Sustainable methods for the synthesis and functionalization of KYNA derivatives

Ph.D. Thesis

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“Be a physical chemist, an analytical chemist, an organic chemist, if you will;
but above all, be a chemist.”

Ira Remsen

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https://doi.org/10.3390/ijms25136966 **IF.: 4.9**

II. **Simon, P.**; Lőrinczi, B.; Szatmári, I.
Novel Eco-friendly, One-Pot Method for the Synthesis of Kynurenic Acid Ethyl Esters
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III. **Simon, P.**; Lőrinczi, B.; Szatmári, I.
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IV. Lőrinczi, B.; **Simon, P.**; Szatmári, I.
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Abbreviations

*a*MA ..... *aza*-Michael addition
BAM..... bisarylmethylene
BINOL..... 1,1′-bi-2-naphthol
BDMS..... bromodimethylsulfonium bromide
BODIPY ..... dipyrrometheneboron difluoride
BPR ..... boron-modified phenolic resin
BSA ..... bovine serum albumin
CDI..... 1,1'-Carbonyldiimidazole
CL..... Conrad–Limpach
DCB..... 1,2-dichlorobenzene
DCM..... dichloromethane
DEAD..... diethyl acetylenedicarboxylate, diethyl buthyndioate
DCC..... *N*,*N*′-Dicyclohexylcarbodiimide
DEC..... diethyl carbonate
DIC ..... *N*,*N*′-Diisopropylcarbodiimide
DM ..... densitometry
EDAC.HCl ..... 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDG..... electron donating group
GC ..... gas chromatography
GVL..... gamma-valerolactone
HCTU ..... *O*-(1*H*-6-Chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HPLC..... high performance liquid chromatography
KYNA ..... kynurenic acid
MOM..... methoxymethyl
MPM..... *p*-methoxybenzyl
MW..... microwave
PPTS..... pyridinium *p*-toluenesulfonate
*p*TsOH ..... *p*-toluenesulfonic acid
QM ..... quinone methide
(q)NMR ..... (quantitative) nuclear magnetic resonance spectroscopy/spectrum
(*R*)-TRIP..... (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
S3MCA..... (*S*)-3-morpholinecarboxylic acid
SDS..... sodium dodecyl sulfate
TBSO..... tert-butyl-dimethylsilyloxy
TEA ..... triethylamine
TFSI-H ..... bistrifluoromethanesulfonimide
TLC ..... thin layer chromatography
TRC ..... thermal ring closure
TRIS ..... tris(hydroxymethyl)aminomethane, tromethamine
UV ..... ultraviolet
V27 ..... mixture of GVL 27 % *V*/*V* and DEC 73 % *V*/*V*
V60 ..... mixture of GVL 60 % *V*/*V* and DEC 40 % *V*/*V*

1. Introduction and aims

Kynurenic acid (KYNA) is an endogenous quinoline derivative, biosynthesized from the essential amino acid L-triptophane *via* the kynurenine pathway. The compound is of great importance due to its neuroprotective properties as aphysiological levels are measured in several neurological disorders such as Parkinson and Huntington disease, epilepsy, and migraine [1–8].

The total synthesis of kynurenic acid and its 5–8 substituted derivatives is conducted most commonly *via* non eco-friendly methods and types of the two-step Conrad–Limpach method. As the method consists of an enamine formation and subsequent cyclization steps, utilizing traditional solvents of high boiling pont such as diphenyl ether [9,10], halogenated arenes [11,12] or catalysts such as polyphosphoric acid [10,13] or *p*TsOH [12] are crucial factors regarding the conduction of the syntheses. In most recent literature, optimalization has been conducted focusing on the heat source or additional work-up processes [12,14].

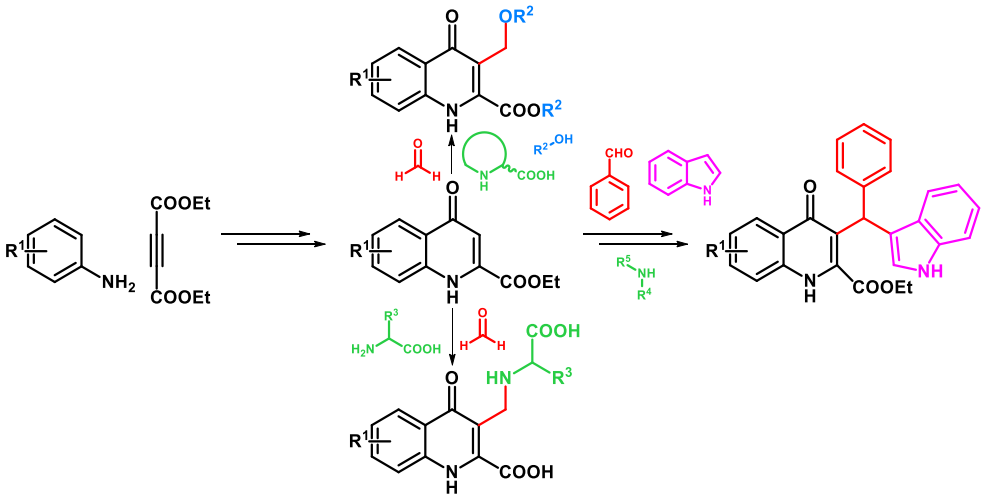
Last milestones of research focused on the further modification of the KYNA skeleton in order to enhance its effectivity and penetrability through the blood–brain barrier. Transformation of its ester precursors towards various amides bearing tertiary nitrogen residues was a versatile means of structural fine tuning [2,15–18]. Certain amides of kynurenic acid are reported to show inhibitory properties on NMDAR related excitotoxicity exerting protective effects in cerebral ischemia and transgenic mouse models of Alzheimers's disease [1] and transgenic mouse models of Huntington disease [2]. However, KYNA being an *aza*-analogue of 1-naphtol, its transformation *via* the Mannich reaction at the C–3 site or at *ortho*-position to its occurring hydroxysubstituents [11,12,16] was possible and cleared the way towards its further modifications. Certain Mannich-bases of KYNA derivatives are reported to show significant inhibiton on field excitatory postsynaptic potentials in the CA1 hippocampal region of rats [11].

The first aim of my PhD work was the design of a sustainable method for the precursor synthesis of kynurenic acid. The Conrad–Limpach method – able to yield various KYNA analogs such as ethyl esters of the biologically and chemically representative methyl-, methoxy- and halogeno derivatives – was aimed to be transferred into green chemical processes utilizing microwave irradiation as heat source on grounds of former improvements in the field. A two-step, one batch method without purification of the intermediates was our objective in order to reduce solvent consumption. The traditional reaction media were targeted to be exchanged to green solvents. Selection of green solvents is a multifactored task as ESH (Environment – Health – Safety) and LCA (Life Cycle Assessment) analysis is required. These classification methods take the environmental impact of the solvent synthesis, eradication, solvent usage in preparative work (*e.g.*

boiling point, volatility) and effect on humans into consideration [19,20]. As a wide-palette of eco-friendly solvents are available nowadays, gamma-valerolactone (GVL) [21–24] and diethyl carbonate (DEC) [25–27] seemed prosperous for the further optimization as these bear the optimal properties to make the solvent for the synthesis of kynurenic acid analogs. Scale-up of the optimized reactions was a further aim regarding the design of a green chemical process for the synthesis of KYNA analogs. Not only the synthetic method itself, but the analytical technique was also targeted to follow the concept of green chemistry.

The second group of aims were the broadening of the scope of the C–3 functionalization of the kynurenic acid *via* the modified Mannich-reaction. Amino acid fragments were chosen to be incorporated in the KYNA scaffold in order to yield zwitterionic Mannich-bases. However, on basis of preliminary research C–3 alkoxymethyl derivatives formed. Since there is a wide array of literature of alkoxyalkylation; the elaboration, optimization and overall investigation of the direct and *N*-nucleophile catalyzed alkoxymethylation of KYNA was targeted by utilizing various cyclic amines, corresponding acetates and amino acids. Broadening the scope of the aforementioned transformation towards different benzyl-ether type KYNA analogs was also plotted. As direct and *retro*-Mannich based alkoxyalkylations are an emerging field of organic syntheses, it was chosen to make the literature background of my thesis.

Further modifications of KYNA derivatives towards indole based triarylmethanes was aimed. Based upon previous research two main routes incorporating *retro*-Mannich reactions were chosen as possible tools for the syntheses [28–31]. Transformations of indole-based Mannich products using KYNA and also, on the contrary, the *retro*-Mannich reaction of Mannich bases of KYNA in the presence of indole was targeted. Optimization of the synthesis of KYNA-indole triarylmethanes and investigation of the scope and limitations of the reaction by utilizing an array of 5–8 substituted kynurenic acid analogs made a general objective of my Ph.D. work.



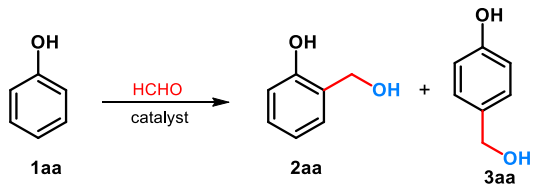
2. Literature background

In the field of organic chemistry, C–C coupling reactions are a unique and versatile means of molecular fine-tuning. Coupling a carbon atom, bearing active hydrogen with an electron deficient carbon (*e.g.* carbonyl) atom has been known to literature. Various methods of synthesizing benzylic-type ethers and alcohols from electron rich arenes have been introduced using aldehydes as carbonyl-compounds and catalysts such as zeolites, base and acid catalysts or organic amines by the degradation of Mannich bases. These types of products earned significance in pharmaceutical, supramolecular and petrol chemistry, as well as preparative organic chemistry, biosensor chemistry, and organic photochemistry.

2.1. Hydroxy- and alkoxyalkylation of electron-rich arenes: direct and catalytic methods

2.1.1. Hydroxy- and alkoxymethylation of monocyclic arenes

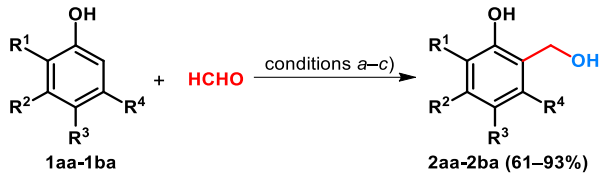
The hydroxymethylation of phenol was examined by using formaldehyde. Due to the activation of hydroxyl function two regioisomeric hydroxymethylated products (**2**, **3**) can be formed. Since both of the products are important chemicals in industry [32,33] or in the synthesis of bioactive compounds [34–36] the selectivity of the reaction is critical (Scheme 1). The effect of the divalent metal salts on the regioselectivity was examined by Komiyama and Morozumi [37]. Without any catalyst, or by using $MgCl_2$, $CuCl_2$ and $FeCl_2$ the ratio **2aa**/**3aa** was 1–1.5. By applying divalent zinc salts such as $Zn(OAc)_2$, $Zn(NO_3)_2$ (and its hexahydrate) or $ZnBr_2$ the selectivity could be shifted toward the formation of **2aa** [37,38]. The prepared salicylic alcohol (**2aa**) was reported to be precursor to synthesize benzofurane derivatives [38] or boron-modified phenolic resin composites (BPR) [39,40].



Scheme 1. Regioselective catalytic hydroxymethylation of phenol with formaldehyde

The C-ortho site-specific monohydroxymethylation of phenol was developed by Casiraghi et al. [41]. Phenol **1aa** was treated in xylene with an excess of paraformaldehyde in the presence of 1 mol equiv. of dimethoxyethane (DME). The synthetic route was then extended for the synthesis of different salicyl alcohols. The ortho-selective monohydroxymethylation of various phenols in the presence of $NaBO_2$ at 40 °C, was described by Wu et al. with the 80–95% yields [42]. Mezzogori

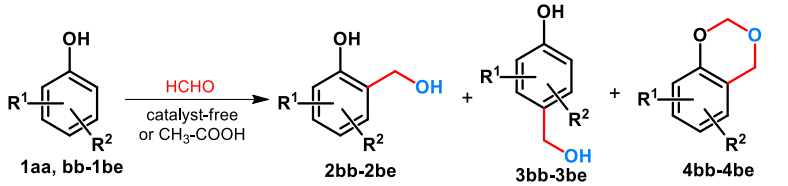
et al. reported that the H-mordenite zeolite catalyzed simultaneous synthesis of *o*- (**2ax**, 70 %), *m*- and *p*-vanillols [43].



R^1=H, Me, ^{c}Hex, *t*Bu, F, OMe, iPe; R^2=H, Me, Br; R^3=H, Me, iBu, *t*Bu, Ph, Cl, Br, I, OH, OMe, OBn; R^4=H, Me, F

Scheme 1. *Ortho*-selective hydroxymethylation of substituted phenols using various catalysts condition *a*) DME/xylene, 135 °C [41] *b*) $NaBO_2$, H_2O, 40 °C [42] *c*) H-mordenite, 80 °C [43]

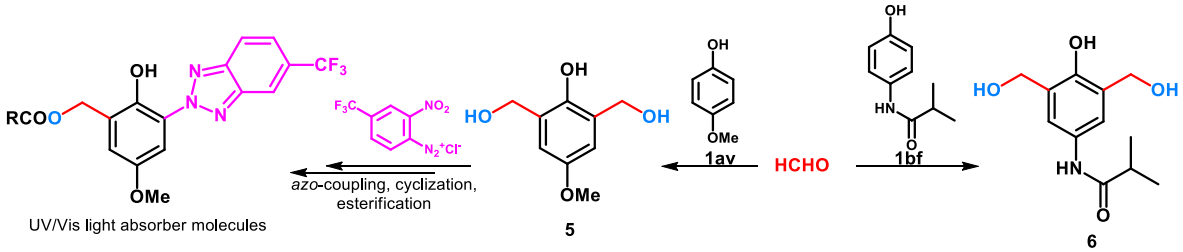
Hydroxymethylation of phenol (**1aa**) and phenolic ketones (**1bb-1be**) was investigated by Goswami *et al.* [44]. Depending on the phenolic substrate : paraformaldehyde ratios, different products could be isolated. It was also assumed that for the formation of 1,3-dioxane derivatives **4**, the necessary paraformaldehyde ratio depended on the phenol or phenolic ketones (**1**) in question.



R^1=H; R^2=H: **aa**; R^1=3-Ac; R^2=H: **bb**; R^1=4-Ac; R^2=H: **bc**; R^1=2-Ac; R^2=4-Me: **bd**; R^1=4-Ac; R^2=2-Me: **be**

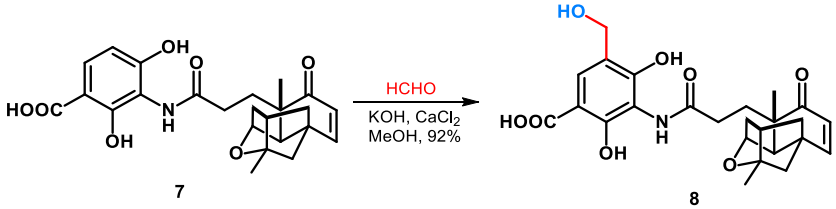
Scheme 2. Divergent hydroxymethylation of phenolic compounds

The previous syntheses tried to avoid the dihydroxymethylation of phenols however, the extra hydroxymethyl function can be further used to build bioactive compounds *e.g.* benzotriazoles [45] and crosslinking agents (Scheme 3) [46].



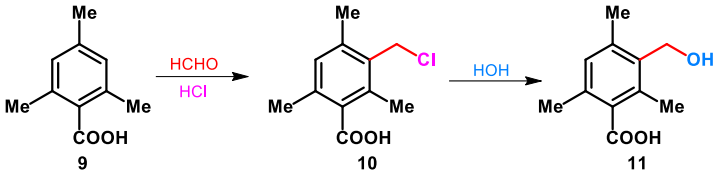
Scheme 3. *Ortho-ortho'* bis-hydroxymethylation of phenol derivatives

Duan *et al.* reported the hydroxymethylation of platensimycin (**7**). The synthesis was performed in MeOH, by using formaldehyde and inorganic additives KOH and $CaCl_2$ leading to the formation of **8** in an excellent yield (Scheme 4) [47].



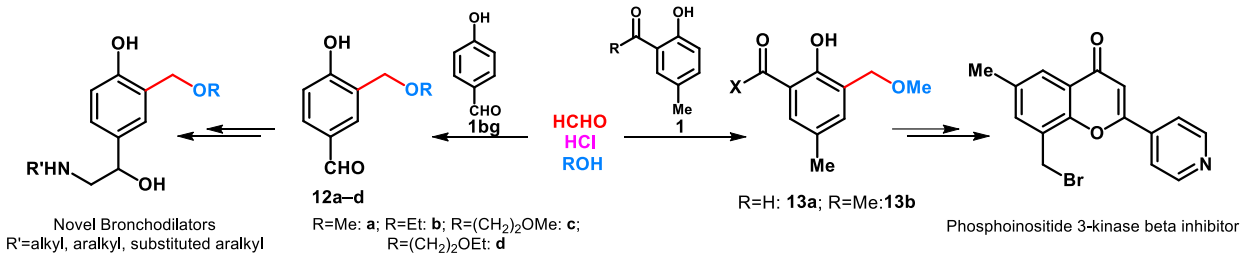
Scheme 4. Hydroxymethylation of plastesimycin

The preparation of compound **11** was reported by Stewart, The synthesis included the chloromethylation of mesitoic acid (**9**) with formaldehyde and hydrochloric acid and its subsequent hydrolysis during the mildly basic aqueous work-up procedure (Scheme 5) [48].



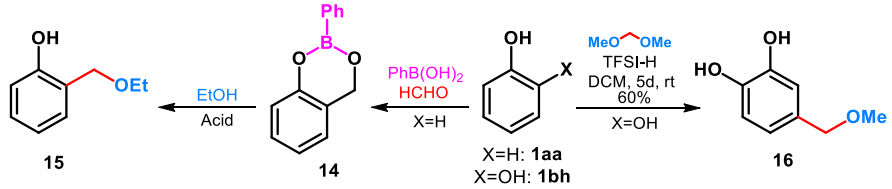
Scheme 5. Chloromethylation and rapid hydrolysis of mesitoic acid

The synthesis of 4-hydroxy-3-alkoxymethylbenzaldehydes (**12a–d**) was reported by Hirose *et al.* The role of hydrochloric acid is to form 3-chloromethyl intermediate that reacts immediately with the alcohols applied in the reaction (Scheme 6) [49]. Methoxymethylation of 2-hydroxy-5-methylbenzaldehyde was published by Jorgensen *et al.* (Scheme 6) [50]. Methoxymethylation of 2-hydroxy-5-methylacetophenone was performed in methanol by using paraformaldehyde in the presence of cc. hydrochloric acid (Scheme 6) [51]. *Ortho*-situated hydroxyl and acetyl functions enabled the building of substituted pyran moiety.



