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Vanillin derivatives affecting the central and peripheral nervous system

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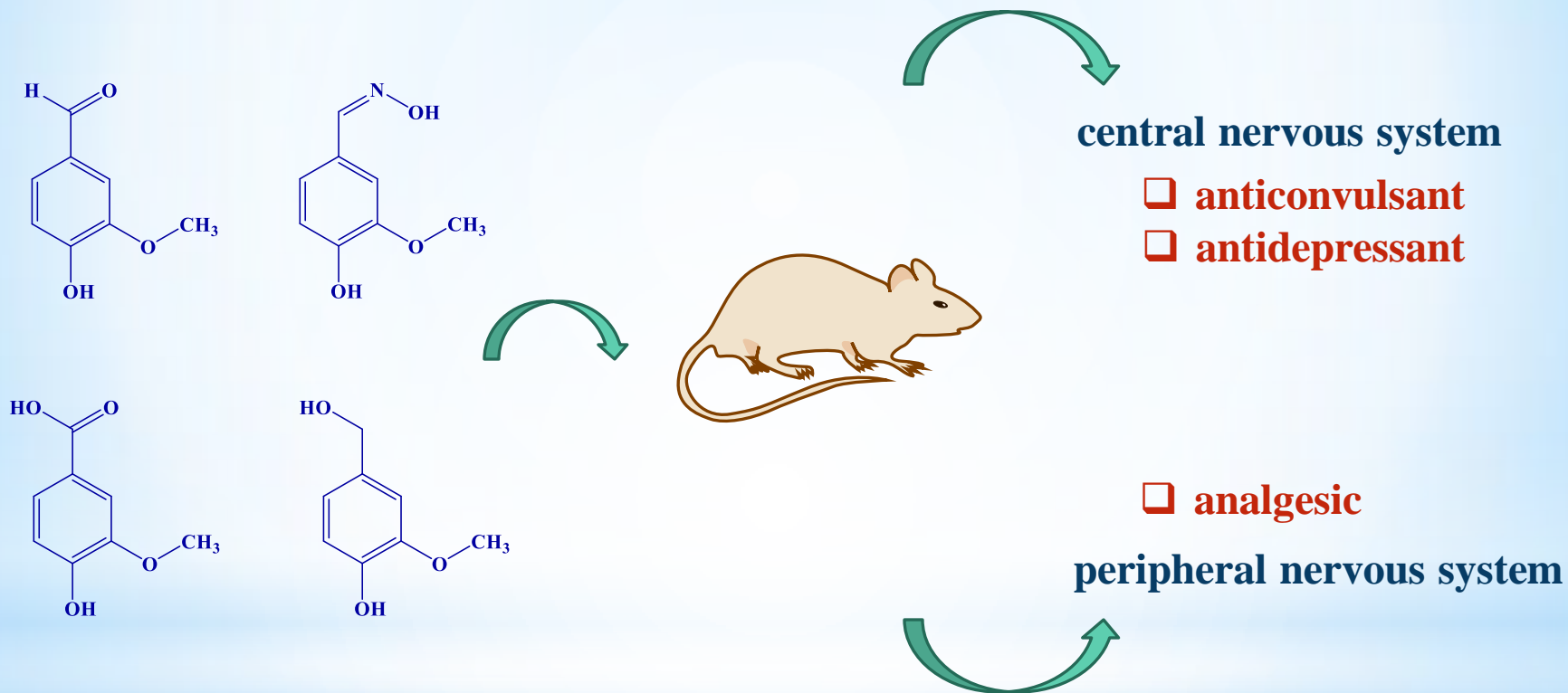
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Vanillin derivatives affecting the central and peripheral nervous system



Abstract:

Nowadays, a significant number of antiepileptic drugs aimed at influencing the main inhibitory transmitter – gamma-aminobutyric acid (GABA). Compounds with various chemical structures, binding to different GABAA sites, potentiate the action of amino acid. Recent studies have reported that phenolic compounds such as vanillin and its derivatives also have actions within the CNS and act as enhancer of GABA potential. On the other hand, vanillin affects the peripheral nervous system as agonist of TRPV1 channels that are involved in the transmission and modulation of pain (nociception) as well as the integration of diverse painful stimuli. At the present study, the influence of vanillin and its derivatives (vanillin oxime, vanillyl alcohol and vanillic acid) on the central and peripheral nervous system was reliably confirmed by evaluating their anticonvulsant, antidepressant and analgesic activity. The present findings indicate that all aforementioned compounds possess antiseizure action after oral administration on PTZ-induced convulsion model. Antidepressant activity, studied by forced swimming test (FST), has been more pronounced manifested for vanillin and vanillic acid during 24 hours after administration. Intriguingly, TRPV1 agonist vanillin and its oxime after transdermal delivery produced hyperalgesia when tested on allylisothiocyanate- and capsaicin-induced models, whereas vanillyl alcohol and vanillic acid were found to reduce the pain sensation.

