RSC Advances

PAPER

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Cite this: *RSC Adv.*, 2016, **6**, 32234

Pyridofuropyrrolo[1,2-*a*]pyrimidines and pyridofuropyrimido[1,2-*a*]azepines: new chemical entities (NCE) with anticonvulsive and psychotropic properties†

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Received 28th January 2016
Accepted 6th March 2016

DOI: 10.1039/c6ra02581a

www.rsc.org/advances

Herein we report the synthesis of several new condensed furo[2,3-*b*]pyridines **3** from the 3-oxo derivatives of cyclopenta[*c*]pyridine, 5,6,7,8-tetrahydroisoquinoline and pyrano[3,4-*c*]pyridine **1**. The obtained furo[2,3-*b*]pyridines **3** were used as starting materials for the synthesis of pyridofuropyrrolo[1,2-*a*]pyrimidines **4** and pyridofuropyrimido[1,2-*a*]azepines **5**. Interestingly enough, derivatives of pyridofuropyrimido[1,2-*a*]azepines **5** exhibited significantly better anticonvulsant activity than the commercial drug ethosuximide (zarontin). Some of them showed a sedative effect, unlike ethosuximide.

1. Introduction

Computer aided structure–activity relationship analysis and molecular modelling are widely used in the finding and optimization of new leads by today's medicinal chemists.[1] The majority of available approaches are focused on a single macromolecular target, the only pharmacological/biochemical action, and/or compounds from the same chemical series. The problem of applicability of the structure–activity relationships found in compounds from one chemical series onto compounds from another chemical series is in general still under discussion.[2] Moreover, the existing structure–activity relationship/quantitative structure–activity relationship (SAR/QSAR) methods deal with a single biological activity, whereas in reality, every compound usually has both main and side (sometimes also negative) pharmacological effects.[3]

Currently in the developed world, a continuous increase of diseases linked to aging or to troubles related to mind problems is observed. As people become older, there is a higher risk of losing cognitive functions such as memory, attention span, ability to concentrate and understand, orientation and comprehension.[4,5] Furthermore, long life can be accompanied by the occurrence of degenerative diseases such as Alzheimer's disease and other dementia types; which affect a third of people over the age of 65.[6] Especially, it becomes critical for people over the age of 80, 25% of whom suffer from serious deterioration of mental capacity. Loss of cognitive function could also be a result of clinical conditions such as stroke, acute and chronic inflammation as well as intoxication, mental retardation in children, cerebrovascular disease, alcoholic organic mental disorders and many others.

The first drug used as a nootropic was Piracetam. Now there is a range of cognition-enhancing (nootropic) drugs that cover a wide spectrum of mechanisms of action, including calcium channel blockers, glutamatergic drugs, antioxidants, cholinomimetics and mnemotropic neuropeptides.[7] Nevertheless, all available nootropics suffer from significant side effects,[8] and thus there is an urgent need for novel cognition enhancers without such adverse reactions.

It is known from the literature that derivatives of fused pyrrolo[1,2-*a*]pyrimidinones and pyrimido[1,2-*a*]azepines (Fig. 1) have a wide spectrum of biological activities such as anticonvulsive,[9] antitubercular,[10] HIV integrase inhibitory,[11,12] fibroblast growth factor receptor 1 kinase inhibitory,[13] molluscicidal, and larvicidal[14] activities. At the same time, the condensed system of pyridofuropyrrolo[1,2-*a*]pyrimidines and pyridofuropyrimido[1,2-*a*]azepines has never been described in the literature (Fig. 2).

For this reason, and in continuation of our work[15–18] on the search for new biologically active heterocyclic compounds, we have developed a method for the synthesis of these condensed compounds, prepared a series of them, and studied their anticonvulsant properties.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra02581a

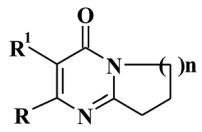


Fig. 1 Structure of known compounds. R = OH, Oalk, aryl; R^1 = CO_2Me, $CONHC_6H_4$-*p*-F; R + R^1 = substituted aryl and heteryl; *n* = 1, 2, 3.

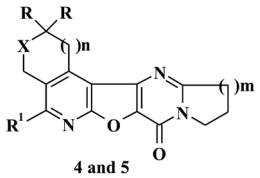


Fig. 2 Structure of compounds **4** and **5** synthesized by us.

2. Results and discussion

2.1. Chemistry

As starting compounds, the already described 3-oxo derivatives of cyclopenta[*c*]pyridine[19] **1a–c**, 5,6,7,8-tetrahydroisoquinoline[20] **1d**, **e** and pyrano[3,4-*c*]pyridine[21] **1f–i** were used. All of these starting materials are very interesting substrates, in fact, all of them are decorated on adjacent carbon atoms of the pyridine ring by two functional groups able to lead the way to compounds with a new condensed ring (a furan ring), which in turn will still contain other reactive groups useful for further chemical transformations.

In fact, compounds **1**, by simple interactions with ethyl chloroacetate in the presence of potassium carbonate, were converted with very good mean yields (>75.5%) into the corresponding O-alkylated compounds **2**,[16,17,22,23] which in turn under the action of sodium ethoxide cyclized, giving the fused furo[2,3-*b*]pyridines **3** (ref. 16, 17, 22 and 23) via the Thorpe–Ziegler reaction (Scheme 1).

We have observed that the cyclization process of the O-alkylated derivatives **2** is very sensitive to humidity and to the reaction time. As a result, we managed to implement the cyclization only in super absolute ethanol (99.95%) reducing the boiling time to 15–20 minutes: in such experimental conditions very good mean yields (>76.5%) were obtained.

In the IR spectra of compounds **3**, the absorption band of the cyano group (2218–2223) characteristic for compounds **2** was not observed. At the same time, the appearance of absorption bands characteristic for the C=O (1664–1674 cm^{-1}) and NH_2 (3330–3550 cm^{-1}) groups is an indication of the formation of compounds **3**.

Their ^{1}H NMR spectra in DMSO/CCl_4 1/3 evidenced the presence of the proton signals of the NH_2 group at 5.70–5.75 ppm.

Aminoesters of furo[2,3-*b*]pyridines **3** still contain functional groups, which can give new cyclization reactions. As a matter of fact, with some lactams, in the presence of phosphorus oxychloride, they led to the simultaneous closing reaction of the two functional groups at once.[9,14,24] As a result, new classes of condensed heterocyclic systems of pyridofuropyrrolo[1,2-*a*]pyrimidines **4** and pyridofuropyrimido[1,2-*a*]azepines **5** were obtained with good or very good mean yields (>61 and 71%, respectively) (Scheme 2).

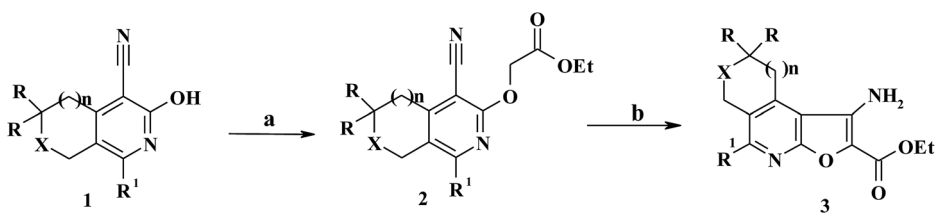
The course of the reaction can be represented as follows: at the first stage of the reaction, the chlorination of 2-pyrrolidinone (or of 2-azepanone) was carried out by the action of phosphorus oxychloride with the formation of corresponding amidochlorides, which were then able to react with the aminoesters of furo[2,3-*b*]pyridine. As a result of this reaction amidines **1** were formed, which in turn were in equilibrium with amidines **2**. Further, an intramolecular cyclization took place, leading to the formation of the desired products **4** and **5** (Scheme 2).[9,14,24]

The IR spectra of compounds **4** and **5** did not show the characteristic bands of the amino group, but showed bands in the range ν 1671–1705 cm^{-1} typical for the carbonyl group.

