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Psychotropic activity of *N*-Aryl derivatives of (adamantan-1-yl)methylamine

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The aim. To investigate the psychotropic activity of a series of *N*-aryl derivatives of (adamantan-1-yl)methylamine and to identify a compound with anxiolytic and anti-phobic effects, devoid of myorelaxant action and not impairing cognitive function.

Materials and methods. For the synthesis of target compounds, (adamantan-1-yl)methylamine, aryl bromides, and zero-valent palladium complexes were used. Product isolation was carried out using column chromatography on silica gel. Experiments were conducted on mice and adult male Wistar rats (12 months old). The psychotropic activity was assessed based on the results of a number of tests: "Open Field," "Elevated Plus Maze," "Novel Object Recognition", and "Extrapolation Escape Task". Anxiolytic activity was further studied in the Vogel conflict test. The assessment of possible myorelaxant effects and impact on motor coordination was performed using the "Rotarod" and "Horizontal-Bar" tests.

Results. A series of *N*-aryl-substituted (adamantan-1-yl)methylamines were synthesized under Buchwald–Hartwig amination conditions. During the optimization of reaction parameters, it was found that the standard catalytic system $Pd(dba)_2$ / BINAP in the presence of 1-bromo-4-fluorobenzene exhibited low efficiency (yield < 45 %). It was established that the use of the phosphine ligand DavePhos facilitates overcoming steric and electronic hindrances and provides a product yield of 74 %. In experiments on mice, compound XF (3 mg/kg) demonstrated significant anxiolytic and anti-phobic activity in the "Open Field" and "Elevated Plus Maze" tests. Regarding the effect on declarative memory, compound XF, along with XCl and XCN, showed a nootropic effect comparable to the reference drug phenotropil. In a second series of experiments on adult Wistar rats (12 months old), the anxiolytic effect of XF was confirmed in the "Open Field", "Elevated Plus Maze", and Vogel conflict tests. It was found that, unlike diazepam, compound XF does not cause a myorelaxant effect and does not impair motor coordination (Rotarod and Horizontal-Bar tests), while preserving cognitive functions.

Conclusion. The obtained results demonstrate that searching within the series of *N*-aryl derivatives of (adamantan-1-yl) methylamine for substances for in-depth investigation of psychotropic properties is promising. The introduction of a fluorine atom into the aryl fragment is considered a strategic tool for expanding the spectrum of pharmacological action of potential neuroprotectors.

Keywords: *N*-aryl-(adamantan-1-yl)methylamine; palladium; catalysis; psychotropic effect; anxiolytic effect; anti-phobic effect; cognitive functions; motor coordination

Abbreviations: OF — Open Field test; EPM — Elevated Plus Maze test; NOR — Novel Object Recognition test; EET — Extrapolation Escape Task; DMSO — dimethyl sulfoxide; DMF — *N,N*-dimethylformamide.

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Психотропная активность *N*-арилпроизводных (адамантан-1-ил)метиламина

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Цель. Исследовать психотропную активность ряда *N*-арилпроизводных (адамантан-1-ил)метиламина и выделить соединение с анксиолитическим и антифобическим действием, лишенного миорелаксирующего действия, не нарушающего когнитивную функцию.

Материалы и методы. Для синтеза целевых соединений использовали (адамантан-1-ил)метиламин, арилбромиды, комплексы нульвалентного палладия, выделение продуктов осуществляли с помощью колоночной хроматографии на силикагеле. Эксперименты выполнены на мышах и взрослых крысах-самцах Wistar (возраст 12 месяцев). Психотропный профиль соединений оценивали по результатам батареи тестов: «Открытое поле», «Приподнятый крестообразный лабиринт», «Распознавание нового объекта» и «Тест экстраполяционного избавления». Анксиолитическую активность дополнительно изучали в тесте конфликтной ситуации по Vogel. Оценку возможного миорелаксирующего действия и влияния на координацию движений проводили с помощью тестов «Ротарод» и «Удержание на горизонтальном канатике».

Результаты. Синтезирован ряд *N*-арилзамещенных (адамантан-1-ил)метиламинов в условиях аминирования по Бухвальду–Хартвигу. В ходе оптимизации параметров реакции выявлено, что стандартная каталитическая система $Pd(dba)_2$/BINAP в присутствии 1-бром-4-фторбензола характеризуется низкой эффективностью (выход <45%). Установлено, что применение донорного фосфинового лиганда DavePhos способствует преодолению стерических и электронных затруднений и обеспечивает выход продукта на уровне 74%. В экспериментах на мышах соединение XF (3 мг/кг) проявляло значимую анксиолитическую и антифобическую активность в тестах «Открытое поле» и «Приподнятый крестообразный лабиринт». По влиянию на декларативную память соединение XF, наряду с XCl и XCN, продемонстрировало ноотропный эффект, сопоставимый с препаратом сравнения фенотропилом. Во второй серии экспериментов на взрослых крысах линии Wistar (12 месяцев) анксиолитическое действие XF подтверждено в тестах «Открытое поле», «Приподнятый крестообразный лабиринт» и конфликтной ситуации по Vogel. Установлено, что, в отличие от диазепама, соединение XF не вызывает миорелаксирующего эффекта и не нарушает координацию движений (тесты «Ротарод» и «горизонтальный канатик»), при этом сохраняя когнитивные функции.

Заключение. Полученные результаты позволяют считать перспективным поиск в ряду *N*-арилпроизводных (адамантан-1-ил)метиламина веществ для углубленного исследования психотропных свойств. Введение атома фтора в арильный фрагмент рассматривается как стратегический инструмент для расширения спектра фармакологического действия потенциальных нейропротекторов.

Ключевые слова: *N*-арил-(адамантан-1-ил)метиламин; палладий; катализ; психотропное действие; анксиолитическое действие; антифобическое действие; когнитивные функции; координация движений

Список сокращений: ОП — тест «Открытое поле», ПКЛ — тест «Приподнятый крестообразный лабиринт», РНО — тест «Распознавание нового объекта», ТЭИ — тест экстраполяционного избавления, ДМСО — диметилсульфоксид, ДМФА — N,N-диметилформамид.

ОРИГИНАЛЬНАЯ СТАТЬЯ
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INTRODUCTION

Anxiety and depressive disorders are among the most pressing problems of modern healthcare. According to global epidemiological data, anxiety disorders rank first among all mental illnesses in terms of prevalence in the population [1–3]. Depressive disorders, in turn, are diagnosed in 280 million people and are the leading cause of disability among working-age individuals [4]. The increase in their prevalence, exacerbated by the consequences of the COVID-19 pandemic and socio-economic instability, necessitates a continuous expansion of the arsenal of effective and safe pharmacological agents for the correction of anxious-depressive states [2, 5]. A key drawback of many classical anxiolytics (e.g., 1,4-benzodiazepine derivatives) is their negative impact on cognitive functions, including impaired memory, attention, and psychomotor reaction speed, as well as a high risk of drug dependence [6, 7]. Therefore, the search for new chemical compounds with pronounced anxiolytic and/or antidepressant activity, devoid of side effects on cognitive functions, is a relevant task.

Compounds containing the adamantane structural fragment have become widespread, primarily due to their diverse biological activity associated with the unique lipophilic properties of the adamantane scaffold and the virtually limitless possibilities for its modification [8]. Among the numerous adamantane compounds exhibiting activity, its amino derivatives hold a crucial place. It is sufficient to note that out of seven medicinal drugs currently registered on the market that include an adamantane fragment in their composition, four are derivatives of adamantane-1-amine, and two are (1-adamantyl)methylamine: α-methyl-1-adamantyl methylamine, which has anti-influenza activity, and saxagliptin, characterized by high hypoglycemic activity. Substances in which the structural unit (1-adamantyl)methylamine is present in one form or another, depending on their structure and the presence of other functional groups and pharmacophore fragments, can possess diverse biological activity. As part of the development of more effective anti-influenza drugs, several structures have been created that combine this structural motif with alicyclic rings of various sizes—from cyclopropane to cycloheptane [9] or with a pyrrolidine fragment [10]. For example, 2-(1-adamantyl)piperidines are active against HIV-1 [11, 12], adamantane-substituted thiazolidinones act as non-nucleoside HIV reverse transcriptase inhibitors [13, 14], and an eremomycin des-(*N*-methyl-*D*-Leu)aglucone modified with adamantane improves the action of anti-HIV drugs [15].

