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Syntheses and transformations of nitrogen-containing naphthol analogues

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SZEGED

2023

A. INTRODUCTION AND AIMS

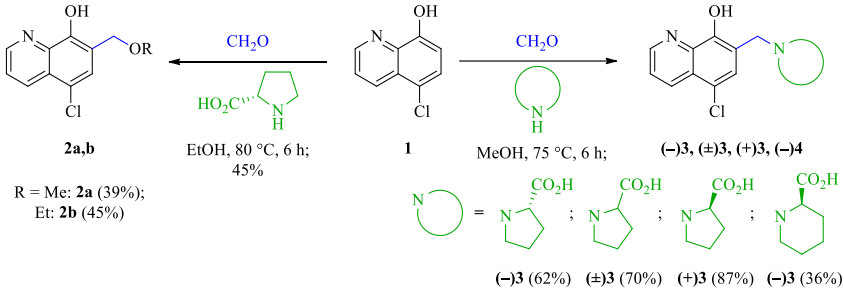
The Mannich reaction is a frequently utilised organic chemical transformation resulting in the formation of a C–C single bond. In this three-component reaction, the components – a primary or secondary amine, an aldehyde and a compound having a hydrogen of pronounced activity – can be converted to the corresponding aminoalkylated product under relatively mild conditions. The essence of the Mannich reaction is that the active H is replaced with an aminomethyl group – if formaldehyde (CH_2O) is the aldehyde component – or a substituted aminoalkyl moiety – if any other aldehyde is applied. During the reaction 1 molar equivalent of H_2O byproduct is formed. The procedure is named after Carl Mannich, whose systematic research in this particular field started in 1912. However, similar condensation reactions were already performed before him, including German patents from 1896 (DE89979) and 1897 (DE90907, DE92309) by Bayer & Co. In the first patent, the procedure included the transformation of dimethylamine, formaldehyde with phenol and naphthol derivatives, as well as the reaction of piperidine, formaldehyde and 1-naphthol. It was suggested that the hydrogen of the phenolic OH group reacts with the aldehyde and amine resulting in alkylaminomethoxy derivatives. The structures in patent DE92309 were corrected, which thus correspond to the structures known today as Mannich products. Franz Sachs published his work on the condensation of piperidine, formaldehyde and phthalimide in 1898 and so did Herm Hildebrandt reporting the condensation of piperidine, formaldehyde and various phenols and 2-naphthol in 1900. Mario Betti's research was launched in 1900, who reacted ammonia, benzaldehyde and 2-naphthol. In recognition of his extensive efforts, when a naphthol or a phenolic compound is the provider of the active hydrogen, the reaction is used to refer to as the Betti reaction and the condensation product as Betti base. Further researchers, who also studied this type of condensation, are van Marle and Tollens, Schäfer and Tollens, Auwers and Dombrowski, Petrenko-Kritschenko and Zoneff, Petrenko-Kritschenko and Petrow, Petrenko-Kritschenko, Petrenko-Kritschenko and Schöttle. In recent times, the process has garnered noteworthy consideration due to the versatile nature of its constituents, the employment of gentle reaction conditions and the potential pharmacological activity of the final products.

One possible extension of the Mannich reaction is the application of nitrogen-containing naphthol analogues, *i.e.*, hydroxyquinolines (HQs) and hydroxyisoquinolines (HIQs). One of the first bioactive HQs discovered is 8-hydroxyquinoline (8HQ), which itself is a well-known antipathogenic and chelating agent. It has many derivatives with more or less similar properties including clioquinol, chlorquinaldol, chloroxine, broxyquinoline, iodoquinol, nitroxoline and tilbroquinol. Procaterol is a β_2 adrenoreceptor agonist used in the treatment of asthma. In contrast, a 4HQ derivative with a propranolamine chain proved to be a more potent β-adrenergic receptor blocker *in vivo* in a rat preparation than propranolol. The first 3-carboxyl-substituted 4-hydroxyquinoline with antibacterial effect was discovered serendipitously. It was an intermediate byproduct in chloroquine synthesis, leading to the development of fluoroquinolone antibiotics. Further 3-carboxylic acid derivatives and approved medicines are elvitegravir (treatment for HIV-1 infection) and ivacaftor (treatment for cystic fibrosis). The 2-carboxylic acid derivative of 4HQ is kynurenic acid (KYNA), which is an endogenous metabolite produced in both humans and rodents; moreover, it is a potential neuroprotective agent. Some 4HQ and 3HIQ derivatives were tested as matrix metalloproteinase inhibitors; nonetheless, some 6HQs are potential antiviral agents against hepatitis B.

