

# MEDICINOS

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# HYPOGLYCEMIC ACTIVITY OF SUBSTITUTED SUCCINAMIC ACIDS

## HIPOGLIKEMINIS PAKEISTŲJŲ SUKcinamo rūgščių AKTYVUMAS

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### SANTRAUKA

**Prasminiai žodžiai:** sukcino rūgštys, hipoglikeminis aktyvumas, cukrinis diabetas, sulfanilslapalas, biguanidai.

Tiriant naujų sukcino rūgščių amidių struktūros ir hipoglikeminio veikimo tarpusavio ryšį nutatyta, kad iš septynių N-acilsuccinamo rūgšties darinių maksimalų hipoglikeminį efektą (26,8%,  $p < 0,05$ ) turėjo 11-as junginys. Pakeitus etilkarboksilo grupę 4-nitrofenilo arba 3-nitrofenilo pakaitu, sumažėjo 11-o junginio hipoglikeminis aktyvumas. N-sulfacilsuccinamo rūgšties dariniai (junginiai 14–19) sumažino cukraus kiekį kraujyje nuo 4,9% iki 29%, N-alkil- $\beta$ -(2-benzimidazolil)succinamo rūgšties dariniai (junginiai 20–27) – nuo 4,0% iki 31,8%. Maksimaliu hipoglikeminiu efektu (38,2%,  $p < 0,05$ ) pasižymėjo sukcino rūgšties alkilamidų 6 darinys, kurio aktyvumas buvo didesnis už karbutamido ir glibenklamido aktyvumą.

### SUMMARY

**Keywords:** succinamic acids, hypoglycemic activity, diabetes mellitus, sulfonylureas, biguanides.

Studying the relationship between the structure of amides of succinamic acid and the hypoglycemic activity it was found that the compound 11 had the maximum hypoglycemic effect (26.8%,  $p < 0.05$ ) in the row of seven derivatives of N-acylsuccinamic acid. The replacement of ethylcarboxial radical by 4-nitrophenyl and 3-nitrophenyl contributes to the decrease of hypoglycemic activity of the compound 11. The derivatives of N-sulfacylsuccinamic acid (compounds 14–19) decreased the sugar level in blood from 4.9% to 29.8%. The derivatives of N-alkyl- $\beta$ -(2-benzimidazolyl) succinamic acid (compounds 20–27) decreased the level of glucose from 4.0% till 31.8%. The most active compound was derivative of succinamic acid alkylamides, which showed the decrease of the sugar in blood plasma for 38.2% ( $p < 0.05$ ). This hypoglycemic effect exceeded the influence of carbutamide and glibenclamide.

**Introduction:** Diabetes mellitus is a widespread endocrine pathology and it is recognized as an actual medical and social problem of 21<sup>st</sup> century [8].

Along with the decrease of factors of risk the decrease of mortality from the diabetes mellitus is related with the rational pharmacotherapy [9]. The priority at the present moment in curing the diabetes mellitus of the II type at clinics is given to the peroral antidiabetical preparations. According to their chemical structure they are divided into the main two groups: derivatives of benzene-

sulfonylurea and biguanides.

The bigger doses of all modern peroral hypoglycemic preparations are effective, but they can cause the side effects (dyspepsia, skin allergy reactions, leucopenia, trombocytopenia, agranulocytosis, liver and kidney function dysfunction, etc.) limiting the clinical use of them [4, 7, 11].

Due to this the actual problem of modern pharmacology is the expansion of the arsenal of national safe hypoglycemic means. Dicarmonic acids take part in many