It is noted [16] that a 7-chloroquinoline derivative of (1-adamantyl)methylamine, an analog of chloroquine, is effective against malaria [16]. There is also data on the effect of adamantane derivatives on the nervous system. For example, a study [17] demonstrated efficacy in blocking recombinant AMPA receptors expressed in *Xenopus laevis* oocytes. An adamantane analog of gabapentin [18, 19], a drug for the treatment of neurological disorders, has been developed, and P2X7 receptor antagonists based on this structural motif have been obtained [20–23]. The (1-adamantyl)methylamine fragment has also shown perspectives when incorporated into natural antibiotics. For instance, an adamantylated analog of gramicidin C is promising as an antibiotic: it penetrates bacterial cells but does not damage mammalian cells [24]. Thus, the synthesis of new derivatives of (1-adamantyl) methylamine and the study of their pharmacological activity is a relevant task.

THE AIM. To investigate the psychotropic activity of a series of *N*-aryl derivatives of (adamantan-1-yl)methylamine and to identify a compound with anxiolytic and anti-phobic effects, devoid of muscle relaxant action and not impairing cognitive function.

MATERIALS AND METHODS

Animals

The study was performed on male outbred white rats aged 13 months and weighing 350–400 g, obtained from the vivarium of the Research Institute of Hygiene, Toxicology, and Occupational Pathology (Russia, Volgograd region, Volgograd).

The conditions for keeping laboratory animals complied with all requirements of Good Laboratory Practice for preclinical studies in the Russian Federation.

After a 2-week quarantine, laboratory animals were housed in the vivarium of the Scientific Center for Innovative Drugs (Volgograd State Medical University) with free access to food. Animals were housed in plastic cages (545 × 395 × 200 mm, Type: T/4V, MEST LLC, Moscow). Soft wood shavings were used as bedding. The lighting regime was 12 hours of light and 12 hours of darkness (automatic light shut-off at 8pm and turn-on at 08am). The ventilation regime ensured 14–15 air changes per hour. Acceptable ranges for microclimate parameters in animal housing rooms were those defined by The Guide for Care and Use of Laboratory Animals (National Academy Press, Washington D.C., 2010). Temperature 20–22 °C, humidity 40–60 %.

Study Design

Two series of experiments were conducted:

1) In *Series 1*, a screening study of the spectrum of psychotropic effects was performed on mice using a set of psychotropic tests: assessment of activity in the "Open Field", "Elevated Plus Maze", "Novel Object Recognition", and "Wire Suspension" tests.

2) In *Series 2*, an extended study was performed on rats of the most active compounds (according to Series 1 data) for psychotropic activity in the "Open Field", "Elevated Plus Maze", "Novel Object Recognition", "Extrapolation Escape Test", "Vogel's Conflict Test", "Wire Suspension", and "Rotarod" tests. The control groups, diazepam, and phenotropil groups consisted of 6 animals each, while the groups receiving the tested compounds consisted of 3 animals each. This corresponds to the principle of Reduction in bioethics (3R): 3 animals per group are sufficient for screening new compounds, while 6 are needed for control and reference drugs for reliable statistics.

The "Open Field" (OF) test allows for the assessment of specific behavioral elements reflecting psychoemotional state, motor activity, and exploratory behavior.

After placing the tested animal in the center of the apparatus, the following parameters are recorded for 3 minutes:

– the number of squares crossed is interpreted as spontaneous motor activity;

– the number of central sectors crossed (a higher number corresponds to lower anxiety);

– the total number of rears and explored holes—interpreted as exploratory behavior;

– the number of defecations and urinations (a higher number is interpreted as vegetative correlates of anxiety).

The "Elevated Plus Maze" (EPM) test is used to study rodent behavior under conditions of variable stress (with free choice of comfortable conditions), allowing for the assessment of the animal's anxiety and fear levels, and is used for screening the anxiolytic and anti-phobic activity of the compounds under study.

The tested animal is placed on the central platform of the EPM with its head towards an open arm, and for 3 minutes, using two stopwatches and a recording template, the following parameters are recorded:

– the latency to leave the central platform into any arm;

– the number of entries and time spent in the open arms (OAs)—the potentially stressful zone of the apparatus;

– the frequency of entries and time spent by animals in the closed arms (CAs), the potentially comfortable zone of the apparatus;

– the number of crossings of the central zone of the apparatus (when entering an open or closed arm) is interpreted as an indicator of motor activity;

– the time to leave the central platform is an indicator of decision-making speed; additionally, the central zone of the EPM is also an illuminated open space, and the time spent in it can be summed with the time spent in the open arms.

Behavioral acts in the EPM test were recorded for 180 seconds.

The "Novel Object Recognition" test allows for the assessment of short-term declarative memory. It consists of two sessions: object familiarization and retrieval. In the training session, two identical objects are placed in the home cage without the top grid, 10 cm apart from each other and 10 cm from each wall of the box, and the animal explores the box and the objects within it for 3 min. The time spent exploring each object is recorded. After exploring the presented objects, the animals are returned to the same home cage. In the retrieval session, 60 minutes after training, the animals are placed in the same box, but one of the objects is replaced with a new one. The objects differ in shape and color but are approximately the same size. Then, the animal freely explores the objects and the box for 3 minutes, and the time spent exploring each object individually is recorded. The discrimination index is used to measure cognitive function, calculated by the formula: (time exploring the novel object – time exploring the "old" object) / (time exploring the novel object + time exploring the "old" object) × 100. After each test, the box is cleaned with 70 % alcohol.

The "Extrapolation Escape Test" (EET) provides data on the speed of solving an extrapolation escape task. During the "training" phase, the animal is placed tail-down in an inner cylinder, and within 3 minutes, it must solve the task: to duck under the edge of the cylinder, after which it is removed from the apparatus. Animals that fail to solve the "extrapolation task" within 3 min are excluded during the first retrieval. The "Retrieval-test No. 2" is conducted 24 hours after the initially performed test (after training). In the Extrapolation Task Test (ETT), the task-solving time is recorded—the time at which the animal dives under the edge of the cylinder (thereby solving the extrapolation task). A shorter time spent by animals in one group receiving the test substance to solve the

ОРИГИНАЛЬНАЯ СТАТЬЯ
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ETT is considered better memory and execution of the strategy to escape the aversive environment. An increase in diving time (task-solving time) is interpreted as amnesia (forgetting) by the animal of the active escape from the aversive environment.

In the **"Punished Water Intake by Vogel"** test, animals were subjected to water deprivation for 48 hours without food restriction. On the experimental day, an electrode was connected to the water dispenser, the rat was placed in the cage for 3 min, and each water intake was punished by applying current to the dispenser (1 mA). The total number of animal approaches to the water dispenser during the observation period was recorded.

The «**Body Retention on a Horizontal Rope"** test assesses the animal's ability to hold onto a horizontal rope with its forepaws, which reflects its muscle strength. For the test, a nylon rope with a diameter of 0.5 cm is placed horizontally at a height of 100 cm from the cage floor, which is filled with a 5 cm layer of shavings. The animal's forepaws are placed on the rope, and its body is released downwards. The time the rat holds onto the rope is recorded. For each rat, 3 repeated placements are performed, and these times are summed. A longer retention time on the rope is considered an increase in strength and performance, indicating no myorelaxant effect.

The **"Rotarod"** test is used to assess animal motor coordination. On the training day, animals were placed on a rotating rod at a speed of 15 rpm. On the following day, the time animals remained on the rotating rod was recorded over 3 trials at the same rotation speed.

The test substances were administered intragastrically at equimolar doses of 1/100 and 1/30 of the molecular weight, which amounted to doses of 3 mg/kg and 9 mg/kg for most compounds (Table 1). The reference drugs phenotropil and diazepam were administered at doses of 30 mg/kg and 1 mg/kg, respectively. Previous studies on the psychotropic activity of compounds structurally similar to those included in this work showed some psychotropic properties at doses of 1/10 and 1/30 of the molecular weight. At the low dose of 1/100, efficacy was practically not observed.