Keywords: vanillin derivatives; combined action; anticonvulsant; analgesic; antidepressant.



Introduction

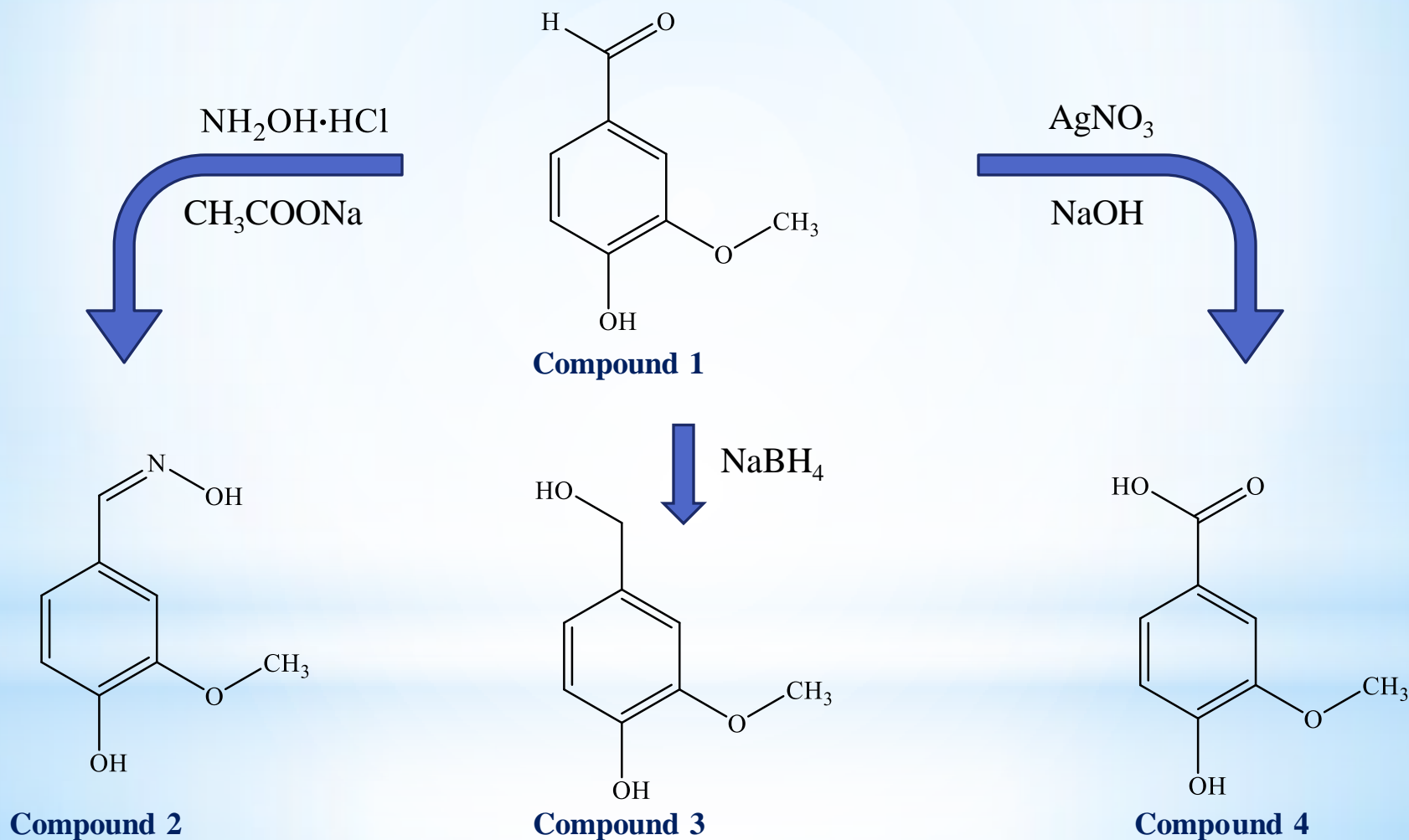
The identification and structure determination of novel pharmacological targets – transient receptor potential (TRP) ion channels – provides an opportunity for the rational design and synthesis of TRP modulators. Numerous studies have shown that representatives of various TRP channel subfamilies are involved in pain perception and inflammatory processes. In this context, TRPA1 and TRPV1 channels are of paramount interest to pharmacologists and practicing surgeons since antagonists of aforementioned receptors are considered promising drugs undergoing clinical trials. These receptors have been established as molecular targets for a variety of phytochemicals among which special attention is paid to phenolic compounds such as vanillin and its derivatives. In addition to affecting the peripheral nervous system through interaction with TRP channels, vanillin was found to act via GABA receptors. Thus, vanillin simultaneously affects both central and peripheral nervous system.

