University of Szeged
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Syntheses and transformations of nitrogen-containing naphthol analogues

Ph.D. Thesis

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Szeged, Hungary
2023

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PUBLICATIONS

Papers related to the thesis

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

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

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

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

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

Other publication

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

Conference lectures

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

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

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

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

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

ABBREVIATIONS

CH_2O – Formaldehyde

β-OH-D-Phe – Beta-hydroxy-D-phenylalanine

β-OH-L-Phe – Beta-hydroxy-L-phenylalanine

Bn – Benzyl

DCM – Dichloromethane

DMF – *N,N*-dimethylformamide

EtOAc – Ethyl acetate

Formalin – Aqueous solution of formaldehyde

GABA – Gamma-aminobutyric acid

Gly – Glycine

HIQ – Hydroxyisoquinoline

HQ – Hydroxyquinoline

KYNA – Kynurenic acid

L-*i*Asn – L-isoasparagine

L-Asp – L-aspartic acid

L-Glu – L-glutamic acid

L-Met – L-methionine

L-Ser – L-serine

MAPK – Mitogen-activated protein kinase

MetAP – Methionine aminopeptidase

MDR – Multidrug resistant

MW – Microwave irradiation

n.d. – No data available

o-QM – *ortho*-quinone methide

p-TSA – *para*-toluenesulfonic acid

Ph – Phenyl

r.t. – Room temperature

Rce1 – Ras converting enzyme 1

TLC – Thin-layer chromatography

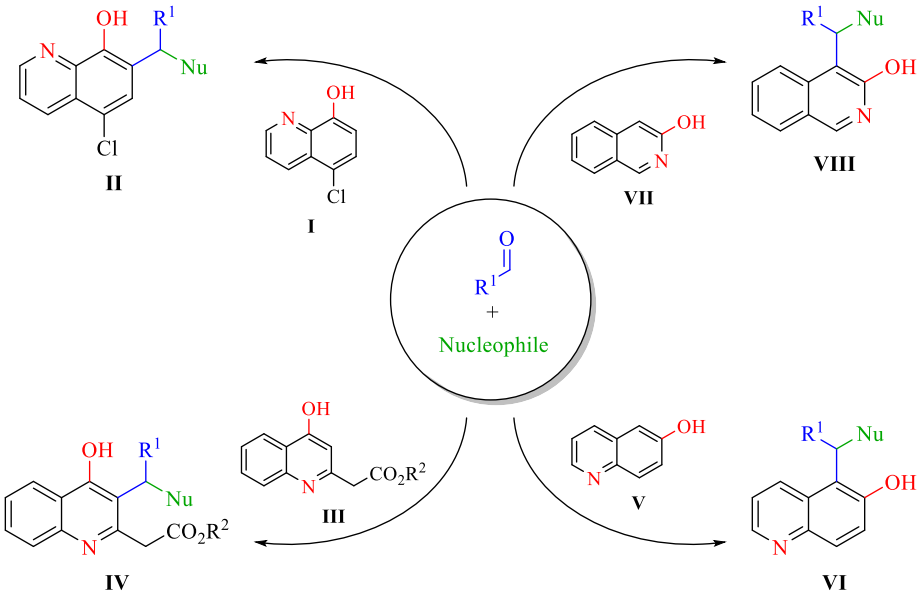
1. INTRODUCTION AND AIMS

The Mannich reaction is a frequently utilised organic chemical transformation resulting in the formation of a C–C single bond. In this three-component reaction, the components – a primary or secondary amine, an aldehyde and a compound having a hydrogen of pronounced activity – can be converted to the corresponding aminoalkylated product under relatively mild conditions. The essence of the Mannich reaction is that the active H is replaced with an aminomethyl group – if formaldehyde (CH_2O) is the aldehyde component – or a substituted aminoalkyl moiety – if any other aldehyde is applied. During the reaction 1 molar equivalent of H_2O byproduct is formed. The procedure is named after Carl Mannich,[1] whose systematic research in this particular field started in 1912.[2] However, similar condensation reactions were already performed before him, including German patents from 1896 (DE89979) and 1897 (DE90907, DE92309) by Bayer & Co.[3–5] In the first patent, the procedure included the transformation of dimethylamine, formaldehyde with phenol and naphthol derivatives, as well as the reaction of piperidine, formaldehyde and 1-naphthol. It was suggested that the hydrogen of the phenolic OH group reacts with the aldehyde and amine resulting in alkylaminomethoxy derivatives. The structures in patent DE92309 were corrected, which thus correspond to the structures known today as Mannich products. Franz Sachs published his work on the condensation of piperidine, formaldehyde and phthalimide in 1898 and so did Herm Hildebrandt reporting the condensation of piperidine, formaldehyde and various phenols and 2-naphthol in 1900.[6,7] Mario Betti's research was launched in 1900, who reacted ammonia, benzaldehyde and 2-naphthol.[8,9] In recognition of his extensive efforts, when a naphthol or a phenolic compound is the provider of the active hydrogen, the reaction is used to refer to as the Betti reaction and the condensation product as Betti base.[10] Further researchers, who also studied this type of condensation, are van Marle and Tollens,[11] Schäfer and Tollens,[12] Auwers and Dombrowski,[13] Petrenko-Kritschenko and Zoneff,[14] Petrenko-Kritschenko and Petrow,[15] Petrenko-Kritschenko,[16] Petrenko-Kritschenko and Schöttle.[17] In recent times, the process has garnered noteworthy consideration due to the versatile nature of its constituents, the employment of gentle reaction conditions and the potential pharmacological activity of the final products.[18–21]

One possible extension of the Mannich reaction is the application of nitrogen-containing naphthol analogues, *i.e.*, hydroxyquinolines (HQs) and hydroxyisoquinolines (HIQs). One of the first bioactive HQs discovered is 8-hydroxyquinoline (8HQ), which itself is a well-known antipathogenic and chelating agent.[22] It has many derivatives with more or less similar properties including clioquinol, chlorquinaldol, chloroxine, broxyquinoline, iodoquinol, nitroxoline and tilbroquinol.[23–29] Procaterol is a β_2 adrenoreceptor agonist used in the treatment of asthma.[30] In

contrast, a 4HQ derivative with a propranolamine chain proved to be a more potent β-adrenergic receptor blocker *in vivo* in a rat preparation than propranolol.[31] The first 3-carboxyl-substituted 4-hydroxyquinoline with antibacterial effect was discovered serendipitously. It was an intermediate byproduct in chloroquine synthesis, leading to the development of fluoroquinolone antibiotics.[32] Further 3-carboxylic acid derivatives and approved medicines are elvitegravir (treatment for HIV-1 infection) and ivacaftor (treatment for cystic fibrosis).[33,34] The 2-carboxylic acid derivative of 4HQ is kynurenic acid (KYNA), which is an endogenous metabolite produced in both humans and rodents; moreover, it is a potential neuroprotective agent.[35] Some 4HQ and 3HIQ derivatives were tested as matrix metalloproteinase inhibitors;[36] nonetheless, some 6HQs are potential antiviral agents against hepatitis B.[37]

My Ph.D. work focused on the investigation of different nitrogen-containing 1- and 2-naphthol analogues in the Mannich reaction and the extension of the reaction using secondary amines and aldehydes. The aminoalkylation of 8HQ derivatives have been studied,[38–41] but the Mannich products possess low water solubility, which is undesirable when biological applicability is in the focus. Therefore, the synthesis of new water-soluble substrates (**II**) starting from 5-Cl-8HQ (**I**) – as a 1-naphthol analogue – was the first aim of my Ph.D. work by using functionalised secondary amines and formaldehyde. The next aim was the investigation of 4HQ derivatives, also as 1-napthol analogues. In earlier studies,[42,43] the reactivity of KYNA has been tested excluding its homologues compound 2-(4-hydroxyquinolin-2-yl) acetic acid (**III**). Accordingly, the synthesis and transformations of this latter compound were planned to obtain Mannich bases (**IV**) by using a secondary amine and formaldehyde or aromatic aldehydes. Since the reaction of 2-naphthol with 2-naphthaldehyde and *N*-benzylmethylamine revealed an unexpected transformation,[44] the final aim was to test the scope and limitations of this reaction starting from 6HQ (**V**) and 3HIQ (**VII**) as *N*-containing 2-naphthol analogues to gain **VI** and **VIII** derivatives.



2. LITERATURE

Syntheses of aminomethylated 8-hydroxyquinolines

Among the near infinite Mannich derivatives of HQs and HIQs, 8HQs have prominent place in medicinal chemistry.[45] In this framework, Mannich derivatives in which the 8HQ and amine function are linked by a CH_2 bridge will be reviewed. These compounds are synthesised by treating the 8HQ core with formaldehyde (paraformaldehyde or formalin, its aqueous solution) and an amine. These derivatives also possess diverse pharmacological activities. The antipathogenic effect is one of the most studied areas, including different mechanisms of action: increasing cell membrane permeability,[46] inhibition of MetAP1,[47,48] ubiquinone synthesis,[49] or type III secretion.[50,51] Antifungal activity of these 8HQs has been assessed among human[48,52,53] and phytopathogens.[54,55] Furthermore, a potential antiprion compound has also been identified.[56] Clamoxyquine is an effective drug for treating whirling disease in rainbow trout.[57] Recently, a large group of aminomethylated 8HQs has been designed to combat cancer. There are derivatives that act via inhibiting DNA biosynthesis,[46,58] MetAP2,[59] JMJD2C,[60] and Rce1.[61] MDR-targeting agents have been studied as well,[39,41] while in some derivatives, the metal-binding property has been utilised to enhance the antiproliferative activity.[62,63] The effect on the MAPK pathway,[63] the caspase-dependent apoptotic pathway[64,65] and survivin have also been examined,[66,67] while some 5-nitro compounds were associated with inhibition of Cathepsin B.[68–71] In the last few years, potential neuroprotective agents have been identified to treat Alzheimer's disease by influencing multiple intramolecular targets.[72–75] Concerning the central nervous system, dopamine D2 receptor[76,77] and inward rectifier potassium channels[78] have also been targeted with 8HQ Mannich products.

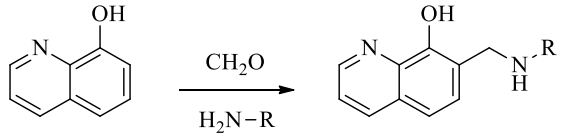
The next sections are divided according to the structure of the applied amine and 8HQ.

2.1. Syntheses of Mannich bases by using primary amines

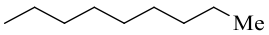
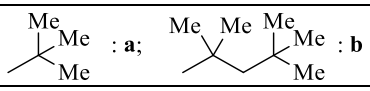
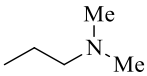
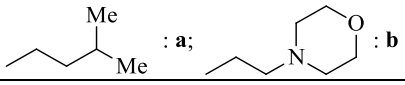
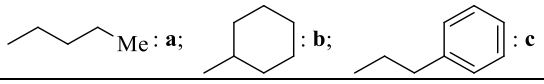
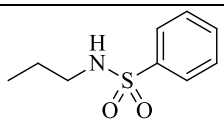
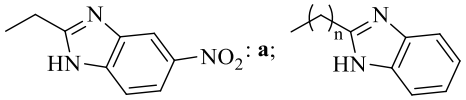
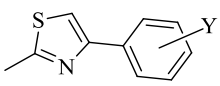
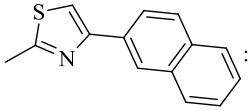
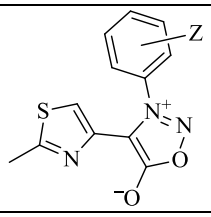
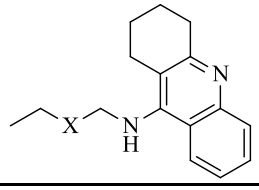
Various primary amines were reacted with 8HQ (**1**) and formaldehyde (CH_2O) resulting in the formation of Mannich bases **2**–**13** (Table 1). Compound **2** was synthesised by Zaoui *et al*. by treating **1** with aqueous solution of CH_2O (37%; hereinafter formalin) and *n*-octylamine in EtOH.[79] Fields carried out the synthesis of **3a,b** in two steps: first an azomethine was obtained from CH_2O and the corresponding amine, and subsequently it was stirred with **1** in benzene (**3a**) or without solvent (**3b**).[80] Burckhalter *et al.* used N^1,N^1-dimethylethane-1,2-diamine and paraformaldehyde to transform **1**. After stirring the components in EtOH and then removing the solvent, the mixture was treated with hydrogen chloride gas in excess, isolating **4** in an excellent yield.[81] Xie and Ding reacted 3-methylbutan-1-amine or 2-morpholinoethylamine with **1** and

paraformaldehyde for 4 hours under reflux conditions, resulting in **5a**,**b**.[60] The synthesis of **6a–c** was performed by Manetti *et al*. by applying **1**, paraformaldehyde and the appropriate amine.[82] The synthesis of various Mannich products were published by Mohammed *et al.,* including 7-((phenylamino)methyl)quinolin-8-ol (**7**) applying paraformaldehyde as the source of CH_2O (for conditions, see Table 1).[61] The synthesis of thiourea derivative **8** was carried out by Abuthir *et al*.[83] Benzensulfonamide derivative **9** was furnished by Shaw *et al*. by dissolving **1**, paraformaldehyde and the amine in dry EtOH at room temperature (r.t.) and then treating the mixture under

Table 1. Reaction of 8HQ, formaldehyde and primary amines.

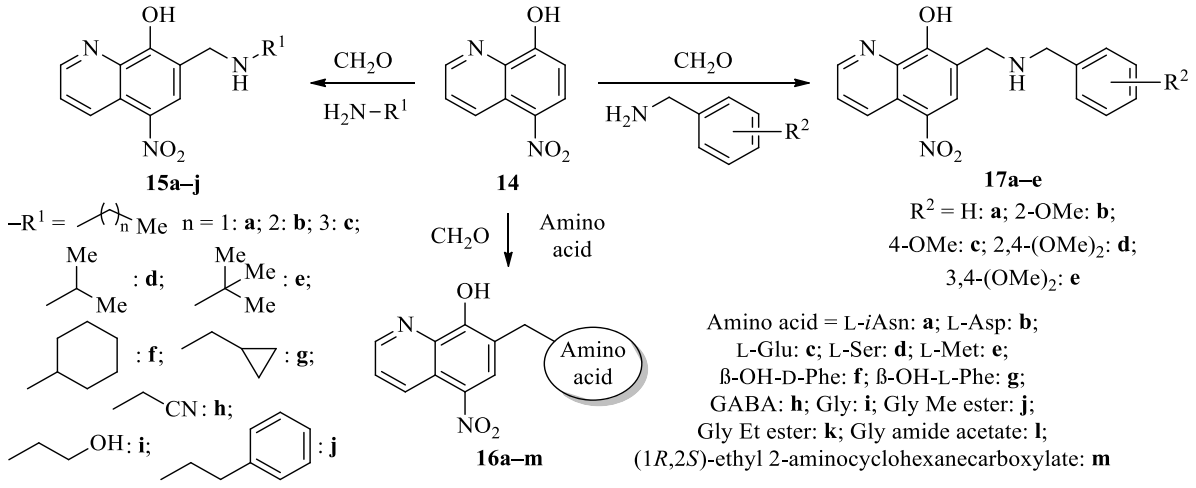


1 **2–13**

Comp.	–R	Conditions	Ref.
2		EtOH, reflux (78 °C), 1 h; Yield: 98%	79
3a,b	 : **a**; : **b**	**a**: Benzene, reflux, 30 min; Yield: n.d. **b**: Neat, 104 °C, 1 h; Yield: n.d.	80
4		EtOH, reflux, 90 min; Yield: 90%	81
5a,b	 : **a**; : **b**	EtOH, reflux, 4 h; Yield: n.d.	60
6a–c	 : **a**; : **b**; : **c**	MeOH, reflux, 12 h; Yield: **a**: 13%; **b**: 3%; **c**: 31%	82
7		EtOH, r.t. 5 min → 120 °C, 12 h; Yield: 52%	61
8		DMF, 60 °C, 6 h; Yield: 92.75%	83
9		EtOH, r.t.→ reflux, 18–22 h; Yield: n.d.	64
10a–c	 : **a**; n = 1: **b**; n = 2: **c**	EtOH, r.t. → 0 °C; Yield: n.d.	84
11a–d	 Y = H: **a**; 4-OH: **b**; 4-OH-3-Me: **c**; Br: **d**; Me: **e**; OMe: **f**;  : **g**	EtOH, reflux, HCl; Yield: **a**: 65%; **b**: 65%; **c**: 68%; **d**: 46%; **e**: 52%; **f**: 54%; **g**: 70%	85 86 87
12a–m	 Z = H: **a**; 3-Cl: **b**; 4-Cl: **c**; 4-Br: **d**; 3-F-4-Cl: **e**; 3-Cl-4-Me: **f**; 4-Cl-2-OMe: **g**; 2-Me: **h**; 4-Me: **i**; 2,5-Me_2: **j**; 3,4-Me_2: **k**; 2-OMe: **l**; 4-OMe: **m**	EtOH, reflux, 8 h, HCl; Yield: **a**: 85%; **b**: 85%; **c**: 80%; **d**: 85%; **e**: 75%; **f**: 75%; **g**: 65%; **h**: 75%; **i**: 82%; **j**: 65%; **k**: 65%; **l**: 70%; **m**: 70%	88
13a–g	 X = $(CH_2)_4$: **a**; $(CH_2)_5$: **b**; $(CH_2)_6$: **c**; $(CH_2)_7$: **d**; $(CH_2)_8$: **e**; $(CH_2)_{10}$: **f**; $(CH_2)_2NCH_3(CH_2)_2$: **g**	EtOH, 90 °C, 6 h → r.t. 18 h; Yield: **a**: 45%; **b**: 38%; **c**: 23%; **d**: 38%; **e**: 20%; **f**: 22%; **g**: 25%	73

reflux conditions.[64] **10a–c** were synthesised by Banerjee *et al*. by stirring CH_2O with the appropriate amine in EtOH. After the addition of **1**, the mixture was cooled on ice, followed by a pH adjustment to 5–6.[84] **11a–g** were prepared by Tripathy *et al.* (**11a**), Sahoo *et al.* (**11b,c,g**) and Bhargava and Sharma (**11d–f**) by means of stirring **1**, 4-substituted-2-aminothiazole and paraformaldehyde in the presence of HCl in EtOH.[85–87] Novel triheterocyclic systems (**12a–m**) were described by Mallur *et al.* applying reaction conditions similar to those used by Sahoo *et al*., Tripathy *et al*. and Bhargava and Sharma.[88] Fernández-Bachiller *et al*. reported tacrine–8HQ hybrids (**13a–g**), synthesised *via* heating paraformaldehyde and the corresponding diamine at 90 °C in EtOH. The mixture was then cooled and 8HQ, dissolved in EtOH, was added dropwise, followed by stirring at r.t.[73]

The 7-aminomethylation of nitroxoline (5-nitro-8HQ, **14**) is achieved by using different primary amine sources: aliphatic amines, amino acids and substituted benzylamines (Scheme 1). Sosič *et al.* synthesised various derivatives, including **15a**, **15h**, **16m** and **17a**, by heating **14** in pyridine and then adding formalin (≥36.5%) and the desired amine.[69] Yin *et al.* carried out the synthesis of **15b–g** in dry EtOH under reflux conditions.[54] One of the first to deal with the Mannich bases of **14** was Movrin *et al*., who synthesised **15i** and **15j** by reacting **14**, paraformaldehyde and the corresponding amine in pyridine.[89] Morvin and Marok were also tested various amino acids in the Mannich reaction, providing **16a–l**.[90] Szakács *et al.* furnished **17b–e** by heating the mixture of **14**, formalin (37%) and substituted benzylamines in pyridine at 50 °C.[39]

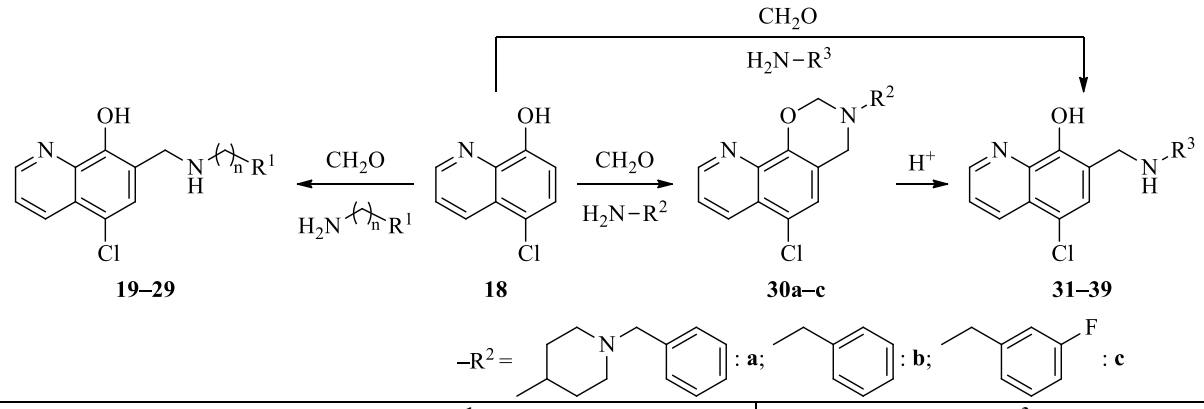


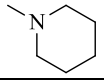
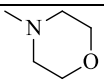
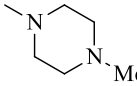
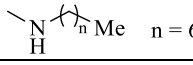
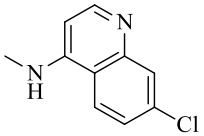
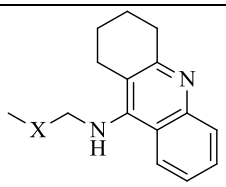
Scheme 1. Reaction of 5-NO_2-8HQ, formaldehyde and primary amines.

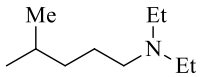
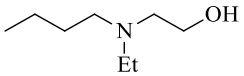
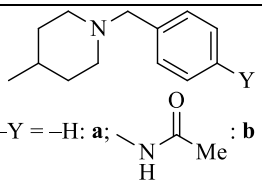
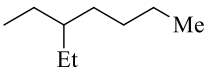
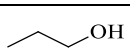
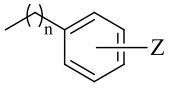
Primary amines applied in 5-chloro-8HQ (**18**) transformations include aliphatic amines, diamines and benzylamines (Table 2). Burckhalter *et al*. did not only synthesise **4**, but they prepared its 5-Cl derivative **19a** and also **20a** in a similar way.[80] In addition, Burckhalter also provided further compounds (**19b**, **20b**, **21**, **22**, **23c**, **24a**, **24b**, **25**, **27b**, **31**, **32**) by treating **18** with paraformaldehyde and the appropriate amines in EtOH under reflux conditions for 90 minutes

followed by a treatment with hydrogen chloride.[91] A single exception is **27a**. In this case, the mixture was heated until a thick oily material remained. Later, **20b** proved to be an efficient antiamoebic and antidiarrheal agent, and became known as clamoxyquine.[92,93,57] Burckhalter *et al.* prepared **20c–e**, **23a**, **23b**, **26**, **34–36**, using the appropriate amine and CH_2O in the form of paraformaldehyde.[94] Bolognesi *et al.* synthesised compound **28** by carrying out the reaction in toluene and using paraformaldehyde.[56] Fernández-Bachiller *et al*. applied not only **1** as starting scaffold for the tacrine–8HQ hybrid, but also **18**, yielding **29a–e**.[73] **33a,b** was furnished *via* stirring **18**, the corresponding amine and 1.1 equivalents of paraformaldehyde in absolute EtOH at

Table 2. Reaction of 5-Cl-8HQ, formaldehyde and primary amines.

