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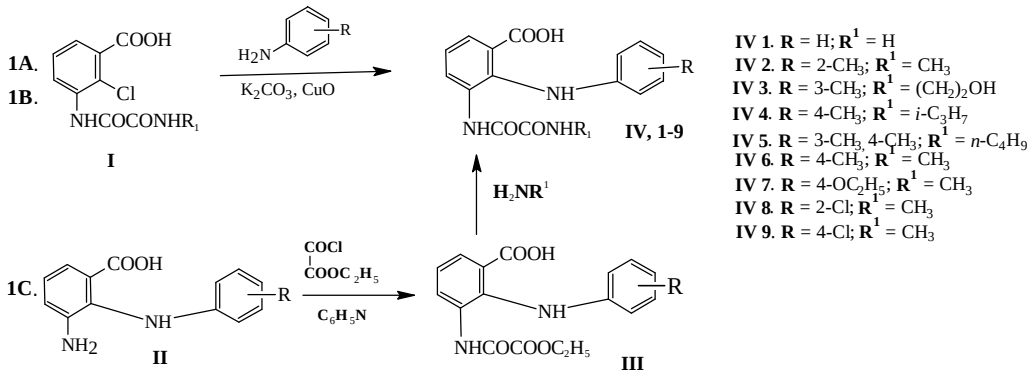
Synthesis of novel 3-(aminooxalyl-amino)-2-phenylamino-benzoic acid derivatives and their anti-inflammatory and analgetic actions evaluation

A few pharmacophoric features combination in the same structure may provide the prominent opportunities for the novel potent biologically active compounds design. Dicarboxylic acids are natural metabolites, the oxalil moiety presence in a substance structure reduces greatly its toxicity and broadens the range of biological effects.

The synthetic reactions leading to 3-(aminooxalyl-amino)-2-phenylamino-benzoic acid (**IV 1**) and its aminooxalil- and phenylamino- moieties substituted derivatives (**IV**, **2-9**) as they are outlined in Scheme 1 belong to Ullmann condensation in the presence of dimethylformamide (DMF) as solvent (1A protocol) or in a solid phase (1B protocol). Ullmann condensation conditions were optimized for the synthesis thus the products best yields were obtained with 0.01 mol of 2-chloro-3-(aminooxalyl-amino)-benzoic acid or its appropriate aminooxalyl moiety alkyl substituted derivative (**I**), 0.04 mol of phenylamine or its appropriate phenyl moiety substituted derivative, 0.01 mol of potassium carbonate, 0.1 g of copper, 145-150 ºC reaction mixture reflux and a reaction time of 8-10 h. For the solid-phase condensation 2-chloro-3-(aminooxalyl-amino)-benzoic acid or its appropriate derivative was treated with phenylamine or its appropriate phenyl moiety substituted derivative as 0.01: 0.01 by moles and 0.0005 mol of copper oxide instead of copper was used. In this case the reaction time was reduced up to for 2 h nevertheless the mixture heating at 180-220 ºC was ensured.



Scheme 1. Synthesis of 3-(aminooxalyl-amino)-2-phenylamino-benzoic acid (**1**) and its aminooxalil- and phenylamino- moieties substituted derivatives (2-9)

For 3-(aminooxalyl-amino)-2-phenylamino-benzoic acid and its aminooxalil- and phenylamino- moieties substituted derivatives preparation we developed also the alternative cross synthesis two-stage procedure (Scheme 1, 1C protocol) which began with 3-amino-2-phenylamino-benzoic acid or its appropriate phenylamino moiety substituted derivative (**II**) acylation by treating it with ethyl chloro(oxo)acetate in concentrated acetic acid medium in the presence of pyridine to afford respective 3-ethoxyoxalyl-amino esters (**III**). On the second stage the esters were involved into the reaction with appropriate alkylamine 25 % aqueous solution in ethanol medium. The structures of the obtained compounds were confirmed by IR and ^{1}H NMR spectroscopy, elemental analysis and approved *via* cross synthesis.

3-(Aminooxalyl-amino)-2-phenylamino-benzoic acid derivatives were testes *in vivo* for anti-inflammatory activity defined as paw volume protection, % to the rat paw, in carrageenin rat paw edema model. The biological activity data as % protection to inflammation were within the range of 17.7-40.6 %. *In vivo* analgetic action study with acetic acid induced writhing test method revealed 19.2-50.1 % protective effect.