Original article

The psycho- and neurotropic profiling of novel 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones *in vivo*

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ABSTRACT

The article presents the study of psycho- and neurotropic properties of novel 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones *in vivo*. The research was carried out using the open field test, elevated plus maze, rotarod test, tail suspension test, passive avoidance test after scopolamine-induced amnesia and acute normobaric hypoxia with hypercapnia. As a result, two promising substances have been found. According to our results 3-[[(4-methoxyphenyl)amino]methyl]-2-methyl-1H-quinolin-4-one in the dose of 10 mg/kg shows a specific sedative effect and a considerable anti-amnesic activity. The most interesting N-[(2-methyl-4-oxo-1H-quinolin-3-yl)methyl]-N-phenylbenzamide (100 mg/kg) combines a potent anti-anxiety action, the anti-amnesic activity and a considerable antihypoxic effect. They are of interest for further profound studies as promising psychoactive compounds.
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1. Introduction

1.1. Background of the research

The idea to study 3-N-R,R′-aminomethyl derivatives of 2-methyl-1H-quinolin-4-ones as psycho- and neurotropic agents appeared in our research team in early 2000s and grounded on certain structural similarity of these compounds with 5-hydroxytryptamine (Zubkov et al., 2005). The first pharmacological study of this new class of compounds was modest and included only six representatives in the doses of 10 mg/kg and 100 mg/kg – four molecules with dimethylaminomethyl substituent in position 3 of quinolone ring and different substituents in aromatic part, one phenylaminomethyl and one 2′-pyridinaminomethyl derivatives (Shtrygol' et al., 2010).

The experimental data of *in vivo* screening confirmed the high anti-amnesic activity of all 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones studied in the passive avoidance test after

scopolamine-induced anterograde amnesia (Shtrygol' et al., 2010). Moreover, some compounds showed additional valuable psychotropic properties. For example, 3-(dimethylaminomethyl)-2,8-dimethyl-1H-quinolin-4-one combined the anti-amnesic activity with the anti-anxiety action (Shtrygol' et al., 2010). However, our attention was attracted by 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one that showed the excellent antidepressant activity in the tail suspension test in the dose of 100 mg/kg (Shtrygol' et al., 2010, 2012). This compound was chosen as a leader for the in-depth research under the code name of "atristamine".

The unique spectrum of additional neuropharmacological properties of this molecule (antihypoxic, anti-amnesic, alco-protective) was investigated (Podolsky et al., 2013a, 2013b, 2014). Using the ELISA method it was shown that a reliable decrease in the concentration of 5-hydroxitriptamine (-16.8%, $p < .05$) was consistent with the increased levels of dopamine ($+22.0\%$) and epinephrine ($+13.0\%$) in the brain of mice after administration of atristamine in the dose of 100 mg/kg (Shtrygol' et al., 2011). It was also proven that atristamine (100 mg/kg) had protective effects against traumatic brain injury in rats (Podolsky and Shtrygol, 2015).

The main results of the previous pharmacological studies of atristamine are briefly presented in Table 1.

Thus, it may be concluded that 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones are, undoubtedly, interesting objects for the further research as psychoactive substances. However, it has been found that the profile of activity for each substance is unpredictable since a minor modification of the chemical structure can

Table 1
The main results of the previous pharmacological studies of 2-methyl-3-(phenylaminomethyl)-1H-quinolin-4-one (atristamine).

Test, indicators		Vehicle control	Atristamine	
			10 mg/kg	100 mg/kg
Tail suspension test	Duration of immobility, s	113.0 ± 23.1	93.2 ± 7.3	32.7 ± 16.3[*] (−71.0%)
Passive avoidance test after scopolamine-induced amnesia	Anti-amnesic activity, %	–	91.6	84.3
Open field test	Square crossings	25.7 ± 5.9	37.4 ± 9.1	40.3 ± 7.8
	Exploratory nose-pokes	13.3 ± 4.0	16.8 ± 1.2	13.7 ± 2.1
	Rearings	4.3 ± 0.9	3.2 ± 1.1	10.7 ± 1.4[*]
	Fecal boli	0.1 ± 0.1	0.4 ± 0.2	0.7 ± 0.5
	Urinations	0	0	0
	Groomings	0.9 ± 0.3	1.4 ± 0.4	2.3 ± 0.6[*]
Acute hypoxia with hypercapnia	The hypoxia tolerance time, min	18.4 ± 0.5	n/s	20.9 ± 0.7[*] (+13.6%)
Weight-loaded forced swimming test	Swimming time, s	4.3 ± 0.8	n/s	12.8 ± 4.0[*] (+298.0%)

n/s – Not studied.
  [*] Significant at p < .05 compared to the corresponding vehicle control group (Student's t-test);

cause profound changes of biological effects right up to diametrically opposite.

1.2. Selection criteria of candidate compounds

The objects of this experimental study **2a-j** and the leader of our previous studies atristamine **1** are presented in Table 2. Moreover, certain computational study of "drug-likeness" properties preceded pharmacological tests to reveal violations of Lipinski's "Rule of 5".