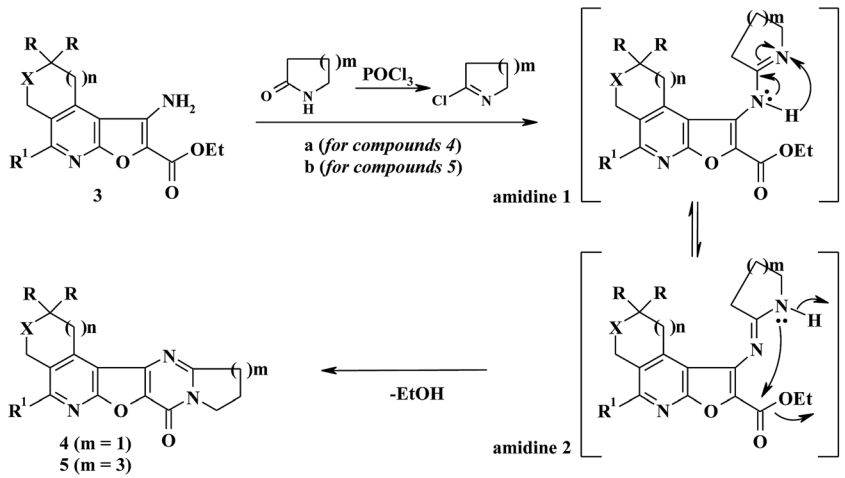
The ^{1}H NMR spectra of compounds **4** and **5** did not show the broad singlet of the NH_2 group at 5.70–5.75 ppm, characteristic for the initial compounds **3**, nor the protons of the COOEt ester group (the triplet of the CH_2 group at 1.40–1.41 ppm, and the quartet of the CH_3 group 4.32–4.33 ppm). The structure of compounds **4** and **5** was also supported by the MS and ^{13}C NMR data.

2.2. PASS predictions of neuroprotective activity

In silico study of the designed compounds was performed by using the computer program PASS, which predicts the biological activity spectra of compounds.



Scheme 1 Synthesis of ethyl 1-aminofuro[2,3-*b*]pyridine-2-carboxylates **3**. (a) $ClCH_2CO_2Et$, K_2CO_2/DMF, 75–80 °C, 2 h, mean yield: >75.5%; (b) EtONa, reflux 15–20 min, mean yield: >76.5%. (**1–3**) **a**: X = CH_2, *n* = 0, R = H, R^1 = *i*-C_3H_7; **b**: X = CH_2, *n* = 0, R = H, R^1 = C_4H_9; **c**: X = CH_2, *n* = 0, R = H, R^1 = Ph; **d**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_3H_7; **e**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_4H_9; **f**: X = O, *n* = 1, R = R^1 = CH_3; **g**: X = O, *n* = 1, R = CH_3, R^1 = C_2H_5; **h**: X = O, *n* = 1, R = CH_3, R^1 = C_4H_9; **i**: X = O, *n* = 1, R = CH_3, R^1 = 2-furyl.



Scheme 2 Synthesis of furopyrrolo[1,2-*a*]pyrimidines **4** and furopyrimido[1,2-*a*]azepines **5**. (a) 2-Pyrrolidinone, $POCl_3$, $C_2H_4Cl_2$, reflux, 25 h, mean yield: >61%; (b) 2-azepanone, $POCl_3$, $C_2H_4Cl_2$, reflux, 20 h, mean yield: >71.5%. (**4**) **a**: X = CH_2, *n* = 0, R = H, R^1 = *i*-C_3H_7; **b**: X = CH_2, *n* = 0, R = H, R^1 = C_4H_9; **c**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_3H_7; **d**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_4H_9; **e**: X = O, *n* = 1, R = R^1 = CH_3; **f**: X = O, *n* = 1, R = CH_3, R^1 = C_2H_5; **g**: X = O, *n* = 1, R = CH_3, R^1 = C_4H_9; **h**: X = O, *n* = 1, R = CH_3, R^1 = 2-furyl. (**5**) **a**: X = CH_2, *n* = 0, R = H, R^1 = *i*-C_3H_7; **b**: X = CH_2, *n* = 0, R = H, R^1 = C_4H_9; **c**: X = CH_2, *n* = 0, R = H, R^1 = Ph; **d**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_3H_7; **e**: X = CH_2, *n* = 1, R = H, R^1 = *i*-C_4H_9; **f**: X = O, *n* = 1, R = R^1 = CH_3; **g**: X = O, *n* = 1, R = CH_3, R^1 = C_2H_5; **h**: X = O, *n* = 1, R = CH_3; R^1 = C_4H_9.

Table 1 Prediction results for the synthesized compounds

Compounds[a]	Predicted activity	Pa
4a	Antineurotic	0.422
4c	Antineurotic	0.422
4e	Anticonvulsant	0.358
4f	Anticonvulsant	0.261
4g	Anticonvulsant	0.280
4h	Neurodegenerative diseases treatment	0.403
	Anticonvulsant	0.288
	Antiparkinsonian	0.244
5a	Nootropic	0.455
5b	Nootropic	0.535
	Cognition disorders treatment	0.431
5c	Nootropic	0.717
	Cognition disorders treatment	0.526
5d	Nootropic	0.455
	Cognition disorders treatment	0.436
5e	Nootropic	0.438
	Cognition disorders treatment	0.410
5f	Anticonvulsant	0.245
5g	Nootropic	0.324
	Cognition disorders treatment	0.324
5h	Nootropic	0.632
	Cognition disorders treatment	0.407

[a] For compounds **4b** and **4d** the anticonvulsant activity was not predicted.

Computer program prediction of activity spectra for substances (PASS)[25–28] is based on a robust analysis of structure–activity relationships[26] in a heterogeneous training set currently including (version PASS 14) about 1 000 000 biologically active compounds from different chemical series. This approach (version PASS2014) can simultaneously predict 7000 different biological activities with an accuracy prediction of 95%. Since only the structural formula of a chemical compound is necessary to obtain PASS predictions, this approach can be used at the earliest stage of investigation (eventually also before the synthesis of new compounds). Literature reports several examples of the successful use of the PASS approach for finding new pharmacologically active species.[29–34]

A biological activity spectrum for a substance is a list of biological activities for which the probability to be revealed (Pa) and the probability not to be revealed (Pi) are calculated. Pa and Pi values are independent and their values vary from 0 to 1.[25] The results of the prediction are valuable for the planning of the experiment, but one should take into account some additional factors, such as particular interest to certain kinds of activity, desirable novelty of a substance, available facilities for experimental testing, *etc.* Actually, each choice is always a compromise between the desirable novelty of the studied substance and the risk of obtaining a negative result in the testing. The higher the Pa value, the lower the probability of false positives in the set of compounds selected for biological testing.

The interpretation of PASS results could be presented as follows. If Pa > 0.7, then the chance of finding this activity in the experiments is high, but in many cases the compound may be a close analogue of known pharmaceutical agents. If 0.5 < Pa < 0.7, the chance of finding the activity in the experiments is lower, because the compound is not so similar to known pharmaceutical agents. If Pa < 0.5, the chance of finding the activity in the experiments is even lower; the compound has a weak similarity with respect to the compounds from the training set, but interestingly enough if the activity will be experimentally observed, the compound may become a 'New Chemical Entity' (NCE).