Synthesis

^{1}H and ^{13}C NMR spectra were recorded at 298 K on a «Bruker Avance-400» spectrometer (operating frequency 400 MHz, internal standard Me_4Si). Positive ion MALDI-TOF mass spectra were obtained on a Bruker Daltonics Autoflex II instrument using 1,8,9-trihydroxyanthracene as the matrix and polyethylene glycols PEG-200 and PEG-300 as internal standards. Preparative column chromatography was performed using "Merck" silica gel (40/60). The starting commercially available compounds: 1-bromo-4-chlorobenzene, 1-bromo-4-fluorobenzene, p-bromobenzonitrile, p-bromoanisole, p-iodoanisole, 4-iodobenzotrifluoride, *rac-2,2'*-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 2-(dicyclohexylphosphino)-2'-dimethylaminobiphenyl (DavePhos), rac-1,1'-bi(2-naphthol) (BINOL), sodium tert-butoxide, cesium carbonate from SigmaAldrich and ABCR were used without special purification. Amine 1 was prepared according to the method described in [28]. $Pd(dba)_2$ was synthesized according to the method described by T. Ukai et al. [29]. DMSO and DMFA of "ch" grade were used without further purification, dioxane was absolutized by distillation over sodium, dichloromethane and petroleum ether for chromatography were freshly distilled.

***N*-(Adamantan-1-ylmethyl)-4-chloroaniline (1).** Method (a). To a 10 mL two-necked flask equipped with a reflux condenser, magnetic stirrer, and filled with argon, were added 1-bromo-4-chlorobenzene (1.1 mmol, 211 mg), $Pd(dba)_2$ (1 mol%, 5.7 mg), BINAP (1.25 mol%, 7.8 mg), 5 mL of dioxane, amine 1 (1 mmol, 165 mg), sodium tert-butoxide (1.5 mmol, 144 mg), and the reaction mixture was heated to reflux for 6 hours. After completion of the reaction, the mixture was cooled, the solution was separated from the precipitate by filtration, the precipitate was washed with 5 mL of dichloromethane, the combined organic fractions were evaporated in a rotary evaporator under vacuum, and the residue was analyzed by ^{1}H NMR spectroscopy. Method (b). Performed analogously to method (a) using $Pd(dba)_2$ (2 mol%, 11.5 mg), BINAP (2.5 mol%, 15.5 mg). Method (c). Performed analogously to method (a) in a 25 mL flask using 1-bromo-4-chlorobenzene (2.2 mmol, 421 mg), $Pd(dba)_2$ (2 mol%, 23 mg), BINAP (2.5 mol%, 31 mg), amine 1 (2 mmol, 330 mg), sodium tert-butoxide (3 mmol, 288 mg), in 10 mL of dioxane. The reaction by method (c) was performed twice. The combined residues from methods (a), (b), and (c) were chromatographed on silica gel using a gradient of eluents: petroleum ether, petroleum ether–dichloromethane (9 : 1–1 : 1). The target compound 2 was isolated with the eluent petroleum ether–dichloromethane 9 : 1. Yield 906 mg (55 %). ^{1}H NMR spectrum, δ, ppm: 1.55–1.57 m (6H,

CH_2(Ad)), 1.63–1.75 m (6H, CH_2(Ad)), 1.99 br. s (3H, CH(Ad)), 2.75 s (2H, CH_2N), 3.96 br. s (1H, NH), 6.56 br. d (2H, $^3J_{obs.}$ = 8.1 Hz, H2,2'(Ar)), 7.06–7.10 m (2H, H3,3'(Ar)). ^{13}C NMR spectrum, δ, ppm: 28.3 (3 CH(Ad)), 33.9 (C(Ad)), 37.0 (3 CH_2(Ad)), 40.6 (3 CH_2(Ad)), 56.3 (CH_2N), 113.5 (C2,2'(Ar)), 120.9 (C4(Ar)), 128.8 (C3,3'(Ar)), 147.1 (C1(Ar)). MALDI-TOF mass spectrum: m/z, found 276.1565 $[M+H]^+$. $C_{17}H_{23}ClN$. Calculated: *M* + H 276.1519.

***N*-(Adamantan-1-ylmethyl)-4-fluoroaniline (2)**. In a 25 mL two-necked flask equipped with a reflux condenser, magnetic stirrer, and filled with argon, were placed 1-bromo-4-fluorobenzene (2.2 mmol, 385 mg), $Pd(dba)_2$ (4 mol%, 46 mg), DavePhos (4.5 mol%, 35 mg), 10 mL of dioxane, amine **1** (2 mmol, 330 mg), sodium tert-butoxide (3 mmol, 288 mg), and the reaction mixture was heated to reflux for 6 hours. After completion of the reaction, the mixture was cooled, the solution was separated from the precipitate by filtration, the precipitate was washed with 5 mL of dichloromethane, the combined organic fractions were evaporated in a rotary evaporator under vacuum, and the residue was analyzed by ^{1}H NMR spectroscopy. The synthesis was performed three times. The combined residues were chromatographed on silica gel using a gradient of eluents: petroleum ether, petroleum ether–dichloromethane (9 : 1–1 : 1). The target compound 3 was isolated with eluents petroleum ether–dichloromethane (1.5 : 1–1 : 1). Yield 970 mg (62 %). ^{1}H NMR spectrum, δ, ppm: 1.57–1.59 m (6H, CH_2(Ad)), 1.66–1.77 m (6H, CH_2(Ad)), 2.02 br. s (3H, CH(Ad)), 2.75 s (2H, CH_2N), 3.54 br. s (1H, NH), 6.56 d. m (2H, $^4J_{HF}$ = 4.4 Hz, H2,2'(Ar)), 6.86–6.90 d. m (2H, $^4J_{HF}$ = 8.7 Hz, H3,3'(Ar)). The spectrum corresponds to that reported in S.P. Panchenko et al. [30].

4-((Adamantan-1-ylmethyl)amino)benzonitrile (3). Method (a). To a 10 mL two-necked flask equipped with a reflux condenser, magnetic stirrer, and filled with argon, were added p-bromobenzonitrile (1.1 mmol, 200 mg), $Pd(dba)_2$ (2 mol%, 11.5 mg), BINAP (2.5 mol%, 15.5 mg), 5 mL of dioxane, amine 1 (1 mmol, 165 mg), sodium tert-butoxide (1.5 mmol, 144 mg), and the reaction mixture was heated to reflux for 6 hours. After completion of the reaction, the mixture was cooled, the solution was separated from the precipitate by filtration, the precipitate was washed with 5 mL of dichloromethane, the combined organic fractions were evaporated in a rotary evaporator under vacuum, and the residue was analyzed by ^{1}H NMR spectroscopy. Method (b). Performed analogously to method (a) in a 25 mL flask using p-bromobenzonitrile (3.3 mmol, 601 mg), $Pd(dba)_2$ (2 mol%, 34 mg), BINAP (2.5 mol%, 46 mg), 15 mL of dioxane, amine 1 (3 mmol, 495 mg), sodium tert-butoxide (4.5 mmol, 432 mg). The combined residues were chromatographed on silica gel using a gradient of eluents: petroleum ether, petroleum ether–dichloromethane (9 : 1–1 : 1), dichloromethane. The target compound **4** was isolated with eluents petroleum ether–dichloromethane (2 : 1–1 : 1). Yield 940 mg (88 %). ^{1}H NMR spectrum, δ, ppm: 1.52–1.54 m (6H, CH_2(Ad)), 1.60–1.72 m (6H, CH_2(Ad)), 1.97 br. s (3H, CH(Ad)), 2.80 s (2H, CH_2N), 4.42 br. s (1H, NH), 6.54–6.56 m (2H, H2,2'(Ar)), 7.33–7.35 m (2H, H3,3'(Ar)). ^{13}C NMR spectrum, δ, ppm: 28.0 (3 CH(Ad)), 34.0 (C(Ad)), 37.0 (3 CH_2(Ad)), 40.3 (3 CH_2(Ad)), 55.0 (CH_2N), 97.2 (C4(Ar)), 111.8 (C2,2'(Ar)), 120.7 (CN), 133.4 (C3,3'(Ar)), 152.2 (C1(Ar)). MALDI-TOF mass spectrum: m/z, found 267.1830 $[M+H]^+$. $C_{18}H_{23}N_2$. Calculated: *M* + H 267.1861.