Structural modification of naturally occurring compounds may result in reducing or enhancing of their pharmacological effects. At the present study, vanillin derivatives obtained by reduction, oxidation or condensation of aldehyde group with hydroxylamine have been investigated as compounds exhibited a range of pharmacological properties such as anticonvulsant, analgesic and antidepressant action.



Results and discussion

Vanillin derivatives are commercially available or might be obtained according to the scheme below.



Anticonvulsant activity vanillin derivatives

Anticonvulsant activity (PTZ test)

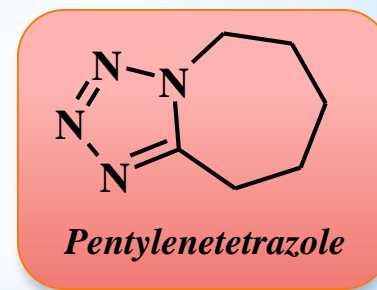
Pentylentetrazole-Induced Convulsions in Mice

The anticonvulsant activity of tested compounds was evaluated by pentylentetrazole model (PTZ), which includes the determination of pentylentetrazole minimum effective doses (MED) inducing clonic-tonic convulsions (CTC) and tonic extension (TE) in test animals upon intravenous infusion of 1% aqueous solution into a tail vein. Doses of pentylentetrazole for inducing clonic-tonic convulsions (DCTC) and tonic extension (DTE) were calculated relative to control. The anticonvulsant effect of compounds was estimated at certain time points (1, 3, 6 and 24 h) from the increase of pentylentetrazole MED compared with a control group. MED in percent was calculated using the formula:

$$\text{MED (\%)} = V/m * 10^4$$

where MED—minimum effective dose of PTZ inducing DCTC or DTE;

V—volume of PTZ solution, ml; m—animal weight, g.