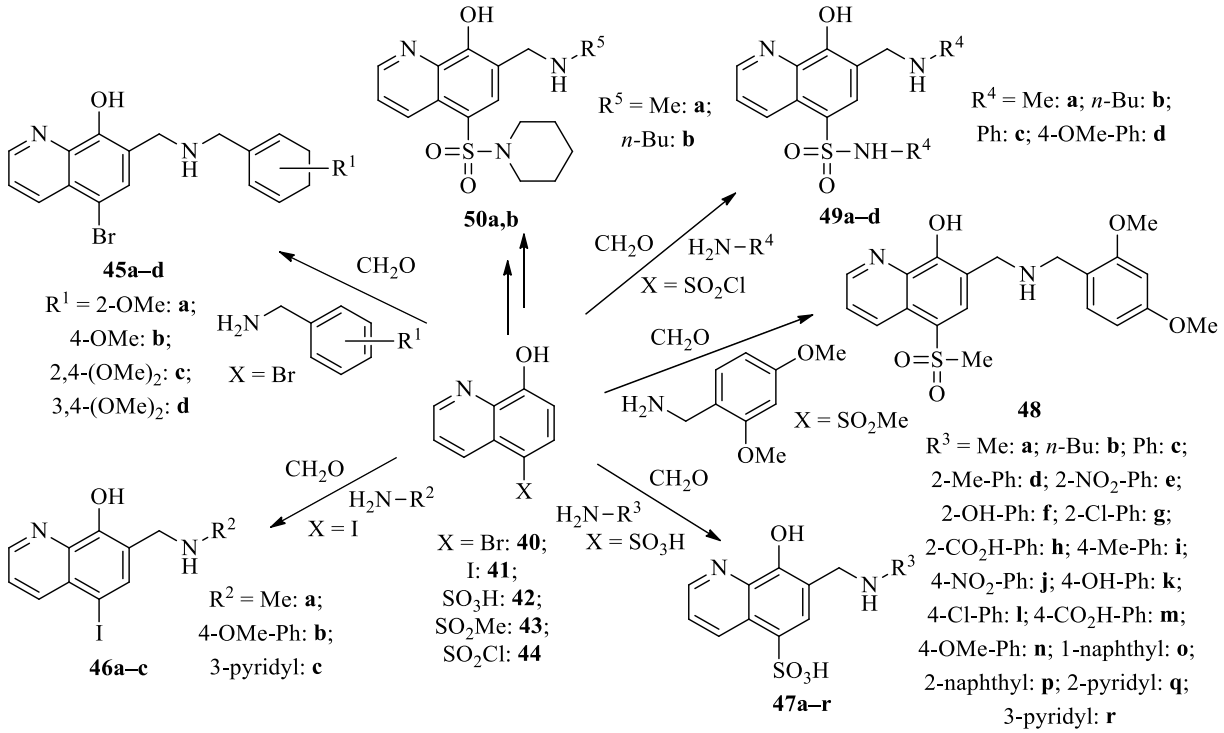


Comp.	n	–R¹	Ref.
19a,b	2: **a**, 3: **b**	NMe_2	80, 91
20a–e	2: **a**, 3: **b**; 4: **c**; 5: **d**; 6: **e**	NEt_2	80, 91, 94
21	3	$N(CH_2CH_2OH)_2$	91
22	3	$N(i\text{-}Pr)_2$	91
23a–c	3: **a**; 4: **b**; 5: **c**		91, 94
24a,b	3: **a**; 5: **b**		91
25	3		91
26	3		94
27a,b	3	 n = 6: **a**; 9: **b**	91
28	3		56
29a–e	1	 X = $(CH_2)_6$: **a**; $(CH_2)_7$: **b**; $(CH_2)_8$: **c**; $(CH_2)_{10}$: **d**; $(CH_2)_2NCH_3(CH_2)_2$: **e**	73

Comp.	–R³	Ref.
31		91
32		91
33a,b	 –Y = –H: **a**; : **b**	72
34		94
35a,b	 n = 6: **a**; 7: **b**	94
36		94
37		95
38		39
39a–e	 n = 1, Z = H: **a**; 2-F: **b**; 4-OMe: **c**; 2,4-$(OMe)_2$: **d**; n = 2, Z = H: **e**	39, 96, 98

60 °C for 16 hours by Ahn *et al.*[72] If 2 molar equivalents of CH_2O were applied in the synthesis of **33a**, the concomitant formation of benzoxazine **30a** was also observed.[72] Kenyon *et al.* published the preparation of **37** using other Mannich bases. The starting compounds were stirred without solvent at 120–150 °C; therefore, the mixture melted forming the desired products.[95] Szakács *et al.* described the synthesis of **38** and **39b–d** from **17b–e** but applying different conditions. To obtain **38** and **39c,d**, the EtOH solution of **18** mixed with cyclohexylamine and formalin solution was stirred under different conditions: 4 days at r.t. (**38**), 14 days at r.t. (**39c**), and 120 hours at 50 °C (**39d**).[39] **39b** was prepared from benzoxazine **30b** under acidic conditions (HCl/EtOH 22%) in 1 hour at r.t.[39] Compound **39a** was synthesised by Combes and Mesnier *via* sulfuric acid treatment of **30c**, which was previously prepared.[96,97] Gianni *et al.* reported the formation of **39e** by treating **18** with formalin and phenethylamine in MeOH at r.t. for 12 hours.[98]

Scheme 2 shows the aminomethylation of additional 5-substituted 8HQs (**40–44**). Szakács *et al.* transformed 5-bromo-8HQ (**40**) to **45a–d** upon stirring **40** with formalin (37%) and the corresponding amine for 1 hour.[39] The Mannich reaction of **41** was performed by Yanni, testing methylamine, *p*-anisidine and 3-aminopyridine, thus acquiring **46a–c**.[99] The substitution of 8-hydroxyquinoline-5-sulfonic acid (**37**) at C-7 with various alkyl- and arylamines was reported by Yanni and Timawy (**47a–r**).[100] **48** was also delivered by Szakács *et al.* by stirring 2,4-dimethoxybenzylamine dissolved in EtOH, formalin (37%) and **43** at 60 °C for 48 hours.[39] Yanni *et al*. accomplished the concomitant formation of the 7-aminomethyl- and 5-sulfonamide-functionalised material starting from **44**, paraformaldehyde and the corresponding amine. The

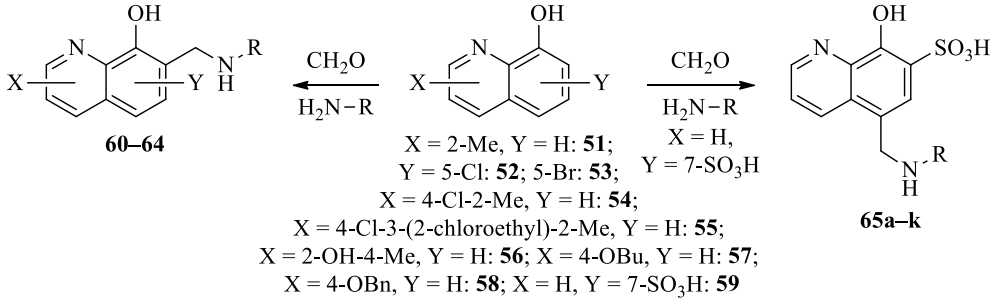


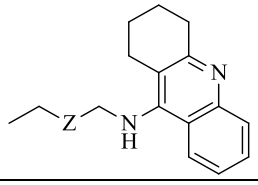
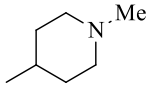
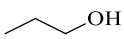
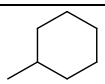
Scheme 2. Reaction of 5-substituted 8HQs, formaldehyde and primary amines.

reaction mixture was treated under reflux conditions in EtOH yielding **49a–d**. Subsequently, they carried out sulfonamidation and then aminomethylation of **39**, giving **50a,b**.[101]

The Mannich transformation of various 8HQs (**51–59**), listed in Table 3, was performed under rather similar conditions, despite the fact that reactions were carried out by different research groups. Fernández-Bachiller *et al.* prepared **60a–e** utilising exactly the same conditions used in the fabrication of **13a–g** and **29a–e**.[73] **61a–c** were synthesised by Bourquin *et al.* applying 1-methylpiperidine as an amine.[102] The transformation of 4-chloro-2-methylquinoline-8-ol (**54**) and 4-chloro-3-(2-chloroethyl)-2-methylquinoline-8-ol (**55**) was performed by Ozawa and Shibuya, resulting in **62a,b**.[103] In addition to **6a–c**, Manetti *et al.* also synthesised **63a,b** from 4-butoxy (**57**) and 4-benzyloxy (**58**) derivatives.[82] The preparation of **64a,b** was reported by Shoeb *et al.* using paraformaldehyde under conditions indicated.[104] Yanni and Mohharam reacted the 7-sulfonic acid derivative of 8HQ, various aromatic and aliphatic amines and paraformaldehyde in the Mannich reaction, which afforded the formation of compounds **65a–k**.[105]

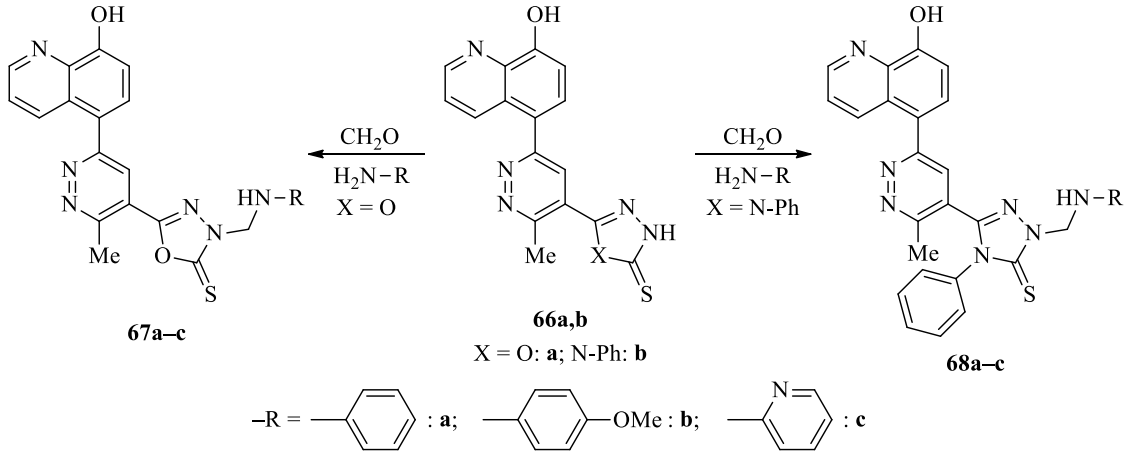
Table 3. Reaction of 8HQ derivatives, formaldehyde and primary amines.



Comp.	X / Y	–R	Conditions	Ref.
60a–e	2-Me	 Z = $(CH_2)_5$: **a**; $(CH_2)_6$: **b**; $(CH_2)_7$: **c**; $(CH_2)_8$: **d**; $(CH_2)_2NCH_3(CH_2)_2$: **e**	EtOH, 90 °C, 6 h → r.t. 18 h; Yield: **a**: 33%; **b**: 35%; **c**: 35%; **d**: 35%; **e**: 27%	73
61a–c	2-Me: **a**; 5-Cl-2-Me: **b**; 5-Br-2-Me: **c**		EtOH, reflux; Yield: n.d.	102
62a,b	4-Cl-2-Me: **a**; 4-Cl-3-(2-chloroethyl)-2-Me: **b**		EtOH, reflux; Yield: **a**: 87%; **b**: 40%	103
63a,b	4-OBu: **a**; 4-OBn: **b**		EtOH, reflux, 12 h; Yield: **a**: 8%; **b**: 53%	82
64a,b	2-OH-4-Me	Me: **a**; *n*-Pr: **b**	EtOH, reflux, 9 h; Yield: **a**: 58%; **b**: 50%	104
65a–k	7-SO_3H	Me: **a**; *n*-Bu: **b**; Ph: **c**; 4-NO_2-Ph: **d**; 4-Cl-Ph: **e**; 4-Me-Ph: **f**; 4-OH-Ph: **g**; 4-CO_2H-Ph: **h**; 4-OMe-Ph: **i**; 1-naphthyl: **j**; 3-piperidyl: **k**	EtOH, reflux, 30–50 h; Yield: 60–70%	105

The transformation of pyridazine-annulated 8HQ was implemented by Abdelmohsen, treating the solution of **66a** or **66b** in absolute EtOH with formalin (40%) and then adding the aromatic amine in EtOH. Subsequently, the mixture was stirred for 3 hours at r.t. and left overnight

with the result of **67a–c** and **68a–c**. An interesting feature is that the Mannich reaction occurred on the side chain rather than at position 7 of the 8HQ core (Scheme 3).[106]



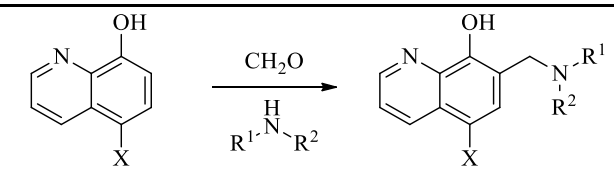
Scheme 3. Reaction of 5-substituted 8HQs, formaldehyde and primary aromatic amines.

2.2. Syntheses of Mannich bases by using acyclic secondary amines

The results of aminomethylation of 8HQ and 5-nitro- and 5-halogeno-8HQs with symmetric and asymmetric acyclic secondary amines are listed in Table 4. One of the earliest utilisations of the Mannich reaction to transform 8HQ (**1**) was performed by Burckhalter *et al.*, when equimolar amounts of dimethylamine, paraformaldehyde and **1** were dissolved in EtOH and treated under reflux for 2 hours (**70a**, yield: 74%).[107] Philips and Fernando prepared **70b** *via* mixing paraformaldehyde and diethylamine, then adding **1** dissolved in EtOH and, after a one-hour standing, the mixture was treated under reflux for 5 hours.[108] Motaleb *et al.* used DMF as solvent and paraformaldehyde as the aldehyde source to synthesise dicarboxylic acid derivative **70c**.[109] The *n*-Pr derivative (**70d**) was prepared by Faydy *et al.* in two steps: first, the Mannich reagent was synthesised *via* mixing dipropylamine and paraformaldehyde in EtOH, and in the second step, 8HQ in EtOH was added. Subsequently, after 1 hour at r.t., the mixture was treated at reflux for 3 hours.[110] The synthetic process of **70e–q** was performed by Ishida and Watanabe. Formalin (35%) was added dropwise to the MeOH solution of **1** and different amines, then the reaction mixture was stirred for 1 hour at r.t. and kept under reflux in 3 hours.[111] Szakács *et al.* also used formalin (37%) to furnish **70r**.[39] **71a** was the product of the reaction of **14** with dimethylamine and paraformaldehyde in pyridine/EtOH under reflux conditions, performed by Shterev *et al.*[112] **71b** was obtained by Burckhalder *et al. via* dissolving the components (**14**, paraformaldehyde and diethylamine) in EtOH and heating at reflux for 90 minutes.[113] Yin *et al.* reported dipropyl homologue derivative **71c**,[54] while Movrin *et al.* described the *i*-Pr and 2-hydroxyethyl derivatives (**61d,e**).[89] Liu *et al.* performed the synthesis of **71f** by dissolving **14** and CH_2O in EtOH, then adding dicyclohexylamine and treating the mixture under reflux for 24 hours.[55] The synthe-

sis of compound **71g** was disclosed by Elofsson,[50] and acetonitriles **71h,i** were prepared by Sosič *et al*.[69] Helin and Vanderwerf synthesised **72** *via* adding paraformaldehyde and diethylamine in EtOH to the 1:1 ether:EtOH solution of 5-fluoro-8HQ (**69**) and leaving it to stand for 30 minutes.[114] The aminomethylation of **18** and **40** leading to the formation of **73** and **74** was studied by Burckhalter *et al*.[80,94,115,116]

Table 4. Reaction of 8HQ and 5-substituted 8HQs, CH_2O and secondary acyclic amines.



X = H: **1**; NO_2: **14**; F: **69**; Cl: **18**; Br: **40**

70–74

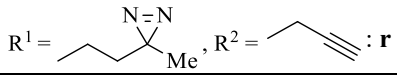
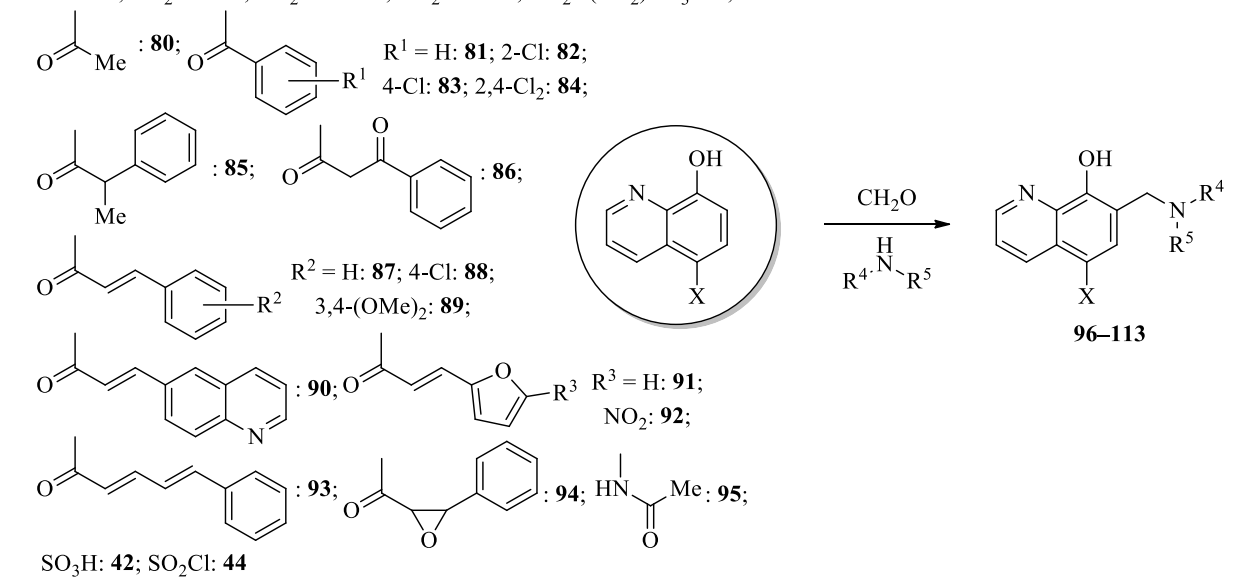
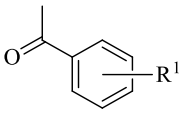
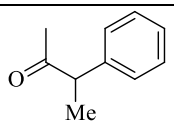
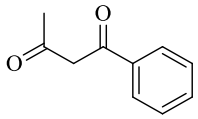
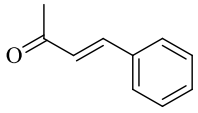
Comp.	X	R^1, R^2	Conditions	Ref.
70a–f	H	R^1=R^2 = Me: **a**; Et: **b**; CH_2CO_2H: **c**; *n*-Pr: **d**; *n*-Bu: **e**; *n*-hexyl: **f**; cyclohexyl: **g**; 2-ethylhexyl: **h**; *n*-octyl: **i**; *n*-dodecyl: **j**; *n*-octadecyl: **k**; *i*-dodecenyl: **l**; Ph: **m**; octylphenyl: **n**; Bn: **o**; 3-(octyloxy)propoxy: **p**; R^1 = *n*-octyl, R^2 = Ph: **q**;  : **r**	**a**: EtOH, reflux, 2 h; Yield: 74% **b**: EtOH, r.t., 1 h → reflux, 5 h; Yield: 55% **c**: DMF, reflux, 24 h; Yield: 27% **d**: EtOH, r.t., 1 h → reflux, 3 h; Yield: 65% **e–q**: MeOH, 20 °C, 1 h → reflux, 3 h; Yield: n.d. **r**: EtOH, reflux 60 °C, 48 h; Yield: 51%	107, 108, 109, 110, 111, 39
71a–i	NO_2	R^1=R^2 = Me: **a**; Et: **b**; *n*-Pr: **c**; *i*-Pr: **d**; $(CH_2)_2OH$: **e**; cyclohexyl: **f**; R^1 = Me, R^2 = cyclohexyl: **g**; R^1 = Me, R^2 = CH_2CN: **h**; R^1 = Bn, R^2 = CH_2CN: **i**	**a**: pyridine:EtOH 1:1, reflux; Yield: n.d. **b**: EtOH, reflux, 90 min; Yield: 83% **c**: EtOH, reflux 80 °C, 24 h; Yield: 14% **d**, **e**: pyridine, 50–60 °C; Yield: 74–84% **f**: EtOH, reflux 80 °C, 24 h; Yield: 19% **g**: n.d. **h**, **i**: pyridine, 60 °C; Yield: 70% / 74%	112, 113, 54, 89, 55, 50, 69
72	F	R^1=R^2 = Et	EtOH, r.t., 30 min; Yield: 42%	114
73a–l	Cl	R^1=R^2 = Me: **a**; Et: **b**; *n*-Pr: **c**; *n*-Bu: **d**; $(CH_2)_2OH$: **e**; CH_2CO_2Et: **f**; CH_2CN: **g**; R^1 = Me, R^2 = $(CH_2)_2NEt_2$: **h**; R^1 = Me, R^2 = $(CH_2)_3NEt_2$: **i**; R^1 = Et, R^2 = $(CH_2)_2NEt_2$: **j**; R^1 = Et, R^2 = $(CH_2)_3NEt_2$: **k**; R^1 = Et, R^2 = $(CH_2)_2OH$: **l**;	**a**: EtOH, reflux, 90 min; Yield: 75% **b**: EtOH, reflux, 90 min; Yield: 74% **c**, **d**: EtOH, reflux, 2 h/30 min; Yield: n.d. **e**: EtOH, reflux, 90 min; Yield: 70% **f**: EtOH, reflux, 2 h; Yield: 79% **g**: EtOH, reflux, 3 h; Yield: 42% **h–k**: EtOH, reflux, 90 min; Yield: n.d. **l**: EtOH, reflux, 90 min; Yield: 80%	80, 115, 116, 94, 91
74a,b	Br	R^1=R^2=Et: **a**; R^1=Me, R^2=Et: **b**	**a**: EtOH, reflux, 90 min; Yield: 51% **b**: EtOH, reflux, 1 h; Yield: n.d.	115, 116

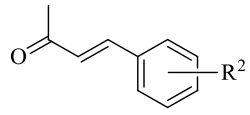
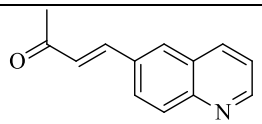
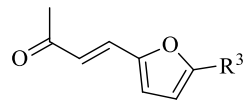
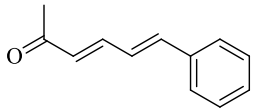
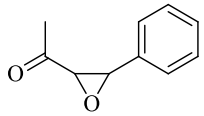
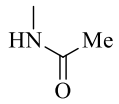
Table 5 shows additional 5-substituted 8HQ derivatives. The synthesis of **96a,b** was performed by Edgerton and Burckhalter, *via* adding **75** in EtOH to the heated EtOH solution of the appropriate amine and paraformaldehyde and exposed the mixture to 1–2 hours of reflux.[117] **97** was furnished *via* mixing **76**, paraformaldehyde and dibenzylamine in abs. EtOH, and treating it under reflux for 4 hours by Himmi *et al*.[118] Venkataramani applied paraformaldehyde as a CH_2O source in the reaction of **77** and **79** with ethanolamine, which yielded **98** and **100**.[119] **99** was synthesised by Burckhalter and Leib *via* treating the EtOH solution of the components (**78**, paraformaldehyde and diethylamine) at reflux for 3 hours.[120] Schraufstätter and Bock extended the reaction to several 5-acyl derivatives delivering **101a**, **102a–e** and **103–109** by stirring the mix-

ture of **80**–**93** each with formalin (30%) and the appropriate amine in EtOH at reflux.[121] **101b** was synthesised by Mangeney and Pechmèze *via* reacting **80**, formalin (30%) and the amine at reflux for 10 hours.[122] **102f** was obtained by Gopalchari and Dhar *via* stirring the starting compounds (**83**, paraformaldehyde and diethylamine) in EtOH at reflux.[123] Möhrle and Schaltenbrand gained epoxy ketone **94** from **87** and subsequently **110a,b** from **94.**[124] **111** was

Table 5. Reaction of 5-substituted 8HQs, formaldehyde and secondary acyclic amines.