***N*-(Adamantan-1-ylmethyl)-4-methoxyaniline (4).** In a hermetically sealed 8 mL vial equipped with a magnetic stirrer, were placed p-iodoanisole (3.75 mmol, 878 mg), CuI (10 mol%, 57 mg), rac-BINOL (20 mol%, 172 mg), amine 1 (3 mmol, 495 mg), cesium carbonate (3.75 mmol, 1.22 g), 6 mL of DMF, and the reaction mixture was stirred with heating at 140°C for 24 hours. After completion of the reaction, the mixture was cooled, the solution was separated from the precipitate by filtration, the precipitate was washed twice with 5 mL of dichloromethane, the combined organic fractions were evaporated in a rotary evaporator under vacuum, and the residue was analyzed by ^{1}H NMR spectroscopy. The synthesis was performed twice. The combined residues were chromatographed on silica gel using a gradient of eluents: petroleum ether, petroleum ether–dichloromethane (5 : 1–1 : 1), dichloromethane. Target compound 5 was isolated with petroleum ether–dichloromethane eluents (2 : 1–1 : 1). Yield 920 mg (57 %). 1H NMR spectrum, δ, ppm: 1.57–1.59 m (6H, CH2(Ad)), 1.65–1.76 m (6H, CH_2(Ad)), 2.00 br s (3H, CH(Ad)), 2.74 s (2H, CH_2N), 3.39 br s (1H, NH), 3.74 s (1H, OMe), 6.57–6.60 m (2H, H2,2'(Ar)), 6.76–6.78 m (2H, H3,3'(Ar)). The spectrum corresponds to that reported in the communication by S.P. Panchenko et al. [30].

***N*-(Adamantan-1-ylmethyl)-4-(trifluoromethyl) aniline (5).** To a hermetically screw-capped 8 ml vial equipped with a magnetic stirrer, p-iodobenzotrifluoride (3.75 mmol, 1.02 g), CuI (10

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2026-14-3-307-322

mol%, 57 mg), rac-BINOL (20 mol%, 172 mg), amine 1 (3 mmol, 495 mg), cesium carbonate (3.75 mmol, 1.22 g), and 6 ml DMF were added. The reaction mixture was stirred and heated at 140 °C for 24 h. After completion of the reaction, the mixture was cooled, the solution was separated from the precipitate by filtration, and the precipitate was washed twice with 5 ml of dichloromethane. The combined organic fractions were evaporated in a vacuum rotary evaporator, and the residue was analyzed by 1H NMR spectroscopy. The synthesis was performed twice. The combined residues were chromatographed on silica gel using petroleum ether as the eluent. Yield 650 mg (35%). 1H NMR spectrum, δ, ppm: 1.55–1.57 m (6H, CH_2(Ad)), 1.63–1.75 m (6H, CH_2(Ad)), 2.00 br s (3H, CH(Ad)), 2.82 s (2H, CH_2N), 4.01 br s (1H, NH), 6.58–6.60 m (2H, H2,2'(Ar)), 7.35–7.37 m (2H, H3,3'(Ar)). The spectrum corresponds to that reported in the communication by S.P. Panchenko et al. [30].

Ethics approval

The study design was approved by the Local Ethics Committee of the Volgograd State Medical University, protocol No. 2022/116 dated March 04, 2022 (IRB registration number 00005839 IORG 0004900 [OHRP]).

The following measures were taken to limit pain and suffering of experimental animals in the studies:

- The minimum possible number of experimental animals was used in the experiment.
- High qualification of personnel involved in the care and all manipulations with animals, which were performed in accordance with the standard operating procedures (SOPs) developed in the laboratory. To exclude the possible negative impact of circadian biorhythms on the research results, all experimental studies were conducted at the same intervals and under the same climatic conditions (all long-term studies were planned so that their completion fell within the same time of year, except for the "holding" stages without manipulations). Handling before experimental sessions allowed for the exclusion of the negative impact of insufficient animal adaptation to the human factor. It also provided an opportunity to assess the health status of laboratory animals for external damage (condition of the coat, mucous membranes, behavior). Euthanasia upon completion of experimental studies was carried out according to the rules of the Guide 1.

Statistical Processing

Statistical analysis was performed using the GraphPad Prism 9.0 software package (GraphPad Software Inc., USA). The conformity of the data to the normal distribution law was assessed using the Shapiro–Wilk test. To determine the statistical significance of differences between groups with normal distribution, one-way ANOVA was used, followed by Dunnett's post-hoc test (for comparing experimental groups with the control). For distributions other than normal, the non-parametric Kruskal-Wallis test was used, followed by Dunn's test. Results were presented as the arithmetic mean and standard error of the mean (M ± SEM). Differences were considered statistically significant at $p < 0.05$.

RESULTS AND DISCUSSION

Synthesis of N-aryl derivatives of (adamantan-1-yl)methylamine

For biological studies, several *N*-aryl derivatives of (adamantan-1-yl)methylamine **(1)** were synthesized, containing various electron-donating and electron-withdrawing substituents in the *para*-position of the phenyl ring. Reactions between amine 1 and the corresponding bromoarenes were carried out under palladium-catalyzed amination conditions, initially in the presence of the $Pd(dba)_2$ / BINAP catalytic system (dba=dibenzylideneacetone, BINAP=*rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), which has proven to be highly versatile, including for *N*-arylation of various adamantane-containing amines [25, 26]. The reactions were carried out using a 10 mol% excess of bromoarenes, in the presence of sodium tert-butoxide base, under reflux in dioxane (amine concentration 0.2 M) for 6 h (Fig. 1).

When performing Pd-catalyzed arylation of primary amines, the lowest possible catalyst loadings should be used to suppress side *N,N*-diarylation of the primary amino group [25, 26]. When using 2 mol% of the catalyst, the reaction of amine 1 with 1-bromo-4-chlorobenzene proceeded with a 61 % yield of the target compound 2 in the reaction mixture. Upon reducing the catalyst loading to 1 mol%, the yield remained unchanged (60 %), while with a higher

[1] Guidelines for conducting preclinical studies of medicines; Scientific Center for Expertise of Medical Products. Part 1. Moscow: Grif and K; 2012. 944 p. EDN: SDEWMP. Russian

catalyst amount, the proportion of *N,N*-diarylation product increased. Therefore, the synthesis scaling was carried out with a Pd(dba)2/BINAP loading of 2/2.5 mol%. After chromatographic purification on silica gel, target product 2 was isolated with a yield of 55%.

In the case of 1-bromo-4-fluorobenzene, reactions in the presence of 2 and 4 mol% of the Pd(dba)2 / BINAP catalytic system were insufficiently effective, with the yield of amination product 3 not exceeding 45% in the reaction mixture. Replacing the BINAP ligand with DavePhos (2-(dicyclohexylphosphino)-2'-dimethylaminobiphenyl) increased the product yield to 74% in the reaction mixture. As a result, compound 3 was isolated chromatographically with a yield of 62 %. When p-bromobenzonitrile was introduced into the reaction, it proceeded excellently in the presence of 2 mol% $Pd(dba)_2$ / BINAP (93 % yield in the reaction mixture), and target product 4 was obtained with a preparative yield of 88 %. However, the palladium-catalyzed reaction with the electron-donating p-bromoanisole proved completely ineffective, with target compound 5 forming in a negligible 13% yield, while C-C coupling occurred to a greater extent, forming 4,4'-dibromobiphenyl (5a) (approximately 50%). Consequently, an alternative copper-catalyzed arylation of amine 1 using *p*-iodoanisole was undertaken (Fig. 2).

We have previously established that copper-catalyzed N-arylation reactions of adamantane-containing amines proceed successfully with CuI catalysis in DMSO at 110°C and in DMF at 140 °C [20]. Copper nanoparticles can also be used when conducting reactions in DMSO. In all cases, the optimal ligand is rac-BINOL (1,1›-bi(2-naphthol)). Reactions are carried out in the presence of cesium carbonate base at an amine concentration of 0.5 M for 24 hours and with a slight excess (25 mol%) of the arylating agent. The reaction of amine 1 with p-iodoanisole proceeded equally successfully in DMSO and DMF, with the yield of target product 5 being over 80 % (in the reaction mixture) in both cases. For simpler isolation during scaling (solvent evaporation without the need for extraction), the reaction in DMF was chosen. After chromatographic isolation, compound 5 was obtained with a preparative yield of 57 %. Under analogous conditions, the reaction with the electron-withdrawing p-iodobenzotrifluoride was also performed, yielding compound 6 with 72 % in the reaction mixture and 35 % after chromatographic purification. Thus, a series of five N-aryl derivatives of (adamantan-1-yl) methylamine of high purity was obtained in quantities of 0.6–1 g, suitable for biological testing.