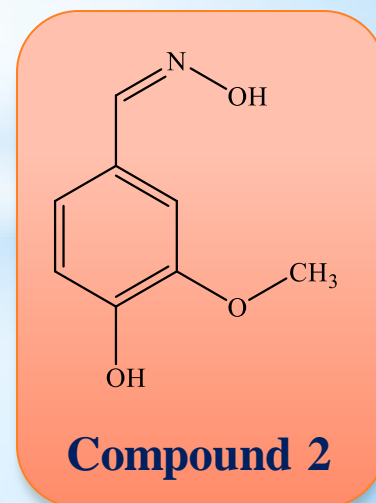
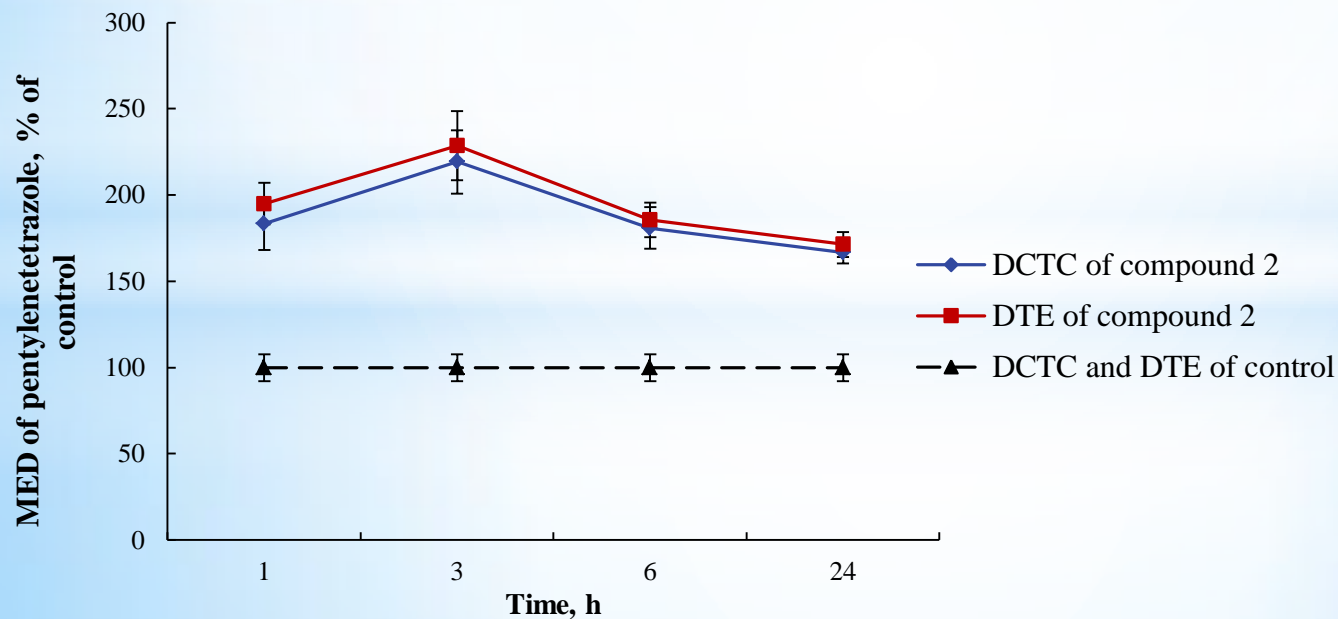
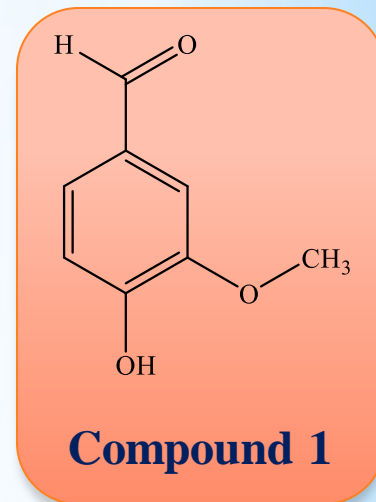
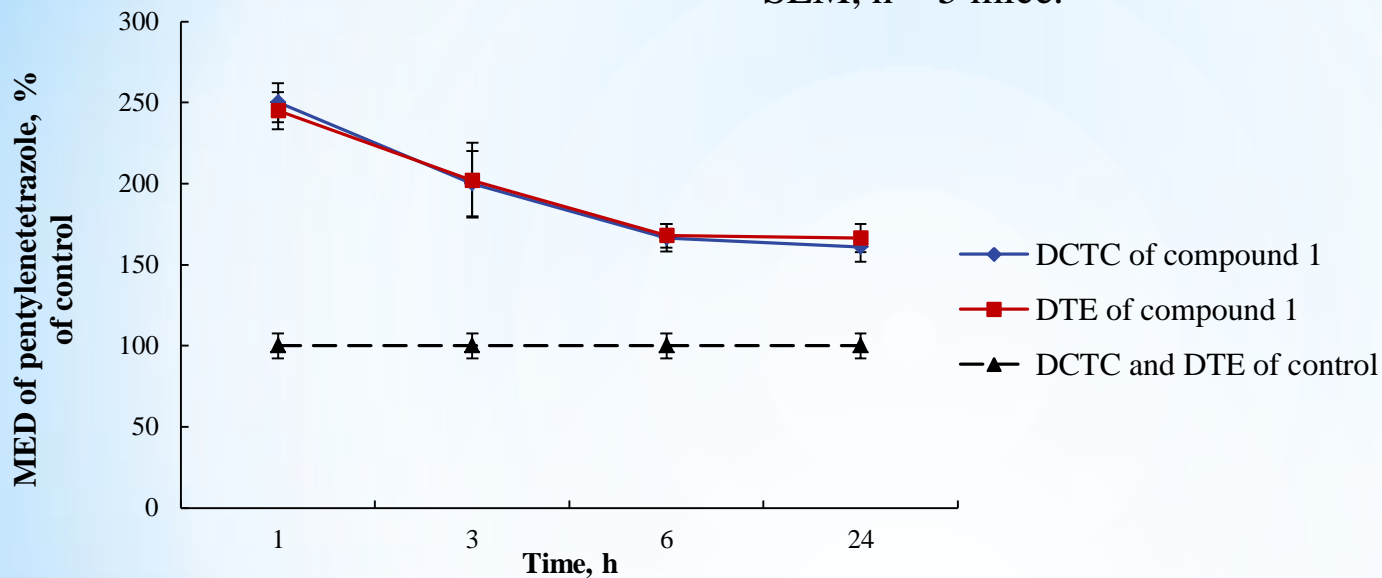
Maximal Electroshock Seizure in Mice

The anticonvulsant activity of the administered substances was studied using acute seizure models reproducible by standard generally accepted methods. The frequency of occurrence of convulsions in the 6-Hz model, and % of the death of animals in the maximum electroshock model were studied.