3-(N-R,R′-Aminomethyl)-2-methyl-1H-quinolin-4-ones with different substituents in various positions of the phenyl moiety **2a-f** constituted the main range of objects to find the effect of the nature and the position of substituents on the spectrum of activity compared to atristamine. 6-Methoxysubstituted analogue of atristamine **2g** was selected taking into account the results of the previous study (Shtrygol' et al., 2010) where 3-(dimethylamino methyl)-6-methoxy-2-methyl-1H-quinolin-4-one showed a high physiological activity (predominantly, anxiogenic) that might be explained by the greater similarity to 5-hydroxytryptamine analogues (5-methoxy-N,N-dimethyltryptamine, 5-methoxy-α-methy ltryptamine, etc.). 3-[[[4-(1-Adamantyl)thiazol-2-yl]amino]methy l]-2-methyl-1H-quinolin-4-one **2h** was added as a heterocyclic analogue of atristamine with the highest values of the molecular weight, Fsp3, clogP and pKa (that is not associated with the hydrogen of the amino group) in spite of violation of Lipinski's "Rule of 5". N-Benzoylated derivatives **2i-j** were chosen to study how the absence of hydrogen in the aminomethyl moiety affects the biological activity.

Thus, present study was undertaken to implement the *in vivo* profiling of psycho- and neurotropic properties of new 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones that are structurally similar to atristamine and reveal the possible "structure-activity relationships" (SAR) features for these derivatives. The open field test, the elevated plus maze, the rotarod test, the tail suspension test, the passive avoidance test and acute normobaric hypoxia with hypercapnia were used for these purposes. The results obtained will expand current knowledge about pharmacological properties of this poorly explored class of compounds and could become the basis for the further researches in this field.

2. Materials and methods

2.1. Chemicals

3-(N-R,R′-Aminomethyl)-2-methyl-1H-quinolin-4-ones was synthesized from 2-methyl-1H-quinolin-4-one *via* aminomethyla-

tion and further interaction of the Mannich base obtained with the corresponding amines as described earlier (Zubkov et al., 2005). N-Benzoylated derivatives were obtained by acylation of 2-methy l-3-(phenylaminomethyl)-1H-quinolin-4-one with benzoyl chloride or *o*-chlorobenzoyl chloride in the appropriate conditions. The identity of the compounds synthesized was confirmed by 1H-NMR spectroscopy.

2.2. Computational data

All computational parameters of compounds, such as molar weight (MW), the number of hydrogen bond donors (HBD) and acceptors (HBA), the fraction of sp³-hybridized carbons (Fsp3), topological polar surface area (TPSA), pKa, clogP and clogS were calculated using a Chemicalize free online service by ChemAxon.

2.3. Animal groups and treatment

Adult random-bred male albino mice (with the body weight of 18–24 g) were included in the present study. The animals were obtained from the vivarium of the Central Research Laboratory (National University of Pharmacy, Kharkiv, Ukraine). All experimental protocols were approved by the Bioethics Commission of the National University of Pharmacy. Experiments were carried out in accordance with "Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes".

The mice were housed in standard polypropylene cages and kept at 20–26 °C and 50% humidity in a well-ventilated room with a 12 h light/dark cycle with free access to food and water (Deacon, 2006).

Considering duration of behavioural tests the general experiment was divided into 5 parts involving 1 control group of animals and 4 test groups per week. Doses of 10 mg/kg and 100 mg/kg for each compound were chosen to make unified comparison with the results of the previous study possible (Shtrygol' et al., 2010).
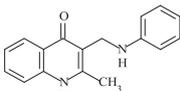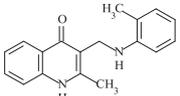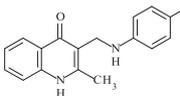
All mice were randomly assigned to 26 groups as presented in Table 3.

Drugs were administered intragastrically as aqueous suspensions stabilized with Tween-80 once a day at the same time. The mice of the control groups received saline intragastrically by the similar scheme. The volume of liquid that the animals in all groups received was similar and equalled to 0.1 mL/10 g.

Each part of the experiment started with the preliminary administration of drugs for two days before behavioural tests. On the third day the open field test, elevated plus maze and rotarod test were performed. On the fourth day the tail suspension test

Table 2
The structures of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones and their main "drug-likeness" properties.

	Formula	MW	Nrot	TPSA	HBD	HBA	Fsp3	pKa	clogP	clogS	Ro5
1		264.3	3	41.13	2	3	0.12	4.23	3.23	−4.04	+
2a		278.4	3	41.13	2	3	0.17	4.18	3.74	−4.31	+
2b		278.4	3	41.13	2	3	0.17	4.67	3.74	−4.54	+
2c		294.4	4	50.36	2	4	0.17	4.58	3.07	−4.04	+
2d		294.4	4	50.36	2	4	0.17	5.27	3.07	−4.04	+
2e		279.3	3	67.15	3	4	0.12	4.55	2.40	−3.86	+
2f		336.4	6	67.43	2	4	0.20	3.25	3.59	−4.53	+
2g		294.4	4	50.36	2	4	0.17	4.23	3.07	−4.04	+
2h		405.6	4	54.02	2	4	0.50	3.45 (not amino-group)	5.31	−6.95	−
2i		368.4	4	49.41	1	3	0.08	–	4.71	−6.40	+
2j		402.9	4	49.41	1	3	0.08	–	5.32	−7.10	−
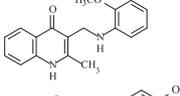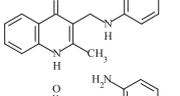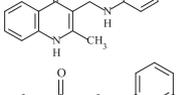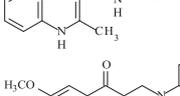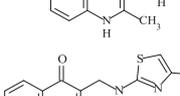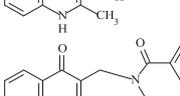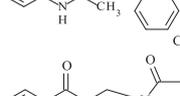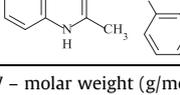
Notes. MW – molar weight (g/mol); Nrot – the number of rotatable bonds; TPSA – the topological polar surface area (Å²); HBD and HBA – the numbers of hydrogen bond donors and acceptors, respectively; Fsp3 – the fraction of sp3-hybridized carbon atoms; pKa – the acid-base dissociation constant; clogP – the logarithm of the partition coefficient calculated at pH = 7.4; clogS – the logarithm (base 10) of aqueous solubility calculated at pH = 7.4; Ro5 – violation of Lipinski's "Rule of 5".

and the training session of passive avoidance test were carried out. The final day started with the test session of the passive avoidance test (in 24 h) and ended with acute normobaric hypoxia with hypercapnia.

