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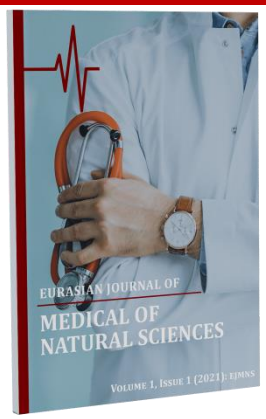

ANTICONVULSANT ACTIVITY OF 1-(4-METHOXYPHENYL)-6.7 DIMETHOXY-1,2,3,4-TETRAHYDROISOQUINOLINE

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1-(4-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, low-toxic, psychopharmacological activity, anticonvulsant activity, carbamazepine, convulex.

ABSTRACT

This article indicates that the synthetic compound 1 - (4 - methoxyphenyl) - 6, 7 –dimethoxy - 1, 2, 3, 4 - tetrahydroisoquinoline belongs to the class of low-toxic, with 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 confirmed by experimental experiments.

ПРОТИВОСУДОРОЖНАЯ АКТИВНОСТЬ 1-(4-МЕТОКСИФЕНИЛ)-6,7 ДИМЕТОКСИ-1,2,3,4-ТЕТРАГИДРОИЗОХИНОЛИНА

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1-(4-метоксифенил)-6,7-диметокси-1,2,3,4-тетрагидроизохинолин, малотоксичен, психофармакологическая активность, противосудорожная активность, карбамазепин, конвулекс.

ABSTRACT

В этой статье указывается, что синтетическое соединение 1-(4-метоксифенил)-6,7-диметокси-1,2,3,4-тетрагидроизохинолин относится к классу малотоксичных, с психофармакологической активностью в дозах 0,1; 0,5; 1,0; 5,0 и 10,0 мг/кг и не уступает сопоставимым противосудорожным препаратам карбамазепину и конвулексу подтверждено экспериментальными опытами.

1-(4´-METOKSIFENIL)-6,7DIMETOKSI-1,2,3,4-TETRAGIDROIZOXINOLINNING TUTQANOQQA QARSHI FAOLLIGI

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1-(4´-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin, kam zaharli, psixofarmakologik faollik, tutqanoqqa qarshi faollik, karbamazepin, konvuleks.

ABSTRACT

Ushbu maqolada sintetik birikma 1-(4´-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin 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.

KIRISH. Epilepsiya-bu har qanday yoshdagi odamlarga yuzaga keladigan keng tarqalgan surunkali nevrologik kasallik. Epilepsiya kamida bitta har qanday bevosita aniqlangan sabab tufayli epileptik tutqanoqning paydo bo‘lishi deb ta’riflanadi [1]. Epilepsiyani davolashning bir qancha usullari mavjud, ammo antiepileptik dorilar eng ko‘p qo‘llaniladigan davolash usuli bo‘lib qolmoqda [2]. 1-(4-aminofenil)-4-metil-7,8-metilendioksi - 5H-2,3-benzodiazepin (GYKI52466, 1) - bu antikonvulsant birikma bo‘lib, uning ta’siri raqobatbardosh bo‘lmagan AMPA tomonidan namoyish etilgan retseptorlari antagonisti va tadqiqotlarda ko‘pchilik uchun qo‘llanma sifatida ishlatilgan [3-10]. Keyinchalik talampanel [2] va CFM-2 [3], bu molekulaning yuqori faolligini ko‘rsatdi va hayvonlarda tutqanoqning turli modellarida yaxshi natijalar aniqlandi [11-13]. *Barreca* va hammualliflar tomonidan o‘tkazilgan 3D farmakofor tadqiqotiga ko‘ra [11] diazepin halqasini tetragidropiridin tizimiga oddiy almashtirish sintezga olib keldi, 2-atsetil-1-aril-6,7-dimetoksi-1,2,3,4 tetragidroizoxinolinlar [4], bu 3D farmakofor gipotezasiga yaxshi mos keladi (ikkita gidrofob guruh, vodorod bog‘lanish akseptorining o‘ziga xos xususiyati va ma’lum bir uch o‘lchovli tartibda bitta aromatik mintaqa) kuchliroq antikonvulsant faollikni ko‘rsatadi [14]. Psixotrop faollikka эga bo‘lgan dori vositalari O‘zbekiston hududida asosan chet mamlakatlardan olib kelinadi. Ushbu dori vositalarining o‘rnini mahalliy preparatlar bilan to‘ldirish hozirgi kunda dolzarb hisoblanadi. Nafaqat O‘zbekistonda, balki butun dunyo olimlari izoxinolin alkaloidlari asosida olingan birikmalarda Shizofreniya [15], Parkinson [16], neyroprotektor [17], antidepressant [18-19] va shunga o‘xshash markaziy nerv tizimi kasalliklari bo‘yicha eksperimental tajribalar olib bormoqda. Shu sababli O‘simlik moddalari kimyosi instituti alkaloidlar kimyosi laboratoriyasida izoxinolin alkaloidlari asosida yangi birikmalarning sintezi amalga oshirilmoqda [20]. Ushbu sintez qilingan birikmalar orasidan atipik neyroleptik [21-22], sedativ anksiolitik [23-24] faollikka эga bo‘lgan moddalar aniqlandi. Shu maqsadda 1-(4´-

