THE PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 4-OXO-3,4-DIHYDROQUINAZOLINE AND ANTHRANILAMIDES CONTAINING A FRAGMENT OF GLYCINE

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Key words: quinazolone; anthranilamide; antidepressant effect; anticonvulsant activity; hypnotic activity

Derivatives of 4-oxo-3,4-dihydroquinazoline are known as a promising class of compounds due to their wide spectrum of the pharmacological activity. Taking into account the PASS data for the substituted anthranilamides synthesized, as well as derivatives of 4-oxo-3,4-dihydroquinazoline containing an “in-built” fragment of amino acid glycine as a pharmacophore, the decision to study their central neurotropic effects was made. While studying the hypnotic, anticonvulsant and antidepressant activities the highest antidepressant properties of N-(1,1-diphenyl-1-hydroxyethyl)-N'-diphenylhydroxyacetylantranilamide (compound 4) have been determined, this compound is slightly inferior the reference drug Imipramine. N-(phenylhydrazidoacetyl)-N'-succinamidoanthranilamide (compound 1) reveals high anticonvulsant properties and is not inferior the classical anticonvulsant drug Depakine. When studying the hypnotic effect the antagonism with Barbamyl for 2-(4-oxo-3,4-dihydro-3-quinazolinyl)acetohydrazide (compound 5) has been found. Methyl-(2-methylcarbonyloxymethyl-4-oxo-3,4-dihydro-3-quinazolinyl)acetate (compound 8) decreased the latent period of “falling asleep” for animals in 1.6 and 1.7 times in the doses of 20 and 200 mg/kg, respectively (the same level with the reference drug), and therefore, it is a promising compound for further research of the hypnotic activity. The analysis of the “structure-activity” relationship gives the possibility to assume that such pronounced pharmacological activity is due to the presence of substituents in position 2 of the quinazoline nucleus. Therefore, the data obtained prove that the study of these derivatives is promising for further search of new biologically active substances with hypnotic, anticonvulsant and antidepressant properties.
It was injected intragastrically in the dose of 300 mg/kg. The control group received intragastrically the same volume of purified water. The aqueous solution of pentylenetetrazol (Sigma) in the dose of 80 mg/kg was injected subcutaneously. The anticonvulsant activity was assessed by the following indicators: the latent period of clonic or tonic convulsions, the number of clonic and tonic paroxysms per 1 mouse and mortality. The results obtained are given in Tab. 2.

The hypnotic activity of compounds 5-8 was assessed using the model of Barbamyl anesthesia in mice [2]. The test substances were injected intragastrically as water suspensions in the preventive mode in the doses of 20 and 200 mg/kg 30 min prior to the experiment. Animals of the comparison group received intragastrically the aqueous solution of Donormyl (doxylamine hydrochloride) in the dose of 20 mg/kg. The control group received intragastrically the same volume of purified water. Barbamyl in the dose of 50 mg/kg was injected intraperitoneally. The hypnotic activity was estimated by the following indicators: the latent period of anesthesia beginning (“falling asleep”), duration of the anesthesia sleep and the number of mice that were anesthetized. The results obtained are given in Tab. 3.

Results and Discussion

When studying the antidepressant activity only \(N-(1,1\text{-diphenyl-1-hydroxyet-2-yl})\)-\(N\text{'-diphenylhydroxyacetylanthranilamide}\) (compound 4) in the dose of 200 mg/kg reliably decreased the general duration of immobile fixation of animals in 1.9 times compared to the control group (at the same level as Imipramine). However, it had no effect on the number of immobility acts. The results ob-

| Group of animals / test compound | Dose, mg/kg | Duration of immobile fixation, s | Number of immobility acts |
|----------------------------------|------------|----------------------------------|---------------------------|
| Control                          | -          | 114.14+/-16.06                   | 19.71+/-3.01              |
| Compound 1                       | 20         | 71.20+/-10.26                    | 15.40+/-1.40              |
|                                  | 200        | 120.80+/-59.56                   | 17.00+/-3.15              |
| Compound 2                       | 20         | 99.20+/-29.57                    | 13.60+/-2.62              |
|                                  | 200        | 75.00+/-23.71                    | 13.40+/-2.58              |
| Compound 3                       | 20         | 94.40+/-37.85                    | 17.60+/-2.29              |
|                                  | 200        | 71.80+/-19.20                    | 16.60+/-1.50              |
| Compound 4                       | 20         | 80.20+/-20.23                    | 14.00+/-2.07              |
|                                  | 200        | 60.00+/-12.40*                   | 18.20+/-3.32              |
| Melipramin                       | 25         | 64.30+/-14.10*                   | 7.60+/-1.71*              |

Note: *significant differences in relation to the control (p<0.05).
tained confirm significant and dose-dependent antidepres-
pressant properties of this compound; they are slightly in-
ferior the reference drug Imipramine.