Biological activity spectra were predicted for all 16 synthesized compounds **4** and **5** with PASS 9.1 version. The results in Table 1 show that the anticonvulsant activity was predicted only

Table 2 Anticonvulsant activity by pentilentetrazol antagonism and toxicity of the examined compounds **4c–h**, **5a**, **5b**, **5f**, and **5h**

Compound	ED_{50}[a], mg kg^{-1}	LD_{50}[a], mg kg^{-1}	TD_{50}[a], mg kg^{-1}	TI	PI
4c	38 ± 4.0	170 ± 2.4	52 ± 2.5	4.5	1.4
4d	32 ± 3.7	250 ± 3.0	48 ± 2.8	7.8	1.5
4e	80 ± 2.5	180 ± 3.3	120 ± 3.5	2.3	1.5
4f	74 ± 2.9	200 ± 3.5	86 ± 4.0	2.7	1.2
4g	120 ± 4.4	175 ± 3.9	150 ± 2.5	1.45	1.25
4h	110 ± 3.1	200 ± 3.2	140 ± 3.1	1.8	1.27
5a	48 ± 3.9	350 ± 4.1	230 ± 2.6	7.3	4.8
5b	62 ± 4.4	2200 ± 4.4	1000 ± 3.8	35.4	16.1
5f	135 ± 3.5	400 ± 3.3	240 ± 2.6	3.0	1.8
5h	30 ± 3.8	1400 ± 3.8	1100 ± 3.75	46.6	36.6
Ethosuximide	155 ± 2.56	1325 ± 2.9	520 ± 2.6	8.5	3.4

[a] $P = 0.05$ at the probability level.

Table 3 Anticonvulsant activity of compounds **4c**, **4d**, **5a**, **5b** and **5h** on the model of thiosemicarbazide (TSC) seizures

Compound	Dose, mg kg^{-1}	Latency of convulsions induced by TSC, min	
		$M \pm m$	I[b]
Control	—	74.8 ± 3.5[a]	1.00
4c	100	95.6 ± 5.3	1.28
4d	100	98.5 ± 8.6	1.32
5a	100	107.4 ± 11.5	1.44
5b	100	102.5 ± 10.9	1.37
5h	100	120.0 ± 13.6	1.60
Ethosuximide	200	75.1 ± 6.2	1.004

[a] $P = 0.05$ at the probability level. [b] I – an increase in the threshold.

for five compounds (**4e–h** and **5f**). The Pa values of these compounds were less than 0.5, indicating that these compounds, if truly active, could be new chemical entities.

Thus, PASS application to pyridofuropyrrolo[1,2-*a*]pyrimidines **4** and pyridofuropyrimido[1,2-*a*]azepines **5** was able to identify prospective pharmacological properties that could be tested and eventually confirmed by experimental studies.

2.3. Biological assay

The study of anticonvulsant activity of 16 new pyridofuropyrrolo [1,2-*a*]pyrimidines **4** and pyridofuropyrimido[1,2-*a*]azepines **5** was carried out in experiments on outbred white mice weighing 18–22 g using two models of seizures caused by pentilentetrazol (PTZ, metrazol, corazol) and by maximal electroshock (MES). The PTZ induced test is considered an experimental model for the clonic component of epilepsy seizures and prognostic anxiolytic activities of the compounds.[35–42] The MES test is used as an animal model for the generalized tonic seizures of epilepsy.[36,37,40–45]

The side effects of the compounds, such as neurotoxicity (movement coordination disorder, myorelaxation, ataxia), were also studied with "rotating rod"[36,46] and acute toxicity tests. The rotating rod performance test is a performance test based on a rotating rod with forced motor activity being applied, usually by a rodent. The test measures parameters such as riding time (seconds) or endurance. In the test, a mouse is placed on a horizontally oriented, rotating cylinder (rod) suspended above a cage floor, which is low enough not to injure the animal, but high enough to induce avoidance of fall. Mice naturally try to stay on the rotating cylinder, or rotating rod, and avoid falling to the ground. The length of time that a given animal stays on this rotating rod is a measure of their balance, coordination, physical condition, and motor-planning. The speed of the rotating rod is mechanically driven, and may either be held constant, or accelerated.[47]

To determine the 50% effective (ED_{50}, causing the anticonvulsant effect in 50% of animals, is calculated by the test antagonism of PTZ), 50% neurotoxic (TD_{50}, causing the

Table 4 Effect of compounds **4c**, **4d**, **5a**, **5b** and **5h** in the research activity in rats in the "open field" test[a]

Compound	Dose, mg kg^{-1}	Amount (absolute data during 5 min)		
		Horizontal displacement	Vertical displacement	Cells
Control	—	25.8 ± 0.8	7.0 ± 1.9	1.5 ± 0.4
4c	50	14.8 ± 0.7	2.0 ± 0.6	1.4 ± 0.3
4d	50	11.8 ± 0.5	2.5 ± 0.8	0.8 ± 0.2
5a	50	11.0 ± 0.3	1.2 ± 0.4	0.9 ± 0.3
5b	50	20.5 ± 0.6	3.6 ± 0.7	1.6 ± 0.4
5h	50	17.3 ± 0.5	3.3 ± 0.8	0.8 ± 0.1
Ethosuximide	200	26.8 ± 3.3	5.6 ± 1.5	1.6 ± 0.5

[a] $P = 0.05$ at a probability level.

Table 5 Effect of compounds **4c**, **4d**, **5a**, **5b** and **5h** on the state of "fear and despair" of mice in the EPM model (observation time 5 min)[a]

Compound	Dose/mg kg^{-1}	Time spent in closed arms/s	Number of entries into the closed arms	Time spent in the center/s
Control	—	278.2 ± 15.8	3.0 ± 0.2	21.8 ± 2.5
4c	100	254.4 ± 11.2	3.2 ± 0.3	45.6 ± 1.1
4d	100	257.8 ± 14.7	3.8 ± 0.5	42.2 ± 8.9
5a	100	242.6 ± 8.6	1.2 ± 0.1	57.4 ± 3.7
5b	100	246.0 ± 10.2	4.4 ± 0.6	54.8 ± 4.6
5h	100	267.8 ± 12.4	4.0 ± 0.5	32.3 ± 2.7
Ethosuximide	200	245.2 ± 32.3	3.0 ± 0.8	25.4 ± 7.4

[a] $P = 0.05$ at a probability level.

myorelaxed effect in 50% of animals, is calculated by the "rotating rod" test) and 50% lethal (LD_{50}, causing death in 50% of animals) doses, a statistical method of probability analysis by Litchfield and Wilcoxon[36,48] was used. From a practical point of view, the therapeutic (TI = LD_{50}/ED_{50}) and protective (PI = TD_{50}/ED_{50}) indexes were identified for the active compounds. Ethosuximide was used as a control.[49]

The evaluation of the anticonvulsant activity of all the synthesised compounds revealed that they, to different degrees, exhibit pentilentetrazol antagonism. The anticonvulsant effects of the most active compounds (derivatives of pyrrolo[1,2-*a*] pyrimidines **4c–h** and derivatives of pyrimido[1,2-*a*]azepines **5a**, **5b**, **5f**, and **5h**) are presented in Table 2. The remaining compounds **4a**, **4b**, **5c–e**, and **5g** revealed weaker action in the studied doses (up to 40%).

The derivatives of pyrimido[1,2-*a*]azepines containing a butyl group, especially (**5b** and **5h**), caused myorelaxation in higher doses and seem to be non-toxic. The ED_{50} values are higher than that of reference drug compared to the derivatives of pyrrolo [1,2-*a*]pyrimidines (**4c–h**). Moreover, these last compounds, in doses slightly higher than TD_{50}, cause tremors and convulsions. Furthermore, compounds **5b** and **5h** are less neurotoxic than the reference drug. Their therapeutic (TI) and protective (PI) indexes are much greater than those of the reference drug (Table 2). It should be mentioned that the compounds presented in Table 2 are more active than ethosuximide according to the PTZ test, while in the test of maximal electroshock, not only the tested compounds but also the reference drug were not active.

