Transformations of electron-rich aromatic compounds toward bioactive scaffolds

Ph.D. Thesis

dr. Dóra Hegedűs

Supervisor:

Prof. Dr. István Szatmári

Institute of Pharmaceutical Chemistry

University of Szeged

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“Don’t focus on what you cannot change. Don’t start to feel sorry for yourself. You just have to focus on what’s next because that’s what you can change.”

Katalin Karikó

Nobel Prize Winner

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PUBLICATIONS

Papers related to the thesis

I. **Dóra Hegedűs**, Nikoletta Szemerédi, Gabriella and István Szatmári
Application of partially aromatic *ortho*-quionone-methides for the synthesis of novel naphthoxazines with improved antibacterial activity
Eur J Med Chem **2022**, *237,* 114391. DOI: 10.1016/j.ejmech.2022.114391 **IF: 6.7**

II. **Dóra Hegedűs**, Nikoletta Szemerédi, Maja Gábor, Judit Sas, Khadija Belasri, István Szatmári and Gabriella Spengler
Cyclic amines coupled to indole derivatives with improved efflux pump inhibiting activity in bacteria and cancer cells
Anticancer Res **2024**, *44,* 1149-1160. DOI:10.21873/anticanres.16910 **IF: 1.6**

III. **Dóra Hegedűs**, Nikoletta Szemerédi, Krisztina Petrinca, Róbert Berkecz, Gabriella Spengler and István Szatmári
Synthesis of tumor selective indole and 8-hydroxyquinoline skeleton containing di-, or triarylmethanes with improved cy-totoxic activity
Molecules **2024,** *29,* 4176. DOI:10.3390/ molecules29174176 **IF: 4.2**

CONFERENCE LECTURES

IV. **Dóra Hegedűs** and István Szatmári
Részlegesen aromás *orto*-kinon metidek szintézise és továbbalakítása
Tudományos Diákköri Konferencia, Szeged, November 16, 2018.

V. **Dóra Hegedűs** and István Szatmári
Részlegesen aromás *orto*-kinon metidek szintézise és továbbalakítása
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VI. **Dóra Hegedűs**, Gabriella Spengler, Nikoletta Szemerédi and István Szatmári
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A módosított Mannich-reakció alkalmazása bioaktív prekurzorok szintézisére és továbbalakításaira
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VIII. **Dóra Hegedűs**, Nikoletta Szemerédi, Gabriella Spengler and István Szatmári
Partially aromatic *ortho*-quionone-methides as precursors for the synthesis of novel naphthoxazines with improved antibacterial activity
22nd Tetrahedron Symposium, Lisbon/Portugal, June 28–July 1, 2022.

IX. **Dóra Hegedűs** and István Szatmári
Synthesis and transformations of bifunctional glycine-type precursors containing 8-hyroxyquinoline skeleton
23rd Tetrahedron Symposium, Göteborg/Sweden, June 27-30, 2023.

X. **Dóra Hegedűs**, Nikoletta Szemerédi, Dorka Gubó, Gabriella Spengler and István Szatmári
Synthesis and transformations of bifunctional 8-hydroxyquinoline skeleton containing glycine-type precursors
Congressus Pharmaceuticus Hungaricus (CPH) XVII. and EUFEPS annual meeting, Debrecen/Hungary, May 23-25, 2024.

XI. **Dóra Hegedűs**, Nikoletta Szemerédi, Krisztina Petrinca, Gabriella Spengler, István Szatmári
Synthesis and cytotoxic activity of bioconjugates consisting of indole and 8-hydroxyquinoline skeleton
24th Tetrahedron Symposium, Montpellier/France, June 18-21, 2024.

1. INTRODUCTION AND AIMS

The Mannich reaction is one of the most important basic reaction types in organic chemistry for C–C and C–N bond formation.[1-5] A special variation of this latter reaction (modified Mannich reaction: *m*MR) uses benzaldehyde rather than formaldehyde, ammonia instead of secondary amine and replacing the C–H acid by an electron-rich aromatic compound, such as 1- or 2-naphthol[6] or nitrogencontaining naphthol analogues leading to chelating compounds with improved antiproliferative activity.[7]

Based on previous studies, an unexpected transformation between 1-α-aminobenzyl-2-naphthol and 3,4-dihydroisoquinoline enabled the synthesis of naphth[1,2-*e*][1,3]oxazino[2,3-*a*]isoquinolines under microwave (MW) irradiation.[8] As a next step, the reaction was extended to 2-aminoalkyl-1-naphthols[9] and other C=N dienophiles (cyclic imines) allowing the synthesis of new naphthoxazino-isoquinoline, -benzazepine and -thienopyridine derivatives.[10] The synthesis of new nonracemic naphth[1,3]oxazino[3,2-*a*]quinoxalinones starting from enantiomeric (4*aS*,8*aS*)-4*a*,5,6,7,8,8*a*-hexahydro-2-quinoxalinone and 1-aminoalkyl-2-naphthols or 2-aminoalkyl-1-naphthols has already been achieved.[11, 12] As a result of a recent work, the reactivity of highly functionalised aminonaphthol[13] or aminophenanthrol derivatives[14] with different cyclic imines was also tested in [4+2] cycloaddition. According to literature data the formation and transformation of aromatic *ortho*-quinone methides (*o*-QM) via [4+2] cycloaddition has been examined.[12] To the best of our knowledge, the stabilisation of partially aromatic *o*-QMs with cyclic imines has not been studied. Consequently, our first aim was to prepare bifunctional glycine-type precursors substituted with 2- and 1-naphthol (Figure 1, compounds **Ia**, **Ib**). The stabilization of precursors via partially aromatic *ortho*-quinone methide intermediate was tested with different cyclic imines in [4+2] cycloaddition (Figure 1, **IIa**, **IIb**).

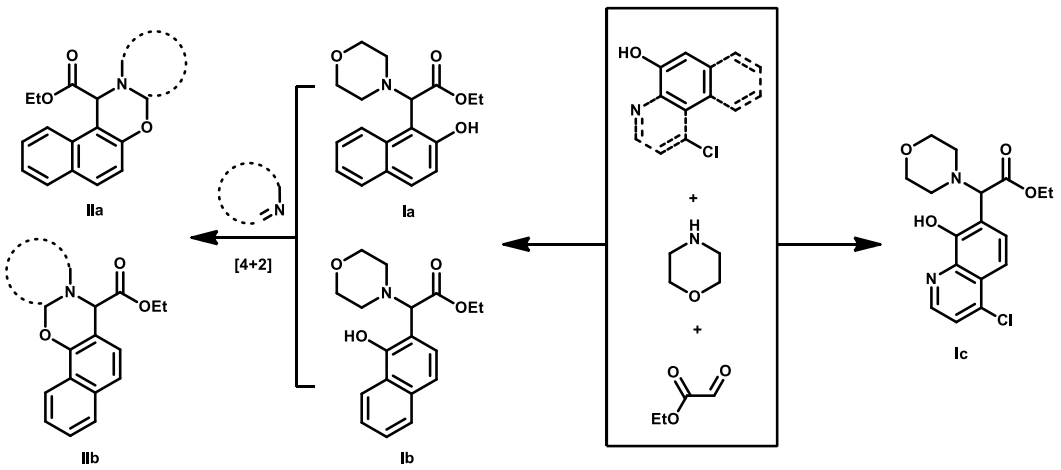


Figure 1

Regarding literature data, 8-hydroxyquinoline (8-OHQ) is a biologically active moiety[7] considered as a potential 1-naphthol analogue. 8-Hydroxyquinoline can be interpreted as potential substrate of the Mannich reaction, which is a privileged structure in many biologically active compounds and several marketed drugs[15] used for the treatment of infectious diseases, neuropathies, and cancers. Taking into consideration that the diverse biological activities of 8-OHQ derivatives can be finetuned by modification of the substitution pattern of the scaffold,[16-19] we proposed to examine the behavior of 5-Cl-8-HQ in the modified Mannich reaction by using ethyl glyoxylate as aldehyde component (Figure 1, compound **Ic**).

In recent studies the formation of triarylmethane derivatives consisting of indole known as potent biological moiety and 2-naphthol[20-22] or the ethyl ester of kynurenic acid[23] has been described. As a further aim of my PhD work, testing the reactivity of glycine derivatives substituted with 2- and 1-naphthol with indole and 7-azaindole was also planned (Figure 2, **IIIa**, **IIIb**). We targeted additionally to study the possibilitiy of transformation of the formed Mannich base consisting 5-Cl-8-HQ skeleton to give diarylmethane derivatives with indole and 7-azaindole as well as the effect of the aldehyde component and the amine part of the Mannich base on the synthetic pathway (Figure 2, **IIIc**).

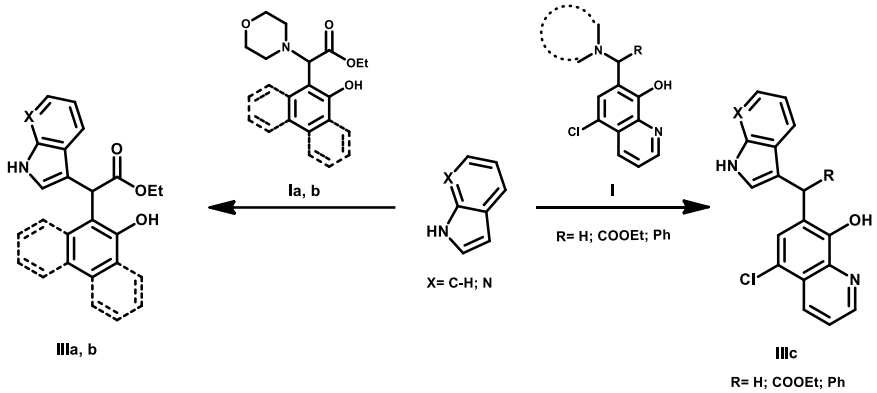


Figure 2

As a special *m*MR ,the modified *aza*-Friedel–Crafts reaction by direct coupling of different cyclic imines and indole derivatives as electron-rich aromatic compounds have been studied.[24-26] To investigate the scope and limitations of the reaction and examine the effect of structural modifications were part of our experiments, which can offer possibilities for having a preliminary overview about the structure–activity relationship for C-3-coupled indole and azaindole derivatives. Therefore, we focused our efforts on resynthesizing selected compounds (3-isoquinolyl-, 3-thieno[3,2-*c*]pyridyl-, 3-*β*-carbolinyl- and 3-benz[*c*]azepinyl-indole and –azaindole derivatives) as well as preparing new derivatives starting from 6,7-dimethoxy-3,4-dihydroisoquinoline, (4*aR*,8*aR*)-4*a*,5,6,7,8,8*a*-hexahydroquinoxalin-2(1*H*)-one and 7-azaindole (Figure 3).

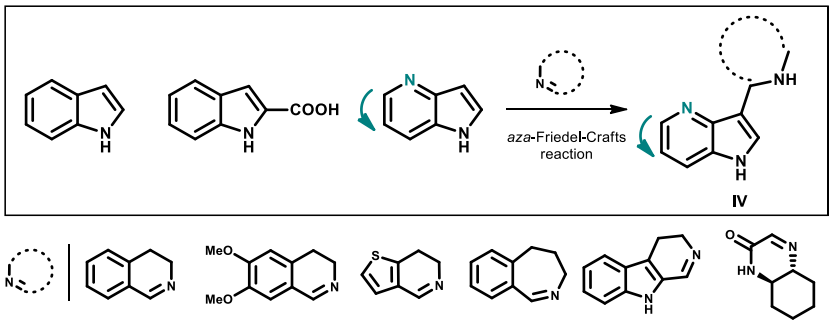


Figure 3

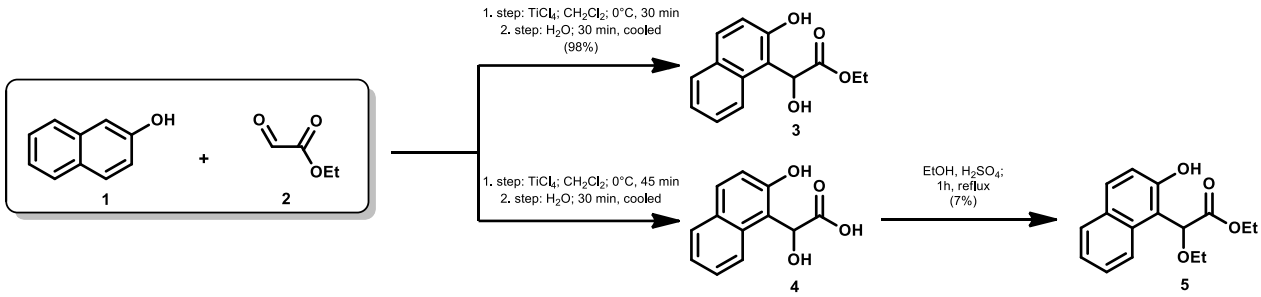
Generally, in favor of having a preliminary overview about the structure–activity relationship, we aimed to test the antibacterial and anticancer activity of synthesized compounds by preliminary biological screening systems.

2. LITERATURE BACKGROUND

2.1. Transformations of 2-naphthol skeleton

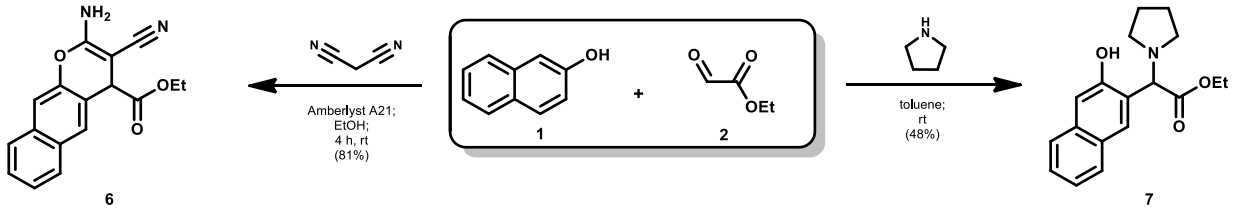
2.1.1. Synthetic methods starting from 2-naphthol and ethyl glyoxylate

For the transformation of 2-naphthol (**1**) and ethyl glyoxalate (**2**), using titanium chloride ($TiCl_4$) two reaction pathways were proposed resulted in preparation of intermediate ethyl 2-hydroxy-2-(2-hydroxynaphthalen-1-yl)acetate (**3**) and ethyl 2-ethoxy-2-(2-hydroxynaphthalen-1-yl)acetate (**5**) (Scheme 1). The invention by Chasset *et al.* provided new antiviral agents, especially anti-retroviral agents, and more particularly anti-HIV compounds.[27]



Scheme 1. Titanium chloride mediated synthesis starting from compounds **1** and **2**

The synthesis of a diverse range of pharmaceutically important pyran annulated heterocycle **6** in the presence of highly reusable ionexchange polystyrene resin Amberlyst A21 as a surrogate solid base catalyst was achieved (Scheme 2).[28] According to a recent study, a redox-neutral strategy was explored, that enables the simultaneous α,β-difunctionalization of amines via transient enamines. The preparation of polycyclic *N,O*-acetals from simple 1-(aminomethyl)-β-naphthols and 2-(aminomethyl)-phenols have been achieved by Chen *et al* (Scheme 2).[29]

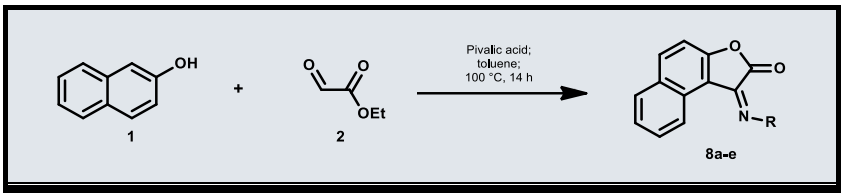


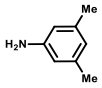
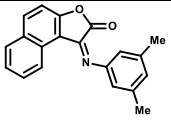
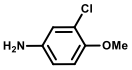
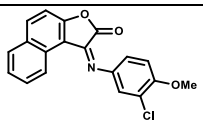
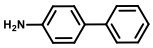
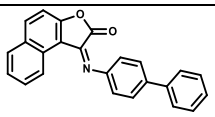
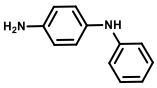
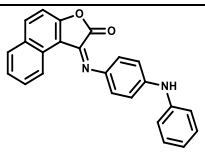
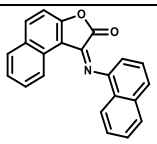
Scheme 2. Transformations of 2-naphthol (**1**) and ethyl glyoxylate (**2**) with malononitrile as well as pyrrolidine

On the base of a recent patent, novel *N*-arylnaphthofuranone imine analogues **8a-e** were developed by using aryl aromatic amines, 2-naphthol analogues, and glyoxylates in the presence of oxygen oxidation.[30] The high adaptability to functional groups (such as alkyl, alkoxy, aryl, halogen,

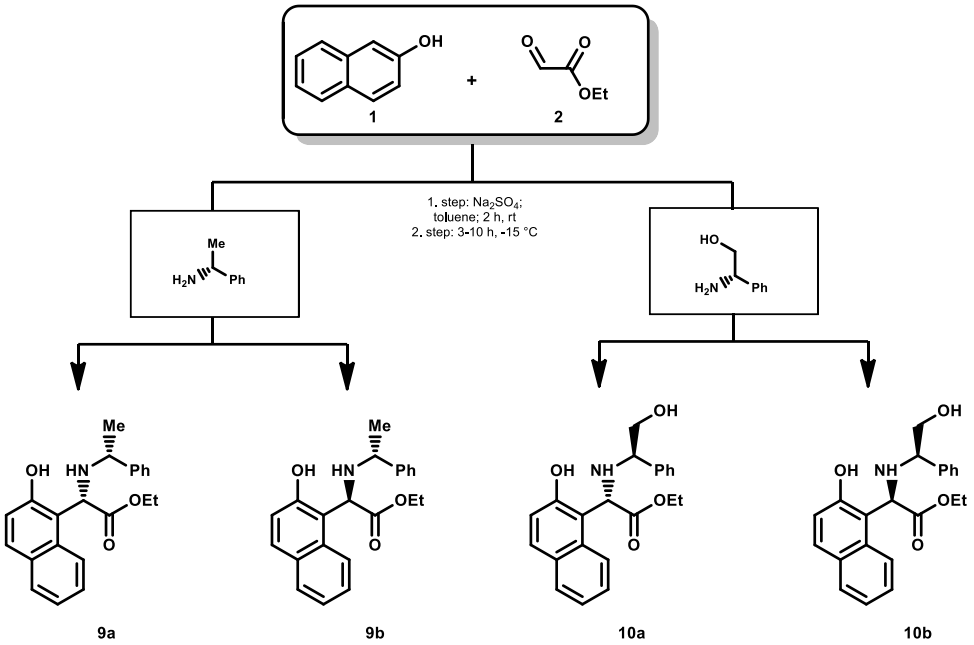
nitro and trifluoromethyl), simple reaction conditions, easy separation of target product, and high yield can be referred as advantages of the method (Table 1).

