Synthesis and transformations of novel precursors *via* modified Mannich and *aza*-Friedel–Crafts reaction

Ph.D. Thesis

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"No amount of experimentation can ever prove me right; a single experiment can prove me wrong"

Albert Einstein

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PUBLICATIONS

Papers related to the thesis

I. István Szatmári, **Khadija Belasri**, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter and Ferenc Fülöp
Ortho-Quinone Methide Driven Synthesis of New *O*,*N*- or *N*,*N*-Heterocycles
ChemistryOpen **2019**, *8*, 961-971. DOI: 10.1002/open.201900150 **IF: 2.205**

II. **Khadija Belasri** , Ferenc Fülöp and István Szatmári
Solvent-Free C-3 Coupling of Azaindoles with Cyclic Imines
Molecules **2019**, *24*, 3578. DOI: 10.3390/molecules24193578 **IF: 3.060**

III. **Khadija Belasri**, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter, Ferenc Fülöp and István Szatmári
Solvent-Free C-3 Coupling of Azaindoles with Cyclic Imines
Molecules **2020**, under publication **IF: 3.060**

Conference lectures

IV. Khadija Belasri, Ferenc Fülöp and István Szatmári:
Ortho-quinonemethid driven synthesis of new *O,N*- or *N,N*-heterocycles
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány előadóülése, May 15, 2018.

V. Khadija Belasri, István Szatmári, Matthias Heydenreich, Andreas Koch, Erich Kleinpeter and Ferenc Fülöp.
Ortho-quinonemethid driven Synthesis of new *O,N*- or *N,N*-heterocycles.
SCT Young Researchers, Paris, France, February 19-21, 2019.

VI. Khadija Belasri, Ferenc Fülöp and István Szatmári:
Catalyst-free coupling of azaindoles with cyclic imines
MTA Alkaloid- és Flavonoidkémiai munkabizottság ülése, April 11-12, 2019.

VII. Khadija Belasri, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp and István Szatmári:
Synthesis and transformations of functionalyzed aminonaphthol derivatives
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése Balatonszemes, June 3-5, 2019.

VIII. István Szatmári, **Khadija Belasri** and Ferenc Fülöp.
Catalyst-free coupling of azaindoles with cyclic imines.
20th Tetrahedron Symposium, Bangkok, Thailand, June 18-21, 2019.

IX. Khadija Belasri, Leila Topal, Ferenc Fülöp and István Szatmári
C-10 substitution of 9-phenanthrol
18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubljana, September 18-21, 2019.

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] The classical Mannich product arises from the condensation reaction of a compound containing at least one active hydrogen atom with formaldehyde and a secondary amine.[6] A special variation of this latter reaction uses benzaldehyde rather than formaldehyde, ammonia instead of secondary amine and replacing the C–H acid by an electron-rich aromatic compound such as 2-naphthol.[7] The reaction was developed by Mario Betti and the aminonaphthol synthesised in this way is known as Betti base.[8–12] This modified three-component Mannich reaction (*m*MR) was then extended to apply 1-naphthol, quinolinol or isoquinolinol as electron-rich aromatic compounds.[8,13]

Mechanistically, the modified *aza*-Friedel–Crafts reaction can be interpreted as a special *m*MR, where electron-rich aromatic compounds such as 1- and 2-naphthol and their *N*-containing analogues are reacted with a wide range of cyclic imines to furnish aminonaphthols,[14–17] aminoquinolinols[15] or aminoisoquinolinols.[15,18] The catalyst-free direct coupling of partially saturated cyclic amines and indole as an electron-rich aromatic compound via a modified *aza*-Friedel–Crafts reaction has recently been published by our research group.[19,20] The reaction has been extended by using indole-2-carboxylic acid as substrate leading to the formation of γ-amino acid derivatives.[19] Most of the methods known already for the synthesis of 3-functionalised 7-azaindole derivatives have applied multistep transformations. Particular efforts have been made to insert other biologically active moieties such as tetrahydroisoquinoline into position 3. In this case, the synthesis of 1-(7-azaindol-3-yl)-1,2,3,4-tetrahydroisoquinoline involved the coupling of 7-azaindole with *N*-protected tetrahydroisoquinoline under iron and copper catalysis.[21,22] Our first aim was to perform a systematic study of the reactivity of azaindole derivatives (4-, 5-, 6- and 7-azaindole) applying the modified *aza*-Friedel–Crafts reaction using cyclic imine substrates leading to new 3-functionalised azaindole derivatives (Figure 1, **I**).

Our next aim was to extend the applicability of the modified *aza*-Friedel–Crafts reaction by using 9-phenanthrol as unique electron-rich aromatic compound and different cyclic imines such as 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-*β*-carboline performing novel aminophenanthrols (Figure 1, **II**). As a further aim, the ring-closing ability of the newly synthesised bifunctional aminophenanthrols with formaldehyde was also planned (Figure 1, **III**).