Scheme 6. Alkoxymethylation of hydroxybenzaldehydes and phenolic ketones

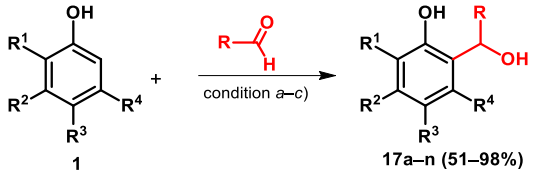
Ortho-selective ethoxymethylation was published by Bélanger *et al.* [52]. Phenol **1aa** was reacted with formaldehyde in the presence of phenylboronic acid leading to compound **14**, which via the treatment with ethanol in the presence of acid catalyst gave the desired 2-ethoxymethylphenol **15**. By treatment of 1,2-dihydroxybenzene (**1bh**) with dimethoxymethane in the presence of bistrifluoromethanesulfonimide (TFSI-H) a regioselective Friedel-Crafts alkylation took place and compound **16** was isolated in a yield of 60% (Scheme 7) [53].



Scheme 7. Alkoxymethylation of catechol and phenol with TFSI-H or phenylboronic acid

The reaction among resorcinol derivatives and flavour-relevant saturated aldehydes were tested by Zomora *et al.* [54]. As a representative reaction, the synthesis of 4-(1-hydroxypentyl)-2-methyl-benzene-1,3-diol (**17a**) was carried out at 60 °C. Thanks to the aliphatic alcohol function,

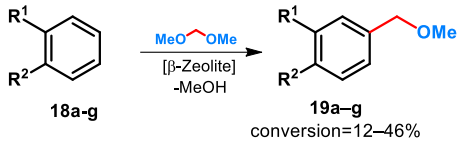
the reaction provided different side products *e.g.* methoxylated **17a**, or its dehydrated derivatives. The asymmetric hydroxyalkylation of different phenols was developed by Casiraghi *et al.* performed in toluene by using chloroacetaldehyde in the presence of chirally modified aluminium chloride derivatives [55]. It was summarized that chiral Lewis acid promoter and the reactants fine-tuned both the regio- and enantioselectivity of the reaction. Ytterbium(III) trifluoromethansulfonate ($Yb(OTf)_3$) catalysed electrophilic aromatic substitution of substituted phenols with ethyl-glyoxilate was published by Wang and Zhang [56]. The reactions were performed at rt, the lowest yield was observed when the starting phenol derivative bore tertiary nitrogen (Scheme 8).



R=Bu, CCl_3, COOEt; R^1=H, Me, iPr, *t*Bu, Br; R^2=H, OH, *t*Bu, NEt_2; R^3=H, Me, *t*Bu, OH, F; R^4=H, Me

Scheme 8. *ortho*-hydroxyalkylation of substituted phenols with different catalysts
condition *a*) DME/xylene, 135 °C [54] *b*) Toluene, 4h, 15 °C [55] *c*) $Yb(OTf)_3/CH_2Cl_2$, 10 h, rt [56]

Methoxymethylation of electron rich monocyclic arenes with formaldehyde-dimethylacetal by using β-Zeolite were performed by Müller *et al.* First, the method was developed starting from cumol (**18a**) [57], that was then extended to other arenes (**18b–g**) (Scheme 9) [58].

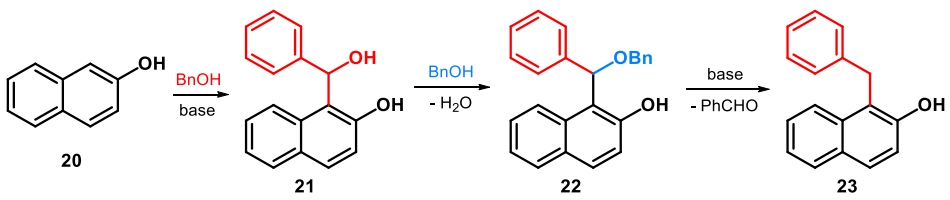


R^1=H, OMe; R^2=iPr; iBu; *t*Bu; OH, OMe

Scheme 9. β-Zeolite catalyzed *para*-methoxymethylation of electron rich benzenes; conditions: 70–120 °C; 3–90h

2.1.2. Hydroxy- and alkoxymethylation of phenol-fused carbocycles

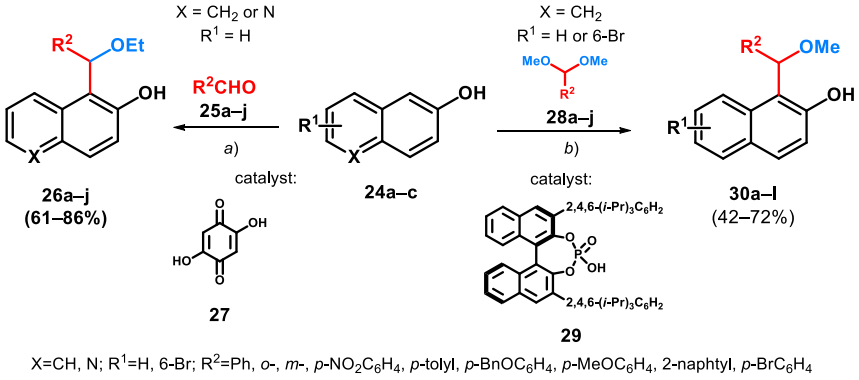
Regarding alkoxyalkylations of naphthol and its derivatives the first synthesis concerns such compounds as hydroxylated/alkoxylated bisarylmethylene (BAM) intermediates. In this regard the reaction of 2-naphthol and benzyl alcohol occurring under high temperature and in the presence of a base –due to which the benzyl alcohol is *in situ* oxidized to benzaldehyde– yields compound **21**. Subsequently **21** has been observed to react with the still present benzyl alcohol yielding compound **22** that *via* a base catalysed elimination, loses benzaldehyde leaving behind the final benzyl substituted product **23** (Scheme 10) [59].



Scheme 10. Synthesis of 1-benzylnaphthalen-2-ol (**23**) from 2-naphthol (**20**) and benzyl alcohol

First synthesis of alkoxylated BAMs concerns the *oxy*-Michael type addition reaction between aromatic aldehydes (**25a–j**), EtOH and 2-naphthol (**24a**) or 6-hydroxyquinoline (**24b**) assisted by 2,5-dihydroxy-1,4-benzoquinone (**27**) in the presence of HCl. The reaction afforded compounds **26a–j** at room temperature with yields 61–86 %. The importance of **27** (1.0–1.0 equiv.) was outlined as without it only xanthene byproducts could be achieved [60].

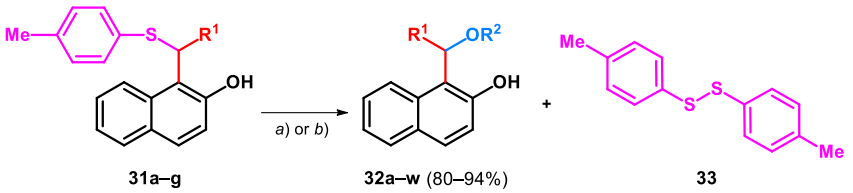
Acetals are widely used in carbon–carbon bond-forming reactions with a variety of nucleophiles for the synthesis of ethers [61,62]. Utilizing TRIP as a chiral Brønsted acids catalyst with acetic acid as additive the synthesis of chiral alkoxylated BAMs from various acetals and naphthols (**24a,c**) was also described. After the optimization of the conditions, (*R*)-TRIP (**29**) could efficiently catalyze the asymmetric Friedel–Crafts reaction of **24a,c** with different aromatic acetals (**28a–j**) affording chiral ethers (**30a–l**) in good enantioselectivity and yield (Scheme 11) [63].



X=CH, N; R^1=H, 6-Br; R^2=Ph, *o*-, *m*-, *p*-$NO_2C_6H_4$, *p*-tolyl, *p*-$BnOC_6H_4$, *p*-$MeOC_6H_4$, 2-naphtyl, *p*-BrC_6H_4

Scheme 11. Substituted bisarylmethelene derivatives of 2-naphthol starting from 2-naphthol. *a*) EtOH/HCl, 100 mol% 27, r.t., 24 h; *b*) abs. $C_2H_4Cl_2$, 20 mol% 29, 20 mol% AcOH, 35 °C

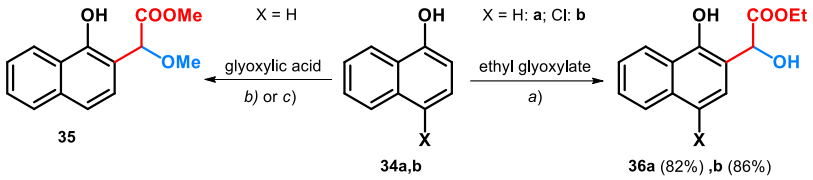
It has been previously demonstrated that organic ammonium tribromides (OATB) and *in situ* generated bromonium ion can be used for *C–S* bond cleavage in deprotection of dithioacetals [64] and in hydrolysis of 1-thioglycosides [65]. Starting out from the corresponding unsymmetrical sulfides (**31a–g**) the synthesis of alkoxylated BAMs (**32a–r**) or hydroxylated 1-benzylnaphthalen-2-ol (**33s–w**) derivatives could be achieved by utilizing BDMS and either the corresponding alcohol or water (Scheme 12) [66].



Scheme 12. Substituted bisarylmethylene derivatives of 2-naphthol starting out from thioethers. *a*) 2 equiv. R^3OH, 1 equiv. BDMS, DCM, r.t., 1-2 min. for 32a–r *b*) 40 µL H_2O, 1 equiv. BDMS, MeCN, r.t., 5 min. for 32s–w

Glyoxylic acid and its esters have also been investigated in the alkoxyalkylation of the electron rich 1- and 2-napthol systems. Starting out from 1-naphthol (**34a**) and glyoxylic acid utilising *tert*-butoxy carbamate or acetamide as catalyst the methyl 2-methoxyacetate derivative of 1-

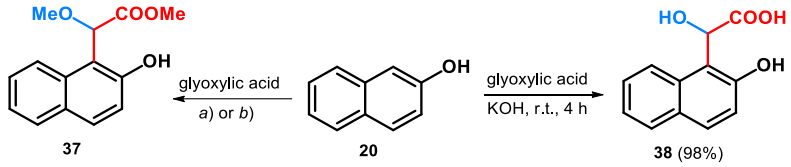
naphthol (**35**) could be achieved (Scheme 13). Though the syntheses yielded alkoxylated derivatives the aim of the described work was to synthesize aminoacid derivatives through a modified Mannich reaction thus highlighting the catalysts as unfavourable [67]. When starting out from ethyl glyoxylate and utilizing ytterbium(III) trifluoromethanesulfonate in DCM beside the previously described phenol derivatives, 1-naphthol (**34a**) and its 4-chloro derivative (**34b**) gave hydroxyl derivatives (**36a**,**b**, Scheme 13) [56].



Scheme 13. *a*) NH_2Boc, *p*TsOH, MeOH, reflux, 98 h, 39%; *b*) acetamide, *p*TsOH, MeOH, reflux, 72 h, 34%; *c*) 5 mol% $Yb(OTf)_3$ CH_2Cl_2, r.t.

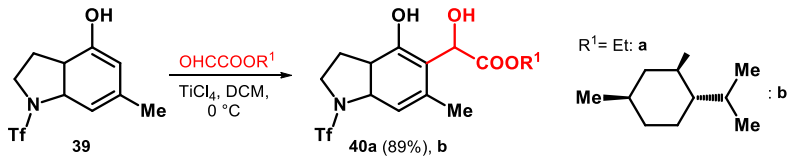
When starting out from 2-naphthol and glyoxylic acid and utilising the same *tert*-butoxy carbamate or acetamide as catalyst similar results could be achieved: the methyl 2-methoxyacetate derivative of 2-naphthol (**37**) could be achieved similar to **35** (Scheme 14) [67].

Without the use of such catalysts, applying only KOH, glyoxylic acid condenses with **20** yielding α-hydroxy-α-(2-hydroxy-1-naphthyl)acetic acid (**38**, Scheme 14) [68].



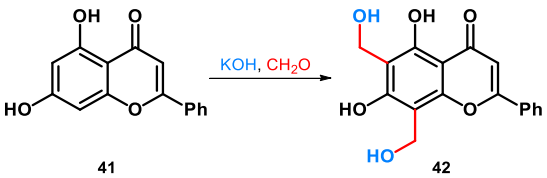
Scheme 14. *a*) NH_2Boc, *p*TsOH, MeOH, reflux, 93 h, 38%; *b*) acetamide, *p*TsOH, MeOH, reflux, 84 h, 32%

Reactions glyoxylic acid esters and phenol-fused heterocycles have been published as well. In case of compound **39** titanium catalyst was needed most probably due to the strong inactivating effect of the triflate protecting group on the pyrrolidine moieties' nitrogen. The reaction yielded the ethyl ester derivative **40a** in high yield (89%); however, there was no published yield for the (–)-menthol ester (**40b**, Scheme 15) [69].



Scheme 15. Alkoxyalkylations of pyrrolidine fused phenol system

Regarding phenol-fused ring-systems another interesting reaction concerns the transformation of chrysin. The reaction conditions specified in the patent were not discoverable, the flavonoid (**41**) was reacted with a formaldehyde source in presence of an alkali hydroxide that gave rise to the formation of the methoxymethylated derivative 16 (Scheme 16) [70].

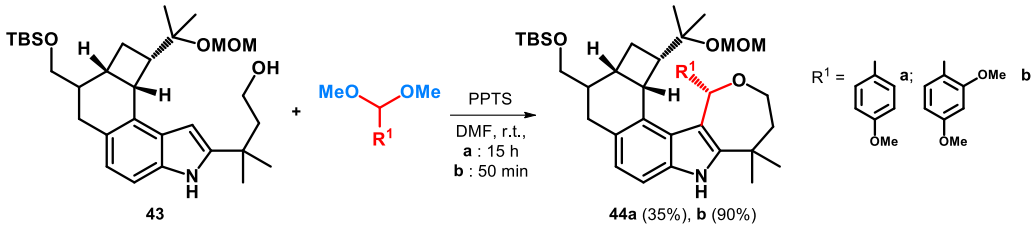


Scheme 16. Synthesis of chrysin based hydroxymethylene derivative **42**

2.1.3. Hydroxy- and alkoxymethylation of *N*-heterocycles

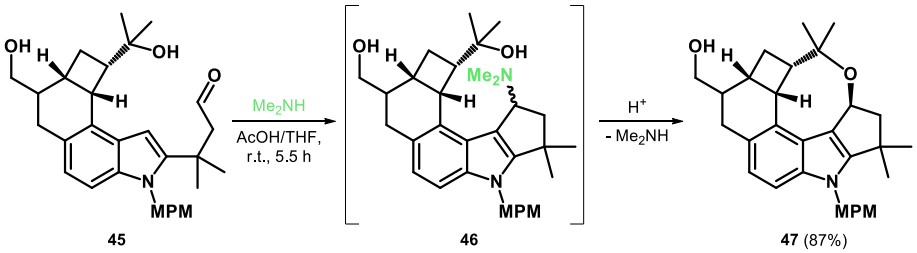
2.1.3.1. Hydroxy- and alkoxymethylation of indoles

During the development of the total synthesis of penitrems, researchers were looking for indole nitrogen protecting groups that are suitable for the modified Mannich reaction. When trying to build in a methoxylated benzyl protecting group starting out from the acetals under acidic conditions on the free alcoholic group yielded alkoxyalkylated BAMs **44a**,**b** (Scheme 17) [71].



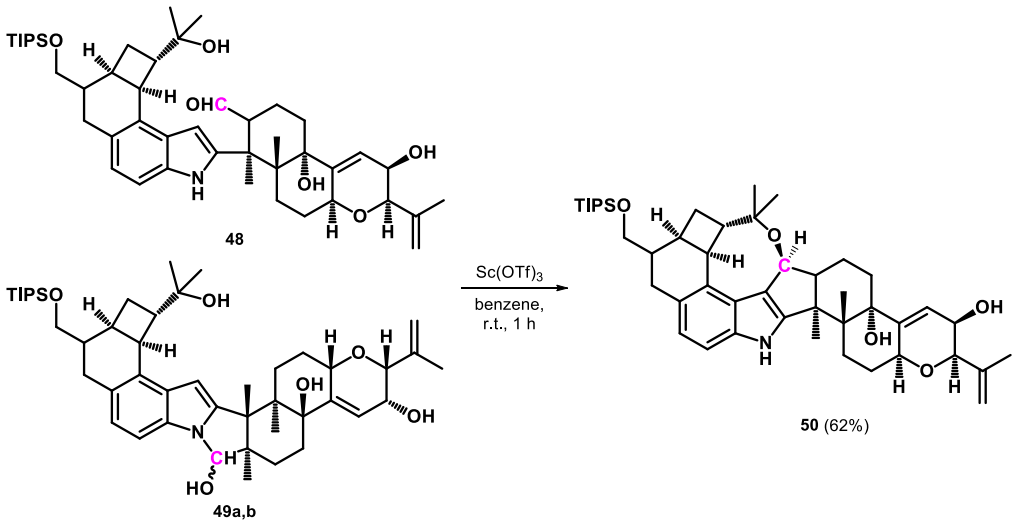
Scheme 17. Unsuccessful protection of indole nitrogen yielding BAMs. PPTS = pyridinium *p*-toluenesulfonate, MOM = methoxymethyl ether

The MPM *N*-protected aldehyde **45** was prepared to take part in the aforementioned modified Mannich reaction yielding the alkoxyalkylated indole-fused oxocine **47** as the final product *via* Mannich-base **46** and a tandem Mannich cyclization/gramine fragmentation sequence (Scheme 18).



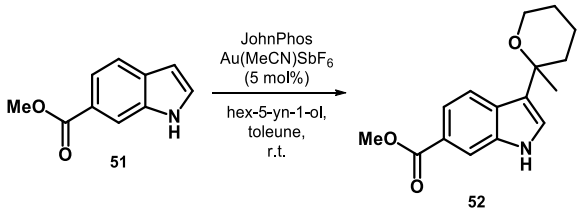
Scheme 18. Tandem Mannich cyclization/gramine fragmentation sequence yielding **47**

The same research group later described the complete total synthesis of the penitrem ring-systems *via* a different reaction route. Alcohols **48** and **49a,b** were synthesized and tandem cyclized into the oxocine-condensed ring-system (**50**) using scandium triflate (Scheme 19) [72].



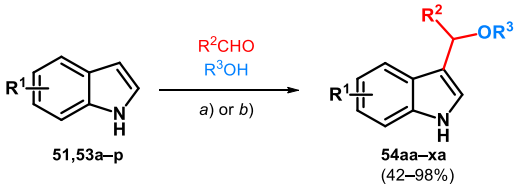
Scheme 19. Transformation of 3 different intermediates (**48**,**49a,b**) into **50** by scandium triflate

Starting out from less functionalised indole derivatives the first publication describes the synthesis of a novel Nav1.7 inhibitor discovery. Compound **52** was synthesized uniquely among the other derivatives described using a gold salt as oxidizer starting out from **51** (Scheme 20) [73].



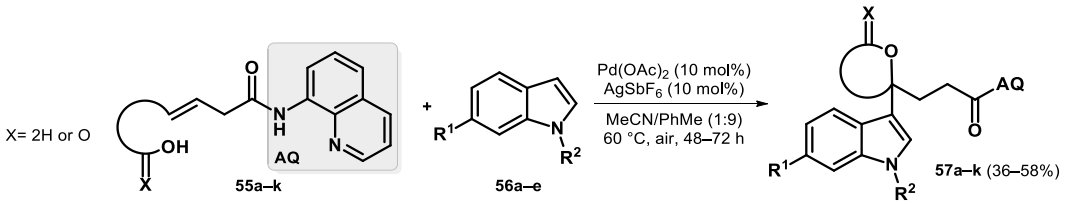
Scheme 20. Synthesis of tetrahydro-2*H*-pyran-2-yl-indole derivative **52**

Two research papers describe the *oxy*-Michael type modification of indole derivatives (**51**,**53a–p**) using aromatic aldehydes and methanol in the presence of NaOH yielding BAMs **54aa–xa** (Scheme 21) [74,75].