Next, the most active compounds with anticonvulsant antagonism *versus* pentilentetrazol (**4c**, **4d**, **5a**, **5b** and **5h**) (Table 3) were selected and studied on the model of thiosemicarbazide (TSC) seizures (affecting the exchange of GABA).[36,50] It was observed that these compounds at a 100 mg kg^{-1} dose increased the latency of convulsions induced by TSC to 1.5 times compared with the control. In this model, ethosuximide (200 mg kg^{-1}) was not effective (Table 3).

Furthermore, these compounds were studied for their anxiolytic activity in some psychotropic models: such as "open field" and elevated plus maze (EPM). In the "open field" test,[51,52] which is a classic model for the evaluation of sedative, activating and anxiolytic properties, the number of the horizontal displacement of the control group of rats was 25.8, vertical was 7.0 and the number of sniffing cells was 1.5. Table 4 shows that the tested compounds **4c**, **4d**, **5a**, **5b** and **5h** at a 50 mg kg^{-1} dose reduce the number of such movements, indicating a sedative effect unlike ethosuximide, which does not exhibit this effect. The number of sniffing cells is almost unchanged, and this is apparently due to the lack of the anxiolytic effect.

In order to assess fear, the methodology of the elevated plus maze (EPM) developed by S. Pellow *et al.* (1986)[53] was used. The elevated plus maze test is one of the most widely used tests for measuring anxiety-like behaviour.[54] The test is based on the natural aversion of mice to open and elevated areas, as well as on their natural spontaneous exploratory behaviour in novel environments due to unsuitability of their locomotor system to jump. The apparatus consists of open arms and closed arms, crossed in the middle perpendicularly to each other, and a centre area. Mice are given access to all of the arms and are allowed to move freely between them. The number of entries into the open arms and the time spent in the open arms are used as indices of open space-induced anxiety in mice.

Thus, administration of compounds **4c**, **4d**, **5a**, **5b**, and **5h** compared with ethosuximide was accompanied by a complete lack of effect and mice stayed in the closed setting like the control group, *i.e.*, it is regarded as a manifestation of fear. In the control group (278.2 s), the animals were in a closed arm for almost most of the time of the observation. The number of entries into a closed arm is almost the same for both groups of rats, the control and rats which received the compounds. Interestingly, the time spent in the center is increased twofold for the tested compounds in contrast to ethosuximide used as a standard. The prolonged presence of animals in the center of the installation allows to consider some protective reaction, located on the border of "fear and despair" of the compounds studied (Table 5).

3. Conclusions

A method, working with good or very good mean yields, for the synthesis of new classes of condensed heterocyclic systems, pyridofuropyrrolo[1,2-*a*]pyrimidines **4** and pyridofuropyrimido [1,2-*a*]azepines **5**, has been developed. The anticonvulsant activity combined with some psychotropic properties of the new compounds was evaluated.

The studied compounds exhibit protection against PTZ seizures, anti-thiosemicarbazide effects, as well as some psychotropic effects.

The biological assays evidenced that some of the studied compounds showed a high anticonvulsant activity by antagonism with pentylenetetrazole. Thus, among the studied compounds some derivatives of pyrimido[1,2-α]azepines **5** were identified as highly active and with a toxicity lower than that of ethosuximide. The anti-thiosemicarbazide effect was not revealed by ethosuximide, in contrast to the selected compounds **4c**, **4d**, **5a**, **5b**, **5h** which increased the latency period of TSC seizures by 1.5 fold. These findings suggest some GABA-ergic mechanism of action of the tested compounds.

According to the results of the psychotropic activity test, it is obvious that the selected compounds have a sedative effect on the model of "open field" and a defense mechanism against the fear in the EPM model, in contrast to ethosuximide. Thus, the studied pyrimidine and azepine derivatives appear as promising New Chemical Entities (NCE) in the field and could be lead compounds for the development of new anticonvulsant agents with psychotropic properties.

4. Experimental section

4.1. Chemistry

^{1}H NMR spectra were recorded in DMSO/CCl_4 1/3 solution on a Varian Mercury 300 V × 300 MHz spectrometer. Chemical shifts are reported as δ (ppm) relative to TMS as the internal standard. IR spectra were recorded on a Nicolet Avatar 330-FT-IR spectrophotometer and the reported wavenumbers are given in cm^{-1}. Mass spectra (MS) were recorded on an MX-1321A spectrometer with direct entry of matter into the ion source at an ionization energy 60 eV, m/z ($I_{rel,\%}$). All melting points were determined in an open capillary and are uncorrected. Elemental analyses were performed on a EuroEA3000 Elemental Analyzer. All compounds showed ≥95% purity.

Compounds **2**, **3a**,[15] **2**, **3c**, **3d**, **3i**,[16] **2**, **3e**,[22] **2**, and **3f** (ref. 23) have already been described.

4.1.1. General procedure for the synthesis of compounds 2b, 2g, and 2h. To a suspension of compound **1** (10 mmol) and potassium carbonate (1520 mg, 11 mmol) in absolute DMF (15 mL), ethyl chloroacetate (1350 mg, 11 mmol) was added dropwise under stirring. The reaction mixture was maintained at 75–80 °C for 2 h, then cooled to room temperature and poured into cold water. The resulting crystals were filtered off, washed with water, dried, and re-crystallized from ethanol.

*Ethyl [(1-butyl-4-cyano-6,7-dihydro-5H-cyclopenta[c]pyridin-3-yl)oxy]acetate (**2b**).* Yield 2.15 g (71%), mp 56–58 °C. IR ν/cm^{-1}: 2218 (C≡N), 1745 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.93 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.28 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.27–1.39 (m, 2H, $C\underline{H}_2CH_3$), 1.56–1.67 (m, 2H, $C\underline{H}_2C_2H_5$), 2.13–2.24 (m, 2H, 6-CH_2), 2.60 (t, J = 7.4 Hz, 2H, $C\underline{H}_2C_3H_7$), 2.86 (t, J = 7.5 Hz, 2H, 7-CH_2), 3.06 (t, J = 7.6 Hz, 2H, 5-CH_2), 4.17 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.89 (s, 2H, OCH_2CO). Anal. calcd for $C_{17}H_{22}N_2O_3$: C 67.53; H 7.33; N 9.26%. Found: C 67.45; H 7.32; N 9.27%.

*Ethyl [(5-cyano-3,3-dimethyl-8-ethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy] acetate (**2g**).* Yield 2.67 g (84%), mp 133–135 °C. IR ν/cm^{-1}: 2223 (C≡N), 1752 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.21 (t, J = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.26 (s, 6H, $C(CH_3)_2$), 1.30 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.58 (q, J = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 2.78 (s, 2H, CH_2), 4.18 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.61 (s, 2H, OCH_2), 4.92 (s, 2H, OCH_2CO). Anal. calcd for $C_{17}H_{22}N_2O_4$: C 64.14; H 6.96; N 8.80%. Found: C 64.03; H 6.97; N 8.81%.