The interval between drug administration and the beginning of the study was 1 h for each mouse. All behavioural tests were conducted from 10 a.m. up to 6 p.m. taking into account the chrono-physiological aspects of the animal behaviour.

2.4. Pharmacology

All behavioural tests were performed in a silence room. The animals were transported from the housing room to the testing area in their home cages and were allowed to adapt for 1 h before testing. The test equipment was thoroughly cleaned with 96% ethanol and sponged over to get rid of residual odours before each mouse was tested.

2.4.1. Combined open field test

The open field test is a common measure of the exploratory behaviour and the general activity in both mice and rats where both the quality and quantity of the activity can be measured (Gould et al., 2009; Vogel, 2008). During the 3-min test period the number of square crossings (the locomotor activity), the number of exploratory nose-pokes and rearing responses (the horizontal and vertical exploratory activity), the number of grooming acts, fecal boli and urinations (emotional reactions) were counted.

2.4.2. Elevated plus maze

The elevated plus maze is a widely used behavioural assay for rodents, and it has been validated to assess the anti-anxiety effects of pharmacological agents (Walf and Frye, 2007). During the test period (5 min) the number of entries into the enclosed arms and into the open arms, the time spent in each compartment were

Table 3
The characteristics of experimental groups of animals.

Group	Compound	Dose, mg/kg	Number of animals, n
I	The vehicle group for training criterion control in the passive avoidance test		9
II	The vehicle control 1 for groups III–VI		8
III	2c	10	8
IV	2c	100	8
V	2d	10	8
VI	2d	100	8
VII	The vehicle control 2 for groups VIII–XI		8
VIII	2a	10	8
IX	2a	100	9
X	2e	10	8
XI	2e	100	8
XII	The vehicle control 3 for groups XIII–XVI		8
XIII	2h	10	8
XIV	2h	100	8
XV	2i	10	8
XVI	2i	100	8
XVII	The vehicle control 4 for groups XVIII–XXI		8
XVIII	2f	10	8
XIX	2f	100	8
XX	2g	10	8
XXI	2g	100	8
XXII	The vehicle control 5 for groups XXIII–XXVI		8
XXIII	2b	10	8
XXIV	2b	100	8
XXV	2j	10	8
XXVI	2j	100	7

recorded. The latency of the first entry into arm, the number of fecal boli and urinations were also registered.

2.4.3. Rotarod test

The rotarod test was used to evaluate the motor coordination and the balance of mice by the apparatus consisting of a rotating rod with separate lanes (Curzon et al., 2009; Shiotsuki et al., 2010).

2.4.4. Tail suspension test

Since its introduction almost 20 years ago the tail suspension test has become one of the most widely used models for assessing the antidepressant-like activity in mice (Cryan et al., 2005). The mice were suspended on the support using the adhesive plaster superimposed on the tip of the tail (Vogel, 2008). The total duration of the animal's immobility was registered within the period of 6 min.

2.4.5. Passive avoidance test after scopolamine-induced amnesia

The passive avoidance test has long been used as a screening test to evaluate drug effects on the memory in rodents (Banfi et al., 1982). This test (Vogel, 2008) was chosen in order to evaluate the effects of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones 2a-j against the scopolamine-induced memory deficit. Scopolamine is a muscarinic receptor antagonist, which induces a cholinergic deficiency modelling to some extent of the memory deficits observed in Alzheimer's disease (Ebert and Kirch, 1998).

All animals were medicated with scopolamine hydrobromide (i. p. in water solution, 1.5 mg/kg) in 30 min before the training session for inducing anterograde amnesia.

The anti-amnesic activity (AA) was calculated using the formula:

$$AA = \frac{\Delta Tc - \Delta Tsc}{\Delta Ti - \Delta Tsc} \cdot 100\%$$

where ΔTc – is the difference between latencies in training and test sessions for the animal group treated with the compound;

ΔTsc – is the difference between latencies in training and test sessions for animals from the group of amnesia control;

ΔTi – is the difference between latencies in training and test sessions for animals from the vehicle control group.

2.4.6. Acute normobaric hypoxia with hypercapnia

Acute normobaric hypoxia with hypercapnia in mice was induced by placing animals in the equal individual transparent jars (200 ml) equipped with leakproof lids. After simultaneous screwing of lids the survival time of mice (the time to stop breathing) was recorded (Karpova et al., 2014).

2.5. Statistical analysis

The results are expressed as the mean (M) ± standard error of the mean (SEM). Statistical differences between groups were analysed using Student's t-test (in the case of normal distribution) and the Fisher's angular transformation (if necessary, with Yates's correction). The level of statistical significance was considered to be p < .05.

3. Results

3.1. Open field test

Analysis of the experimental data presented in Table 4 shows that animals treated with compounds **2a**, **2b**, **2h** and **2i** have no significant differences in indicators compared to the corresponding vehicle control groups.