Biological Studies

Results of Series 1 Studies

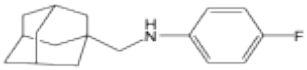
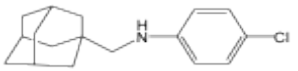
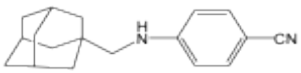
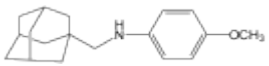
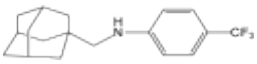
Series 1 studies on the effect of a series of adamantane derivatives with substituents -F, -Cl, -CN, -OMe, -CF3 at the 4-position showed that they exert an activating effect. Based on this, phenotropil, which has activating and nootropic effects, was chosen as the reference drug. In the OF test with mice that received compounds XF, XCF3, and the reference drug phenotropil, higher spontaneous motor activity was observed (82 ± 2, 93.7 ± 6.8, 80.7 ± 13.3, respectively), and compound XF also showed higher exploratory activity (19.5 ± 9.5). Animals receiving compounds XF made more transitions in the central zone of the illuminated arena (37 ± 4), and at a dose of 3 mg/kg, only individual animals showed a lower number of fecal boli, which are considered markers of vegetative signs of anxious behavior (Fig. 3).

In the EPM test, animals that were administered compound XF at a dose of 3 mg/kg 60 minutes before testing, left the central platform faster, made more transitions between arms, and spent more time in the open arms of the apparatus where they performed head-dipping (Fig. 4).

The presented results of animal behavior in the OF and EPM allow us to conclude that compound XF exhibits anxiolytic and antiphobic effects. Considering these properties of substance XF, which are characteristic of benzodiazepine-class substances whose undesirable effect is muscle relaxation, we planned the "Animal Hanging on a Horizontal Rope" test. Based on the time animals spent on the rope (over 30 sec) compared to the control group, a conclusion was drawn about the presence of muscle relaxant effects. If animals held on for a shorter time compared to the control group, it indicated the presence of muscle relaxant effects, and if they held on for the same or longer time than the control group, it indicated the absence of muscle relaxant effects (possibly even an increase in grip strength and anterior paw muscle contraction force). In our experiment, the tested substances did not exhibit muscle relaxant effects, and animals receiving compound XF at a dose of 9 mg/kg held on to the horizontal rope longer than others (Fig. 5).

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2026-14-3-307-322

Table 1 — Test Compounds

№	Name	Structural Formula	Molecular Weight, g/mol	Multiplicity to Mr	Dose of Substance, mg/kg	Designation
1	*N*-((3R,5R,7R)-adamantan-1-ylmethyl)-4-fluoroaniline		259.36	1/100	3	F_100
				1/30	9	F_30
2	*N*-((3R,5R,7R)-adamantan-1-ylmethyl)-4-chloroaniline		275.82	1/100	3	Cl_100
				1/30	9	Cl_30
3	4-(((3R,5R,7R)-adamantan-1-ylmethyl)amino)benzonitrile		266.38	1/100	3	CN_100
				1/30	9	CN_30
4	*N*-((3R,5R,7R)-adamantan-1-ylmethyl)-4-methoxyaniline		271.40	1/100	3	OMe_100
				1/30	9	OMe_30
5	*N*-((3R,5R,7R)-adamantan-1-ylmethyl)-4-(trifluoromethyl) aniline		309.37	1/100	3	CF3_100
				1/30	10	CF3_30

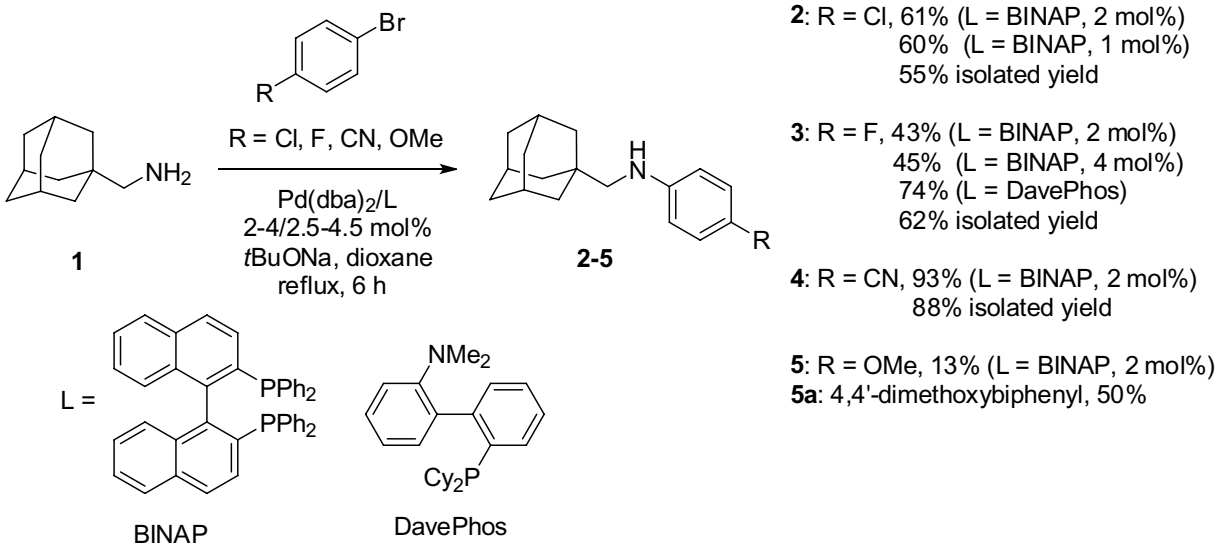


Figure 1 — Synthesis of N-aryl derivatives of adamantanamines under palladium-catalyzed amination conditions.

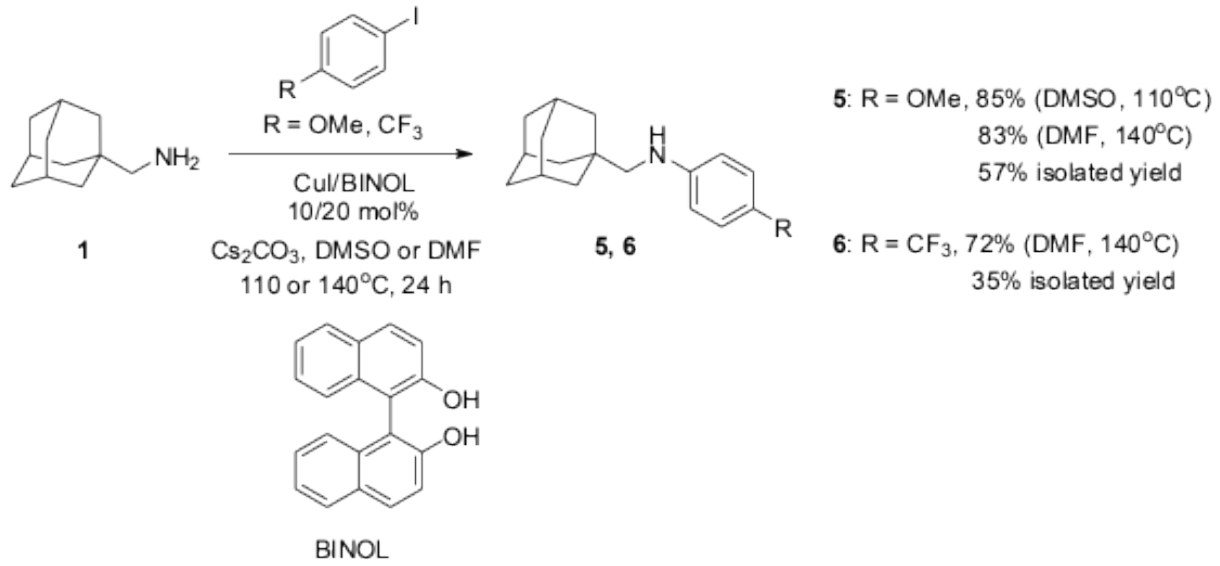


Figure 2 — Synthesis of *N*-aryl derivatives under copper compound catalysis.