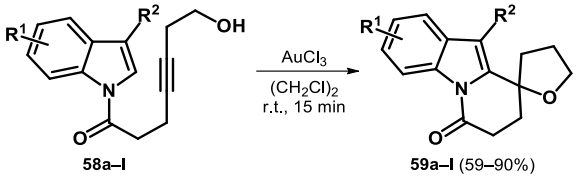
Scheme 21. *a*) 2 equiv. NaOH, 120 °C, 2–24 h for **54aa–ea** *b*) 1.5 equiv. NaOH, 20 °C, 24 h, for **54fa–xa.**

The site-selective 1,1-difunctionalization of unactivated alkenes was described that was enabled by cationic palladium catalysis. The scope and limitations of the synthesis was investigated in case of alkenes comprising alcohols and carboxylic acids (**55a–k**) utilising palladium(II) acetate and silver hexafluoroantimonate(V) as catalysts yielding **57a–k** (Scheme 22). It is worth mentioning that for the reaction to take place directing group **AQ** was necessary and crucial [76].



Scheme 22. Substituents and yields of final products**.**

Another reaction concerns the synthesis of spiro-pyridoindolone derivatives (**59**), in which the alkyne moiety reacts with an alcohol –intramolecularly in **58**– in the presence of gold salt catalyst (Scheme 23) [77].

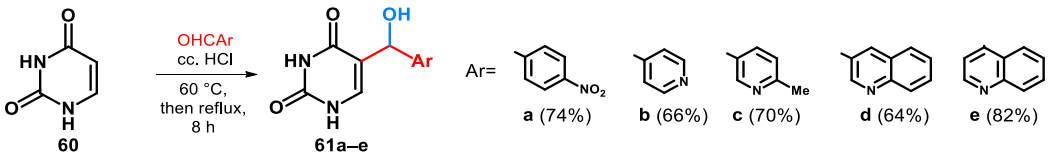


R[1]=H, 5-OMe, 5-Me, 5-F, 5-Cl, 5-Br, 5-I, 6-F, 6-Cl, 6-Br, 4-Br, 7-Me

Scheme 23. Gold-catalysed intramolecular alkynol cyclisation/hydroindolylation

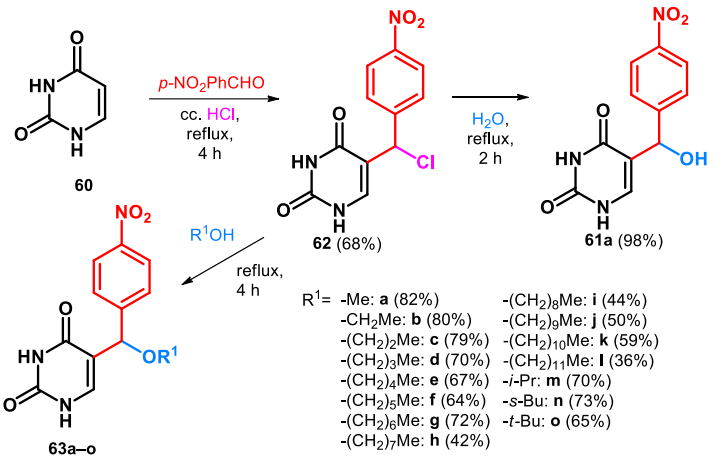
2.1.3.2. Hydroxy- and alkoxymethylation of uracil

Uracil (**60**) bearing an enamino ketone character was successfully utilized in a hydroxyalkylation reaction using electron-deficient aromatic aldehydes in water. Instead of the more commonly used halogeno derivatives of aromatic aldehydes the scope and limitations was investigated beside *p*-nitrobenzaldehyde with heteroaromatic aldehyde derivatives, showing moderate yields (Scheme 24) [78].



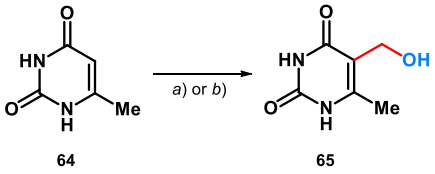
Scheme 24. Synthesis and achieved yields of 5-(arylhydroxymethyl)uracil derivatives

Building upon these transformations Hlavác *et. al*. described the synthesis of **61a** in very similar reaction conditions. However, they obtained the chloro derivative (**62**) that had to be further hydrolysed. The scope and limitations was also investigated by supplementing water with different aliphatic alcohols all yielding the alkoxymethylated BAMs incorporating the uracil moiety (**63a–o**, Scheme 25) [79].



Scheme 25. Synthesis of alkoxymethylated BAMs incorporating uracil moiety

Beside aromatic aldehydes, paraformaldehyde was also investigated in two publications regarding 6-methyluracil. Using KOH as additive and in both cases the final product was a hydroxymethylated derivative (**65**). One method describes no solvent and a much longer reaction [80], while the other describes the solvent and despite only a 5 °C difference half the reaction time and much better yields (Scheme 26) [81].

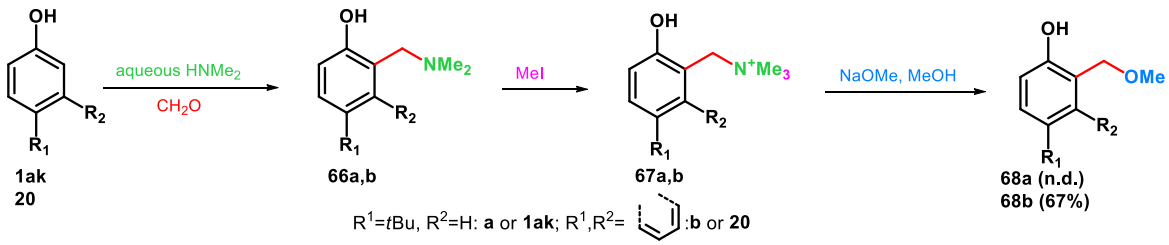


Scheme 26. *a*) $(CH_2O)_n$, KOH, 50°C, 73 h (76%) [80]; *b*) $(CH_2O)_n$, KOH, H_2O, 0°C then 55°C for 36 h (98%)

2.2. Hydroxy- and alkoxyalkylation of electron rich arenes *via* aminoalkyl intermediates

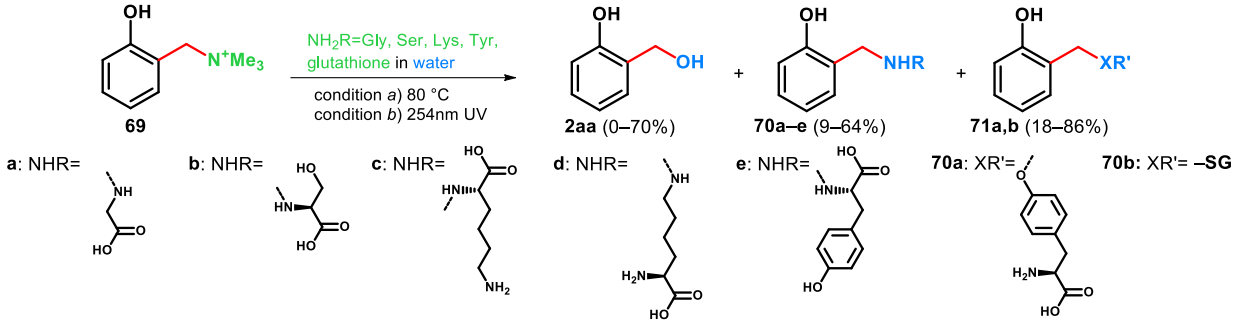
2.2.1. Transformations of phenolic Mannich-bases

Transformations of benzylamines with various nucleophiles have been widely investigated. Applying conditions on these substances, which favour the *retro*-Mannich degradation yield *ortho*-quinonemethides (*o*QM). As these compounds are prone to rearomatization, nucleophilic attack on the methylidene group leads to novel molecules bearing benzylalcohol or benzyl-alkyl ethers. By the methylation of compounds **66a,b**, unstable quaternary ammonium species formed (**67a,b**) which are easily transformed to benzyl-methyl ethers **68a,b** [82] (Scheme 27).



Scheme 27. Mannich subsequent *retro*-Mannich reaction of phenols towards benzyl-methyl ethers

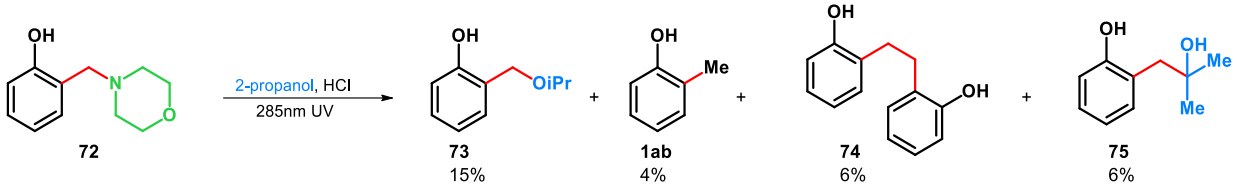
Freccero *et al.*, published various transformations of *o*-hydroxybenzyl-trimethylammonium iodide (**69**) testing multiple *N*- (and *S*-) nucleophiles and conditions. UV- and heat-driven eliminative deamination and subsequent nucleophilic addition methods were tested in pH-buffered aqueous solutions [83] (Scheme 28).



Scheme 28. Transformations of **69** with amino acids and glutathione as *N*-, *O*- or *S*-nucleophiles

It was proved that in aqueous conditions, not only is the used *N*-nucleophile capable of the addition towards compounds **70a–e**, the solvent acting as a nucleophile **2aa** formed. *Via* thermodeamination, pH=6–7 favored the formation of compound **2aa**, while higher pH favoured **70a–e**. Using photodeaminative methods (UV 254 nm), the ratio of **2aa** went higher than formerly. Using tyrosine, *O*-alkylation was observed at pH=10–12 besides the *N*-alkykation.

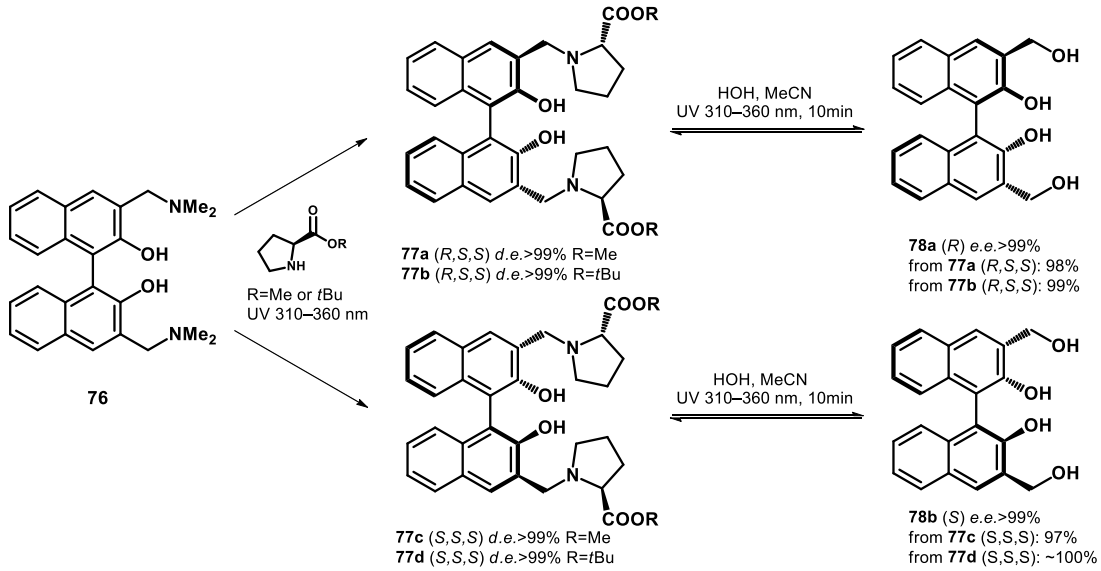
Roth and Michel found that the photodeamination-driven transformation can be applied on tertiary amine **72** in 2-propanol-HCl medium, yielding products **1ab**, **73–75** (Scheme 29) [84]. The radical deamination favoured the formation of **73**.



Scheme 29. UV-driven *retro*-Mannich reactions of *o*-morpholinomethyl phenol Mannich base

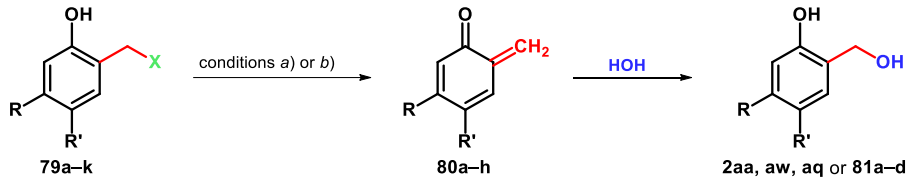
Saito *et al.* published the [85] highly efficient *o*QM formation of dimethylaminomethyl phenols and subsequent transformations toward different acetals. They investigated the *o*QM formation of *o*-hydroxybenzyl alcohols, however it was found that Mannich bases are much more prone to transformation.

Freccero *et al.* transformed Mannich-bases of BINOLs towards L-proline-ester based diastereomers (*d.e.*>99%), which were subsequently transformed to chiral hydroxymethyl derivatives (*e.e.*>99%). They reported the reversibility of the ligand exchange step (**77a–d** and **78a,b**, Scheme 30) [86].



Scheme 30. Enantio- and diastereoselective photochemical synthesis of bis-hydroxymethyl BINOLs

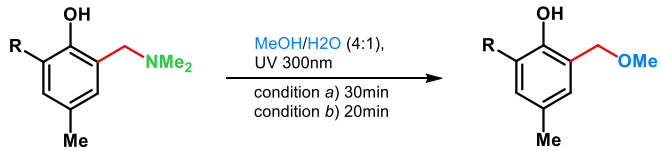
They reported that using thermal incubation or flash photolysis tests, electron donating substituents facilitate the formation of *o*QMs and suppress the rearomative transformation stabilizing the *o*QM (Scheme 31). Electron withdrawing groups suppress the deamination and they facilitate the rearomatization. During flash photolysis test, quaternary ammonium compounds had significantly higher quantum yields, than the corresponding tertiary amines. [87]



X= 4-morpholinyl, N^+Me_3; R= H, OMe, COOMe; R'=H, OMe, COOMe, Cl, CN

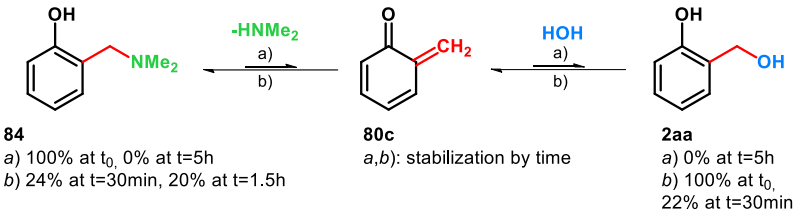
Scheme 31. Thermal- and photochemical degradation of Mannich bases **79a–k**
a) incubation at 100 °C, *b*) laser flash photolysis, 266 nm

Basarić *et al.* also supported the statement while testing the photodeamination of *p*-cresol derived tertiary amines and their hydrochlorides *via* laser flash photolysis at 266 nm. The quantum yield could be elevated by protonation. (Scheme 32) [88].



Scheme 32. Acid driven photodeamination of tertiary Mannich base **82a,b**

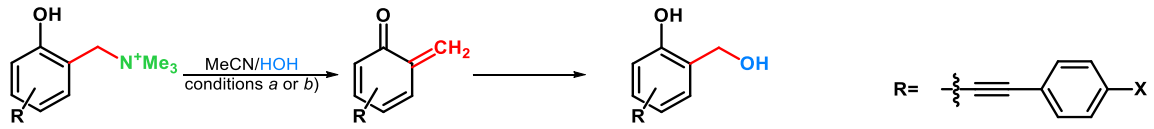
Takaki *et al.* while synthetizing chromene derivatives starting from Mannich-bases or α-substituted salicyl alcohols, tested the equilibrium of compounds **83, 80c and 2aa**. (Scheme 33)



Scheme 33. Equilibrium between Mannich-base 84 and salicyl alcohol (2aa). Conditions: UV 280nm, D_2O/CD_3CN, Ph_2CH_2 (an internal standard); (*a*) **84** 100% at t_0, $HNMe_2$ (40 wt.% in H_2O, ~1 equiv.); (*b*) **2aa** 100% at t_0, H_2O (~1 equiv.).

In contrast to using quaternary benzylammonium salts, treating secondary Mannich-base **84** with water under UV irradiation, no trace of **2aa** was observable (via ^{1}H-NMR analysis) (condition *a*); however, starting from **2aa** and reacting it with $HNMe_2$ under the same reaction conditions, full conversion was achievable towards **80c** and **84** (condition *b*) [89]. These findings prove the importance of the formation of quaternary ammonium salts of elevated leaving properties regarding *retro*-Mannich transformations. However, elevation of the leaving property of a tertiary amine can be applied through protonation [84,88].

Later, Freccero's research group broadened the investigations in 2016. Various Mannich bases were synthesized from phenols, bearing 4- or 5-arylethynyl substituents for the investigation of the substituent effect on the photogeneration of *o*QM. An aspect of the *o*QM detection was the study of reactivity with water or mercaptoethanol. The good-leaving quaternary ammonium moiety is needed for a good quantum-yield photolysis, the 5-arylethynyl derivatives showed lower reactivity and that the electron donating substituents fasten the formation of *o*QMs. Compounds **85a–c** were transformed to hydroxymethyl derivatives in water-trapping probes of **86a–c** (Scheme 34) [90].



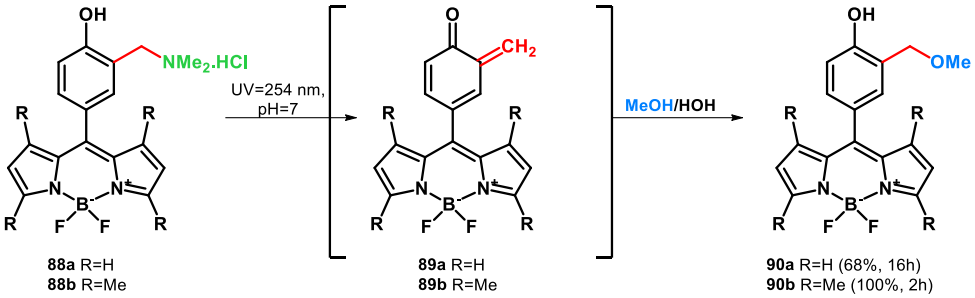
85a 4-R, X=H
85b 4-R, X=NO_2
85c 5-R, X=H

86a 4-R, X=H
86b 4-R, X=NO_2
86c 5-R, X=H

87a 4-R, X=H (89%, condition *a*))
87a 4-R, X=NO_2 (97.5%, condition *b*))
87a 5-R, X=H (64%, condition *a*))

Scheme 34. Study on substituent effects in correspondence with oQM generation condition (a) UV 310nm, 5 min; condition (b) UV 360nm, 450 min

Basarić *et al.* synthesized fluorescent BODIPY-Mannich dyes which, *via o*QM state, can react with the thiol-groups of BSA (bovine serum albumin). Hydrochlorides of Mannich bases (**88a,b**) were successfully probed for the transformation with methanol, and the photomethanolysis occurred via irradiation (Scheme 35) [91].