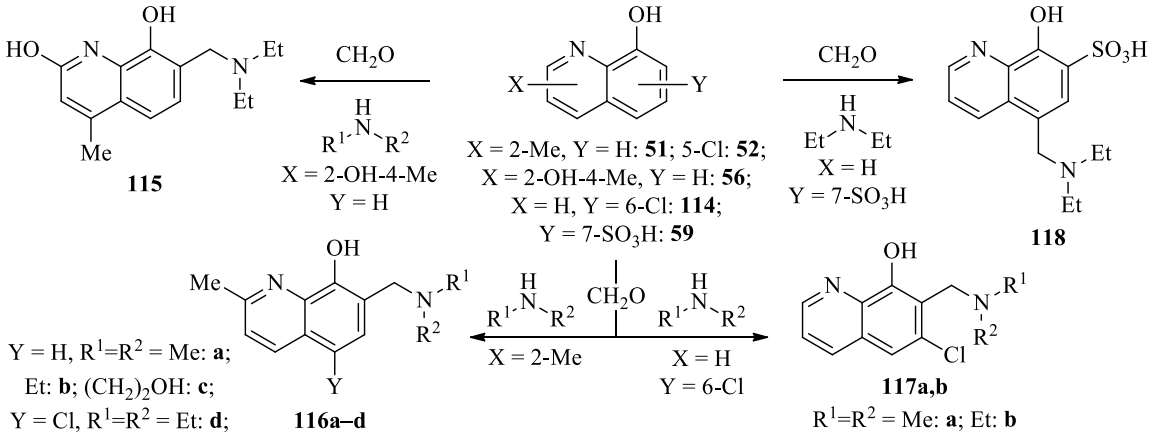


Comp.	X	R^4, R^5	Ref.
96a,b	Me	R^4=R^5 = Et: **a**; R^4 = Et, R^5 = $(CH_2)_2OH$: **b**	117
97	CH_2CN	R^4=R^5 = Bn	118
98	CH_2OMe	R^4=R^5 = $(CH_2)_2OH$	118
99	CH_2OEt	R^4=R^5= Et	120
100	$CH_2O(CH_2)CH_3$	R^4=R^5 = $(CH_2)_2OH$	118
101a,b		R^4=R^5 = Me: **a**; R^4=$(CH_2)_2CN$, R^5=$C_{12}H_{25}$: **b**	121, 122
102a–f		R^1 = H, R^4=R^5 = Me: **a**; R^4 = Et, R^5 = $(CH_2)_2NEt_2$: **b**; R^1 = 2-Cl, R^4=R^5 = Me: **c**; R^1 = 4-Cl, R^4=R^5 = Me: **d**; R^1 = 2,4-Cl_2, R^4=R^5 = Me: **e**; R^1 = 4-Cl, R^4=R^5 = Et: **f**	121, 123
103		R^1=R^2 = Me	121
104		R^1=R^2 = Me	121
105a–h		R^4=R^5=Me: **a**; Et: **b**; *n*-Bu: **c**; $(CH_2)_2OH$: **d**; $(CH_2)_2NEt_2$: **e**; R^4 = Me, R^5 = Bn: **f**; R^4 = Me, R^5 = $C_{12}H_{25}$: **g**; R^4 = Et, R^5 = $(CH_2)_2NEt_2$: **h**	121

Comp.	X	R^4, R^5	Ref.
106a,b		R^2 = 4-Cl, R^4=R^5 = Me: **a**; R^2 = 3,4-$(OMe)_2$, R^4=R^5 = Me: **b**	121
107		R^4=R^5 = Me	121
108a,b		R^3 = H, R^4=R^5 = Me: **a**; R^3 = NO_2, R^4=R^5 = Me: **b**	121
109		R^4=R^5 = Me	121
110a,b		R^4=R^5 = Me: **a**; Et: **b**	124
111		R^4=R^5 = Et	113
112a–f	SO_3H	R^4=R^5=Me: **a**; Et: **b**; *n*-Pr: **c**; *n*-Bu: **d**; *i*-Bu: **e**; $(CH_2)_2OH$: **f**	125
113	SO_2NEt_2	R^4=R^5 = Et	101

synthesised by Burckhalter *et al.* from **95** in a yield of 74%.[113] Sen and Kulkarni transformed **42**, applying paraformaldehyde and several dialkylamines providing products **112a–f**.[125] Yanni *et al.* treated **44** with diethylamine and paraformaldehyde, leading to the formation of **113**.[101]

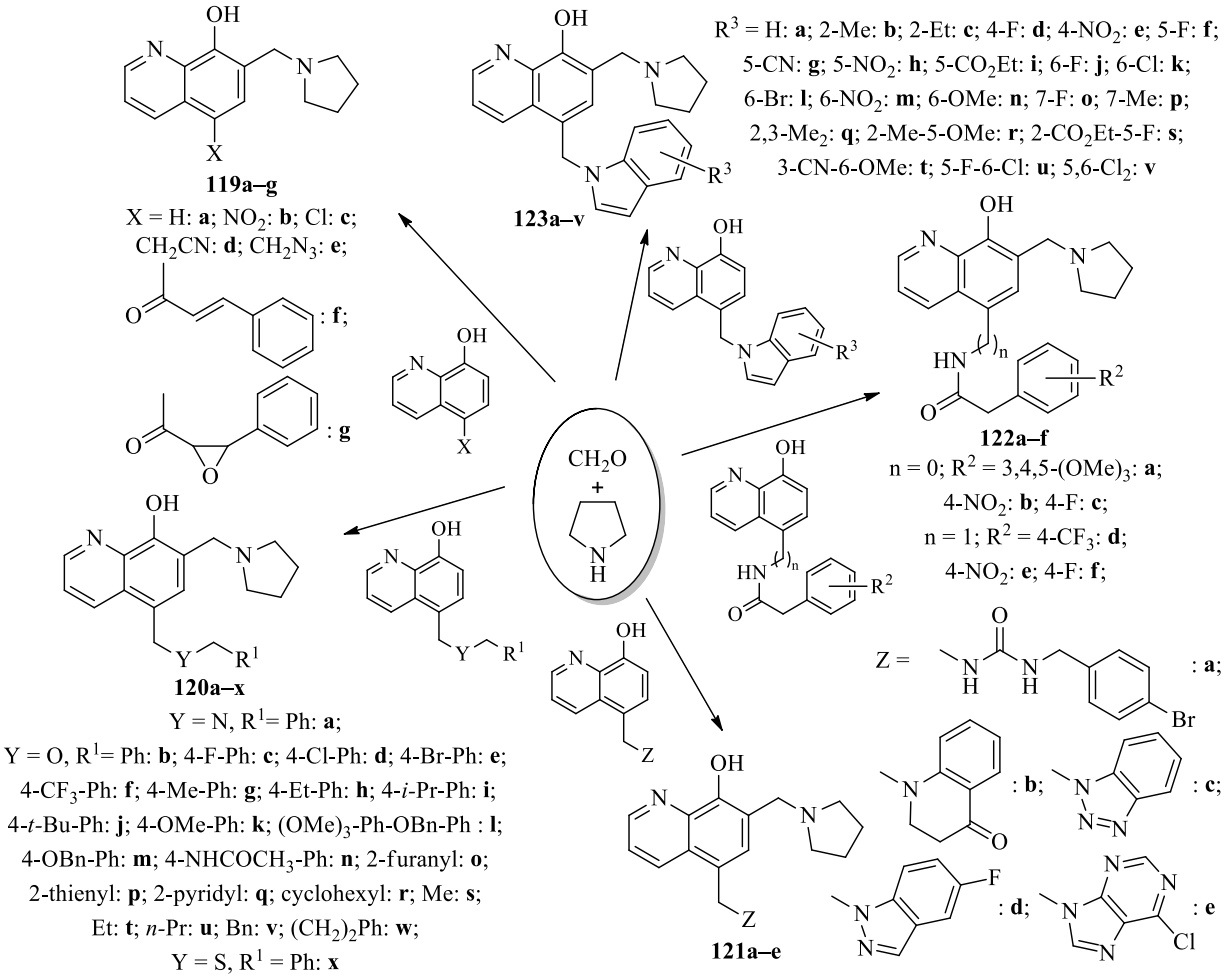
Scheme 4 includes further aminomethylated 8HQs. In addition to the preparation of **64a,b**, the synthesis of **115** was also carried out by Shoeb *et al.*[104] The dimethyl and diethyl derivatives of quinaldine (**116a,b**) were first reported by Bourquin *et al.,* and then the synthesis of **116d** was shown to be efficient from both **52** *via* the Mannich reaction and **116b** *via* chlorination.[102] **116c** was furnished using diethanolamine and CH_2O by Ozawa and Shibuya with the finding that the reaction occurred at position 7, not involving the 2-Me group.[126] The transformation of 6-chloro-8-hydroxyquinoline (**114**) to **117a,b** was performed by Burckhalter *et al.* Their interest was motivated by the biological importance of these isomeric structures (**73a,b**).[80,116] The synthesis of **117a** was performed in EtOH, but the synthesis of **117b** could be carried out efficiently in both MeOH and EtOH using paraformaldehyde as the CH_2O source. Yanni and Mohharam prepared **118** similar to the method applied in the synthesis of primary amine derivatives **65a–k**.[105]



Scheme 4. Reaction of 8HQ derivatives, formaldehyde and acyclic secondary amines.

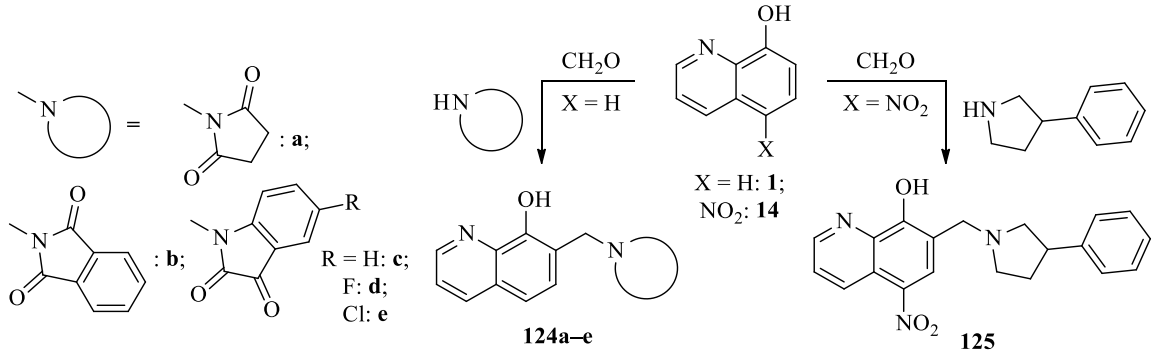
2.3. Syntheses of Mannich bases by using cyclic secondary amines

This subsection covers Mannich reactions carried out with the use of cyclic amines. Scheme 5 depicts the transformation of 8HQ derivatives by pyrrolidine and CH_2O. **119a**, the simplest core, was reported by Goyal and Chaturvedi.[127] The synthesis of **119b–g** is an extension of methods described previously by Movrin *et al.* (**119b**),[89] Burckhalter *et al.* (**119c**),[80] Himmi *et al.* (**119d,e**),[118] Schraufstätter and Bock (**119f**)[121] and Möhrle and Schaltenbrand (**119g**).[124] Numerous 5-substituted 7-pyrrolidinylmethyl derivatives (**120a**, **120c–x**) were obtained by Xiao *et al.* on the basis of **120b** (UC-112) by reacting the appropriate functionalised 8HQs with paraformaldehyde and pyrrolidine in EtOH.[66] Note that this approach was previously studied by Wang and Li.[65] Based on these findings, the synthesis of additional UC-112 analogues (**121**–**123**) was carried out under the same conditions by Wang *et al.*[67]



Scheme 5. Reaction of 8HQ/5-substituted 8HQs, formaldehyde and pyrrolidine.

Scheme 6 shows the application of additional nitrogen-containing five-membered ring systems described by Mohamed *et al.* and the Elofsson group, including phthalimide, isatin and 5-halogenoisatins, succinimide and 3-phenylpyrrolidine affording **124a–e** and **125**.[128,50]

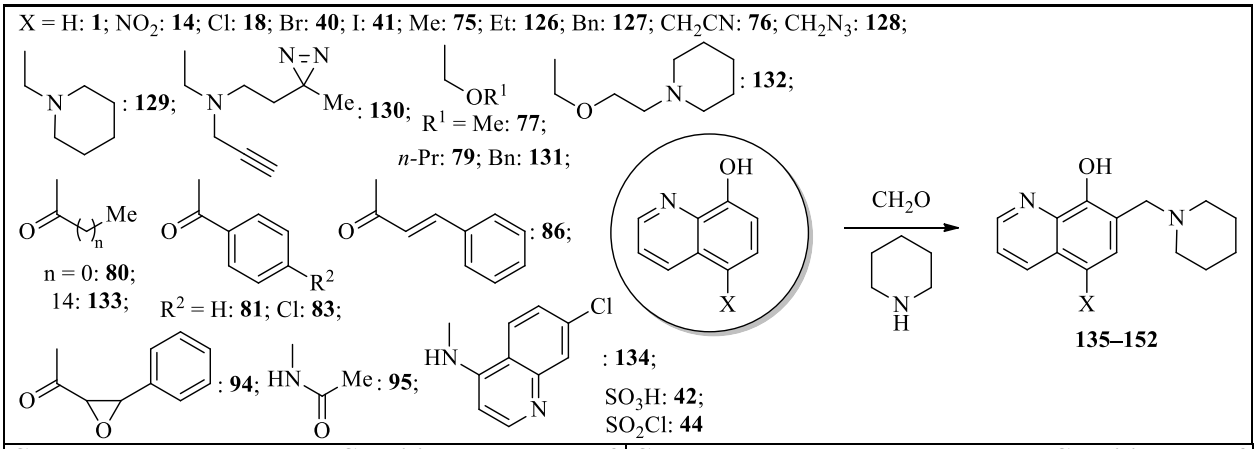


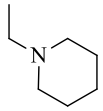
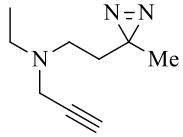
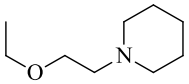
Scheme 6. Reaction of 8HQ and substituted 8HQs, CH_2O and pyrrolidine derivatives.

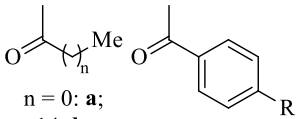
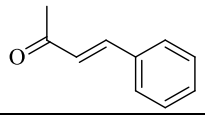
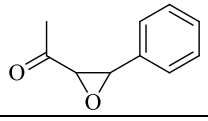
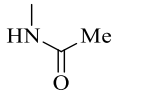
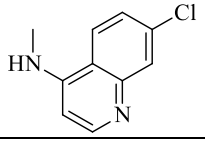
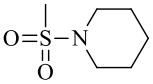
Piperidine, a secondary amine, has been frequently utilised in the Mannich reaction (see Table 6), which is probably due to its stability and reactivity. Note that it was the first amine to be applied for the aminomethylation of 8HQ, described in a German patent in 1897.[5] 14 kg of 8HQ (**1**) was dissolved in EtOH, then 8 kg of formalin (40%) and 8.5 kg of piperidine were added and the mixture was stirred for 6 hours under reflux. After distillation, the free base (**135**) was

crystallised. Its hydrochloride salt was prepared by Burckhalter *et al.*[106] The reaction conditions for the compounds in Table 6 are almost identical. EtOH was used as solvent, except for compound **142**, which was performed in a solventless process by Burckhalter and Leib (for **144a,b**, **146d** and **148** details were not available).[120,118,124] Reaction mixtures were treated primarily at reflux or at unspecified heated temperature with the exception of **143**, synthesised at r.t.[39] Additional examples are **136**, **137**, **149**, **150** (Burckhalter *et al.*);[113,80] **138**, **145** (Burckhalter and Leib);[120] **139** (Yanni);[99] **140a–c**, **146a–c** (Edgerton and Burckhalter);[117] **141a,b** (Himmi *et al.*);[118] **144c** (Xiao *et al.*);[66] **147** (Schraufstätter and Bock);[121] **151** (Sen and Kulkarni)[124] and **152** (Yanni).[101] In the case of **152**, reactions were started from **44**, and both aminomethylation and concomitant sulfodamidation were achieved.

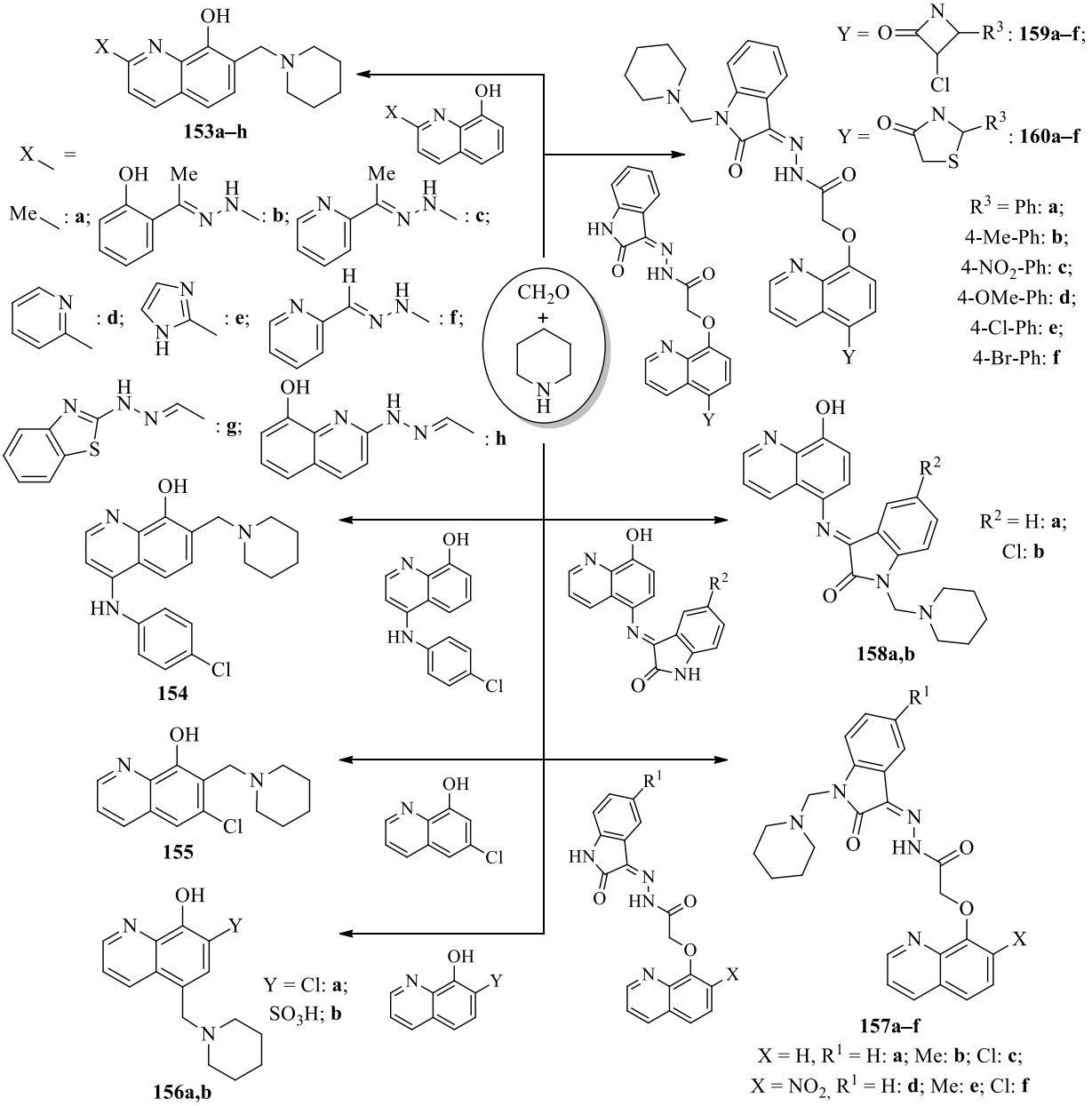
Table 6. Reaction of 8HQ/5-substituted 8HQs, formaldehyde and piperidine.



