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**ANTI-INFLAMMATORY ACTIVITY OF COMPLEX COMPOUNDS TIN
(IV) CHLORIDE (SnCl_4) WITH SALICYLOYL HYDRAZONES
BENZALDEHYDE AND 4-BROMOBENZALDEHYDE ON
CARRAGEENAN AND FORMALIN-INDUCED INFLAMMATION**

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**ПРОТИЗАПАЛЬНА АКТИВНІСТЬ НОВИХ КОМПЛЕКСІВ SnCl_4 З
САЛІЦІЛОІЛГІДРАЗОНАМИ БЕНЗАЛЬДЕГІДУ І 4-
БРОМБЕНЗАЛЬДЕГІДУ НА МОДЕЛЯХ КАРРАГІНАН- І
ФОРМАЛІН-ІНДУКОВАНОГО ЗАПАЛЕННЯ**

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**ПРОТИВОВОСПАЛИТЕЛЬНАЯ АКТИВНОСТЬ НОВЫХ
КОМПЛЕКСОВ SnCl_4 С САЛИЦИЛОИЛГИДРАЗОНАМИ
БЕНЗАЛЬДЕГИДА И 4-БРОМБЕНЗАЛЬДЕГИДА НА МОДЕЛЯХ
КАРРАГИНАН- И ФОРМАЛИН-ИНДУЦИРОВАННОГО
ВОСПАЛЕНИЯ**

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Резюме/Summary

Anti-inflammatory properties of new complexes of SnCl_4 with benzaldehyde and 4-bromobenzaldehyde salicyloyl hydrazones the were studied in the rats using models on carrageenan and formalin-induced inflammation of paw. Solutions of benzaldehyde, 4-bromobenzaldehyde and salicylic acid were also used to determine their contribution to the anti-inflammatory activity of the complexes. The development of inflammatory process was assessed by changes in the volume and width of the inflamed paw. The use of complexes of SnCl_4 with benzaldehyde and 4- bromobenzaldehyde salicyloyl hydrazones for treatment resulted in normalization of the width and volume of the inflamed paw following 3 days of treatment. . Six days after the start of the experiment (carrageenan model), the volume of the affected limb almost reached the control values in animals that received complex compounds I and II, benzaldehyde and salicylic acid. During the experiment it was determined that complex compounds I and II demonstrated the best anti-inflammatory activity in both models of inflammation

Key words: *anti-inflammatory activity, complex compound, benzaldehyde, carrageenan, formalin.*

Протизапальні властивості нових комплексних сполук SnCl_4 з бензальдегідом

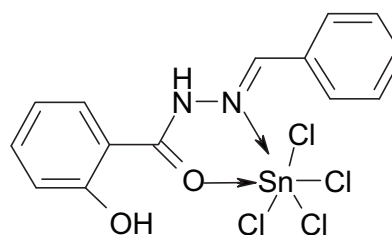
і 4-бромбензальдегідом саліцілоілгідрозонів вивчали на щурах на моделях каррагінан- і формалін-індукованого набряку лапи. Розчини бензальдегіду, 4-бромбензальдегіду і саліцилової кислоти також використовувалися для визначення вкладу їх функціональних груп у протизапальну активність комплексів. Розвиток запального процесу оцінювали за змінами об'єму і ширини запаленої лапи. Застосування комплексних сполук SnCl_4 бензальдегіду і 4-бромбензальдегіду саліцілоілгідрозонів призводило до нормалізації ширини і об'єму запаленої лапи через 3 дні після початку лікування. У тварин, які отримували лікування комплексними сполуками I і II, бензальдегідом і саліцилової кислотою, вже через шість днів після початку експерименту (на моделі каррагінан-індукованого запалення) обсяг ураженої кінцівки практично досяг контрольних значень. В ході експерименту було встановлено, що комплексні сполуки I і II продемонстрували найкращу протизапальну активність на обох моделях запалення.

Ключові слова: протизапальна активність, комплексні сполуки, бензальдегід, каррагінан, формалін.