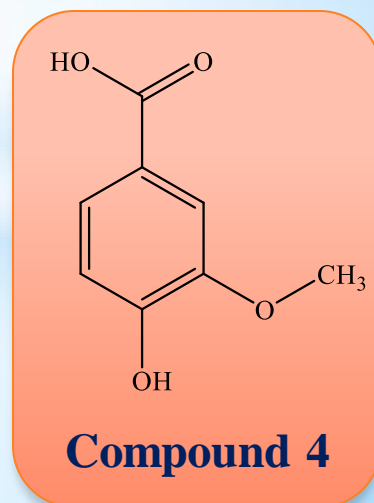
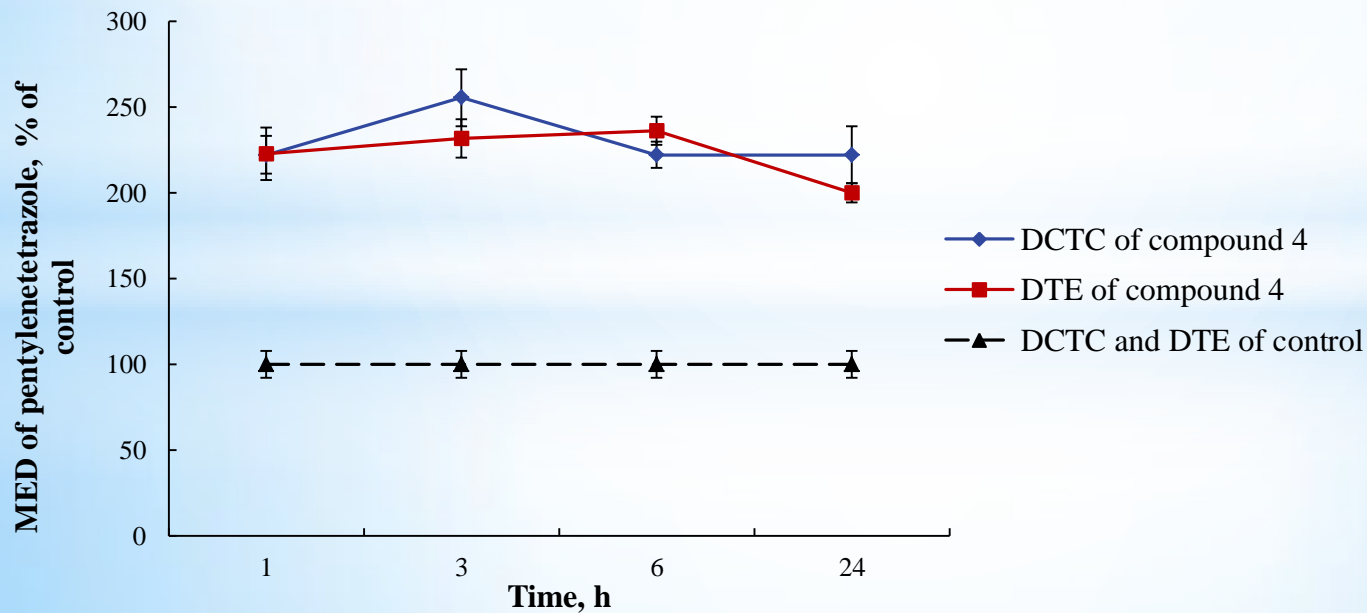
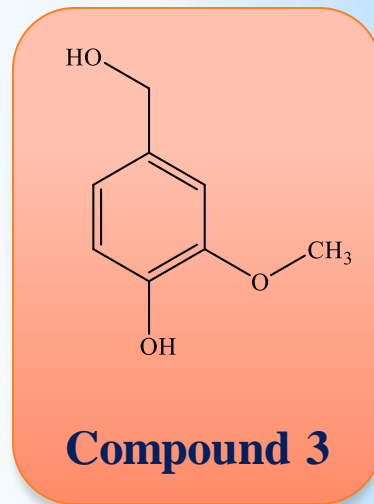
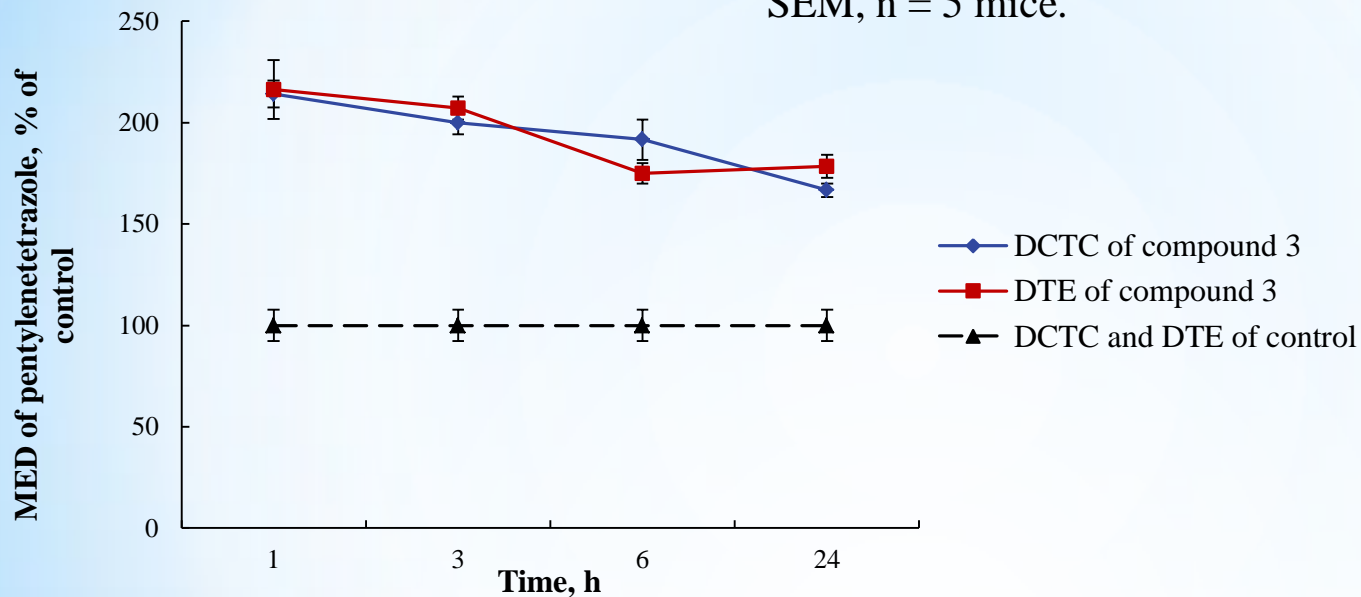
Anticonvulsant activity of vanillin derivatives