My Ph.D. work focused on the investigation of different nitrogen-containing 1- and 2-naphthol analogues in the Mannich reaction and the extension of the reaction using secondary amines and aldehydes. The aminoalkylation of 8HQ derivatives have been studied, but the Mannich products possess low water solubility, which is undesirable when biological applicability is in the focus. Therefore, the synthesis of new water-soluble substrates starting from 5-Cl-8HQ – as a 1-naphthol analogue – was the first aim of my Ph.D. work by using functionalised secondary amines and formaldehyde. The next aim was the investigation of 4HQ derivatives, also as 1-napthol analogues. In earlier studies, the reactivity of KYNA has been tested excluding its homologues compound 2-(4-hydroxyquinolin-2-yl) acetic acid. Accordingly, the synthesis and transformations of this latter compound were planned to obtain Mannich bases by using a secondary amine and formaldehyde or aromatic aldehydes. Since the reaction of 2-naphthol with 2-naphthaldehyde and *N*-benzylmethylamine revealed an unexpected transformation, the final aim was to test the scope and limitations of this reaction starting from 6HQ and 3HIQ as *N*-containing 2-naphthol analogues.

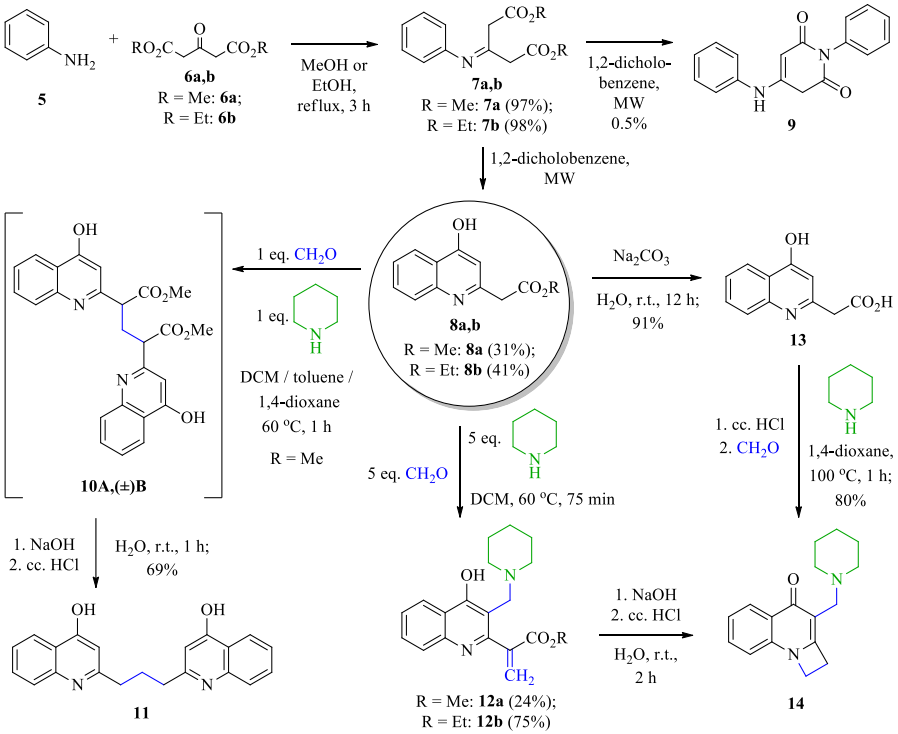
B. RESULTS AND DISCUSSION

1. 5-Chloro-8-hydroxyquinoline (**1**) was applied in the Mannich reaction as 1-naphthol analogue (Scheme 1). The reaction of **1**, L-proline and formalin (38%) in MeOH and EtOH at 80 °C resulted in the formation of methoxymethyl (**2a**) and ethoxymethyl (**2b**) derivatives, respectively. Lowering the temperature to 75 °C, the reaction in MeOH gave the desired Mannich product **(–)3**. The optimised molar equivalents of the starting compounds eased the purification process and only a recrystallisation was required to reach the desired purity. The reaction was extended for other α-amino acids, including racemic proline, D-proline and D-homoproline, which afforded **(±)3**, **(+)3**, and **(–)4**, respectively.



Scheme 1.