Table 1. Synthesis of *N*-arylnaphthofuranone imine analogues



Ent-ry	Reactant (amines)	Product	Yields (%)	Lit.
1.		 8a	94	30
2.		 8b	85	
3.		 8c	88	
4.		 8d	90	
5.		 8e	88	

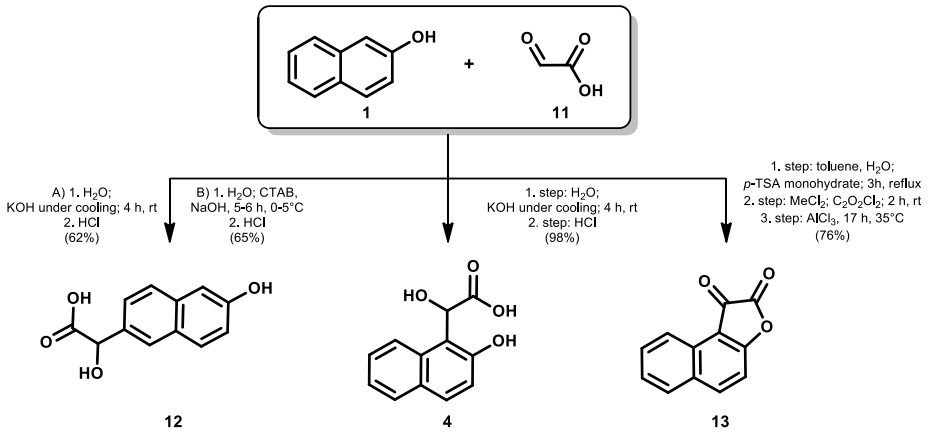
In previous investigations, a novel synthesis of enantiomerically pure arylglycinates **9, 10** via the spontaneous reaction between either phenol or naphthol derivatives and enantiopure glyoxylate imine in the absence of an acid catalyst was accomplished (Scheme 3). Diastereoisomerically pure aryl glycinates were obtained via flash chromatographic separation of the crude reaction mixture. The diastereomeric ratio of **9a**:**9b** was found to be 82:18, **10a**:**10b** was found to be 77:23. Optical rotations were measured in the case of compounds **9a,b** and **10a**.[31] Additionally, the research group found that the free naphthol OH moiety probably promoted a cyclic transition state, activating the imino group in situ via intermolecular hydrogen bonding, and promoting the reaction in the absence of an acid catalyst.



Scheme 3. Preparation of enantiomerically pure arylglycinates

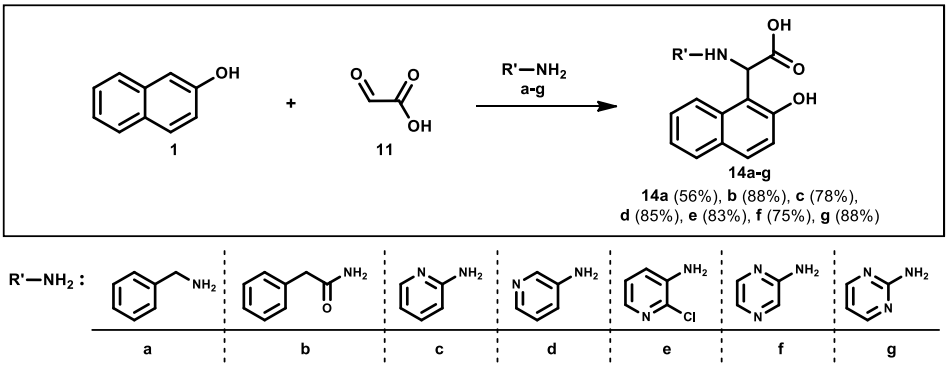
2.1.2. Synthetic methods starting from 2-naphthol and glyoxylic acid

In the case of the synthesis of 2-hydroxy-2-(6-hydroxynaphthalen-2-yl)acetic acid (**12**), the method presented in the literature involved the reaction starting from 2-napthol (**1**), glyoxylic acid monohydrate (**11**), KOH under cooling (Method A) (Scheme 4).[32] Along further synthetic route,[33] substituted mandelic acids were prepared by reacting a mixture of NaOH solution, corresponding substituted phenols and glyoxalic acid (**11**) in the presence of a phase transfer catalyst (cetyl trimethyl ammonium bromide - CTAB) (Method B) and transformed to 2-(1,3-dioxo-2,3-dihydro-1*H*-2-isoindolyl) ethyl 2-hydroxy-2-(substituted phenyl) acetates by using *N*-(2-hydroxy ethyl) phthalimide. By a base-catalyzed condensation of 2-naphthol (**1**) with glyoxylic acid (**11**) the synthesis of racemic α-hydroxy-α-(2-hydroxy-1-naphthyl)acetic (**4**) acid was achieved.[34] The synthesis of benzofuran-2-ones **13** which in particular possess good solubilities in addition to giving good performance properties such as heat and light fastness and strong, transparent and bright colorations were described by a patent (Scheme 4).[35]



Scheme 4. Methods for reacting 2-naphthol (**1**) with glyoxylic acid (**11**)

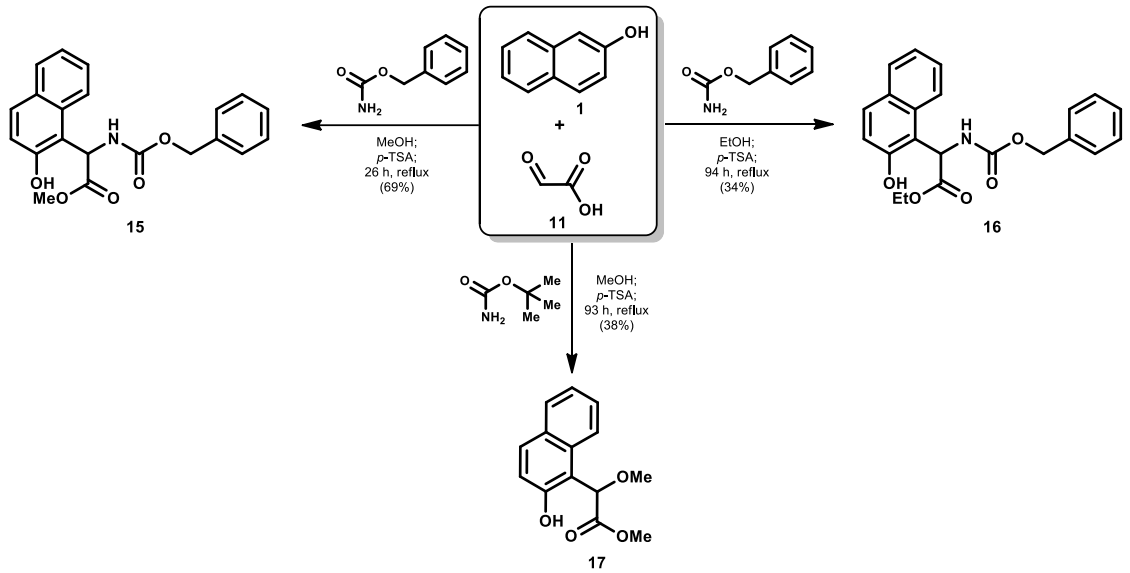
When 2-naphthol (**1**) was reacted with glyoxylic acid (**11**) in the presence of benzylamine, the formation of *N*-benzyl-(2-hydroxy-1-naphthyl)glycine (**14a**) was obtained (Scheme 5).[36] Based on recent investigations, amido-alkylation of electron-rich arene **1** with phenylacetamide and glyoxylic acid (**11**) resulted in *N*-phenylacetylated arylglycine **14b** that are suited for immediate enzymatic resolution by penicillin G acylase.[37] One-step synthesis of *N*-heteroaryl α-naphthylglycines **14c-g** were carried out by the reaction of 2-naphthol (**1**), aqueous glyoxalic acid (**11**) with heteroaryl amines (2-aminopyridine, 3-aminopyridine, 3-amino-2-chloropyridine, 2-aminopyrazine, 2-aminopyrimidine) in water at ambient temperature and under reflux conditions.[38]



Scheme 5. Synthesis of *N*-aryl α-naphthylglycines starting from derivatives **1** and **11** in the presence of various amines

An efficient one-pot synthesis of hydroxynaphthyl-substituted glycine derivatives **15, 16** from 2- naphthol (**1**), glyoxylic acid (**11**), and benzyl carbamate in the presence of *p*-TSA via a modified Mannich reaction is described.[39] As next steps, after removal of the benzyloxycarbonyl group by catalytic (Pd/C) hydrogenation, hydrolysis (5% aq HCl) was carried out. Csütörtöki *et al.* extended the synthetic method by testing MeOH as well as EtOH as solvent. To test other carbamates, in the reaction of 2-naphthol (**1**) with glyoxylic acid (**11**) in the presence of *p*-TSA using MeOH as solvent, *tert*-butoxy carbamate (NH_2Boc) was applied (Scheme 6). Developing an analytical protocol for the

enantioseparation of the synthesized racemic aminoesters was part of the study, the absolute configurations were determined by CD analysis supported by TDDFT CD calculations.

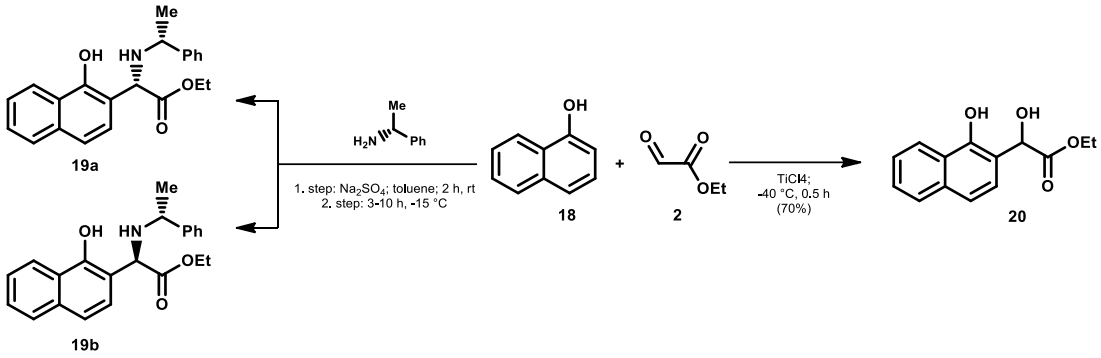


Scheme 6. Preparation of hydroxynaphthyl-substituted glycine derivatives by testing different carbamates

2.2. Transformations of 1-naphthol skeleton

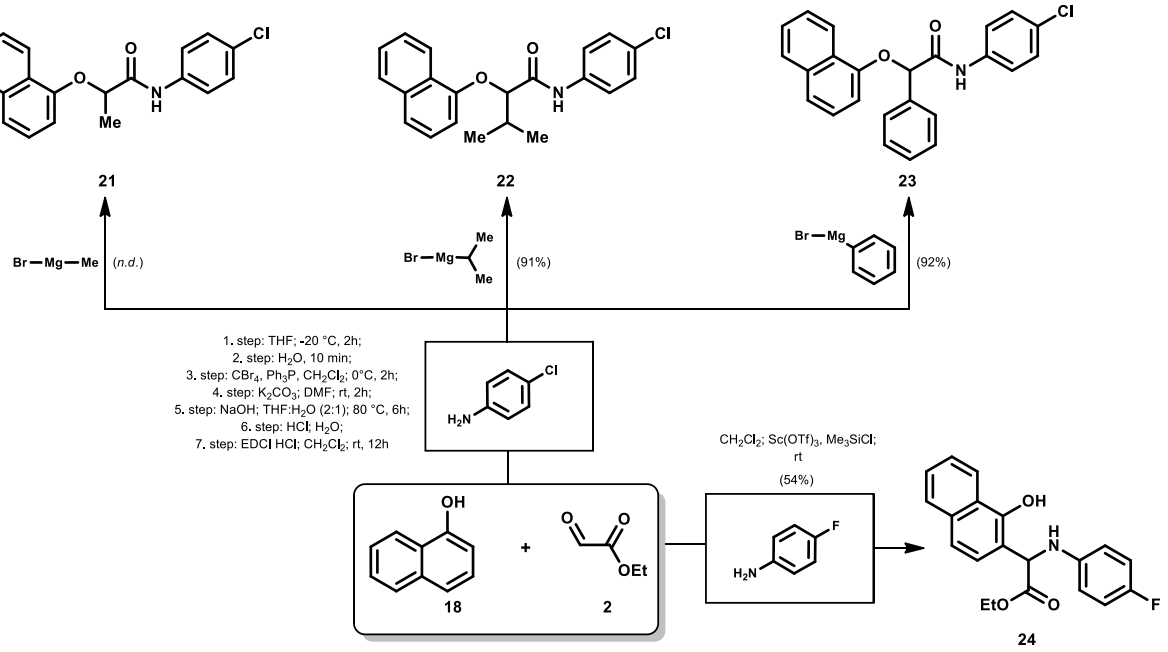
2.2.1. Synthetic methods starting from 1-naphthol and ethyl glyoxylate

On the base of literature data, the spontaneous reaction between either naphthol or phenol derivatives and ethyl glyoxylate imines, in toluene at -15 °C, without the use of an acid catalyst was accomplished, which led to arylglicinate **19** with moderate to high yields obtained after a few hours (Scheme 7). A variety of substituted phenol or naphthol glycinates were obtained in good yields and high diastereoselectivities. Diastereoisomerically pure aryl glycinates were obtained via flash chromatographic separation of the crude reaction mixture. The diastereomeric ratio of **19a**:**19b** was found to be 81:19. Optical rotation were measured in the case of compound **19a**.[31] The synthetic method starting from 2-naphthol (**1**) was presented in chapter 2.1.1. The reaction of α-keto esters with phenols in the presence of a Lewis acid (mainly chlorides of metals in high oxidation state) provided in high yields (*o*-hydroxyaryl)-glycolic acid derivative **20** (Scheme 7).[40]



Scheme 7. Transformations of 1-naphthol (**18**) with ethyl glyoxylate (**2**) without the use of an acid catalyst or in the presence of a Lewis acid

As a result of a previous research, various analogues of the *α*-phenoxide anilide derivative considered as moderately potent and very selective inhibitor of *C. parvum* IMPDH that contain the amide functional group were prepared. Ethyl glyoxylate (**2**) was allowed to react with MeMgBr, PhMgBr and *i*-PrMgBr to give a corresponding alcohol that was subsequently converted to bromide with carbon tetrabromide and triphenylphosphine. Treatment of the product with 1-naphthol (**18**) in the presence of base gave ester. The ester was saponified with sodium hydroxide in THF to give acid, which was subsequently converted to amide **21-23** with the aid of EDCI·HCl in anhydrous dichloromethane (Scheme 8).[41]



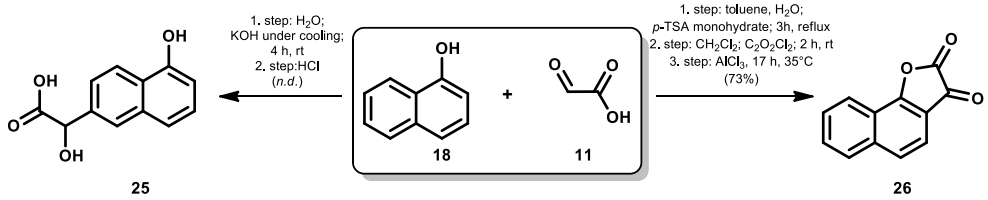
Scheme 8. Reacting 1-naphthol (**18**) with ethyl glyoxylate (**2**) in the presence of 4-chloroaniline and 4-fluoroaniline

Recently, amino acid derivatives are generated by a scandium triflate-catalyzed three-component reaction of phenols, glyoxylates and amines. The three-component/one-pot reaction

starting from 1-naphthol (**18**), ethyl glyoxylate (**2**) and 4-fluoroaniline afforded the corresponding product **24** (Scheme 8). The applied $Sc(OTf)_3$ could be recovered and reused. In the presence of Me_3SiCl, the yield of the product was improved considerably.[42]

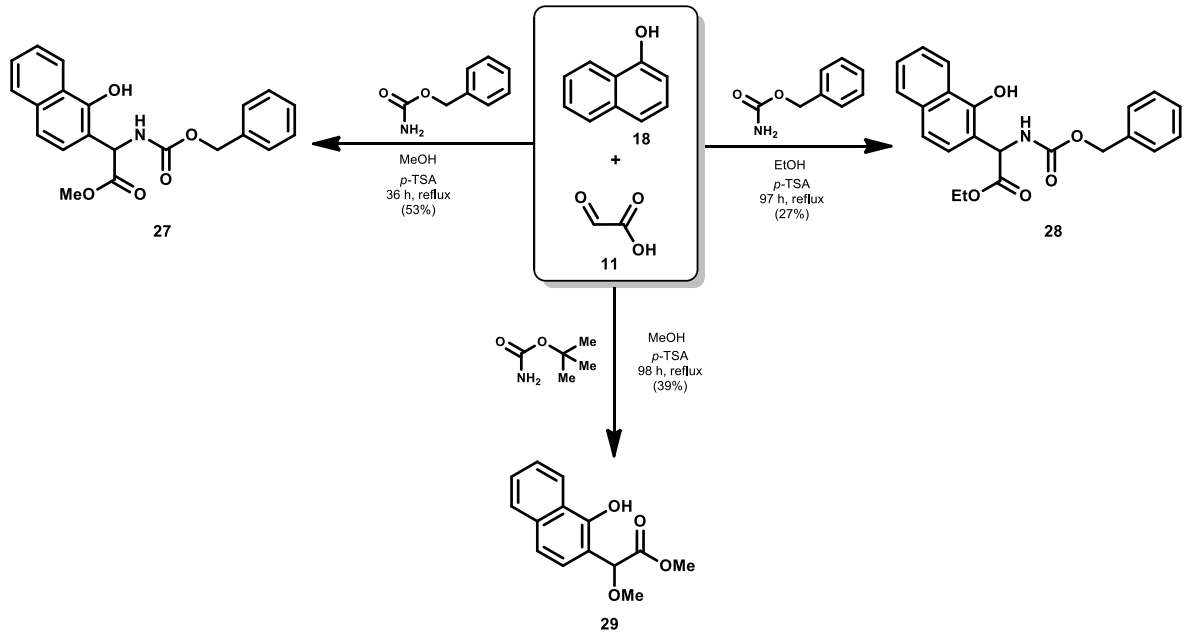
2.2.2. Synthetic methods starting from 1-naphthol and glyoxylic acid

The procedure applied by Rani *et al.* afforded the formation of 2-hydroxy-2-(5-hydroxynaphthalen-2-yl)acetic acid (**25**) in water with the aid of KOH under cooling in order to synthesize new hydroxy-(substituted-naphthalen-1-yl)-acetic acid 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl esters.[32] An invention described the preparation of 3-oxo-1-naphthofuranone (**26**) and the application as colorants for organic materials, especially organic materials of high or low molecular weight (Scheme 9).[35] In the case of both synthetic pathways for the preparation of corresponding compounds either from 2-naphthol were subjected in chapter 2.1.2.