Comp.	X	Conditions	Ref.
135	H	EtOH, reflux, 6 h; Yield: n. d.	5
136	NO_2	EtOH, heat; Yield: 83%	113
137	Cl	EtOH, reflux, 1.5 h; Yield: 80%	80
138	Br	EtOH, reflux, 1 h; Yield: 65%	120
139	I	EtOH, reflux; Yield: 60%	99
140a–c	Me: **a**; Et: **b**; Bn: **c**	EtOH, reflux, 1–2 h; Yield: **a**: 97%; **b**: 95%; **c**: 56%	117
141a,b	CH_2CN: **a**; CH_2N_3: **b**	EtOH, reflux, 4 h; Yield: **a**: 78%; **b**: 81%	118
142		Neat conditions, heat, 3 h; Yield: 90%	120
143		EtOH, r. t., 3 days; Yield: 68%	39
144a–c	 R1 = Me: **a**; *n*-Pr: **b**; Bn: **c**	**a**, **b**: n. d. **c**: EtOH, reflux, 4 h; Yield: n. d.	118, 66
145		EtOH, reflux, 3h; Yield: 88%	120

Comp.	X	Conditions	Ref.
146a–c	 n = 0: **a**; 14: **b**; R = H: **c**; Cl: **d**	EtOH, reflux, 1–4 h; Yield: **a**: 67%; **b**: 81%; **c**: 54% **d**: n.d.	117, 121
147		EtOH, reflux, 8 h; Yield: n.d.	121
148		n.d.; Yield: 67–90%	124
149		EtOH, reflux, 1 h; Yield: 92%	113
150		EtOH, reflux, 2 h; Yield: 93%	113
151	SO_3H	EtOH, reflux, 6 h, Yield: 80%	124
152		EtOH, reflux, 30–40 h; Yield: 70%	101

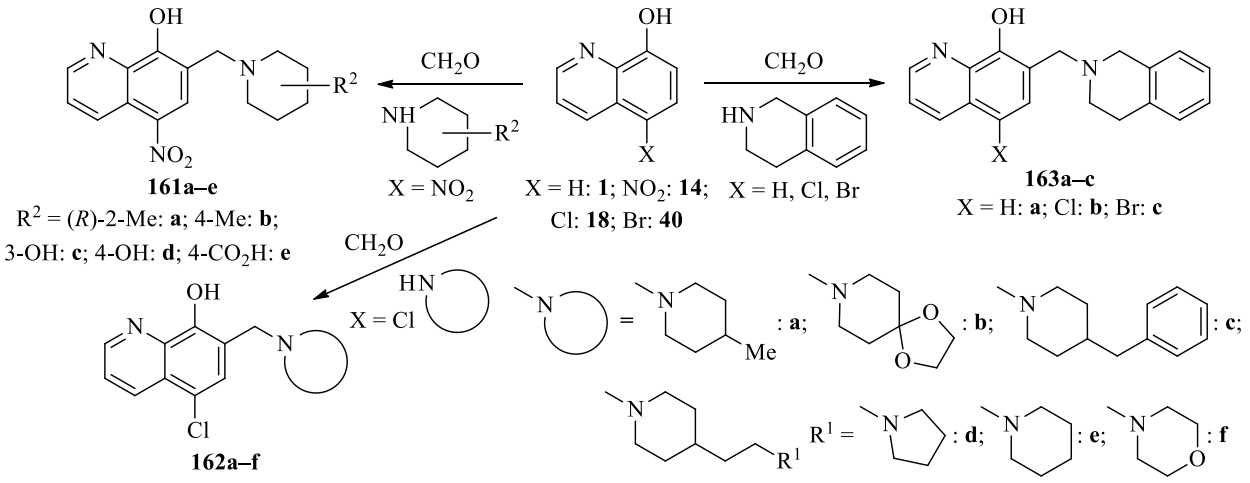
Additional piperidylmethyl-substituted 8HQs are included in Scheme 7. Quinaldine **153a** was obtained by reacting equimolar amounts of 8-hydroxyquinaldine, paraformaldehyde and piperidine in EtOH for 3 hours under reflux conditions by Rose *et al.*[129] Szakács *et al.* transformed some 2-functionalised 8HQs by stirring the mixture of piperidine and formalin (35%) in EtOH for 1 hour, then, after adding the appropriate 8HQ, stirring was continued at r.t. for 2 days (**153d**), 3 days (**153e**–**h**) or 4 days (**153b,c**).[39] 4-(4-Chloroanilino)-8-hydroxyquinoline was added to the heated ethanolic solution of piperidine and paraformaldehyde, and then heated at boiling for 25 minutes to obtain **154** by Burckhalter and Edgerton, who also synthesised **155** in 72%.[115] To provide **156a**, 7-chloro-8-hydroxyquinoline, piperidine and paraformaldehyde were dissolved in MeOH and heated at reflux for 90 minutes.[80] Among the 8-hydroxyquinoline-7-sulfonic acids previously described, **156b** was reported by Yanni and Mohharam.[105] Compounds



Scheme 7. Reaction of 8HQ derivatives, formaldehyde and piperidine.

157a–f were synthesised by Meenakshi *et al.*,[130] and derivatives **158a,b** were published by Chhajed and Padwal.[131] **159a–f** and **160a–f** were prepared by Madhu *et al*. The starting 8HQ, piperidine and water were mixed and, after adding H_2O and DMF to this clear solution, stirring was continued in an ice-bath for 2 hours followed by leaving it at r.t. overnight.[132,133] Similar to **67a–c** and **68a–c**, the synthesis of **157–160** are also exceptional, since piperidine and CH_2O did not appear to react with the 8HQ nuclei but resulted in *N*-functionalisation of the isatin core.

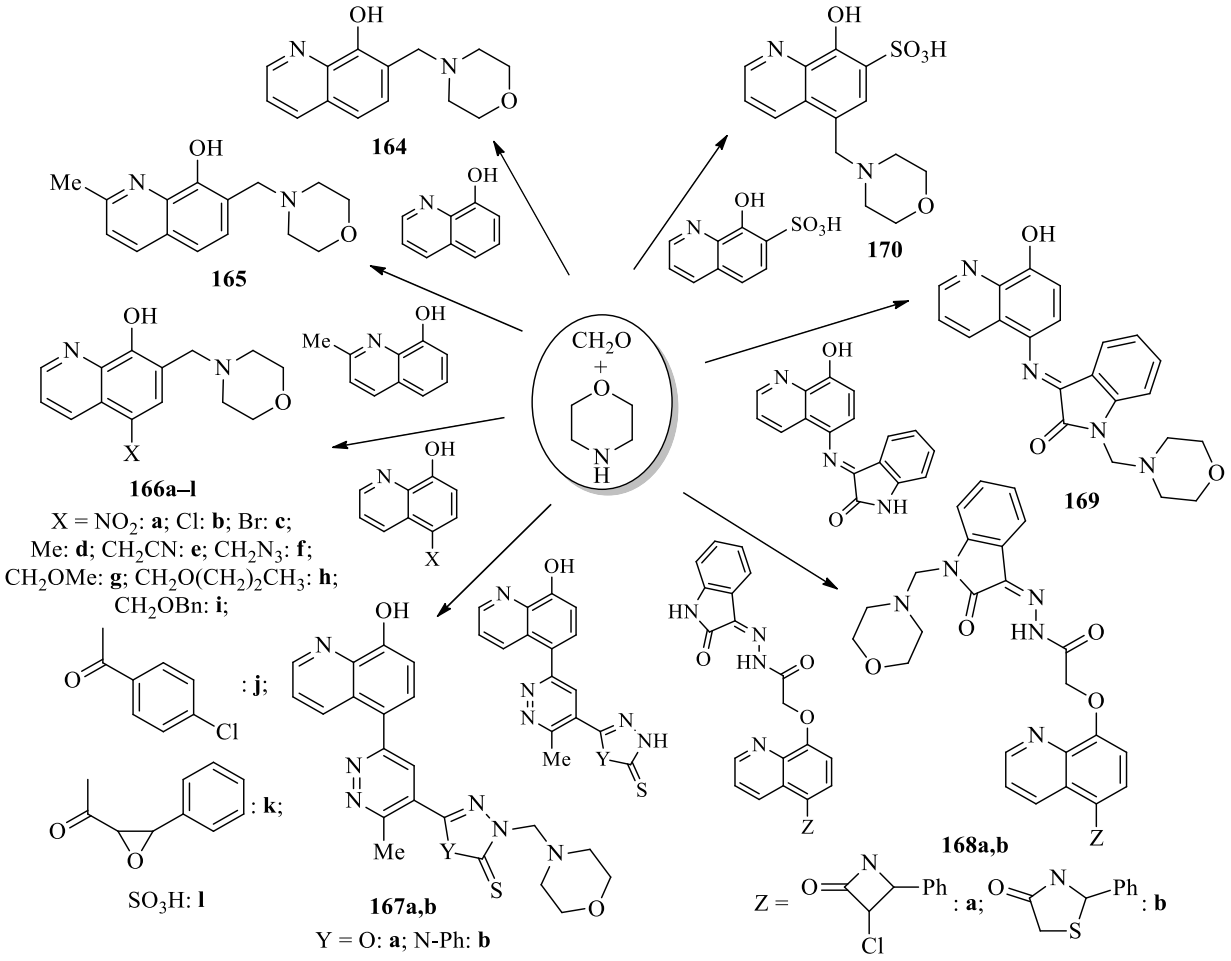
Scheme 8 depicts the Mannich reaction of 8HQs with various piperidine derivatives. **161a** was synthesised *via* dissolving **14** in pyridine at 60 °C and then reacting it with formalin (36.5%) and (*R*)-2-methyl-piperidine.[69] The synthesis **161b** was disclosed by Mirković *et al.*[68] **161c–e** were prepared by Shterev *et al. via* treating **14** with piperazines and paraformaldehyde in the 1:1 mixture of pyridine and EtOH.[112] Only a few examples were reported on the utilisation of MW in the Mannich reaction of 8HQ. In one of them demonstrated by Swale *et al.*, 20–30 minutes of MW irradiation to maintain 140 °C and EtOH were applied to gain **162a–c**.[78] **162d–f** were obtained by Chough in the reaction of **18**, paraformaldehyde and the appropriate 4-(2-cyclic-aminoethyl)-piperidine.[134] The incorporation of 1,2,3,4-tetrahydroisoquinoline (**163a–c**) was achieved by Chakravorti *et al*. *via* adding paraformaldehyde and 1,2,3,4-tetrahydroisoquinoline to the solution of 8HQ (**1**, **18** or **40**) in EtOH and treating the mixture under reflux for 5 hours.[135]



Scheme 8. Reaction of 8HQ and 5-substituted 8HQs, CH_2O and piperidine derivatives.

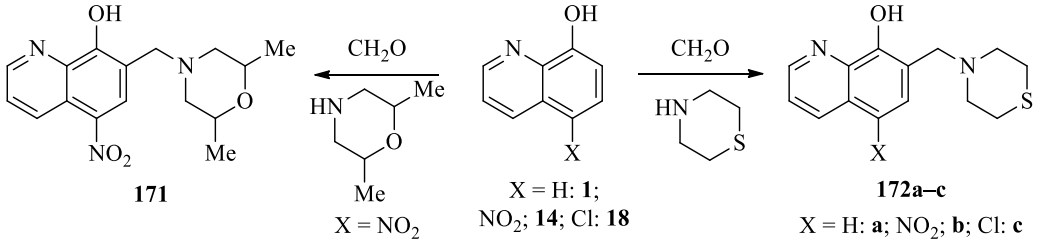
In addition to piperidine, morpholine, too, was applied rather frequently in the Mannich reaction (Scheme 9). The simplest core in this framework is **164**, which was disclosed by Grzycka and Miłkowska.[136] Similar to **153a**, **165** was also described by Rose *et al.*[129] Petrow and Sturgeon prepared **166a** *via* treating 5-NO_2-8HQ in EtOH under reflux with formalin (36%) and morpholine.[137] The synthesis of **166b** in a yield of 78% was reported by Burckhalter *et al.*; however, its synthesis later appeared in several publications.[80] The 5-bromo analogue **166c** was disclosed by Kim *et al.*[138] The preparation of **166d–l** and **167–170** is extensions of synthetic proce-

dures described previously by Edgerton and Burckhalter (**166d**),[117] Himmi *et al*. (**166e,f**),[118] Venkataramani (**166g,h**),[118] Xiao *et al.* (**166i**),[66] Gopalchari and Dhar (**166j**),[123] Möhrle and Schaltenbrand (**166k**),[124] Sen and Kulkarni (**166l**),[124] Abdelmohsen (**167a,b**),[106] Madhu *et al.* (**168a,b**),[132,133] Chhajed and Padwal (**169**)[131] and Yanni and Mohharam (**170**).[105]



Scheme 9. Reaction of 8HQ and substituted 8HQs, formaldehyde and morpholine.

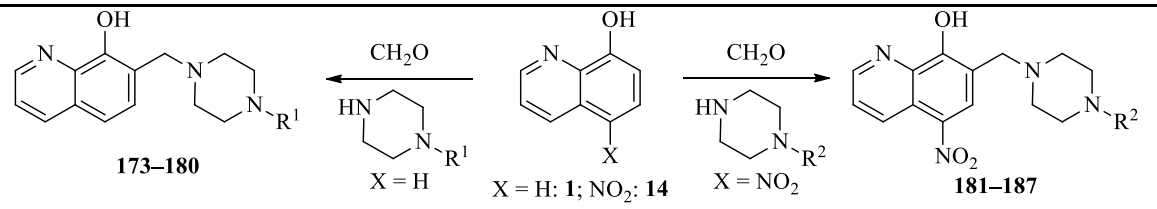
Thiomorpholine and 2,6-dimethylmorpholine were also applied in the Mannich reaction (Scheme 10). Synthesis of the latter (**171**) was disclosed by Elofsson.[50] **172a** was prepared *via* stirring the components in EtOH (**1**, thiomorpholine and formalin) for 12 hours at r.t. by Zaoui *et al.*[79] The synthesis of **172b** and **172c** was carried out by Wangtrakuldee *et al*. by treating the appropriate 8HQ, CH_2O and thiomorpholine in dry EtOH at 80 °C for 24 hours.[47]

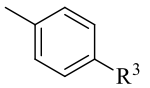
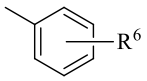
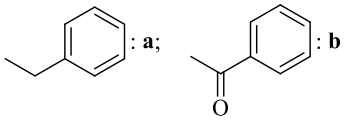
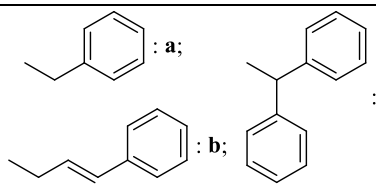
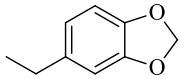
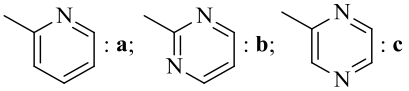
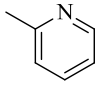
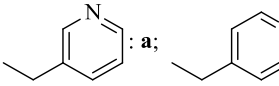
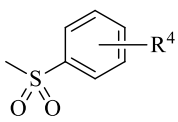
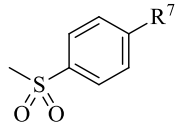


Scheme 10. Reaction of 8HQ and 5-substituted 8HQs, CH_2O and morpholine derivatives.

In the following, the application of piperazine and *N*-substituted piperazines as secondary amines is demonstrated in the reaction of 8HQ (**1**) and 5-NO_2-8HQ (**14**) (Table 7). Another example of the use of MW is the study by Prati *et al.* to synthesise **173** *via* adding **1** and paraformaldehyde to the dry EtOH solution of piperazine and stirring it at r.t. for 10 minutes, then treating the mixture at 130 °C for 45 minutes under MW irradiation.[74] This research group used **173** to synthesise further derivatives, including **176a**, *via* classical S_N2 nucleophilic substitution with the appropriate benzyl chloride. Shaw *et al*., in turn, synthesised **176a** directly from **1**, *N*-benzylpiperazine and paraformaldehyde upon stirring the components in dry EtOH at reflux.[64] Shaw *et al.* used this method successfully for compounds **176b**, **179b**–**o**, **180a,b** and **187a,b**.[64] Derivatives **174**, **175a,c** and **177** were prepared by Faydy *et al*. *via* adding the EtOH solution of **1** to the EtOH solution of paraformaldehyde and the amine kept under reflux, then stirring at reflux for 3 hours.[139,140] The preparation of **175b** and **183b** was reported by Enquist *et al.* reacting CH_2O and 4-fluorophenylpiperazine under cooling on ice, then adding the resulting precipitation portionwise to **1** or **14** in pyridine at 50 °C.[51] **178** was synthesised by Free *et al.*[76] Chen *et al.* carried out the synthesis of **179a** and **187c** *via* dissolving the components in dry EtOH and

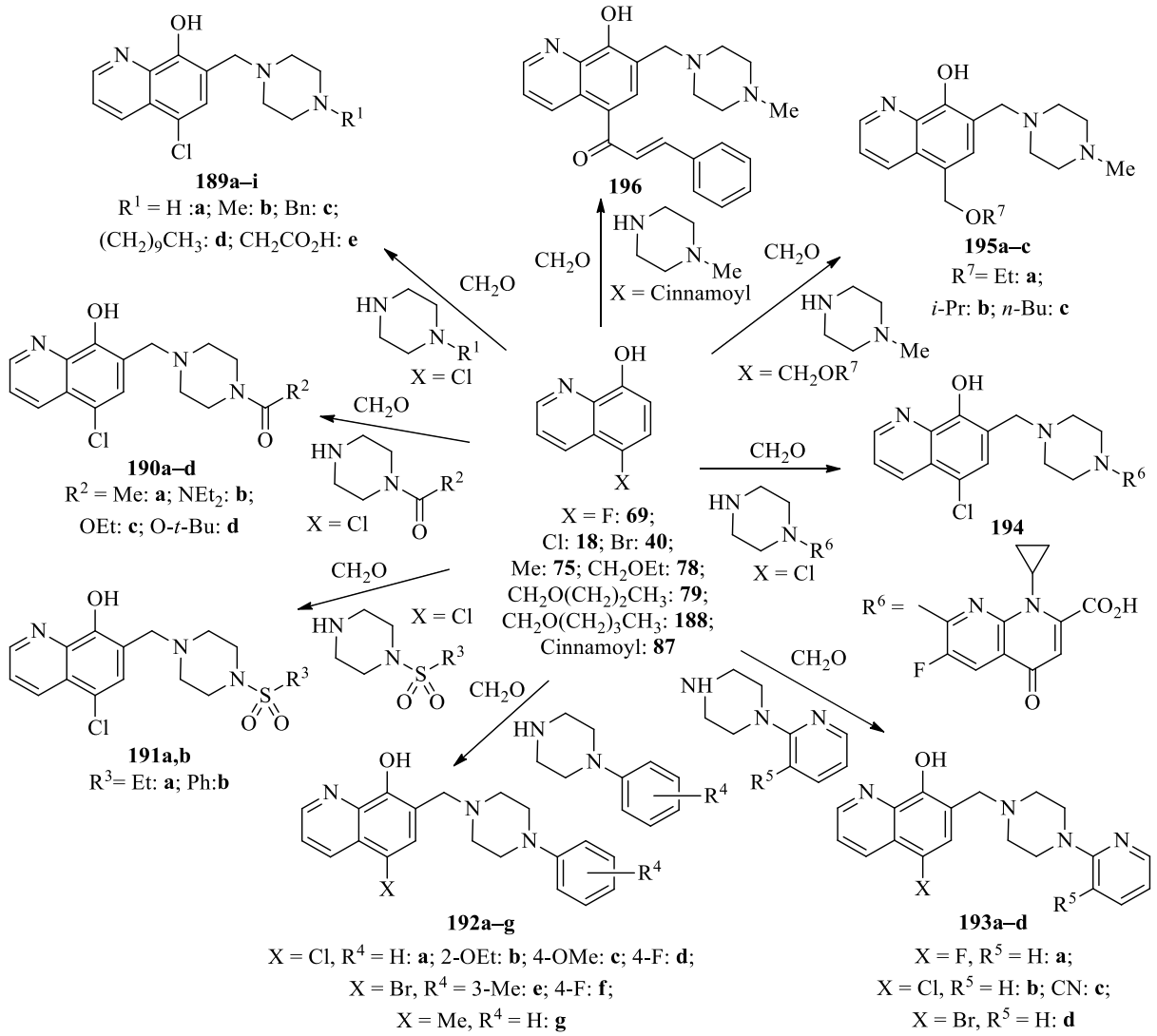
Table 7. Reaction of 8HQ/5-NO_2-8HQ, formaldehyde and piperazine derivatives.



