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Synthesis and anti-inflammatory activity of new 1,2,4-triazole derivatives

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ABSTRACT

The series of new 1,2,4-triazole derivatives with methacrylic acid moiety were synthesized and characterized by NMR and IR spectroscopy as well as X-ray crystallography. The influence of newly synthesized compounds on the inflammation on the level of cytokine production and the proliferation of human peripheral blood mononuclear cells (PBMC) were experimentally evaluated. Obtained triazoles showed antiproliferative activity and diverse effects on cytokine production. Two compounds demonstrated potentially anti-inflammatory activity and comparable effects with ibuprofen.

Inflammation is a common state during infections and a number of diseases from hay fever, periodontitis, atherosclerosis, rheumatoid arthritis to cancer. Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) provide analgesic and antipyretic effects as well as anti-inflammatory in higher doses. The therapeutics are prevalent, however they seriously increase vascular and gastrointestinal risks.[1] Because heart failure risk was roughly doubled by all NSAIDs cardiovascular risk needs to be taken into account when prescribing any medicine of this group.[2] Over one hundred years after inventing aspirin there is still a need for a safe anti-inflammatory drug.

Searching for new potentially active substances, we combined the methacrylic acid with 1,2,4-triazole core. Compounds possessing triazole ring are known for their wide range of biological activities, and anti-inflammatory properties among them.[3–6] Methacrylic acid resembles propanoic acid present in the structure of some NSAIDs like ibuprofen, naproxen and ketoprofen. Anti-inflammatory activity of compounds containing methacrylic acid moiety has been reported.[7] However, 1,2,4-triazoles combined with this acid were never examined as anti-inflammatory agents.

In present work we describe the syntheses of new 1,2,4-triazoles substituted with methacrylic acid and their influence on the inflammation on the level of proliferation of peripheral blood mononuclear cells (PBMC) and cytokine production.

The series of novel 1,2,4-triazole derivatives **8**–**14** containing methacrylic acid moiety were synthesised in reaction of N^3-substituted amidrazones **1**–**7**[8] with itaconic anhydride (Fig. 1). All compounds were obtained with satisfactory yields (50–91%), except derivative **14** possessing 2-pyridyl and 4-nitrophenyl groups (about 15% yield). According to the method described previously[9] we obtained triazole **14** with better efficiency by cheating crude precipitate obtained in general reaction in 2% NaOH solution. It is noteworthy that the reaction of amidrazones **6** and **7** with itaconic anhydride conducted by the same procedure leaded to complete isomerisation to (*E*)-3-(4,5-diaryl)-4*H*-1,2,4-triazol-3-yl)-2-methylacrylic acids **15** and **16**. In our study compound **14** was obtained in alkaline solution with 56% yield and isomerisation product was not found. Obtained derivatives were characterized by spectroscopic

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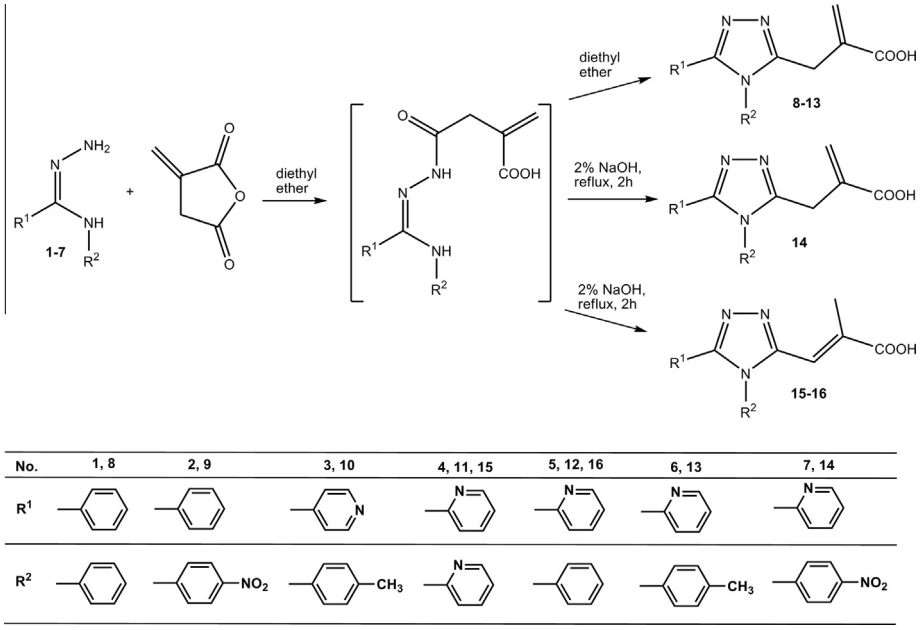

Figure 1. The synthesis and structures of compounds **8**–**16**.