Scheme 9. Synthesis of 2-hydroxy-2-(5-hydroxynaphthalen-2-yl)acetic acid (**25**) and 3-oxo-1-naphthofuranone (**26**)

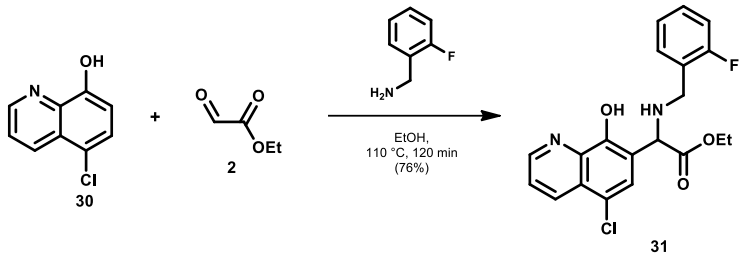
The one-pot synthesis of hydroxynaphthyl-substituted α-amino acid derivatives **15-17** starting from 2- naphthol (**1**), glyoxylic acid (**11**), and benzyl carbamate or *tert*-butoxy carbamate in the presence of *p*-TSA via a modified Mannich reaction was presented in chapter 2.1.2. (Scheme 6). Next, to study the applicability of the reaction, the optimized reaction conditions were extended to 1-naphthol (**18**) as substrate (Scheme 10).[39]



Scheme 10. Preparation of hydroxynaphthyl-substituted α-amino acid derivatives by testing different carbamates extended to 1-naphthol (**18**) as substrate

2.2.3. Synthetic method starting from 8-hydroxyquinoline as 1-naphthol analogue and ethyl glyoxylate

A review of the scientific literature identified 8-hydroxyquinoline derivatives possessing multidrug-resistance reversing activity with improved selectivity and increased cytotoxicity towards multidrug-resistant cancer cells. In favor to form ethyl 2-(5-chloro-8-hydroxyquinolin-7-yl)-2-{[(2-fluorophenyl)methyl]amino}acetate (**31**), 5-chloro-8-hydroxyquinoline (**30**) considered as 1-naphthol analogue was reacted with 2-fluorobenzylamine and ethyl glyoxylate (**2**) in ethanol (Scheme 11).[43]

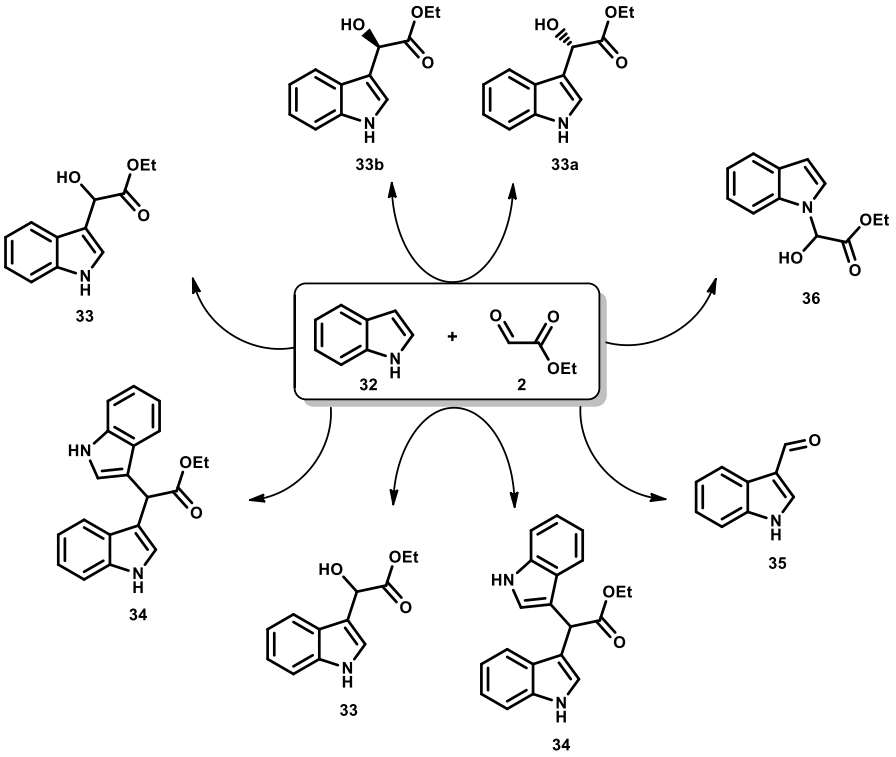


Scheme 11. Reaction starting from 5-chloro-8-hydroxyquinoline (**30**) as 1-naphthol analogue with ethyl glyoxylate (**2**)

2.3. Transformations of indole skeleton

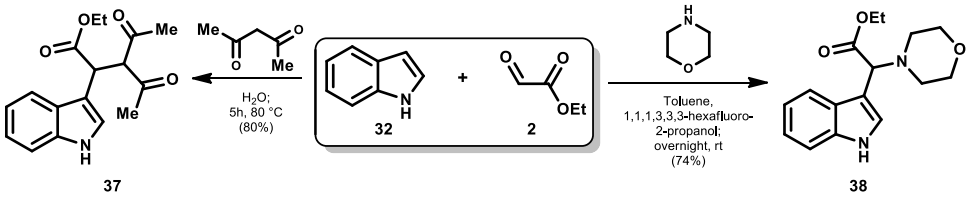
2.3.1. Synthetic methods starting from indole and ethyl glyoxylate

Indole and imidazo[1,2-a]pyridine are known as important structural units frequently found in many natural products, pharmaceuticals, and agrochemicals.[44] Regarding functionalization reactions, hydroxyalkylation at the C3-position of indole and imidazo[1,2-*a*]pyridine is accomplished by (*i*) Friedel−Crafts acylation/Vilsmeier−Haack formylation followed by reduction, and (*ii*) Friedel−Crafts hydroxyalkylation in the presence of acids including reaction with excess formalin in acetic acid. On the base of literature data of recent years, various synthetic protocols for Friedel−Crafts hydroxyalkylation of heterocycle ethyl-2-hydroxy-2-(1*H*-indol-3-yl)acetate (**33**) were reported. Among them, zinc triflate,[45] magnesium iodide,[46] scandium triflate,[47] *N*,*N*-dioxide,[47] titanium isopropoxide,[48] (-)-binol[48] were shown to be efficient catalysts for certain reactions. For the synthesis of compound **34**, besides the reaction of indole (**32**) with ethyl glyoxylate (**2**), iodine and sodium thiosulfate;[49] *N*-phenyl-*N*-2-piridinurea;[50] 1*H*-benzimidazolium,3,3′-(1,3-phenylene)bis[2-iodo-1-methyl-,1,1,1 trifluoromethanesulfonate (1:2);[51] sodium dodecyl sulfate and ytterbium triflate;[52] triethylborane;[53] indion 225;[54] carbon tetrabromide, benzenesulfonic acid, 3-(diphenylphosphino)-, sodium salt (1:1);[55] silica, sodium iodide, cerium trichloride[56] were applied as reagents or catalyst. Soueidan *et al.* examined the reaction of ethyl glyoxylate (**2**) with indole (**32**) as aromatic compound in the presence of 10 mol % samarium diiodide. As result, the desired α-hydroxy-ester **33** (38%) and product **34** (22%) identified as arising from a double Friedel–Crafts reaction with dehydration.[57] The nickel-catalyzed dehydrogenative–decarboxylative coupling of indole (**32**) with ethyl 2-oxoacetate enabled the generation of 3-formylindole (**35**).[58] Furthermore, various indole hemiaminals **36** was prepared by organocatalyzed indole *N*-1 nucleophilic addition of α-oxoaldehydes.[59] The catalytic enantioselective Friedel–Crafts alkylation of indole with ethyl glyoxylate in 1,1,1,3,3-pentafluorobutane in the presence of fluorous cinchona alkaloid catalysts was achieved and resulted is products **33a** and **33b**.[60] Based on a patent, the asymmetric Friedel-Crafts alkylation catalyzed by bifunctional cinchona alkaloids led to the same products.[61] The transformations are summarized in Scheme 12.



Scheme 12. Various synthetic protocols for transformation of indole (**32**) with ethyl glyoxylate (**2**)

In the field of multicomponent reactions, catalyst-free three-component reaction of ethyl glyoxylate (**2**), a 1,3-dicarbonyl compound, and indole (**32**) as nucleophile was developed by using water as the solvent, which produced 1,4-diketone **37**.[62] Li *et al.* developed a 1,1,1,3,3,3-hexafluoro-2-propanol-promoted de novo synthesis of nonnatural α-arylated amino ester **38** from morpholine, ethyl glyoxylate (**2**) and indole (**32**) as electronrich arene (Scheme 13).[63]

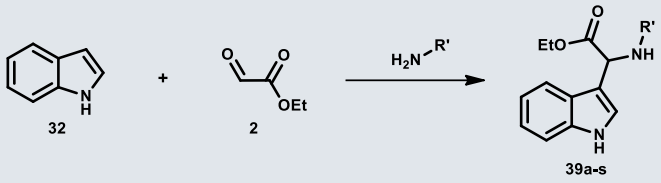


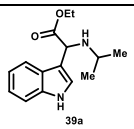
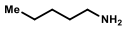
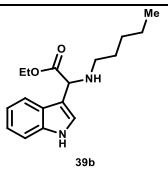
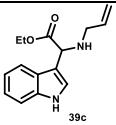
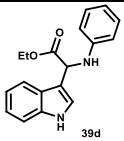
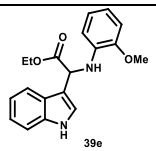
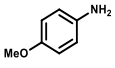
Scheme 13. Preparation of derivatives **37** and **38** by using 1,3-dicarbonyl compound and morpholine as applied reactants

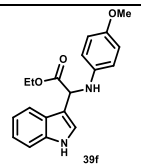
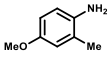
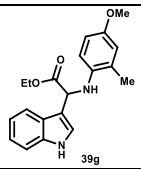
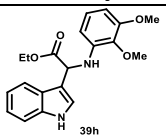
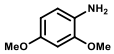
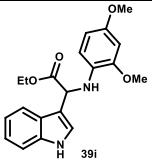
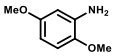
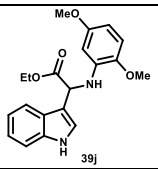
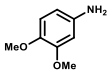
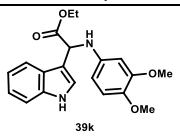
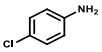
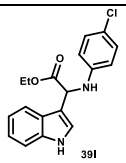
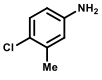
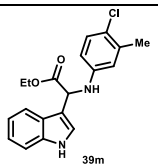
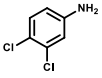
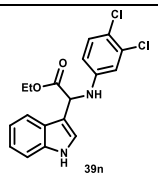
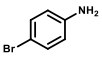
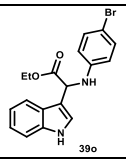
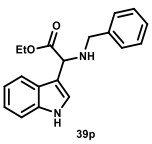
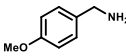
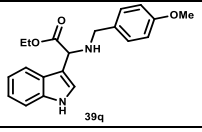
Based on a previous study on the multi-component Friedel–Crafts alkylation reaction between indole (**32**), ethyl glyoxylate (**2**) and anilines, the expected ethyl 2-(arylamino)-2-(1*H*-indol-3-yl)acetates were formed (Table 2, entries 4-5, 7, 12-14, 17). The reactions between starting compounds with scandium triflate (5 mol%) in dichloromethane applying different reaction conditions (temperature, time) were investigated.[64] Kang *et al.* studied the chiral phosphoric acid-catalyzed enantioselective Friedel–Crafts reaction of indole (**32**) with ethyl glyoxylate imines,

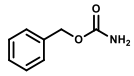
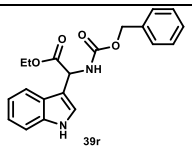
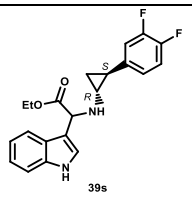
therethrough optically active (3-indolyl)glycine derivatives with excellent yields and high enantioselectivities were synthesized (Table 2, entries 9-10).[65] Furthermore, a novel class of potential herbicides, 3-indolylglycines were synthesized via *aza*-Friedel-Crafts in a water/sodium dodecyl sulfate system (Table 2, entries 6, 16, 20-21).[66] To produce unnatural tryptophan derivatives, benzylamine was combined with ethyl glyoxylate to form the intermediate imine which in the presence of catalytic amount of $Yb(OTf)_3$ underwent electrophilic substitution on the 3-position of a variety of indoles (Table 2, entry 24).[67] A novel acetyl chloride-mediated cascade transformation was investigated by a patent using benzyl carbamate, ethyl glyoxylate and arene nucleophiles (Table 2, entry 26).[68] In addition to the presented experiments[64-68] the reaction conditions for the further synthesis[69-72] of new 3-indolylglycine derivatives are summarised in Table 2.

Table 2. Synthesis of 3-indolylglycine derivatives

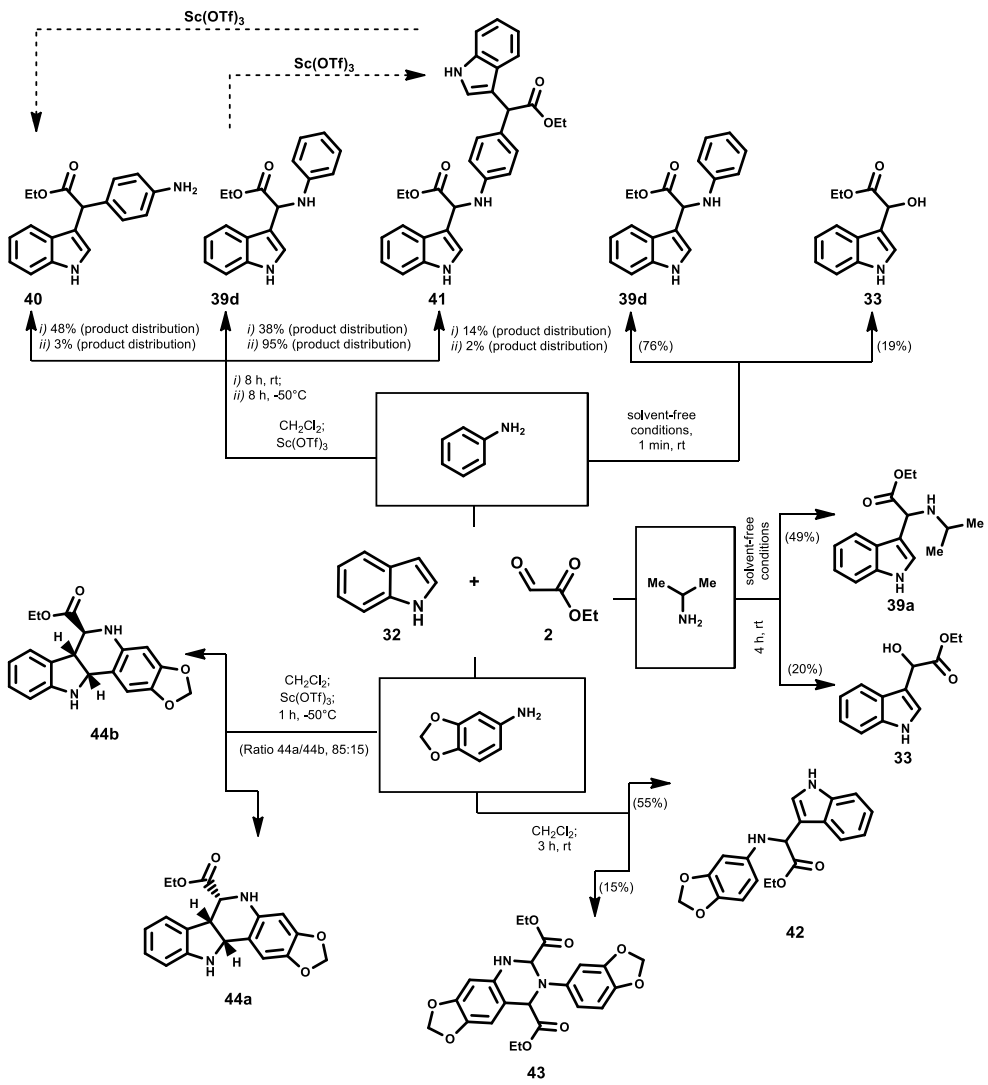


Entry	Reactant (amine)	Product	Reaction conditions				Yields (%)	Lit.
			Reagents	Catalyst	Solvent	T (°C), t (h)		
1		 39a	$H_2O_4S{\cdot}Mg$ (1:1)	-	toluene	rt, 73	33	69
2		 39b	$H_2O_4S{\cdot}Mg$ (1:1)	-	toluene	rt, 73	49	69
3		 39c	-	-	-	rt, 1	61	70
4		 39d	-	-	CH_2Cl_2	rt, 20	85	64
5		 39e	-	-	CH_2Cl_2	rt, 15	75	64
6			-	$CH_3(CH_2)_{11}OSO_3Na$	H_2O	50, 0.5	98	66
7			-	$Sc(OTf)_3$	CH_2Cl_2	-50, 0.5	88	64
8			$H_2O_4S{\cdot}Mg$ (1:1)	-	toluene	rt, 13	89	69

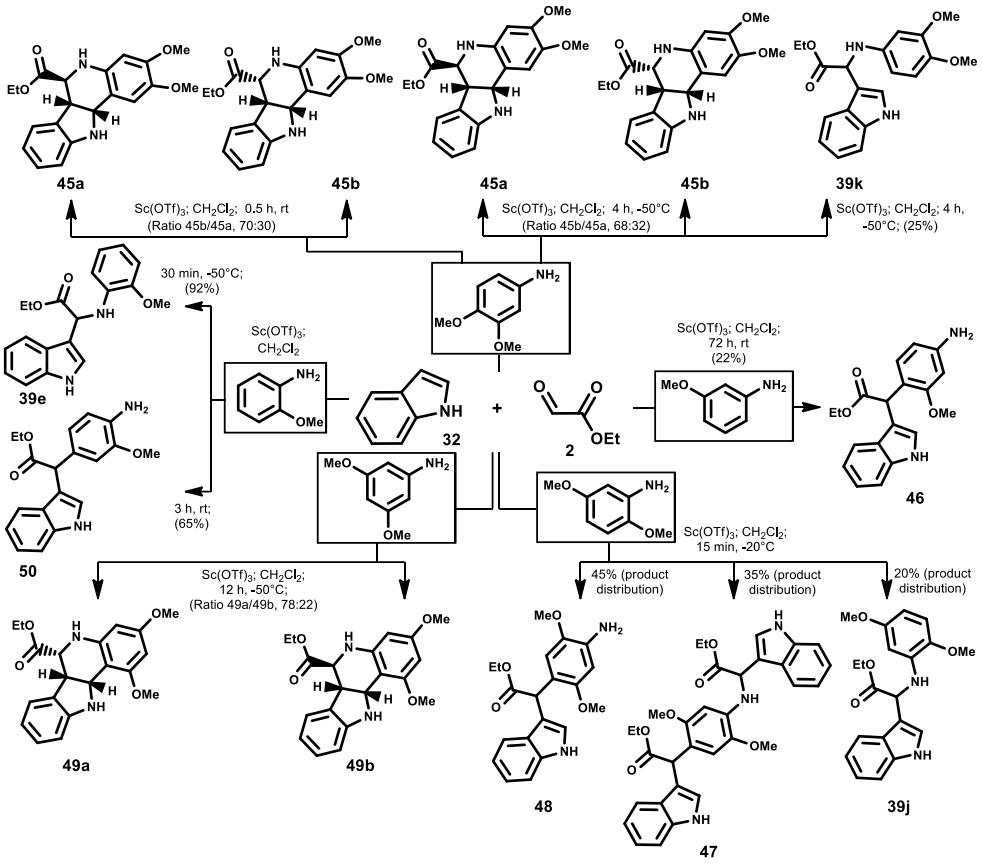
9		 39f	$NaHCO_3$	chiral phosphoric acid	toluene, H_2O	rt, 0.2; -40, 1.5;	99	65
10		 39g	$NaHCO_3$	chiral phosphoric acid	toluene, H_2O	rt, 0.2; -50, 1.5;	92	65
11		 39h	-	$Sc(OTf)_3$	CH_2Cl_2	-50, 12	73	71
12		 39i	-	$Sc(OTf)_3$	CH_2Cl_2	-50, 0.5	98	64
13		 39j	-	-	CH_2Cl_2	rt, 6	54	64
14			-	$Sc(OTf)_3$	CH_2Cl_2	-50, 6	35	64
15		 39k	-	-	CH_2Cl_2	rt, 24	55	71
16		 39l	-	$CH_3(CH_2)_{11}OSO_3Na$	H_2O	50, 0.4	96	66
17			-	-	CH_2Cl_2	rt, 24	75	64
18		 39m	-	$Sc(OTf)_3$	CH_2Cl_2	-50, 12	83	71
19		 39n	-	$Sc(OTf)_3$	CH_2Cl_2	-50, 12	93	71
20		 39o	-	$CH_3(CH_2)_{11}OSO_3Na$	H_2O	50, 0.4	88	66
21		 39p	-	$CH_3(CH_2)_{11}OSO_3Na$	H_2O	50, 0.7	77	66
22			-	-	-	rt, 0.5	80	70
23			$H_2O_4S{\cdot}Mg$ (1:1)	-	toluene	rt, 49	61	69
24			Na_2SO_4	$Yb(OTf)_3$	CH_2Cl_2	-, -	82	67
25		 39q	$H_2O_4S{\cdot}Mg$ (1:1)	-	toluene	rt, 73	46	69