Comp.	R^1	Ref.	Comp.	R^2	Ref.
173	H	74	**181**	H	112
174	Me	139	**182a–c**	Me: **a**; Et: **b**; CO_2Et: **c**	89, 54, 69
175a–c		R^3 = H: **a**; F: **b**; Cl: **c**	139, 140, 51	**183a–m**		R^6 = H: **a**; 4-F: **b**; 2-F: **c**; 2,4-F_2: **d**; 4-Cl: **e**; 2,4-Cl_2: **f**; 4-NO_2: **g**; 2-Me: **h**; 3-Me: **i**; 4-Me: **j**; 3-OMe: **k**; 4-OMe: **l**; 2-OMe: **m**	51, 89, 54, 50
176a,b		: **a**; : **b**	64	**184a–c**		: **a**; : **b**; : **c**	112
177			140	**185a–c**		: **a**; : **b**; : **c**	54
178			76	**186a,b**		: **a**; : **b**	69
179a–o		R^4 = H: **a**; 2-NO_2: **b**; 4-NO_2: **c**; 4-F: **d**; 4-Cl: **e**; 4-Br: **f**; 4-Me: **g**; 4-CF_3: **h**; 4-*i*-Pr: **i**; 4-*t*-Bu: **j**; 4-Ph: **k**; 4-OMe: **l**; 3,4-$(OMe)_2$: **m**; 3-OMe: **n**; 4-OCF_3: **o**	63, 64	**187a–c**		R^7 = H: **a**; NO_2: **b**; Me: **c**	64, 63
180a,b		R^5 = 1-naphtyl: **a**; 2-naphtyl: **b**	64				

then treating the mixture at reflux.[63] **181** and **184a–c** were obtained by Shterev *et al.* utilising the same method as applied for **71a** and **161c–e**.[112] **182a** and **183a** were prepared by Movrin *et al*. upon reacting the components in pyridine at 50–60 °C.[89] Yin *et al.* accomplished the transformation of **14** in pyridine with the appropriate amine at 50 °C, resulting in **182b**, **183c**–**n** and **185a**–**c**.[54] Sosič *et al.* also applied pyridine as a solvent to acquire **182c** and **186a,b**.[69] Elofsson *et al.* disclosed the fabrication of **183m**.[50]

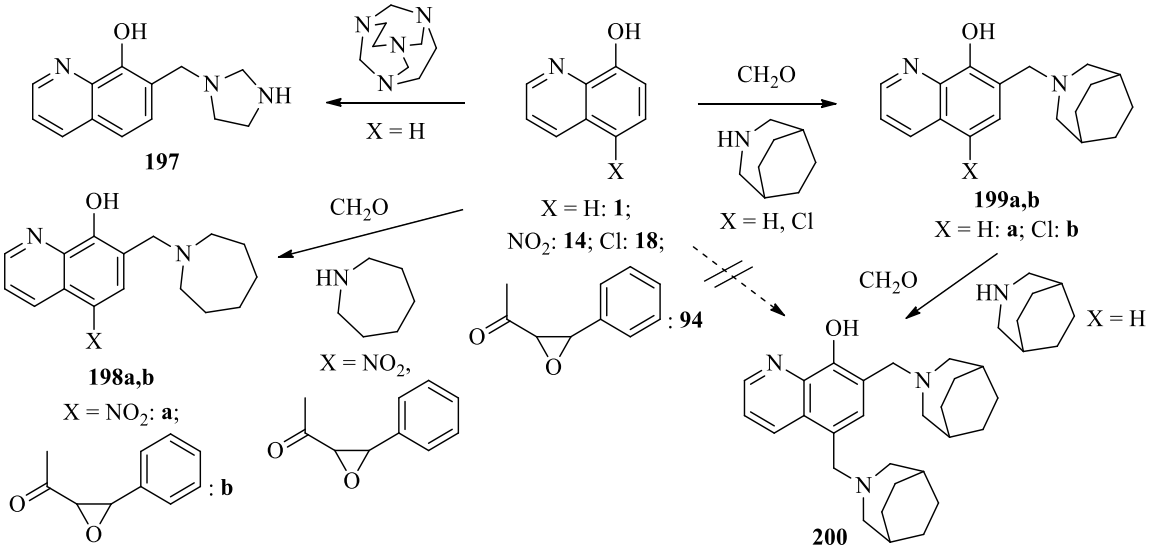
The results of aminoalkylation of 5-halogeno, 5-alkyl and 5-alkoxy 8HQs by piperazine and *N*-substituted piperazines are included in Scheme 11. Prati *et al.* synthesised **189a** similar to that used for **173**.[74] **189b–e**, **190b,c** and **191a** were prepared by Burckhalter *et al.* They also made **189a**; however, not *via* Mannich reaction, but treating **190c** with cc. HCl and then NH_4OH.[80] Moreover, they prepared **191a** both *via* the Mannich route and, alternatively, by the treatment of **189a** with ethanesulfonyl chloride. **190a** and **190d** were made by Thinnes *et al. via* stirring **18**, paraformaldehyde and 1-acyl/Boc-piperazine in the presence of triethylamine in EtOH.[141] Compound **191b** was described by Shaw *et al*.[64] The synthesis of **192a,b,e** was carried



Scheme 11. Reactions of 5-Hlg-8HQs, formaldehyde and piperazine derivatives.

out by Enquist *et al.*, using the same method applied for **175b** and **183b**.[51] The treatment of **18** in absolute EtOH, paraformaldehyde and 1-(4-methoxyphenyl)piperazine in the presence of triethylamine delivered **192c** (Bhat *et al.*).[59] The synthesis of **192d**, **192f** and **193b** were disclosed by Elofsson.[50] Among the compounds mentioned previously, **192g** was reported by Edgerton and Burckhalter as well.[117] The syntheses of **193a** and **193d** from **69**/**40**, 1-(pyridin-2-yl)piperazine and formalin (37%) were achieved by Chan *et al.*, stirring the mixture of components at 80 °C.[77] The synthesis of compound **193c** was reported by Free *et al.*[76] In a rather remarkable study by Fu *et al.,* an 8HQ–ciprofloxacin hybrid was synthesised. The treatment of the dry EtOH solution of **18** with paraformaldehyde and ciprofloxacin as secondary amine for 8 hours under reflux gave the desired **194**.[142] Burckhalter and Leib extended their research on **195a**–**c**, whereby the EtOH solution of *N*-methylpiperazine and paraformaldehyde was added to the EtOH solution of 5-alkoxy-8HQs (**78**, **79** or **189**) followed by heating under reflux.[120] In addition to previous acyl derivatives, 5-cinnamoyl **196** was also described by Schraufstätter and Bock using formalin (30%) as the CH_2O provider.[121]

Scheme 12 depicts the application of 7-membered ring systems. Rivera *et al.* reported a modification of the Mannich reaction. Instead of using CH_2O and an amine as reactants, 1,3,6,8-tetraazatricyclo-[4.4.1.1]dodecane (TATD) was added to **1** and isolating **197**. The process was described as a solvent-free Mannich-type reaction.[143] Shterev *et al.* extended their investigation to the synthesis of **198a** as well.[112] Möhrle and Schaltenbrand applied azepine similar to Shterev *et al*., and the synthesis of **198b** was accomplished starting from **94**.[124] Magarian and Nobles used formalin (37%), 3-azabicyclo[3.2.2]nonane and 8HQ (**1** or **14**) in EtOH at reflux to acquire **199a,b**.[144] Disubstituted products are not usual in the Mannich reaction, but Magarian and Nobles could achieve the synthesis of **200**; however, it could be synthesised only from **199a**, rather than from **1**.



Scheme 12. Reaction of 8HQ and 5-substituted 8HQs, CH_2O and 7-membered cyclic amines.

3. RESULTS AND DISCUSSION

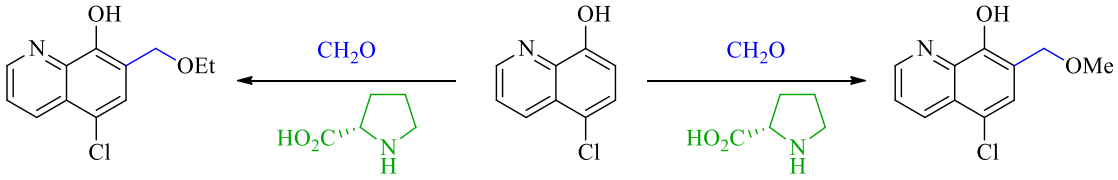
3.1. Syntheses and transformations of *N*-containing 1-naphthol analogues

The nitrogen-containing 1-naphthol analogues discussed in this subsection include 5-chloro-8-hydroxyquinoline and 4-hydroxyquionoline acetates.

3.1.1. Transformations of 5-chloro-8-hydroxyquinoline

The aminoalkylation of 5-chloro-8-hydroxyquinoline at position 7 using various aldehydes and amine components has been widely explored as summarised in the literature part. The water solubility of the reviewed compounds is rather limited, which might affect the biological activity and the pharmacological applicability in some cases. To overcome to this limitation, our primary objective was to synthesise compounds with increased water solubility, which was planned to be achieved *via* the incorporation of zwitterionic α-amino acids.

In our first experiment, L-proline was reacted with **18** and formalin (38%) in EtOH stirring the reaction mixture in an oil bath at 80 °C. The performed TLC showed a new spot, and the reaction was worked up after 6 hours. The ^{1}H NMR spectrum of the isolated product revealed the lack of signals associated with L-proline from the aliphatic region. In contrast, a new quartet and a triplet signal appeared, indicating CH_2 and CH_3 groups, i.e., the formation of an ethoxymethyl group at C-7 (Scheme 13, **201**). Hon *et al.* obtained a similar product,[145] namely 5,7-bis(ethoxymethyl)quinolin-8-ol from the reaction of 8HQ (**1**), paraformaldehyde and hydrochloride salt of diethylamine in EtOH.

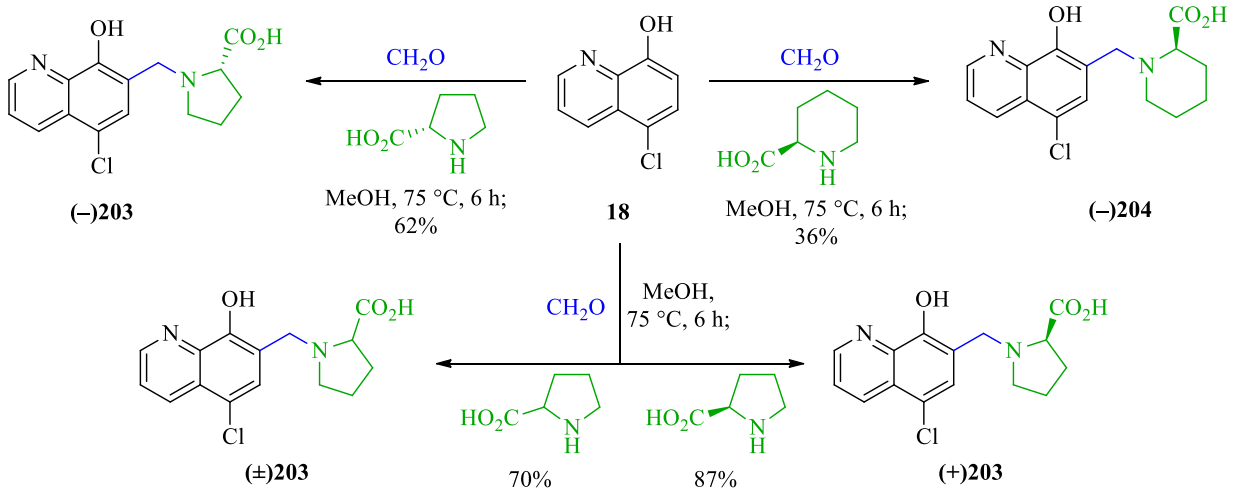


201 **18** **202**

Scheme 13. Reaction of 5-Cl-8HQ, formalin (38%) and L-proline in EtOH and MeOH.

The synthesis was repeated in various solvents (1,4-dioxane, DMF, H_2O, toluene, MeOH), but the reaction did not afford assessable results, and observable transformation occurred only in MeOH. However, after the analysis of the ^{1}H NMR of the isolated product, it was found, that the compound was another ether derivative (**202**), and it was MeOH acting as a nucleophile instead of L-proline. Subsequently, the temperature was reduced to 75 °C, and the mixture of 5-Cl-8HQ with formalin (38%) and L-proline in MeOH was stirred for 6 hours, and then the solvent was removed (Scheme 14). After isolation, the ^{1}H NMR spectrum of the compound confirmed both

the structure of **(–)203** and the necessity of purification. Due to the similar physical properties of the product and L-proline, the attempts to remove the unreacted L-proline was problematic. The practical solution for this issue was that L-proline was used in a molar equivalent lower than that of **18**. Therefore, when L-proline was no longer available in the reaction, the excess of 5-Cl-8HQ could be removed conveniently *via* recrystallisation. As an extension, the reaction was carried out with racemic proline, D-proline, and D-homoproline (pipecolic acid) under the previously optimised conditions, leading to **(±)203**, **(+)203** and **(–)204**, respectively.



Scheme 14. Reaction of 5-Cl-8HQ, formalin (38%) and α-amino acids.

The purity of the synthesised prolinomethyl compounds were checked via HPLC (*n*-Hex *i*PA 80:20; 0.2 ml/min; Chiralpak® IA). According to Figure 1, the transformation did not affect the chirality centre of the proline moiety.

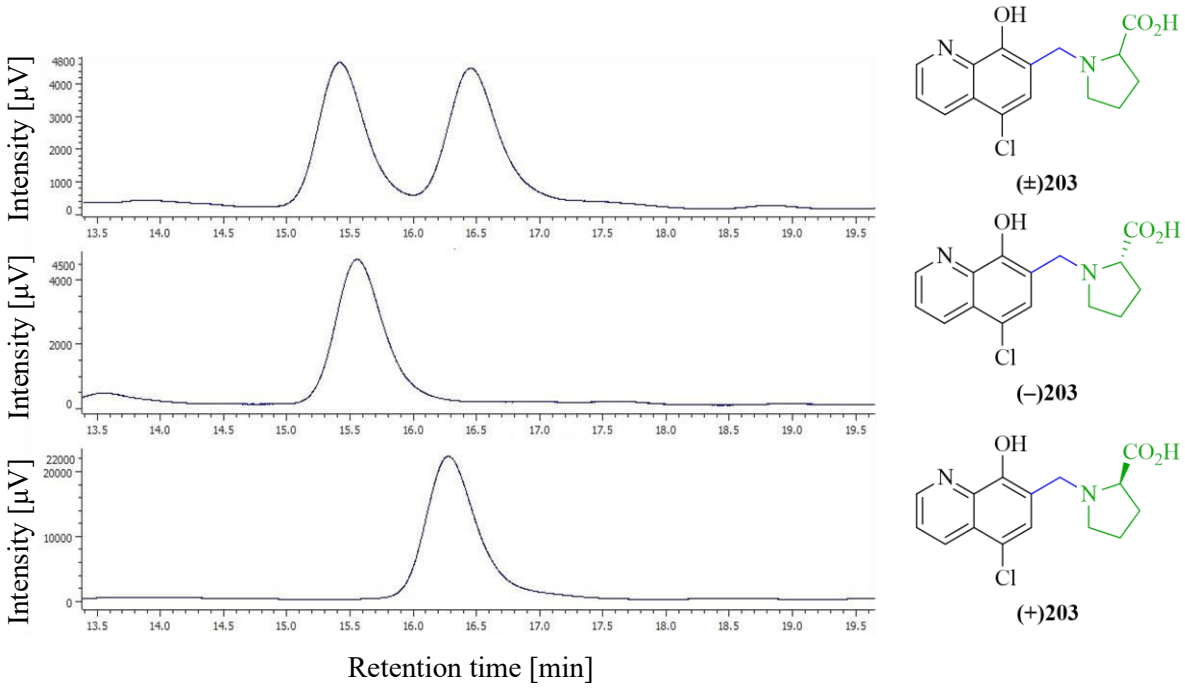


Figure 1. The investigation of synthesised compounds via HPLC.

The solution chemical properties of synthesised compounds **(–)203**, **(+)203** and **(–)204** were investigated in complex formation with half-sandwich organometallic ruthenium and rhodium cations. The antiproliferative and cytotoxic evaluation of the compounds and their complexes were performed *in vitro*, and their MDR selectivity was assessed.

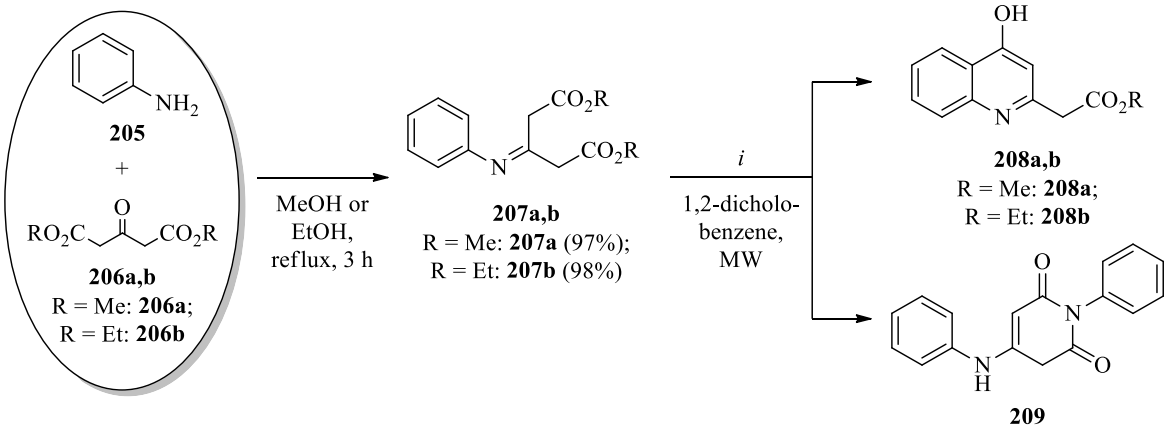
3.1.2. Syntheses and transformations of 4-hydroxyquinoline acetates

Our next aim was to test the reactivity of 2-(4-hydroxyquinolin-2-yl) acetates in the Mannich reaction, using piperidine as amine with formaldehyde or aromatic aldehydes. A further aim was to develop tumour-selective anticancer drugs that are potent against cancer cells and exert low toxicity towards normal cells.

3.1.2.1. Syntheses of 4-hydroxyquinolines

The synthesis of ethyl 2-(4-hydroxyquinolin-2-yl) acetate is known as the Conrad–Limpach reaction.[146–148] However, Rahn *et al.* revealed an alternative synthetic method, when 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene was reacted with 2-nitrobenzoyl chlorides followed by the hydrogenation of the condensation products resulting in substituted 2-(4-hydroxyquinolin-2-yl) acetates.[149] In our study, the Conrad–Limpach reaction was used with some fine-tuned modifications (Scheme 15).

Aniline (**205**) and dimethyl- or diethyl-1,3-acetonedicarboxylate (**206a,b**) were dissolved in methanol or ethanol, respectively. The mixture was treated under reflux conditions for 6 hours, affording intermediate enamines **207a** or **207b**. The alcohol was evaporated by vacuum distillation, and the residue was dissolved in 1,2-dichlorobenzene.



Scheme 15. Reaction of aniline and dialkyl-1,3-acetonedicarboxylates.

According to the literature, ring closure requires high temperature for a short period of time. The boiling point of 1,2-dichlorobenzene is 180 °C, but the required temperature was higher. Therefore, the reaction was performed in closed, pressurised vials with heating in a micro-

wave reactor, enabling a temperature higher than that of the boiling point of the solvent. Several conditions [Scheme 15, (*i*)] were tested, which are included in Table 8. After MW irradiation, the mixture was cooled in iced water and crystals formed were filtered out.

Table 8. Reaction conditions (*i*) for the synthesis of **208a,b** and **209**.

Product	Time (min)	Temperature (°C)	Yield of 208a / 208b (%)	Yield of 209 (%)
208a	20	240	28	0
	20	245	31	0
	20	250	27	0
	20	245	0	53 [1]
208b	20	220	7	0.5
	20	230	16	0.6
	20	235	28	0.3
	20	240	35	0.1
	20	245	41	0
	20	250	35	0
	15	245	37	0
	30	245	36	0

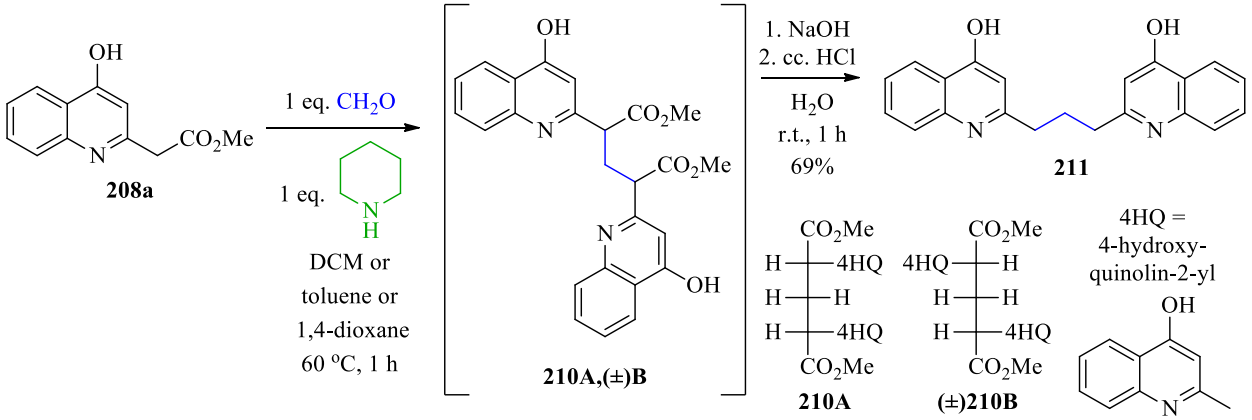
[1] With added *para*-toluenesulfonic acid (*p*-TSA).

At lower temperatures, the presence of byproduct **209** was observed, but its formation could be lowered by increasing the temperature. The critical reaction temperature was 245 °C, since at lower temperatures, the presence of **209** could be perceived. However, according to the literature,[150] 4 hours at 120 °C, followed by a 2-hour heating at 180 °C are the optimum conditions for the formation of **209**. In contrast to some earlier studies,[151] our observation was that an acidic catalyst (*e.g.*, *p*-TSA) did not afford the formation of the quinoline skeleton and only pyridinedione **209** was detected.

3.1.2.2. Reaction of 4-hydroxyquinolines with paraformaldehyde and piperidine

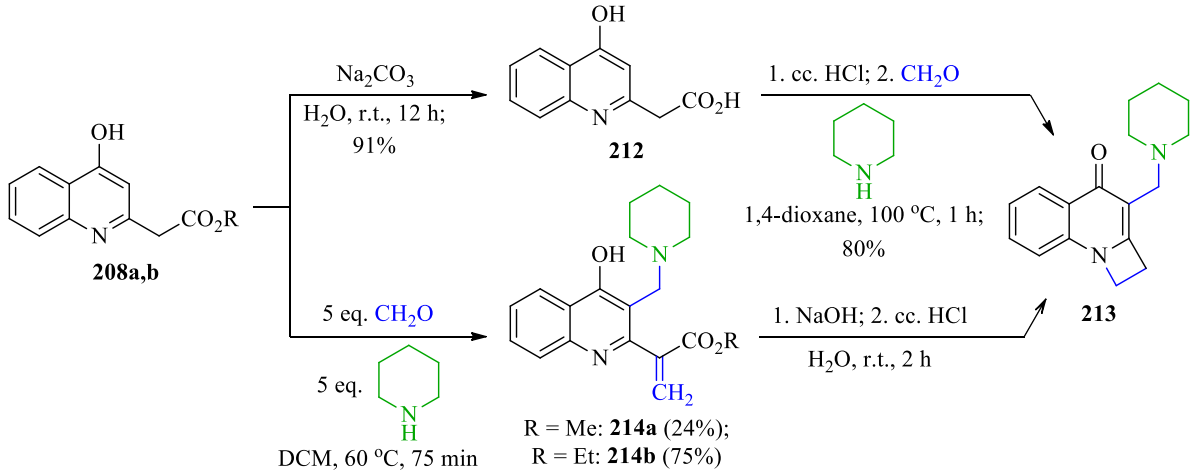
Our first attempt was the aminoalkylation of **208a** *via* reacting piperidine and paraformaldehyde in dichloromethane (DCM) under reflux. After a 1-hour reaction, formed crystals were filtered out. The crude ^{1}H NMR spectrum showed that the product was not the desired 3-aminometylquinolinol. The spectrum was remarkably similar to that found by Tatemitsu *et al.* studying *meso*- and (±)-diphenylglutaric acid.[152] Valdéz-Camacho *et al.* also isolated the mixture of *erythro* and *threo* dimethyl 2,4-diphenylpentanedioate byproducts.[153] Möhrle and Schaltenbrand gained aminomethylated methylenebis compounds under conventional Mannich conditions, instead of the classical Mannich product.[154] According to these observations, we assumed that the reaction afforded the mixture of *meso* compound **210A** and racemic compound **(±)210B** (Scheme 16). Our attempts to separate these compounds were unsuccessful, but in order to confirm the structures synthetically, decarboxylation was tested. The saponification of **208b** furnishes the 2-methyl derivative, i.e., quinaldine.[146] Note that similar bisquinolines have been synthesised and transformed via decarboxylation by Ayad *et al.* applying NaOH.[155] Accordingly,

NaOH treatment was followed by neutralisation. In the ^{1}H NMR spectrum of the isolated product, a quintet with 2 integrals at 2.12 ppm and a triplet with 4 integrals at 2.70 ppm were present. These multiplicities appear, when a –$(CH_2)_3$– chain is located between aromatic rings,[156] which is consistent with the structure of **211**.