*Ethyl [(8-butyl-5-cyano-3,3-dimethyl-3,4-dihydro-1H-pyrano[3,4-c]pyridin-6-yl)oxy] acetate (**2h**).* Yield 2.49 g (72%), mp 93–95 °C. IR ν/cm^{-1}: 2222 (C≡N), 1675 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.93 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.27 (s, 6H, $C(CH_3)_2$), 1.27 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.30–1.41 (m, 2H, $C\underline{H}_2CH_3$), 1.57–1.68 (m, 2H, $C\underline{H}_2C_2H_5$), 2.50–2.55 (m, 2H, $C\underline{H}_2C_3H_7$), 2.78 (s, 2H, CH_2), 4.17 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.62 (s, 2H, OCH_2), 4.91 (s, 2H, OCH_2CO). Anal. calcd for $C_{19}H_{26}N_2O_4$: C 65.88; H 7.56; N 8.09%. Found: C 65.78; H 7.54; N 8.11%.

4.1.2. General procedure for the synthesis of compounds 3b3g, and 3h. To a solution of sodium ethoxide [253 mg (11 mmol) in absolute ethanol (300 mL)], compound **2** (10 mmol) was added. The mixture was refluxed for 15–20 min, cooled, and poured onto ice. The formed crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

*Ethyl 1-amino-5-butyl-7,8-dihydro-6H-cyclopenta[d]furo[2,3-b]pyridine-2-carboxylate (**3b**).* Yield 2.27 g (75%), mp 98–100 °C. IR ν/cm^{-1}: 3550, 3330 (NH_2), 1674 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.95 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.32–1.45 (m, 2H, $C\underline{H}_2CH_3$), 1.40 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.63–1.75 (m, 2H, $C\underline{H}_2C_2H_5$), 2.15–2.27 (m, 2H, 7-CH_2), 2.68–2.74 (m, 2H, $C\underline{H}_2C_3H_7$), 2.89 (t, J = 7.5 Hz, 2H, 6-CH_2), 3.27 (t, J = 7.6 Hz, 2H, 8-CH_2), 4.32 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 5.70 (br s, 2H, NH_2). Anal. calcd for $C_{17}H_{22}N_2O_3$: C 67.53; H 7.33; N 9.26%. Found: C 67.64; H 7.32; N 9.29%.

*Ethyl 1-amino-8,8-dimethyl-5-ethyl-8,9-dihydro-6H-furo[2,3-b]pyrano[4,3-d]pyridine-2-carboxylate (**3g**).* Yield 2.71 g (85%), mp 165–166 °C. IR ν/cm^{-1}: 3456, 3330 (NH_2), 1665 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.29 (t, J = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.30 (s, 6H, $C(CH_3)_2$), 1.41 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 2.65 (q, J = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 3.11 (s, 2H, CH_2), 4.33 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.71 (s, 2H, OCH_2), 5.74 (br s, 2H, NH_2). Anal. calcd for $C_{17}H_{22}N_2O_4$: C 64.14; H 6.96; N 8.80%. Found: C 64.04; H 6.94; N 8.83%.

*Ethyl 1-amino-8,8-dimethyl-5-butyl-8,9-dihydro-6H-furo[2,3-b]pyrano[4,3-d]pyridine-2-carboxylate (**3h**).* Yield 2.42 g (70%), mp 159–161 °C. IR ν/cm^{-1}: 3451, 3332 (NH_2), 1664 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.97 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.29 (s, 6H, $C(CH_3)_2$), 1.35–1.48 (m, 2H, $C\underline{H}_2CH_3$), 1.40 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.65–1.76 (m, 2H, $C\underline{H}_2C_2H_5$), 2.61 (t, J = 7.5 Hz, 2H, $C\underline{H}_2C_3H_7$), 3.11 (s, 2H, CH_2), 4.33 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.71 (s, 2H, OCH_2), 5.75 (br s, 2H, NH_2). Anal. calcd for $C_{19}H_{26}N_2O_4$: C 65.88; H 7.56; N 8.09%. Found: C 65.80; H 7.54; N 8.06%.

4.1.3. General procedure for the synthesis of compounds 4a–h. A mixture of furo[2,3-*b*]pyridine **3** (10 mmol), 2-

pyrrolidinone (1700 mg, 20 mmol) and phosphorus oxychloride (1.86 mL, 20 mmol) in absolute 1,2-dichloroethane (50 mL) was refluxed for 25 h. The solvent was distilled off to dryness and water (50 mL) was added to the residue. The separated crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

*4-Isopropyl-2,3,10,11-tetrahydro-1H-cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-7(9H)-one (**4a**).* Yield 2.01 g (65%), mp 209–211 °C. IR ν/cm^{-1}: 1671 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.31 (d, J = 6.6 Hz, 6H, CH(C$\underline{H}_3$)$_2$), 2.20–2.41 (m, 4H, 2-CH_2, 10-CH_2), 3.02 (t, J = 7.4 Hz, 2H, 3-CH_2), 3.19 (t, J = 7.8 Hz, 2H, 11-CH_2), 3.20 (sp, J = 6.7 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.35 (t, J = 7.6 Hz, 2H, 1-CH_2), 4.18–4.24 (m, 2H, 9-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 19.6, 21.0, 24.5, 29.1, 31.1, 31.6, 32.8, 46.5, 109.2, 133.2, 135.5, 142.6, 149.6, 150.8, 160.7, 161.4, 161.8. Anal. calcd for $C_{18}H_{19}N_3O_2$: C 69.88; H 6.19; N 13.58%. Found: C 69.95; H 6.20; N 13.56%.

*4-Butyl-2,3,10,11-tetrahydro-1H-cyclopenta[4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-7(9H)-one (**4b**).* Yield 2.30 g (71%), mp 184–186 °C. IR ν/cm^{-1}: 1685 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.98 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.37–1.50 (m, 2H, C$\underline{H}_2$CH$_3$), 1.70–1.80 (m, 2H, C$\underline{H}_2C_2H_5$), 2.23–2.41 (m, 4H, 2-CH_2, 10-CH_2), 2.80 (t, J = 7.5 Hz, 2H, C$\underline{H}_2C_3H_7$), 2.99 (t, J = 7.4 Hz, 2H, 3-CH_2), 3.19 (t, J = 7.9 Hz, 2H, 11-CH_2), 3.34 (t, J = 7.6 Hz, 2H, 1-CH_2), 4.18–4.24 (m, 2H, 9-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 13.5, 19.6, 21.9, 24.4, 29.3, 29.8, 31.1, 31.6, 34.9, 46.5, 109.1, 134.1, 135.4, 142.5, 149.3, 150.8, 156.9, 160.6, 161.6. MS, m/z ($I_{rel,\%}$), [M$^+$] 323 (4), 280 (100), 267 (1), 251 (9). Anal. calcd for $C_{19}H_{21}N_3O_2$: C 70.57; H 6.55; N 12.99%. Found: C 70.50; H 6.53; N 13.03%.

*5-Isopropyl-1,2,3,4,11,12-hexahydropyrrolo[1″,2″:1′,2′]pyrimido[4′,5′:4,5]furo[2,3-c]-isoquinolin-8(10H)-one (**4c**).* Yield 2.23 g (69%), mp 236–238 °C. IR ν/cm^{-1}: 1690 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.28 (d, J = 6.6 Hz, 6H, CH(C$\underline{H}_3$)$_2$), 1.83–1.98 (m, 4H, 2,3-CH_2), 2.29–2.40 (m, 2H, 11-CH_2), 2.82–2.88 (m, 2H, 4-CH_2), 3.18 (t, J = 7.9 Hz, 2H, 12-CH_2), 3.30–3.38 (m, 3H, 1-CH_2, C$\underline{H}$(CH$_3$)$_2$), 4.17–4.23 (m, 2H, 10-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 19.5, 20.8, 21.3, 22.4, 24.7, 26.5, 30.4, 31.7, 46.4, 109.9, 125.1, 135.1, 143.5, 143.9, 150.8, 160.2, 160.3, 164.9. Anal. calcd for $C_{19}H_{21}N_3O_2$: C 70.57; H 6.54; N 12.99%. Found: C 70.69; H 6.55; N 12.95%.