metoksifenil)-6,7dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidi sintezlanib, psixofarmakologik izlanishlar olib borildi.

TADQIQOT UCHUN ISHLATILGAN MATERIAL VA METODLAR. Farmakologik tadqiqotlar vivariy sharoitida 14 kun karantinda saqlangan massasi 18-24 g. bo‘lgan oq sichqonlarda olib borildi. Hayvonlar bilan o‘tkazilgan barcha tajribalar umurtqali hayvonlarni himoya qilish bo‘yicha Yevropa konvensiyasining xalqaro tavsiyalari talablariga muvofiq amalga oshirildi [25]. Har bir guruh 8-10 tadan tajriba hayvonlari joylashtirildi. O‘rganiluvchi modda suvda yaxshi eriydigan 1-(4′-metoksifenil)-6,7dimetoksi-1,2,3,4-tetragidroizoxinolinning gidroxlorid tuzi O‘simlik moddadari kimyosi instituti alkaloidlar kimyosi laboratoriyasi olimlari tomonidan sintez qilingan. Tadqiqotlar uchun pentilentetrazol, strixninlar Sigma-Aldrich® kompaniyasi maxsulotlari va galoperidoldan katalepsiya modellarida foydalanildi. 1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin turli xil psixofarmakologik [26] tajriba modellarida amalga oshirildi. Birikmaning o‘tkir zaharliligi 100 mg/kg dan to 1200 mg/kg dozagacha og‘iz orqali yuborilib o‘rganildi. 0.1; 0.5; 1.0; 5.0 va 10.0 mg/kg dozada harakatlanish aktivligi, etaminal-natriy 40 mg/kg dozada qorin bo‘shlig‘iga yuborish yordamida chaqirilgan uyqu davomiyligiga, strixnin, pentilentetrazol (korazol) ta’sirida chaqirilgan tutqanoqqa ta’siri, galoperidoldan yuzaga keladigan katalepsiya dovomiyligini ta’siri o‘rganib chiqildi. O‘rganiluvchi modda va referens preparatlar (karbamazepin, konvuleks) analizatorlardan 60 daqiqa oldin yuborildi. Tajribalardan olingan natijalar statistik tahlil usullari yordamida qayta ishlandi. O‘zgarishlar aniqligi p≤0,05 ko‘rsatkichi bo‘yicha hisoblandi.

NATIJALAR

1-(4′-metoksifenil)-6,7dimetoksi-1,2,3,4-tetragidroizoxinolinning o‘tkir zaharliligini o‘rganish. 1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidi o‘tkir zaharliligi oq sichqonlarda o‘tkazildi. O‘rganiluvchi modda 100 mg/kg dozadan 1200 mg/kg dozagacha og‘iz orqali maxsus metal zond yordamida yuborildi. 500 mg/kg dozada harakat qo‘zg‘aluvchanligi, 700 mg/kg dozadan boshlab, tutqanoq xurujlari, 1000 va 1200 mg/kg dozalarda nafas yetishmovchiligi tufayli nobud bo‘ldi (1-jadval).

