida chaqirilgan tutqanoqqa ta’sirini baholash (n=8)

O‘rganilgan modda	Doza, mg/kg	Tutqanoq boshlanish vaqti (daqiqa)	Tutqanoqlar soni	O‘lim vaqti (daqiqa)	O‘lgan soni
Nazorat (pentilentetrazol t/o)	90.0	4.75±0.93	7.00±2.17	15.75±2.79	8
	10.0	13.25±3.41*	5.00±1.86*	25.50±2.79*	6

D-280	5.0	13.00±0.93*	5.00±0.93*	40.00±4.96*	8
	1.0	12.25±4.34*	2.00±0.62*	26.00±11.16*	8
	0.5	10.00±5.58*	4.25±1.24*	24.00±6.20*	6*
	0.1	15.50±1.24*	3.50±0.62*	24.25±7.13*	8
Karbamazepin	20.0	2.70±0.93	2.75±0.31*	5.50±1.24*	8
	50.0	3.05±1.24	2.50±0.62*	9.75±2.79*	8
Konvuleks	100.0	4.60±0.93	5.20±1.24*	12.75±5.20*	7*
	200.0	5.00±0.93*	3.40±1.24*	12.20±2.79*	8

Eslatma.*P≤0.05 nazorat guruhiga nisbatan

Shunday qilib, D-280 birikmasi $GAMK_A$ antagonisti hisoblangan pentilentetrazolga qarshi faolligini inobatga olsak, birikmalar yuqori darajada $GAMK_A$ retseptorlari faolligini oshirganligini ko‘rishimiz mumkin. Solishtirma preparatlardan qolishmasligini amalda namoyon etganligini ko‘rishimiz mumkin.

Xulosa. D-280 birikmasining o‘tkir zaharliligi Stefanov tasnifi bo‘yicha IV sinf kam zaharli birikmalar qatoriga kiradi. Harakatlanish aktivligi va “ochiq maydon”usulida harakat va qidiruv faolligini oshirganligini ko‘rishimiz mumkin. Pentilentetrazol yordamida chaqirilgan tutqanoqlarda tutqanoq yashirin davrini uzayishiga, yashash davomiyligini oshishiga va o‘limlar sonini kamayishiga olib keldi. Tutqanoqqa qarshi faolligi bo‘yicha tibbiyot amaliyotida keng qo‘llaniladigan preparatlar karbamazepin va konvuleksdan qolishmasligi hatto ba’zi holatlarda ulardan ustunligini tajribalar ko‘rsatdi. Ushbu natijalarga asoslanib, tutqanoq yuzaga kelishida muhim o‘rin tutadigan glitsinergik va $GAMK_A$ retseptorlari sistemasiga yetarli darajada ta’sir ko‘rsatganligini ko‘rishimiz mumkin.

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