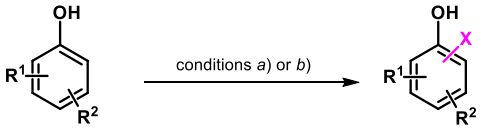
88a R=H
88b R=Me

89a R=H
89b R=Me

90a R=H (68%, 16h)
90b R=Me (100%, 2h)

Scheme 35. Photomethanolysis probe on BODIPY-Mannich dyes

Polarized *N*-centers favor the retro-Mannich transformation towards *o*QMs. Non-UV-driven base and acid catalysis have also been reported to promote such transformations towards *O*-alkylated products. Regarding the synthesis of various chromanecarboxylic acids, the alkoxylmethylation step was reported *via* the usage of acetic acid additive [92]. However, it was found that a Mannich reaction of disubstituted phenols in alcohols gave alkoxymethylated products while synthesizing antioxidant molecules [93] (Scheme 36).

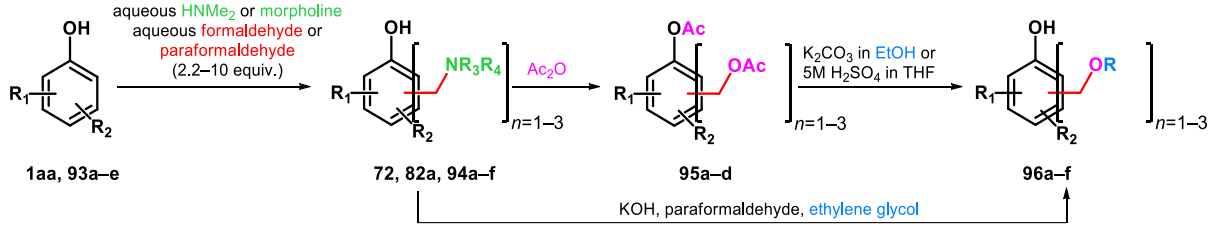


91a R^1=2-Me, R^2=6-Me
91b R^1=2-Me, R^2=6-iPr
91c R^1=2-iPr, R^2=6-Me
91d R^1=2-*t*Bu, R^2=4-*t*Bu

92a R^1=2-Me, R^2=6-Me, X=4-CH_2OMe (condition *a*), 100 °C, 6h)
92b R^1=2-Me, R^2=6-iPr, X=4-CH_2OMe (condition *a*), 120 °C, 4h)
92c R^1=2-iPr, R^2=6-Me, X=4-CH_2OMe (condition *a*), 120 °C, 4h)
92d R^1=6-*t*Bu, R^2=4-*t*Bu, X=2-CH_2OnBu (91%, condition *b*), reflux, 10h)

Scheme 36. One-pot alkoxymethylation of phenols via subsequent Mannich–*retro*-Mannich reactions: condition (*a*) $HNEt_2$ (0.14 equiv.), paraformaldehyde (0.87 equiv.), MeOH; condition (*b*) $HN(nBu)_2$ (0.10 equiv.), paraformaldehyde (1.7 equiv.), HOAc (0.5 equiv.), *n*BuOH

For the alkoxymetylation of substituted (alkyl, halogeno, or *2H*-benzo[*d*][1,2,3]triazol-2-yl) phenols, numerous examples were reported *via* degradation of Mannich-bases. Treating Mannich bases with acetic anhydride yielded *O*-acetyl-*O*-acetyloxymethyl phenols, which under acidic [94] or basic [95] conditions gave the *O*-alkyl products. It was found by Crisp and Turner that under mild basic conditions in water, hydroxymethyl derivatives were also able to form, and by the multi-step Mannich and subsequent retro-Mannich route, in contrast to alkali-mediated hydroxymethylation, higher yields can be achieved (Scheme 37) [96].

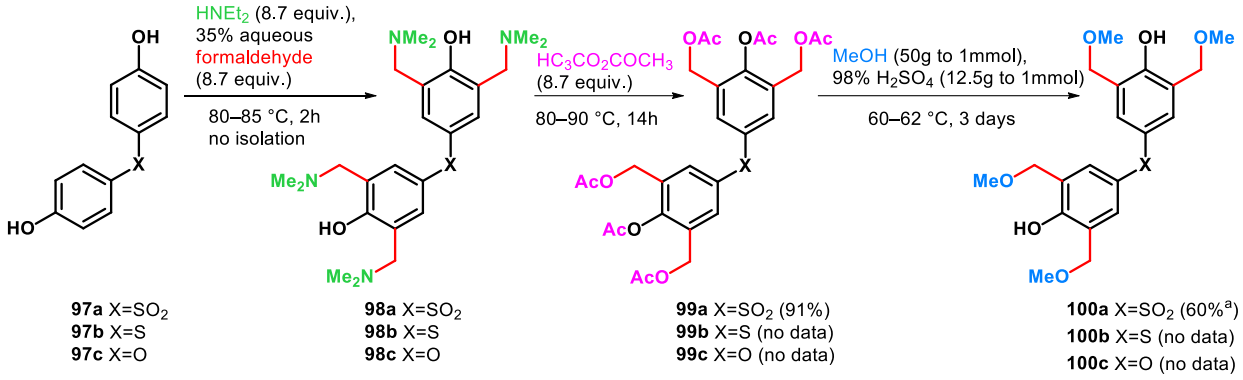


1aa, 93a–e | **72, 82a, 94a–f** | **95a–d** | **96a–f**

R^1=H, 4-Br, 2-(*2H*-benzo[*d*][1,2,3]triazol-2-yl); R^2=H, *t*-Bu, 1-(2-hydroxy)ethyl, 1-(2,2,4,4-tetramethyl)butyl;
$CH_2NR^3R^4$=2- or 2,4,6-CH_2NMe_2, 2,6-morpholinomethyl; 2,6 or 2,4,6-OAc; CH_2OR=2-$CH_2O(CH_2)_2OH$, 2,4,6-CH_2OEt or 2,6-CH_2OH

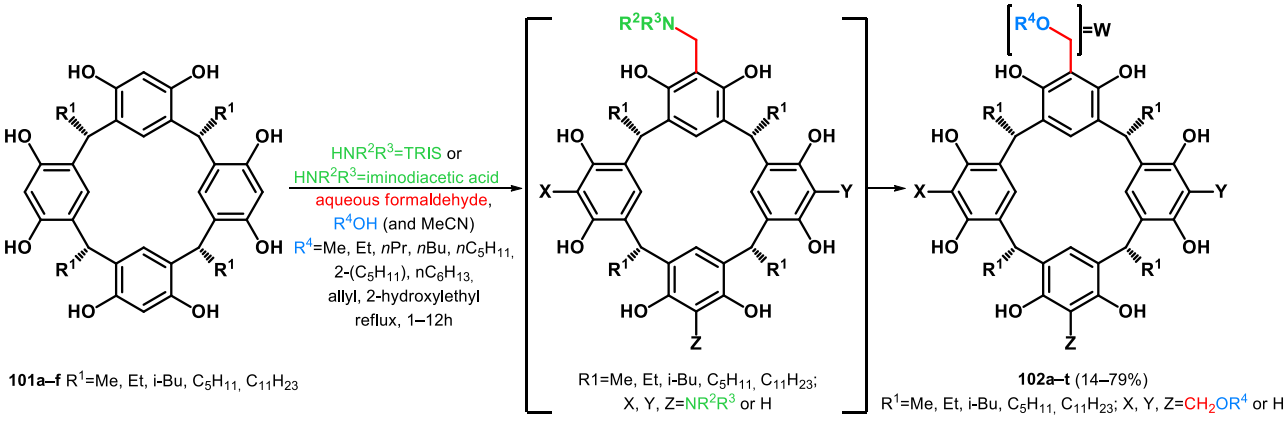
Scheme 37. Mannich and subsequent *retro*-Mannich reaction of substituted phenols *via* acetyloxylation and hydro- or alcoholysis

The method itself can be applied to yield tetrakisalkoxymethylated bisphenols as resin raw materials of high storage stability, heat resistance and good optical properties (Scheme 38) [97].



Scheme 38. Methoxymethylation of bisphenols **97a–c** *via* Mannich–*retro*-Mannich reactions

Alkoxymethylation methods are studied in correspondence with resorcinarene chemistry. Resorcinarenes, which are versatile building blocks for supramolecular chemistry, have been modified yielding alkoxymethylated products. Rissanen, Shivanyuk *et al.* conducted the synthesis of tetrakis(alkoxymethyl)resorcinarenes. Testing reaction conditions, no conversion was observable without using tromethamine, thus hypothesizing an *in situ* Mannich reaction by which products transform towards the desired alkoxymethylated products (Scheme 39) [98]. Urbaniak et al. carried on the study using iminodiacetic acid as an *N*-nucleophile. Iminodiacetic acid acts as both *N*-nucleophile and an in situ protonating agent, being an optimal additive for the transformation of electron-rich arenes towards their alkoxymethyl derivatives. It was found that a 9.4 mol% catalytic amount of iminodiacetic acid was sufficient. They proposed a reaction mechanism which involves autoprotonation of the Mannich-type intermediate [99]. Later, selective alkoxymethylation was carried via the shortening of the reaction time (Scheme 39) [100].

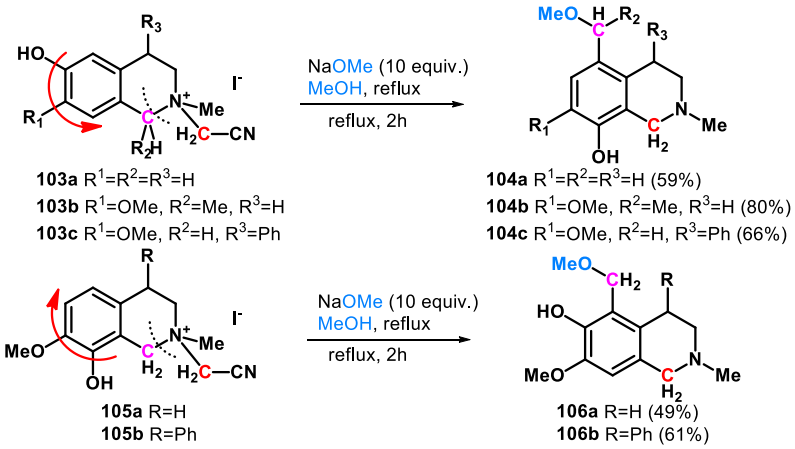


Scheme 39. Alkoxymethylation of resorcinarenes using tromethamine or iminodiacetic acid catalyst

2.2.2. Transformations of semi-synthetic phenols and *N*-heterocycles

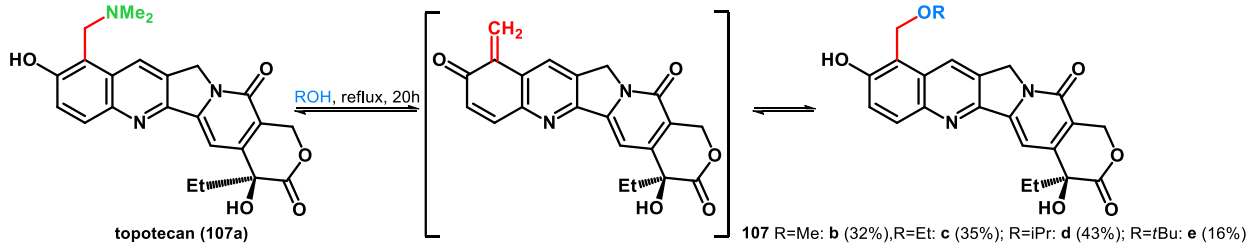
2.2.2.1. Transformations of phenol-fused molecules

Numerous Mannich–*retro*-Mannich driven hydroxy- and alkoxymethylation reactions have been reported in correspondence with hydroxyfunctionalized heterocycles. Hara *et al.* reported unexpected the methoxymethylation side-reaction of tetrahydroisoquinolines (**103a–c**, **105a**,**b**). The reaction is driven by an intramolecular *retro*-Mannich type reaction in which *o*- or *p*QM molecules form with simultaneous ring opening and turnover (Scheme 40) [101].



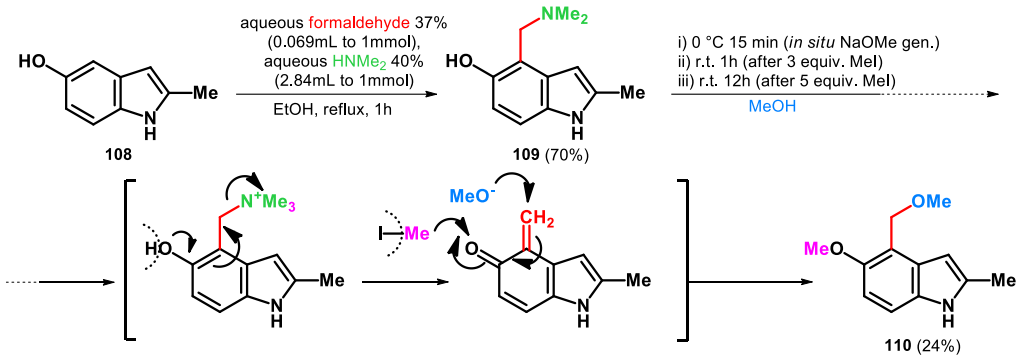
Scheme 40. Intramolecular *retro*-Mannich reaction and ring turnover of tetrahydroisoqionolines **103a–c** and **105a,b** yielding methoxymethyl derivatives

Zhang *et al.* preformed the alcoholysis of the Mannich-base topotecan [102,103]. The already presented equilibrium was also found between topotecan (107a) and compounds 107b–e, which was explained with the hydrogen bonding ability between the dimethylamino and the phenolic hydroxyl group positively polarizing the nitrogen atom. Compound 106e showed lower IC50 values than the parent molecule on HepG2 and C26 cell lines [104]. The same research group broadened the scope of the reaction using thiols and enol-ethers (Scheme 41) [105].



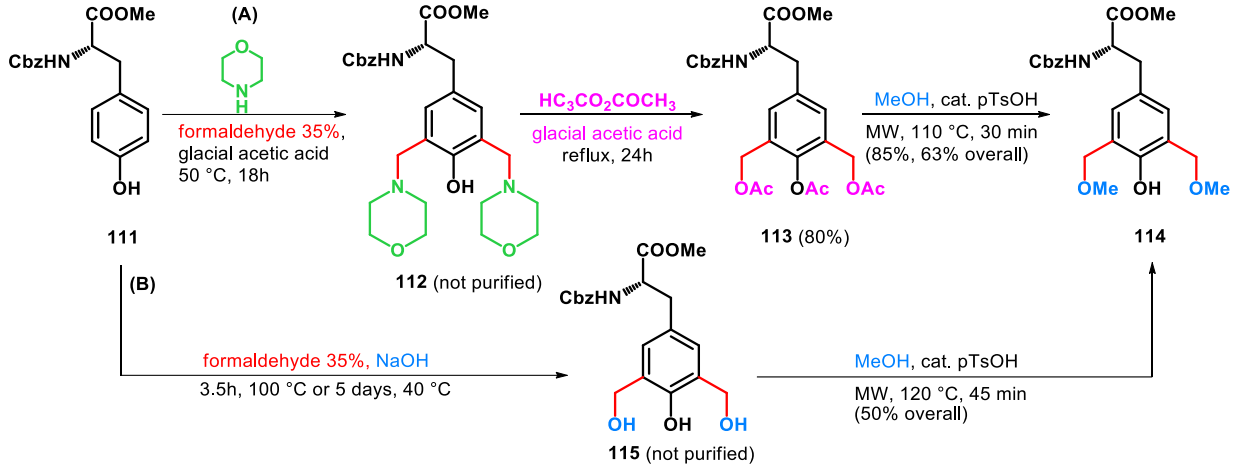
Scheme 41. *retro*-Mannich driven *N–O* swap of topotecan, a widely known Mannich base

Homer and Sperry in 2018 targeted the total synthesis of *Tricholoma* alkaloids [106]. The synthesis started from the Mannich reaction of 5-hydroxy-2-methylindole (**108**) [107] yielding **109** which was subsequently transformed in one-batch towards **110** with moderate yields (Scheme 30). MeI additive functioned as an *N*-methylating agent [83], facilitating the *retro*-Mannich reaction and simultaneously methylating the phenolic hydroxyl group (Scheme 42).



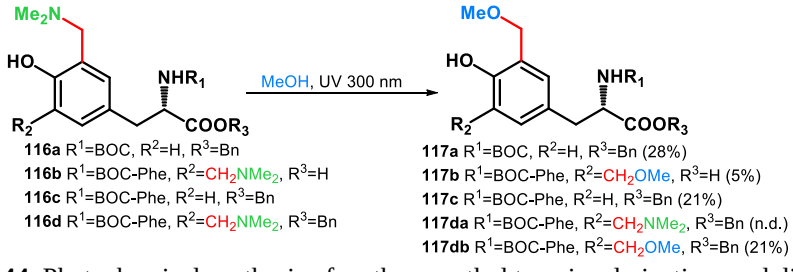
Scheme 42. Total synthesis of tricholoma alkaloid **110** utilizing *N–O* swap

Bew *et al.* reported the synthesis of methylene-bridged (*S*)-tyrosine-phenol dimers. One method exploited the potential of *retro*-Mannich reactions, the other utilized inorganic additives while reducing reaction steps. *Via* pathway **A**, higher yields could be achieved than utilizing **B**, despite the greater number of steps and longer reaction time (Scheme 43) [108].



Scheme 43. Synthesis of bis-methoxymethyl compound **114**, a building block for methylene-bridged tyrosine derivatives

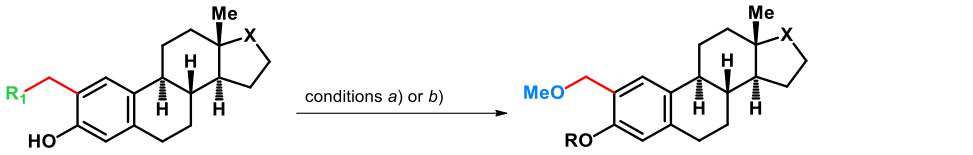
Basarić *et al.* reported the photochemical transformations of dipeptides drivatives **116**, presenting photoswitchable units for peptide modification [109]. Compound **116d** was investigated in the reaction towards **117da,db**. At 30 min reaction time, the ratio was 1:1, running the reaction for a longer time, 68% conversion of **117db** was achieved (Scheme 44).