Compounds 1-3 in both doses (except for compound 1
in the dose of 200 mg/kg) revealed a tendency to de-
crease the total duration of immobile fixation and the num-
ber of immobility acts. However, this difference did not
reach the level of statistical significance because of high
depression of data. The high activity of compound 4
can be associated with the presence of two fragments of ben-
zylic (diphenylhydroxyacetic) acid in the structure of a
molecule.

The results of the anticonvulsant activity study pre-

Table 2

The effect of the test substances on pentylenetetrazol convulsions in mice

| Group of animals / test compound | Dose, mg/kg | The latent period, min | Number of clonic and tonic paroxysms per 1 mouse | Mortality, % |
|---------------------------------|------------|------------------------|---------------------------------|-------------|
| Control                         | –          | 6.34+/-.79             | 2.86+/-.51                      | 71          |
| Compound 1                      | 20         | 6.43+/-.71             | 2.60+/-.81                      | 40          |
|                                 | 200        | 11.05+/-.197*         | 1.40+/-.025*                    | 20**        |
| Compound 2                      | 20         | 6.12+/-.103            | 2.80+/-.49                      | 60          |
|                                 | 200        | 4.14+/-.044            | 3.00+/-.55                      | 80          |
| Compound 3                      | 20         | 4.40+/-.103            | 2.40+/-.75                      | 80          |
|                                 | 200        | 5.56+/-.141            | 2.00+/-.32                      | 80          |
| Compound 4                      | 20         | 5.45+/-.64             | 2.20+/-.58                      | 60          |
|                                 | 200        | 5.55+/-.95             | 2.60+/-.40                      | 60          |
| Depakine                        | 300        | 12.16+/-.88*           | 1.20+/-.41*                     | 17**        |

Note: significant differences in relation to the control (p<0.05); * – by the Student’s t-criterion; ** – by the Fisher angular transformation.

Table 3

The effect of the test substances on the Barbamyl anesthesia in mice

| Group of animals / test compound | Dose, mg/kg | The latent period, min | Duration of anesthesia, min | % of mice that were anesthetized |
|---------------------------------|------------|------------------------|-----------------------------|---------------------------------|
| Control                         | –          | 21.56+/-.238           | 45.50+/-.444                | 100                             |
| Compound 5                      | 20         | –                      | 0.00+/-.00***               | 0**                             |
|                                 | 200        | 32.20                  | 11.25*                      | 20**                             |
| Compound 6                      | 20         | 18.53+/-.169           | 15.95+/-.312***             | 100                             |
|                                 | 200        | 9.47+/-.48**           | 15.40+/-.60**               | 100                             |
| Compound 7                      | 20         | 14.46+/-.346           | 25.02+/-.63*                | 100                             |
|                                 | 200        | 12.00+/-.272*          | 34.11+/-.68                 | 100                             |
| Compound 8                      | 20         | 13.68+/-.202*          | 45.82+/-.75                 | 100                             |
|                                 | 200        | 12.61+/-.280*          | 43.60+/-.67                 | 100                             |
| Donormyl                        | 20         | 11.72+/-.146*          | 50.36+/-.52                 | 100                             |

Note: significant differences in relation to the control: * – by the Student’s t-criterion (p<0.05); ** – by the Student’s t-criterion (p<0.01); *** – by the Student’s t-criterion; # – by the Fisher angular transformation (p<0.05); ## – by the Fisher angular transformation (p<0.01).

Compounds 1-3 in both doses (except for compound 1
in the dose of 200 mg/kg) revealed a tendency to de-
crease the total duration of immobile fixation and the num-
ber of immobility acts. However, this difference did not
reach the level of statistical significance because of high
depression of data. The high activity of compound 4 can
be associated with the presence of two fragments of ben-
zylic (diphenylhydroxyacetic) acid in the structure of a
molecule.

The results of the anticonvulsant activity study pre-

by 51% (p<0.05) compared to the control group. The anti-
convulsant effect of this compound is dose-dependent:
in the dose of 20 mg/kg compound 1 does not affect the
latent period and the number of convulsions per 1 mouse,
and it only insignificantly reduces the mortality index in
the group by 31% compared to the control group. In ge-
neral, the anticonvulsant effect of this compound in the
dose of 200 mg/kg is not inferior the classical anticon-
vulsant drug Depakine in the dose of 300 mg/kg. It cau-
sed a significant prolongation of the latent period of the first
paroxysm development in the group in 1.9 times, as well as
decrease in the number of convulsions in 2.4 times and the
mortality index (54%) compared to the control group.