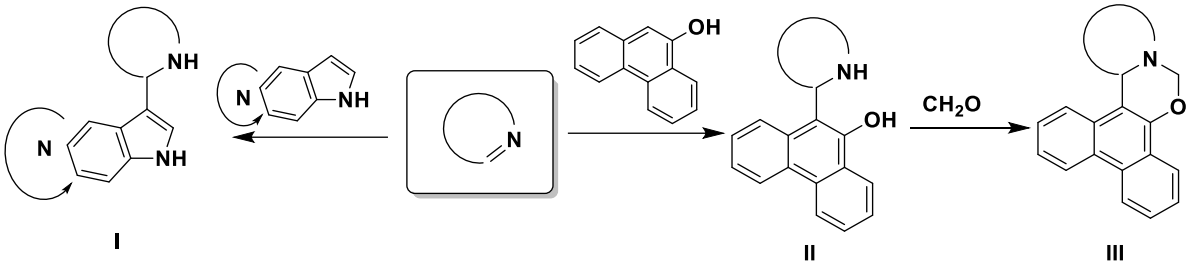


Figure 1

The transformation of *ortho*-quinone methide (*o*-QMs) generated from Mannich bases to condensed polyheterocycles is a relatively new area of chemistry.[23,24] In this case, [4+2] cycloaddition takes place between the *o*-QMs and cyclic imines containing C=N bond. Our research group was the first to develop the reaction of 1-aminoalkyl-2-naphthols with 3,4-dihydroisoquinoline as the cyclic imine.[25] The reaction was then extended starting from 2-aminoalkyl-1-naphthols and other C=N dienophiles preparing naphthoxazino-isoquinoline, -benzazepine and -thienopyridine derivatives.[26] Accordingly, another aim of my PhD work was the synthesis of new 9-phenanthrol based precursor **IV** (Figure 2) and to investigate its reactivity in [4+2] cycloaddition forming new phenanthroxazine derivatives (Figure 2, **V**).

To the best of our knowledge, the transformation of bifunctional Mannich bases, which can serve as two different types of *o*-QMs has not been studied. Consequently, our aim was to synthesise new functionalised aminonaphthol derivatives (Figure 2, **VI**) and to study the scope and limitations of the applicability of these aminonaphthols in [4+2] cycloaddition. Furthermore, we wanted to investigate the influence of the relative stability of the formed *o*-QMs and/or the dienophile on the structure of the final products **VII** (Figure 2). Our next aim was to synthesise functionalised aminobenzylphenanthrols (Figure 2, **VIII**) and to study their reactivity with cyclic imines as novel precursor Mannich bases in [4+2] cycloaddition (Figure 2, **IX**). Finally, we wanted to explore both the structure and conformational behaviour of the novel polyheterocycles by NMR spectroscopy and theoretical quantum chemical (QC) calculations.