Scheme 44. Photochemical synthesis of methoxymethyl tyrosine derivatives and dipeptides

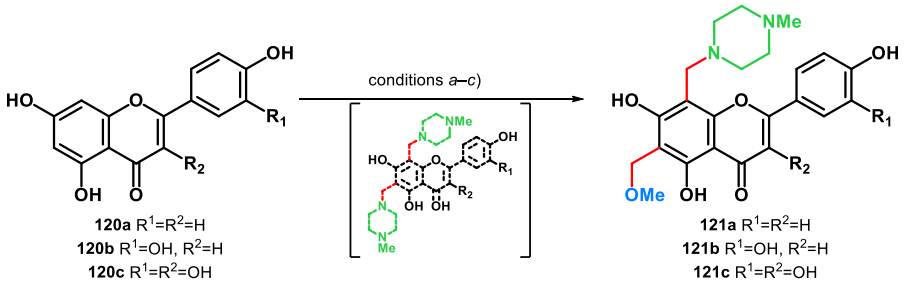
Two research groups have successfully synthesized 2-methoxymethyl estrone or 2-methoxymethyl-17α-estradiol derivatives starting from Mannich bases **118a–c** [110,111]. The

usage of dimethyl sulfate as an initiator of the *retro*-Mannich subreaction (condition *a*), being an aggressive alkylating agent also alkylated the 3-OH group (**119b**). While using MeI (condition *b*)) no *O*-alkylation was observed under the investigated conditions (Scheme 45).



Scheme 45. *N–O* swap of estrogen-based Mannich bases **118a,b** (*a*) (*i*) MeI (26 equiv.), in Et_2O 20h, r.t.; isolated (*ii*) KOH (excess), MeOH, 3h, reflux (*b*) MeOH, 17% aqueous KOH (in 2 steps, 12 + 2 weight equiv.), Me_2SO_4 (9–10 molar equiv.), 60 °C, 5 h

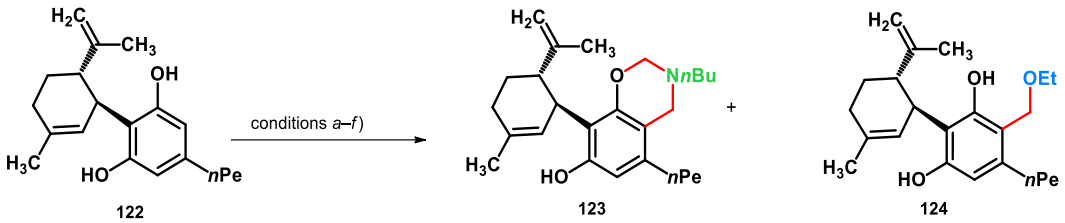
Transformations of apigenin (**120a**), luteolin (**120b**) and quercetin (**120c**) *via* Mannich reaction were reported [112]. Under the investigated conditions (*a–c*), running the reaction in MeOH, simultaneous methoxymethylation (at position C–6) and aminomethylation (at position C–8) took place yielding products **121a–c**. It is noteworthy that a C–6,8 bis-(4-methylpiperazino)methyl derivative is hypothetically possible to form in the reaction mixture, which however, might be prone to transformation towards **121a–c** based on the polarizing properties of the proximal two hydroxyl groups [104] or acidity of the parent molecules [99] (Scheme 46).



Scheme 46. Transformation of flavonoids **120a–c** yielding methoxymethyl–morpholinomethyl derivatives: condition (*a*) MeOH, 2.5 equiv. HCHO, 0.8 equiv. *N*-Me-piperazine, 63 °C, 1 h; condition (*b*) MeOH, 1.5 equiv. HCHO, 1.5 equiv. *N*-Me-piperazine, 20 °C, 12 h; condition (*c*) MeOH, 2.0 equiv. HCHO, 1.2 equiv. *N*-Me-piperazine, 46 °C, 6 h

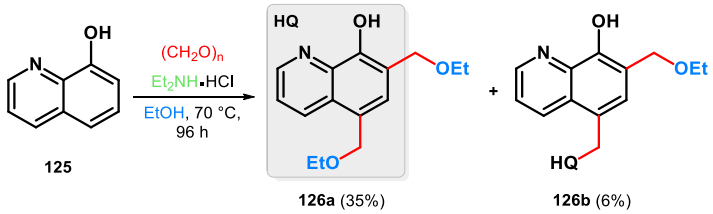
Bereczki *et al.* synthesized Mannich derivatives of cannabidiol (**122**) in order to enhance their penetrability and/or water solubility [113]. Conducting Mannich-reaction using *n*-buthylamine in ethanol, formation of the ethoxymethylated side-product **124** (21 %)**,** in addition to **123** (64 %), was observed (condition *b*) (Scheme 47). The conditions were thoroughly investigated and optimized. The alkoxymethylation did not take place in methanol (condition (*a*) **123**: ~89 %), neither did it using ethanol at lower temperatures (condition (*c*) **123**: ~100 %) or 1,4-dioxane (condition (*d*) **123**: 60 %). The formation of **124** was investigated. Without an amine component (condition *f*), the desired product did not form. Under condition *e* [54], **124** was isolable with moderate yields (30 %). Since an equilibrium was found [89] between alkoxymethyl and aminomethyl phenolic compounds,

and that product **124** did not form at lower temperatures, suggests that the mentioned equilibrium can be shifted towards the alkoxymethyl compounds by raising temperature.



Scheme 47. Mannich-type modifications of (–)-cannabidiol under different conditions

Modified Mannich reaction of 8-hydroxyquinoline, a widely cited bioactive agent [114–118] (**125**), was reported using diethylamine hydrochloride and paraformaldehyde in ethanol; however, the isolated products were not Mannich bases. The ethanol solvent served as an *O*-nucleophile on the intermediate Mannich base and exchanged the diethylamino function giving 5,7-bis(ethoxymethyl)quinolin-8-ol (**126a**) as a major product, however dimer (**126b**) was also isolated (Scheme 48) [119].

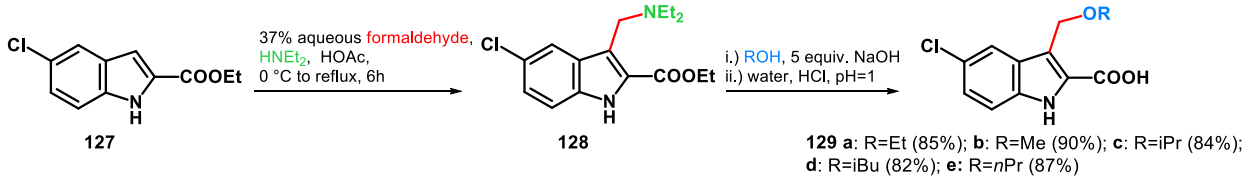


Scheme 48. Synthesis of 8-hydroxyquinoline-derived ethoxymethylene derivatives **126a,b**

Taking the aforementioned information into consideration, a hypothetical reason behind the formation of **126a** can be the *in situ* protonating ability of the diethylamine hydrochloride.

2.2.2.2. Transformations of *N*-heterocycles

Youssif *et al.* synthesized antiproliferative 3-alkoxymethyl or 3-phenyl indole-2-carboxamides, which showed good activity on MCF7 and HCT116 cell lines (Scheme 49) [120].



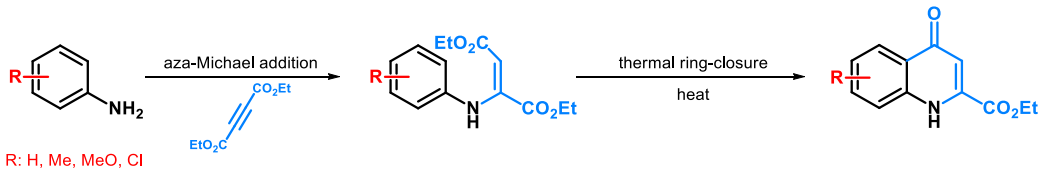
Scheme 49. Design of 3-alkoxymethyl indole-2-carboxylic acid antiproliferative agents

Transformation of **128** towards **129a–e** was conducted in the corresponding alcohols and NaOH with excellent yields. Theoretically, the proximal carboxylic function could act as an autoprotonating agent if the reaction mixture reaches neutral pH and ester function is hydrolized while the aminomethyl moiety is still intact. Also, the *retro*-Mannich reaction can be conducted under acidic conditions which is present while work-up.

3. Results and discussions

3.1. Eco-friendly, one-pot method for the synthesis of kynurenic acid ethyl esters

During my PhD work a novel, one-batch two-step MW-assisted method, using only a single solvent system for the total synthesis of KYNA and its derivatives was designed. The CL method itself consists of two main steps: *i*) the reaction between an aniline derivative and diethyl acetylenedicarboxylate (DEAD) forms an enamine through *aza*-Michael addition (*a*MA); *ii*) the final product is synthesised *via* the thermal ring closure (TRC) (Scheme 50).

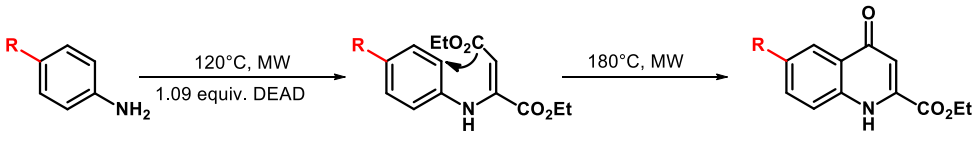


Scheme 50. Synthesis of substituted kynurenic acid ethyl esters using the CL method

In order to economize solvent consumption, neither chromatographic purification nor distillation were used between the steps. Advantages of MW-assisted heating techniques have been reported in scientific literature, regarding preparative methods or digestion for analysis. Using closed reaction system, temperatures above boiling points of solvents or reagents can be achieved, minimizing the environmental impact. Moreover, specific microwave effects take place in MW-conducted reactions. Such (thermal) effects are overheating effect of solvents, selective heating of reagents of catalysts in the reaction media, formation of hotspots (by direct coupling of reagents) and the bulk-heating model (lack of "wall-effect") which leads to homologous temperature profile in the reaction chamber. There are recent debates over such athermal effects of the electromagnetic irradiation on dipolar molecules which can alter the pre-exponential factor or the activation energy of a reaction. It is important to note that in the case of microwave-assisted syntheses, reaction conditions can be precisely set and handled [121–124].

3.1.1. Syntheses of C-6-substituted KYNA analogs

Starting from aniline derivatives, through the formation of enamines **130–132**, KYNA analogs **133–135** were synthesised (Scheme 51).



Scheme 51. CL synthesis of C-6-substituted KYNA ethyl esters

Designing the reaction methods suitable for one-pot microwave-assisted synthesis, several factors were taken into consideration regarding starting materials, MW-parameters and solvents (Figure 1).

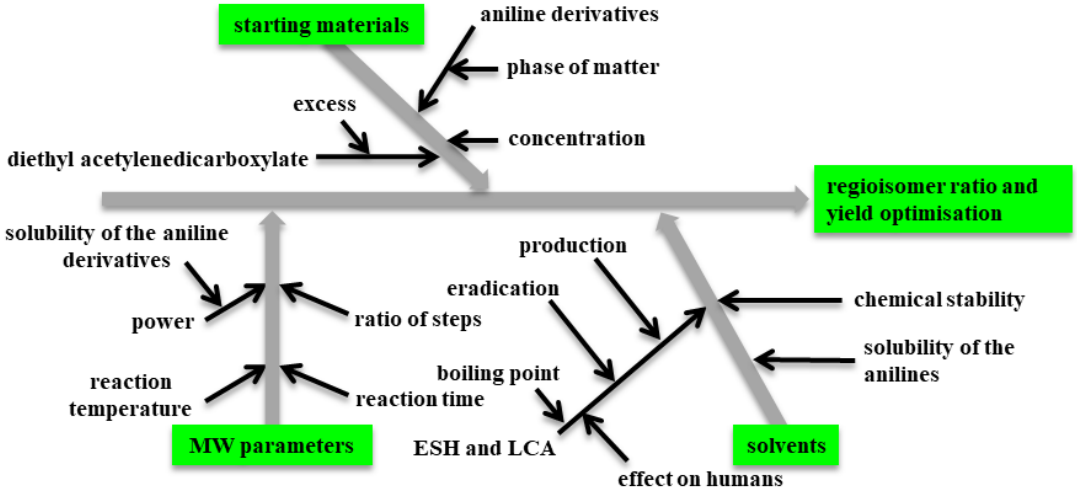


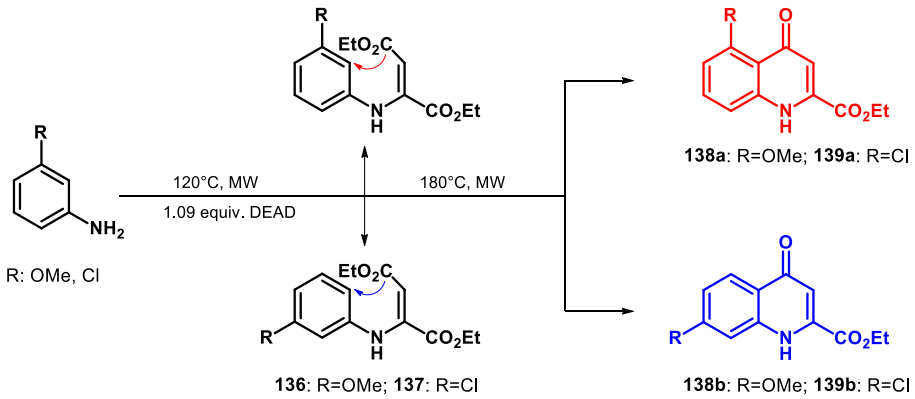
Figure 1. Factors taken into consideration while designing the MW-assisted reactions

Reaction conditions of each step were precisely set as follows: *Volume:* a 5.0-mL reaction volume was investigated. *Concentration:* in the case of anilines derivatives, a concentration of 0.5 M of the selected solvents was found to be optimal. At higher concentrations (*e.g.* 1.5–5 M), maleimide-type side-products formed and the conversion decreased [12]. *Reagent excess:* the excess of diethyl acetylenedicarboxylate (DEAD) was determined to be 1.09 equivalents, since problematic side-products were occasionally formed above 1.1 equivalents. *Solubility:* Regarding the starting materials (in the case of solid aniline derivatives), solubility was taken into consideration, as undissolved fractions of anilines are prone to degradation. *Reaction temperature: i*) in the test reactions utilising 1,2-dichlorobenzene (DCB) solvent, 120 °C was found to be the optimal temperature for the *a*MA reaction step. This was presumably observed due to the slower enamine formation in this media, compared with methods using ethanol. It is important to note, that the boiling point of DEAD is 107–110 °C; therefore, a closed reaction system was needed. *ii*) The TRC step of the syntheses was conducted at 180 °C. Temperatures above 180 °C did not lead to significantly higher yields; however, in some cases, side-products were formed. It is also important to mention that in order to avoid the formation of maleimides (usually at about 150 °C), heating up from 120 °C to the next phase should be as fast as possible. *Reaction time:* For each synthesis, individual reaction times were determined in order to maximize conversion (Table 2). *Green solvent systems:* Reaction conditions finally being set, our further experiments focused on the exchange of 1,2 dichlorobenzene (DCB) to green solvents, without altering reaction times. From two solvents (GVL and DEC), selected by their physicochemical properties (boiling point, stability, Environment–Safety–Health data and Life Cycle Assessment), four green solvent systems were

prepared. Ultimately, test reactions were conducted in DCB, GVL, DEC and two mixtures of the latter [1:2 (V27) and 2:1 (V60), given in n_{GVL}/n_{DEC} molar ratios].

3.1.2. Syntheses of C-5- and C-7-substituted KYNA analogs

Further experiments focused on KYNA ethyl esters formed as regioisomer pairs (Scheme 52).



Scheme 52. CL syntheses of C-5- and C-7-substituted KYNA ethyl esters

Reaction conditions were set on the basis of the same conclusions as mentioned before, *i.e.*, 0.5 M concentration of the aniline derivative, 5.0 mL reaction volume, 1.09 equivalents of DEAD, 120 °C temperature for step *i*), and 180 °C for step *ii*). Reaction times are summarized in Table 2. Compound pairs **138a–b** and **139a–b** having been synthesised in DCB, our next aim was to alter reaction conditions in order to affect regioisomeric ratios. First, temperatures at which the TRCs were conducted were tested in the range of 160–220 °C by 20 °C. At 160 °C no or only trace of products formed, above 180 °C side-product formation was observed without the change in regioisomeric ratio. Results of the former experiments led to the deduction, that regarding the synthesis of unsubstituted and 6-Me-, 5-, 6-, 7-MeO- and 5-, 7-Cl-substituted KYNA ethyl esters via CL method, a green solvent system of GVL and DEC can be prepared for each test reaction in which the synthesis can be conducted with nearly the same (or higher) conversion compared to the use of DCB. Furthermore, a solvent effect on regioisomeric ratios was observed in the four green solvent systems (Table 1).

Table 1. Different reaction times of both step (*i*) and (*ii*) used in the synthesis of KYNA-derivatives

Product	**Reaction time (min)**	
	aza-Michael addition (*i*)	thermal ring closure (*ii*)
133	60	60
134	90	120
135	60	60
138a–b	90	60
139a–b	120	60

3.1.3. Determination of conversion

In order to quantify the exact mass of the dissolved products, several methods were taken into consideration. Due to the complexity of the crude product, the HPLC method seemed to be problematic regarding its costly column. GC methods would not be applicable, due to the low volatility of products and matrices. Two methods were considered to be adequate, because of the difference in their physicochemical principles.

3.1.3.1. Quantitative NMR

Quantitative NMR was first chosen to quantify the dissolved products using *p*-methoxybenzoic acid as internal standard. However, due to the complex matrices and occasional modest conversions and/or overlapping peaks, the method was found to be not universal (Figure 2). At high temperatures, formation of substituted *N*-(4-hydroxy)valeroyl aniline or *N*-ethoxycarbonyl aniline by-products can be hypothesized, although the thorough analysis of the crude NMR spectra proved that these compounds were under the limit of detection.

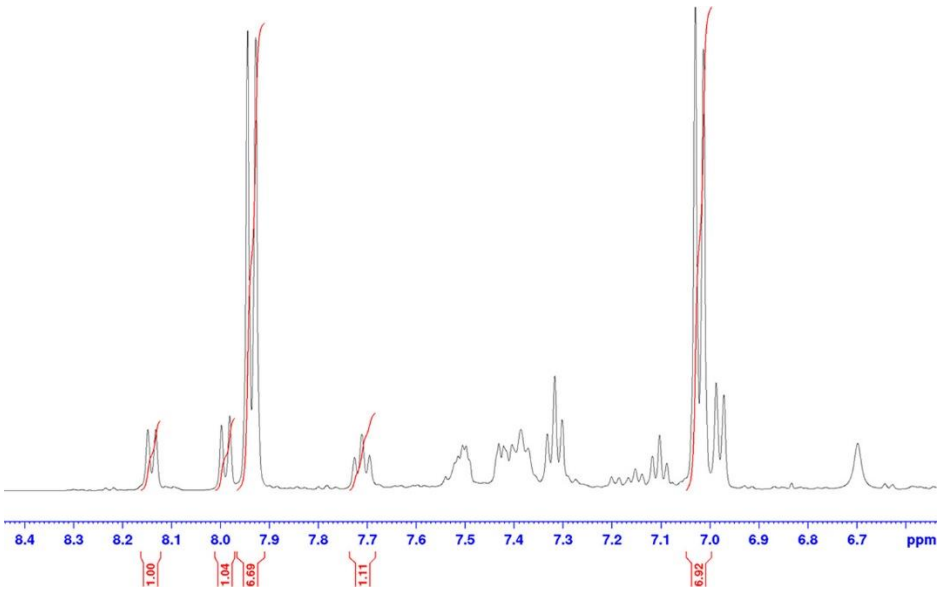


Figure 2. Quantitative NMR spectrum of the crude reaction mixture of the synthesis of compound **133** in GVL using *p*-methoxybenzoic acid as internal standard (aromatic region)

3.1.3.2. TLC-densitometric measurements

TLC densitometry was found to be a universal, eco-friendly method for determining dissolved products with a limit-of-quantification of nanograms. The method was taken into consideration, because of the great difference of retention factors between the products, the side-products and the remaining reactants. Furthermore, the products have characteristic UV activity. TLC densitometry has been introduced in scientific literature due to its advantages [125–128]. It is mostly utilized in the field of pharmacognosy, quantifying bioactive components of drugs and food materials such as L-theanine, histamine, cadaverine, spermidine, tyramine, putrescine, rosmarinic acid and flavonoids

[125–130]. The authors also introduced new aspects of TLC-densitometry, specifically, the use of a densitometer was changed to the use of digital cameras or even newer smartphones with camera [131]. The principle of the method relies on the simultaneous elution and recording of the reference matter (as a calibration series) and the analyte sample on the very same TLC plate. The results were calculated using the linear regression equation (Figure 3).