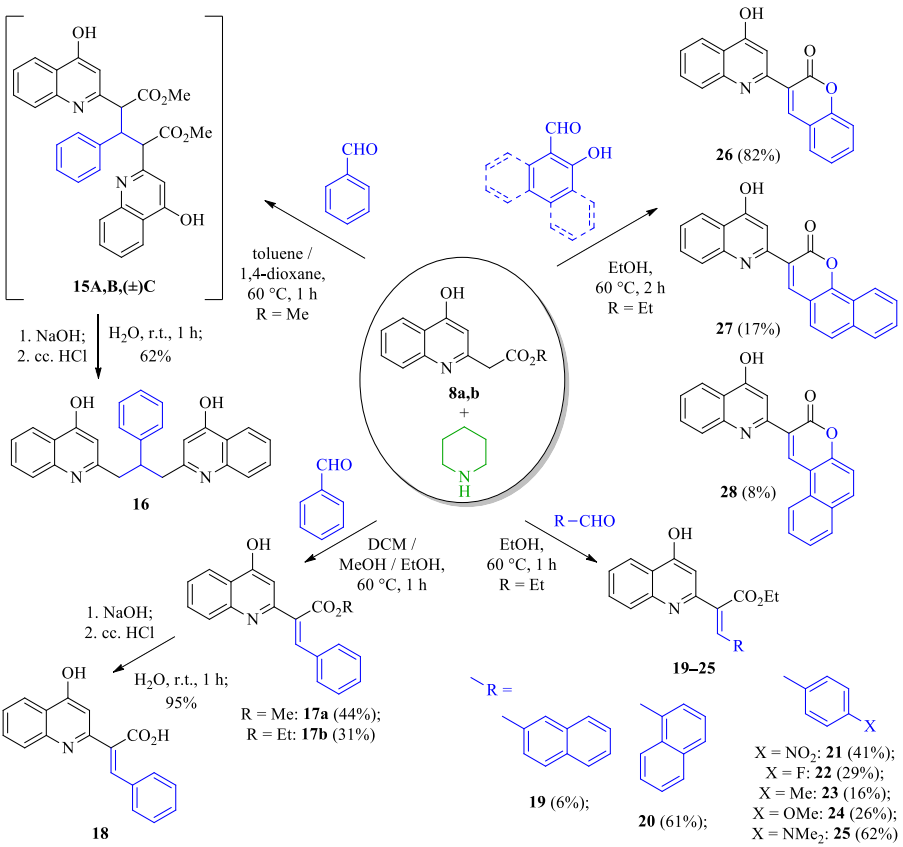
2. The Conrad–Limpach reaction for methyl and ethyl 2-(4-hydroxyquinolin-2-yl) acetate (**8a,b**) was optimised and the undesired formation of **9** byproduct was reduced (Scheme 2). The reaction of **8a,b**, piperidine and paraformaldehyde afforded either methylenebis compound **10A,(±)B** or a Mannich base with α-methylenation (**12a,b**), depending on the solvent and the equivalents used. The hydrolysis of **10A,(±)B** led to 2,2′-(propane-1,3-diyl)bis(quinolin-4-ol) (**11**) *via* decarboxylation. The hydrolysis of 3-piperidine-1-yl-methyl acrylates (**12a,b**) with NaOH led to a novel 1*H*-azeto [1,2-*a*]quinoline (**14**), which was also synthesised starting from 2-(4-hydroxyquinolin-2-yl)acetic acid (**13**).



Scheme 2.

3. In order to investigate the scope and limitations of the transformations of **8a,b**, aromatic aldehydes were used instead of formaldehyde (Scheme 3). The application of benzaldehyde resulted in the formation of phenylmethylenebis derivatives (**15A**,**B**,(±)**C**), and subsequent hydrolysis produced the corresponding phenylpropane **16**. The alteration of the reaction conditions did not lead to a Mannich reaction, but a Knoevenagel condensation took place (**17a,b**). Hydrolysis of **17a** led to the carboxylic acid derivative **18**; decarboxylation was not observed. The synthesis was extended to 2- and 1-naphthaldehydes as well as a series of *para*-substituted (nitro-, fluoro-, methyl-, methoxy-, dimethylamino-) benzaldehydes (**19**–**25**). When *ortho*-hydroxybenzaldehyde (salicylaldehyde) was applied, an intramolecular ring closure took place affording a lactone-containing skeleton (**26**), which

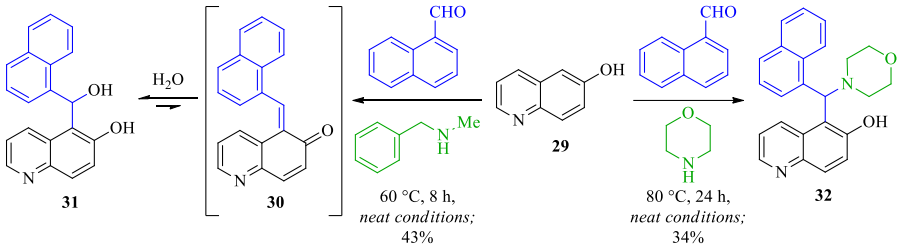
is a 4-hydroxyquinoline–coumarin hybrid. Benzocoumarin derivatives (**27** and **28**) were synthesised by using the appropriate hydroxynaphthaldehydes. Regarding the biological results, some derivatives possess selectivity towards cancer cells and calculated pIC50 values and the Hammett–Brown substituent showed a good correlation.