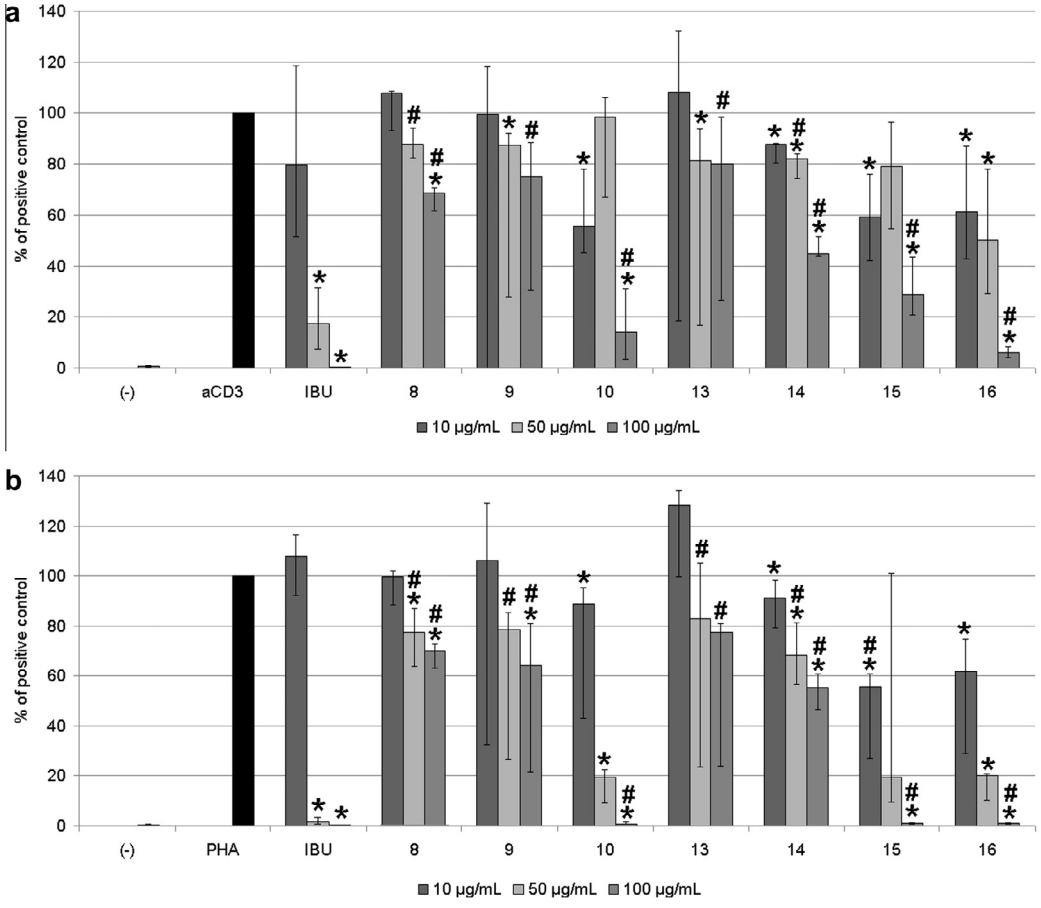

Figure 2. The effect of compounds **8**–**10**, **13**–**16** on proliferation of human peripheral blood mononuclear cells (PBMC) induced by the anti-CD3 antibody (a) or PHA (b). Cells were treated with anti-CD3 antibody (4 µg/mL) or PHA (0.5 µg/mL) and compounds **8**–**10**, **13**–**16** at concentrations 10, 50, 100 µg/mL. Ibuprofen (IBU) was used as reference drug, negative control (−) – no additions. After 72/h incubation, the proliferation of PBMC were measured using ^{3}H thymidine incorporation assay. The results were shown as percentage of positive control (anti-CD3 antibody or PHA). Values expressed as medians from five independent experiments and interquartile ranges [Q1–Q3], ∗ – indicates significant difference compared to anti-CD3 antibody alone (a) or PHA alone (b) at p <0.05; # – indicates significant difference compared to ibuprofen at p <0.05.