The tendency towards decrease of the locomotor activity and the total sum of emotional reactions for *ortho*-methoxyphenylaminomethyl substituted **2c** in the dose of 10 mg/kg should be noted, and it can be the evidence of a weak sedative effect on mice which disappears in the 10-fold greater dose.

The results for *para*-methoxy derivative **2d** were more interesting – in the dose of 10 mg/kg the 3-fold decrease of square crossings (p < .01), a considerable reduction of defecations (p < .05) and, as a result, the 2-fold decrease of the total activity sum (p < .01) were observed. However, these changes in the locomotor activity and emotional reactions were not accompanied by the explorative activity impairment. This reflects a certain selectivity of sedation that can be a positive feature of this compound. In the dose of 100 mg/kg effects on behavioural indicators were the same but less pronounced.

The 6-methoxy substituted analogue of atristamine **2g** also attracted our attention. As can be seen from Table 4, in the dose of 10 mg/kg this compound increased the locomotor activity to 50% (p < .05) without any influence on another behavioural indicators. However, in a 10-fold greater dose in addition to the increased ambulation (to 43%, p < .05) the elevated number of rearing responses (to 89%, p < .05) indicating intensification of the psychostimulative action was observed. At the same time, the absence of any impact on emotional reactions in both doses should be noted as a positive feature of this compound.

A significant stimulating effect of **2f** in a higher dose (predominantly, on ambulation) and the anxiogenic action for **2j** in a lower dose (by the increased number of defecations) should be noted.

3.2. Elevated plus maze

Analysis of the experimental data presented in Table 5 shows that N-benzoylated derivatives **2i** and **2j** are the most interesting

Table 4
The effect of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones on the behavioural responses of mice in the combined open field test.

Animal group, compound	Dose, mg/kg	Square crossings	Exploratory nose-pokes	Rearings	Total explorative activity	Groomings	Fecal boli	Urinations	Total sum of emotional reactions	Total activity sum
Vehicle control 1		61.4 ± 8.7	21.9 ± 4.3	8.9 ± 2.7	30.8 ± 5.5	2.9 ± 1.2	1.5 ± 0.5	0.4 ± 0.2	4.8 ± 1.5	96.9 ± 12.8
2c	10	39.3 ± 8.0	26.9 ± 3.8	7.1 ± 2.1	34.0 ± 5.3	1.1 ± 0.3	0.6 ± 0.4	0.1 ± 0.1	1.5 ± 0.8	75.1 ± 12.7