26		 39r	CH_3COCl, $NaHCO_3$	CH_3COOH	$CHCl_3$, H_2O	60, 12; 0, 2	64	68
27		 39s	-	-	toluene, 1,1,1,3,3,3-hexafluoro-2-propanol	rt, 6.5	68	72

According the synthetic methods summarized in Scheme 14-15, when the reactions are catalysed by 5 mol-% scandium triflate $ScO(Tf)_3$, in cases when e.g. aniline, 2-methoxyaniline, 2,5-dimethoxyaniline were applied, rearrangements involving the arylamino fragments were observed. In certain cases, these unusual conversions through intermediate **41**, **47** were occured. The proposed mechanism for the Sc^{III}-catalysed rearrangements from ethyl 2-(arylamino)-2-(1*H*-indol-3-yl)acetates to the products of the rearrangement was reported.[64] Next, the effect induced by the position of a methoxy group on the regioselectivity of the scandium-catalysed rearrangement of acetates obtained from the multicomponent reaction between indole (**32**), ethyl glyoxylate (**2**) and anilines (e.g. benzo[*d*][1,3]dioxol-5-amine, 3,4-dimethoxyaniline, 3,5-dimethoxyaniline) was defined. It was found that the reaction followed a different pathway, and two pairs of diastereomeric *aza*- Diels-Alder adducts (**45b**, **44a**, **49a** and **45a**, **44b**, **49b**) were isolated.[71] On the base of a recent investigation, the solvent-free and catalyst-free three-component Friedel–Crafts alkylation of indole (**32**), amines, and ethyl glyoxylate (**2**) was developed for the synthesis of (3-indolyl)glycine derivatives. When aniline and propan-2-amine were used as amine components, the reaction were complete within one minute and 4 hours to give the aminoalkylation products **39d, 39a** as well as ethyl 2-hydroxy-2-(1*H*-indol-3-yl)acetate (**33**). It was found that the yield of the reaction was dependent on the addition order of the starting materials. These results prove that the reaction of ethyl glyoxilate with amines is faster than that with indole and that the product of the Friedel–Crafts reaction of indole with in situ generated glyoxylate imine predominates in the solvent-free three-component reaction.[70]



Scheme 14. Synthetic protocols for transformation of indole (**32**) with ethyl glyoxylate (**2**) by applying aniline, propan-2-amine, benzo[*d*][1,3]dioxol-5-amine as amine components

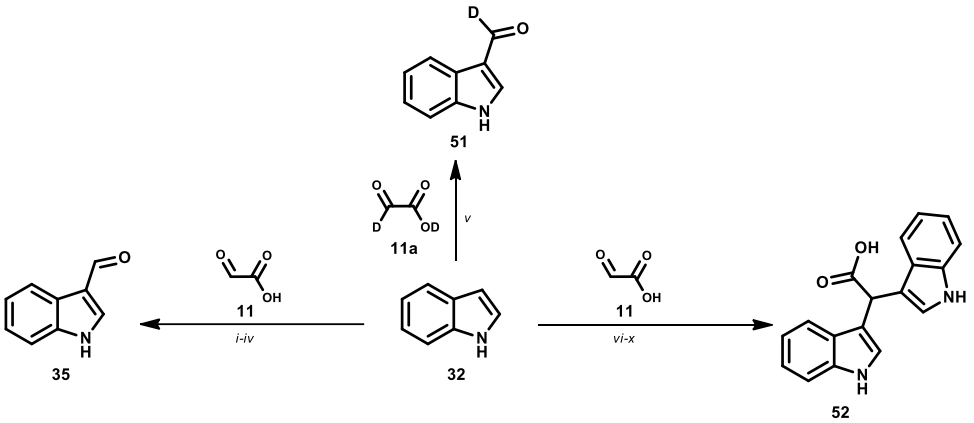


Scheme 15. Reactions between indole (**32**) and ethyl glyoxylate (**2**) by using different anilines with methoxy group(s)

2.3.2. Synthetic methods starting from indole and glyoxylic acid

A literature survey on the application of indole (**32**) revealed that its reactivity with glyoxylic acid (**11**) has been tested in a few model reactions resulting in 3-formylindole (**35**) (Scheme 16). For instance, a highly efficient methodology by electro-chemical decarboxylation of glyoxylic acid using amine (aniline) as a dual function catalyst was reported (method *i*).[73] In addition, photoredox[74]- (method *ii*) as well as $(NH_4)_2S_2O_8$-mediated[75] (method *iii*) and photochemical[76] (method *iv*) formylation of indole (**32**) using reaction conditions summarized in Table 3 has been published. The synthesis of C-1 deuterated 3-formylindole **51** by organophotoredox catalysed direct formylation of indole (**32**) with deuterated glyoxylic acid **11a** was achieved (method *v*).[74] For the synthesis of bis(indolyl)methane derivative **52**, reactions of indole (**32**) with glyoxylic acid (**11**) were carried out in the presence of 1-phenyl-3-(2-pyridyl)thiourea[50] (method *vi*) or zirconium oxychloride octahydrate[77] (method *vii*) or tungstophosphoric acid[78] (method *viii*) or scandium triflate[79] (method *ix*) as catalysts. In addition a patent revealed the synthesis of bis-heterocyclic compounds and their use as anti-inflammatory agents. Accordingly, one equivalent of indole (**32**)

was suspended in water and one equivalent of glyoxylic acid (**11**) was added (method *x*). The mixture was stirred at 85°C for three hours.[80] Reaction conditions are summarized in Table 3.

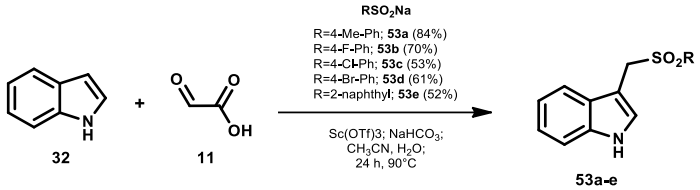


Scheme 16. Preparation of compounds **35**, **51** and **52** by using glyoxylic acid (**11**) or deuterated glyoxylic acid (**11a**)

Table 3. Reaction conditions for the synthesis of derivatives **35**, **51** and **52**

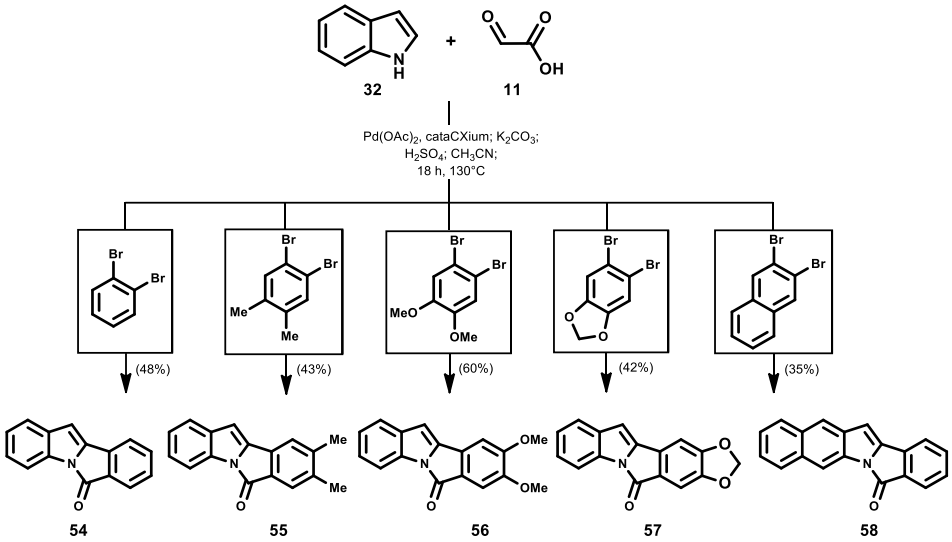
Reac-tion	Reagent	Catalyst	Solvent	T (°C)	t (h)	Yield (%)	Lit.
i	$NaClO_4$	aniline, Platinum foils	$(CH_3)_2SO$, H_2O	rt	7	73	73
ii	CH_3COONa, O_2	-	CH_3CN	rt	84	84	74
iii	$(NH_4)_2S_2O_8$	-	$(CH_3)_2SO$, H_2O	rt	3	72	75
iv	-	-	CH_3CN, H_2O	rt	6	65	76
v	CH_3COONa, O_2	-	CH_3CN	rt	24	67	74
vi	-	1-phenyl-3-(2-pyridyl)thiourea ($C_{12}H_{11}N_3S$)	$C_2H_4Cl_2$	60	-	50	50
vii	-	$ZrOCl_2 \cdot 8H_2O$	EtOH, H_2O	rt	5	90	77
viii	-	tungstophosphoric acid ($H_3[PW_{12}O_{40}]$)	H_2O	rt	4	86	78
ix	-	$Sc(OTf)_3$	CH_3CN	rt	12	88	79
x	-	-	H_2O	85	3	85	80

Further investigations on transformations of indole skeleton (Scheme 17), an efficient methodology for C(sp^2)–*H* sulfonylmethylation of indole using glyoxylic acid (**11**) as the C1 source and sodium sulfinates as the sulfone source was developed. The reactions were performed in the presence of $Sc(OTf)_3$ (10 mol%) and acetonitrile was applied as solvent.[81]



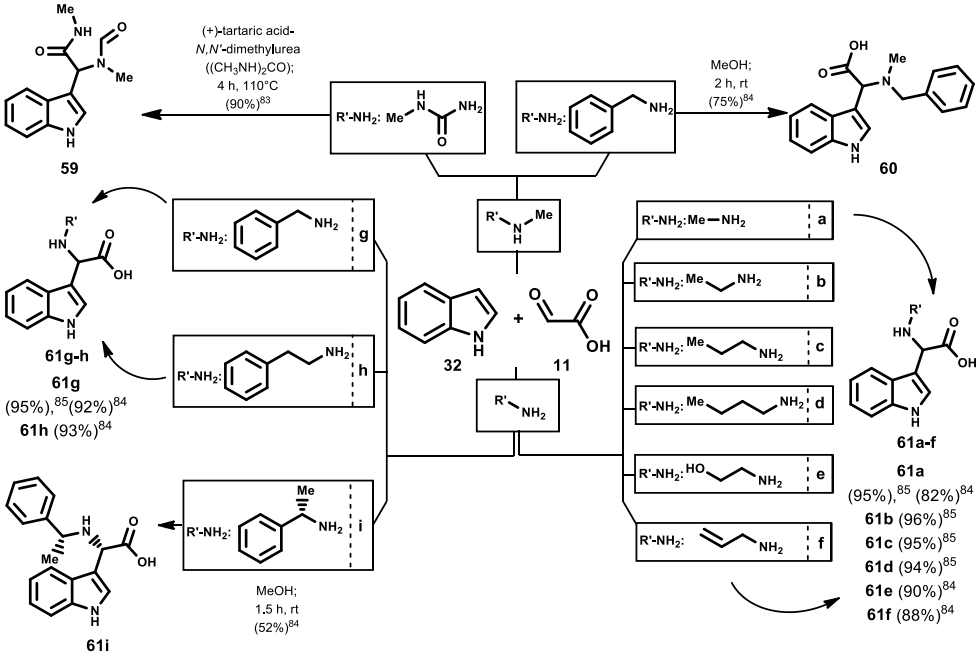
Scheme 17. Method for C(sp^2)–*H* sulfonylmethylation of indole in the presence of $Sc(OTf)_3$

Čarný *et al.* reported a one-step protocol for the construction of the isoindolo[2,1-*a*]indol-6-one framework through tandem Pd-catalyzed aminocarbonylation and intramolecular cross-coupling reaction via C−H activation. In favor to test the applicability of the proposed method, numerous dibromoarenes and indole were reacted by using $Pd(OAc)_2$ and cataCXium as catalysts (Scheme 18).[82]



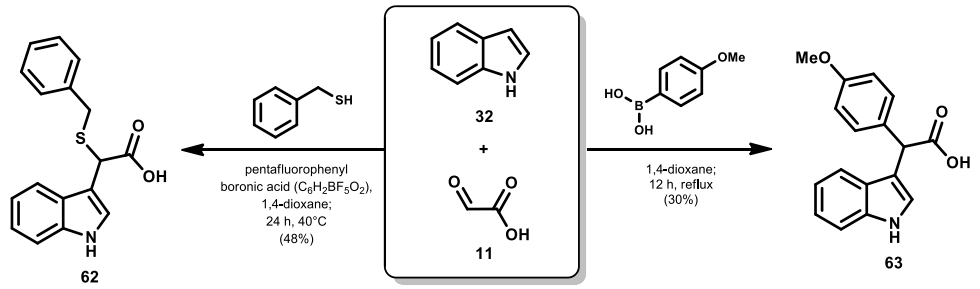
Scheme 18. Reacting various dibromoarenes with indole (**32**)

As shown by Scheme 19, by the reaction of indole (**32**) with glyoxylic acid (**11**) using (+)-tartaric acid-*N*,*N'*-dimethylurea as a deep eutectic solution, a cascade approach for the synthesis of 5-(indol-3-yl)hydantoin (**59**) was developed.[83] Based on a recent paper, the synthesis of novel *N*-substituted 3-indolylglycines via three-component Mannich reaction of indole (**32**) and free glyoxylic acid (**11**) in the presence of primary and secondary aliphatic amines were achieved. A series of racemic 3-indolylglycines **60**, **61a**, **61e-f**, **61g-i** using e.g. methanamine, 2-aminoethanol, prop-2-en-1-amine, benzylamine, *N*-methyl-1-phenylmethanamine and 2-phenylethanamine as amine components, as well as the optically pure (*S*)-3-indolylglycine using *R*-1-phenylethylamine as chiral pool were synthetized. In the case of latter transformation, precise tuning of reaction conditions using methanol allowed the research group to isolate the major (*R*,*S*)-diastereomer in excellent diastereomeric purity. Regarding the reaction conditions, the transformations were performed in methanol at room temperature.[84] The three-component reaction of primary aliphatic amines, glyoxalic acid (**11**) and indole (**32**) in water at ambient temperature afforded indol-3-yl-glycines **61a-c, 61g**. The procedure is based on the uncatalyzed Friedel-Crafts condensation between indole (**32**) and various iminoacids formed in situ from glyoxalic acid (**11**) and primary aliphatic amines. Among the amines used are methanamine, ethanamine, propan-1-amine, butan-1-amine, and benzylamine.[85]



Scheme 19. Synthesis of 5-(indol-3-yl)hydantoin (**59**) and *N*-substituted 3-indolylglycines (**60**, **61a-i**)

As further transformation (Scheme 20), a novel boronic acid accelerated three-component reaction of indole (**32**), thiol, and glyoxylic acid (**11**) was published, providing a unique class of α-sulfanyl-substituted indole derivative **62** containing free carboxylic acids via the formation of α-hydroxycarboxylic acids. Additionally, the research group demonstrated that simultaneous activation of the α-hydroxy group with a boronic acid catalyst and internal carboxylic acid is key to promoting the reaction.[86] Furthermore, indoles can serve as substrates for the Petasis boronic acid-Mannich reaction, providing a practical synthetic route for C–C bond formation in α-(*N*-substituted indole)carboxylic acids. When (4-methoxyphenyl)boronic acid was subjected to give the corresponding product **63**, it was obtained in poor yields (30%) after purification.[87]

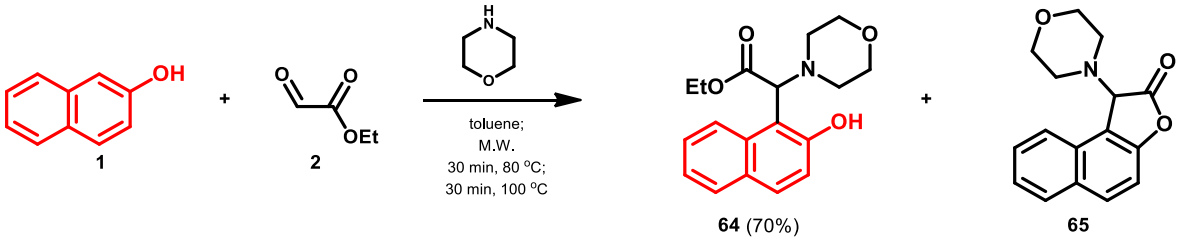


Scheme 20. Applying pentafluorophenyl boronic acid, thiol and (4-methoxyphenyl)boronic acid in the reaction of indole (**32**) and glyoxylic acid (**11**)

3. RESULTS AND DISCUSSION

3.1. Synthesis of naphthol and quinoline type precursors

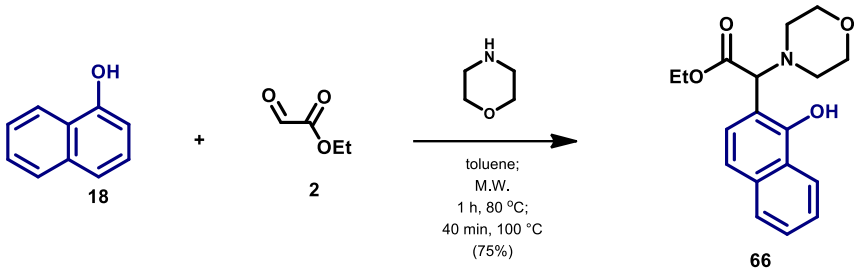
In order to prepare 2-naphthol-substituted bifunctional glycine-type precursor, the electron-rich aromatic compound (**1**) and morpholine were reacted in the presence of ethyl glyoxylate (**2**) as an aldehyde component (Scheme 21). The crude reaction mixtures formed under microwave irradiation in 30 min at 80 °C and in 30 min at 100 °C in toluene were examined by ^{1}H-NMR measurements. It is interesting to note that using conventional heating, the formation of the desired product **64** could not be detected. After optimisation of reaction conditions, the reaction was repeated and TLC proved the presence of two main products; therefore, column chromatographic purification was required. After separation of the desired glycine precursor **64** from side-product **65**, we aimed to investigate the reaction mechanism. A detailed NMR spectroscopic and mass spectrometry analysis of product **65** indicated the formation of a lactone via intramolecular loss of ethanol. Based on literature data (melting point, NMR spectroscopy), the structure of **65** was verified.[88] It is worth mentioning that Matuszczak published the reaction of 2-naphthol and *N*-acetyl-α-hydroxyglycinate furnishing lactone **65** by using acetic anhydride.[89] In contrast, in our case the formation of lactone was achieved in situ in toluene under microwave irradiation.