Anticonvulsant activity of compound 1 and 2; time-response relationship. Values are given as mean \pm SEM, n = 5 mice.



Anticonvulsant activity of vanillin derivatives

Anticonvulsant activity of compound **3** and **4**; time-response relationship. Values are given as mean \pm SEM, n = 5 mice.



Study of the anticonvulsant effect of vanillin derivatives on maximal electroshock seizure in mice

Experimental groups of animals	Administration time 1 h.		Administration time 3 h.	
	6 Hz, % animals with seizures	Max electroshock, % lethality	6 Hz, % animals with seizures	Max electroshock, % lethality
Control	70	60	70	60
Vanillin	90	10	40	20
Vanillin oxime	0	0	0	0
Vanillyl alcohol	40	10	70	10
Vanillic acid	100	20	90	10

White outbred male mice weighing 18–25 g were used in the work. All animals were randomly divided into equal groups (5 animals per group). Solution of vanillin, vanillin oxime, vanillic acid, vanillin alcohol at a dose of 200 mg/kg was orally administered animals of the experimental groups.

In the maximum electroshock test, the survival of animals in the experimental groups ranged from 80 to 100%, with a survival rate of 40% in the control group at 1-hour administration, for 3-hour administration, the survival rate did not differ significantly from the 1-hour. In the case of a 6-Hz model of convulsions, the administered substances can both potentiate and inhibit the seizure activity.



Experimental methods of pain induction

Chemical methods of induction



- ✓ **Capsaicin-induced licking** 20 μ l (6 μ g/paw) of solution
- ✓ **AITC-induced licking** 20 μ l of 0,5% solution



Dosage form: 2% ointment

Base: PEG – PEO – 1,2-Propyleneglycol

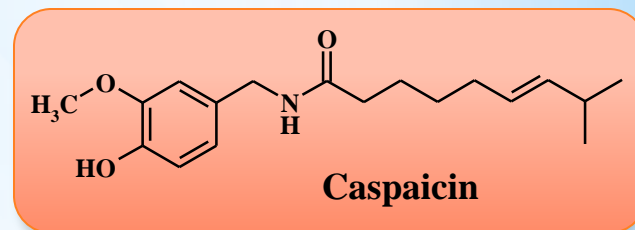
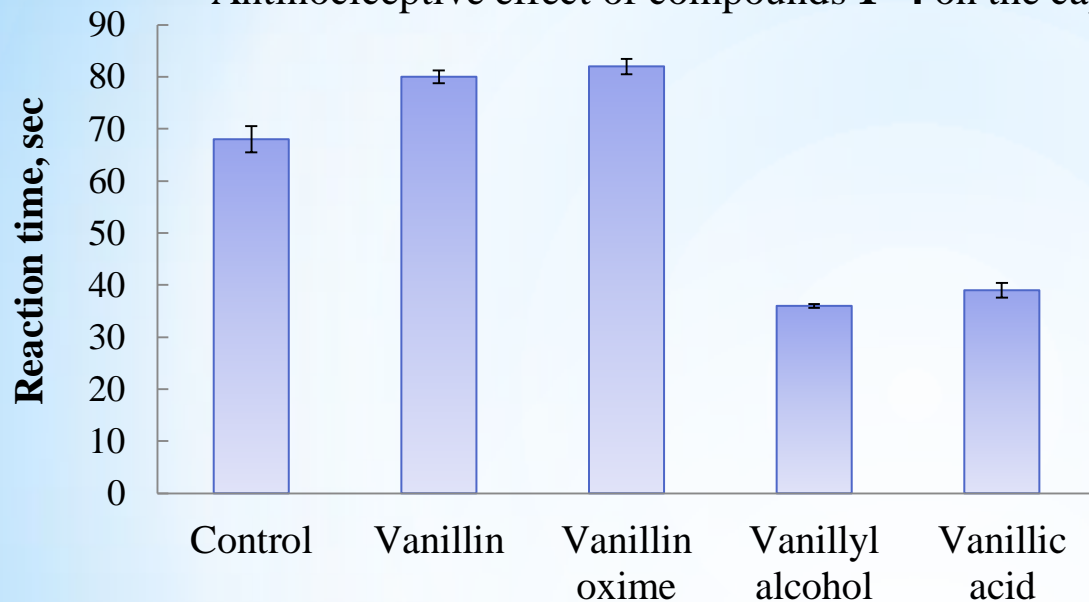