1-jadval

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolinning o‘tkir zaharliligi

№	Yuborilayotgan modda	Doza	Tirik qolgan hayvonlar soni	O‘lgan hayvonlar soni
1.	1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin	100 mg/kg	10	0
2.		300 mg/kg	10	0
3.		500 mg/kg	1	9
4.		700 mg/kg	7	3
5.		800 mg/kg	5	5
6.		1000 mg/kg	3	7
7.		1200 mg/kg	0	10

Olib borilgan statistik hisoblashlar natijasida o‘rtacha o‘lim dozasi LD_{50}=820 mg/kg ni tashkil etdi.

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidining bir martalik yuborilgandagi harakatlanish faolligini aniqlash. Harakat faolligi oq

sichqonlarda 0.1; 0.5; 1.0; 5.0 va 10 mg/kg dozalarda og‘iz orqali yuborib, 4-soat davomida kuzatildi. Olingan natijalarga ko‘ra, 0.5 mg/kg dozada harakat aktivligini nazorat guruhiga nisbatan oshirganligini ko‘rishimiz mumkin. Qolgan barcha dozalarda dastlabki soatlardan harakatlanish aktivligini susaytirgan. 10 mg/kg dozada esa dastlab harakat aktivligin oshirib, keyinchalik barcha soatlarda harakat aktivligini susaytirdi. Olingan natijalar quyidagi 2-jadvalda keltirilgan.

2-jadval

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidining bir martalik yuborilgandagi harakatlanish aktivligiga ta’siri (n=10)

№	Modda	Dastlabki holat	1 soat	2 soat	3 soat	4 soat
1.	*Nazorat guruhi*	14.3±1.2 (100%)	10.5±0.72 (73%)	8.0±0.48 (56%)	6.5±0.24 (45%)	8.0±0.48 (56%)
2.	*0.1 mg/kg p.o.*	14.2±0.72 (100%)	16.8±1.44* (118%)	15.2±1.2* (107%)	11.6±0.96* (82%)	10.8±0.48* (76%)
3.	*0.5 mg/kg p.o.*	15.6±0.72 (100%)	18.6±1.44* (119%)	19.2±1.2* (123%)	13.6±0.96* (87%)	9.8±0.48* (63%)
4.	*1.0 mg/kg p.o.*	9.5±0.48 (100%)	6.5±0.48* (68%)	3.5±0.24* (37%)	3.0±0.24* (31%)	5.0±0.48* (53%)
5.	*5.0 mg/kg p.o.*	13.4±0.96 (100%)	10.3±0.72 (77%)	9.8±0.48 (73%)	7.9±0.24 (59%)	6.2±0.24* (46%)
6.	*10.0 mg/kg p.o.*	8.25±0.48 (100%)	9.5±0.24* (115%)	3.0±0.24* (36%)	1.5±0.24* (18%)	0.75±0.24* (9%)

Eslatma.*P≤0.05 nazorat guruhiga nisbatan

Kuzatishlar natijasi bo‘yicha moddaning doza oshib borish tartibida harakatlanish aktivligi pasayishi, ya’ni sedativ xossasi mavjudligi to‘g‘risida xulosaga kelish mumkin.

Etaminal-natriy yordamida chaqirilgan uyqu davomiyligi 1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidining ta’siri. Tajribalar etaminal-natriy 40 mg/kg qorin bo‘shlig‘iga yuborishdan 60 daqiqa oldin sintetik moddaning 0.5; 1.0; 5.0 va 10 mg/kg dozalarining ta’siri o‘rganib chiqildi. Nazorat guruhida uyqu davomiyligi 63 daqiqani o‘rganiluvchi moddada mos ravishda 48; 59; 95 va 106 daqiqani tashkil etdi. Bundan ko‘rinib turibdiki, 0.5 va 1.0 mg/kg dozalarda xuddi yuqoridagi harakatlanish aktivligiga bog‘liq holda uyqu davomiyligini qisqartirganligi, doza oshgan sari esa uyqu davomiyligini nisbatan oshirganligini ko‘rish mumkin.