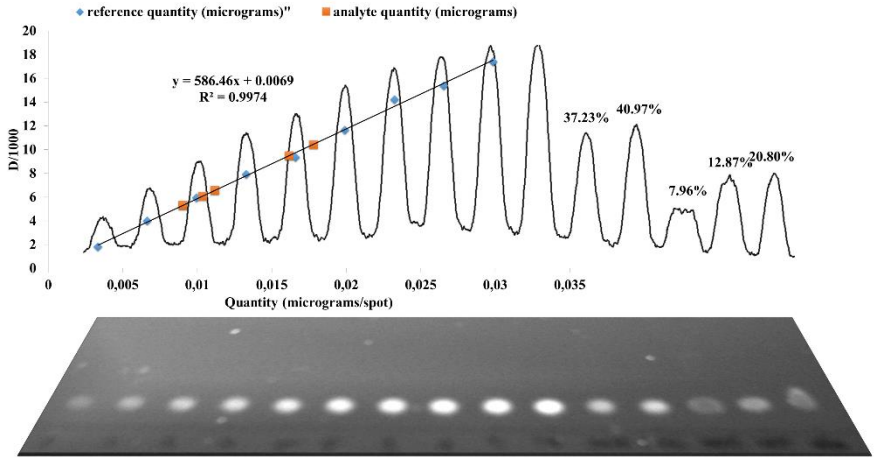


Figure 3. TLC densitometric analysis of compound **133**: record of the plate, densitogram, regression curve on graph (quantity of desired compound [μg] → optical density divided by 1000) and calculated dissolved products, conversion × selectivity [%])

TLC densitometry was found to be the universal method to quantify dissolved products, although qNMR, in the case of each test reaction, was able to validate the measurements. The results of compounds **133–135** are summarized in Table 2, while those of **138a–b** and **139a–b** are collected in Table 3. The conversions achievable in DCB could be reached or surpassed in the case of the synthesis of each compound. In the case of compound **133**, compound **134** and compound **135**, GVL, V60 and V27 were, respectively, the optimal green solvent to replace the traditional solvent, while achieving higher conversions.

Table 2. Molar percentage of dissolved product compared to the corresponding starting aniline derivative [%] in the synthesis of compounds **133–135** in DCB, GVL, DEC, V27 and V60 solvents, measured with DM and qNMR

Product	Solvent system	Dissolved product [%] (densitometry)	Dissolved product [%] (qNMR)
133	DCB	33.75	31.50
	GVL	38.34	39.45
	DEC	5.02	4.74
	V27	12.25	12.94
	V60	20.56	23.95
134	DCB	72.28	72.99
	GVL	43.34	38.25
	DEC	12.08	12.28
	V27	56.01	52.66
	V60	73.07	72.16
135	DCB	34.82	48.35a
	GVL	9.41	9.88
	DEC	10.61	5.31a
	V27	38.09	40.76
	V60	10.85	14.70a

[a] Outliers due to overlapping peaks in the 1H NMR spectra of crude products

In the case of regioisomer pair **138a–b** (Table 3), it was also demonstrated that by changing the composition of the binary solvent, a significant change can be achieved regarding regioisomeric ratios (from [2.38;3.32] : 1 (Entry 1) can be changed to [1.10;1.20] : 1). With the proposed tuneable solvent systems, a major elevation was achieved regarding the ratio of the 5-substituted product (Entry 5). Compound **138a** was not thoroughly characterized in literature. A major signal widening was found while analyzing its NMR spectra, measured in DMSO-*d6*. A chemical equilibrium was hypothesized between the enolic **138aA** and its oxo-tautomer **138aB**, thus new measurements were conducted at 285 K in $CDCl_3$ (Figure 4).

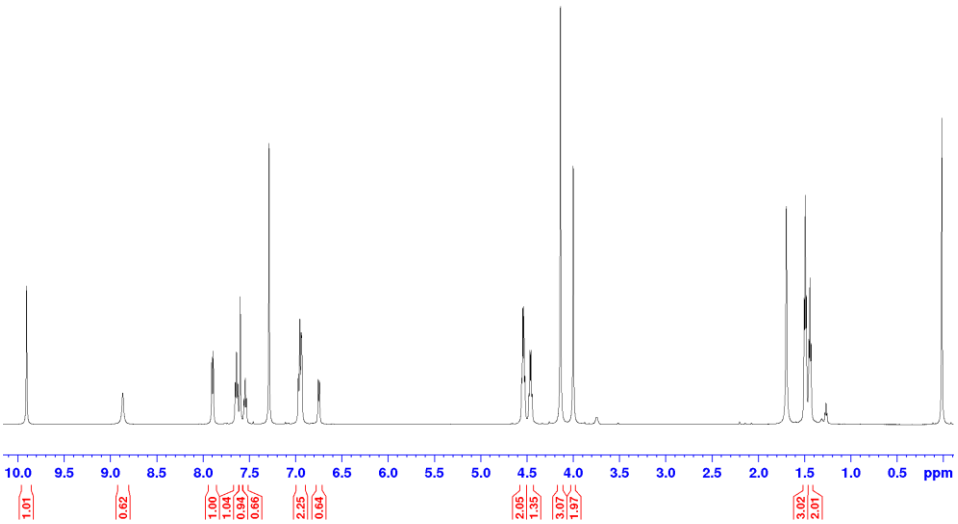


Figure 4. ^{1}H-NMR spectrum of **138a** in $CDCl_3$ at 285 K, with adequate multiplicity and the two tautomers visible

The latter measurements supported the hypothesis, at 285 K, in chloroform a chemical equilibrium is present, the enolic **138aA** being the major tautomer and the oxo-form (**138aB**) being the minor tautomer with the ratio of 1 : ~0.6. The structure of the two tautomers were proved by the assignment of protons and carbon atoms NMR analysis (Figure 5).

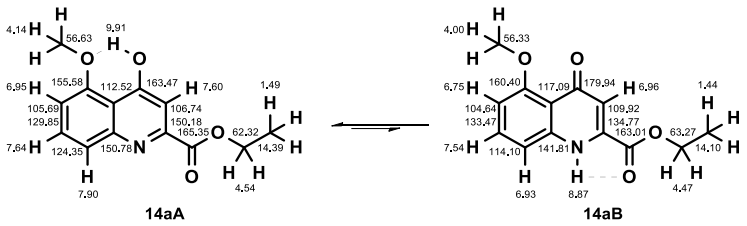


Figure 5. Oxo-enol tautomerism of **138a**, with full signal assignment

The tautomeric ratio can be explained by a hydrogen bond formation of the hydroxylic hydrogen (δ 9.91) and the oxygen of the C–5-methoxy group, forming a non-strained six membered ring in **138aA** tautomer. However, in **138aB**, only a more strained five membered ring can be hypothesized by the formation of a hydrogen bond between the *N*–H hydrogen (δ 8.87) and the oxo-group of the ethoxycarbonyl function.

Analysing regioisomer pair **139a–b**, it is proved that regioisomer ratio can be modified from 0.78 : 1 (Table 4. / Entry 7) to 1.23 : 1 (Table 4. / Entry 8), although compound **139b** had the highest dissolved quantity in V60, with the regioisomer ratio of 1.09 (Table 4. / Entry 10). We presume that the difference between the regioisomeric ratios of the two compound pairs is rooted in the substituent effect. The chloro substituent is an electron-withdrawing group, with no ability to form hydrogen bonds, while the methoxy moiety is a hydrogen-bond acceptor with high potential to form secondary bonds with the solvents either intra- or intermolecular manner. Furthermore, it has electron-donating effect towards the aromatic ring. The methoxy group also has a higher steric hindrance than the chloro substituent. Consequently, compound **138b** is the more favoured product (Table 4. / Entry 2). The ability to interfere with the ratio is more apparent in the case of compound **138** than in **139**, which can be explained by the ability of hydrogen-bond formation and the steric hindrance of the methoxy group. It can be deduced, that in the synthesis of kynurenic acid and its derivatives (**133–135**, **138a–b** and **139a–b**) prepared via the CL method, GVL and DEC can serve as green substitutes for DCB (and other non-renewable solvents) with a possibility to change regioisomeric ratios.

Table 3. Molar percentage of dissolved product compared to the corresponding starting aniline derivative [%] in the synthesis of compounds **138a–b** and **139a–b** in DCB, GVL, DEC, V27 and V60 solvents, measured with densitometry and quantitative NMR of the crude products

Product pairs	Entry #	Solvent system	Dissolved product [%]				Regioisomeric ratio [n_b/n_a]	
			Regioisomer a		Regioisomer b			
			qNMR	DM	qNMR	DM	qNMR	DM
138	1	DCB	11.26	9.43	26.8	31.28	2.38	3.32
	2	GVL	19.08	25.55	66.29	68.63	3.47	2.69
	3	DEC	no trace of product				n.d.[a]	n.d.[a]
	4	V27	13.09	12.88	27.19	23.8	2.08	1.85
	5	V60	25.66	23.9	28.21	28.6	1.10	1.20
139	6	DCB	21.17	20.54	19.23	19.77	0.91	0.96
	7	GVL	n.d.[b]	22.91	13.44	17.85	n.d.[c]	0.78
	8	DEC	n.d.[b]	7.05	6.46	8.71	n.d.[c]	1.23
	9	V27	n.d.[b]	10.49	15.30	12.78	n.d.[c]	1.21
	10	V60	n.d.[b]	19.28	19.6	21.12	n.d.[c]	1.09

[a] Regiosiomeric ratio cannot be determined due to lack of products. [b] Signals of protons could not be assigned due to overlapping peaks in the ^{1}H-NMR spectra of crude products. [c] Regiosiomeric ratio cannot be determined by qNMR due to unreliability of spectra.

3.1.4. Scale-up and isolation

After finding the optimal reaction conditions, major scale-up and adequate isolation were conducted resulting in the formation of gram-scale products **133–135**, **138a–b** and **139a–b**. Conditions of the scale-up procedures remained the same as of the test reactions, only the reaction volume was modified to 25 mL. The isolated quantities, as well as used solvent are summarized in Table 4.

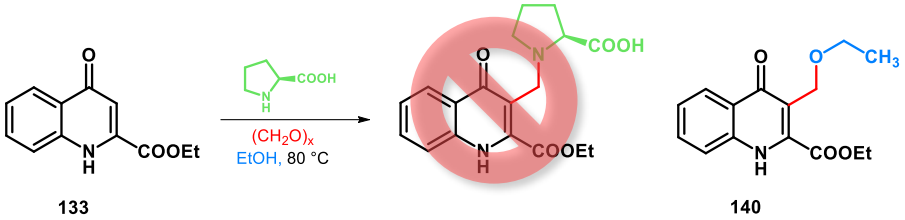
Table 4. Isolated quantities of scaled-up synthesis of compounds **133–135, 138, 139**

Compound	133	134	135	138a	138b	139a	139b
Traditional Solvent	DCB						
Isolated quantity	1.11 g (41 %)	1.07 g (37 %)	1.57 g (51 %)	0.25 g (8 %)	0.87 g (28 %)	0.81 g (25 %)	0.81 g (25 %)
Green solvent	GVL	V60	V27	GVL	GVL	GVL	GVL
Isolated quantity	1.14 g (42 %)	1.53 g (53 %)	1.64 g (53 %)	0.68 g (22 %)	1.91 g (62 %)	0.84 g (26 %)	0.81 g (25 %)

3.2. Transformation of kynurenic acid esters towards C–3 alkoxymethyl derivatives

The reaction of the ethyl ester of KYNA (**133**) with paraformaldehyde and L-proline 1.0 was conducted in absolute ethanol at 80 °C in order to yield Mannich-bases of KYNA bearing amino acid moieties. The solvent was chosen on the basis of the ability of dissolving each reactant. After reaching a maximal conversion and then purification of the reaction mixture, the analysis of the product proved that the amino acid moiety is not present in the molecule. Instead, an unexpected

product (**140**) bearing an ethoxymethylene moiety at the C–3 position was formed. Solvent ethanol acted as an *O*-nucleophile under the examined conditions, thus yielding an ether-type compound (Scheme 53).



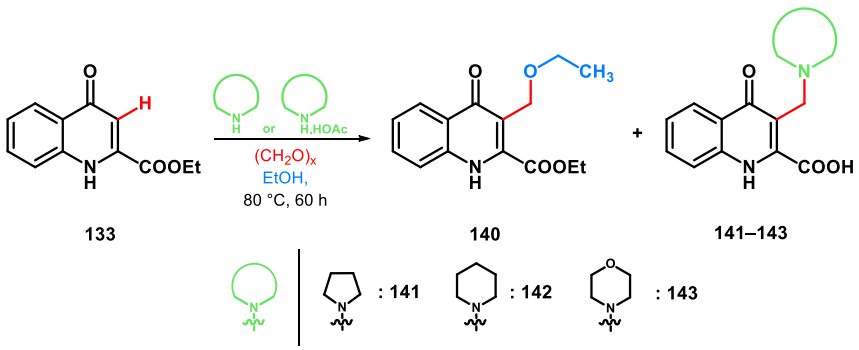
133 140

Scheme 53. Modified Mannich reaction of **133** with L-proline and paraformaldehyde

Product **140** attracted our attention, since it is a novel C–3 modified kynurenic acid derivative, able to broaden the spectrum of the possible neuroactive KYNA analogues. In the literature a wide palette of alkoxyalkylation reactions of aromatic compounds bearing active hydrogen were published.

3.2.1. Catalyst screening for the C–3 ethoxymethylation of KYNA

Having results of the preliminary reaction at hand, test reactions were conducted using common strong or weak acid or base additives *i.e.* NaOEt, Et_3N, acetic acid or *p*-TsOH (1.0 equiv.). Monitoring the reaction after 60 hours indicated no conversion. Similar observation was made in microwave-assisted reactions at 100 and 120 °C temperatures. These findings led to the conclusion that for the formation of compound **140** a secondary *N*-nucleophile is necessary. In the next step, **133** was reacted with 1.0 equiv. paraformaldehyde and 1.0 equiv. cyclic amines (pyrrolidine, piperidine and morpholine) in abs. ethanol in a pressure-resistant vessel for 60 hours to reach maximum conversion [16]. Upon monitoring the reaction, crude NMR spectra and TLC-analysis showed that using pyrrolidine and piperidine, no trace of **140** was observed. The only reaction products were aminoalkylated derivatives (**141, 142**). When morpholine, a significantly weaker base containing an *O*-heteroatom was used, ethoxymethylated compound **140** was detectable along with aminoalkylated product **143** (Scheme 53, Table 5).



133 140 141–143

Scheme 53. Reaction of **133** with cyclic amines or cyclic ammonium acetates and paraformaldehyde in ethanol

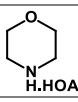
Table 5. Maximal conversion per cents measured in the reaction of **133** with cyclic amines and paraformaldehyde in ethanol

Used nucleophile		**Maximal conversion**		
Structure	pKa	Mannich base		Compound **140**
	11.00	**141**	75%[a]	-
	11.00	**142**	98%[a]	-
	8.51	**143**	92%[a]	4%[b]

[a] measured in 22.5-hour reactions at plateau, b: measured in 8-hour reaction (**140** decomposed upon longer treatment**)**

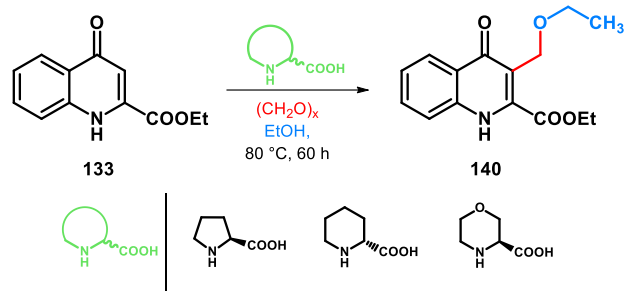
Based on this information, a series of reactions was conducted using pyrrolidine-, piperidine- and morpholine acetate, as these compounds are able to mimic the corresponding amino acids on the grounds of acidity as pyrrolidine acetate mimicked L-proline used previously. Compound **133** was reacted with 1.0 equiv. paraformaldehyde and acetates in abs. ethanol until no change was detectable in conversion (Scheme 53). Both crude NMR spectra and TLC-analysis showed that the conversion per cents of Mannich bases **141**–**143** dropped significantly in each reaction and compound **140** was detectable (Table 6).

Table 6. Maximal conversion per cents in the reaction of **133** with cyclic ammonium acetates and paraformaldehyde in ethanol

Used nucleophile			**Maximal conversion (at reaction time)**		
#		pK_a	Mannich bases		Compound **140**
	HOAc: 4.54	11.00	**141**	56% (28 h)	3% (1–3 h)
		11.00	**142**	34% (20 h)	5% (1–5 h)
		8.51	**143**	60% (12 h)	20% (9 h)

Full conversion per cents of **140** in the three test reactions were in the order of pyrrolidine acetate < piperidine acetate < morpholine acetate. These findings can be explained by either the electron-withdrawing ability of the oxygen atom in morpholine (thus making it the weakest base and strongest conjugate acid of the three compounds) or the presence of oxygen itself as a hydrogen-bond acceptor, able to coordinate an ethanol molecule.

Additional test reactions were run with L-proline (pK_a=1.94, 10.33), D-pipecolic acid (pK_a=2.06, 10.39), and (*S*)-morpholine-3-carboxylic acid (S3MCA) (pK_a=1.61, 8.52) as *N*-nucleophiles. Compound **133** was reacted with 1.0 equiv. paraformaldehyde and the mentioned amino acids in abs. ethanol until no change in conversion was detectable. Having the crude NMR spectra at hand, it was found that C–3 aminoalkylated products could not be detected in either reaction (Scheme 54).



Scheme 54. Reaction of **133** with cyclic amino acids and paraformaldehyde in ethanol

In accordance with our previous results, maximal conversion per cents of **140** in the three test reactions were in the order of nucleophiles L-proline < D-pipecolic acid < S3MCA used. These findings support the hypothesis of the importance of the oxygen heteroatom and prove that the acidic condition is necessary but it is not a sufficient factor regarding the formation of the ethoxymethylated product (Figure 6). The differences between conversions while using nucleophiles L-proline or pyrrolidine acetate and D-pipecolic acid or piperidine acetate can be explained with the steric effects regarding the ability of the nucleophilic attack between the 5-membered and 6-membered rings.