Scheme 21. Synthesis of 2-naphthol-substituted glycine precursor **64**

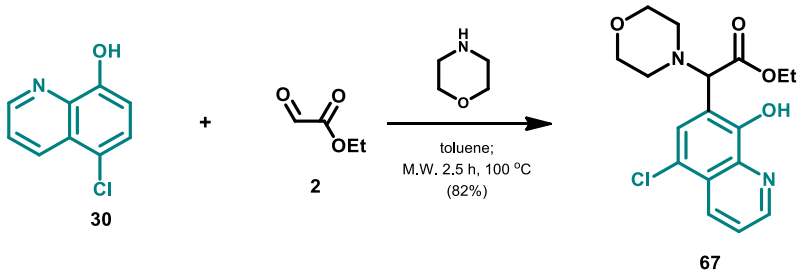
The synthesis of precursor **66** was achieved by reacting 1-naphthol (**18**) as an electron-rich aromatic compound and morpholine with ethyl glyoxylate (**2**) as the aldehyde component. According to TLC, after 1 hour in toluene at 80 °C and 40 minutes at 100 °C under MW irradiation, desired product **66** was formed. The NMR investigation of the crude product proved the presence of initial compounds; therefore, column chromatographic purification was applied.

It is interesting to mention that previously Li *et al.* have developed the first HFIP-promoted denovo synthesis of various nonnatural α-arylated amino esters from readily available amines (such as morpholine), ethyl glyoxylate and electron-rich arenes (such as 1-naphthol) under mild conditions. Additionally, the possible reaction mechanism was proposed, revealing that the products probably formed via the unstable imine salt inter-mediates, rather than via the mandelic acid ester intermediates.[90]



Scheme 22. Preparation of 1-naphthol-substituted glycine precursor **66**

Based on literature data, 8-hydroxyquinoline is a biologically active moiety[7] interpreted as a potential 1-naphthol analogue. To examine the behavior of 5-Cl-8-HQ in Mannich reaction, derivative **30** was reacted with morpholine in the presence of ethyl glyoxylate (**2**) as an aldehyde component. According to TLC and NMR investigation of the crude reaction mixture, the formation of a single product and the presence of initial compounds were observed. New compound **67** was isolated and purified by crystallization and recrystallization from *i*Pr_2O.



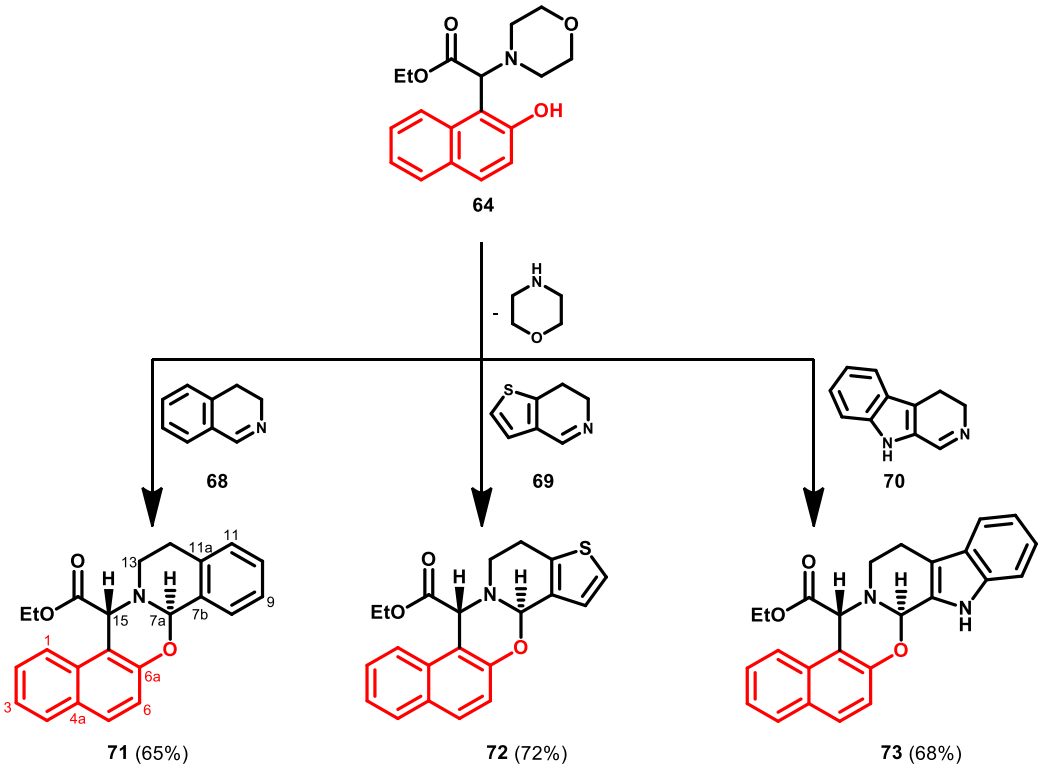
Scheme 23. Application of 5-Cl-8-HQ as electron-rich compound to the synthesis of Mannich base **67**

3.2. Transformations of the synthesized precursors via [4+2] cycloaddition reactions

3.2.1. Application of ethyl 2-(2-hydroxynaphthalen-1-yl)-2-morpholinoacetate in [4+2] cycloaddition reactions

In the frame of this work, with aminonaphthol derivative **64** in hand, its reaction with different cyclic imines via [4+2] cycloaddition was tested (Scheme 24). Mechanistically, during the reaction via loss of morpholine, the presence of partially aromatic *ortho*-quinone methide intermediate has been proved and it was transformed with different dienophiles to new α-amino acid esters. First, we wanted to investigate the reaction of bifunctional precursor **64** with 3,4-dihydroisoquinoline (**68**)[91] in [4+2] cycloaddition. The reaction was performed first at 80 °C under microwave irradiation for 60 min in 1,4-dioxane. The progress of the synthesis was monitored by TLC that showed the formation of a new spot next to those of the starting materials. By using higher temperatures and longer reactions (100 °C, 300 min), the desired product was isolated in a relatively higher amount.

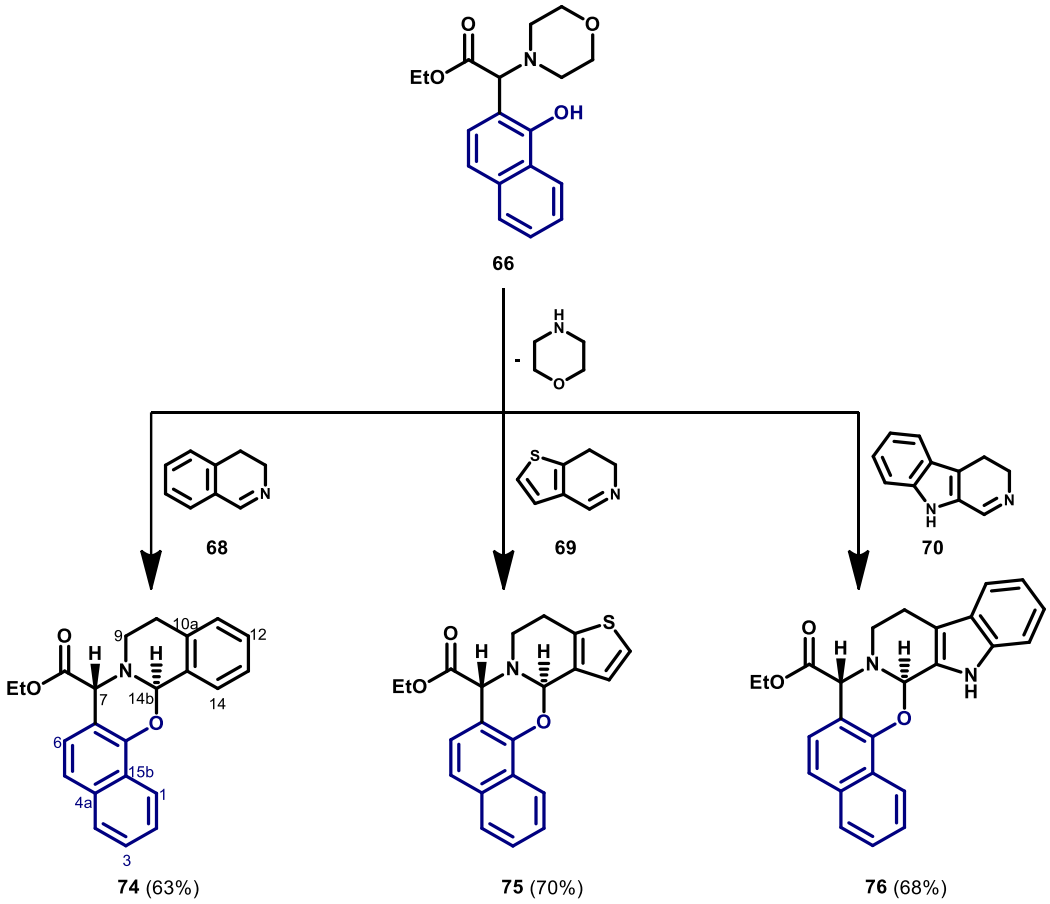
Based on ^{1}H-NMR analysis of the crude reaction mixture, the formation of a single product has been assumed. In order to determine the relative configuration of the newly formed two stereogenic centres, 2D-NMR technique was applied. The relatively weak cross peak on the NOE spectrum of **71** proved that the arrangement of H-7a and H-15 is *trans*. Then we focused on testing the possibility to extend the reaction by using 6,7-dihydrothieno[3,2-*c*]pyridine (**69**)[92] and 3,4-dihydro-*β*-carboline (**70**)[93] as initial cyclic imine dienophiles. The [4+2] cycloaddition reactions were performed at 80 °C and 100 °C in 1,4-dioxane. The formation of the desired naphthoxazines was monitored by both TLC and the NMR analysis of the crude products. This latter method proved that all reactions led to the formation of a single product. In order to separate the desired polycycles from unreacted starting materials, column chromatographic purification was required. Finally, the target compounds were isolated by crystallisation. In the case of [4+2] cycloaddition, 100 °C and reaction times of 280–360 min were found to be the optimal reaction conditions (Table 4). By using 2D-NMR technique (NOE measurements) the relative configurations of the newly formed stereogenic centres was proved to be *trans*. Comparing the reactivity of cyclic imines (3,4-dihydroisoquinoline (**68**), 6,7-dihydrothieno[3,2-c]pyridine (**69**), and 3,4-dihydro-*β*-carboline (**70**), the reaction of **69** gave compound **72** isolated as a pure product in a relatively good yield of 72%.



Scheme 24. [4+2] Cycloaddition reactions starting from derivative **64**

3.2.2. Application of ethyl 2-(1-hydroxynaphthalen-2-yl)-2-morpholinoacetate in [4+2] cycloaddition reactions

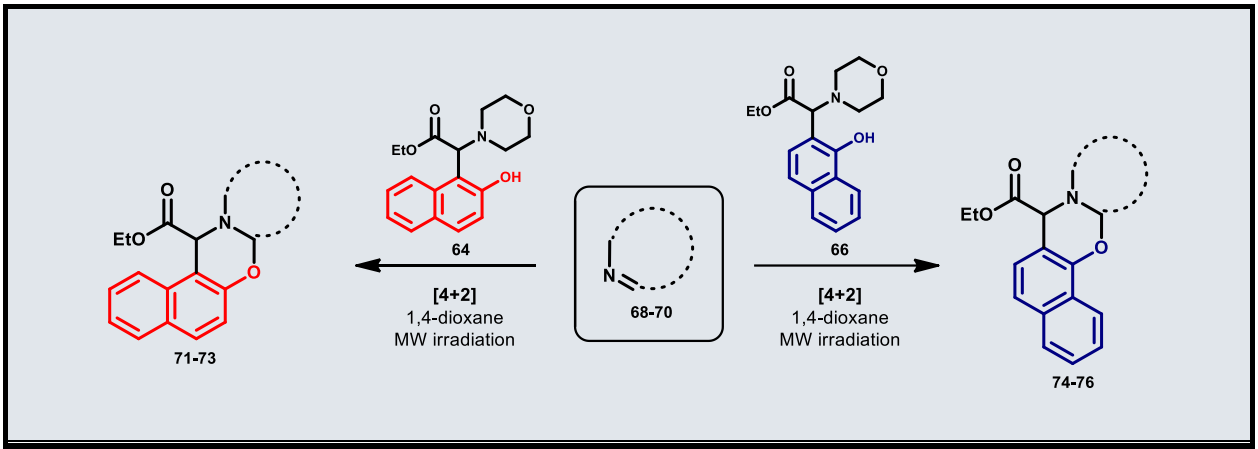
By extending the modified Mannich reaction, the stabilisation of aminonaphthol derivative **66** via partially aromatic *ortho*-quinone methide intermediate was tested with different cyclic imines in [4+2] cycloaddition (Scheme 25). Accordingly, 1-naphthol-substituted glycine precursor **66** was reacted with 3,4-dihydroisoquinoline (**68**) at 100 °C under MW irradiation in 1,4-dioxane. After a reaction time of 80 min, the formation of two new spots in TLC were observed. According to the ^{1}H-NMR spectrum of the crude reaction mixture, the decomposition of the desired naphthoxazino derivative **74** was proved. The separation of product **74** from the side product was achieved by using column chromatographic purification. Next, we focused on avoiding the formation of the side product by controlling reaction conditions. Therefore, the reaction was repeated at lower temperature (80 °C). The progress of synthesis was monitored in every 20 minutes by TLC showing the formation of a single product after 80 minutes. After optimising reaction conditions, the crude reaction mixture was purified by column chromatography.



Scheme 25. [4+2] Cycloaddition reactions starting from derivative **66**

Based on previous experiments, we wanted to investigate the behaviour of other dienophiles in [4+2] cycloaddition, namely 6,7-dihydrothieno[3,2-*c*]pyridine (**69**) and 3,4-dihydro-*β*-carboline (**70**) (Table 4). TLC and crude product NMR analysis, in each case, indicated the formation of a single product. In the case of newly formed stereogenic centres via [4+2] cycloaddition, NOE measurements proved that the relative configuration is *trans*. In conclusion, 80–120 °C and reaction times of 80–260 minutes were found to be the optimal reaction conditions. Purification of crude mixtures were achieved by column chromatography.

Table 4. Reaction conditions for preparation of naphthoxazino derivates via [4+2] cycloaddition (**71–73**, **74–76**)



Product	Cyclic imine	Time (min)	Temperature (°C)	Conversion[a] (%)	Yield[b] (%)
71	**68**	60	80	65	
		300	**100**	**73**	**65**
72	**69**	60	80	70	
		280	**100**	**77**	**72**
73	**70**	80	80	67	
		360	**100**	**75**	**68**
74	**68**	20	80	55	
		80	**80**	**70**	**63**
75	**69**	60	100	68	
		80	**100**	**78**	**70**
76	**70**	20	80	65	
		40	100	72	
		260	**120**	**75**	**68**

[a] Determined from crude NMR spectra.
[b] Isolated yields. Work-up was performed in the case of each product from its reaction at the highest conversion.

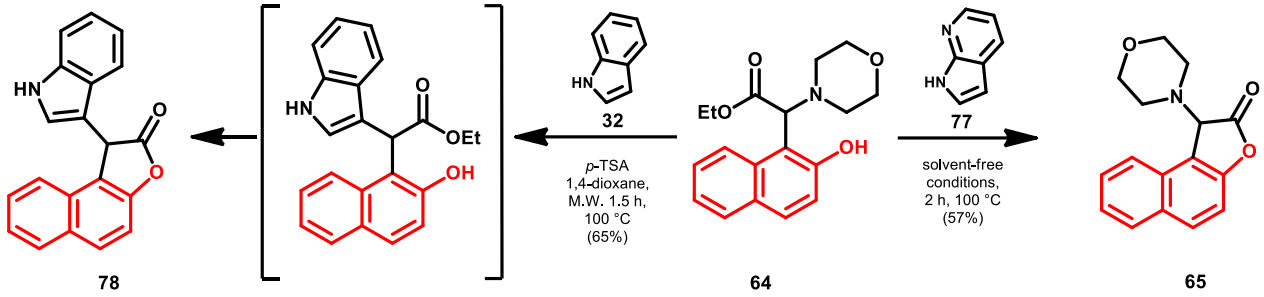
As observed on the performed investigations, although longer reaction times and a higher temperature accelerated the [4+2] cycloaddition reactions, conversions were maximised at around 78%. Based on our results, the transformation of new α-amino acid esters seemed to proceed under equilibrium condititons. Accordingly, morpholine, because of its nucleophilic property, is able to stabilize *ortho*-quinone methide to recover the initial aminonaphthol derivative thereby inhibiting [4+2] cycloaddition.

3.3. Synthesis of indole and naphthol or 8-hydroxyquinolin skeleton containing di- or triarylmethane derivatives

3.3.1. Arylation of ethyl 2-(2-hydroxynaphthalen-1-yl)-2-morpholinoacetate and ethyl 2-(1-hydroxynaphthalen-2-yl)-2-morpholinoacetate with indole or 7-azaindole

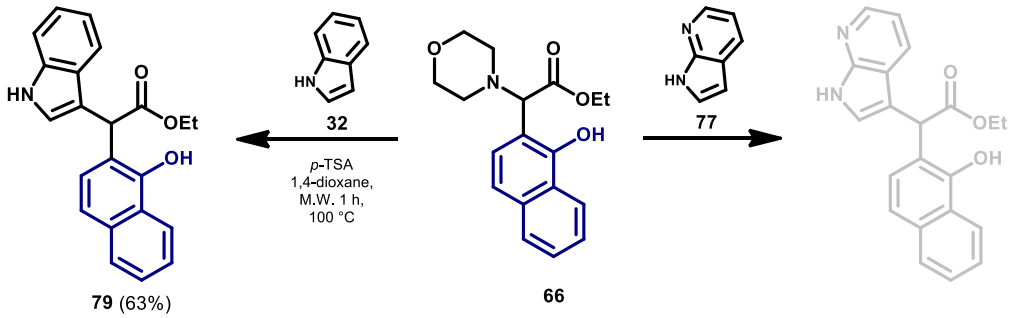
On the basis of available studies, the indole skeleton proves to be a potent biological moiety[94] and the structure−activity relationships trough structural modifications were examined.[20-23] Taking into consideration of previous investigations that glycine derivatives substituted with 2- and 1-naphthol were found to be excellent precursors to participate in [4+2] cycloaddition with different cyclic imines, we desired to test their reactivity with indole and 7-azaindole (Scheme 26). Having in hand 2-naphthol-substituted glycine precursor **64** reported previously and indole (**32**), the reaction was performed at 100 °C in 1,4-dioxane under microwave conditions. *p*-Toluenesulfonic acid (*p*-TSA) is considered to be an acid catalyst applied frequently in the modified Mannich reaction,[39] we decided to investigate its effect on the reaction. After a reaction time of 1.5 h, the formation of **78** through ester intermediate was observed. The synthesis of 1-(1*H*-indol-3-yl)naphtho[2,1-*b*]furan-2(1*H*)-one (**78**) was already described by Jadhav *et al.* utilizing a different synthetic pathway, starting from ethyl2-(4-fluorophenylamino)-2-(1*H*-indol-3-yl) acetate and 2-naphthol using scandium triflate in 1,2 dichloroethane via arylation−cyclization.[95] Applying different reaction conditions (modification of solvent, temperature, additive) led to the same product. In our next experiment, precursor **64** was reacted with 7-azaindole (**77**) in the presence of 10 mol% *p*-TSA at 100 °C under MW irradiation in 1,4-dioxane. Based on ^{1}H NMR analysis of the crude reaction mixture and thin-layer chromatography (TLC), we concluded that the synthesis did not result in the desired derivative. When the reaction was repeated in toluene as solvent, the formation of a multi-spot reaction mixture was monitored by TLC. Unfortunately, the desired product could not be isolated even by using column chromatography. Next, the reaction was carried out in solvent-free conditions under microwave irradiation at 100 °C. A detailed NMR spectroscopic

analysis of the product indicated the formation of a lactone structure (compound **65**) via intramolecular loss of ethanol. It is worth mentioning, that the formation and structure of this lactone as side-product was reported in our previous examinations (chapter 3.1.).