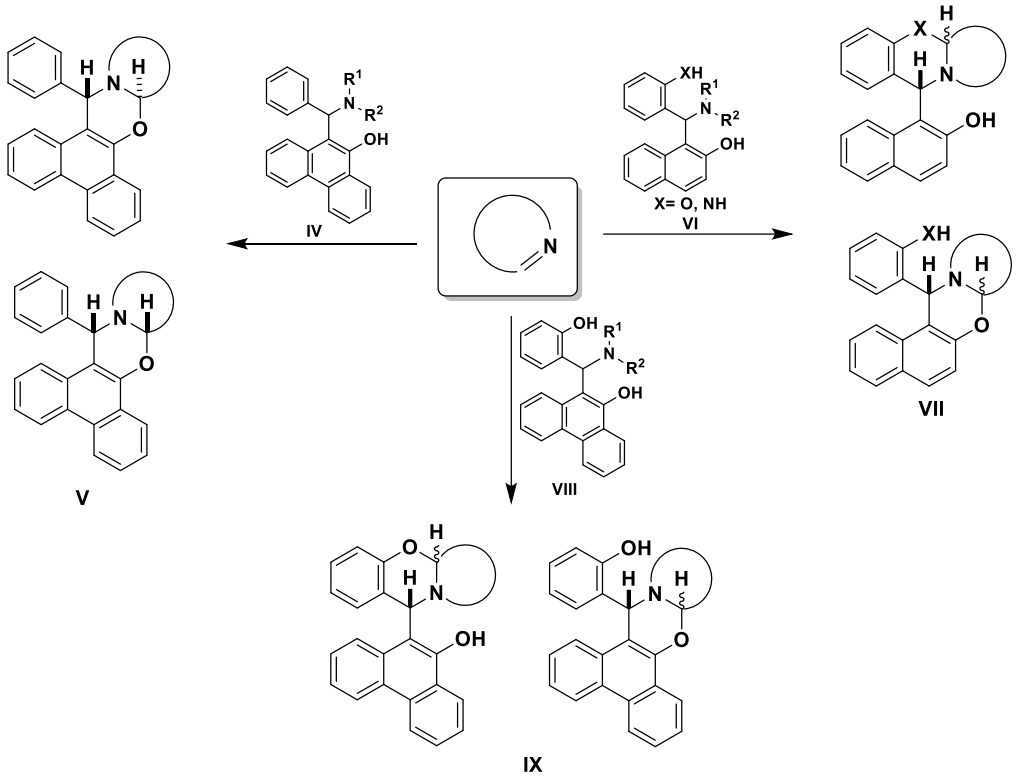


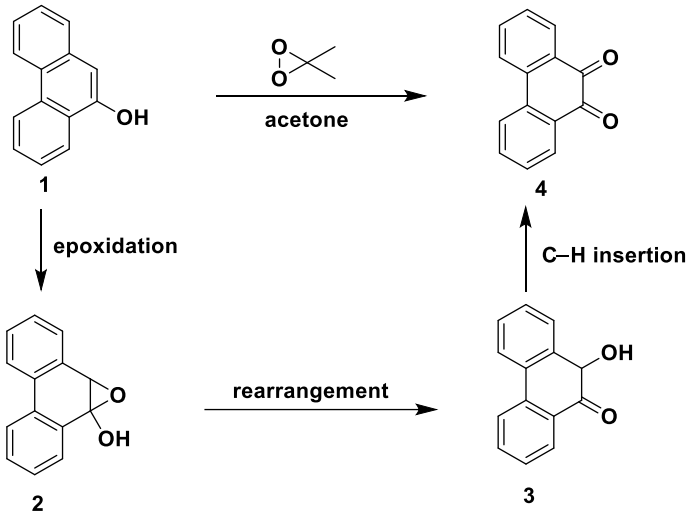
Figure 2

2. LITERATURE BACKGROUND

2.1. The transformation of 9-phenanthrols at position 10

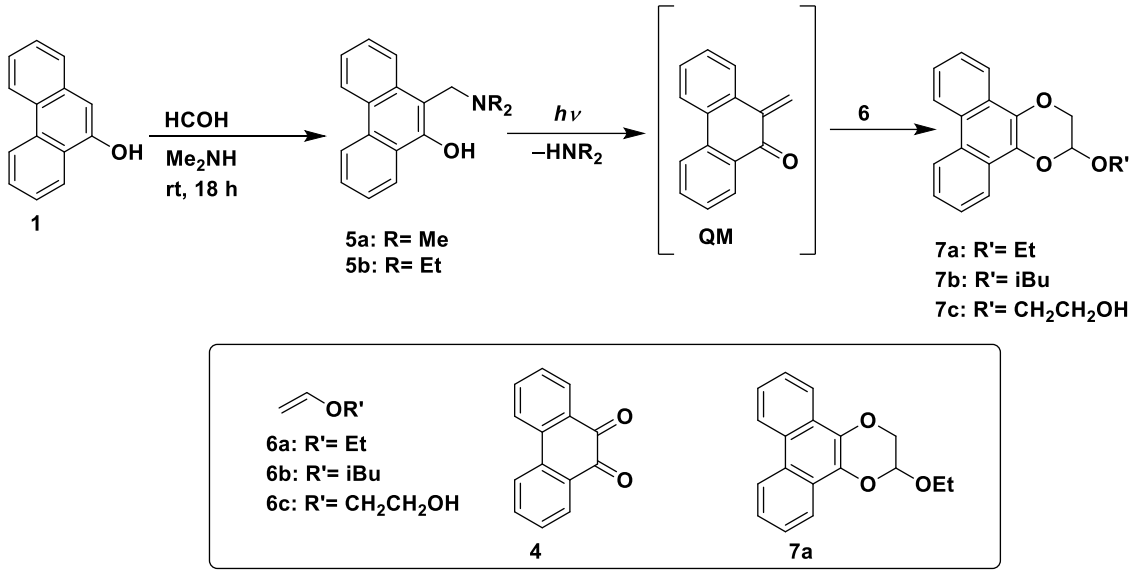
9-Phenanthrol is a unique electron-rich aromatic compound with C-10 as the most reactive centre, because of the position of its phenolic hydroxy function. This chapter collects related publications of the field.

For the synthesis of quinone derivative **4**, two reaction pathways were proposed by Crandal et al.[27] The first included the epoxidation of 9-phenanthrol leading to the formation of **2**, a labile compound, which underwent a rearrangement and gave compound **4** via C–H insertion. As a simpler synthetic route, Crandal et al. achieved the transformation of 9-phenanthrol to provide the stable 9,10-phenanthroquinone (**4**) in good yield via an oxidation protocol by using dimethyldioxirane (DMD) in acetone (Scheme 1).[27]



Scheme 1. DMD oxidation of 9-phenanthrol

Photochemical and thermal transformations of *N*,*N*-dialkyl-9-aminomethyl-10-phenanthrols (**5**) and their naphthalene analogs, which act as *o*-QM precursors, have been studied by Yasuda et al. (Scheme 2).[28]