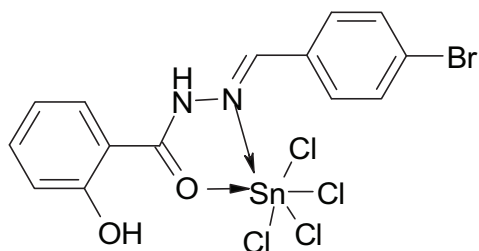
Противовоспалительные свойства новых комплексных соединений SnCl_4 с бензальдегидом и 4-бромбензальдегидом салицилоилгидразонов изучали на крысах на моделях каррагинан- и формалин-индуцированного отёка лапы. Растворы бензальдегида, 4-бромбензальдегида и салициловой кислоты также использовались для определения вклада их функциональных групп в противовоспалительную активность комплексов. Развитие воспалительного процесса оценивали по изменениям объема и ширины воспаленной лапы. Применение комплексных соединений SnCl_4 бензальдегида и 4-бромбензальдегида салицилоилгидразонов приводило к нормализации ширины и объема воспаленной лапы спустя 3 дня после начала лечения. У животных, которые получали лечение комплексными соединениями I и II, бензальдегидом и салициловой кислотой, уже через шесть дней после начала эксперимента (на модели каррагинан-индуцированного воспаления) объем пораженной конечности практически достиг контрольных значений. В ходе эксперимента было установлено, что комплексные соединения I и II продемонстрировали наилучшую противовоспалительную активность на обеих моделях воспаления.

Ключевые слова: противовоспалительная активность, комплексные соединения, бензальдегид, каррагинан, формалин.

Complex compounds tin (IV) chloride (SnCl_4) with salicyloyl hydrazones benzaldehyde and 4-bromobenzaldehyde [1] were previously synthesized at the Department of General Chemistry and Polymers and anti-inflammatory activity of these compounds was determined on models of trypsin, histamine and carrageenan-induced inflammation [2, 3]. Among obtained compounds, it was interesting to study anti-inflammatory activity of benzaldehyde, 4-bromobenzaldehyde and salicylic acid on carrageenan- and formalin-induced inflammation in order to determine their role in the anti-inflammatory activity of complex compounds SnCl_4 with salicyloyl hydrazones benzaldehyde and 4-bromobenzaldehyde.



Complex compound I



Complex compound II

Carrageenan-induced inflammation is an acute inflammation that is easily to replicate in the lab and used for studying the new prospective anti-inflammatory medicine, as well as the mechanism of development of the inflammatory process. Oedema, hyperalgesia and erythema develop immediately after inoculation of the of phlogogen injection, the mechanism of inflammation is based on increasing the release of inflammatory mediators (bradykinin, serotonin, histamine), nitric oxide and prostaglandins [4], as well as accompanied by nociceptive changes and the migration of inflammatory cells to the site of phlogogen inoculation. Development mechanism of the anti-inflammatory activity is due to the involvement of cyclooxygenase-2 (COX-2) that is induced by COX isozyme and it develops in the cells and tissues during development of the inflammatory reaction.

Formalin inflammation is the sub-acute inflammation and along with the local inflammation development and hyperaemia it also manifests itself as a systematic reaction that leads to chronic and localized pain [5], as a result, the inflammatory mediators such as biogenic amines, bradykinins, etc. start to produce. Also, the model of formalin inflammation is used for replication of arthritis in rats that is similar to human arthritis [6,7].

Anti-inflammatory activity of benzaldehyde and 4-bromobenzaldehyde was investigated and demonstrated in previously conducted studies using trypsin and

histamine inflammation model [8].

Materials and methods

Experiments were performed on Wistar male rats with weight around 180-220 g that were kept in vivarium conditions on the standard diet with free access to water and nutrition. All studies conformed to the rules of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) [9] and the principles of the Ukrainian National Congress on Bioethics (Kiev, 2003) [10].

Inflammatory reaction for each type of inflammation was induced by subplantar inoculation 0.2 ml of 0.2% aqueous solution of carrageenan (Sigma) and 0.1 ml of 2% formation (Sigma) solution [11,12] into the back surface of the rat's hind limb.

