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SEARCH FOR BIOLOGICALLY ACTIVE ANTI-INFLAMMATORY AGENTS AMONG DERIVATIVES OF N-R-N'-(3-OXO-2,3-DIHYDRO-1H-INDAZOL-7-YL)BUTANEDIAMIDE

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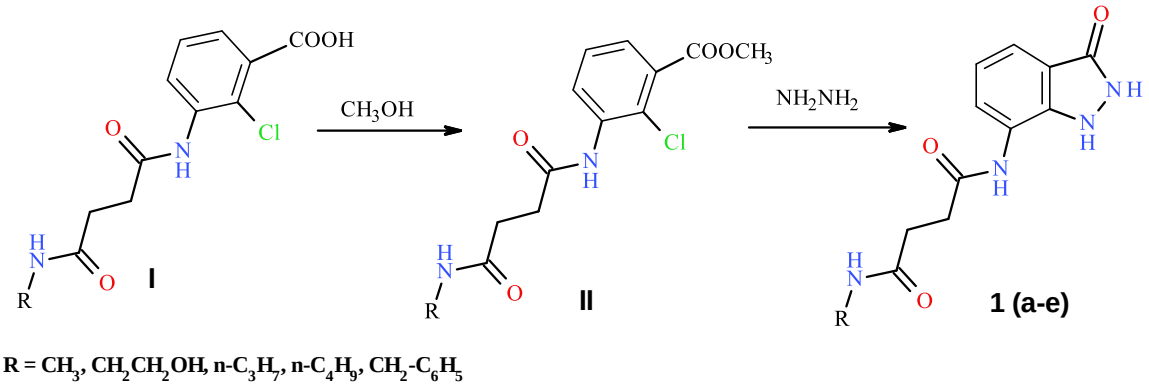
Abstract. New N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamide derivatives are synthesized. The structure and purity of the obtained compounds were confirmed by modern physicochemical methods: ^{1}H-NMR spectroscopy, elemental analysis and chromatography in a thin layer of sorbent. According to the results of the screening, the synthesized substances have a moderate anti-inflammatory activity.
Key words. Synthesis, N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamide derivatives, anti-inflammatory activity.

Indazole is a promising chemical agent in the formation of drug-like molecules [1, p. 1509] [2, p. 47]. According to the literature, biologically active substances having antitumor [3, p. 1503], anti-inflammatory [4, p. 871], antimicrobial [5, p. 2960] and neuroprotective [6, p. 6679] activity have already been obtained by modification of indazole substitutes of various electronic nature. Now such medicines as Benzadac,

Granisetron and Lonidamine have been developed based on indazole. In our opinion, the introduction of the succinic acid residue into the indazole molecule at the 7 position of the cycle should lead to the expansion of the range and increase of pharmacological activity and reduction of toxicity, given that succinic acid is a natural metabolite in humans. Therefore, the combination of indazole cycle, dicarboxylic acid residue, aromatic and aliphatic substituents in one molecule, saturation of the pyrazole moiety by Oxygen is a relevant research area that will have practical and theoretical value.

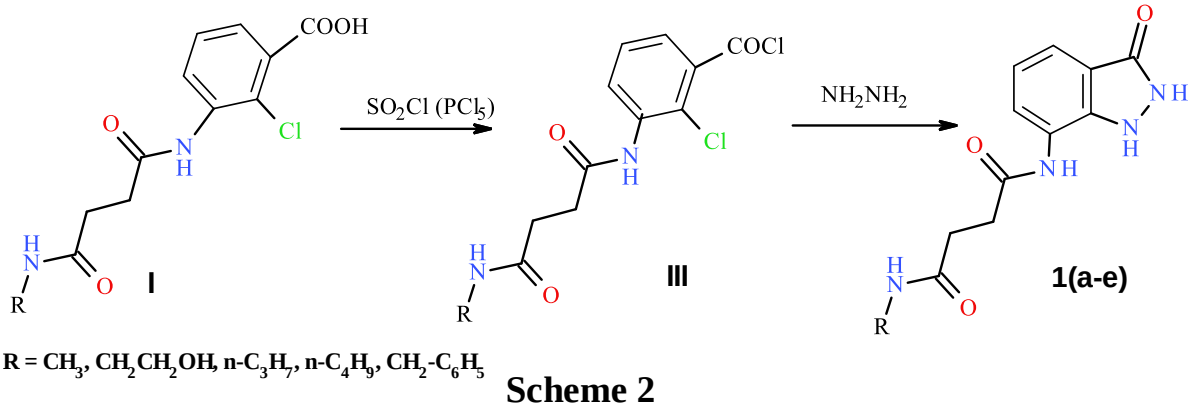
3-carboxy-2-chlorosuccinanilic acid amides ***I*** were used as starting materials for synthesis of N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamides ***1(a-e).*** The starting amides ***I*** were esterified with methyl alcohol in the presence of a catalyst - conc. H_2SO_4. The target compounds ***1(a-e)*** were obtained by reaction of methyl esters of amides of 3-carboxy-2-chlorosuccinanilic acid ***II*** with hydrazine hydrate when heated for 30-40 minutes (method A) (Scheme 1).