	100	48.9 ± 7.4	27.9 ± 4.0	6.1 ± 2.0	34.0 ± 4.9	1.0 ± 0.2	0.6 ± 0.5	0.0 ± 0.0	1.9 ± 0.9	84.5 ± 9.8
2d	10	20.0 ± 5.2**	17.4 ± 2.4	5.8 ± 1.9	23.1 ± 4.2	1.6 ± 0.8	0.0 ± 0.0*	0.0 ± 0.0	1.5 ± 0.6	44.8 ± 8.3**
	100	37.3 ± 4.7*	22.3 ± 1.7	7.8 ± 1.4	30.0 ± 1.5	1.9 ± 0.9	0.0 ± 0.0*	0.0 ± 0.0	1.6 ± 0.5	69.1 ± 5.0
Vehicle control 2		39.8 ± 7.9	30.3 ± 3.6	3.1 ± 1.5	33.4 ± 3.9	0.6 ± 0.3	0.7 ± 0.5	0.1 ± 0.1	1.5 ± 0.5	74.6 ± 11.3
2a	10	29.1 ± 2.9	29.0 ± 3.3	2.8 ± 0.5	31.8 ± 3.8	0.6 ± 0.3	0.6 ± 0.3	0.1 ± 0.1	1.4 ± 0.6	62.3 ± 5.7
	100	35.0 ± 5.4	32.3 ± 1.6	4.4 ± 1.4	36.8 ± 2.3	0.7 ± 0.2	1.9 ± 0.7	0.0 ± 0.0	2.6 ± 0.8	74.3 ± 6.1
2e	10	54.4 ± 6.7	32.6 ± 2.3	7.4 ± 1.2*	40.0 ± 2.6	0.7 ± 0.2	1.1 ± 0.6	0.3 ± 0.2	2.1 ± 0.5	96.5 ± 6.9
	100	47.1 ± 5.0	30.3 ± 2. 6	5.5 ± 1.6	35.8 ± 3.4	0.7 ± 0.2	1.0 ± 0.4	0.0 ± 0.0	1.8 ± 0.4	84.6 ± 7.2
Vehicle control 3		38.8 ± 6.3	27.5 ± 3.3	8.8 ± 2.8	36.3 ± 5.4	0.7 ± 0.4	0.4 ± 0.2	0.3 ± 0.2	1.4 ± 0.5	76.4 ± 11.6
2h	10	32.4 ± 7.6	27.6 ± 3.2	3.5 ± 1.9	31.1 ± 4.3	1.1 ± 0.6	0.7 ± 0.4	0.0 ± 0.0	1.9 ± 0.9	65.4 ± 10.0
	100	38.9 ± 5.7	32.9 ± 3.0	5.3 ± 1.7	38.1 ± 3.4	0.4 ± 0.2	1.9 ± 0.8	0.0 ± 0.0	2.3 ± 0.8	79.3 ± 7.7
2i	10	38.9 ± 4.1	35.4 ± 2.1$	4.1 ± 1.4	39.5 ± 2.6	0.5 ± 0.4	0.7 ± 0.4	0.1 ± 0.1	1.4 ± 0.5	79.8 ± 5.4
	100	33.1 ± 6.2	23.9 ± 4.6$	4.0 ± 1.9	27.9 ± 5.5	0.0 ± 0.0	0.7 ± 0.41	0.0 ± 0.0	0.8 ± 0.4	61.8 ± 11.5
Vehicle control 4		34.4 ± 5.0	41.8 ± 3.8	6.1 ± 1.0	47.9 ± 4.3	0.3 ± 0.2	0.9 ± 0.6	0.1 ± 0.1	1.3 ± 0.8	83.5 ± 7.6
2g	10	51.5 ± 4.0*	44.1 ± 2.9	7.8 ± 1.9	51.9 ± 2.2	0.0 ± 0.0	1.0 ± 0.5	0.0 ± 0.0	1.0 ± 0.5	104.4 ± 4.5*
	100	49.1 ± 4.2*	44.1 ± 3.2	11.5 ± 2.3*	55.6 ± 4.1	0.1 ± 0.1	0.5 ± 0.2	0.0 ± 0.0	0.6 ± 0.3	105.4 ± 5.7*
2f	10	51.3 ± 8.0	51.1 ± 3.7	6.5 ± 2.5	57.6 ± 5.7	0.3 ± 0.2	0.0 ± 0.0	0.3 ± 0.2	0.5 ± 0.2	109.4 ± 13.2
	100	50.3 ± 3.4*	47.4 ± 3.3	8.6 ± 1.5	56.0 ± 3.8	0.7 ± 0.4	0.6 ± 0.4	0.1 ± 0.1	1.5 ± 0.5	107.8 ± 3.6*
Vehicle control 5		39.5 ± 4.8	32.0 ± 3.8	9.5 ± 2.2	41.5 ± 5.8	0.6 ± 0.3	0.5 ± 0.3	0.1 ± 0.1	1.3 ± 0.5	82.3 ± 9.4
2b	10	35.0 ± 3.5	26.6 ± 2.8	6.6 ± 2.0	33.3 ± 3.4	0.9 ± 0.3	1.4 ± 0.6	0.0 ± 0.0	2.3 ± 0.6	70.5 ± 4.4
	100	36.8 ± 9.6	26.5 ± 3.6	6.5 ± 2.6	33.0 ± 4.6	0.6 ± 0.2	0.1 ± 0.1	0.4 ± 0.2	1.1 ± 0.4	70.9 ± 12.9
2j	10	37.3 ± 3.5	31.8 ± 3.3	4.3 ± 1.3	36.0 ± 3.5	1.4 ± 0.4	2.3 ± 0.7*	0.0 ± 0.0	3.6 ± 0.9*	76.9 ± 6.1
	100	33.4 ± 4.9	27.6 ± 4.3	4.6 ± 1.6	32.1 ± 4.6	1.0 ± 0.3	1.3 ± 0.5	0.6 ± 0.3	2.9 ± 0.6	68.4 ± 9.4