Scheme 26. Reactions of 2-(2-hydroxynaphthalen-1-yl)-2-morpholinoacetate (**64**) with indole (**32**) and 7-azaindole (**77**)

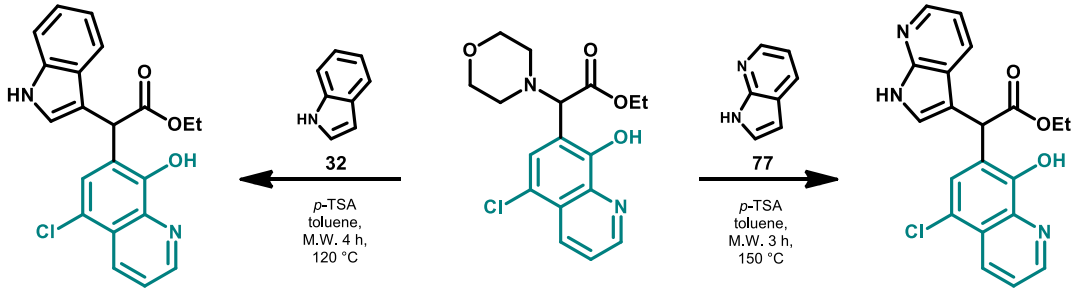
In view of the findings on the field of transformation of 2-naphthol-substituted precursor **64** with indole and 7-azaindole, we focused on testing the reaction from 1-naphthol-substituted precursor **66** (Scheme 27). Accordingly, **66** and indole (**32**) were reacted in the presence of 10 mol% *p*-TSA at 100 °C for 60 min under MW irradiation in 1,4-dioxane. The progress of the synthesis was monitored by TLC showing the formation of a new spot. On the basis of ^{1}H-NMR analysis of the crude reaction mixture, the formation of **79** as a single product was assumed. On the basis of previous observations, the reaction was carried out under other conditions as well, applying toluene as solvent in the presence of 10 mol% *p*-TSA. However, formation of the desired product did not take place. A similar result was found by running the reaction under solvent-free conditions. In favor of examining the possibility of extending the reaction scope, 7-azaindole (**77**) was reacted with precursor **66**. However, even by applying different solvents (toluene, 1,4-dioxane), using solvent-free conditions, and testing different temperatures (80 °C, 100 °C, 120 °C, 150 °C), the target compound did not form.



Scheme 27. Preparation of target compound **79** from 1-naphthol-substituted precursor **66**

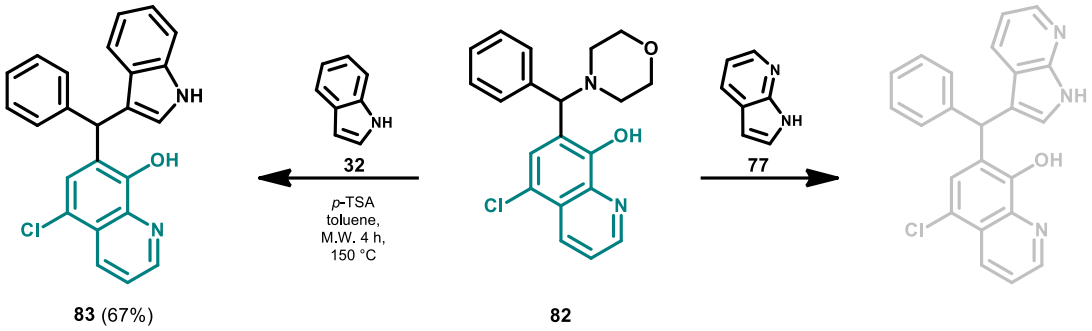
3.3.2. Arylation of 8-hydroxyquinoline skeleton containing precursors with indole or 7-azaindole

To investigate the scope and limitations of the reaction, the synthesis of new diarylmethane derivatives starting from a precursor substituted with 8-hydroxyquinoline skeleton as well as indole and 7-azaindole were accomplished. The preparation of **80** starting from **67** and indole (**32**) in the presence of 10 mol% *p*-TSA was achieved (Scheme 28). In this case, **80** was isolated with a yield of 70% in 4 h at 120 °C. To study the scope and limitations of the reaction, the synthesis of **81** was planned through the reaction of the precursor **67** with 7-azaindole (**77**). The reaction was tested first in toluene at 120 °C by monitoring the conversion of the starting compounds by TLC analysis. Since the yield was not satisfactory, the reaction was repeated at 150 °C (Scheme 28). By using higher temperature and longer reaction (3 h), the desired product was isolated by crystallization from the reaction mixture.



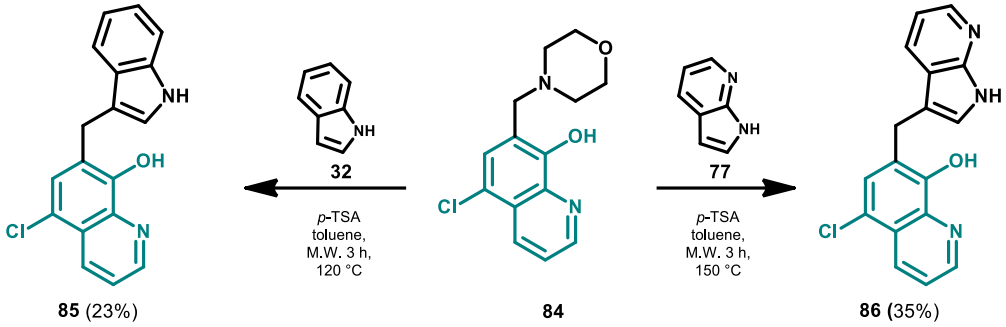
Scheme 28. The transformation of compound **67** bearing the 5-chloro-8-hydroxyquinoline moiety with indole (**32**) and 7-azaindole (**77**)

In order to study the effect of the aldehyde component on the synthetic pathway, 5-Cl-8-HQ and morpholine were fixed and the aldehyde moiety was varied among benzaldehyde and paraformaldehyde. The re-synthesis of precursors **82** was achieved based on the previously published synthetic method.[96] When precursor **82** was reacted with indole (**32**) at 150 °C for 4 h, the desired triarylmethane **83** was isolated in a yield of 67% after purification by column chromatography (Scheme 29). In contrast, the reaction between **82** and 7-azaindole (**77**) did not show any transformation upon testing various reaction conditions (solvent, reaction time, reaction temperature) (Scheme 29).



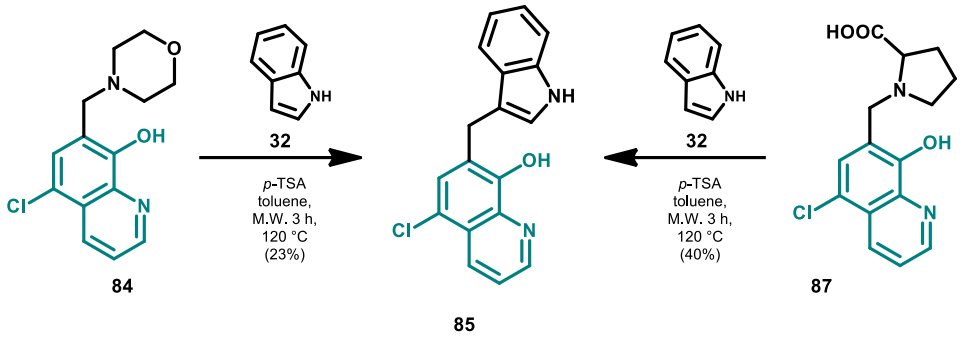
Scheme 29. The reaction of precursor **82** with indole (**32**) and 7-azaindole (**77**)

In the next step, we focused our efforts to investigate the transformations of precursors that were originally prepared from paraformaldehyde as the aldehyde component. For this reason, the re-synthesis of Mannich base **84** was accomplished applying a synthetic method published previously.[96] Starting from precursor **84** and indole (**32**) and 7-azaindole (**77**), the formation of target compounds **85** and **86** were isolated with low yield in relatively long reactions at high temperatures (Scheme 30).



Scheme 30. The transformation of **84** containing paraformaldehyde as aldehyde component

Since derivative **85** is postulated to be formed in the reaction of indole with *ortho*-quinone methide evolving from Mannich base **84**, we carried out a systematic investigation of the synthesis of **85**. According to previous observations, the amine moiety of the Mannich base can be interpreted as a leaving group. Consequently, two precursors have been selected. These were compound **84** bearing the morpholine skeleton and Mannich base **87** having the L-proline motif. This latter precursor was re-synthesized by using our synthetic pathway published earlier,[97] starting from 5-chloro-8-hydroxyquinoline, L-proline, and aqueous formaldehyde. The parallel arylation of precursors **84** and **87** with indole was also investigated (Scheme 31).



Scheme 31. Synthesis of compound **85** starting from different precursors

This latter reaction offered a possibility to compare the effect of the leaving groups on conversion (Figure 4). The reaction was monitored by TLC and NMR analysis of the crude reaction mixtures in every 30 minutes. These systematic investigations allowed us to conclude that starting from precursor **87** the desired diaryl derivative was formed in higher conversion. This may be explained by the better leaving group character of L-proline compared with that of morpholine.

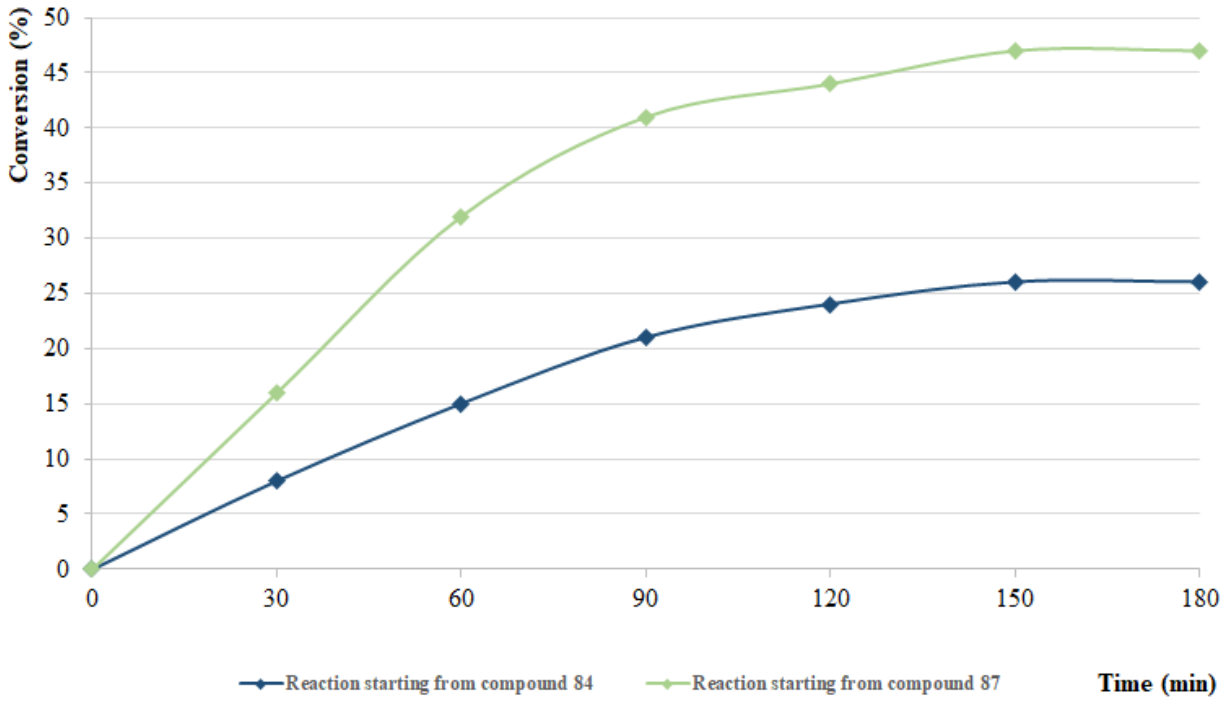


Figure 4. Systematic investigation on compound **84** and **87** to determine the effect of the leaving groups

3.4. Systematically designed series of cyclic amines coupled indole and azaindole derivatives

In previous studies the scope and limitations of the modified *aza*-Friedel–Crafts reaction by direct coupling of different cyclic imines and indole derivatives as electron-rich aromatic compounds have been examined.[24-26] In addition, regarding the widespread biological activity of

the indole skeleton or their application as pharmaceuticals,[98] we desired to perform a systematic biological examination of 3-isoquinolyl-, 3-thieno[3,2-*c*]pyridyl-, 3-*β*-carbolinyl- and 3-benz[*c*]azepinyl-indole and -azaindole derivatives. In favour of drawing the inference, we decided to resynthesize the selected derivatives and to extend the synthetic pathway to the preparation of new derivatives to have a preliminary overview about the structure–activity relationship for C-3-coupled indole and azaindole derivatives.

To examine the effect of the indole skeleton in primary biological screening (Figure 5), the isoquinoline part was stabilized and the C-1 coupled (relative to tetrahydroisoquinoline core) indole moiety was varied among indole, indole-2-carboxylic acid, and 4-, 5- and 6-azaindoles (Figure 5). The synthesis of 3-(1,2,3,4-tetrahydroisoquinolin-1- yl)indole (**88**) and 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)indole-2-carboxylic acid (**89**) was accelerated under microwave irradiation as described earlier by our research group.[24] To investigate the role of the heteroatom (nitrogen) on the activity, 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)azaindoles (**90-93**) have also been resynthesized.[26]

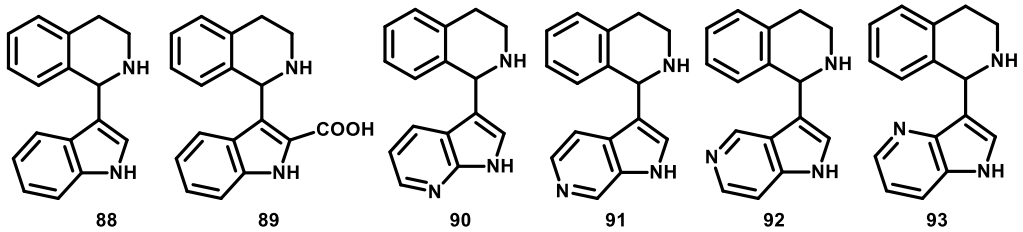


Figure 5. C-1 substituted 1,2,3,4-tetrahydroisoquinolines

Next, we selected compounds **94-98**, with the indole skeleton connected to varied partially saturated cyclic amines, to investigate the influence of the cationic centre (amine) on the biological activity (Figure 6). The selected derivatives were synthesized based on the research protocol published previously by direct *aza*-Friedel–Crafts reaction of indole with 6,7-dimethoxy-3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 4,6-dihydro-3*H*benzo[*c*]azepine and 4,9-dihydro-3*H*-*β*-carboline.[24,25] Microwave irradiation, as the optimal reaction condition, has been used that led to the formation of the desired **94-97** products in good yields. Recently, the applicability of (4*aR*,8*aR*)-4*a*,5,6,7,8,8*a*-hexahydroquinoxalin-2(1*H*)-one as chiral imine in the modified aza-Friedel–Crafts reaction has been tested by Iwanejko *et al*.[99] Compounds **98a** and **98b** were synthesized followed by isolation (separation) by column chromatography and determining the absolute configuration of the newly generated asymmetric centre. This allowed to identify the diastoremers by comparing the published characteristic data of **98a** and **98b** with those measured (melting points, ^{1}H-NMR chemical shifts and rotation values).[99]

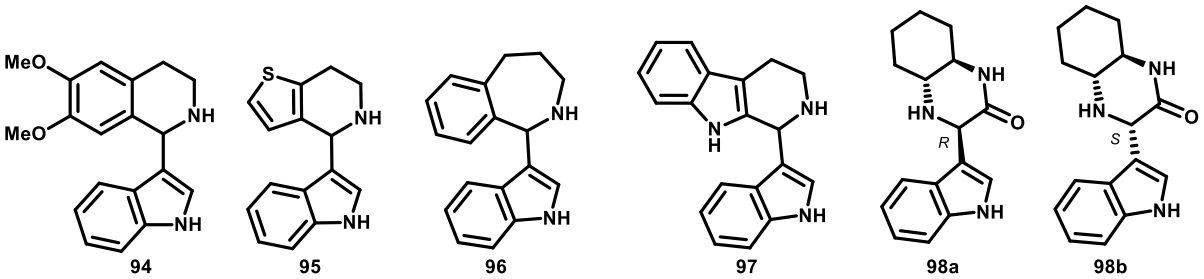


Figure 6. C-3-substituted indole derivatives

Regarding the biological activity of the azaindole skeleton, 7-azaindole derivatives have been found to be a hingebinding element in kinase inhibition.[100] Mechanistically, because of its structural characteristics, 7-azaindole is able to form bidentate hydrogen bonds with the hinge region of kinase. Vemurafenib has been described as 7-azaindole-based kinase drug for the treatment of melanoma.[101] Accordingly, our next selected set of compounds was designed with the 7-azaindole skeleton connected to partially saturated cyclic amines. The direct coupling of 7-azaindole with cyclic imines, such as 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-*β*-carboline and 4,5-dihydro-3*H*-benz[*c*]azepine, was performed utilizing the solvent-free method previously described leading to the formation of compounds **100**-**102** (Figure 7).[26]

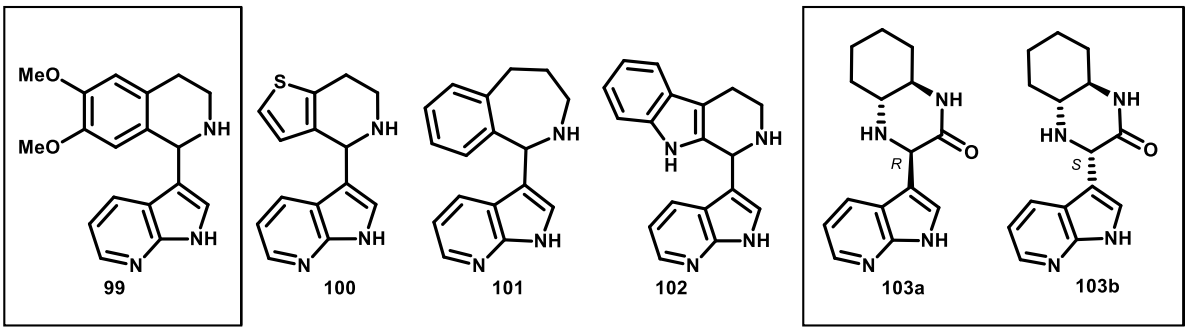
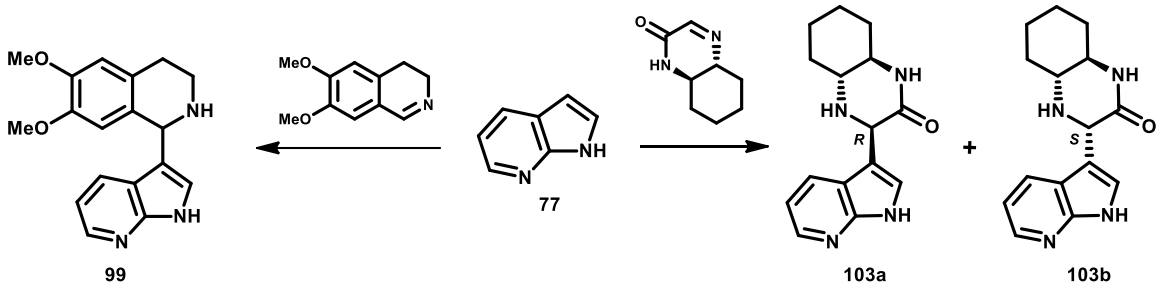


Figure 7. C-3-substituted 7-azaindole derivatives

To have an overview about the influence of the dimethoxy-substituents tetrahydoisoquinoline skeleton on activity, 3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-7-azaindole (**99**) as new precursor was also synthesized starting from 6,7-dimethoxy-3,4-dihydroisoquinoline as cyclic imine and 7-azaindole (**77**). The reaction was performed under solvent-free conditions by applying microwave irradiation (2.5 h, 100 °C; 1 h, 110 °C) as the optimal condition (Scheme 32).