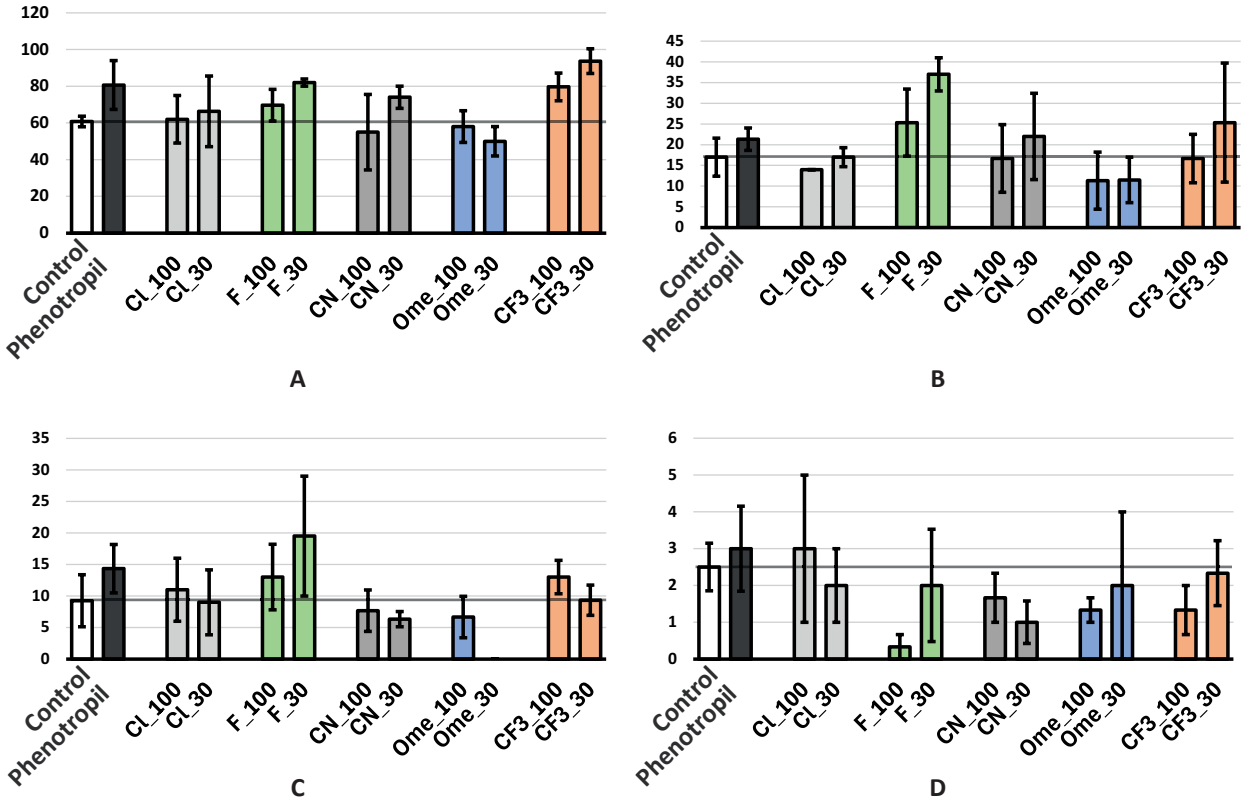


Figure 3 — Behavior of mice in the "Open Field" test.

Note: A: number of crossed squares; B: number of crossed squares in the central zone; C: total exploratory activity; D: number of fecal pellets.

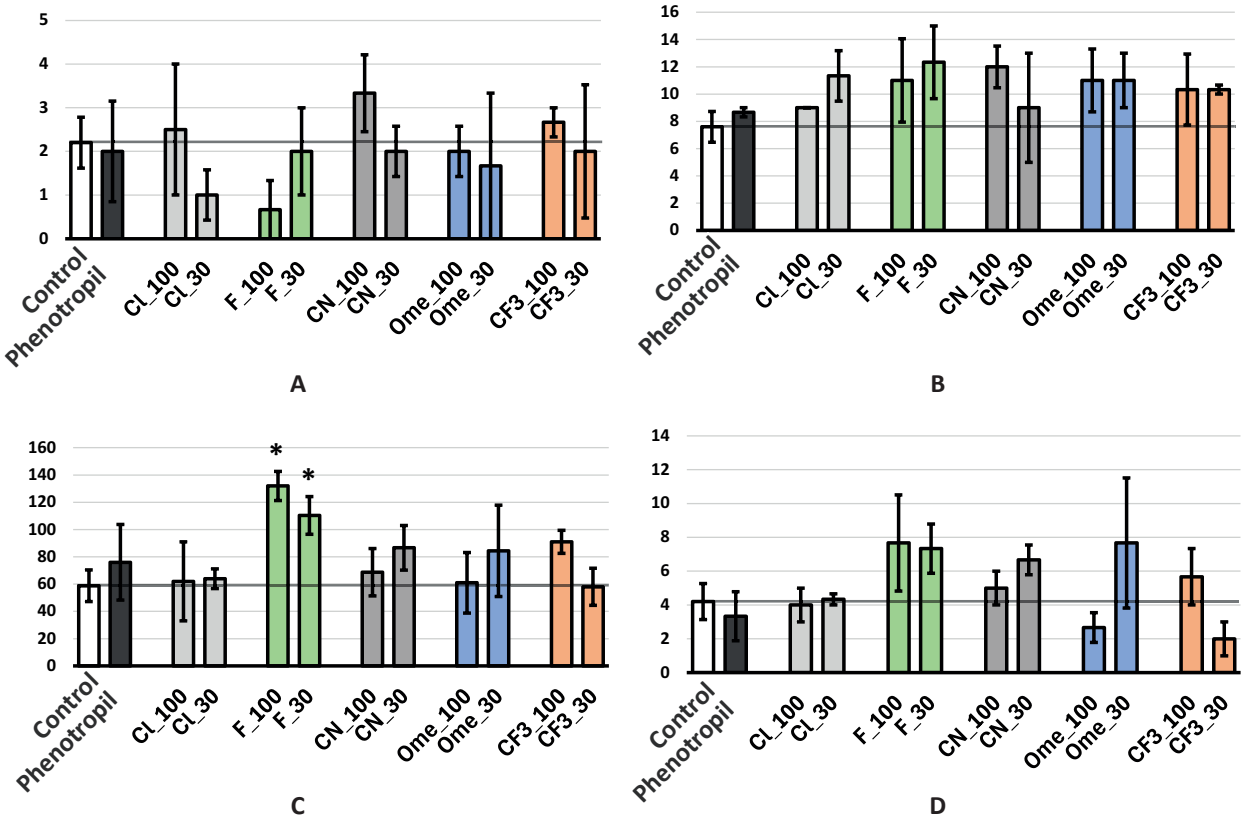


Figure 4 — Behavior of mice in the "Elevated Plus Maze" test.

Note: A: latency (s) to exit the center; B: number of transitions between arms; C: time (s) in the open arm of the apparatus; D: number of head dips from the open arm; * value is statistically significant compared to the control group ($p < 0.05$), Kruskal-Wallis test followed by Dunn's test.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2026-14-3-307-322

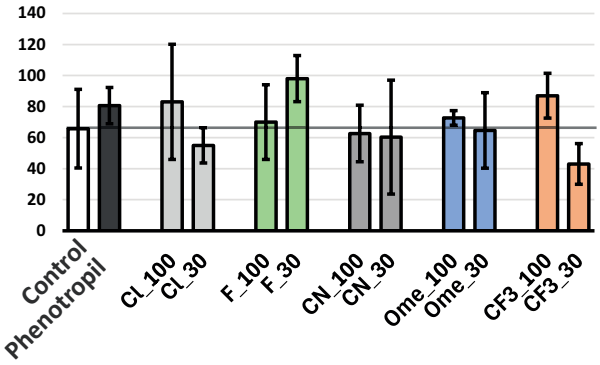


Figure 5 — Behavior of mice in the "Body Retention on a Horizontal Rope" test.

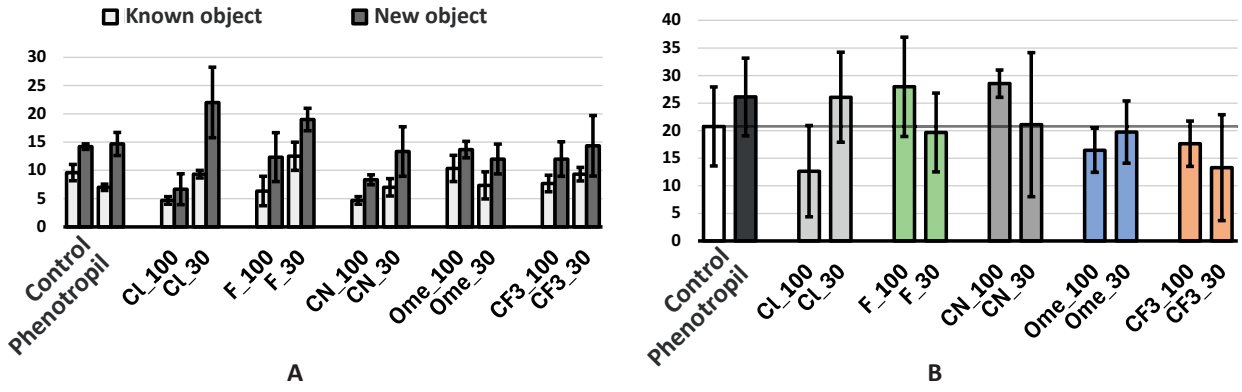


Figure 6 – Behavior of mice in the "Novel Object Recognition" test.
Note: A: time (s) of object investigation; B: discrimination ratio.