* Significant at p < .05 compared to the corresponding vehicle control group.
** Significant at p < .01 compared to the corresponding vehicle control group.
$ Significant at p < .05 compared to the group of animals receiving another dose of the drug.

Table 5
The effect of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones on the behavioural responses of mice in the elevated plus maze.

Animal group, compound	Dose, mg/kg	Latency of the first entry, s	Time spent in open arms, s	Inter-arm crossings	Number of open-arm entries	Number of fecal boli	Number of urinations
Vehicle control 1		4.9 ± 1.2	67.9 ± 19.0	10.9 ± 2.7	1.4 ± 0.4	0.6 ± 0.4	0.1 ± 0.1
2c	10	4.9 ± 1.2	47.4 ± 14.1	6.4 ± 2.4	1.3 ± 0.5	0.1 ± 0.1	0.0 ± 0.0
	100	4.8 ± 2.8	106.3 ± 32.4	9.6 ± 2.9	1.1 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
2d	10	6.8 ± 2.8	53.4 ± 27.4	2.4 ± 1.1*	0.4 ± 0.3	1.3 ± 0.7	0.0 ± 0.0
	100	3.0 ± 0.9	45.4 ± 15.6	7.1 ± 2.3	1.1 ± 0.3	0.0 ± 0.0	0.0 ± 0.0
Vehicle control 2		8.5 ± 3.4	46.0 ± 8.3	7.5 ± 2.1	0.8 ± 0.4	0.0 ± 0.0	0.0 ± 0.0
2a	10	18.0 ± 8.4	61.5 ± 17.5	6.0 ± 2.0	0.8 ± 0.4	0.6 ± 0.6	0.0 ± 0.0
	100	44.4 ± 29.5	60.1 ± 28.0	1.7 ± 0.9*	0.1 ± 0.1	0.8 ± 0.4	0.2 ± 0.2
2e	10	10.0 ± 3.5	23.9 ± 5.9*	2.0 ± 0.6*	0.1 ± 0.1	1.1 ± 0.5*	0.0 ± 0.0
	100	15.5 ± 8.7	63.6 ± 30.3	3.5 ± 1.2	0.5 ± 0.3	0.4 ± 0.3	0.0 ± 0.0
Vehicle control 3		11.0 ± 4.0	47.5 ± 14.0	5.0 ± 2.1	0.5 ± 0.3	0.9 ± 0.4	0.0 ± 0.0
2h	10	47.0 ± 36.4	87.4 ± 34.3	4.8 ± 1.7	0.4 ± 0.3	1.5 ± 0.8	0.0 ± 0.0
	100	26.6 ± 11.1	59.6 ± 12.6	5.1 ± 1.6	0.3 ± 0.2	0.8 ± 0.6	0.0 ± 0.0
2i	10	13.6 ± 5.9	98.8 ± 35.0	6.6 ± 1.8	0.6 ± 0.5	0.4 ± 0.3	0.1 ± 0.1
	100	28.0 ± 9.2	117.0 ± 28.5*	5.6 ± 1.9	1.1 ± 0.5	1.4 ± 0.5	0.0 ± 0.0
Vehicle control 4		10.9 ± 3.4	68.9 ± 16.2	8.3 ± 2.4	1.6 ± 0.8	0.0 ± 0.0	0.0 ± 0.0
2g	10	4.4 ± 1.2	67.8 ± 24.3	6.3 ± 1.7	0.9 ± 0.5	0.0 ± 0.0	0.0 ± 0.0
	100	5.5 ± 1.5	87.4 ± 20.8	11.1 ± 1.9	2.3 ± 1.0	0.0 ± 0.0	0.0 ± 0.0
2f	10	13.5 ± 3.9	84.3 ± 10.5	8.0 ± 1.1	1.3 ± 0.5	0.9 ± 0.4*	0.0 ± 0.0
	100	17.5 ± 4.9	106.6 ± 9.2	11.1 ± 1.1	1.6 ± 0.5	0.6 ± 0.4	0.0 ± 0.0
Vehicle control 5		14.5 ± 3.9	56.9 ± 11.3	6.8 ± 1.1	0.4 ± 0.3	0.6 ± 0.3	0.0 ± 0.0
2b	10	10.3 ± 2.6	42.8 ± 11.3	5.4 ± 1.1	1.3 ± 0.3	1.3 ± 0.6	0.0 ± 0.0
	100	21.1 ± 6.3	69.0 ± 10.5	4.9 ± 1.1	0.6 ± 0.3	1.6 ± 0.6	0.1 ± 0.1
2j	10	15.1 ± 5.3	75.4 ± 15.7	4.0 ± 0.9	0.5 ± 0.2	0.3 ± 0.2	0.0 ± 0.0
	100	30.0 ± 8.7	118.9 ± 25.0*	5.3 ± 1.6	0.6 ± 0.4	0.6 ± 0.3	0.0 ± 0.0

* Significant at p < .05 compared to the corresponding vehicle control group.

substances by their effect on the main marker of anxiety behaviour – the total time spent in open arms. Animals treated with **2i** in the dose of 100 mg/kg stayed in the open arms of the maze almost by 2.5 times longer (p < .05) than animals from the vehicle control group 3. The difference in this measure for the animal group

administered 100 mg/kg of **2j** compared to the vehicle control group 5 was 2.1 times (p < .05). This fact reveals the anti-anxiety properties of N-benzoylated analogues.

For *ortho*-aminophenyl substituted derivative **2e** in a lower dose the pronounced anxiogenic action was proven. It was

determined by a significant 2-fold decrease of the time spent in open arms (p < .05), almost 4 times more rare inter-arm crossings (p < .05) and the increased number of defecations (p < .05).

3.3. Rotarod test

To avoid presentation of a wide data array it can be briefly stated that there are no substances impairing motor coordination of mice among 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones studied.

3.4. Passive avoidance test

The results obtained in the passive avoidance test generally confirmed our assumptions about inherency of the anti-amnesic activity to 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones grounded on the previous screening study (Shtrygol' et al., 2010). As can be seen from Table 6, most of the substances tested in one or both doses displayed a considerable protective effect against chemo-induced amnesia. The only exception was heterocyclic derivative **2h**, which was almost inactive in both doses. It is important to note that N-benzoylated **2i** and **2j** showed a slightly weaker activity compared to phenylamino derivatives. This confirms the importance of the secondary amino group existence in the molecule structure for exhibiting the anti-amnesic effect.

3.5. Tail suspension test

Since atristamine, the leader of the previous studies, has a considerable antidepressant activity, a special interest to the results of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones in the tail suspension test is completely predictable.

As can be seen from Table 7, there were no substances which showed a significant antidepressant action. But some derivatives have interesting features. For example, derivatives **2a** and **2b**, being structurally most relative to atristamine, tended to show the antidepressant activity in one or both doses. Substance **2e** with the amino group in the ortho-position of the phenyl moiety, conversely, insignificantly increases duration of the mice immobility in both doses. A special attention was attracted by 6-methoxysubstituted **2g** and N-(2′-chlorobenzoyl)-N-phenylderivative **2j**, which displayed the dose-dependent reversal of the effect (p < .05 for **2g** and p < .01 for **2j**). This is quite common peculiarity of psychotropic drugs, which, however, greatly restricts their use.

3.6. Acute normobaric hypoxia with hypercapnia

As well known, most psychoactive substances in therapeutic doses increase the hypoxia tolerance in rodents due to their effects on trophic factor cascades and apoptosis (Drzyzga et al., 2009). Therefore, it was interesting to evaluate the effect of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones on the survival time of mice under conditions of acute hypoxia with hypercapnia as the final stage of the general experiment (Luk'janova, 1990). Unfortu-

Table 6
The effect of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones on the results of the passive avoidance test after scopolamine-induced amnesia.