Studies were conducted on 12 groups of animals (6 groups for each type of inflammation), 3 rats each. Animals were treated directly after 24 hours after inflammation development. Control animal group received no treatment. Each tested animal group received treatment peroral: groups 2 and 3 received emulsion solutions of complexes SnCl_4 with salicyloyl hydrazones benzaldehyde and 4-bromobenzaldehyde prospectively; group 4 received emulsion of benzaldehyde in Twin; group 5 received emulsion of 4-bromobenzaldehyde in Twin; group 6 received solution of salicylic acid (40 mg/kg).

Result evaluation of the experimental study was based on volume changes of limb (using digital plethysmometer 37140 (Ugo Basile, China)) and the width of the affected limb (using an electronic calliper YT-7201 (YATO, Poland)) before and after 24-hours, as well as in the dynamics throughout the experiment. Obtained experimental data were statistically processed by standard methods using

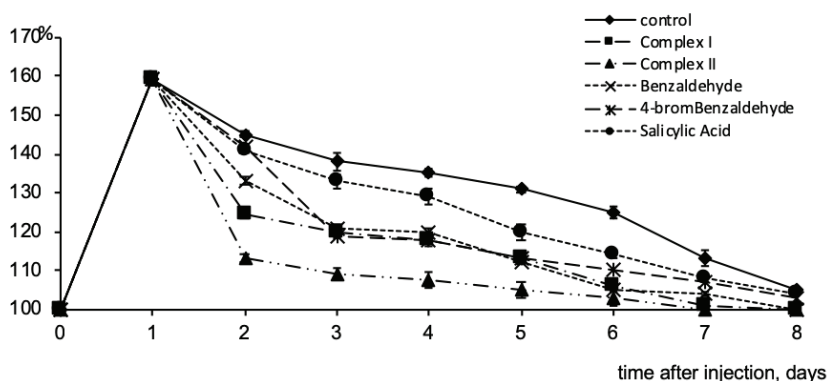


Fig.1. The volume change of the affected limb with carrageenan-induced inflammation (% of control)

Thus, within one day after the start of the experiment, increased volume of the affected limb for complex II compound was only 13%, for complex compound I – 24%. Then, for complex compound II there was a gradual reduction in volume of the affected limb within five days from the start of the experiment and achieving the volume measures of intact animals. Considering that salicylic acid and benzaldehydes are part of the complex compounds I and II, it was assumed that they might play the main contribution to their anti-inflammatory activity. From the obtained data it is

Table 1
Dynamics of changes in the width of the affected limb using carrageenan-induced inflammation model

Compound Time, days	Control group	Complex I	Complex II	Benzaldehyde	4-bromobenzaldehyde	SA
0 (control)	100 ± 2,4	100 ± 2,3	100 ± 2,4	100 ± 3,0	100 ± 3,0	100 ± 2,4
1	157 ± 3,4	157,3 ± 3,4	157 ± 3,4	135 ± 7,0	135 ± 7,0	157 ± 3,4
2	158 ± 3,9	128 ± 2,6	109 ± 4,6	132 ± 2,0	134 ± 8,0	142 ± 4,5
3	148 ± 8,3	125,6 ± 7,3	109 ± 4,9	125 ± 3,0	128 ± 9,0	128 ± 4,4
4	151 ± 4,7	124,4 ± 5	107 ± 4,2	123 ± 4,0	137 ± 8,0	125 ± 4,7
5	143 ± 4,0	119,3 ± 5,0	113 ± 5,0	116 ± 3,0	123 ± 5,0	117 ± 5,3
6	139 ± 3,8	111,7 ± 3,3	111 ± 4,0	112 ± 2,0	115 ± 3,0	110 ± 2,8
7	126 ± 6,8	102,7 ± 1,8	109 ± 5,0	106 ± 3,0	109 ± 4,0	105 ± 1,3
8	122 ± 5,4	100,2 ± 3,1	101 ± 2,0	101 ± 2,0	102 ± 2,0	107 ± 6,8

the values of the arithmetic mean (M), standard deviation of arithmetic mean (m), Student's *t*-test and confidence factor. Anti-inflammatory activity of studied compounds was expressed as a percentage inhibition of oedema.