Scheme 16. Reaction of 4HQ acetates with paraformaldehyde in the presence of piperidine.

The reaction in toluene and 1,4-dioxane afforded the bisquinoline derivatives as well. In order to gain an aminomethyl product, it was necessary to synthesise the carboxylic acid derivatives of **208a,b** and then to transform them *via* Mannich reaction. As mentioned, the saponification of **208a,b** with NaOH affords quinaldine; consequently, alternative reagents were tested. Acidic ester hydrolysis by cc. HCl furnished **212**, but after a few hours, spontaneous decarboxylation took place resulting in quinaldine. Immediately after isolation of **212**, without waiting for undesired decarboxylation, paraformaldehyde and piperidine were added, and the mixture was stirred in 1,4-dioxane for 1 hour. The formed white solid was isolated and analysed. In the ^{1}H NMR spectrum, two triplets were observed with 2-2 integrals, which indicates the presence of two –CH_2– neighbouring groups. In addition, the signs of piperidine and the methylene bridge were also present. These were not consistent with the structure hypothesised previously, but the formation of **213** was assumed (Scheme 17).



Scheme 17. Synthetic routes to 1*H*-azeto[1,2-*a*]quinolin **213**.

In order to gain the stable 2-(4-hydroxyquinolin-2-yl)acetic acid (**212**), **208a** was treated with Na_2CO_3. The hydrolysis required a longer reaction, but a stable compound was formed. It was reacted with paraformaldehyde and piperidine in 1,4-dioxane, but no reaction occurred. The reaction was modified by first using cc. HCl followed by adding the other reagents (paraformaldehyde and piperidine). A new spot appeared on the TLC, and the isolated product was identical to that synthesised previously (compound **213**).

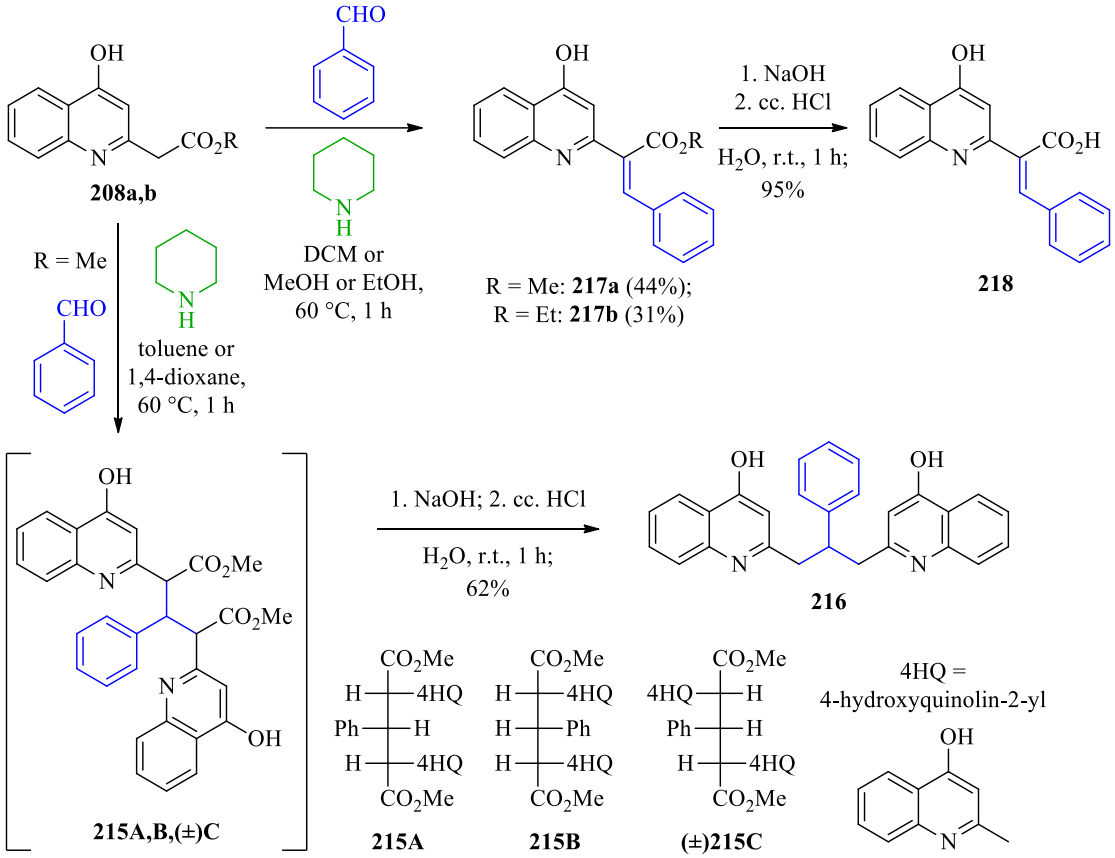
The aminomethylation presumably took place on **212**; therefore, the reaction of **208a** was repeated with an increased amount of paraformaldehyde and piperidine using 5 equivalents each. The reaction was carried out in DCM stirring for 75 minutes. After isolation, the corresponding spectra were studied. The ^{1}H NMR spectrum seemingly indicated the 3-(piperidin-1-ylmethyl) derivative of **208a**, since the signs of piperidine and the –CH_2– bridge could be observed. However, the MS spectrum showed a higher molecular weight; therefore, it was presumed that Mannich reaction and α-methylenation took place concomitantly, resulting in the structure of **214a**. The synthesis of **214b** was carried out in a similar manner providing a higher yield compared to that of the methyl ester. The saponification of the two esters was carried out, and in both cases, the reactions afforded the same spot observed by TLC and the same ^{1}H NMR spectrum. The spectra were also identical to the spectrum of **213**, which confirmed its structure, that is a new 1*H*-azeto[1,2-*a*]quinoline derivative was isolated. This reaction also undoubtedly proves that **214a** and **214b** are acrylate derivatives with 3-(piperidin-1-ylmethyl) substitution.

3.1.2.3. Reaction of 4-hydroxyquinolines with aromatic aldehydes and piperidine

Our next goal was to change paraformaldehyde to aromatic aldehydes to explore reactivities. First, benzaldehyde, piperidine, and **208a** were reacted (Scheme 18). Toluene and 1,4-dioxane were tested as solvents, but in both cases, the experiments led to the formation of bisquinolines (**215A**,**B**,(±)**C**). Synthetic verification was also desired performed by hydrolysis with NaOH, followed by neutralisation delivering **216** in good yields.

Thereafter, the solvent was changed to DCM. The expected compound was a Mannich product. However, after isolation of the main product, its ^{1}H NMR spectrum showed that the presence of the CH_2 group of the starting compound (**208a**) disappeared and the piperidine moiety was not incorporated. In the spectrum, the presence of ten aromatic protons could be observed. According to these findings, the formation of methyl 4-hydroxyquinoline-3-phenyl acrylate (**217a**) was assumed, rather than that of the desired Mannich product (Scheme 18). The process can be explained by the Knoevenagel condensation,[157] a reaction between the activated CH_2 group and benzaldehyde. A solvent change was carried out as MeOH was tested, and a higher

yield was observed. **217b** was furnished in a similar manner, starting from **208b** and applying EtOH as solvent.

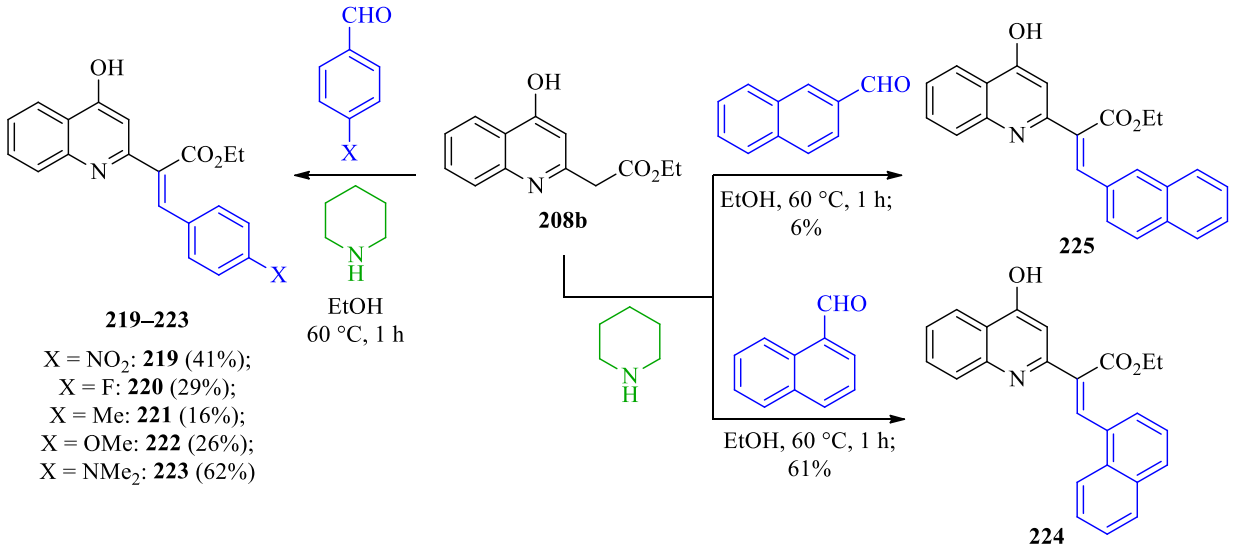


Scheme 18. Reaction of 4HQs with benzaldehyde in the presence of piperidine.

Furthermore, decarboxylation experienced previously was also tested, hypothesising that a styrylquinoline derivative would form. Styrylquinolines possess a rather wide range of biological activities, including antiproliferative,[158–161] antiviral and antibacterial activities.[162] Therefore, **217a** was stirred with NaOH in water at r.t., then the reaction mixture was neutralised with cc. HCl. According to the ^{1}H NMR spectrum, there was no additional proton sign, which would have indicated decarboxylation. Mass spectrometry also supported that only ester hydrolysis took place. The reaction was repeated at a higher temperature but again, only the carboxylic acid derivative was isolated (**218**).

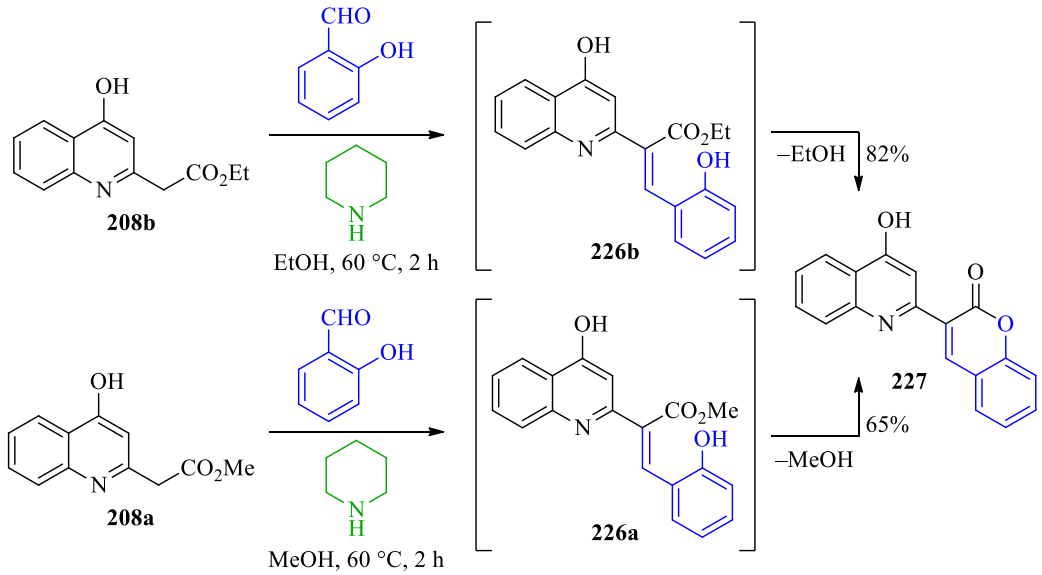
In order to investigate the extensibility of the reaction, the aldehyde component was modified. Since the yield from starting compound **208b** was higher than that of **208a**, we continued our work with only the ethyl ester (Scheme 19). Five *para*-substituted (*p*-NO_2, *p*-F, *p*-Me, *p*-OMe, *p*-NMe_2) benzaldehydes were tested. The corresponding benzaldehyde, **208b**, and piperidine were dissolved in EtOH and the mixture was treated at reflux temperature for 1–10 hours. The solubility of products in EtOH was lower than that of the starting compounds and, consequently, the formed substances were crystallised from EtOH. In all cases, NMR confirmed the structures of the new *p*-substituted benzylidenes (**219**–**223**). The reactivity of 1- and 2-

naphthaldehyde was tested, and **224** was isolated in a good yield, but **225** was formed in a much lower yield. A possible explanation is that the 1-naphthyl ring promotes condensation, but the 2-naphthyl group sterically inhibits it.



Scheme 19. Reaction of **208b** with aromatic aldehydes in the presence of piperidine.

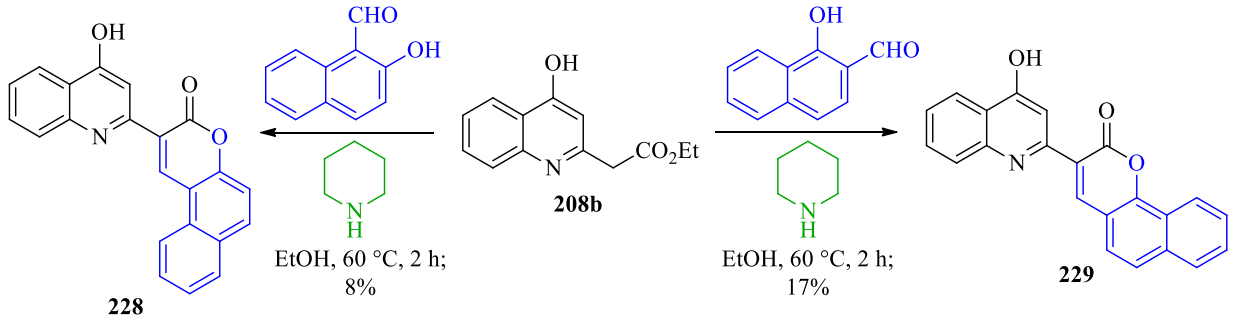
In further investigation, salicylaldehyde, an *ortho*-substituted benzaldehyde was tested. It was treated at reflux temperature with **208b** in the presence of piperidine in EtOH, which led to the formation of a single product after a short reaction of 2 hours. The ^{1}H NMR spectrum of the isolated solid showed the absence of the ethyl ester group. This clearly indicates that compound **226b** is an intermediate product (Scheme 20), and an intramolecular ring closure takes place via EtOH loss; thus, a new 2*H*-chromen-2-one derivative (**227**) was isolated. Our hypothesis, i.e., spontaneous ring closure *via* alcohol loss, was confirmed by repeating the reaction with **208a**. As expected, the synthesis led to the formation of the same chromanone derivative (**227**).



Scheme 20. Reaction of 4HQs with salicylaldehyde in the presence of piperidine.

The *Z*/*E* isomerism of benzylidenes (**217a,b**, **218**, **219**–**225**) synthesised previously has not been described. The ring closure of **227** can only take place if the intermediate products (**226a,b**) are *Z*-isomers, because the functional groups, involved in ring closure, are located in a sterically appropriate arrangement. This indirectly proves that all isolated compounds are *Z*-isomers.

There are known synthesis pathways for 2-quinolyl coumarins,[163–166] but our reaction (Scheme 20) provides a more convenient alternative synthetic route. The reaction was further tested for functionalised aromatic aldehydes such as 2-hydroxy-1-naphthaldehyde and 1-hydroxy-2-naphthaldehyde. In these cases, the expected intramolecular ring closure took place and compounds **228** and **229** were isolated (Scheme 21). The ring closure can only happen, provided the intermediates are *Z* isomers, which is a further support to our hypothesis about *Z*/*E* isomerism of the synthesised benzylidene derivatives.



Scheme 21. Reaction of **208b** with hydroxynaphthaldehydes in the presence of piperidine.

3.1.2.4. Biological evaluation of the synthesised compounds

The cytotoxic activity of the derivatives was evaluated using doxorubicin-sensitive and -resistant colon adenocarcinoma cell lines (Colo 205 and Colo 320, respectively) and normal human embryonic MRC-5 fibroblasts (Table 9). The IC_{50} values below 20 μM were considered as cytotoxic. In this regard, the following compounds were cytotoxic on the resistant cancer cell line Colo 320 (IC_{50} values are expressed in μM): **219** (IC_{50}: 4.61), **217b** (IC_{50}: 4.58), **217a** (IC_{50}: 8.19), **228** (IC_{50}: 9.86), **225** (IC_{50}: 11), **221** (IC_{50}: 12.29), **227** (IC_{50}: 14.08). Compounds **219** (IC_{50}: 2.34), **217b** (IC_{50}: 8.1), **221** (IC_{50}: 11.79), **217a** (IC_{50}: 11.86), **225** (IC_{50}: 12.63), **220** (IC_{50}: 16.54) exerted cytotoxic activity on the chemosensitive tumour cell line Colo 205.

The selectivity of the compounds towards cancer cells compared to normal cells was calculated using the non-tumoural MRC-5 human embryonic lung fibroblast cell line, as reported previously.[167] The different selectivity indexes (SI) were evaluated as the quotient of the IC_{50} value in the non-tumoural cells divided by the IC_{50} in the cancer cell line. The compounds' activity towards cancer cells is considered to be strongly selective, if the selectivity index (SI) value is higher than 6, moderately selective if $3 < SI < 6$, slightly selective if $1 < SI < 3$ and non-selective if SI is lower than 1. The most selective derivative towards the resistant Colo 320 cell line was

228 showing an SI higher than 6 (Table 10). Moderate selectivity towards MDR cancer cells was obtained in the presence of compounds **217b** and **217a**, with the selectivity indices 4.14 and 3.49, respectively. In addition, moderate selectivity was observed towards the sensitive cancer cell line Colo 205 with compound **219** (SI: 4.23).

Table 9. Cytotoxic activity of the synthesised compounds on Colo 205 and Colo 320 cell lines, and normal human embryonic MRC-5 fibroblasts.

Compound	Colo 205 IC_{50} (µM)		Colo 320 IC_{50} (µM)		MRC-5 IC_{50} (µM)	
	Mean	SD (+/−)	Mean	SD (+/−)	Mean	SD (+/−)
208a	>100	−	92.78	1.68	>100	−
208b	>100	−	>100	−	>100	−
209	>100	−	>100	−	>100	−
211	>100	−	>100	−	>100	−
212	>100	−	>100	−	>100	−
213	>100	−	>100	−	>100	−
214a	>100	−	>100	−	>100	−
214b	>100	−	>100	−	>100	−
216	>100	−	>100	−	>100	−
217a	11.86	1.07	8.19	1.35	28.56	1.11
217b	8.10	0.11	4.58	0.18	18.94	1.83
218	>100	−	>100	−	>100	−
219	2.34	0.24	4.61	0.24	9.89	0.00
220	16.54	1.97	42.65	2.26	21.94	0.82
221	11.79	0.27	12.29	0.55	30.64	0.64
222	42.76	2.35	>100	−	65.18	1.13
223	>100	−	>100	−	>100	−
224	>100	−	32.40	3.37	36.54	1.01
225	12.63	0.49	11.00	0.37	17.58	0.27
227	>100	−	14.08	0.35	6.52	0.46
228	>100	−	9.86	0.90	>100	−
229	>100	−	>100	−	>100	−
DOXO	2.30	0.12	3.61	0.34	>10	−

DOXO: doxorubicin

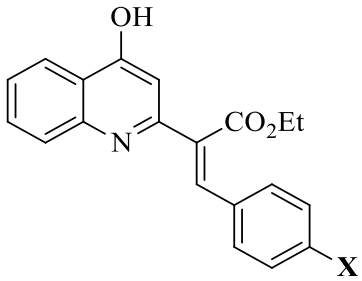
Table 10. The selectivity index of the synthesised compounds based on their IC_{50}.

Comp.	SI (Selectivity Index)		Comp.	SI (Selectivity Index)	
	MRC-5/Colo 205	MRC-5/Colo 320		MRC-5/Colo 205	MRC-5/Colo 320
208a	−	−	**218**	−	−
208b	−	−	**219**	4.23	2.15
209	−	−	**220**	1.33	0.51
211	−	−	**221**	2.60	2.49
212	−	−	**222**	1.52	−
213	−	−	**223**	−	−
214a	−	−	**224**	−	1.13
214b	−	−	**225**	1.39	1.60
216	−	−	**227**	−	0.46
217a	2.41	3.49	**228**	−	>6
217b	2.34	4.14	**229**	−	−

Selectivity index = $IC_{50\ (MRC\text{-}5)}/IC_{50\ (Colo205)}$ or $IC_{50\ (MRC\text{-}5)}/IC_{50\ (Colo320)}$.

Overseeing the results, mainly *para*-substituted benzylidene derivatives proved to be active compounds as cytotoxic agents. It was realised that the activity might correlate with a certain effect of the functional groups. A well-known descriptor is the Hammett–Brown substituent σ^+ (σ_p^+ for *para*-substituted derivatives), which sums up the electronic effect of a substituted group on a benzene ring.[168] Table 11 includes the constant σ_p^+ and the pIC_{50} obtained from IC_{50}.

Table 11. The Hammett–Brown constant (σ_p^+) for substituents (X) at the *para* position and the corresponding negative logarithm of IC_{50} (pIC_{50}).



Comp.	X	σ_p^+	Colo 205 pIC_{50}	Colo 320 pIC_{50}
219	NO_2	0.79	5.63	5.34
217b	H	0.00	5.09	5.34
220	F	–0.07	4.78	4.37
221	Me	–0.31	4.93	4.91
222	OMe	–0.78	4.37	<4.00
223	NMe_2	–1.70	<4.00	<4.00

The Hammett–Brown substituent was correlated to the pIC_{50} values. The correlations are depicted in Figure 2. In the case of Colo 205, the R^2 is 0.94, while Colo 320 showed a lower R^2 value of 0.66.