Animal group, compound	Dose, mg/kg	Latency to entry, s			Animals achieved training criterion		Anti-amnesic activity
		Initial	In 24 h	Δ	abs.	%	
Vehicle control, n = 9		17.7 ± 2.3	157.4 ± 13.3	139.8 ± 12.6	6/9	66.7	–
Control of amnesia 1, n = 7 (scopolamine, 1.5 mg/kg)		8.1 ± 2.4	60.9 ± 29.6	52.7 ± 28.1	1/7	14.3	–
2c	10 (n = 7)	26.1 ± 8.2	129.7 ± 30.7	103.6 ± 28.8	4/7	57.1[&]	58.4
	100 (n = 8)	43.0 ± 9.5	168.5 ± 11.5	125.5 ± 11.3[*]	7/8	87.5[&&]	83.6
2d	10 (n = 8)	31.4 ± 9.2	160.6 ± 18.1	129.3 ± 19.6[*]	6/8	75.0[&&]	87.9
	100 (n = 8)	17.4 ± 2.6	138.6 ± 21.7	121.3 ± 22.1	5/8	62.5[&]	78.7
Control of amnesia 2, n = 8 (scopolamine, 1.5 mg/kg)		13.9 ± 2.5	54.5 ± 10.2	40.6 ± 10.0	0/8	0.0	–
2a	10 (n = 8)	15.0 ± 3.3	161.1 ± 11.5	146.1 ± 10.6[***]	5/8	62.5[&&]	106.4
	100 (n = 9)	17.1 ± 2.6	155.2 ± 12.7	138.1 ± 14.3[***]	6/9	66.7[&&]	98.3
2e	10 (n = 8)	16.3 ± 3.0	152.3 ± 12.6	136.0 ± 10.8[***]	4/8	50.0[&&]	96.2
	100 (n = 8)	18.0 ± 2.4	130.6 ± 16.0	112.6 ± 15.9[**]	3/8	37.5[&&]	72.6
Control of amnesia 3, n = 8 (scopolamine, 1.5 mg/kg)		19.6 ± 4.2	53.0 ± 14.0	33.4 ± 14.2	0/8	0.0	–
2h	10 (n = 8)	20.0 ± 4.4	74.3 ± 16.6	54.3 ± 16.4	1/8	12.5	19.6
	100 (n = 8)	20.4 ± 4.0	88.5 ± 21.7	68.1 ± 22.6	2/8	25.0[&]	32.7
2i	10 (n = 8)	23.9 ± 6.2	112.9 ± 22.5	89.0 ± 22.7	3/8	37.5[&&]	52.3
	100 (n = 8)	15.6 ± 4.6	117.5 ± 26.1	101.9 ± 25.7[*]	4/8	50.0[&&]	64.4
Control of amnesia 4, n = 8 (scopolamine, 1.5 mg/kg)		15.0 ± 3.4	69.5 ± 16.7	54.5 ± 16.0	1/8	12.5	–
2g	10 (n = 8)	19.9 ± 4.3	143.6 ± 17.3	123.8 ± 17.3[*]	4/8	50.0[&]	81.2
	100 (n = 8)	23.5 ± 3.3	156.8 ± 16.2	133.3 ± 17.2[**]	6/8	75.0[&&]	92.3
2f	10 (n = 8)	17.1 ± 3.5	124.1 ± 18.1	107.0 ± 17.1[*]	3/8	37.5	61.5
	100 (n = 8)	21.8 ± 4.5	125.4 ± 21.9	103.6 ± 20.7	4/8	50.0[&]	57.6
Control of amnesia 5, n = 8 (scopolamine, 1.5 mg/kg)		19.0 ± 4.9	65.1 ± 14.9	46.1 ± 17.6	0/8	0.0	–
2b	10 (n = 8)	17.5 ± 3.3	127.3 ± 21.1	109.8 ± 19.0[*]	4/8	50.0[&&]	67.9
	100 (n = 8)	16.9 ± 4.9	145.0 ± 18.9	128.1 ± 20.3[**]	5/8	62.5[&&]	87.5
2j	10 (n = 8)	19.4 ± 5.0	118.3 ± 20.2	98.9 ± 19.3	3/8	37.5[&&]	56.3
	100 (n = 7)	16.7 ± 3.7	123.3 ± 20.4	106.6 ± 19.2[*]	3/7	42.9[&&]	64.5

[*] Significant at p < .05 respectively, compared to the corresponding vehicle control group (Student's *t*-test);

[**] Significant at p < .01 respectively, compared to the corresponding vehicle control group (Student's *t*-test);

[***] Significant at p < .001, respectively, compared to the corresponding vehicle control group (Student's *t*-test);

[&] Significant at p < .05 respectively, compared to the corresponding vehicle control group (Fisher's angular transformation).

[&&] Significant at p < .01, respectively, compared to the corresponding vehicle control group (Fisher's angular transformation).

Table 7
The effect of 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones on the results of the tail suspension test and acute normobaric hypoxia with hypercapnia.