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidini galoperidol ta’sirida chaqirilgan katalepsiyaga ta’sirini o‘rganish. Tipik neyroleptiklar dofaminergik D_2 retseptorlarini to‘q qamal qilishi hisobiga kam harakatlilik yoki harakatsiz holatga olib kelishi barchamizga ayon. Tipik neyroleptik dofaminoblokator galoperidolning 0.3 mg/kg dozasi yordamida katalepsiya davomiyligi 6-soat davomida kuzatildi. O‘rganiluvchi modda 0.5; 1.0; 5.0 va 10.0 mg/kg dozalarda og‘iz orqali yuborib, katalepsiya davomiyligi katta dozada 3-4 soatgacha, kichik dozalar esa to‘liq 6-soatgacha yaqqol antogonizmni yuzaga keltirdi. Olingan natijalar 1-rasmda keltirilgan.

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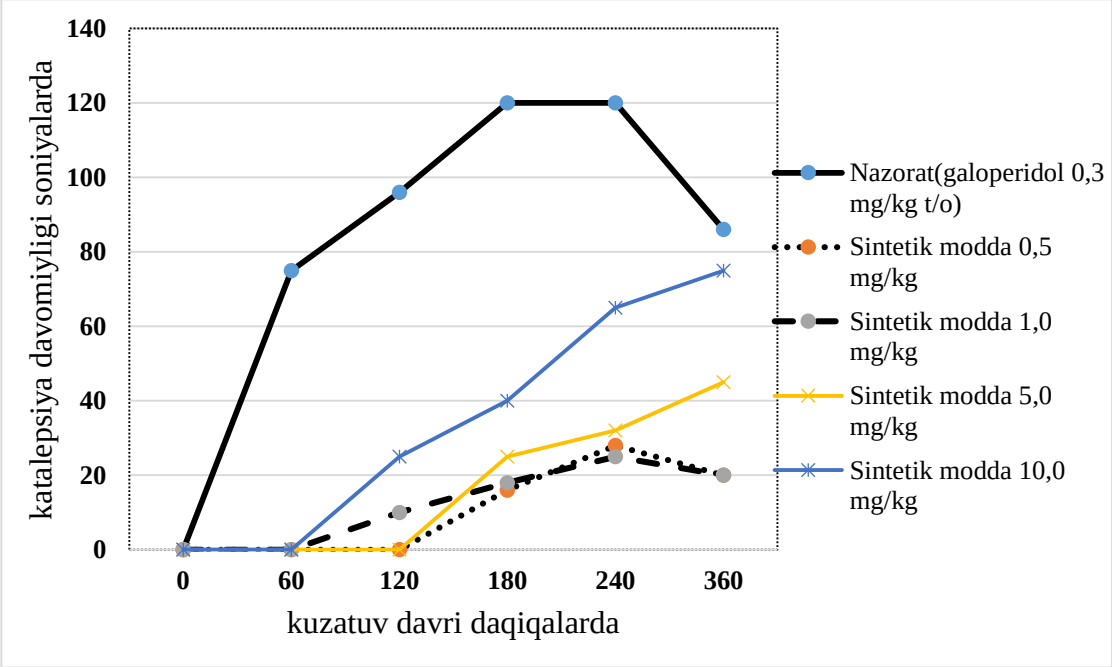

1-rasm. 1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidini galoperidol ta'sirida chaqirilgan katalepsiyaga ta'siri

1-rasmdan ko'rinib turibdiki, dastlabki 3-4 soat davomida barcha dozalarda katalepsiyaga qarshi yaqqol samara vaqt o'tgan sari ta'sirining susayganligini ko'rish mumkin. Barcha dozalarda nazorat guruhi qaraganda yaqqol dofaminopozitiv faollikni namoyon qilgan.