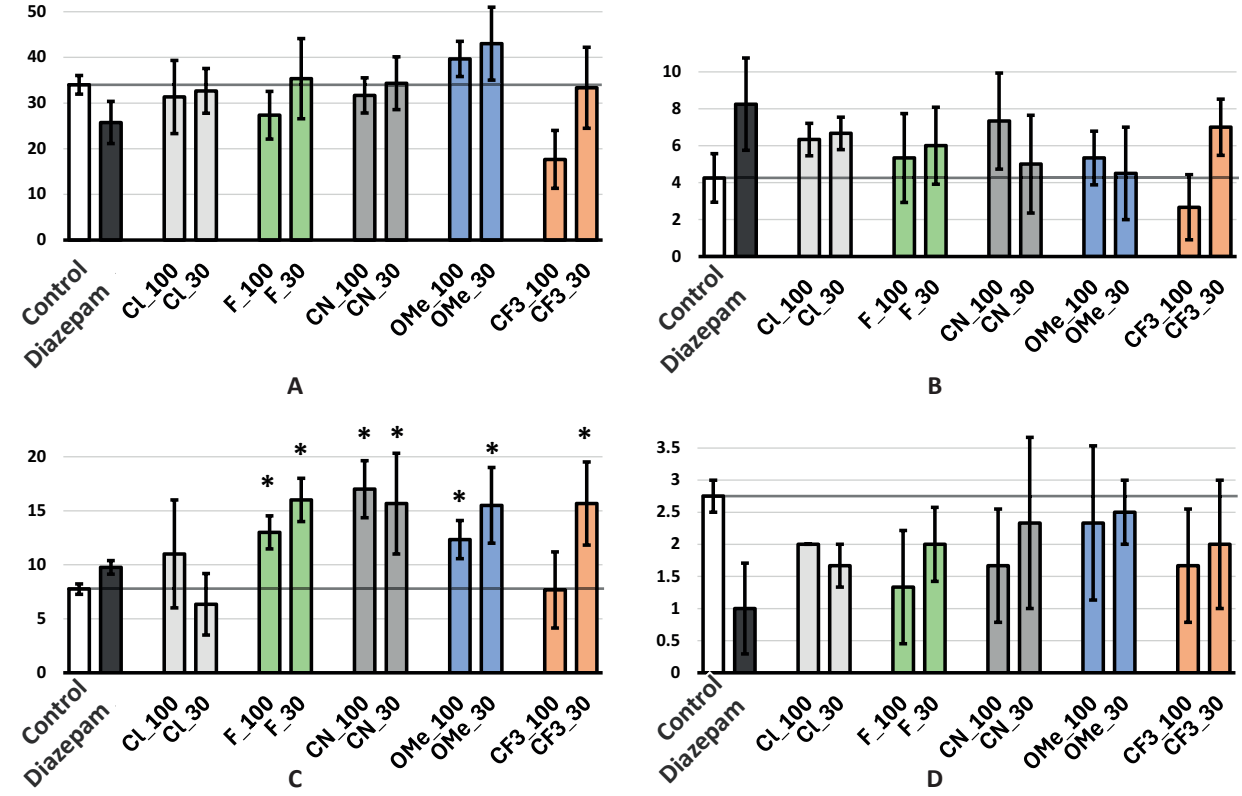


Figure 7 — Behavior of rats in the "Open Field" test.
Note: A: number of crossed squares; B: number of crossed squares in the central zone; C: total exploratory activity; D: number of fecal pellets; * value is statistically significant compared to the control group ($p < 0.05$), Kruskal-Wallis test followed by Dunn's test.

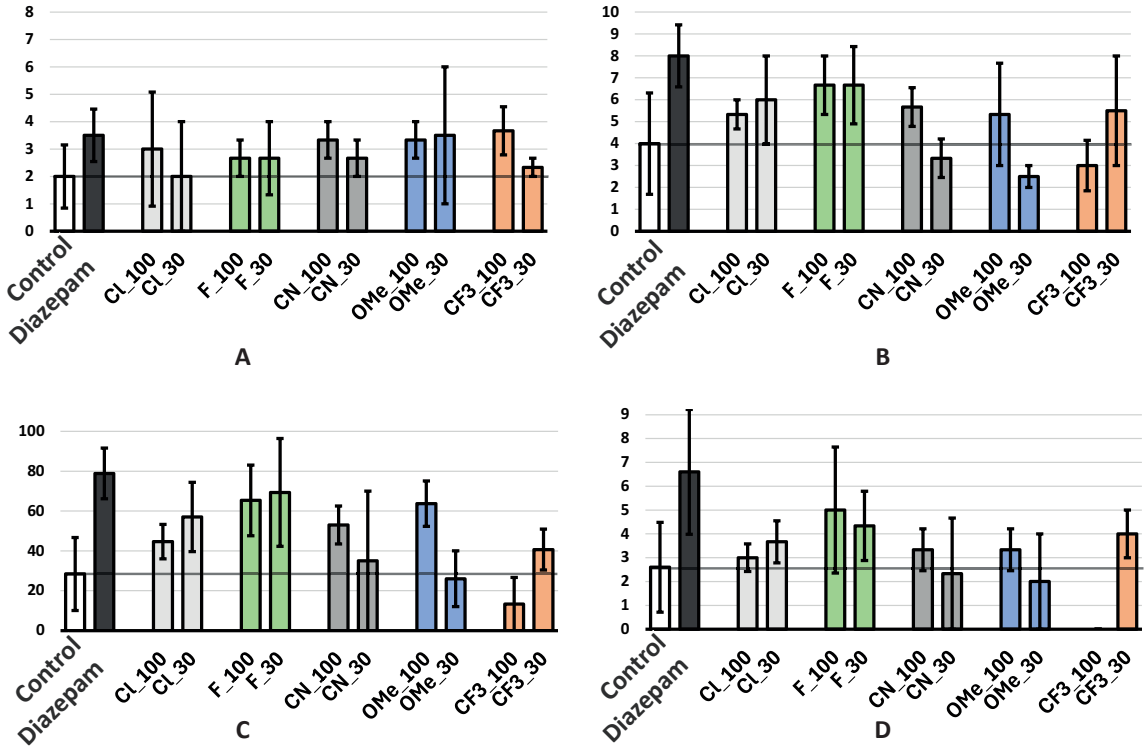


Рисунок 8 — Показатели поведения крыс в тесте «Приподнятый крестообразный лабиринт».

Примечание: А — латентный период (с) выхода из центра; Б — количество переходов между рукавами; В — время (с) в открытом рукаве установки; Г — количество свешиваний с открытого рукава.

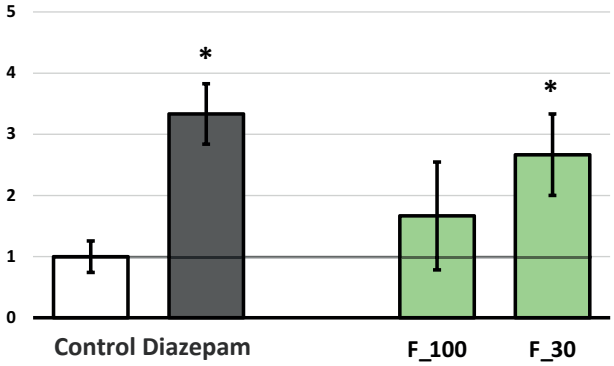


Figure 9 — Behavior of rats in the "Vogel's Punished Water Intake" test.

Note: * value is statistically significant compared to the control group ($p < 0.05$), Kruskal-Wallis test followed by Dunn's test.