R = CH_3, CH_2CH_2OH, n-C_3H_7, n-C_4H_9, CH_2-C_6H_5

Scheme 1

The target compounds ***1(a-e)*** are also formed by hydrazinolysis of the corresponding chloro anhydrides of amides of 3-carboxy-2-chlorosuccinanilic acid ***III*** (method B). N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamides ***1(a-d)*** can be synthesized in one step without isolation of the corresponding chloro anhydrides ***III*** with direct action on the starting alkylamides ***I*** by thionyl chloride or phosphorus pentachloride, followed by the addition of hydrazine hydrate. The reaction takes place in 10 minutes with high yield (Scheme 2).



R = CH_3, CH_2CH_2OH, n-C_3H_7, n-C_4H_9, CH_2-C_6H_5

Scheme 2

The obtained compounds are white crystalline substances with clear melting points, soluble in methanol, dioxane, dimethylformamide, insoluble in water.

The structure and personality of new derivatives of N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamide were confirmed by elemental analysis, ^{1}H NMR spectroscopy and thin layer chromatography.

The study of anti-inflammatory activity was performed on a model of carrageenan edema in mice by subplantar injection of 0.1 ml of carrageenan solution. Test substances ***1(a-e)*** and the reference drug (diclofenac sodium) were injected intragastrically at a dose of 10 mg/kg one hour before phlogogen injection. Distilled water was injected for animals of the control group. The effectiveness of the test substance was evaluated by the degree of inhibition of the growth of inflammatory edema in percent relative to the control (table. 1).

Table 1

Anti-inflammatory activity of new derivatives of N-R-N'-(3-oxo-2,3-dihydro-1H-indazol-7-yl)butanediamide ***1(a-e)***

Compound	Increase in edema after 3 hours,%	Inhibition of edema, % to control
1(a)	61,41±4,38	20,8*
1(b)	59,33±4,12	22,4**
1(c)	54,16±3,65	30,5*
1(d)	55,6±3,95	45,3*
1(e)	57,12±3,48	31,7*
Control	74,30±5,19	0,0
Diclofenac sodium (at a dose of 10 mg/kg)	44,27±2,01	52**

*p<0,05 – compared to control, ** p<0,01 – compared to control.

According to the results of the screening, the synthesized substances have a moderate anti-inflammatory effect (table 1).

REFERENCES

1. Thangadurai A., Minu M., Wakode S., et al. Indazole: a medicinally important heterocyclic moiety // Med. Chem. Res. – 2012. – 21(7). – P. 1509-23.
2. Büchel G.E., Stepanenko I.N., Hejl M., et al. Osmium (IV) complexes with 1H-and 2H-indazoles: tautomer identity versus spectroscopic properties and antiproliferative activity // J. Inorg. Biochem. – 2012. – 113. – P. 47-54.
3. Bhutia Y.D., Babu E. and Ganapathy V. Re-programming tumour cell metabolism to treat cancer: no lone target for lonidamine // Biochemical Journal. – 2016. – 473(11). – P. 1503-6.
4. Cerecetto H., Gerpe A., González M., et al. Pharmacological properties of indazole derivatives: recent developments. Mini-Rev // Med. Chem. – 2005. – 5(10). – P. 869-78.
5. Minu M., Thangadurai A., Wakode S.R., et al. Synthesis, antimicrobial activity and QSAR studies of new 2, 3-disubstituted-3, 3a, 4, 5, 6, 7-hexahydro-2 Hindazoles // Bioorg. Med. Chem. Lett. – 2009. – 19(11). – P. 2960-64.
6. Tzvetkov N.T., Hinz S., Küppers P., Gastreich M., Müller C.E. Indazole-and indole5-carboxamides: selective and reversible monoamine oxidase B inhibitors with subnanomolar potency // J. Med. Chem. – 2014. – 57(15). – P. 6679-703.