Table. Hypoglycemic activity of derivatives of succinamic acid

Compound No	Dose mg/kg	Reduction of sugar content in blood with regard to the initial level, % within ....hour				
		2	4	6	8	24
1	3.5	2.3±0.06	10.4±0.07	14.5±0.06	10.2±0.09	4.3±0.06
2	3.4	4.1±0.10	12.9±0.07	16.2±0.07	12.3±0.06	2.1±0.08
3	3.2	7.0±0.12	11.2±0.06	13.8±0.12	10.1±0.11	4.4±0.05
4	2.9	8.4±0.11	18.4±0.21	20.4±0.12	17.2±0.10	7.3±0.07
5	2.7	3.2±0.04	6.8±0.08	13.5±0.12	7.2±0.11	3.2±0.08
6	2.3	15.2±0.12	27.3±0.16	38.2±0.14	24.1±0.12	12.7±0.04
7	2.2	10.7±0.14	24.2±0.07	30.9±0.14*	21.2±0.11*	12.1±0.05
8	3.0	10.9±0.12	18.8±0.31*	23.4±0.13*	15.7±0.12*	7.3±0.11
9	2.1	5.6±0.07	15.4±0.08	24.2±0.13*	18.4±0.07*	9.5±0.06
10	1.8	6.9±0.07	17.2±0.17	25.1±0.22*	15.3±0.04	6.3±0.08
11	5.8	12.1±0.09	19.2±0.07*	26.8±0.08*	22.1±0.11*	10.2±0.06
12	5.2	—	8.6±0.06	14.2±0.07	10.4±0.05	v
13	4.8	—	12.1±0.07*	18.2±0.05*	13.4±0.08	3.4±0.04
14	5.9	—	—	9.2±0.06	—	—
15	5.4	—	—	—	—	—
16	18.4	4.9±0.11	15.4±0.17*	18.1±0.12*	8.1±0.05	—
17	15.8	5.2±0.14*	25.0±0.13*	29.8±0.26*	17.1±0.12*	3.6±0.08
18	16.5	8.2±0.16	19.8±0.13	26.1±0.31	10.4±0.11	3.0±0.09
19	21.0	7.1±0.12*	22.3±0.21*	14.7±0.17*	13.5±0.24*	5.3±0.07
20	20.6	12.2±0.12	26.9±0.21*	31.8±0.15*	18.1±0.12*	5.4±0.05
21	18.7	12.5±0.13	15.4±0.14	21.1±0.14*	10.3±0.11	4.2±0.04
22	8.7	4.0±0.31	7.5±0.04*	14.3±0.05*	7.9±0.06*	4.4±0.07
23	5.4	10.1±0.31	17.1±0.16	19.1±0.12	12.2±0.10	6.4±0.06
24	8.2	12.5±0.14	19.7±0.21	14.4±0.22	10.8±0.12	5.7±0.15
25	9.1	8.7±0.12	15.4±0.19	11.5±0.22	8.3±0.11	4.1±0.04
26	9.3	4.9±0.14	9.4±0.27	10.1±0.12	6.4±0.13	—
27	5.3	2.6±0.11	5.7±0.21	13.6±0.15	7.6±0.12	—
28	7.5	8.9±0.08	10.9±0.08	14.7±0.08	4.5±0.05	—
29	8.6	7.6±0.12	14.7±0.13	19.4±0.21	14.4±0.14	5.7±0.10
30	6.2	6.2±0.11	11.9±0.17	18.2±0.12	11.6±0.13	—
31	6.8	8.4±0.13	19.2±0.13	24.4±0.09*	17.4±0.08	8.4±0.12
32	5.1	9.2±0.11	17.7±0.11	14.3±0.13	8.7±0.05	—
33	4.7	8.4±0.32	10.8±0.33	14.5±0.12	7.6±0.08	—
34	4.2	10.4±0.23	16.9±0.17	13.2±0.05	10.9±0.11	2.8±0.07
35	3.9	11.9±0.09	19.2±0.11	21.8±0.37*	15.0±0.21	6.1±0.06
36	12.5	14.3±0.17	23.4±0.13*	32.1±0.15**	24.8±0.18*	13.7±0.12
37	10.3	15.6±0.13	30.5±0.17*	28.6±0.12*	14.2±0.02	8.5±0.14
38	8.5	10.3±0.21	27.3±0.19	32.6±0.21*	14.3±0.8	7.2±0.04
39	7.4	14.9±0.13	29.4±0.12*	36.1±0.14*	21.8±0.37*	12.4±0.04
40	8.0	10.7±0.34	16.9±0.21	24.1±0.16*	14.2±0.11	5.3±0.12
41	7.1	11.4±0.24	19.4±0.12	24.5±0.21*	15.7±0.14	7.2±0.06
42	6.5	14.1±0.22	21.4±0.21*	24.5±0.28*	12.4±0.31	6.1±0.05
43	4.3	17.5±0.31	23.1±0.42*	28.5±0.23*	16.2±0.27	7.2±0.09
44	4.0	4.0±0.22	8.1±0.41	10.8±0.46	8.7±0.13	—
45	5.2	16.5±0.27	27.9±0.31	19.8±0.42*	10.4±0.21	5.8±0.14
46	10.0	12.7±0.13	18.7±0.22	23.1±0.19*	8.6±0.12	7.3±0.05
47	4.1	9.5±0.22	19.7±0.21	29.5±0.32*	18.2±0.21	6.1±0.11
48	5.4	12.4±0.32	25.8±0.33	31.5±0.25*	23.7±0.16	10.1±0.07
49	6.9	17.5±0.09	28.1±0.08	30.5±0.06	21.7±0.13	8.1±0.08
50	2.7	6.8±0.33	8.6±0.18	13.5±0.32*	4.1±0.11	—
51	3.3	10.4±0.11	16.7±0.14*	18.2±0.22*	10.2±0.14	6.1±0.07
52	2.7	10.1±0.14	17.2±0.12	22.3±0.17*	12.4±0.09	4.8±0.09
53	4.6	11.2±0.14*	16.8±0.31	24.2±0.24*	11.6±0.06	3.2±0.06
54	5.0	12.9±0.32	27.4±0.23	32.5±0.12*	21.7±0.14	10.9±0.08
Bucarbon	50.0	10.9±0.3	29.1±0.23*	35.2±0.27*	29.3±0.2*	14.2±0.16
Glibenclamide	1.0	9.3±0.4	28.5±0.4*	30.8±0.21*	25.2±0.27*	11.5±0.19