Scheme 3.

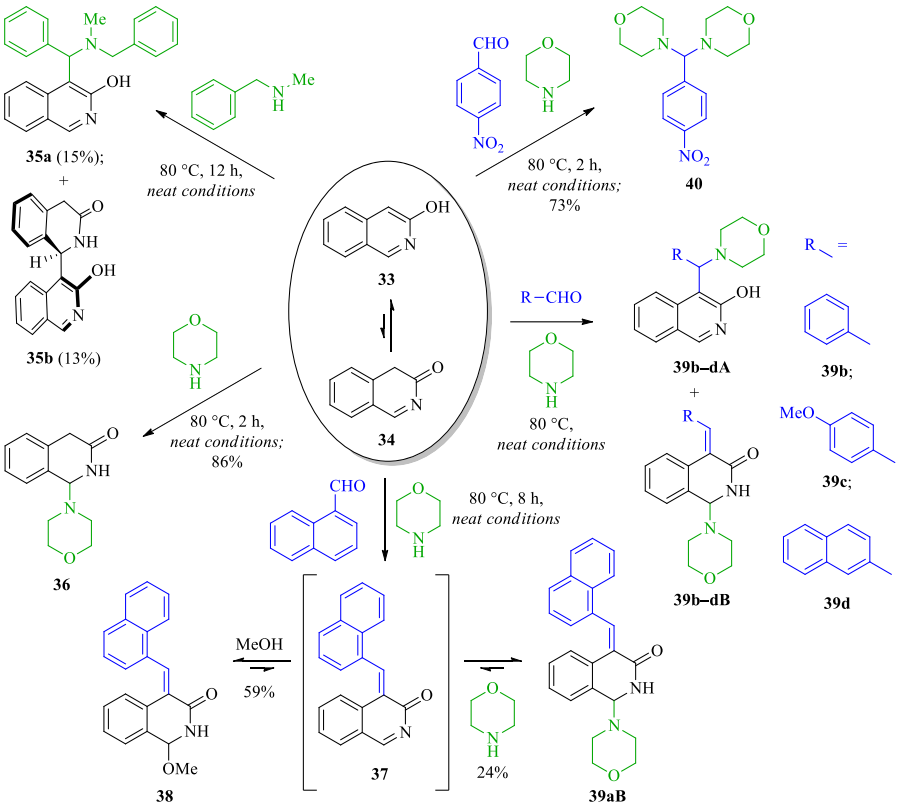
4. 6-Hydroxyquinoline (**29**) was tested in Mannich reaction as *N*-containing 2-naphthol analogue (Scheme 4). The outcomes of the attempted Mannich reactions were strongly influenced by the amine components. Aminoalkylation of this substrate with reagents

1-naphthaldehyde and *N*-benzylmethylamine led to the isolation of diol **31** regarded as a stabilised water adduct of an *ortho*-quinone methide (**30**). Its formation can be ascribed to the presence of a hydroxide ion in a relatively higher concentration generated by the bulky and basic amine component with decreased nucleophilicity. Classical Mannich base **32** was isolated as a single product, when the amine component was replaced by morpholine, featuring nucleophilicity rather than basic character under the applied reaction conditions.



Scheme 4.

5. The reactivity of 3-hydroxyisoquinoline (**33**) was explored and, rather unexpectedly, transformations were observed even if only amines were applied, which can be rationalised by the equilibrium formation of tautomer **34** (Scheme 5). *N*-Benzylmethylamine with **33** produced **35a,b** – due to its decomposition –, and morpholine with **33** produced the aminal **36**, but no reaction with MeOH was observed. When the reaction of **33**, 1-naphtaldehyde and morpholine was worked up with the use of MeOH on column chromatography, the methoxy-substituted lactam **38** was identified. However, when purification and isolation was performed without MeOH, it led to arylidene derivative **39aB**. When other aldehydes (benzaldehyde, 2-naphthaldehyde, *p*-OMe-benzaldehyde) were applied, the ^{1}H NMR analyses revealed the parallel formation of the classical Mannich product (**39b**–**dA**) and arylidene derivative **39b**–**dB**. In the case of *p*-NO_2-benzaldehyde, the reaction took place without the involvement of **33**, producing 4,4'-((4-nitrophenyl)methylene)dimorpholine (**40**) as the main product. DFT modelling studies were undertaken to rationalise the preparative results.