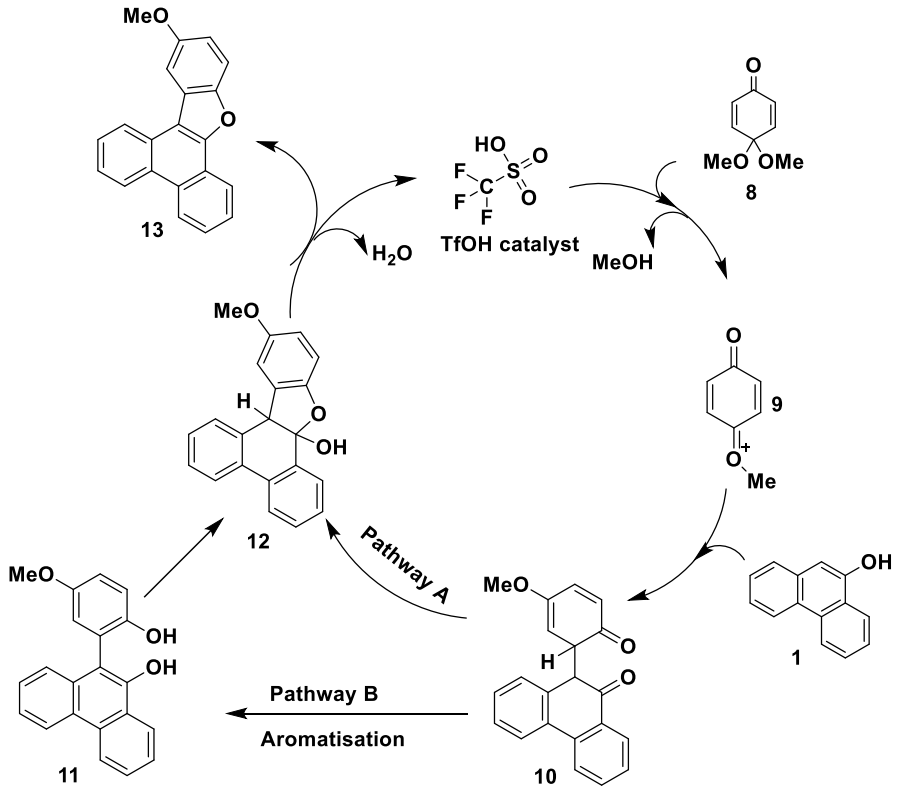
Scheme 2. Photoreaction of **1** with dienophyl type **6**

The precursor *N,N*-dialkyl-9-aminomethyl-10-phenanthrols (**5a,b**) were easily prepared by the Mannich reaction of 9-phenanthrol with alkylamines in the presence of formaldehyde. The thermal reaction of *N,N*-dimethyl-9-aminomethyl-10-phenanthrol (**5a**) with ethyl vinyl ether (**6a**) proceeded in aqueous MeOH, acetonitrile (MeCN), dimethylformamide (DMF) or THF solutions at 50 ^{o}C to give 2-ethoxydibenzo[*f,h*]chroman **7a**. Interesting to note that the reaction did not take place in water-free MeOH and THF. 9,10-Phenanthrenequinone (**4**) was found as a by-product in the thermal reaction of **5a,b** in MeCN–H_2O and DMF–H_2O. Photoreactions of **5** with vinyl ethers (**6**) were carried out by irradiating a degassed solution containing **5** and **6** by a high-pressure mercury lamp through a Pyrex filter (lO 280 nm) at 20 ^{o}C. The photoreaction of **5a** with ethyl vinyl ether (**6a**) in MeCN–H_2O (6:4) gave selectively **7a** in a yield of 74% without the formation of **4**. However, the photoreaction of **1** at higher temperature in MeCN–H_2O gave 2-ethoxy-4-oxodibenzo[*f,h*]-chroman **7a** formed as a consequence of the photoreaction of **4** with **6a**. The reaction yields depended on the solvent used. Photoreaction of **1** with **6a** proceeded more efficiently in aqueous MeCN compared with those in MeOH–H_2O and THF–H_2O. It is noteworthy that no reaction occurred in water-free solvents and not even in MeOH regardless of the presence of hydroxy group. Therefore, water was a requisite for the efficient formation of **7** in both photochemical and thermal reactions.

Wan et al. reported the photochemical generation of *o*-QMs by the elimination of water from *o*-(hydroxymethyl)phenol derivatives. Among these, 9-hydroxymethyl-10-phenanthrol was also described to form 2-ethoxy-4-oxodibenzo[*f,h*]-chroman (**7a**) with ethyl vinyl ether (**6a**).[29]

Biju et al.[30] developed a metal-free synthesis of phenanthrobenzofuran derivatives via the Brønsted acid-catalysed dehydrative, formal [3+2] annulation of 9-phenanthrol with quinone