physiological processes and introduce a perspective group for this search [1–3, 5, 6].

**Materials and methods:** In this research the influence of investigated substitutions of succinamic acid to the sugar content in blood was studied in the experiments on white rats (140–170 g weight) and chinchilla rabbits (2.4–3.2 kg weight). The sugar content in blood was determined by ortotulidinal and lucozoxidant methods using the glucozimeter "Eksan-G" [10]. The investigated substitutions of succinamic acid were put into the blood of rabbits' introgastrically by means of a special metallic probe. The rabbits without the input of the analyzed material were the control group. The blood for analysis was taken from the ear vein of rabbits within 2, 4, and 24 hour's period after the granted dose of analyzed compounds. The content of the sugar in blood plasma of the controlled groups of animals was defined after the same period of time as in the testing groups. The medical preparations of carbutamide (bucarbon) and glibenclamide (glyburide) were used in the maximum effective doses for the comparison of hypoglycemic activity. Every preparation was tested on the animals. The evaluation of hypoglycemic activity was carried comparing the sugar content in animals' blood with the initial one before the input of the analyzed substances which were taken by 100 % [1, 2].

**Results and discussions:** The obtained data of experimental investigations are presented in *Table* and *Figure*. The analysis of the obtained results showed that the majority of alkylamides of succinamic acid (comb. 1–6) displayed the moderated hypoglycemic activity. The most active compound from it decreased the sugar in blood plasma for 38.2% ( $p < 0.05$ ) within 6 hours.

The majority of substances showed the more expressed sugar decreasing activity in the row of derivatives of N-acylsuccinamic acid (compounds 7–13). The maximum hypoglycemic effect (26.8%,  $p < 0.05$ ) was seen after 6 hours from the intake of compound 11. The replacement of ethylcarboxial (compound 11) radical by 4-nitrophenyl (compound 9) and 3-nitrophenyl (compound 10) contributes to the decrease of hypoglycemic activity.

The majority of derivatives of N-sulfacylsuccinamic acid (compounds 14–19) showed the more expressed hypoglycemic activity. After the shot they caused the

decrease of the sugar level in blood in comparison to the initial level from 4.9% to 29.8% after the period of 6 hours. The compound 17 was the most effective and it decreased the sugar level in blood by 29.8% ( $p < 0.05$ ) within the period of 6 hours from the intake. The sugar decreasing effect was reached by the shift of nitro groups into the 2<sup>nd</sup> position or change of 4-nitrogroups into the atom of chlorine (compounds 18, 19), atom of hydrogen (compound 14) and 4-aminocarboxymethyl radical. The derivatives of N-alkyl- $\beta$ -(2-benzimidazolyl) succinamic acid (compounds 20–27) showed the hypoglycemic activity. They decreased the level of glucose in the blood from 4.0% till 31.8% within the period of 6 hours from the shot.

The compound 39 showed the most expressive hypoglycemic activity among the derivatives of N-alkylamide succinamic acid (compounds 28–42). It decreased the level of the sugar in blood by 36.1% within the period of 6 hours. The change of propyl radical in the cycle of benzoxazolyl (compound 39) to the atom of hydrogen (compound 35) led to the reduction of hypoglycemic activity.

The compound 54 showed the expressed hypoglycemic activity (32.5%) between the N-arylamide succinamic acid derivatives (compounds 43–54) within the period of 6 hours from the intake. The other substances in this group also showed the moderate hypoglycemic activity, the reduction of sugar level in blood was from 6.8 till 31.5%.