*5-Isobutyl-1,2,3,4,11,12-hexahydropyrrolo[1″,2″:1′,2′]pyrimido[4′,5′:4,5]furo[2,3-c]isoquinolin-8(10H)-one (**4d**).* Yield 2.29 g (68%), mp 191–193 °C. IR ν/cm^{-1}: 1703 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.00 (d, J = 6.6 Hz, 6H, CH(C$\underline{H}_3$)$_2$), 1.83–1.97 (m, 4H, 2,3-CH_2), 2.21–2.40 (m, 3H, C$\underline{H}$(CH$_3$)$_2$, 11-CH_2), 2.68 (d, J = 7.0 Hz, 2H, CHC$\underline{H}_2$), 2.76–2.82 (m, 2H, 4-CH_2), 3.18 (t, J = 7.9 Hz, 2H, 12-CH_2), 3.31–3.37 (m, 2H, 1-CH_2), 4.17–4.23 (m, 2H, 10-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 19.6, 20.8, 22.2, 22.3, 25.2, 26.4, 27.1, 31.7, 42.9, 46.4, 109.9, 126.4, 135.0, 143.4, 143.6, 150.8, 159.7, 159.9, 160.3. Anal. calcd for $C_{20}H_{23}N_3O_2$: C 71.19; H 6.87; N 12.45%. Found: C 71.08; H 6.85; N 12.42%.

*2,2,5-Trimethyl-1,4,11,12-tetrahydro-2H-pyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-8(10H)-one (**4e**).* Yield 2.28 g (70%), mp 251–253 °C. IR ν/cm^{-1}: 1700 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.33 (s, 6H, C(CH$_3$)$_2$), 2.30–2.41 (m, 2H, 11-CH_2), 2.48 (s, 3H, CH_3), 3.19 (s, 2H, CH_2), 3.20 (t, J = 7.9 Hz, 2H, 12-CH_2), 4.20 (t, J = 7.3 Hz, 2H, 10-CH_2), 4.74 (s, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 19.6, 20.8, 25.8, 31.7, 36.3, 46.5, 60.0, 68.6, 110.1, 123.7, 135.1, 139.6, 143.0, 150.7, 153.5, 160.3, 160.7. Anal. calcd for $C_{18}H_{19}N_3O_3$: C 66.45; H 5.89; N 12.91%. Found: C 66.55; H 5.90; N 12.93%.

*2,2-Dimethyl-5-ethyl-1,4,11,12-tetrahydro-2H-pyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-8(10H)-one (**4f**).* Yield 2.21 g (65%), mp 219–221 °C. IR ν/cm^{-1}: 1690 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.33 (s, 6H, C(CH$_3$)$_2$), 1.35 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 2.30–2.41 (m, 2H, 11-CH_2), 2.74 (t, J = 7.3 Hz, 2H, C$\underline{H}_2$CH$_3$), 3.20 (t, J = 7.9 Hz, 2H, 12-CH_2), 3.22 (s, 2H, CH_2), 4.18–4.24 (t, J = 7.3 Hz, 2H, 10-CH_2), 4.79 (s, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 11.3, 19.6, 25.8, 26.4, 31.7, 36.4, 46.5, 59.7, 68.5, 109.9, 123.1, 135.2, 139.7, 143.0, 150.7, 157.9, 160.6, 160.7. Anal. calcd for $C_{19}H_{21}N_3O_3$: C 67.24; H 6.24; N 12.38%. Found: C 67.13; H 6.25; N 12.41%.

*5-Butyl-2,2-dimethyl-1,4,11,12-tetrahydro-2H-pyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-8(10H)-one (**4g**).* Yield 2.57 g (70%), mp 188–190 °C. IR ν/cm^{-1}: 1690 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.99 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.33 (s, 6H, C(CH$_3$)$_2$), 1.39–1.52 (m, 2H, C$\underline{H}_2$CH$_3$), 1.71–1.82 (m, 2H, C$\underline{H}_2C_2H_5$), 2.30–2.41 (m, 2H, 11-CH_2), 2.66–2.73 (m, 2H, C$\underline{H}_2C_3H_7$), 3.20 (t, J = 7.9 Hz, 2H, 12-CH_2), 3.22 (s, 2H, CH_2), 4.18–4.25 (t, J = 7.3 Hz, 2H, 10-CH_2), 4.80 (s, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 13.5, 19.6, 21.9, 25.8, 29.4, 31.7, 33.0, 36.5, 46.5, 59.8, 68.6, 110.1, 123.3, 135.2, 139.9, 143.1, 150.7, 157.3, 160.6, 160.7. Anal. calcd for $C_{21}H_{25}N_3O_3$: C 68.64; H 6.86; N 11.44%. Found: C 68.53; H 6.88; N 11.46%.

*2,2-Dimethyl-5-(2-furyl)-1,4,11,12-tetrahydro-2H-pyrano[4″,3″:4′,5′]pyrido[3′,2′:4,5]furo[3,2-d]pyrrolo[1,2-a]pyrimidin-8(10H)-one (**4h**).* Yield 2.75 g (73%), mp 343–345 °C. IR ν/cm^{-1}: 1687 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.37 (s, 6H, C(CH$_3$)$_2$), 2.28–2.39 (m, 2H, 11-CH_2), 3.21 (t, J = 7.9 Hz, 2H, 12-CH_2), 3.30 (s, 2H, CH_2), 4.17–4.23 (t, J = 7.3 Hz, 2H, 10-CH_2), 5.14 (s, 2H, OCH_2), 6.67 (dd, J = 3.5, 1.7 Hz, 1H, 4-CH, furyl), 7.22 (dd, J = 3.5, 0.7 Hz, 1H, 3-CH, furyl), 7.83 (dd, J = 1.7, 0.7 Hz, 1H, 5-CH, furyl). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 21.7, 25.8, 31.6, 36.5, 46.5, 60.0, 68.7, 107.8, 109.7, 110.1, 123.8, 135.0, 139.8, 140.9, 144.2, 152.7, 153.5, 155.7, 160.7, 161.9. Anal. calcd for $C_{21}H_{19}N_3O_4$: C 66.83; H 5.07; N 11.13%. Found: C 66.71; H 5.08; N 11.11%.

4.1.4. General procedure for the synthesis of compounds 5a–h. A mixture of furo[2,3-*b*]pyridine **3** (10 mmol), 2-azepanone (2260 mg, 20 mmol) and phosphorus oxychloride (1.86 mL, 20 mmol) in absolute 1,2-dichloroethane (50 mL) was refluxed for 20 h. The solvent was distilled off to dryness and water (50 mL) was added. The separated crystals were filtered off, washed with water, dried, and recrystallized from ethanol.

*4-Isopropyl-2,3,10,11,12,13-hexahydro-1H-cyclopenta[4″,5″]pyrido[3″,2″:4′,5′]furo[3′,2′:4,5]-pyrimido[1,2-a]azepin-7(9H)-one (**5a**).* Yield 2.43 g (72%), mp 163–165 °C. IR ν/cm^{-1}: 1702 (C=O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.31 (d, J = 6.7 Hz, 6H, CH(C$\underline{H}_3$)$_2$), 1.76–1.93 (m, 6H, 10,11,12-CH_2), 2.23–2.34 (m, 2H, 2-CH_2), 3.02 (t, J = 7.4 Hz, 2H, 3-CH_2), 3.12–3.17 (m, 2H, 13-CH_2), 3.19 (sp, J = 6.7 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.36 (t, J = 7.6 Hz, 2H, 1-CH_2), 4.41–4.46 (m, 2H, 9-CH_2). ^{13}C NMR (75 MHz, DMSO/

CCl_4, 1/3) δ: 20.9, 24.5, 27.1, 28.7, 29.0, 31.1, 32.8, 36.6, 41.9, 109.2, 133.1, 135.1, 140.4, 149.7, 151.8, 160.9, 161.5, 161.8. Anal. calcd for $C_{20}H_{23}N_3O_2$: C 71.19; H 6.87; N 12.45%. Found: C 71.10; H 6.85; N 12.48%.