Scheme 32. Synthesis of new derivatives starting from 7-azaindole (**77**) as an electron-rich aromatic compound

As a further structural modification, we wanted to observe the effect of saturated nonracemic cyclic amine coupled with 7-azaindole. Accordingly, 7-azaindole (**77**) and 1.0 equivalent of (4*aR*,8*aR*)-4*a*,5,6,7,8,8*a*-hexahydroquinoxalin-2(1*H*)-one as chiral imine were reacted at room temperature in dichloromethane. After a relatively long reaction (23 h), the NMR spectrum of the crude reaction mixture proved the appearance of both possible products **103a** and **103b**. In this case, the ratio of **103a**:**103b** was found to be 5:1. Since the conversion was not satisfactory, the synthesis was repeated by using a twostep microwave reaction (1.5 h, 40˚C; 1.5 h, 50˚C). A further increase of the temperature (100˚C) under microwave conditions resulted in the formation of **103a** and **103b** in a conversion of 57%. Before the work-up procedure, the diastereomeric ratio of **103a**:**103b** was also measured and found to be 5:1 again. It means that the diastereoselectivity of the reaction is not influenced by the reaction temperature (Table 5). The desired products **103a** and **103b** were isolated by column chromatography and the configurations of the newly created stereogenic centres (Scheme 32) were determined by comparing the measured characteristic data (melting points, ^{1}H-NMR chemical shifts and rotation values) with the published data found for the analogues **98a** and **98b** (Figure 6).[99]

Table 5. Reaction conditions for the synthesis of 3-[(1*R*,4*R*,6*R*)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-7-azaindole (**103a**) and 3-[(1*R*,4*S*,6*R*)-3-oxo-2,5-diazabicyclo[4.4.0]dec-4-yl]-7azaindole (**103b**)

Entry	Time (h)	Heating technique	Temperature (°C)	Conversion[a] (%)	*d.r.*
1	23	classical heating (oil bath)	room temperature	11	**103a**:**103b** 5:1
2	1.5 1.5	MW	40 50	9	**103a**:**103b** 5:1
3	1.5	MW	80	12	**103a**:**103b** 5:1
4	2	MW	100	57	**103a**:**103b** 5:1
[a] Determined from crude NMR spectra.					

Regarding the antibacterial activity (Table 6), the compounds were tested on Gram-negative *Escherichia coli* and Gram-positive methicillin susceptible and resistant *Staphylococcus aureus* strains. Two derivatives exerted a moderate antibacterial effect on the reference *S. aureus* strains: **101** and **97** had an MIC of 50 μM. The other derivatives had an MIC of 100 μM or >100 μM on the tested bacterial strains.

The efflux pump inhibiting (EPI) properties of the compounds were assessed on Gram-negative and Gram-positive bacterial strains, such as AcrAB-TolC pump expressing *E. coli* AG100, its AcrAB-TolC-deleted mutant strain *E. coli* AG100A and methicillin susceptible *S. aureus* ATCC 25923 reference strain, methicillin resistant *S. aureus* MRSA 272123 clinical strains, respectively. The EPI activity was compared to the positive control and in the case of the *E coli* strains, an RFI value above 0.30 was considered as an effective efflux pump inhibitor (the positive control CCCP had an RFI of 0.74 on the pump expressing and pump deleted strains). Compound **90** was effective on *E. coli* AG100 (RFI: 0.33) and caused higher EB accumulation in the mutant *E. coli* strain (RFI: 0.52). Similar activity was obtained on *E. coli* AG100 in the presence of compounds **91** (RFI: 0.47) and **93** (RFI: 0.37). Furthermore, the compounds were also more active on the mutant strain indicating that AcrAB-TolC is crucial in the defense mechanisms of bacteria against toxic compounds. Compounds **94** and **96** were potent EPIs at 50 μM with RFIs of 0.33 and 0.36 on *E. coli* AG100, respectively. Furthermore, their activity was near the same on the mutant *E. coli* strain, because they have more targets in the bacterial cells, *e.g.* membrane destabilizing activity without affecting efflux pumps. The most potent EPI of the AcrAB-TolC system was **95** with RFI of 0.56 on the *E. coli* AG100 strain at 50 μM, and lower activity was observed on the pump mutant strain (RFI: 0.43). On the Gram-positive strains the positive control was reserpine: it was more active on the methicillin susceptible reference strain (RFI: 0.32) than on the MRSA clinical isolate (RFI: 0.23). None of the compounds had EPI properties on the MRSA strain. On the methicillin susceptible strain the most potent EPIs at 50 μM are the following: **95** (RFI: 0.68), **96** (RFI: 0.30), **99** (RFI: 0.30), **94** (RFI: 0.17). Considering the antibacterial evaluations, the indole skeleton connected with 6,7-dihydrothieno[3,2-*c*]pyridine as a partially saturated cyclic amine has been found to be the most effective (Table 6, Entry 8).

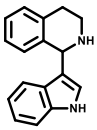
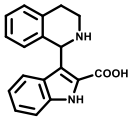
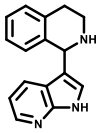
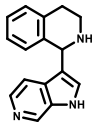
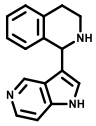
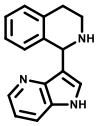
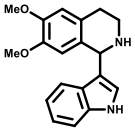
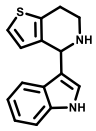
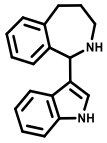
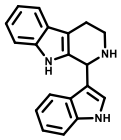
Using the bacterial strains mentioned above, the anti-biofilm activity of the derivatives was determined using crystal violet staining. No biofilm inhibition was observed on the pump-deleted mutant *E. coli* AG100A and on the methicillin susceptible *S. aureus* ATCC 25923 strains. Three derivatives could inhibit the biofilm formation of *E. coli* AG100 with inhibition degree of nearly 30%: **99** (inhibition: 38.34%), **98b** (inhibition: 31.45%) at 100 μM and **98a** (inhibition: 34.30%) at 50 μM. Four derivatives could inhibit the biofilm formation of the MRSA strain: the most potent

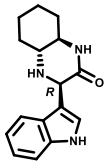
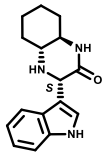
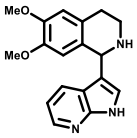
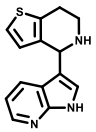
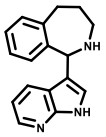
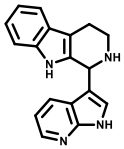
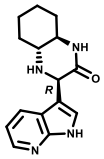
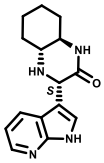
one was **102** demonstrating an inhibition of 33.38% at 50 μM, then **97** with an inhibition of 29.17% at 100 μM. Furthermore, **103a** (an inhibition of 21.96% at 50 μM) and the weakest activity of 19.13% was detected in the presence of **99** at 100 μM. In point of correlation between structure and biological activity, 7-azaindole as an electron-rich aromatic compound could be identified as a significant moiety (Table 6, Entry 13, 16).

The cytotoxic activity of the derivatives was determined using sensitive (Colo 205) and ABCB1 efflux pump expressing (Colo 320) colon adenocarcinoma cell lines and a normal, non-cancerous fibroblast cell line MRC-5. The most potent derivatives were **97**, **88**, **95**, **90** and **96**. The highest anticancer activity was measured in the presence of **95** and **97** on Colo 205 cells (IC_{50}: 21.81 and 24.71 μM, respectively) and Colo 320 cells (IC_{50}: 12.94 and 13.55 μM, respectively). However, compound **97** showed moderate toxicity on normal cells too (IC_{50}: 22.86 μM), whereas compound **95** had no toxic effect on normal cells. The IC_{50} values of **88** and **95** were between 10 and 30 μM on the colon adenocarcinoma cells and, fortunately, these derivatives were not toxic on normal MRC-5 fibroblasts (IC_{50} > 100 μM). In the case of **90** and **96**, the derivatives were more effective on the resistant cell line (IC_{50} of 53.52 and 41.06 μM, respectively) compared to the sensitive one (IC_{50} of 64.35 and 97.85 μM, respectively). In addition, they were not toxic on normal fibroblasts (IC_{50} > 100 μM for both compounds). Derivative **94** was more toxic on the sensitive cells (IC_{50}: 47.38 μM) than on the resistant ones (IC_{50}: 60.38 μM). Compounds **101** and **102** showed mild cytotoxic activity on cancer cells (IC_{50}: 50-80 μM) and they did not affect the viability of normal cells (IC_{50} > 100 μM). To conclude, in favour of improved cytotoxic activity, the presence of the indole skeleton and 6,7-dihydrothieno[3,2-*c*]pyridine as well as 3,4-dihydro-*β*-carboline as cyclic imine is relevant (Table 7, Entry 8, 10).

Since the difference between the sensitive and resistant colon adenocarcinoma cell lines is the expression of the MDR efflux transporter ABCB1 (P-glycoprotein), the activity of the compounds was assessed on the inhibition of ABCB1. The ABCB1 inhibitory activity was compared based on the fluorescence activity ratio (FAR) values at 2 and 20 μM. FAR values above 2 are considered as active ABCB1 modulators. Out of all derivatives, **94**, **95**, **96**, **97** and **101** showed inhibitory effect. The most potent efflux pump inhibitor (EPI) was **94** showing inhibition in both 2 and 20 μM (FAR: 2.34 and 4.04). The other compounds exerted inhibition only at 20 μM: **95** (FAR: 5.14), **101** (FAR: 3.10), **96** (FAR: 2.60) and **97** (FAR: 2.26). In the case of inhibition of P-glycoprotein, the indole moiety has been described as the most active electron-rich aromatic component. With respect to the coupled cyclic amine side, 6,7-dimethoxyisoquinoline has been interpreted to be a beneficial structural element (Table 7, Entry 7).

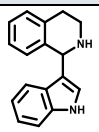
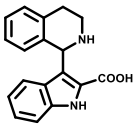
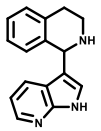
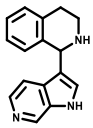
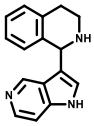
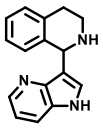
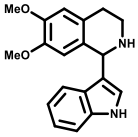
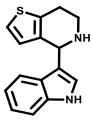
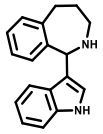
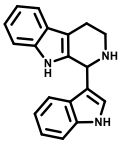
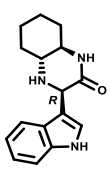
Table 6. Antibacterial effectivity of synthesized compounds

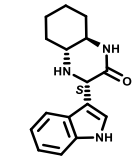
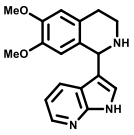
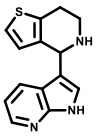
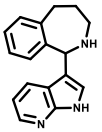
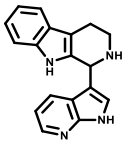
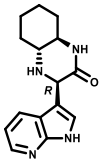
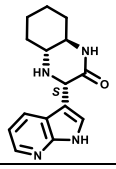
Entry	Product	Structure	Antibacterial activity								
			Anti-biofilm activity					RFI			
			E. coli AG100[a]								
			S.aureus MRSA 272123[b]								
			cc. µM, µg/mL	AV.	SD	comp. OD	Inh. %	cc. µM	*E. coli* AG100	*E. coli* AG100A	*S. aureus* ATCC 25923	*S. aureus* MRSA 272123
1	88		50 100	0.96[a] 0.71[b] 0.67[a] 0.89[b]	0.42[a] 0.06[b] 0.09[a] 0.02[b]	0.81[a] 0.55[b] 0.52[a] 0.74[b]	-151.92[a] -42.08[b] -62.92[a] -90.25[b]	50	0.20	0.52	-0.18	-0.03
2	89		50 100	0.75[a] 0.76[b] 0.60[a] 0.78[b]	0.28[a] 0.12[b] 0.10[a] 0.11[b]	0.60[a] 0.61[b] 0.45[a] 0.63[b]	-88.57[a] -56.75[b] -40.16[a] -62.19[b]	50	-0.01	-0.01	-0.14	0.01
3	90		50 100	0.65[a] 0.68[b] 0.54[a] 0.70[b]	0.24[a] 0.07[b] 0.09[a] 0.25[b]	0.50[a] 0.53[b] 0.39[a] 0.54[b]	-56.12[a] -36.37[b] -20.45[a] -39.38[b]	50	0.33	0.52	-0.22	0.09
4	91		50 100	0.64[a] 0.64[b] 0.72[a] 0.58[b]	0.27[a] 0.11[b] 0.06[a] 0.08[b]	0.49[a] 0.48[b] 0.57[a] 0.42[b]	-54.32[a] -24.38[b] -77.10[a] -8.41[b]	50	0.47	0.53	-0.09	0.10
5	92		50 100	0.48[a] 0.71[b] 0.48[a] 0.53[b]	0.08[a] 0.05[b] 0.14[a] 0.07[b]	0.33[a] 0.56[b] 0.32[a] 0.37[b]	-4.03[a] -43.49[b] -1.37[a] 3.95[b]	50	0.04	0.42	-0.17	0.00
6	93		50 100	0.82[a] 0.65[b] 0.56[a] 0.67[b]	0.32[a] 0.11[b] 0.02[a] 0.13[b]	0.67[a] 0.49[b] 0.40[a] 0.51[b]	-109.61[a] -26.68[b] -26.63[a] -31.40[b]	50	0.37	0.66	-0.14	0.02
7	94		50 100	0.84[a] 0.94[b] 0.51[a] 0.50[b]	0.33[a] 0.03[b] 0.11[a] 0.14[b]	0.69[a] 0.78[b] 0.36[a] 0.35[b]	-115.71[a] -100.97[b] -12.66[a] 10.12[b]	50 100	0.33 0.44	0.34 0.40	0.17 0.38	0.04 0.11
8	95		50 100	1.03[a] 0.75[b] 0.63[a] 0.89[b]	0.35[a] 0.12[b] 0.13[a] 0.24[b]	0.88[a] 0.59[b] 0.48[a] 0.74[b]	-174.29[a] -52.76[b] -49.78[a] -89.75[b]	50 100	0.56 0.71	0.43 0.85	0.68 -	0.07 0.17
9	96		50 100	1.08[a] 0.55[b] 0.67[a] 0.50[b]	0.24[a] 0.03[b] 0.11[a] 0.03[b]	0.93[a] 0.40[b] 0.52[a] 0.35[b]	-189.93[a] -2.23[b] -63.44[a] 9.87[b]	50 100	0.36 0.33	0.36 0.26	0.30 -	-0.09 0.03
10	97		50 100	0.45[a] 0.62[b] 0.48[a] 0.43[b]	0.03[a] 0.08[b] 0.05[a] 0.08[b]	0.29[a] 0.46[b] 0.33[a] 0.28[b]	8.02[a] -18.53[b] -2.78[a] 29.17[b]	25 50 100	- 0.24 0.25	- 0.22 0.36	0.16 - -	- 0.01 -0.10

11	**98a**		50 100	0.36[a] 0.75[b] 0.47[a] 0.65[b]	0.03[a] 0.06[b] 0.06[a] 0.06[b]	0.21[a] 0.60[b] 0.32[a] 0.50[b]	34.30[a] -53.96[b] 0.04[a] -27.41[b]	50 100	0.20 0.11	0.18 -0.07	0.14 0.24	-0.06 -0.08
12	**98b**		50 100	0.43[a] 0.74[b] 0.37[a] 0.84[b]	0.03[a] 0.05[b] 0.04[a] 0.04[b]	0.28[a] 0.58[b] 0.22[a] 0.68[b]	13.80[a] -49.75[b] 31.45[a] -75.58[b]	50 100	0.17 0.12	-0.10 -0.02	0.05 0.14	-0.02 0.01
13	**99**		50 100	0.45[a] 0.73[b] 0.35[a] 0.47[b]	0.11[a] 0.07[b] 0.05[a] 0.08[b]	0.30[a] 0.57[b] 0.20[a] 0.31[b]	6.53[a] -47.18[b] 38.34[a] 19.13[b]	50 100	0.27 0.26	0.17 0.40	0.30 0.16	0.02 0.02
14	**100**		50 100	0.49[a] 0.53[b] 0.43[a] 0.59[b]	0.03[a] 0.01[b] 0.02[a] 0.14[b]	0.34[a] 0.38[b] 0.28[a] 0.44[b]	-6.06[a] 2.49[b] 12.06[a] -12.95[b]	50	0.06	0.29	-0.10	-0.01
15	**101**		50 100	0.48[a] 0.49[b] 0.45[a] -	0.03[a] 0.07[b] 0.04[a] -	0.33[a] 0.33[b] 0.30[a] -	-3.17[a] 13.90[b] 5.83[a] -	50	0.12	0.57	-0.16	0.06
16	**102**		50 100	0.57[a] 0.41[b] 0.41[a] 0.55[b]	0.10[a] 0.28[b] 0.03[a] 0.15[b]	0.42[a] 0.26[b] 0.26[a] 0.39[b]	-32.34[a] 33.38[b] 19.98[a] -1.29[b]	50	0.01	0.30	-0.25	-0.02
17	**103a**		50 100	0.46[a] 0.46[b] 0.41[a] 0.61[b]	0.10[a] 0.01[b] 0.06[a] 0.02[b]	0.31[a] 0.30[b] 0.26[a] 0.46[b]	3.71[a] 21.96[b] 18.73[a] -17.93[b]	50 100	0.17 0.06	0.04 -0.03	-0.01 0.33	0.01 0.02
18	**103b**		50 100	0.51[a] 0.52[b] 0.42[a] 0.57[b]	0.09[a] 0.26[b] 0.03[a] 0.12[b]	0.36[a] 0.37[b] 0.27[a] 0.41[b]	-11.22[a] 4.71[b] 14.82[a] -5.75[b]	50 100	0.17 -0.01	0.30 0.14	0.10 0.12	-0.02 -0.05
		CCCP							0.74	0.74	-	-
		Reserpine (RES)									0.32	0.23

[a] Determined anti-biofilm activity on *E. coli* AG100 strain. [b] Determined anti-biofilm activity on S. aureus MRSA 272123 strain.