The hypoglycemic activity of the investigated compounds was compared with carbutamide and glibenclamide, which were shot intragastrically 50 mg/kg and 1.0 mg/kg accordingly. It was determined that the hypoglycemic effect of compound 6 exceeds the effect of carbutamide and glibenclamide.

## CONCLUSION

The hypoglycemic activity of the compound 6 was confronted with the comparative preparations – carbutamide and glibenclamide.

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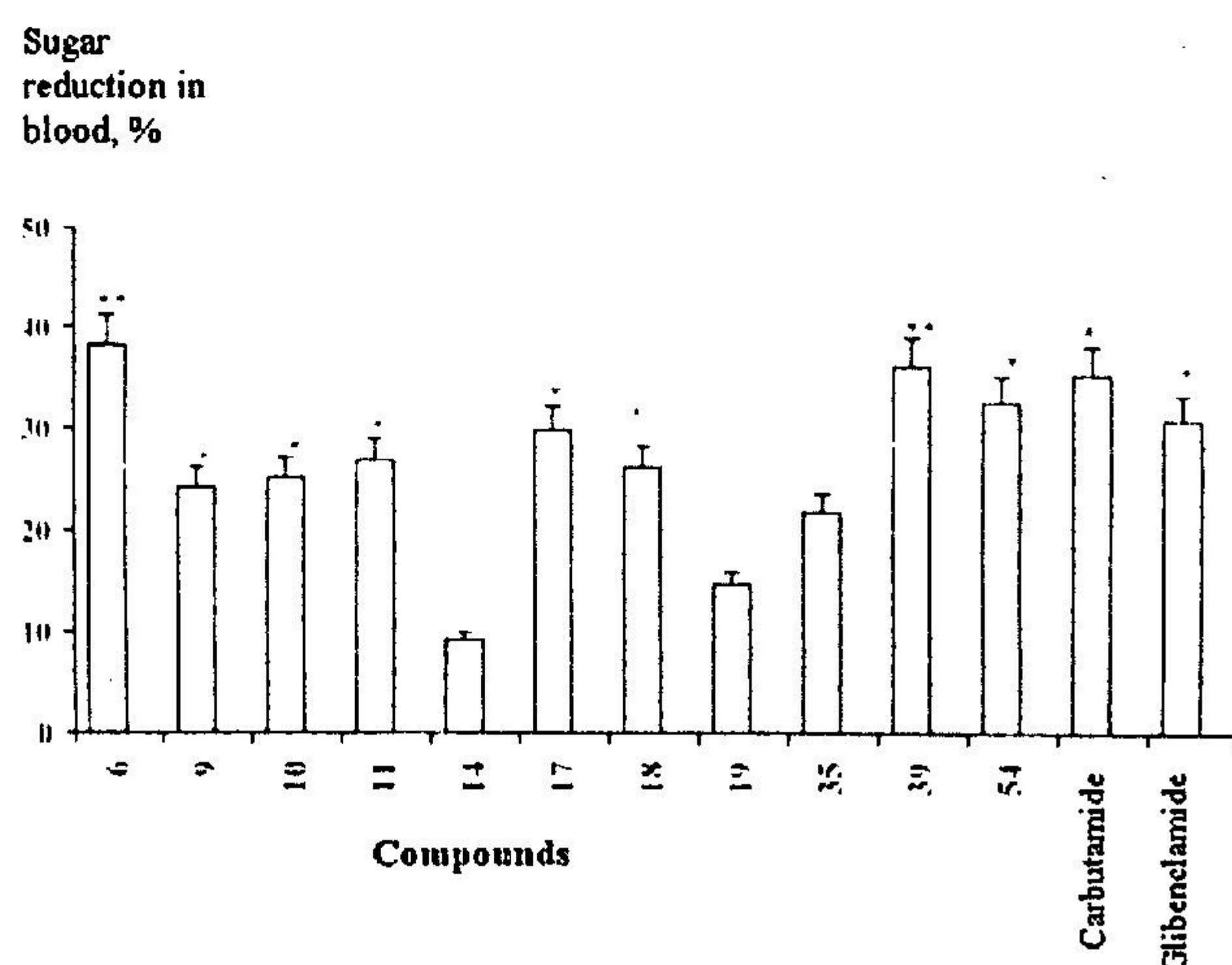


Figure. The hypoglycemic activity of succinamic acid derivatives

\*, \*\* – reliability of results at  $p < 0.05$  and  $p < 0.01$  comparing with the initial standard