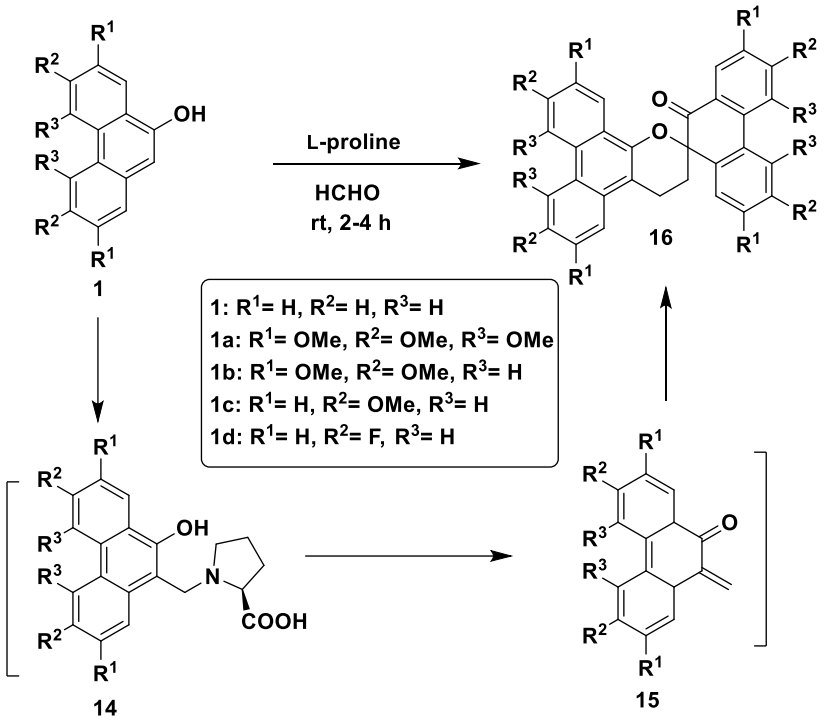
monoacetals (QMAs). Products were formed in moderate to good yields with a reasonable substrate scope (Scheme 3).



Scheme 3. Tentative mechanism of the reaction

The mechanistic rationale for this Brønsted acid-catalysed annulation can be advanced along the following lines. The reaction is likely initiated by the activation of the quinone monoacetal by triflic acid (TfOH), leading to the generation of highly electrophilic oxocarbenium intermediate **9**. This is followed by the nucleophilic addition of 9-phenanthrol to **9**, forming diketone intermediate **10**. Intramolecular cyclisation generates the intermediate and subsequent elimination of a water molecule delivers phenanthrobenzofuran **12** (pathway A). Alternatively, intermediate **10** can undergo aromatisation via proton transfer to form phenol biaryl **11**, which can be converted into **13** via intermediate **12** (pathway B). Demethylation of phenanthrobenzofuran can easily be achieved under the BBr_3 conditions.[30]

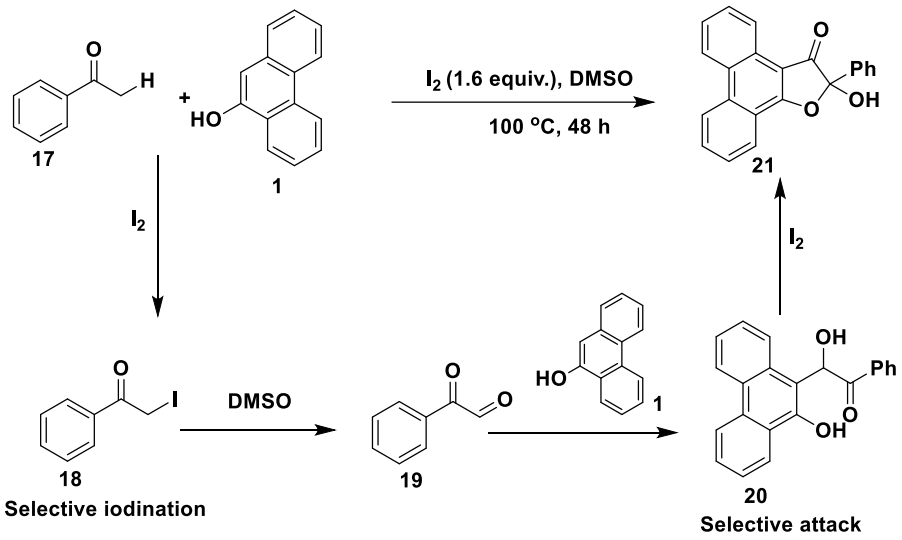
The polymethoxyaromatic skeleton is known to impart important biological activities to some natural products.[31–34] Recently, You et al.[35] published the synthesis of a new class of spiro polymethoxyaromatics type **16** (Scheme 4).



Scheme 4. Synthesis of spirophenanthrones

Condensation of 9-phenanthrol (**1, 1a–c**) with formaldehyde catalysed by proline at room temperature gave directly the target spirophenanthrone product. Substrate 9-phenanthrol first underwent a Mannich reaction affording the expected Mannich base (**14**), which proved to be unstable. Elimination of proline then produced 10-methylene-9-phenanthrone intermediate **15**, which was highly reactive and readily dimerised via a hetero Diels–Alder reaction to form **16**. It was summarised that substrates with electron-donating substituents (**1a**–**c**) gave moderate to good yields. Among these, 2,3,4,5,6,7-hexamethoxy-9-phenanthrol **1a** gave the highest yield (85%). When the substituent was electron withdrawing (**1d**), the product was formed in a lower yield. It was reasoned that the Mannich reaction occurs more readily with electron-rich aromatic compounds.