The animal then was placed in an individual plexiglass cage. The time spent licking the injected paw was measured during 5/10 min after capsaicin/AITC administration and was considered as an indicator of pain response.

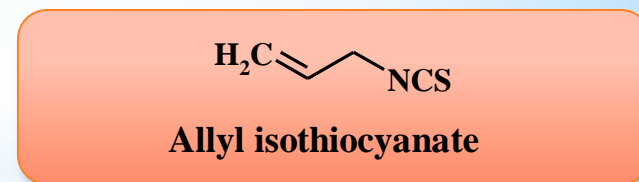
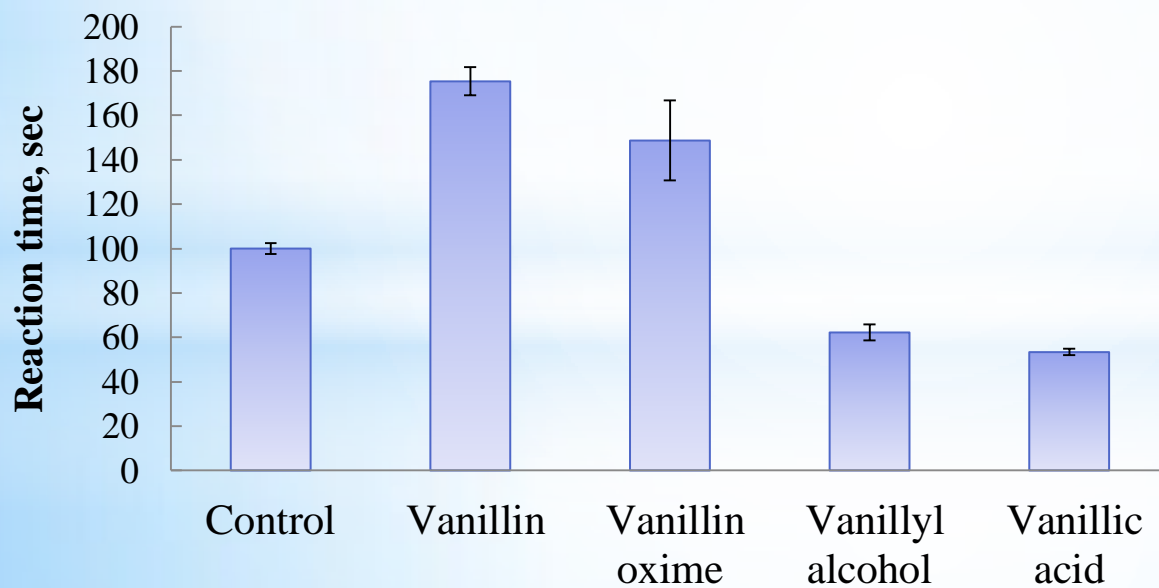