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidi strixnin ta'sirida chaqirilgan tutqanoqqa qarshi ta'sirini o'rganish. Bu test odamlarda birlamchi-tarqalgan tutqanoqqa o'xshash holatlarni yuzaga chiqaradi [27]. Ushbu modeldagi birikmalarning antikonvulsant faolligi glitsinga sezgir retseptorlarning bevosita faollashishi va glitsin va GAMK-ergik faollikning birgalikda kuchayishi bilan bog'liq bo'lishi mumkin [28]. Strixnin yuborilgandan so'ng, nazorat hayvonlarining 100% tonik-klonik tutqanoqlar rivojlandi. Tajribalar oq sichqonlarda 1.1 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 nisbatan oshirdi, tutqanoqlar soni hamda o'lim yuzaga kelishishi 50% gacha kamaytirdi. Tajriba guruhlari antikonvulsant faollikni namoyon etdi. Olingan natijalar 3-jadvalda ko'rsatilgan.

3-jadval

1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin 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)	1.1	7.50±0.93	3.25±0.93	8.25±1.86	8
1-(4′-metoksifenil)-	10.0	9.25±1.55*	1.00±0.00*	12.00±1.55*	4*

6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin	5.0	7.00±1.55	1.00±0.00*	9.00±2.17	6*
	1.0	8.25±1.24	2.00±0.62*	10.00±2.79*	5*
	0.5	8.50±1.24	1.25±0.31*	9.50±0.93	8
	0.1	8.50±0.93	1.00±0.00*	9.25±0.93	8
Konvuleks	50.0	7.00±1.24	1.25±0.31*	7.00±1.24	8
	100.0	6.00±0.62	1.25±0.31*	6.25±0.31	8
	200.0	7.25±1.24	1.00±0.00*	8.25±0.31	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 nisbatan yuqori 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 yuqori miqdorda ta’sir ko‘rsatishini ko‘rsatadi.

1-(4´-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidi 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 1,5-2 barobar uzaytirganligi va o‘lim yuzaga kelishini kamaytirganligini ko‘rish mumkin (4-jadval).

4-jadval

1-(4´-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin 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
1.	Nazorat (pentilentetrazol t/o)	90.0	4.75±0.93	7.0±2.17	15.75±2.79	8
2.	1-(4´-metoksifenil)-	10.0	10.25±1.24*	7.75±1.55	22.25±8.37*	6*

3.	6,7dimetoksi-1,2,3,4-tetragidroizoxinolin	5.0	9.50±1.24*	5.00±1.24	22.00±2.79*	6*
4.		1.0	9.75±3.41*	4.50±1.24	23.25±5.58*	8
5.		0.5	9.25±1.24*	5.00±1.86	19.75±6.20*	8
6.		0.1	11.50±4.65*	3.00±0.93*	18.25±2.79*	8
7.	Karbamazepin	20.0	2.70±0.93*	2.75±0.31*	5.50±1.24*	8
8.		50.0	3.05±1.24*	2.50±0.62*	9.75±2.79*	8
9.	Konvuleks	100.0	4.60±0.93	5.20±1.24*	12.75±5.20	7*
10.		200.0	5.00±0.93	3.40±1.24*	12.20±2.79	8

Eslatma.*P≤0.05 nazorat guruhiga nisbatan

Shunday qilib, sintetik birikma $GAMK_A$ 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. 1-(4′-metoksifenil)-6,7-dimetoksi-1,2,3,4-tetragidroizoxinolin alkaloidining o‘tkir zaharliligi Stefanov tasnifi bo‘yicha IV sinf kam zaharli birikmalar qatoriga kiradi. Harakatlanish aktivligi va uyqu davomiyligi bo‘yicha kichik dozalarda kuchli faollashtiruvchi, nisbatan katta dozalarda sedativ faollikni nomoyon qildi. Strixnin va pentilentetrazol yordamida chaqirilgan tutqanoqlarda tutqanoq yashirin davrini uzayishiga va o‘limlar sonini kamayishiga olib keldi. Galoperidoldan yuzaga keladigan katalepsiyaga qarshi 6 soatda qarama-qarshi ta’sir ko‘rsatib, dofaminopozitiv faollikni va 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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