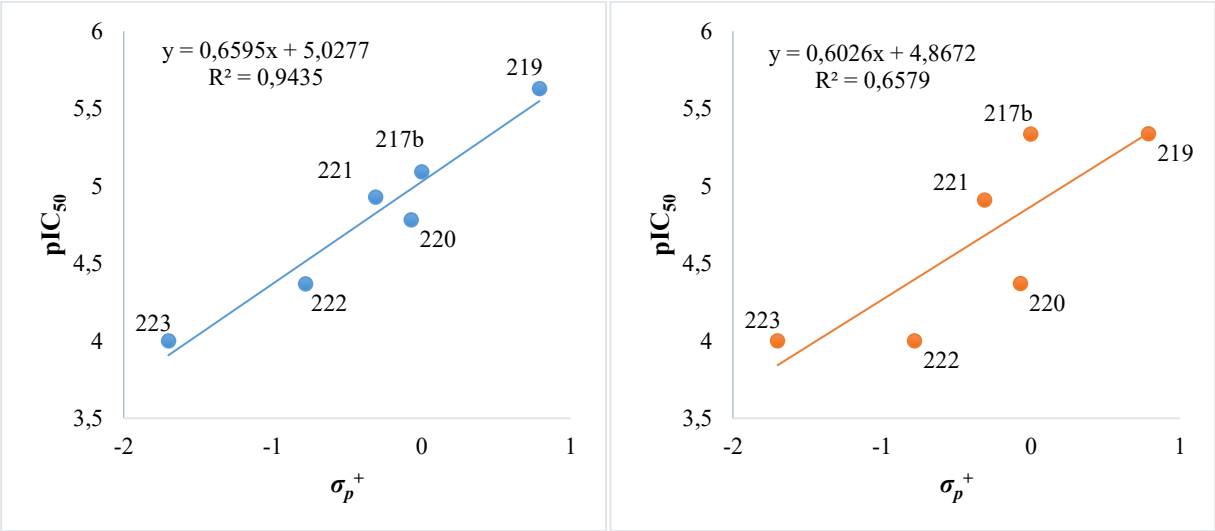


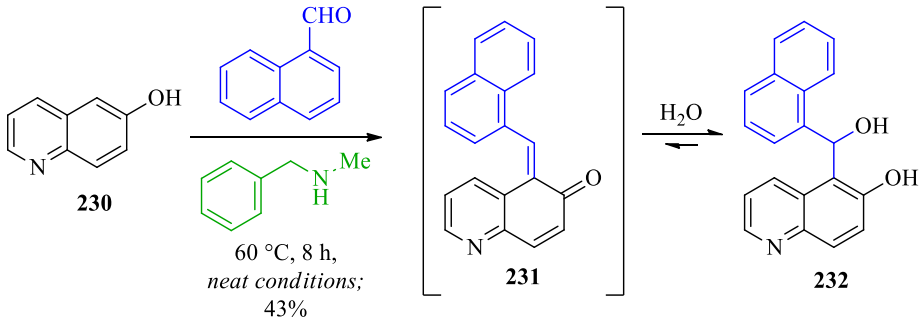
Figure 2. A correlation of the Hammet–Brown constant (σ_p^+) and pIC_{50} for compounds **217b**, **219**–**223**; regression lines and regression coefficients are given.

3.2. Syntheses and transformations of *N*-containing 2-naphthol analogues

As final aim of my Ph.D. work, application of 6-hydroxyquinoline and 3-hydroxyisoquinoline in the Mannich reactions as *N*-containing 2-naphthol derivatives are discussed.

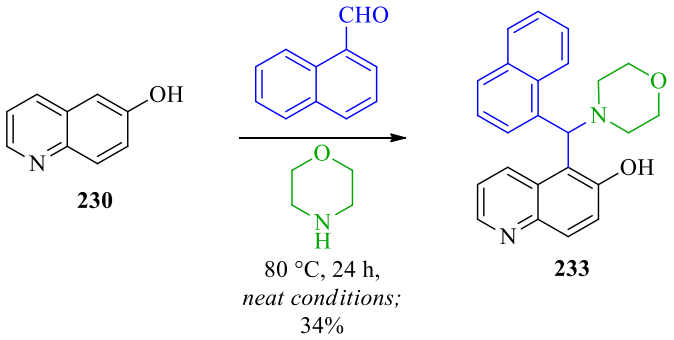
3.2.1. Transformations of 6-hydroxyquinoline

In our first experiments, 6HQ (**230**) was reacted with 1-naphthaldehyde and *N*-benzylmethylamine under neat conditions (Scheme 22). Of the tested temperatures (60 °C, 80 °C and 100 °C), 60 °C was found to be optimal, which was provided by classical heating (an oil bath). After 8 hours, in the course of the workup of the reaction mixture, the crude product was subjected to column chromatography. Subsequent crystallisation from methanol gave a mixture with hydrate **232** as the main component, which is the stabilised form of *ortho*-quinone methide **231** as disclosed by combined NMR methods. An analogous product was isolated in our previous work when 2-naphthol was attempted to be aminoalkylated with *N*-benzylmethylamine in the presence of 1-naphthaldehyde.[44]



Scheme 22. Formation of *ortho*-quinone methide (**231**) and its stabilisation to hydrate (**232**).

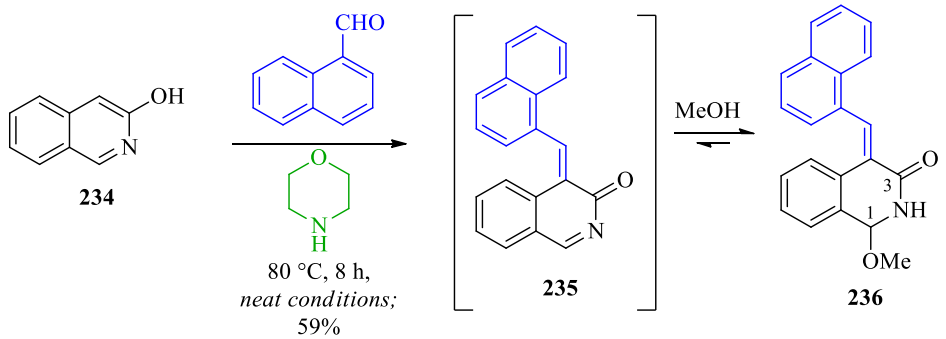
In order to evaluate the role of the amines, morpholine as a secondary cyclic amine was reacted with **230** and 1-naphthaldehyde under conditions that were previously optimised (Scheme 23). TLC confirmed the formation of a single product, which was then isolated by crystallisation. The NMR spectra provided evidence that the use of morpholine as an amine component led to the formation of the classical Mannich product **233**. The differences between the reaction pathways can be explained in terms of the different steric demands and the basicity of the applied amines (pK_b = 4.25 and 5.64 for *N*-benzylmethylamine and morpholine, respectively). Since *N*-benzylmethylamine is bulkier and at least tenfold more basic than morpholine, it can be more prone to activate water molecules as a nucleophile rather than to attack the potential electrophilic species present in the reaction mixture.



Scheme 23. Aminoalkylation of 6HQ, i.e., formation of the classical Mannich product **233**.

3.2.2. Transformations of 3-hydroxyisoquinoline and DFT modelling

In order to explore further structure–reactivity relationships, 3HIQ (**234**), a nitrogen-containing electron-rich aromatic substrate, was selected for subsequent studies. Accordingly, **234**, 1-naphthaldehyde and *N*-benzylmethylamine were reacted under neat conditions. After 30 minutes of reaction time at 60 °C, the prepared TLC was multi-spotted, and no well-defined component could be isolated from the reaction mixture. Thereafter, morpholine was applied instead of *N*-benzylmethylamine. A prolonged reaction time (6 hours) at 80 °C was necessary for the appearance of a few new spots on the TLC. By means of column chromatography, using EtOAc:MeOH (20:1) as an eluent, we isolated methoxy-substituted lactam **236** as a distinct compound (Scheme 24). In the ^{1}H NMR spectrum of **236**, the typical singlet of 3H intensity at 3.35 ppm and the amide-type NH doublet at 9.25 ppm along with ^{1}H-^{13}C-HMBC connectivity between signal pairs O$\underline{C}$H$_3$/C-1, H-1/O$\underline{C}$H$_3$, H-1/C-3, NH/C-3 and NH/C-4 unambiguously proved its structure. The formation of this product can be explained via the formation of the *ortho*-quinone methide intermediate (**235**). Then it reacted at the most electrophilic *N*-acylimine site with methanol present in the solvent mixture used in the chromatographic purification.

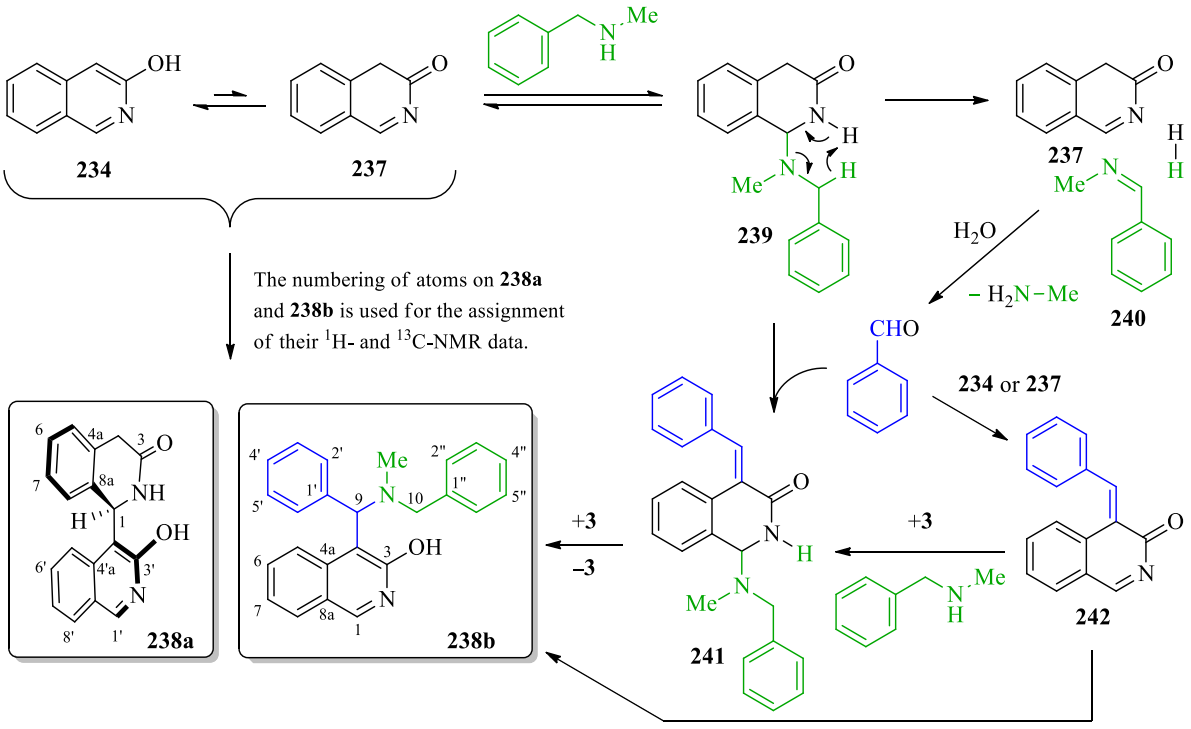


Scheme 24. Nucleophilic attack of MeOH on *o*-QM **235** resulting in C-1 substitution.

To investigate the influence of the arylidene moiety on the apparently unexpected nucleophilic attack of MeOH at position 1, 3HIQ (**234**) and MeOH were stirred at 80 °C. Since, even after a prolonged reaction time (20 hours), TLC indicated only the presence of the starting com-

pounds, the reaction was repeated at 100 °C and 120 °C. Because mixing **234** with MeOH at a higher temperature gave again the unchanged starting compounds, we focused our attention on the evaluation of the effects of stronger nucleophiles, such as *N*-benzylmethylamine and morpholine, on the outcome of the reactions.

First, *N*-benzylmethylamine and **234** were reacted at 80 °C under neat conditions. Surprisingly, after 12 hours of reaction time, TLC showed the formation of a multicomponent mixture. After purification by column chromatography, two components with characteristic compositions (**238a** and **238b**: Scheme 25) could be isolated and identified by combined NMR methods, including the use of highly diagnostic ^{1}H-^{13}C-HMBC. These apparently intriguing transformations can be rationalised by the equilibrium formation of tautomer **237**, the key intermediate of subsequent transformations. On one hand, the nucleophilic attack of tautomer **234** on the highly-electrophilic C-1 centre of this activated *N*-acyl-imine results in the formation of the racemic mixture of chiral dimer **238a**. On the other hand, upon nucleophilic attack of *N*-benzylmethylamine, tautomer **237** is converted into adduct **239**. The latter undergoes a synchronous imine- and dihydrogen-forming fragmentation, leading to Schiff base **240** with the simultaneous regeneration of **237**. Hydrolysis of **240** gives benzaldehyde and methylamine. Upon condensation with benzaldehyde**,** saturated aminal adduct **239** is transformed into **241**. This enone-containing aminal intermediate then undergoes sequential addition and elimination of *N*-benzylmethylamine, eventually affording **238b**, the other isolated aromatic product. Finally,

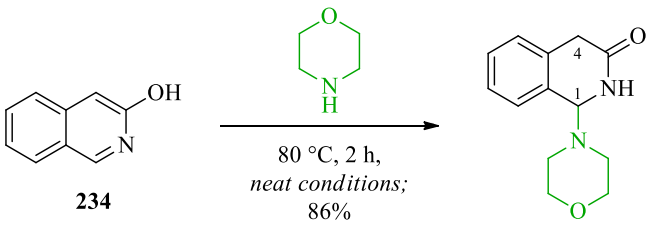


For the sake of simplicity, only a single enantiomer is presented for the racemic **238a** comprising the elements of central and axial chirality. Naturally, **238b** with a single stereogenic centre is also formed as a racemic mixture.

Scheme 25. Unexpected transformations of **234** in the presence of *N*-benzylmethylamine.

either of the two equilibrating tautomers of the heterocyclic precursor (**234** or **237**) might also react with benzaldehyde to construct enone **242**. The *aza*-Michael addition of the latter with *N*-benzylmethylamine also leads to **238b**.

Since *N*-benzylmethylamine was expected to undergo uncontrolled decomposition, leading to a wide range of side products, morpholine was applied in our subsequent experiments. This stable secondary cyclic amine was stirred with **234** at 80 °C under neat conditions. After 2 hours, the spot indicating 3HIQ disappeared on a TLC; therefore, the mixture was worked up by neutral column chromatography to produce aminal **243** as a single isolated product (Scheme 26). In its ^{1}H NMR spectrum, the separated AB signals (J = 20 Hz) of the diastereotopic H-4 protons discernible at 3.37 ppm and 3.64 ppm indicated its lactam-type skeletal structure with a stereogenic centre at position 1. This structure was also supported by the chemical shift of C-1 (171.4 ppm) and by HMBC cross peaks revealing correlations between ^{1}H/^{13}C coupled pairs H-4A/C-1, H-4B/C-1, H-1/C-1 and NH/C-1.

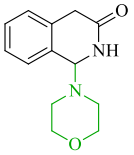
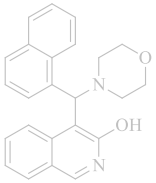
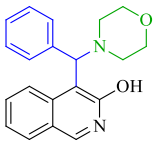
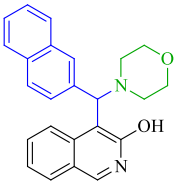
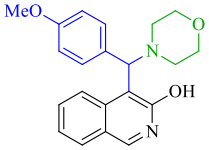
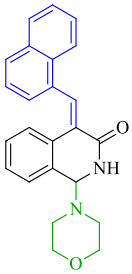
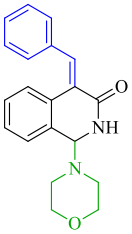
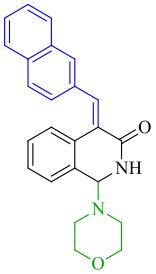
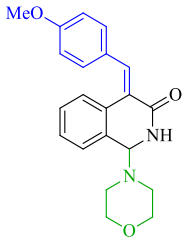
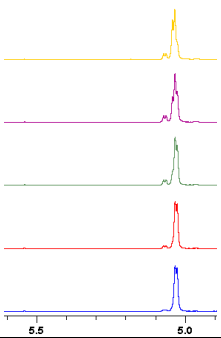
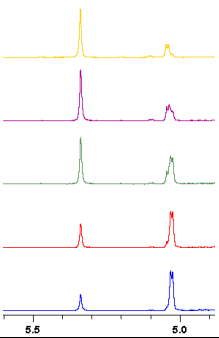
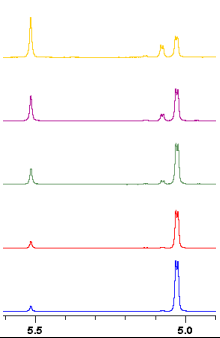
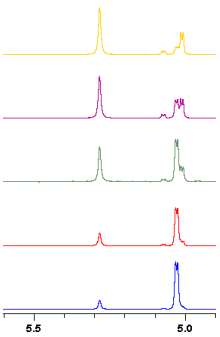


Scheme 26. Reaction of 3-hydroxyisoquinoline with morpholine, leading to aminal **243**.

In order to unambiguously clarify the role of the amine and the aldehyde in this reaction and to avoid the rather unpredictable reactivity and decomposition of *N*-benzylmethylamine, **234** was reacted with morpholine and aromatic aldehydes (1-naphthaldehyde, benzaldehyde, 2-naphthaldehyde, *p*-methoxybenzaldehyde and *p*-nitrobenzaldehyde; reactions **244a–e**, respectively) under neat conditions. Since the incorporation of the methoxy group (as in the case of **236**) was also undesirable, the composition of the crude reaction mixtures was analysed using ^{1}H NMR without any further purification. In accord with our previous findings with morpholine as the amine nucleophile, in addition to **243**, the ^{1}H NMR analyses revealed the parallel formation of the classical Mannich product (**244b**–**dA**) and the corresponding arylidene derivative (**244b**–**dB**) when benzaldehyde, 2-naphthaldehyde and *p*-methoxybenzaldehyde were applied as the carbonyl component. The increase and decrease of characteristic proton ratios were observed to be rather time-dependent; therefore, the crude products were analysed at five different reaction times (1 h, 2 h, 4 h, 8 h and 16 h). The ratio of the regioisomers and **243** was obtained as the relative intensity of the diagnostic proton signals of particular components. Namely a singlet in the range of 5.3–5.5 ppm is characteristic of Mannich adducts type **244A**, and a doublet in the range

of 5.0–5.1 ppm is diagnostic for enone aminals of type **244B**. The relative amount of **243** could also be calculated by the intensity of the characteristic proton signals at 5.03 ppm. However, independently of the reaction time, when 1-naphthaldehyde was used as a coupling partner, reactions led to the formation of the arylidene derivative **244aB**, which could be isolated as a single product. This might be associated with the steric bulk of the 1-naphthyl group.

Table 12. Structures and diagnostic ^{1}H NMR signals of Mannich products (type **244A**) and arylidene derivatives (type **244B**) and the corresponding ^{1}H NMR section.

Reaction	**244a**	**244b**	**244c**	**244d**
	Structures appearing in the reactions			
Compound **243**	 **243**			
Mannich products (Product type A) **244a–dA**	 244aA	 **244bA**	 **244cA**	 **244dA**
Arylidene products (Product type B) **244a–dB**	 **244aB**	 **244bB**	 **244cB**	 **244dB**
	Characteristic proton signals appearing in reaction mixtures			
Compound **243**	**243**: 5.03 ppm			
Mannich product (Product type A)	**244aA**: –	**244bA**: 5.34 ppm	**244cA**: 5.51 ppm	**244dA**: 5.28 ppm
Arylidene product (Product type B)	**244aB**: 5.04 ppm	**244bB**: 5.05 ppm	**244cB**: 5.09 ppm	**244dB**: 5.02 ppm
	Relevant part of ^{1}H NMR spectra in the depicted reaction times			
16 hours 8 hours 4 hours 2 hours 1 hour				

In general, the first-appearing NMR signals can unambiguously be assigned to the protons of **243**. In the progress of the experiments, the ratio of **243** gradually decreased, while the ratios of other products increased. It must be pointed out that enones **244b–dB** were slowly transformed into the appropriate Mannich-type products **244b–dA** as highlighted by the ^{1}H NMR spectra of the reaction mixtures that were registered at different times (Table 12). As a representative example, the transformation of **244d** – which includes **243**, **244dA** and **244dB** – is demonstrated in Figure 3.