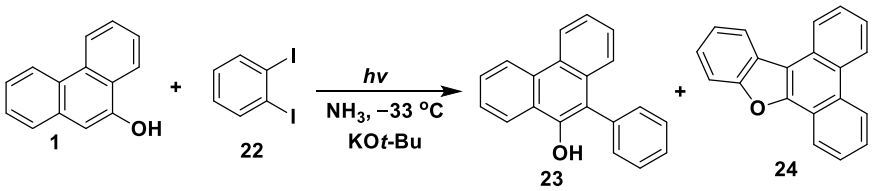
Wu et al.[36] reported a highly efficient and selective I_2-promoted oxidative cross-coupling/annulation with the direct use of 9-phenanthrol and methyl ketones as nucleophiles for the construction of phenanthro[9,10-*b*]furan-3(2*H*)-one (**21**) with a quaternary centre. Initial studies of the mechanism suggest that this reaction could have occurred through a self-sequenced iodination/Kornblum oxidation/Friedel−Crafts alkylation/oxidation/cyclisation cascade reaction (Scheme 5).



Scheme 5. Selective I_2-promoted oxidative coupling of 9-phenanthrols with methyl ketones

The most important direct C−H bond activation step is thought to be the formation of a new carbon−iodine bond, known as the *in situ* iodination-based oxidative coupling pathway. It is envisioned that if the selective iodination of the C(sp^3)−H bond of acetophenone is feasible by molecular iodine, *in situ* oxidation of the carbon−iodine bond could generate an electrophilic α-ketoaldehyde intermediate liable to selective attack by the C−H of 9-phenanthrol. Oxidation followed by cyclisation furnished the desired phenanthro[9,10-*b*]furan-3(2*H*)-one (**21**) with a quaternary centre.

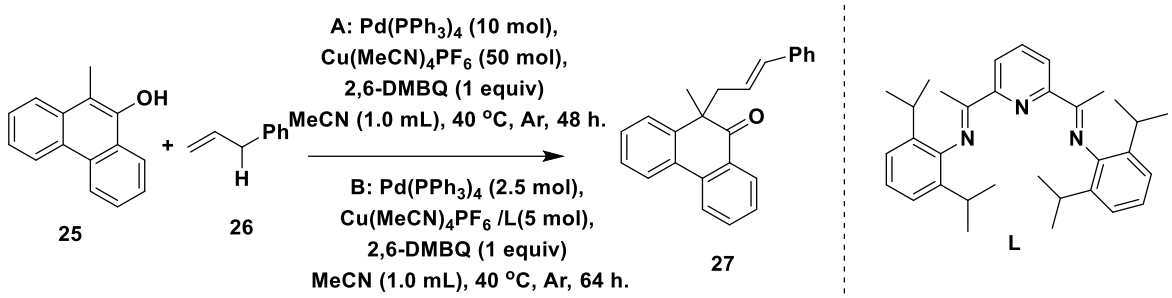
Baumgartner et al.[37] reported the synthesis of 10-aryl-9-phenanthrols by reacting the anion of 9-phenanthrol with aryl halides. Interesting to note that by using *o*-diiodobenzene, product **23** was formed in a relatively low yield (26%). It was attributed to a parallel ring-closure reaction leading to the formation of oxa-indeno[1,2-*l*]phenanthrene **24** (Scheme 6).



Scheme 6. The synthesis of the products **23** and **24**

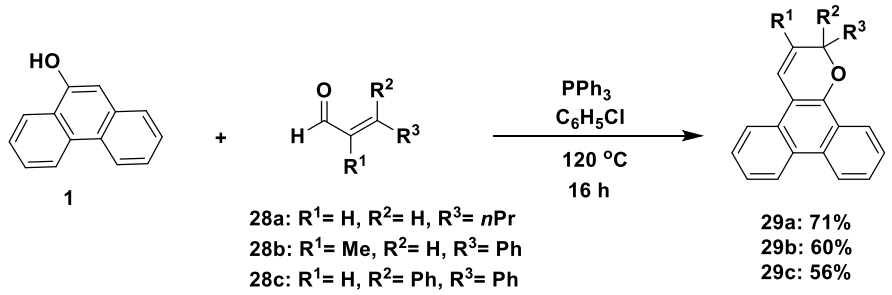
Cyclohexadienones with *ortho*-quaternary carbon centres are pivotal skeletons with special bioactivities[38] for drug discovery, excellent photoelectric performance for material science[39] and great importance in the total synthesis of natural products.[40,41] Accordingly, Yang et al.[42] explored the scope of oxidative allylic C−H alkylation of varied cyclohexadienones, including 10-methyl-9-

phenanthrol (**25**). The synthesis of the desired cyclohexadienones, among others, compound **27**, was accomplished with excellent chemoselectivities and broad substrate scope through $Pd(PPh_3)_4/Cu(MeCN)_4PF_6$ cooperative catalysis with 2,6-dimethoxybenzoquinone (2,6-DMBQ) under mild, base-free conditions. The transformation provided a general protocol to obtain functionalised cyclohexadienones with quaternary carbon centres under two alternative sets of conditions (**A** and **B**, Scheme 7) and it serves as a complementary catalytic system for the dearomatisation of 9-phenanthrols.