Table 7. Cytotoxic applicability of prepared derivatives

Entry	Product	Structure	Cytotoxic activity Colo 205		Colo 320		MRC-5		Inhibition of P-glycoprotein				
			IC50 µM	SD±	IC50 µM	SD±	IC50 µM	SD±	cc. µM	FSC	SSC	FL-1	FAR
1	**88**		22.37	2.04	30.76	0.86	>100	-	2 20	2010 2032	1041 1026	3.34 6.49	0.86 1.66
2	**89**		>100	-	53.58	1.52	>100	-	2 20	2016 2016	1041 1024	3.74 2.62	0.96 0.67
3	**90**		64.35	2.17	53.52	0.90	>100	-	2 20	1621 1594	896 917	9.64 9.75	1.47 1.48
4	**91**		>100	-	>100	-	98.80	2.17	2 20	1999 1963	1045 1027	3.61 3.26	0.92 0.83
5	**92**		>100	-	>100	-	>100	-	2 20	2033 2054	1042 1038	3.93 2.84	1.01 0.73
6	**93**		>100	-	>100	-	>100	-	2 20	1633 1623	901 896	6.51 6.58	0.99 1.00
7	**94**		47.38	0.97	60.38	1.61	>100	-	2 20	1612 1591	876 883	15.40 26.60	2.34 4.04
8	**95**		21.81	1.33	12.94	0.26	>100	-	2 20	1615 1618	865 910	6.48 33.80	0.99 5.14
9	**96**		97.85	0.61	41.06	1.20	>100	-	2 20	1609 1596	888 897	7.26 17.10	1.10 2.60
10	**97**		24.71	0.10	13.55	0.98	22.86	0.57	2 20	1643 1627	1030 992	4.13 13.00	0.72 2.26
11	**98a**		>100	-	>100	-	>100	-	2 20	1655 1629	1028 1041	3.79 3.07	0.66 0.53

12	**98b**		>100	-	>100	-	>100	-	2 20	1670 1636	1014 1043	3.39 3.27	0.59 0.57
13	**99**		>100	-	>100	-	>100	-	2 20	1669 1668	1040 1036	3.38 2.96	0.59 0.52
14	**100**		>100	-	>100	-	>100	-	2 20	1974 2007	1009 1058	6.86 7.46	1.76 1.91
15	**101**		79.56	4.20	68.47	6.06	>100	-	2 20	2014 2006	1024 1017	4.79 12.10	1.23 3.10
16	**102**		66.79	1.52	54.23	1.70	>100	-	2 20	2025 2023	1011 1022	5.68 6.38	1.45 1.63
17	**103a**		>100	-	>100	-	>100	-	2 20	1652 1639	1016 1040	4.44 3.55	0.77 0.62
18	**103b**		>100	-	>100	-	>100	-	2 20	1660 1662	1033 1048	2.68 2.51	0.47 0.44

3.5. Biological evaluations on synthesized compounds

The biological evaluations described in this section were carried out by our co-operating and co-author partner Gabriella Spengler. The acquired results show the importance of the synthetic transformations carried out and were deemed worthy of mentioning in a separate paragraph.

3.5.1. Biological properties of synthesised 2- and 1-naphthol-substituted glycine derivatives and α-amino acid esters

In order to investigate the biological properties of prepared derivatives, antibacterial and efflux pump inhibiting activities were examined. According to the data no significant antibacterial effect was observed for most of the compounds on either Gram-negative or Gram-positive strains. However, compound **76** exhibited antibacterial effect on the reference *S. aureus* ATCC 25923 strain. The activity of the compounds on efflux pump inhibition can be assessed by real-time fluorimetry applying a fluorochrome (e.g. ethidium bromide), a substrate of the bacterial efflux

pumps. Since the compounds, with the exception of **76**, had no antibacterial activity, they were tested at 50 and 100 μM concentrations. In the real-time ethidium bromide accumulation assay, compounds with an efflux pump inhibitory (EPI) effect have a higher relative fluorescence index (RFI) compared to that of the untreated control. The derivatives were not effective on the Gram-negative *Escherichia coli* AG100 strains. However, they had potent EPI activity on the susceptible and resistant *S. aureus* strains (Figure 8). In the case of the susceptible reference *S. aureus* ATCC 25923, **64** and **74** were effective EPIs at 100 μM. In addition, **64**, **74** and **75** showed EPI activity at 50 μM. Since **76** had antibacterial activity on this *S. aureus* strain, the compound was applied at MIC/2 concentration and presented an RFI of 0.26 (Table 8).

With respect to the resistant *S. aureus* MRSA ATCC 43300, **74** and **75** were effective at both concentrations tested (Table 9).

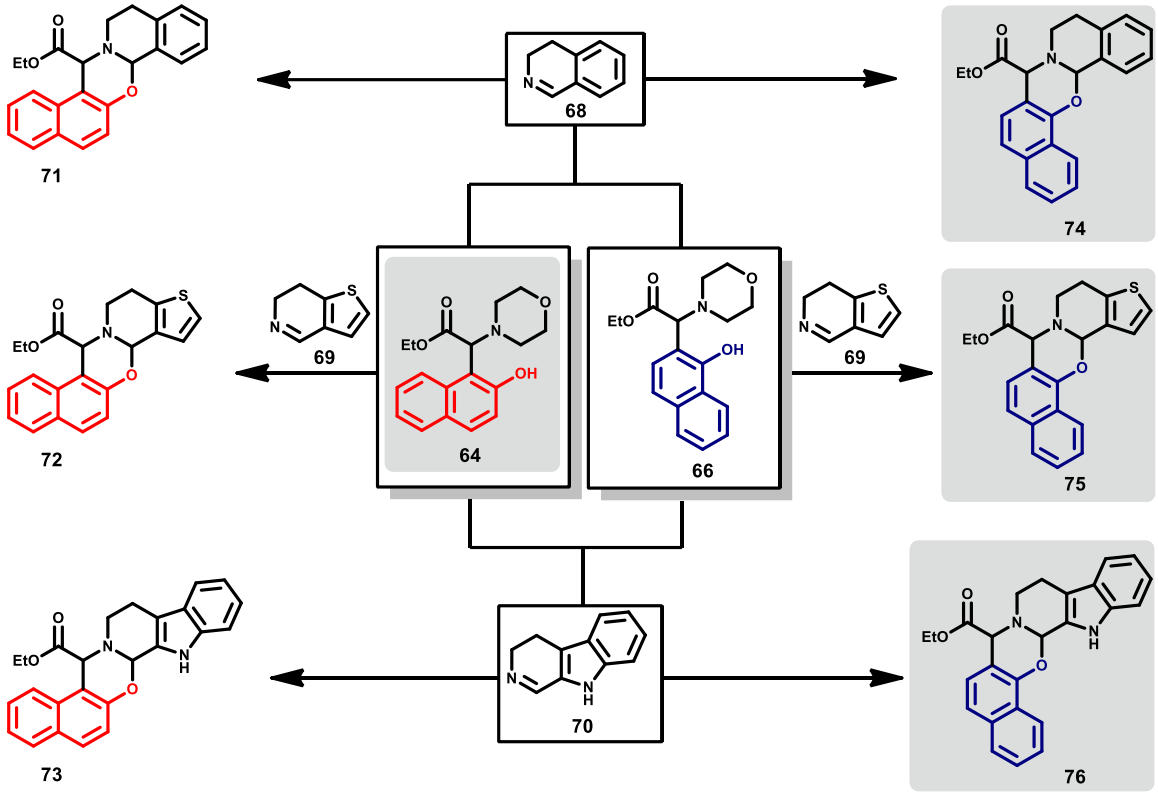


Figure 8. The most effective compounds with antibacterial activity

Table 8. Efflux pump inhibiting activity of the derivatives on *S. aureus* ATCC 25923 strain

RFI		***S.aureus* ATCC 25923**	
Concentration			
50 µM	**Mean**	**SD**	**RFI**
64	58168.67	865.83	**1.10**
71	31759.00	1778.37	0.15
72	29306.00	1165.51	0.06
73	27892.33	884.07	0.01
66	11677.33	1308.70	-0.58
74	44414.33	946.94	**0.61**
75	36826.67	2499.36	0.33

100 µM	**Mean**	**SD**	**RFI**
64	51721.00	905.77	**0.87**
71	31231.67	894.65	0.13
72	33816.67	3255.64	0.22
73	29131.67	2453.80	0.05
66	7624.33	1372.54	-0.72
74	42864.00	2360.31	**0.55**
75	77859.67	5158.78	**1.82**

3.125 µM	**Mean**	**SD**	**RFI**
76	34824.33	1646.59	0.26

	Mean	**SD**	**RFI**
DMSO	27636.67	1089.18	0.00
Reserpine	54056.00	829.47	**0.96**

Table 9. Efflux pump inhibiting activity of the derivatives on *S.aureus* MRSA ATCC 43300 strain

	***Staphylococcus aureus* MRSA ATCC 43300**		
Concentration			
50 µM	**Mean**	**SD**	**RFI**
64	87762.67	3187.90	0.12
71	92734.00	528.62	0.19
72	88184.67	666.65	0.13
73	76072.00	1171.02	-0.03
66	56126.33	299.38	-0.28
74	111300.67	1782.32	**0.43**

75	101450.33	1316.67	**0.30**
76	84683.00	455.64	0.09

100 µM	**Mean**	**SD**	**RFI**
64	84280.00	1539.30	0.08
71	93822.67	4081.38	0.20
72	88655.67	1118.00	0.14
73	78009.00	1574.59	0.00
66	18886.00	648.23	-0.76
74	114226.00	744.67	**0.46**
75	103410.00	1139.71	**0.33**
76	90479.33	1534.61	0.16

	Mean	**SD**	**RFI**
DMSO	78039.33	1254.261	
Reserpine	101532.7	3878.731	**0.30**

3.5.2. Biological activity of indole and 8-hydroxyquinoline, 2- and 1-naphthol skeleton containing di- or triarylmethane derivatives

Based on the obtained results, the compounds showed a potent toxic activity against the sensitive Colo205 and resistant Colo320 cell lines (IC50 values were between 1.72 µM and 53.64 µM) (Table 10). Overall, it was observed that the tested compounds were more effective on the Colo320 cell line, with the exception of the compound **83**. **79** and **78** showed no effect on Colo205 cells, and **78** had no effect on Colo320 either. Only derivatives **80**, **81**, and **83** exerted a mild cytotoxic effect on the normal MRC-5 cell line compared to the cancer cell lines. This means that the compounds can be considered selective, as they were not toxic to normal fibroblast cells (Table 10). Doxorubicin was applied as a positive control, and DMSO was the solvent control. In our research the selectivity of the compounds towards cancer cells (when the activity is compared to normal cells) was investigated. The potential collateral selectivity of the derivatives was also tested applying sensitive Colo 205 colon adenocarcinoma cells and ABCB1 and LRP expressing resistant Colo 320 cells.[102] Relative resistance (RR) values were calculated as the ratio between the IC50 of a compound against the resistant cells and the IC50 against the corresponding sensitive cells (Table 11). Compounds with RR < 1 show selectivity against resistant cells, whereas RR ≤ 0.5 means that the compounds are highly selective towards resistant cells. All derivatives, with the exception of **83**, were selective towards resistant tumor cells. Furthermore, **85** exerted high potency to eliminate

the MDR Colo320 cells (RR=0.37), and this derivative showed no toxicity on normal MRC-5 cells being the most powerful scaffold in the series (Figure 9).

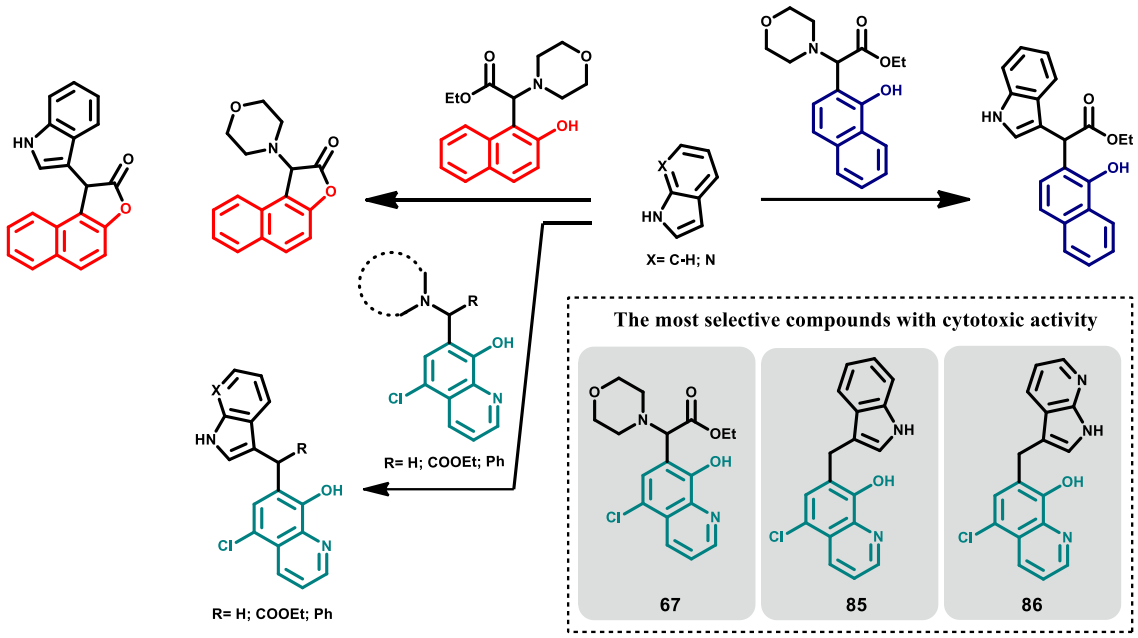


Figure 9. The most selective compounds with cytotoxic activity based on evaluations on sensitive (Colo205) and resistant (Colo320) colon adenocarcinoma, and MRC-5 normal embryonal fibroblast cell lines

Table 10. Cytotoxic effect of the compounds on sensitive (Colo205) and resistant (Colo320) colon adenocarcinoma, and MRC-5 normal embryonal fibroblast cell lines. Doxorubicin was used as a positive control. AV: average of 3 parallel experiment, SD: standard deviation

	Colo205 (µM)					Colo320 (µM)					MRC-5 (µM)			
				AV.	**SD**				**AV.**	**SD**			**AV.**	**SD**
78	-	-	-	**>100**	-	-	-	-	**>100**	-	-	-	**>100**	-
79	-	-	-	**>100**	-	53.82	54.92	52.18	**53.64**	1.38	-	-	**>100**	-
67	2.07	2.06	2.02	**2.05**	0.02	1.565	1.813	1.79	**1.72**	0.14	-	-	**>100**	-
80	5.51	4.71	4.42	**4.88**	0.56	4.636	4.832	4.957	**4.81**	0.16	54.46	55.08	**54.77**	0.44
81	8.05	7.42	8.84	**8.11**	0.71	5.157	4.923	5.109	**5.06**	0.12	46.9	45.56	**46.23**	0.95
83	2.49	2.49	2.63	**2.53**	0.08	2.552	2.84	2.781	**2.72**	0.15	30.08	29.28	**29.68**	0.57
85	13.56	13.37	12.26	**13.06**	0.70	4.967	4.74	4.91	**4.87**	0.12	-	-	**>100**	-
86	36.49	39.42	40.40	**38.77**	2.03	22.98	21.89	22.54	**22.47**	0.55	-	-	**>100**	-
DOX	0.84	0.89	0.81	**0.85**	0.04	3.117	3.12	2.961	**3.07**	0.09	-	-	**>8.62**	-
DMSO	-	-	-	**>2%**	-	-	-	-	**>2%**	-	-	-	**>2%**	-

Table 11. Selectivity indexes (SI) and relative resistance (RR) of the compounds

	MRC-5/Colo205	MRC-5/Colo320	Colo320/Colo205
	SI		RR
78	-	-	NA
79	-	NA	NA
67	>6	>6	0.83
80	11.2	11.4	0.98
81	5.7	9.1	0.62
83	11.7	11	1.07
85	>6	>6	0.37
86	NA	NA	0.57

4. SUMMARY

1. In the frame of my PhD work, new bifunctional precursors substituted with 2- and 1-naphthol or 5-chloro-8-hydroxyquinoline were synthesised by the reaction of 2- and 1-naphthol or 5-chloro-8-hydroxyquinoline, morpholine and ethyl glyoxylate as the aldehyde component by using a modified Mannich-type synthetic pathway.

2. The stabilization of Mannich bases via partially aromatic *ortho*-quinone methide intermediate was tested with different cyclic imines in [4+2] cycloaddition. Based on ^{1}H-NMR analysis, in the case of new α-amino acid esters the formation of a single product has been assumed. The NOE spectrum proved that the relative configuration of the newly formed stereogenic centres was *trans*.

3. Glycine derivatives bearing 2- and 1-naphthol were reacted with indole and 7-azaindole. Reactions were found to depend on the naphthol skeleton. Starting from the 2-naphthol-substituted precursor, lactam-type ring-closed products were isolated. The transformation of 1-naphthol, in turn, led to the formation of the desired biaryl ester. The formed Mannich base substituted with 5-chloro-8-hydroxyquinoline was subjected to give diarylmethane derivatives with indole and 7-azaindole. The effect of the aldehyde component and the amine part of the Mannich base on the synthetic pathway was also investigated.

4. A series of cyclic amines coupled with indole and azaindole derivatives has been systematically designed. The investigated precursors were synthesized by the coupling of indole with cyclic imines such as 3,4-dihydroisoquinoline, 6,7-dimethoxy-3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-β-carboline, 4,5-dihydro-3*H*-benz[*c*]azepine and (4*aR*,8*aR*)-4*a*,5,6,7,8,8*a*-hexahydroquinoxalin-2(1*H*)-one. By fixing the isoquinoline part, the influence of the indole skeleton was also varied among indole-2-carboxylic acid, 4-, 5-, 6- and 7-azaindoles. To have a comprehensive analysis about the correlation between structure and biological activity, the 7-azaindole analogues of the previously mentioned C-3-substituted indoles were also resynthesized or synthesized by using the modified *aza*-Friedel–Crafts reaction. The preparation of new 7-azaindole derivatives starting from 6,7-dimethoxy-3,4-dihydroisoquinoline as cyclic imine and (4*aR*,8*aR*)-4*a*,5,6,7,8,8*a*-hexahydroquinoxalin-2(1*H*)-one as chiral cyclic imine were also achieved by using microwave conditions.

5. In favor of having a preliminary overview about the structure–activity relationships, our efforts were focused on having an overview about biological activity of synthesized

compounds by preliminary biological screening systems. In the frame of biological evaluations of 2- and 1-naphthol-substituted glycine derivatives and α-amino acid esters, in the case of derivatives **64**, **74**, **75** and **76** efflux pump inhibitory (EPI) activity on *S. aureus* ATCC 25923 strain was observed. In addition, **74** and **75** were effective on the resistant *S. aureus* MRSA ATCC 43300. In point of correlation between structure and biological activity, in the case of of α-amino acid esters, 1-naphthol as electron-rich aromatic compound could be identified as a significant moiety. Regarding the cytotoxic effect of indole and 8-hydroxyquinoline, 2- and 1-naphthol skeleton containing di- or triarylmethane derivatives, the biaryl structural element and 5-chloro-8-hydroxyquinoline skeleton could be identified as a significant moiety (compound **85**). For improved cytotoxic activity, the presence of morpholine bearing cationic centre and 5-chloro-8-hydroxyquinoline is beneficial (compound **67**). In the case of cyclic amines coupled indole and azaindole derivatives, the most significant EPI activity was observed referring to 6,7-dihydrothieno[3,2-*c*]pyridine coupled indole derivative on *E. coli* AG100 strain. The reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline with 7-azaindole resulted in the most potent biofilm formation inhibitor product. Applying indole and dihydro-β-carboline as well as dihydrothieno[3,2-*c*]pyridine led to the formation of C-3-coupled compound with the highest anticancer activity. 6,7-Dimethoxy-3,4-dihydroisoquinoline as electron-rich aromatic compound and indole skeleton have been found to be effective in the inhibition of ABCB1.

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ANNEX

I.

II.

III.