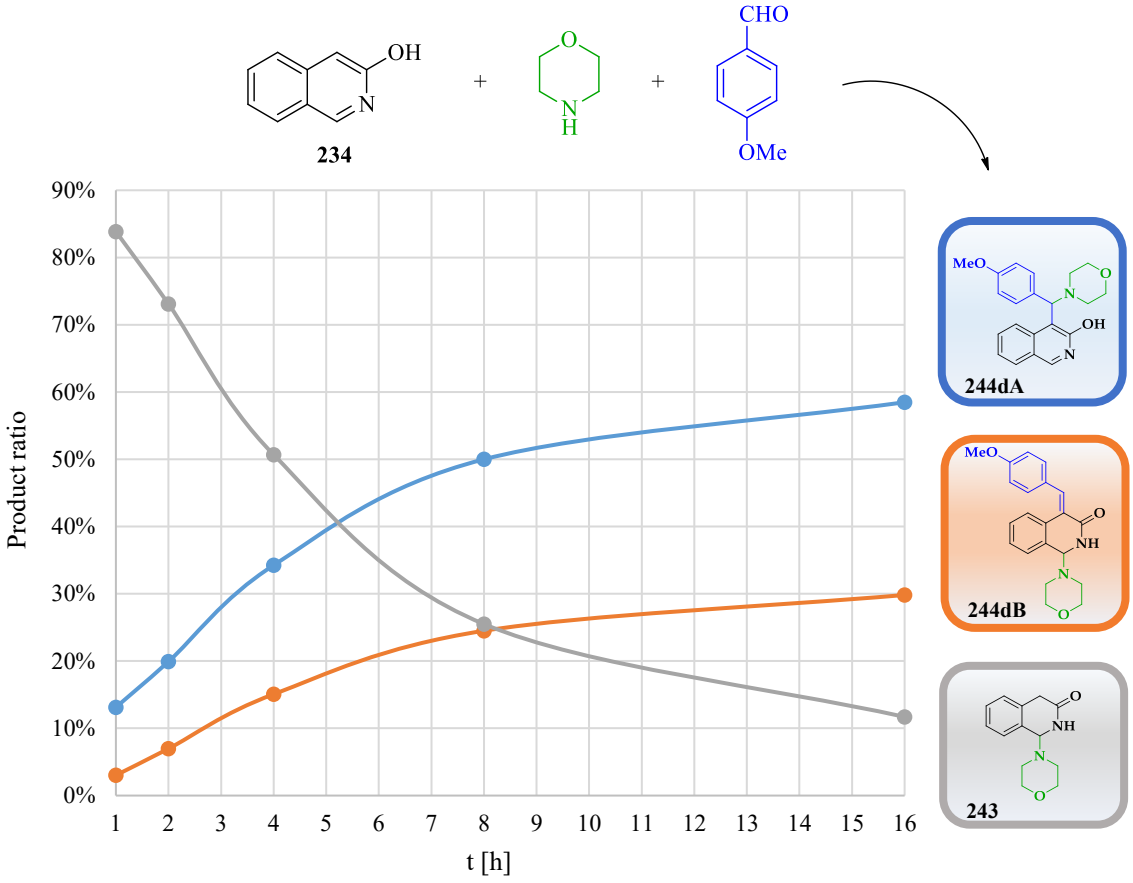
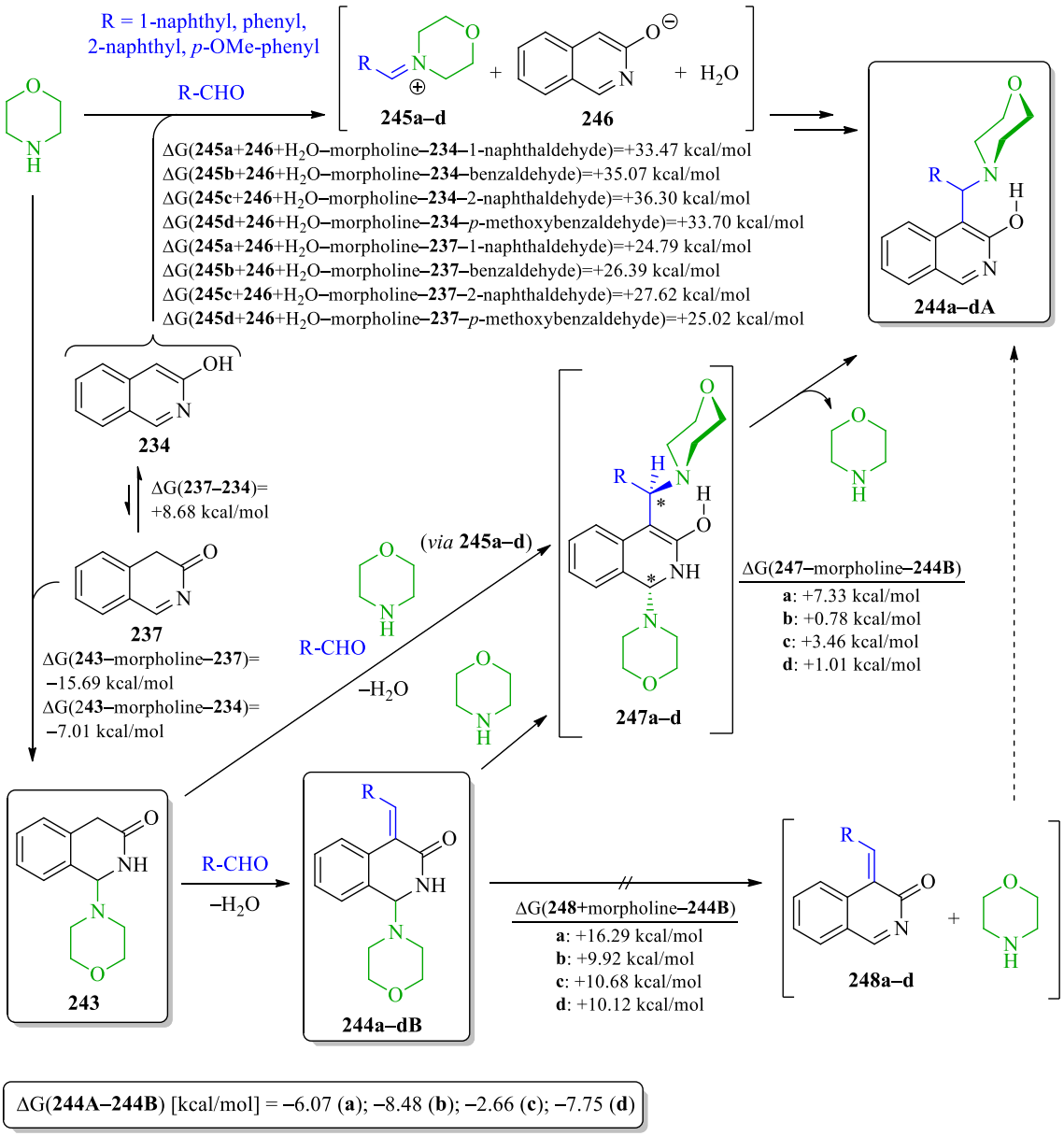


Figure 3. The time-dependent ratios of morpholino-hydroxyquinoline adduct **243**, Mannich product **244dA** and benzylidene derivative **244dB** as determined by ^{1}H NMR.

In order to rationalise all aforementioned aryl-group-dependent experimental findings as well as the exceptional reactivity of 4-nitrobenzaldehyde manifested in its analogue transformation to obtain the Mannich-type product (discussed later), comparative DFT modelling studies were undertaken on the aryl-group-dependent progress of the formation and possible interconversion of **243** and compound types **244A** and **244B**. We hypothesised that these transformations might take place along the pathways outlined on Scheme 27. The feasibility of this assumption was assessed by the relative energetics of particular elementary steps and by the analysis of the acceptor orbitals (LUMO and LUMO+1) of the possible electrophilic species involved in these Mannich-type and related conversions (Figure 4).



Scheme 27. Mechanism of the formation of Mannich and arylidene products (types **244A** and **244B**, respectively) and products proposed on the basis of the aryl-group-dependent relative thermodynamics of the assumed transformations obtained using DFT modelling.

First, the classical Mannich products were expected to be formed through an ion pair incorporating iminium cations **245a**–**d** and a heterocyclic anion **246** generated by the nucleophilic attack of morpholine on the aldehyde component followed by elimination of water promoted by 3-hydroxyisoquinoline. However, on the basis of the assumed relatively small amount of the ion pair **245b**–**d**/**246** [cf., the changes in Gibbs free energy (ΔG) accompanying their formation by implication of either tautomers **234** or **237**, as presented on Scheme 27] and the dominance of **243** in the reaction mixtures obtained after 1 hour, the share of these pathways was negligible in the construction of compounds type **244A**. On the other hand, the rapid and dominant primary

formation of **243** could be ascribed to the pronounced electrophilicity of **237**, mainly assigned to its low-energy LUMO, with a significant share on the C-1 atom. Accordingly, except for 4-nitrobenzaldehyde, the other arylaldehyde components had markedly higher LUMO energy relative to that of **237**. This oxo-tautomer could be regarded as the main precursor of **243**, even though the calculated ΔG value suggested that its tautomer **8** must be present in the reaction mixture in a substantially higher concentration. In the subsequent steps, **243** could have undergone condensation with the appropriate aldehyde to construct arylidenes **244B**. Alternatively, with the involvement of morpholine generating iminium ions **245a**–**d**, **243** could have been converted into *bis*-morpholine intermediates type **247**. Morpholine elimination from the aminal residue of **247** gave the corresponding Mannich product (**244A**). It is of note that due to the thermodynamically unfavoured formation of **245a**–**d** under slightly acidic conditions, this condensation–elimination sequence can be considered as a less feasible pathway. Since the relative energetic data calculated for all investigated isomer pairs **244A**/**244B** [(ΔG(**244B**–**244A**), see Scheme 27] suggested that **244a**–**dA** are formed under thermodynamic control, the isomerisation of **244B** into **244A** can also be taken into account as a realistic process taking place under the applied conditions. In this regard, the calculated energetic data [(ΔG(**248**+morpholine–**244B**)] practically rule out the elimination–addition sequence **244B**→**248**→**244A** as a realistic pathway. The reason is that the competitive addition–elimination sequence proceeding via *bis*-morpholine intermediates **247** seems to be more feasible as indicated again by the relative energetics calculated for the critical addition step [(ΔG(**247**–morpholine–**244B**)].

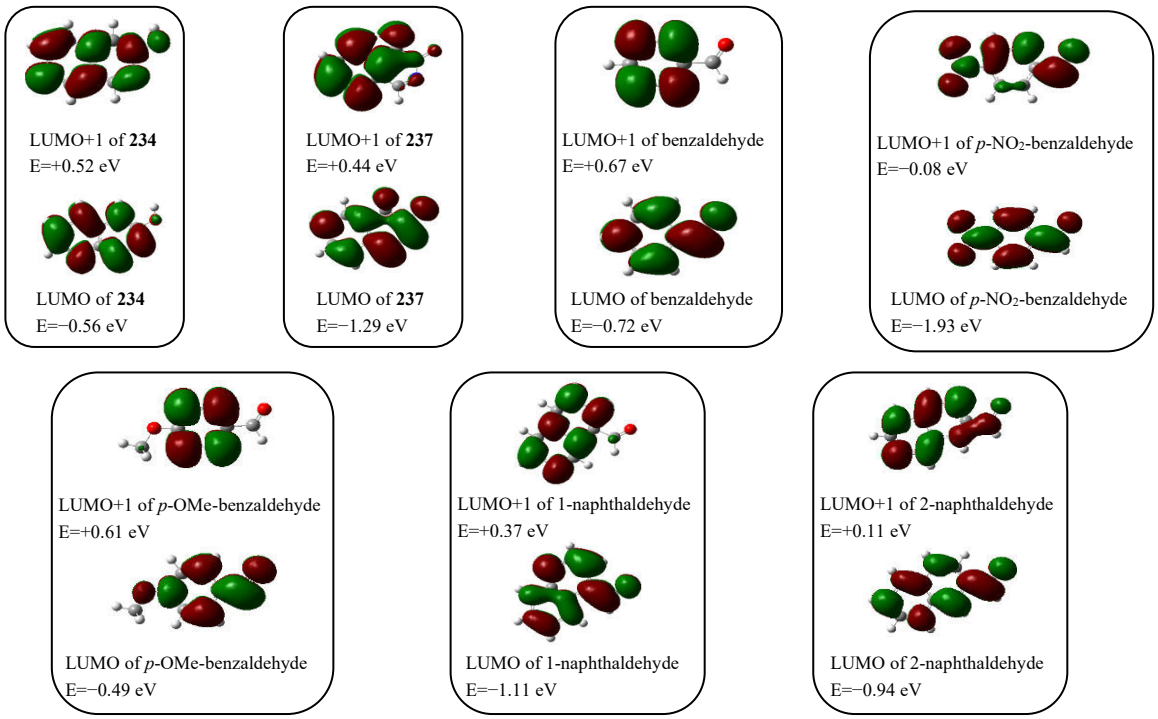
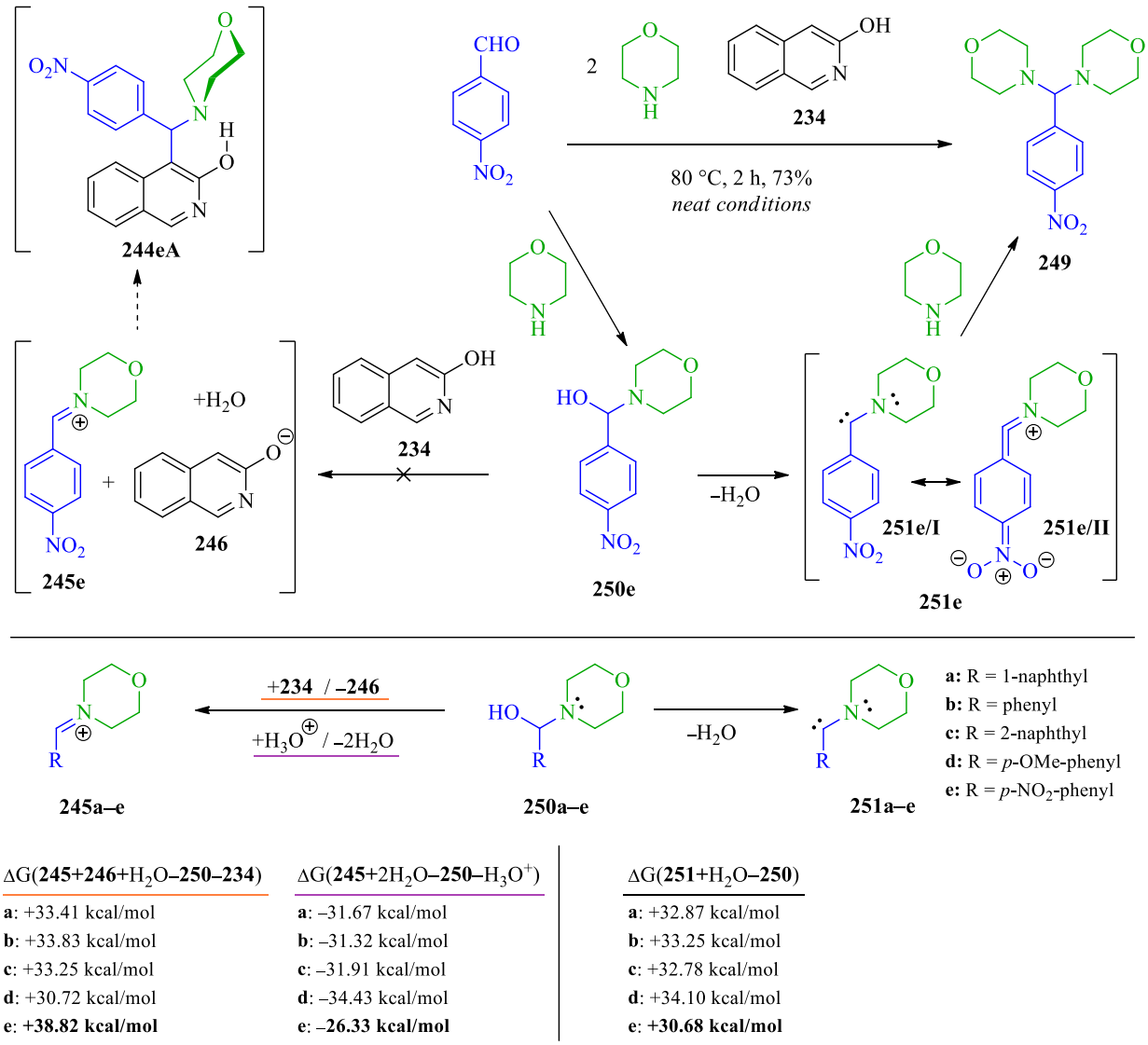


Figure 4. Acceptor orbitals (LUMO and LUMO+1) of the electrophilic components involved in the Mannich-type reactions obtained using MO analysis of the optimised structures.

The reaction of **234** and morpholine with *p*-nitrobenzaldehyde was an exceptional case, because neither the expected Mannich product **244eA** nor the appropriate benzylidene product **244eB** could be isolated. Instead, 4,4'-((4-nitrophenyl)methylene)dimorpholine (**249**)[169–171] was formed as the main product (Scheme 28). This unique conversion of *p*-nitrobenzaldehyde, proceeding without the implication of equilibrating heterocyclic tautomers (**234** and **237**), can be interpreted by its LUMO energy being markedly lower than that of **237** (Figure 4). Furthermore, the relatively low-energy LUMO+1, also available to nucleophilic attack with significant share on the carbonyl group, further attenuates the electrophilicity of this reactive aldehyde. On the other hand, the tendency in the calculated energetic data – in accord with the general qualitative expectations – clearly shows that 3-hydroxyisoquinoline-promoted generation of ion pair **245e**/**246** is a less favoured process, than the formation of ion pairs **245a**–**d**/**246** containing a positively charged nitrogen atom without a strong electron-withdrawing substituent on the aryl



ΔG(**245**+**246**+H_2O–**250**–**234**)	ΔG(**245**+2H_2O–**250**–H_3O^+)	ΔG(**251**+H_2O–**250**)
a: +33.41 kcal/mol	**a**: –31.67 kcal/mol	**a**: +32.87 kcal/mol
b: +33.83 kcal/mol	**b**: –31.32 kcal/mol	**b**: +33.25 kcal/mol
c: +33.25 kcal/mol	**c**: –31.91 kcal/mol	**c**: +32.78 kcal/mol
d: +30.72 kcal/mol	**d**: –34.43 kcal/mol	**d**: +34.10 kcal/mol
e: **+38.82 kcal/mol**	**e**: **–26.33 kcal/mol**	**e**: **+30.68 kcal/mol**

Scheme 28. DFT-supported rationale of the unique reactivity of 4-nitrobenzaldehyde manifested in its attempted Mannich condensation with morpholine and **234**.

group. It must be pointed out here, that the readiness of iminium generation is strongly dependent on the proton source as shown by the energetic data obtained by replacing **234** with a hydroxonium ion in the calculations. The extreme difference between the two series of energetic data, otherwise both demonstrating the same tendency in the function of the electronic character of the aryl groups, can be considered as a strong indication of the dramatic dependence of the thermochemistry of ion-pair formation on a number of factors, that might influence the stability of the charged particles, including, e.g., coulombic interaction, solvation and other intermolecular contacts. Avoiding unrealistically demanding computations, except for the estimated polarity of the reaction mixture, the aforementioned factors were neglected in the course of our DFT modelling studies.

Finally, we proposed a mechanism for the formation of **249**, accounting for taking place without the implication of **234**. Thus, according to our assumption, reductive elimination of the elements of the water molecule from adduct **250e**, generated in a selective manner, gives carbene **251e** stabilised by the 4-nitrophenyl group as represented by resonance hybrids **251e/I** and **251e/II**, which then reacts with morpholine in an oxidative addition step affording **249** as the single isolable product (Scheme 28). In this sequence, carbene formation is the critical step with indispensable assistance of the nitrophenyl group. This view was supported by the comparison of the relative energetics of water elimination from adducts **250a**–**e** (Scheme 28). The calculated data [(ΔG(**251**+H_2O–**250**)] unambiguously indicated that the process **250e**→**251e**+H_2O is significantly less endoergic and, consequently, it is more feasible than the analogous reaction steps **250a**–**d**→**251a**–**d**+H_2O. It must be emphasised again, that it is the tendency of the relative energetics that must be regarded to have diagnostic value in the assessment of the substituent effect. Note that solvation of the involved species along with other stabilising and destabilising interactions – which were not modelled in the calculations – are also expected to determine the real thermochemistry of the studied conversions. It is also of note that carbene **251e** reacts with morpholine rather than with **234**. This substrate selectivity might be associated with the enhanced nucleophilicity of morpholine compared to that of the neutral **234** of which the deprotonation-generated ion pair **245e**/**246** with the highly reactive anion **246**, a real competitor of morpholine, is suppressed by the nitrophenyl group as discussed above.

4. SUMMARY

1. 5-Chloro-8-hydroxyquinoline (**18**) was applied in the Mannich reaction as 1-naphthol analogue. The reaction of **18**, L-proline and formalin (38%) in EtOH and MeOH at 80 °C resulted in the formation of ethoxymethyl (**201**) and methoxymethyl (**202**) derivatives, respectively. Lowering the temperature to 75 °C, the reaction in MeOH gave the desired Mannich product **(–)203**. The optimised molar equivalents of the starting compounds eased the purification process and only a recrystallisation was required to reach the desired purity. The reaction was extended for other α-amino acids, including racemic proline, D-proline and D-homoproline, which afforded **(±)203**, **(+)203**, and **(–)204**, respectively.

2. The Conrad–Limpach reaction for methyl and ethyl 2-(4-hydroxyquinolin-2-yl) acetate (**208a,b**) was optimised and the undesired formation of **209** byproduct was reduced. The reaction of **208a,b**, piperidine and paraformaldehyde afforded either methylenebis compound **210A,(±)B** or a Mannich base with α-methylenation (**214a,b**), depending on the solvent and the equivalents used. The hydrolysis of **210A,(±)B** led to 2,2′-(propane-1,3-diyl)bis(quinolin-4-ol) (**211**) *via* decarboxylation. The hydrolysis of 3-piperidine-1-yl-methyl acrylates (**214a,b**) with NaOH gave a novel 1*H*-azeto [1,2-*a*]quinoline (**213**), which was also synthesised starting from 2-(4-hydroxyquinolin-2-yl)acetic acid (**212**).

3. In order to investigate the scope and limitations of the transformations of **208a,b**, aromatic aldehydes were used instead of formaldehyde. The application of benzaldehyde resulted in the formation of phenylmethylenebis derivatives (**215A**,**B**,(±)**C**), and subsequent hydrolysis produced the corresponding phenylpropane **216**. The alteration of the reaction conditions did not lead to a Mannich reaction, but a Knoevenagel condensation took place (**217a,b**). The synthesis was extended to a series of *para*-substituted (nitro-, fluoro-, methyl-, methoxy-, dimethylamino-) benzaldehydes as well as 1- and 2-naphthaldehydes (**219–225**). When *ortho*-hydroxybenzaldehyde (salicylaldehyde) was applied, an intramolecular ring closure took place affording a lactone-containing skeleton (**227**), which is a 4-hydroxyquinoline–coumarin hybrid. Benzocoumarin derivatives (**228** and **229**) were synthesised by using the appropriate hydroxynaphthaldehydes. Regarding the biological results, some derivatives possess selectivity towards cancer cells and calculated pIC50 values and the Hammett–Brown substituent showed a good correlation.

4. 6-Hydroxyquinoline (**230**) was tested in Mannich reaction as *N*-containing 2-naphthol analogue. The outcomes of the attempted Mannich reactions were strongly influenced by the amine components. Aminoalkylation of this substrate with reagents 1-naphthaldehyde and *N*-benzylmethylamine led to the isolation of diol **232** regarded as a stabilised water adduct of an *ortho*-quinone methide (*o*-QM). Its formation can be ascribed to the presence of a hydroxide ion in a relatively higher concentration generated by the bulky and basic amine component with decreased nucleophilicity. Classical Mannich base **233** was isolated as a single product, when the amine component was replaced by morpholine, featuring nucleophilicity rather than basic character under the applied reaction conditions.

5. The reactivity of 3-hydroxyisoquinoline (**234**) was explored and, rather unexpectedly, transformations were observed even if only amines were applied. *N*-Benzylmethylamine with **234** produced **238a,b** – due to its decomposition –, and morpholine with **234** produced the aminal **243**, but no reaction with MeOH was observed. When the reaction of **234**, 1-naphtaldehyde and morpholine was worked up with the use of MeOH on column chromatography, the methoxy-substituted lactam **236** was identified. However, when purification and isolation was performed without MeOH, it led to arylidene derivative **244aB**. When other aldehydes (benzaldehyde, 2-naphthaldehyde, *p*-OMe-benzaldehyde) were applied, the ^{1}H NMR analyses revealed the parallel formation of the classical Mannich product (**244b**–**dA**) and arylidene derivative **244b**–**dB**. In the case of *p*-NO_2-benzaldehyde, the reaction took place without the involvement of **234**, producing 4,4'-((4-nitrophenyl)methylene)dimorpholine (**249**) as the main product. DFT modelling studies were undertaken to rationalise the preparative results.

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ACKNOWLEDGEMENTS

This work was carried out in the Institute of Pharmaceutical Chemistry, University of Szeged, during the period of 2018–2022.

I would like to express my appreciation to my supervisor Prof. Dr. István Szatmári, head of the Institute, in particular for his guidance of my work, continuous support, and motivating discussions. His advice and help have been priceless during my Ph.D. studies.

I would like to thank all members of the Institute of Pharmaceutical Chemistry, especially the former and active members of Research Laboratory 4 for their assistance and friendship.

Finally, I would like to give my heartfelt gratitude to my family, friends, and companion for their encouragement and support, as well as for providing all circumstances that allowed me to complete my Ph.D. work. Thank you.

ANNEX