Scheme 7. Allylic alkylation of substituted phenanthrol **27**

Flavonoids, a common group of polyphenol compounds in fruits and vegetables, have been shown to exhibit a wide range of pharmacological effects including anti-inflammatory, anti-aging and anticancer activities.[43,44] Yi et al.[45] published the synthesis of novel flavonoid derivatives (**29a–c**) starting from 9-phenanthrol and *α,β*-unsaturated aldehydes (**28a–c**). The structures of the flavonoid derivatives are depicted in Scheme 8.



Scheme 8. The synthesis of the products **29**

The formation of the corresponding polycyclic enol ether products **29a–c** was explained by *ortho*-C–H acylation followed by conjugate addition and dehydrative annulation sequences.

2.2. Synthesis and applications of 10,10'-dihydroxy-9,9'-biphenanthryl (BANOL) based catalysts

Noyori first reported the application of nonracemic 1,1'-bi-2-naphthol (BINOL) in asymmetric catalysis in 1979.[46] Since then BINOL derivatives have played a significant role in asymmetric synthesis and have attracted a great deal of interest.[47,48] Numerous new examples have emerged in this field, because the enantiomers of BINOL are inexpensive and commercially available compounds.[49] By modifying the BINOL scaffold, chemists can easily and effectively tune both the steric and electronic character of chiral metal–BINOL complexes. Using the techniques of parallel synthesis, diverse BINOL derivatives can be synthesised and screened in a particular reaction with the ultimate goal of finding the best catalyst/substrate combination.[50] Nakajima et al. have demonstrated the first example of the enantioselective addition of Grignard reagents to ketones promoted by a BINOL derivative bearing alkyl chains at positions 3,3′. This is the first asymmetric direct aryl Grignard addition to ketones. A variety of tertiary diaryl alcohols could be obtained in high yields and enantioselectivities without using any other metal source.[51] On the other hand, Kyuetngsoo et al. developed an enantiodivergent approach to chiral BINOLs using two different 2-naphthol activation modes: intermolecular coupling by a mononuclear vanadium(V) catalyst and coupling by a dinuclear vanadium(V) catalyst in an intramolecular manner. The unusually high coupling reactivity of 4-substituted 2-naphthols has been the key to elucidate the intricate reaction mechanisms and selectivities of asymmetric oxidative coupling of 2-naphthols, even in the presence of low catalyst loadings of 0.5−5 mol%.[52]

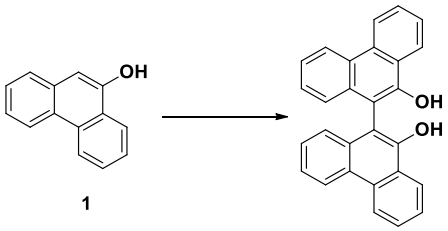
As it has been demonstrated, the substitution of BINOL catalysts at position 3 and/or 4 is critical for their enantioinduction. Structurally 9-phenanthrol can be interpreted as a special condensed 2-naphthol analogue. Enantioselective oxidative coupling of 9-phenanthrol at position 10 is a useful method for the synthesis of biphenanthrol derivatives and this synthetic route is one of the most important transformations of 9-phenanthrol, using its special reactivity at position 10. Accordingly, this chapter collects synthetic methods to achieve biphenanthrols, their transformations to new chiral ligands as well as their applications as chiral ligands in asymmetric synthesis.

2.2.1. Preparation of 10,10'-dihydroxy-9,9'-biphenanthryl derivatives

The preparation of chiral 10,10'-dihydroxy-9,9'-biphenanthryl called also BANOL is of great importance because of their utility in asymmetric synthesis. Among the synthetic methods to access enantiomerically pure BANOLs, catalytic asymmetric oxidative coupling of 9-phenanthrols is one of the most straightforward processes.

In one of the earliest publications on the subject, Kocovsky et al.[53] described their experiments performed under argon thereby achieving anaerobic conditions. $CuCl_2$ applied in the reactions had a double role. It catalysed the process by forming a complex with (−)-spartiene *in situ* and, on the other hand, through its reduction, provided the necessary conditions for oxidative coupling (Table 1, entry 1).

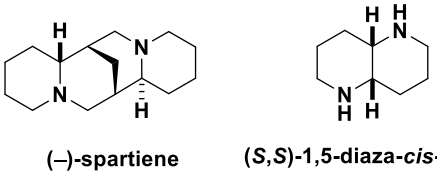
Table 1. Synthesis of 10,10'-dihydroxy-9,9'-biphenanthryl