Animal group, compound	Dose, mg/kg	Tail suspension test – duration of immobility, s	Acute hypoxia with hypercapnia – the hypoxia tolerance time, min
Vehicle control 1		78.1 ± 11.5	n/s
2c	10	76.3 ± 16.5	n/s
	100	87.6 ± 11.8	n/s
2d	10	77.1 ± 11.9	n/s
	100	81.4 ± 9.8	n/s
Vehicle control 2		91.6 ± 12.7	26.4 ± 1.6
2a	10	67.3 ± 8.2 (−26.5%)	31.5 ± 1.2[*] (+19.4%)
	100	79.2 ± 15.0 (−13.2%)	28.3 ± 1.6
2e	10	109.0 ± 15.5 (+19.0%)	27.0 ± 1.4
	100	105.0 ± 13.0 (+14.6%)	29.5 ± 1.6
Vehicle control 3		84.8 ± 20.0	22.3 ± 0.7
2h	10	77.3 ± 14.4	24.1 ± 1.5
	100	89.0 ± 13.7	21.9 ± 1.4
2i	10	106.9 ± 18.6 (+26.1%)	23.8 ± 1.0
	100	84.1 ± 13.9	28.3 ± 0.9[***] (+27.3%)
Vehicle control 4		86.3 ± 13.8	26.4 ± 1.8
2g	10	62.5 ± 13.1[$] (−27.6%)	22.1 ± 1.1 (−16.3%)
	100	126.1 ± 18.3[$] (+46.1%)	22.2 ± 0.8[*] (−15.9%)
2f	10	90.4 ± 12.1	24.8 ± 2.0
	100	96.6 ± 14.7	26.3 ± 1.9
Vehicle control 5		97.5 ± 15.1	24.0 ± 1.0
2b	10	99.8 ± 14.2	21.7 ± 0.9
	100	76.6 ± 10.3 (−21.4%)	24.0 ± 1.6
2j	10	70.3 ± 12.8[$$] (−27.9%)	24.1 ± 0.8
	100	123.9 ± 7.9[$$] (+27.1%)	25.2 ± 1.4

n/s – Not studied.

[*] Significant at p < .05 compared to the corresponding vehicle control group.

[***] Significant at p < .001 compared to the corresponding vehicle control group.

[$] Significant at p < .05 compared to the group of animals receiving another dose of the drug.

[$$] Significant at p < .01 compared to the group of animals receiving another dose of the drug.

nately, the results for methoxyphenyl derivatives **2c** and **2d** were not obtained in this test due to some organizational aspects of the experiment.

The present model of hypoxia is quite rigorous and not very sensitive, but allows us to uncover real "hits" with a considerable antihypoxic activity. Analysis of the experimental data presented in Table 7 has proven that most of the substances studied have no effect on the hypoxia tolerance time in mice.

However, animals treated with **2a** in the dose of 10 mg/kg increased the hypoxia tolerance (+19.4%, p < .05). This may be explained by the greatest structural likeness among 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones tested with atristamine with the antihypoxic activity proven in our previous studies (Podolsky et al., 2013a).

Moreover, substance **2i** showed a pronounced antihypoxic effect (+27.3%, p < .001) in the dose of 100 mg/kg, and it correlated well with its anti-anxiety action in the similar dose.

However, the substance with prohypoxic properties was found in this test. 6–Methoxysubstituted analogue of atristamine **2g** in the dose of 100 mg/kg displayed a significant reduction of the hypoxia tolerance time in mice (−15.9%, p < .05). This fact may be explained by stimulating effects of **2g** revealed in the open field test. Hyperactivity that causes hyperventilation increases the total oxygen consumption leading to rapid death. Besides, in a lower dose this effect was also observed at the same level, but without the appropriate level of significance.

4. Discussion

The present study was undertaken as the sequel of the previous research of the novel class of chemical compounds with the

psycho- and neurotropic spectrum of the biological action. Taking into account the modest scope of testing the impressive conclusions concerning SAR regularities cannot be made. Furthermore, doubts are cast upon feasibility of the activity profile prediction for 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones due to complicated results obtained in behavioural tests. These facts indicate the delicacy of the mechanism of action and sensitivity to minor modifications of the chemical structure. However, certain SAR features were revealed.

It became absolutely apparent that compounds with the phenylaminomethyl fragment have pronounced mnemotropic effects against scopolamine-induced amnesia. Substitution of this fragment with the heterocyclic moiety or N-benzoylation leads to the action weakening. Being the most structurally similar to atristamine, 3-[[(2-methylphenyl)amino]methyl]-2-methyl-1H-quinolin-4-one **2a** has the same profile of activity. But, if other substituents are present in the phenyl moiety (**2b-f**), there is rather large dispersion of results in behavioural tests. According to the data obtained N-benzoylation of atristamine results in appearance of the potent anti-anxiety action, but an ambiguous influence on depressive behaviour at the same time. It should be emphasized that the methoxy group in position 6 of the quinolone fragment causes great differences in the profile of the biological activity compared to atristamine. This fact correlates well with the results for 3-(dimethylaminomethyl)-6–methoxy-2-methyl-1H-quinolin-4-one in the previous study (Shtrygol' et al., 2010), i.e. a high physiological activity without valuable outcomes for drug development.

5. Conclusions

The article presents the psycho- and neurotropic profiling of novel 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones *in vivo*. Certain regularities of the "structure–activity relationships" revealed have been discussed. Some compounds that deserve a deeper and more detailed pharmacological study have been found. 3-[[(4-Methoxyphenyl)amino]methyl]-2-methyl-1H-quinolin-4-one exhibiting a specific sedative effect and a considerable anti-amnesic activity, as well as N-[(2-methyl-4-oxo-1H-quinolin-3-yl)methyl]-N-phenylbenzamide, which combines the anti-anxiety action, anti-amnesic activity and antihypoxic effect, are among them as promising psychoactive agents. The results of this study expand current knowledge about pharmacological properties of this class of compounds and allow us to outline directions for the further purposeful searches of promising psyco- and neurotropic agents among 3-(N-R,R′-aminomethyl)-2-methyl-1H-quinolin-4-ones.

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