As can be seen from Tab. 3, a well-proven hypnotic
drug Donormyl (doxylamine hydrochloride) in the dose
of 20 mg/kg statistically significantly reduced the latent
period of animals’ anesthesia beginning in 1.8 times com-
pared to the control group; however, it had no effect on the
sleep duration.

Compound 5 revealed the antagonism to Barbamyl:
in the dose of 20 mg/kg none of the animals were anes-
that is a promising compound for further research of the hypnotic activity since it substantially decreases the time of “falling asleep” and does not affect duration of sleep. The analysis of the “structure-activity” relationship gives the possibility to assume that such pronounced pharmacological activity is due to the presence of substituents in position 2 of the quinazoline nucleus.

CONCLUSIONS
1. For N-(1,1-diphenyl-1-hydroxyeth-2-yl)-N’-diphenylhydroxyacetlanthranilamide (compound 5) the highest level of the antidepressant activity has been determined, it is slightly inferior than that for the reference drug Imipramine.

2. N-(phenyllhazidoacetyl)-N’-succinamidoanthranilamide (compound 1) reveals high anticonvulsant properties and is not inferior the action of the classical anticonvulsant drug Depakine.

3. It has been found that 2-(4-oxo-3,4-dihydro-3-quinazolinyl)acetohydrazide (compound 5) shows the antagonistic effect in relation to Barbamyl.

4. Methyl-(2-methylcarbonyloxyethyl-4-oxo-3,4-dihydro-3-quinazolinyl)acetate (compound 8) decreases the latent period of “falling asleep” for animals, and therefore, it is a promising biologically active substance for further research of the hypnotic activity.

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(сполука 8) в дозах 20 та 200 мг/кг достовірно на рівні препарату порівняння зменшує ла-
tентний період «засинання» тварин у 1,6 та 1,7 рази відповідно і є перспективною БАР для
подальших досліджень снодійної активності. Аналіз зв’язку «структура-дія» дає можливість
припустити, що виразний прояв фармакологічної активності обумовлений наявністю заміс-
ників у положенні 2 хіназолінового ядра. Отримані дані дозволяють зробити висновок, що до-
слідження зазначених похідних є перспективним для подальшого пошуку нових біологічно ак-
тивних речовин зі снодійною, противосудорожною та антидепресивною властивостями.

ФАРМАКОЛОГІЧЕСКАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ 3,4-ДИГИДРО-
4-ОКСОХИНАЗОЛИНА И АНТРАНИЛАМИДОВ, КОТОРЫЕ СОДЕРЖАТ ОСТАТОК ГЛИЦИНА
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Ключевые слова: хиназолон; антраниламид; антидепрессивный эффект;
противосудорожная активность; снотворная активность

Производные 3,4-дигидро-4-оксохиназолина известны как перспективный класс химических
соединений, проявляющих широкий спектр фармакологической активности. С учетом дан-
ных PASS-прогноза для полученных нами замещенных антраниламидов и производных 4-оксо-
3,4-дигидрохиназолинов, которые содержат «встроенный» остаток аминокислоты глутамин
в качестве фармакофора, возникли основания для исследования центральных нейротропных
эфектов. При изучении снотворной, противосудорожной и антидепрессивной активности
установлено высокие антидепрессивные свойства N-(1,1-дифенил-1-гидроксил-2-ил)-N’-ди-
фенилгидразидоантраниламиды (соединение 4), который несколько уступает препа-
рату сравнения имипрамину. N-(фенилгидразидоацетил)-N’-сукинимидаантраниламид (соее-
динение 1) проявляет высокие противосудорожные свойства и не уступает классическому
противосудорожному средству депакину. При изучении снотворного эффекта установлено,
что 2-(4-оксо-3,4-дигидро-3-хиназолинил)ацетогидразид (соединение 5) проявляет антаго-
nistическое влияние относительно барбамила. Метил-(2-метилкарбонилоксиметил-4-оксо-
3,4-дигидро-3-хиназолинил)ацетат (соединение 8) в дозах 20 и 200 мг/кг достоверно на уровне
препарата сравнения уменьшает латентный период «засыпания» животных в 1,6 и 1,7 раза
соответственно и является перспективным БАВ для дальнейших исследований снотворной
активности. Анализ связи «структура-действие» дает возможность предположить, что
выраженное проявление фармакологической активности обусловлено наличием заместите-
лей в положении 2 хиназолинового ядра. Полученные данные позволяют сделать вывод, что
исследования данных производных являются перспективными для дальнейшего поиска но-
вых биологически активных веществ со снотворными, противосудорожными и антидепрес-
сивными свойствами.