*4-Butyl-2,3,10,11,12,13-hexahydro-1H-cyclopenta[4″,5″]pyrido[3″,2″:4′,5′]furo[3′,2′:4,5]-pyrimido[1,2-a]azepin-7(9H)-one (**5b**).* Yield 2.46 g (70%), mp 172–174 °C. IR ν/cm^{-1}: 1689 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.98 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.36–1.49 (m, 2H, $C\underline{H}_2CH_3$), 1.69–1.93 (m, 8H, $C\underline{H}_2C_2H_5$, 10,11,12-CH_2), 2.23–2.33 (m, 2H, 2-CH_2), 2.80 (t, J = 7.6 Hz, 2H, $C\underline{H}_2C_3H_7$), 2.99 (t, J = 7.4 Hz, 2H, 3-CH_2), 3.11–3.16 (m, 2H, 13-CH_2), 3.34 (t, J = 7.6 Hz, 2H, 1-CH_2), 4.40–4.45 (m, 2H, 9-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 13.5, 21.9, 24.4, 24.5, 27.1, 28.7, 29.2, 29.7, 31.1, 34.9, 36.6, 41.9, 109.2, 134.1, 134.9, 140.4, 149.4, 151.8, 156.9, 160.9, 161.6. Anal. calcd for $C_{21}H_{25}N_3O_2$: C 71.77; H 7.17; N 11.96%. Found: C 71.90; H 7.14; N 12.00%.

*4-Phenyl-2,3,10,11,12,13-hexahydro-1H-cyclopenta[4″,5″]pyrido[3″,2″:4′,5′]furo-[3′,2′:4,5]pyrimido[1,2-a]azepin-7(9H)-one (**5c**).* Yield 2.53 g (68%), mp 309 °C. IR ν/cm^{-1}: 1685 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.78–1.95 (m, 6H, CH_2, 10,11,12-CH_2), 2.23–2.35 (m, 2H, 2-CH_2), 3.13–3.20 (m, 2H, 13-CH_2), 3.24 (t, J = 7.3 Hz, 2H, 3-CH_2), 3.43 (t, J = 7.5 Hz, 2H, 1-CH_2), 4.41–4.49 (m, 2H, NCH_2), 7.38–7.51 and 7.83–7.88 (both m, 3H and 2H, Ph). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 24.4, 25.7, 26.9, 28.6, 31.2, 31.8, 36.6, 42.1, 110.2, 127.9, 128.4, 128.5, 134.2, 135.9, 138.6, 140.3, 151.8, 152.0, 152.3, 161.5, 161.8. Anal. calcd for $C_{23}H_{21}N_3O_2$: C 74.37; H 5.70; N 11.31%. Found: C 74.47; H 5.68; N 11.34%.

*5-Isopropyl-1,2,3,4,11,12,13,14-octahydroazepino[1″,2″:1′,2′]pyrimido[4′,5′:4,5]furo[2,3-c]isoquinolin-8(10H)-one (**5d**).* Yield 2.57 g (73%), mp 183–185 °C. IR ν/cm^{-1}: 1702 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.28 (d, J = 6.7 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.75–1.98 (m, 10H, 2,3-CH_2 and 11,12,13-CH_2), 2.82–2.88 (m, 2H, 4-CH_2), 3.11–3.16 (m, 2H, 14-CH_2), 3.33 (sp, J = 6.7 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.32–3.38 (m, 2H, 1-CH_2), 4.40–4.45 (m, 2H, 10-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 20.7, 21.3, 22.4, 24.5, 24.7, 26.5, 27.1, 28.7, 30.4, 36.7, 41.8, 109.9, 124.9, 134.6, 141.3, 144.0, 151.7, 160.3, 160.6, 164.9. Anal. calcd for $C_{21}H_{25}N_3O_2$: C 71.77; H 7.17; N 11.96%. Found: C 71.90; H 7.15; N 12.00%.

*5-Isobutyl-1,2,3,4,11,12,13,14-octahydroazepino[1″,2″:1′,2′]pyrimido[4′,5′:4,5]furo[2,3-c]isoquinolin-8(10H)-one (**5e**).* Yield 2.70 g (74%), mp 192–194 °C. IR ν/cm^{-1}: 1705 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.99 (d, J = 6.6 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.75–1.97 (m, 10H, 2,3-CH_2 and 11,12,13-CH_2), 2.21–2.34 (m, 1H, $C\underline{H}(CH_3)_2$), 2.68 (d, J = 7.0 Hz, 2H, $CHC\underline{H}_2$), 2.76–2.82 (m, 2H, 4-CH_2), 3.11–3.17 (m, 2H, 14-CH_2), 3.32–3.38 (m, 2H, 1-CH_2), 4.40–4.45 (m, 2H, 10-CH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 20.8, 22.2, 22.4, 24.5, 25.2, 26.3, 27.1, 28.7, 36.7, 41.8, 42.9, 109.9, 126.4, 134.6, 141.3, 143.8, 151.8, 159.8, 159.9, 160.6. Anal. calcd for $C_{22}H_{27}N_3O_2$: C 72.30; H 7.45; N 11.50%. Found: C 72.41; H 7.44; N 11.52%.

*2,2,5-Trimethyl-1,4,11,12,13,14-hexahydro-2H-pyrano[4‴,3‴:4″,5″]pyrido[3″,2″:4′,5′]furo[3′,2′:4,5]pyrimido[1,2-a]azepin-8(10H)-one (**5f**).* Yield 2.54 g (72%), mp 211–213 °C. IR ν/cm^{-1}: 1688 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.34 (s, 6H, $C(CH_3)_2$), 1.76–1.94 (m, 6H, 11,12,13-CH_2), 2.49 (s, 3H, CH_3), 3.14–3.20 (m, 2H, 14-CH_2), 3.22 (s, 2H, CH_2), 4.41–4.46 (m, 2H, 10-CH_2), 4.75 (c, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 20.8, 24.5, 25.8, 27.0, 28.7, 36.3, 36.6, 41.9, 60.0, 68.6, 110.2, 123.7, 134.7, 139.7, 140.8, 151.7, 153.6, 160.4, 161.0. Anal. calcd for $C_{20}H_{23}N_3O_3$: C 67.97; H 6.56; N 11.89%. Found: C 68.05; H 6.57; N 11.91%.

*2,2-Dimethyl-5-ethyl-1,4,11,12,13,14-hexahydro-2H-pyrano[4‴,3‴:4″,5″]pyrido[3″,2″:4′,5′]furo[3′,2′:4,5]pyrimido[1,2-a]azepin-8(10H)-one (**5g**).* Yield 2.76 g (75%), mp 224–226 °C. IR ν/cm^{-1}: 1694 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 1.34 (s, 6H, $C(CH_3)_2$), 1.35 (t, J = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.76–1.94 (m, 6H, 11,12,13-CH_2), 2.74 (q, J = 7.4 Hz, 2H, $C\underline{H}_2CH_3$), 3.14–3.20 (m, 2H, 14-CH_2), 3.23 (s, 2H, CH_2), 4.41–4.47 (m, 2H, 10-CH_2), 4.80 (s, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 11.3, 24.5, 25.8, 26.4, 27.1, 28.7, 36.4, 36.6, 41.9, 59.7, 68.6, 110.1, 123.1, 134.8, 139.8, 140.9, 151.7, 158.0, 160.7, 161.0. Anal. calcd for $C_{21}H_{25}N_3O_3$: C 68.64; H 6.86; N 11.44%. Found: C 68.55; H 6.85; N 11.47%.