Analgesic properties of vanillin derivatives

Antinociceptive effect of compounds 1–4 on the capsaicin and AITC tests in mice

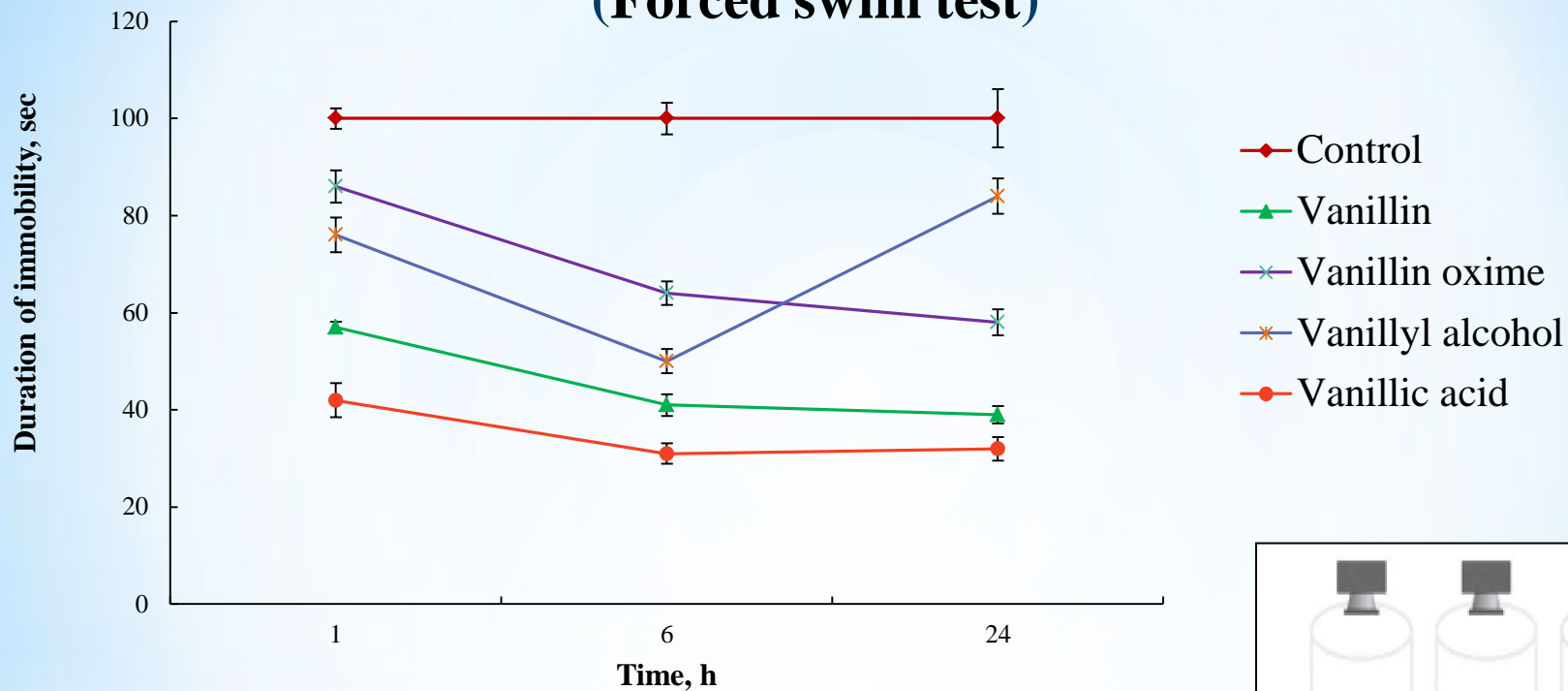


AITC or capsaicin-induced licking:
Following the adaptation to the experimental conditions, 20 μL of 0.5% (w/w) allyl isothiocyanate (AITC) or 20 μL of capsaicin solution (6 $\mu\text{g}/\text{paw}$) was injected subcutaneously under the skin of the dorsal surface of the right hindpaw.

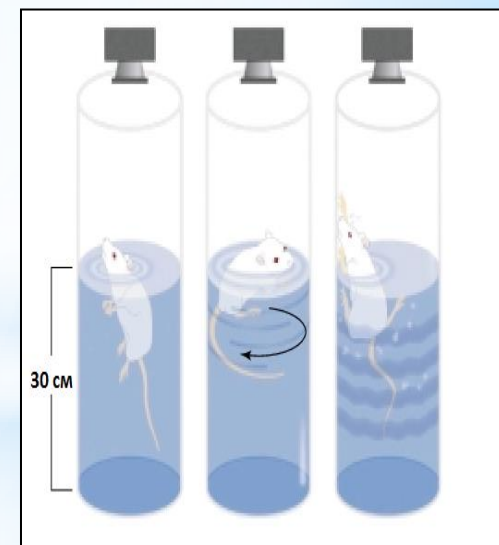


The animal then was placed in an individual plexiglass cage. The time spent licking the injected paw was measured 5/10 min after capsaicin/AITC administration and was considered as an indicator of pain response.

Antidepressant properties of vanillin derivatives (Forced swim test)



For the forced swim test (FST), white male mice were individually forced to swim in an open cylindrical container. Vanillin derivatives were administered orally 1, 6 and 24 h prior to study. All animals were forced to swim for 3 min and the duration of immobility was recorded. A decrease in the duration of immobility is indicative of an antidepressant activity.



Conclusions

In this study, the effect of vanillin and its derivatives (vanillin oxime, vanillyl alcohol and vanillic acid) on the central and peripheral nervous system was reliably proved by evaluating their anticonvulsant, antidepressant and analgesic activity. According to the obtained results, all aforementioned compounds possess antiseizure action after oral administration on PTZ-induced convulsion model. Antidepressant activity, studied by forced swimming test (FST), has been more pronounced manifested for vanillin and vanillic acid during 24 hours after administration. Intriguingly, TRPV1 agonist vanillin and its oxime after transdermal delivery produced hyperalgesia when tested on allylthiocyanate- and capsaicin-induced models, whereas vanillyl alcohol and vanillic acid were found to reduce the pain sensation.