Results and discussions

Carrageenan-induced model

Represented data [figure 1] indicated that the volume of affected limbs of all tested animals after 24 hours after phlogogen inoculation (carrageenan) increased by 60%, but 2 days after the start of the experiment there was a clear trend of decreasing of the inflammatory foci in animals that perorally received complex compounds I and II.

known that salicylic acid, as well as benzaldehyde and 4-bromobenzaldehyde, has an anti-inflammatory effect, which leads to a decrease in the inflammatory process during the first days of the experiment. Six days after the start of the experiment, the volume of the affected limb almost reached the control values in animals that received complex compounds I and II, benzaldehyde and salicylic acid.

It should be noted that dynamic change in the width of the affected limb (Table 1) was similar to the volume changes of the affected limb and demonstrated no statistical differences.

Formalin-induced inflammation.

According to obtained data, [figure 2] demonstrated that both complex com-

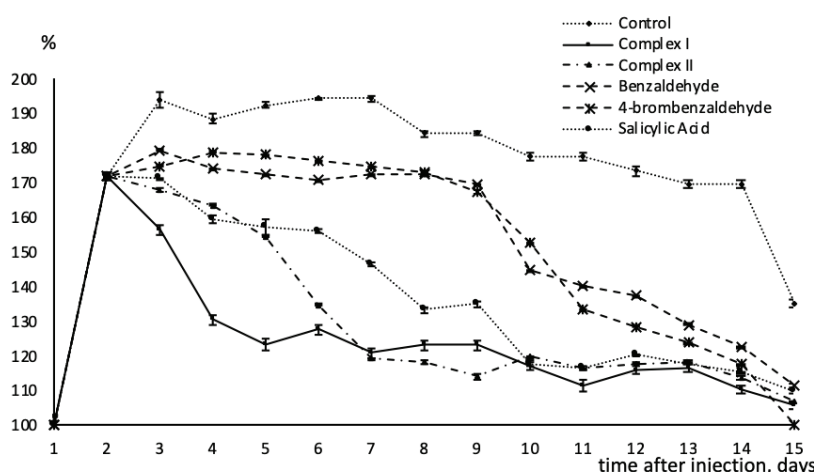


Fig. 2. The volume change of the affected limb with formalin-induced inflammation (% of control).

pounds absolutely showed an anti-inflammatory effect using the formalin inflammation model.

Thus, three days after formalin inoculation the volume of affected limbs in rats of all tested groups increased by 72% comparing to intact values. Starting from the second day of the treatment with perorally inoculation of the complex compound I, the volume of affected limbs of rats decreased by around 19% and this tendency continued in the following days of the experiment. After 16 days of observation (14th days of treatment) values of the group that was treated with perorally inoculation of complex compound I, almost reached the values of intact group of animals. During the peroral inoculation of the complex compound II the anti-inflammatory effect was also observed. Until 8th days of observation the decreasing of the volume of affected rat limb was slower than it was in the rat group that were treated with complex compound I and it was 5-9% per day in average. However, all value of the volume of the affected rat limbs reached the control on the 14th day of treatment. Benzaldehyde and 4-bromobenzaldehyde also demonstrated some anti-inflammatory activity throughout the experiment, on the 16th day of observa-

tion (14th day of treatment) the volume of the affected limbs reached initial values. Salicylic acid demonstrated the best anti-inflammatory activity and on the 7th day of treatment the values of the affected limbs of rats decreased by around 37%, but the values of volume of affected limbs in rats did not return to the intact level until the end of the experiment

in this investigation. During the visual observation of the rat limbs demonstrated no external signs of inflammation, in contrast to the control group of animals, which signs of inflammation were sufficiently pronounced on the 16th day of observation.

Obtained data from the determination of the width of affected limbs of rats using the formalin-induced model demonstrated that, in general, the dynamic changes of the width of affected limbs matched with dynamic change of the volume, during the usage of all tested compounds, the values did not reach the control values, and 16 days after phlogogen inoculation which, apparently, related with physiology of resorption.

Conclusion

Thus, during the experiment it was determined that complex compounds I and II demonstrated the best anti-inflammatory activity in both models of inflammation. Obviously, the components of complex compounds I and II – salicylic acid and benzaldehydes were involved in the anti-inflammatory activity of these complexes.

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