35a (15%);
+
35b (13%)
80 °C, 12 h,
neat conditions
33
34
80 °C, 2 h,
neat conditions;
73%
40
R−CHO
80 °C,
neat conditions
39b–dA
+
39b–dB
39b;
39c;
39d
80 °C, 2 h,
neat conditions;
86%
36
80 °C, 8 h,
neat conditions
MeOH
59%
38
37
24%
39aB

Scheme 5.

C. PUBLICATIONS

Papers related to the thesis

I. Mészáros, J. P.; Poljarević, J. M.; Szatmári, I.; **Csuvik, O.**; Fülöp, F.; Szoboszlai, N.; Spengler, G.; Enyedy, É. A.
An 8-Hydroxyquinoline–Proline Hybrid with Multidrug Resistance Reversal Activity and the Solution Chemistry of Its Half-Sandwich Organometallic Ru and Rh Complexes.
Dalton Trans. **2020**, *49*, 7977–7992. DOI: 10.1039/D0DT01256D. **IF.: 4.390**

II. Pivarcsik, T.; Dömötör, O.; Mészáros, J. P.; May, N. V.; Spengler, G.; **Csuvik, O.**; Szatmári, I.; Enyedy, É. A.
8-Hydroxyquinoline-Amino Acid Hybrids and Their Half-Sandwich Rh and Ru Complexes: Synthesis, Anticancer Activities, Solution Chemistry and Interaction with Biomolecules.
Int. J. Mol. Sci. **2021**, *22*, 11281. DOI: 10.3390/ijms222011281. **IF.: 6.208**

III. **Csuvik, O.**; Szemerédi, N.; Spengler, G.; Szatmári I.
Synthesis of 4-Hydroxyquinolines as Potential Cytotoxic Agents.
Int. J. Mol. Sci. **2022**, *23*, 9688. DOI: 10.3390/ijms23179688. **IF.: 5.600**

IV. **Csuvik, O.**; Barta, P.; Csámpai, A.; Szatmári I.
Fine-Tuned Reactivity of N-Containing Naphthol Analogues.
Int. J. Mol. Sci. **2022**, *23*, 12329. DOI: 10.3390/ijms232012329. **IF.: 5.600**

V. **Csuvik, O.**; Szatmári I.
Synthesis of Bioactive Aminomethylated 8-Hydroxyquinolines via the Modified Mannich Reaction.
Int. J. Mol. Sci. **2023**, *24*, 7915. DOI: 10.3390/ijms24097915. **IF.: 5.600**

Total IF.: 27.398

Other publication

VI. Dobričić, V.; Turković, N.; Ivković, B.; **Csuvik, O.**; Vujić, Z.
Evaluation of the Lipophilicity of Chalcones by RP-TLC and Computational Methods.
JPC-J Planar Chromat **2020**, *33*, 245–253. DOI: 10.1007/s00764-020-00029-w. **IF.: 0.856**

D. CONFERENCE LECTURES

1. **Oszkár Csuvik**, Ferenc Fülöp, and István Szatmári
   Synthesis of hydroxyquinoline-derivatives with antiproliferative activity
   19th Tetrahedron Symposium
   26–29 June 2018, Riva del Garda, Italy

2. **Oszkár Csuvik**
   Homológ kinurénsav-származékok szintézise és továbbalakításai
   XLI. Kémiai Előadói Napok
   15–17 October 2018, Szeged, Hungary

3. **Oszkár Csuvik**, Ferenc Fülöp, Gabriella Spengler, and István Szatmári
   Synthesis of new 4-hydroxyquinolyl acetic acid derivatives
   1st Hungarian-Polish Interdisciplinary Scientific Symposium; The pharmaceutical and biological potential of natural origin substances
   26–27 September 2019, Szeged, Hungary

4. **Oszkár Csuvik**, Ferenc Fülöp, and István Szatmári
   Selective Substitutions of Homologue Kynurenic Acids
   25th International Conference on Chemistry
   24–26 October 2019, Cluj-Napoca, Romania

5. **Oszkár Csuvik**, Ferenc Fülöp, Antal Csámpai, and István Szatmári
   The transformation of nitrogen-containing analogues of 2-naphthol
   26th International Conference on Chemistry
   30 October 2020, Cluj-Napoca, Romania (online)