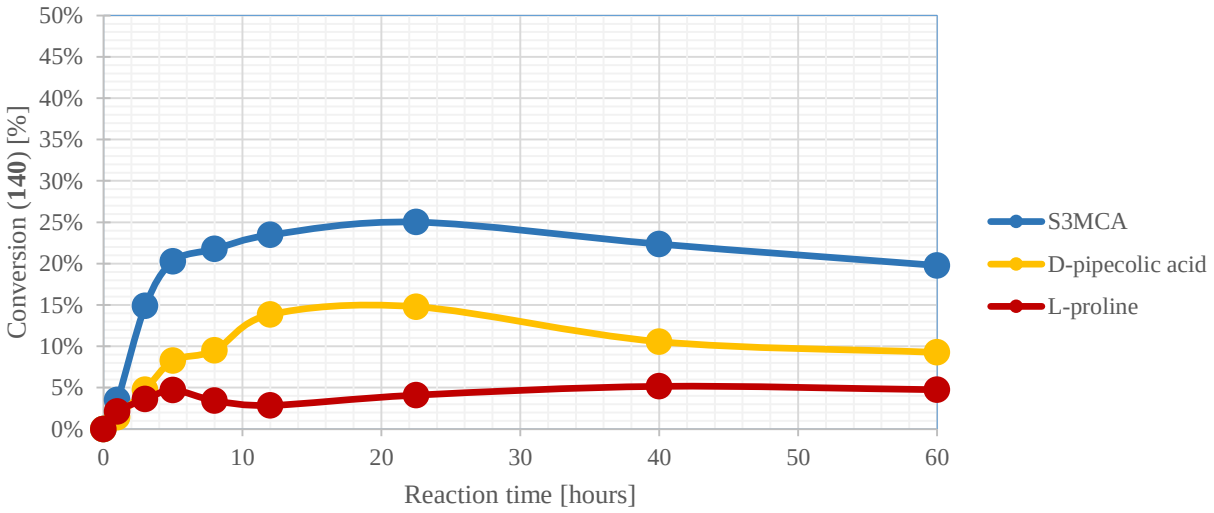
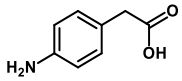
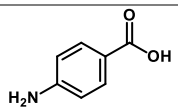
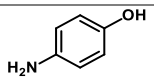
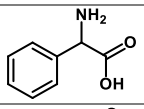
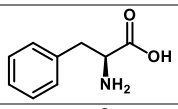
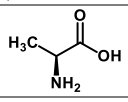
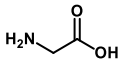
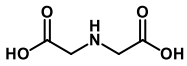


Figure 6. Conversion curves of **140** depending of the used amino acid

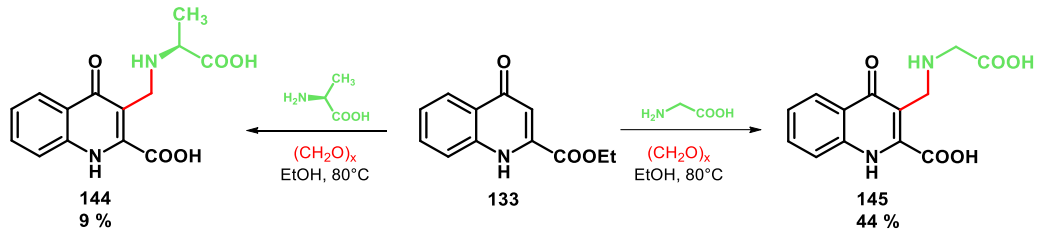
In order to clarify the previous results, eight more zwitterionic *N*-nucleophiles were utilized in the test reactions (Table 7). Compound **133** was reacted with 1.0 equiv. paraformaldehyde and the nucleophiles in abs. ethanol in a pressure-resistant vessel for 60 hours to reach maximum conversion.

Table 7. Conversion per cents in the reactions of **133** with additional zwitterionic nucleophiles and paraformaldehyde in ethanol

Entry #	Structure	pK_a	Amine character	Acid character	Outcome
1		3.39, 5.51	Primary aromatic	Aliphatic	No conversion
2		2.69, 4.77	Primary aromatic	Aromatic	No conversion
3		5.43, 10.40	Primary aromatic	Weak phenolic	No conversion
4		2.29, 8.64	Primary aliphatic, at benzylic site	Aliphatic	No conversion
5		2.47, 9.45	Primary aliphatic	Aliphatic, large side-chain	No conversion
6		2.47, 9.48	Primary aliphatic	Aliphatic, short side-chain	Aminoalkylated product (**144**)
7		2.31, 9.24	Primary aliphatic	Aliphatic, no alkyl side-chain	Aminoalkylated product (**145**)
8		2.12, 2.90, 9.63	Secondary aliphatic	Aliphatic dicarboxylic acid	15% conversion (**140**)

Both crude NMR spectra and TLC-analysis showed no conversion of **133** in the case of nucleophiles in entries 1–5. Utilizing iminodiacetic acid (Table 7. / Entry 8), the maximal conversion per cent of **140** was found to be 15%, which is significantly lower than that achieved with S3MCA additive. This information led to the deduction that only secondary *N*-nucleophiles facilitate the formation of compound **140**. Iminodacetic acid being a potent acidic secondary amine nucleophile, the hypothesis is verified that for the ethoxymethylation reaction, an acid functional group on the nucleophile is necessary but not sufficient. Furthermore, the hydrogen-bond acceptor *O*-heteroatom is proposed to coordinate ethanol.

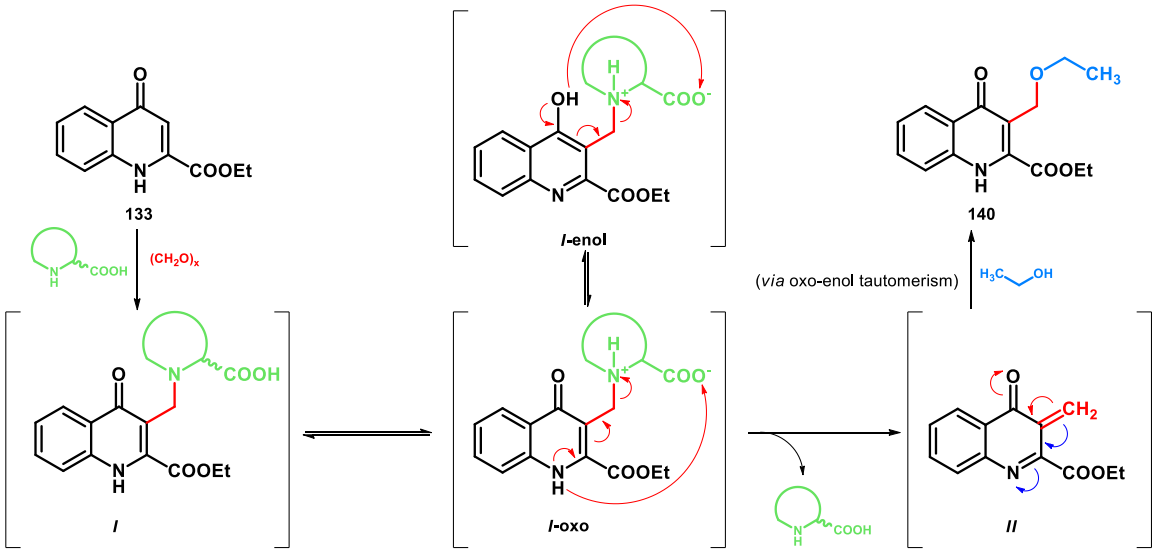
In the case of primary amino acid nucleophiles with side chains of negligible steric hindrance L-alanine and glycine, stable Mannich bases **144**, **145** formed (Table 7. / Entries 6,7). It should be emphasized that in the case of compound **145** fair conversion and yield could be achieved (44%), although **144** formed in a significantly lower conversion and yield (9%) thus setting the scope and limitations of the original aim of the modified Mannich reaction of KYNA esters with amino acids (Scheme 55).



Scheme 55. Reaction of **133** with primary amino acids and paraformaldehyde in ethanol

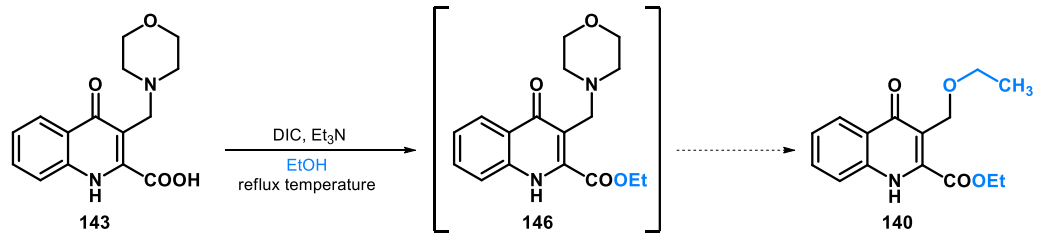
3.2.2. Mechanism assessment *via* analogous transformations

In addition, we aimed to explore the mechanism of the ethoxymethylation reaction. It was hypothesized that first an unstable Mannich base forms (***I*** and zwitterionic ***I*-enol** and ***I*-oxo**) with the secondary amino acids. Next, upon the elimination of the amino acid, an *ortho*-quinone methide (***II***) forms which, *via* Michael addition, leads to compound **140** (Scheme 56).



Scheme 56. Proposed mechanism of formation of **140** starting from compound **133**, using secondary amino acids and paraformaldehyde in ethanol

In order to elaborate the previous mechanism, esterification of compound **143** was conducted. Since utilizing thionyl chloride yielded complex reaction mixture, other coupling reagents (DIC, DCC, EDAC.HCl, CDI, HCTU, Ac_2O) were tested. Among these, *N*,*N*'-diisopropylcarbodiimide (DIC) in abs. ethanol at reflux temperature gave the highest conversion (Scheme 57).



Scheme 57. Esterification of Mannich base **143** with coupling agent DIC in ethanol

TLC and crude NMR analysis showed full converison of compound **143** (Figure 7/A and B). Besides the formation of the aminoester (**146**), **140** also started to form as a side-product with

approximately 1 to 7.7 molar ratio (Figure 7/B). Characteristic signals could be assigned to compound **146**. Note, however, that the signals of compound **140** are also detectable. The reaction was quenched and worked-up at that point. Surprisingly, after the work-up process and chromatographic purification, **140** was found to be present in significantly higher (2 to 3) molar ratio in comparison to **146** (Figure 7/C) thus proving that compound **146** is highly prone to transformation to **140** also encumbering its isolation.

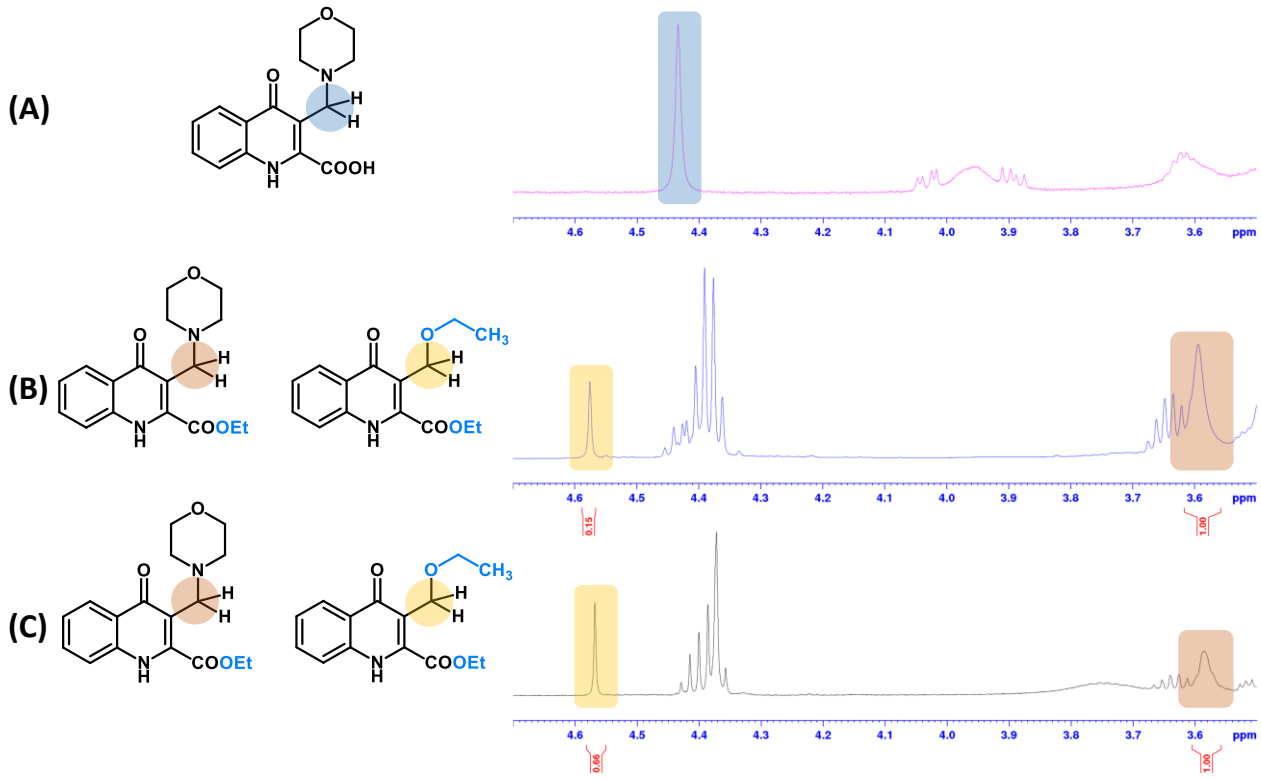


Figure 7. Crude NMR spectra of the esterification reaction of **143** with coupling agent DIC in ethanol

Formation of **140** indirectly proved the unstable amino acid Mannich ester (***I***) → *ortho*-quinone methide (***II***) → **140** route shown in Scheme 56. According to our proposed explanation, first the unisolable Mannich product ***I*** forms. Thanks to its zwitterionic trait, autoprotonation occurs yielding a quaternary ammonium compound at the benzylic site with good leaving group property. After the *retro*-Mannich type elimination of the amino acid, *ortho*-quinone methide (***II***), an excellent Michael acceptor forms, which readily reacts with the *O*-nucleophile solvent ethanol to form **140**.

3.2.3. Condition optimalization and broadening scope

As a next step the optimal equivalence of (*S*)-morpholine-3-carboxylic acid was investigated in the reaction. It was chosen for equivalence optimization as the highest conversion towards **140** could be achieved with this additive. In order to clarify the role of the catalyst, additive or reagent in the reaction, four test reactions were conducted with different equivalences. Compound **133** was

reacted with paraformaldehyde and S3MCA (0.1, 0.5, 1.0, and 2.0 equiv.) in abs. ethanol until maximum conversions were observed. Crude NMR spectra of samples taken from the reaction chambers were analyzed and conversion curves were drawn (Figure 7).

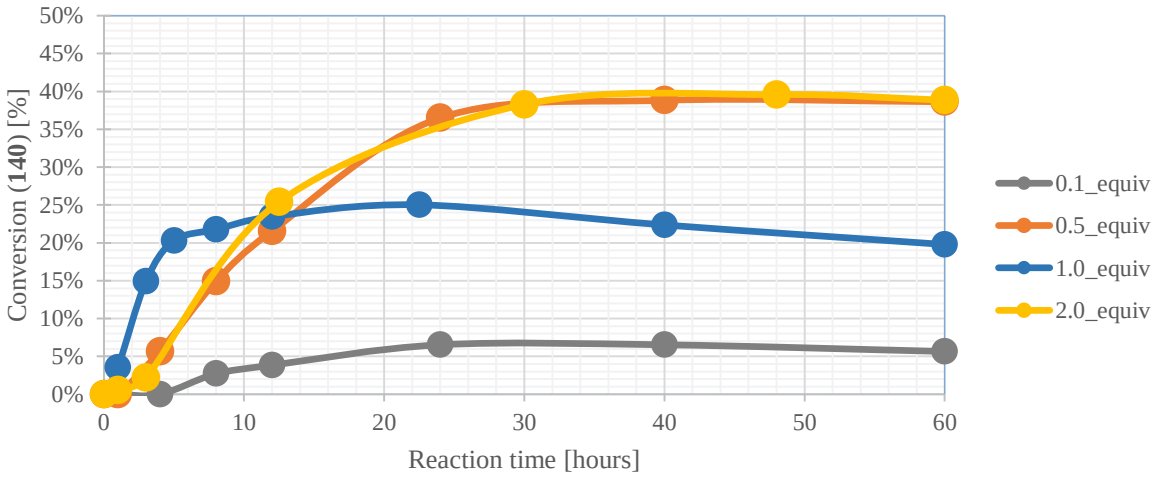


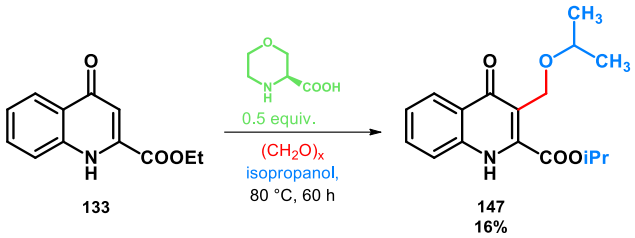
Figure 8. Conversion curves (**140**) of the C–3 ethoxymethylation of **133** using different equivalents of S3MCA

The curves showed that a significant decrease in conversion occurred when applying 0.1 equiv. in contrast to the utilization of 1.0 equivalent. When using 2.0 equiv., the conversion of **140** measurably increased thanks to the higher molar ratio of the nucleophile. Interestingly, the optimal equivalent of S3MCA was found to be 0.5, an additive-range equivalent. Analyzing crude NMR spectra it can be hypothesized that lower nucleophile concentration subdues certain side reactions thus leading to higher conversion. These findings are supported by crude NMR-spectra since, in the case of the reaction with 0.5 equiv. S3MCA, less unidentifiable signals can be observed in contrast to using 1.0 or 2.0 equivalents of additive.

Our next objective was to expand the scope of the reaction with diverse aldehyde or alcohol components. First, we changed the aldehyde. Compound **133** was reacted with 1.0 equiv. of the corresponding aldehyde (benzaldehyde, butyraldehyde, and phenylacetaldehyde) and 0.5 equiv. S3MCA additive in abs. ethanol. Both TLC and crude NMR analyses showed no conversion. A possible explanation of the failure of the reaction is the steric hindrance of the corresponding aldehydes. Next, we modified the alcohol component in the reaction. We started with methanol the simplest alcohol followed by using bulkier primary, secondary, and tertiary alcohols. Kynurenic acid methyl ester [132] was reacted with 1.0 equiv. paraformaldehyde and 0.5 equiv. S3MCA in methanol for 60 hours at 80 °C in a closed vessel. TLC and crude NMR analyses showed the formation of a complex reaction mixture from which the desired product was not possible to isolate.

Henceforth, compound **133** was reacted with 1.0 equiv. paraformaldehyde and 0.5 equiv. S3MCA in isopropyl alcohol for 60 hours at 80 °C in a pressure-resistant vessel in order to produce

the alkoxymethylated product. It was found that transesterification to the isopropyl ester occurred simultaneously to isopropoxymethylation. Only compound **147** formed (21% maximal conversion in 26-hour reaction, Scheme 58).