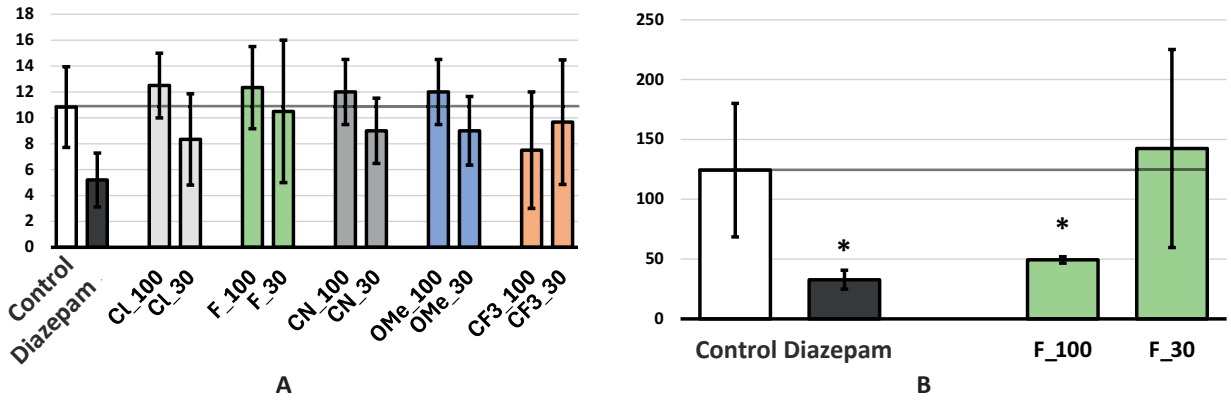


Figure 10 — Behavior of rats in the "Body Retention on a Horizontal Rope" and "Rotarod" tests.

Note: A: time (s) of retention on the rope; B: time of retention in the Rotarod test; * value is statistically significant compared to the control group ($p < 0.05$), Kruskal-Wallis test followed by Dunn's test.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2026-14-3-307-322

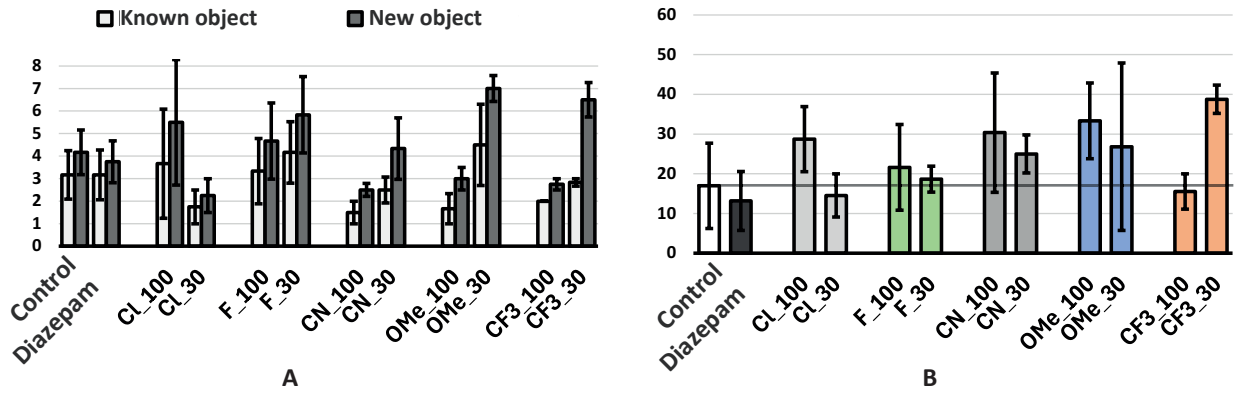


Figure 11 — Behavior of rats in the "Novel Object Recognition" test.
Note: A: time (s) of object investigation; B: discrimination ratio.

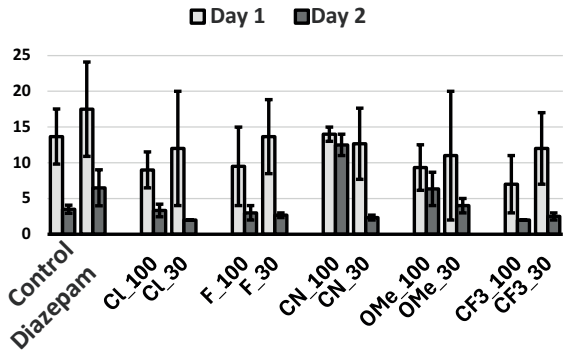


Figure 12 — Behavior of rats in the "Extrapolation Escape" test.

In the NOR test in mice, it was noted that all animals that received phenotropil, as a reference drug, as well as those that received compounds XCl at a dose of 9 mg/kg, XF, and XCN, studied the new object significantly longer than the familiar one, after a preliminary familiarization session with the objects. The presented data suggest that compounds XCl, XF, and XCN, similar to and comparable with phenotropil, improve declarative memory (Fig. 6).

The presented data on the spectrum and severity of the psychotropic effects of adamantane derivatives with substituents -F, -Cl, -CN, -OMe, -CF3 at the 4-position showed that the most pronounced anxiolytic and antiphobic effect of compound XF prompted us to re-investigate these effects in an experiment on rats with the reference drug diazepam.

Results of Series 2 Studies

The following presents data from *Series 2* experiments conducted on adult male rats aged 12 months.

In the OF test, animals in almost all groups crossed an equal number of squares, but animals administered diazepam, and to a lesser extent XCl, XF, XCN, crossed more squares in the central zone than animals in the control group. Overall exploratory activity was statistically significantly higher in the groups administered substances XF, XCN, XOMe, and XCF3 than in the control group animals. All animals receiving the tested substances showed fewer fecal boli compared to the control animals (Fig. 7).

In the variable stress test "Elevated Plus Maze" (EPM), animals left the central platform within the first 3–4 seconds after placement. However, a greater number of transitions between arms was observed only in animals receiving diazepam. Nevertheless, longer time spent in the open arm and the number of head-dips were observed only in animals receiving the reference drug diazepam and compound XF (Fig. 8).

Thus, based on the data obtained in the OF and EPM tests, some anxiolytic and antiphobic effects were noted in animals receiving the reference drug diazepam and, to a lesser extent, compound XF, which is consistent with the data obtained in mice.

To confirm the anxiogenic effect, animals were tested in the Vogel test (punished drinking). After 48 hours of water deprivation, animals administered compound XF at a dose of 9 mg/kg approached the

water dispenser statistically significantly more often than animals in the control group, but less often than animals receiving diazepam (Fig. 9).

In the tests of body retention on a horizontal rope and Rotarod, the time of retention on the rope and rotating rod did not differ from the indicators of the control group, which received purified water. Animals receiving diazepam held on to the rope and rotating rod for a shorter time than animals in the control group, which is explained by the muscle relaxant effect inherent in almost all benzodiazepine-class anxiolytics. The remaining animals receiving the tested substances held on to the rope for the same duration as the control group animals. The data indicate that the tested compounds do not exert a muscle relaxant effect. In the Rotarod test, animals receiving diazepam and compound XF at a dose of 3 mg/kg held on to the rotating rod for a shorter time (Fig. 10).

In the NOR test on rats, it was noted that all animals receiving the tested substances did not show impairment of attention and declarative memory (Fig. 11).

In the test of extrapolative avoidance, neither improvement nor deterioration in the formation of memory trace and declarative memory was revealed upon administration of all tested drugs (Fig. 12).

Study Limitations

The limitations of this study include the unevenness and small sample size: experimental groups included 3 animals each, while control groups had 6, which could have affected the statistical power in assessing behavioral reactions. Furthermore, the psychotropic profile of the synthesized compounds was assessed exclusively under conditions of single intragastric administration.

CONCLUSION

Thus, the study of the spectrum of psychotropic effects of adamantane derivatives with substituents -F, -Cl, -CN, -OMe, -CF3 revealed fluoraniline, which exhibits pronounced anxiolytic and antiphobic effects, does not cause muscle relaxation, and does not impair motor coordination or cognitive function. Based on the presented data, it is considered expedient to further investigate the psychotropic and neurotropic properties of compound XF, including the development of its improved structures, possibly with greater activity and a different spectrum of psychotropic action.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

CONTRIBUTION OF THE AUTHORS

Nikita S. Bolokhov, Alexander A. Pokhlebin — investigation, validation, writing—original draft; Ivan N. Tyurenkov — conceptualization, writing—review & editing; Evgenii N. Savel'ev, Elena A. Alykova — investigation; Ivan A. Novakov — conceptualization; Arina V. Murashkina, Alexei D. Averin — investigation; Irina P. Beletskaya – administration, conceptualization. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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