*5-Butyl-2,2-dimethyl-1,4,11,12,13,14-hexahydro-2H-pyrano[4‴,3‴:4″,5″]pyrido-[3″,2″:4′,5′]furo[3′,2′:4,5]pyrimido[1,2-a]azepin-8(10H)-one (**5h**).* Yield 2.69 g (68%), mp 150–152 °C. IR ν/cm^{-1}: 1701 (C═O). ^{1}H NMR (300 MHz, DMSO/CCl_4, 1/3) δ 0.99 (t, J = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.33 (s, 6H, $C(CH_3)_2$), 1.38–1.51 (m, 2H, $C\underline{H}_2CH_3$), 1.71–1.94 (m, 8H, $\underline{CH}_2C_2H_5$, 11,12,13-CH_2), 2.69 (t, J = 7.6 Hz, 2H, $C\underline{H}_2C_3H_7$), 3.13–3.20 (m, 2H, 14-CH_2), 3.23 (s, 2H, CH_2), 4.40–4.47 (m, 2H, 10-CH_2), 4.80 (s, 2H, OCH_2). ^{13}C NMR (75 MHz, DMSO/CCl_4, 1/3) δ: 13.5, 21.9, 24.5, 25.8, 27.1, 28.7, 29.4, 32.9, 36.5, 36.6, 41.9, 59.8, 68.6, 110.2, 123.3, 134.8, 139.9, 140.9, 151.8, 157.3, 160.7, 161.0. MS, m/z ($I_{rel,\%}$), [M^+] 395 (28), 353 (100), 325 (14), 283 (10). Anal. calcd for $C_{23}H_{29}N_3O_3$: C 69.85; H 7.39; N 10.62%. Found: C 69.77; H 7.41; N 10.65%.

4.2. PASS

Prediction of biological activity spectra for the designed *in silico* compounds was performed by PASS version 2014.

This version of PASS predicts simultaneously about 7000 types of biological activities with a mean accuracy of ~95% based on analysis of structure–activity relationships for the training set, including information about 1 000 000 substances. The PASS approach is described in more detail elsewhere.[25,26] Recent news about PASS improvement and extension, as well as several examples of PASS applications, may be found on the PASS web-site.[25]

4.3. Biological evaluation

Biological investigations of all compounds described in the paper were carried out using outbred white rats (Vistar line) weighing 120 ± 150 g and mice (Albino line) weighing 18 ± 22 g of both sexes. All groups of animals were maintained at 25 ± 2 °C in the same room, on a common food ration. All the experimental protocols were approved by the Committee of Ethics of the Yerevan State Medical University (YSMU) (Yerevan, Armenia), followed the "Principles of laboratory animal care" and carried out in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).[55]

4.3.1. Evaluation of the anticonvulsant activity of the synthesized compounds. Pentylenetetrazole (PTZ) is a common

convulsant agent used in animal models to investigate the mechanisms of seizures.[35–42] PTZ was injected subcutaneously at 90 mg kg^{-1}, which induced convulsions in 95% of animals ($CD_{95\%}$). Each animal was placed into an individual plastic cage for observation lasting 1 hour. Seizure and clonic convulsions were recorded. Substances were administered intraperitoneally (i.p.) at doses of 10, 25, 50, 75, 100, 150, 200 mg kg^{-1} in carboxymethylcellulose and Tween-80 suspension 45 min before the administration of PTZ and applying electrical stimulation. To the control animals the emulsion was injected. Every dose of each test compound was studied in 6 animals. As a reference compound, the known antiepileptic drug ethosuximide (zarontin) was used.[49]

MES test was used as an animal model for the generalized tonic seizures of epilepsy.[43–45] The parameters of MES were: 50 mA, duration of 0.2 s, and oscillation frequency of 50 imp per s. The anticonvulsant properties of compounds were assessed by the prevention of tonic-extensor phase of convulsions.

Thiosemicarbazide, being an antimetabolite of the GABA inhibitor (glutamic acid decarboxylase) in the brain,[36,50] was administered subcutaneously to mice at a dose of 18 mg kg^{-1} as a 0.5% solution causing clonic convulsions in animals. Antithiosemicarbazide activity was evaluated on latency time of the onset of seizures. Substances were administered intraperitoneally (i.p.) at doses of 100 mg kg^{-1} in carboxymethylcellulose suspension with Tween-80 45 min before administration of thiosemicarbazide. The comparative drug zarontin was given in 200 mg kg^{-1} doses.

4.3.2. Evaluation of the anxiolytic effect of the synthesized compounds

Open field test. An open field apparatus (a square with a side of 58 cm and a height of 20 cm) was used, the bottom of which is divided into squares and has holes (cells). Within 5 minutes of the experiment, the number of spontaneous horizontal displacements (the intersection of squares), those sniffing cells and those standing on their hind legs (vertical movement) in the experimental and control groups of animals was determined.[51,52]

Experiments were carried out in the daytime (in natural light). Registration of spontaneous behaviour of each individual animal was carried out for 5 min. The presence of sedating and activating effects was judged by the number of horizontal (the intersection of squares) and vertical (rising on their hind legs) movements, while the anxiolytic effect was evaluated by the number of examined cells from the experimental and control groups of animals. For each compound, as well as for the diazepam group used as the control, a group of eight animals was used. Test compounds were administered to mice in the most effective dose of 50 mg kg^{-1} intraperitoneally as a suspension with methylcarboxycellulose and Tween-80. The compounds were administered to mice 45 minutes before placing the animals in the "open field" conditions.

Modified elevated plus maze test for mice. The modified contact labyrinth is raised above the floor in a cruciform system having a pair of opposed open and closed arms. When placing the animals in the cruciform EPM system,[53] antagonism was observed in the research aimed at familiarizing the mice with the whole maze, as the fear of falling appeared. Normal animals prefer to spend most of their time in the closed (dark) arms of the maze. The anxiolytic effect of the drug is estimated by the increase of the number of entries into the open arm and the time spent in them, without increasing the overall motor activity. Studies were conducted on mice. The animal was placed in the center of the installation – at the intersection of the arms. The fixed time spent in the closed arms and the number of attempts to enter the center of the installation were measured. The tested compounds (100 mg kg^{-1}) and reference drug ethosuximide (200 mg kg^{-1}) were administered intraperitoneally before the experiments. Control animals received an emulsifier. The results were processed statistically ($P = 0.05$).

4.3.3. Evaluation of the incoordination of movements in the rotating rod test and acute toxicity. Muscle relaxant properties were studied using the "rotating rod" test.[36,46,47] Mice were placed on a horizontal rod 4 cm in diameter rotating at a speed of 5 revolutions per minute. The failure of animals under the influence of a substance to keep their balance on the rod for 2 minutes was regarded as a manifestation of the lack of coordination of movement. The compounds were injected i.p in doses of 25–1800 mg kg^{-1}.

The acute toxicity (LD_{50}), was determined by calculating the number of dead animals after 24 h of exposure (i.p. injection) in doses of 100–2200 mg kg^{-1}. Ethosuximide was used as a control.

It should be mentioned that all experiments were performed in compliance with the relevant laws and institutional guidelines, and also the institutional committee(s) on animal experimentation have approved the experiments.

Acknowledgements

The chemical part of this work was made possible in part by a research grant from the Armenian National Science and Education Fund (ANSEF, Chemorg-3824) based in New York, USA. The biological part of this work was supported by the State Committee Science MES RA, in frame of the research project No. SCS "13-3D145".

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