Scheme 58. Reaction of **133** with paraformaldehyde in isopropyl alcohol

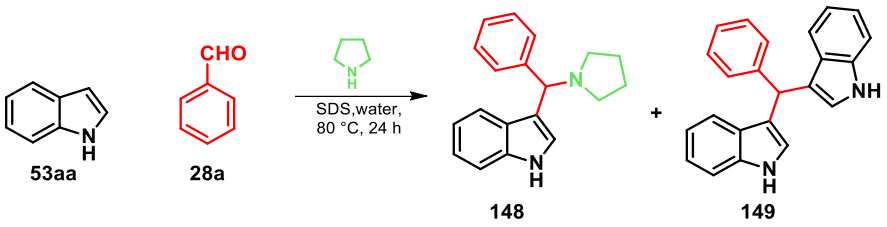
Conducting the reaction in *t*BuOH, a bulky tertiary alcohol, no conversion was observed after 60 hours under the previously set conditions, thus setting the scope and limitations of the secondary aminoacid-mediated alkoxyalkylation reaction of kynurenic acid esters.

3.3. Synthesis of indole-coupled KYNA triarylmethanes *via retro*-Mannich reaction

The following research focused on the transformation of kynurenic acid towards indole-coupled triarylmethane derivatives *via* the exploitation of the Mannich-subsequent *retro*-Mannich reaction.

3.3.1. Reactions of indole based Mannich-derivatives with KYNA ethyl-ester

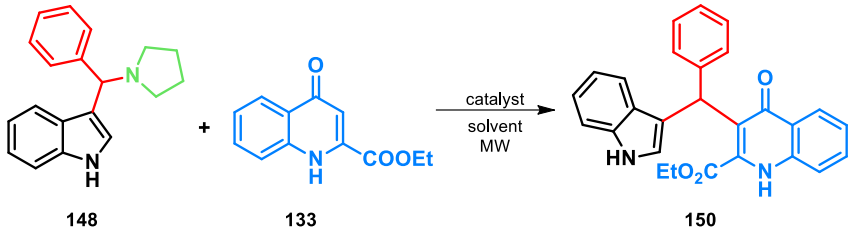
First, the reaction between the Mannich base of indole and KYNA ethyl ester was planned (route A). To synthesize the Mannich base of indole (**148**), several literature methods have been explored. Reactions utilizing catalysts, such as ferric phosphate [133] and iodine [134] or protic solvents such as ethanol, methanol [135], and ethylene glycol [136], resulted mainly in bisindole derivative **149** mentioned in the corresponding literatures as a byproduct. However, Mannich base **148** could be synthesized under neat conditions applying only indole, benzaldehyde, and pyrrolidine (with or without L-proline as catalyst [31,137]). Surprisingly, the highest yield was achieved through the application of the surfactant sodium dodecyl sulfate (SDS, Scheme 59) [138].



Scheme 59. The synthesis of aminoalkylated indole derivatives

The starting material having been synthesized, in the first C–C bond-forming reactions, **148** was reacted with the ethyl ester of KYNA (**133**) in MeCN at 100 °C (under MW conditions) with

thiourea as catalyst, based on the work of Baruah *et al.* [28] (Scheme 60). The conversion determined by NMR spectrometry was low; thus, the best conditions used for the alternative reaction route [29] were investigated showing promising results (Table 8). Fortunately, the still low yield of **150** could be further improved by raising the reaction temperature to 160 °C. However, any further increase caused the decomposition of the starting materials.



Scheme 60. Route A: synthesis of KYNA TRAMs through indole-based Mannich products

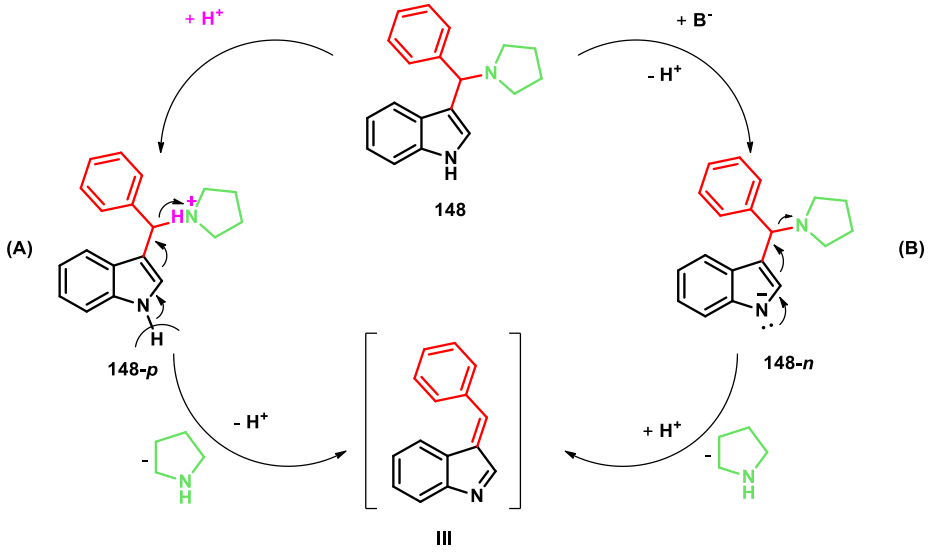
Table 8. Optimization of the synthesis of **150.**

Entry #	Solvent	Catalyst	Temperature (°C)	Time (min.)	Conversion (%)[a]
1	MeCN	thiourea	100	10	5
2	toluene	*p*TsOH	100	180	20
3	toluene	*p*TsOH	130	180	60
4	toluene	*p*TsOH	160	90	80[b]
5	toluene	-	160	90	5
6	toluene	thiourea	160	90	40
7	toluene	L-proline	160	90	65
8	toluene	TEA	160	90	70
9	DCB	*p*TsOH	160	90	0
10	MeCN	*p*TsOH	160	90	10
11	anisole	*p*TsOH	160	90	5
12	EtOH	*p*TsOH	160	90	0
13	water	SDS	160	60	0

[a] determined from crude NMR spectra
[b] work-up performed to isolate 150 (yield: 62%)

The use of a catalyst was crucial, as the desired TRAM did not form without the use of a base or an acid catalyst. Although acid catalysis resulted in somewhat higher conversion, both acid and base catalysis could enhance the synthesis of **150**. Baruah *et al.* hypothesized that the reaction taking place between the indole derivative and varied electron-rich aromatic structures involves the formation of intermediate **III** [28,29]. In their proposed elimination–addition pathway starting from a Mannich base of indole, thiourea activates the amine moiety of the aminoalkyl function through double hydrogen bonding and converts it into a better leaving group. Concerning triethylamine (TEA), used in our reactions, a hydrogen bond is unable to form and, therefore, a more direct form of catalysis is proposed. Through the application of high temperature and TEA, the deprotonation of the indole moiety takes place followed by a subsequent rearrangement of the indole anion into benzylidene intermediate **III**. Then the latter is attacked by a molecule of the electron-rich KYNA

yielding compound **150**. It is also surmised that the C–*N* bond cleavage of the indole derivative could also take place through the elimination of pyrrolidine *via* the protonation of the amine moiety elevating its leaving property, thus leading to intermediate **III**.

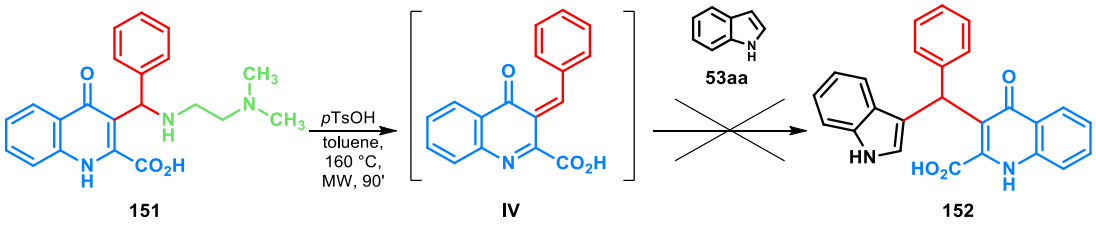


Scheme 61. Proposed mechanisms in the case of acid (A) or base (B) catalysis

Further optimization of the reaction involved the change of solvent from the aprotic and apolar toluene to solvents representing a wider range of the aprotic–protic and apolar–polar scale (Table 8). It is hypothesized that toluene may be the best solvent because of the lack of H-bridge bonds and polarity of the solvent can contribute to a more unstable, thus more reactive intermediate.

3.3.2. Reactions of KYNA based Mannich-derivatives with indole

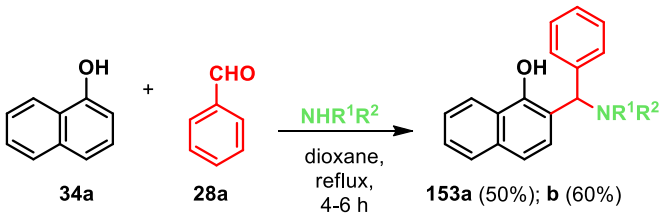
After successfully optimizing the reaction through route A, the synthesis of **150** was planned through the reaction of the KYNA Mannich base with indole (route B). KYNA Mannich derivatives synthesized previously are abundant [16]; however, compounds containing the crucial phenol structure were narrowed down only to a single compound (**151**, Scheme 62). Unfortunately, using this derivative in the reaction under conditions optimized previously did not result in the desired compound.



Scheme 62. Route B: synthesis of KYNA TRAM through aminoalkylated KYNA

It is presumed that this may be due to the *N*,*N*-dimethylaminoethyl moiety being a bad leaving group. In order to fully support this hypothesis a synthetic procedure was applied. Unfortunately, a Mannich base of KYNA containing a secondary amine function, could not be synthesized, which is

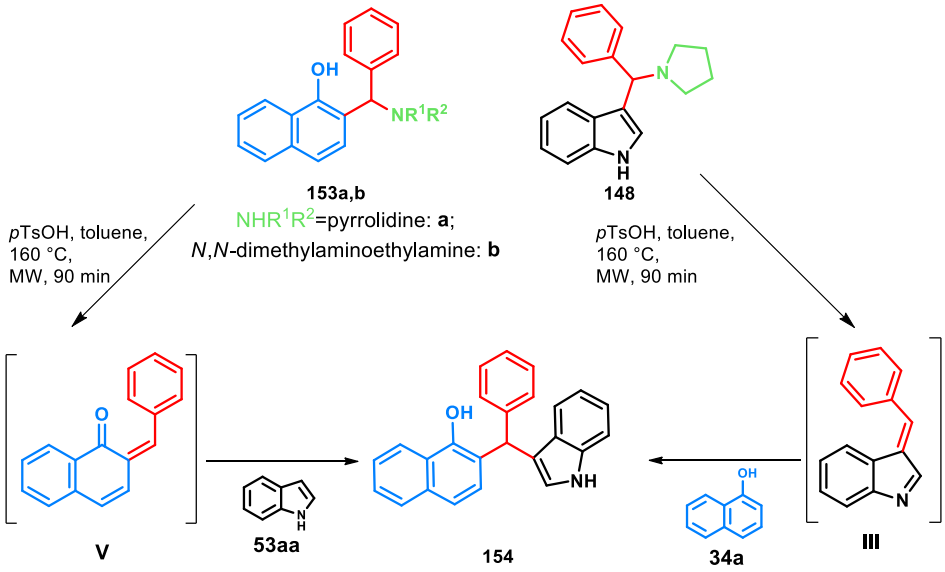
probably due to steric hindrance. Thus, considering the similarity of 1-naphthol to KYNA [16], the synthesis of Mannich bases **153a,b** was carried out as shown in Scheme 63.



NHR^1R^2=pyrrolidine: **a**; *N*,*N*-dimethylaminoethylamine: **b**

Scheme 63. Synthesis of aminoalkylated 1-naphthol derivatives **153a,b.**

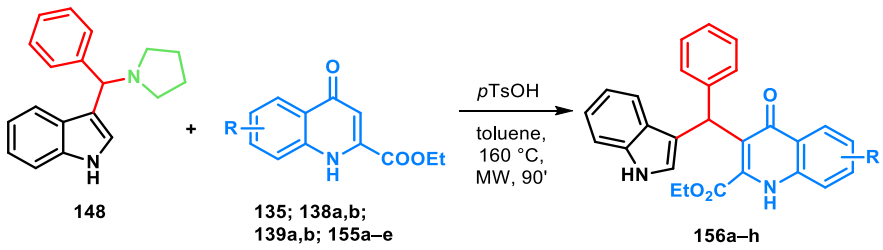
A comparison of the reaction of 1-naphthol with **133** and the reactions of **153a**,**b** with indole (Scheme 64) allows to arrive at two conclusions: (*a*) Mannich bases containing secondary amines are less prone to undergo the transformation because of a bad leaving group character, and (*b*) reactions through intermediate **III** are more preferred compared to reactions via possible *ortho*-quinone methide intermediates **IV** and **V** derived either from **148** or from the Mannich bases of 1-naphthol (**153a,b**). This may be due to a possible hydrogen bridge between the hydroxy/oxo group in **153a,b** and **148** and the amine moiety, making the protonated form a more stable intermediate.



Scheme 64. Comparison of the syntheses of **154**. Conversions: starting from **153a** 10 %, **153b** ~1 %, **148** 99 %. Yield of **154** starting from **148**: 70%.

3.3.3. Broadening the scope of the synthesis of KYNA-indol triarylmethanes

To further investigate the scope and limitations of the reaction, the synthesis of TRAMs containing different KYNA derivatives was planned (Scheme 65). The reactions were carried out applying the optimized conditions (see Table 9, Entry #4) starting from KYNA derivatives substituted at the B ring. The reactions resulted in a diverse range of compounds (**156a-h**).



R=5-Cl: **139a, 156a**; 6-Cl:**155a, 156b**; 7-Cl:**139b, 156c**; 8-Cl:**155b, 156d**;
5-OMe: **138a, 156e**; 6-OMe: **135, 156f**; 7-OMe: **138b, 156g**; 8-OMe: **155c, 156h**

Scheme 65. Synthesis of 5–8 substituted KYNA-indole triarylmethanes

Table 9. Comparison of the reactivity of substituted KYNA derivatives

Entry #	Precursor	Temperature	Time (h)	Conversion (%)[a]	Yield (%)
1	**139a**	160	3	60	44
2		reflux	8	99	91
3	**155a**	160	3	60	49
4		reflux	8	90	83
5	**139b**	160	3	70	62
6		reflux	8	85	76
7	**155b**	160	3	60	53
8		reflux	8	50	38
9	**138a**	160	3	30	18
10		reflux	8	90	81
11	**135**	160	3	45	34
12		reflux	8	70	58
13	**138b**	160	3	60	48
14		reflux	5	99	95
15	**155c**	160	3	10	5
16		reflux	18	20	10

[a] determined from crude NMR spectra

In the case of derivative **138a**, the reaction applying microwave as a heat source resulted in an exceptionally low conversion. To test whether a kinetic control takes place during the transformation, a longer reflux treatment was carried out. As the result with an almost full conversion was promising, reflux conditions were applied to the other derivatives as well, showing a general increase in conversions supporting our hypothesis.

It is interesting to mention that the type of substituents on the B ring influenced the reactions to a lesser extent (*e.g.*, Table 9, Entry #2 and #10) compared to the position of the substituents (*e.g.*, Table 9, #10 and #16). Both chloro- and methoxy-KYNA derivatives, with substituents at C–5 and C–7, showed somewhat lower reactivity compared to the ethyl ester of KYNA (longer reaction times were needed). However, the same substituents in positions C–6 and C–8 caused a significant decrease in reactivity of the KYNA skeleton.

4. Summary

1. Synthesis of biologically prosperous kynurenic acid derivatives were investigated and optimized for one-batch, two-step microwave-assisted reactions. Utilizing both chemically and biologically representative non-, methyl-, methoxy- and chlorosubstituted aniline derivatives, in catalyst-free conditions, 2–3.5 hour timeframe syntheses of seven kynurenic acid derivatives were introduced. Crucial parameters including reaction time, reaction temperature, solubility, concentration and molar ratio of substrates along with overall reaction volume were determined, investigated and optimized. Four green, tuneable solvent systems made of DEC and GVL were introduced as substitutes for DCB as reaction medium in each synthesis. The performance of the green solvent systems was highlighted, because of their ability to be used in microwave-assisted reactions. Yields are not lower than those found in traditional solvents. Moreover, the potential of the tuneable solvent system to regulate regioisomeric ratios in CL synthesis was emphasised.
2. Both the synthetic method itself and the analytical technique were designed on the basis of the concept of green chemistry. The benefits of TLC-densitometry, a rapid, eco-friendly, inexpensive analytical technique, were revealed in the case of reaction monitoring and conversion analysis compared to quantitative NMR. Gram-scale scale-up was accomplished in the halogenated solvent DCB and, most importantly, in green substitutes with the solvent-performance similar to preliminary experiments. These synthetic methods facilitated the CL synthesis of unsubstituted and several substituted kynurenic acid analogues.
3. Novel C–3 alkoxymethylated derivatives of kynurenic acid were synthesized with cyclic secondary alpha amino acid additives *via* the hypothesized retro-Mannich cleavage of the intermediates. The importance of a secondary acidic N-nucleophile was proven. Test reactions were conducted using common organic additives, including cyclic amines and their acetate salts, as well as using other acidic N-nucleophiles. Result showed the importance of the local acidic conditions, particularly when using amino acids. The importance of the corresponding heterocycle and its ability to coordinate the *O*-nucleophile were also highlighted.
4. A mechanism of the alkoxyalkylation of kynurenic acid ethyl esters was proposed on basis of the literature of *retro*-Mannich C–*N* cleavage of Mannich bases moreover, via the conduction of analogous reactions, indirect proof was presented regarding the reaction mechanism. The optimal equivalence of the amino acid was found considering both economic and preparative reasons. The findings supported that the used amino acid should be in the additive-range (*i.e.* 0.5 equiv.) which both elevates conversion and selectivity towards the desired products, also subdue side-reactions encumbering the work-up processes.

5. Two novel kynurenic acid derivatives, containing glycine or L-alanine fragments were synthesized, thus proving the scope and limitations of the aminoalkylation reaction of kynurenic acid ethyl ester using alpha amino acids. Limitations were set of alkoxyalkylation reactions and two novel kynurenic acid derivatives were synthesized bearing ethoxymethyl or isopropoxymethyl moieties at the site C-3.
6. The synthesis of TRAM bioconjugates consisting of indole and the ethyl ester of kynurenic acid has been accomplished. The reactions took place through the cleavage of the C–*N* bond of indole Mannich bases and subsequent C–C bond formation between the benzylidene intermediate and KYNA. On the basis of acid and base catalysis, two possible catalytic pathways are hypothesized, both promoting the elimination of the amine moiety. An alternative reaction route starting with the Mannich bases of KYNA and its structural analogue 1-naphthol was also investigated showing a prominent tilt toward the synthesis applying the Mannich base of indole involving the benzylidene intermediate.
7. To further investigate the scope and limitations of the reaction, KYNA derivatives bearing chemically and biologically prosperous chloro and methoxy groups were also reacted yielding a wide variety of new TRAM KYNA derivatives with possible bioactivities.

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ANNEX