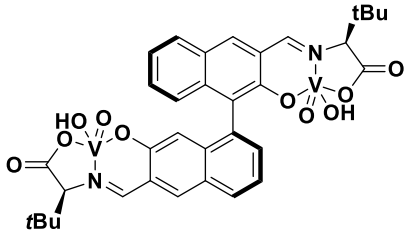


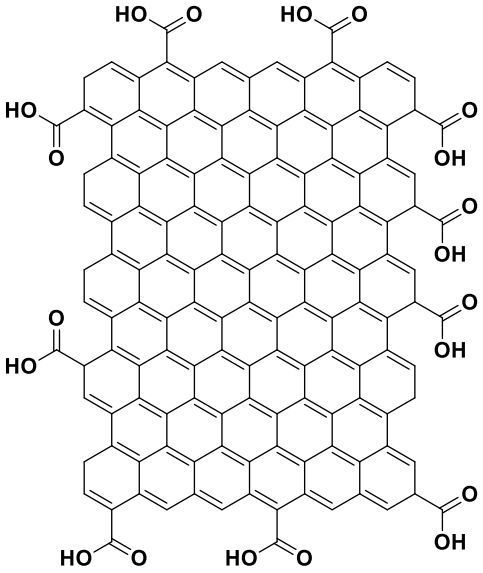
1 30

Entry	Reaction Conditions					Yields (%)	*ee* (%)	Lit.
	Catalyst	Solvent	Oxidant	Temp. (°C)	time (h)			
1	$CuCl_2$-(−)-sparteine complex	MeOH	Cu(II)/ Cu(I) system	rt.	72	80	76	[53]
2	CuCl-1,5-diaza-*cis*-decalin complex	$ClCH_2CH_2Cl$	Air	rt.	6	63	10	[54]
3	CuCl-1,5-diaza-*cis*-decalin complex	$ClCH_2CH_2Cl$	O_2	rt.	3	53	11	
4	vanadium complex	CH_2Cl_2	O_2	0	24	92	84	[55] [56]
5	vanadium complex	MeCN	O_2	-5	70	92	89	
6	vanadium complex	CH_2Cl_2	O_2	-5	36	94	88	

7	vanadium complex	CH_2Cl_2	Air	-5	74	80	76	
8	vanadium complex	Toluene	O_2	-5	72	80	86	
9	vanadium complex	$CHCl_3$	O_2	-5	60	90	54	
10	vanadium complex	CH_2Cl_2	O_2	-10	48	quant.	93	
11	vanadium complex	CH_2Cl_2	O_2	-10	48	quant.	90	[57]
12	Graphene oxide (GO)	Toluene	Air	100	-	91	-	[58]







The oxidative coupling of 9-phenanthrol in the presence of CuCl and (*S*,*S*)-1,5-diaza-*cis*-decalin was performed by Kozlowski et al.[54] At medium production rates, very low enantioselectivities were observed (Table 1, entries 2, 3).

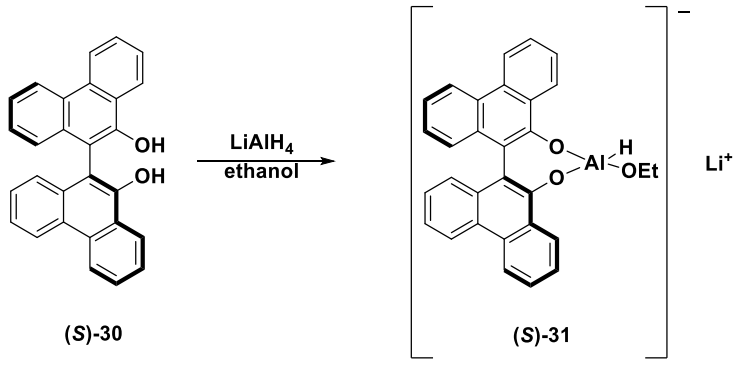
In order to achieve better results, it was necessary to optimize reaction conditions. The exchange of copper-based catalysts with bivalent vanadium complexes increased both the yields and enantioselectivities. Most of the publications have used dual-core vanadium complexes as catalysts,[59,60] having the advantage of being capable of oxidative coupling of compounds with various functional groups, even under mild conditions. The oxidative catalysis of the vanadium complex is characterised by the fact that only water is produced as a by-product during the synthesis.[61] Sasai et al. tested the application of dinuclear vanadium catalyst to promote the oxidative coupling of **1** to give **30** (Table 1, entries 4–11).[55,56] Yields were found to be between 80–92% with good enantioselectivities in most cases. Of the applied solvents, CH_2Cl_2 provided the highest enantioselectivity in a relatively short (24 h) reaction time (Table 1, entry 4). It was also

established that by using air as oxidant, the enantioselectivity decreased (Table 1, entry 7). The same research group found that decreasing the reaction temperature to –10 °C, coupling product **30** could be isolated in quantitative yield and with 93% *ee* (Table 1, entry 10). The yield after recrystallisation was 80%, while the *ee* value was found to be >99%.[56] Under these optimal conditions, Sasai et al. published the gram-scale (6.0 g) synthesis of (*S*)-**30** (Table 1, entry 11). In the last step of the procedure, a single recrystallisation afforded the desired product in 79% yield and with >99% *ee*.[56,57]

An environmentally benign green method for the synthesis of racemic **30** was published by Ranganath et al. The oxidative coupling of 9-phenanthrol has been performed in a metal-free synthesis.[58] The advantage of the process was the use of inexpensive graphene oxide (GO) as catalyst. The reaction was performed in toluene and **30** was isolated in a yield of 91% (Table 1, entry 12).[58]

2.2.2. Synthesis of 10,10'-dihydroxy-9,9'-biphenanthryl (BANOL) based catalysts

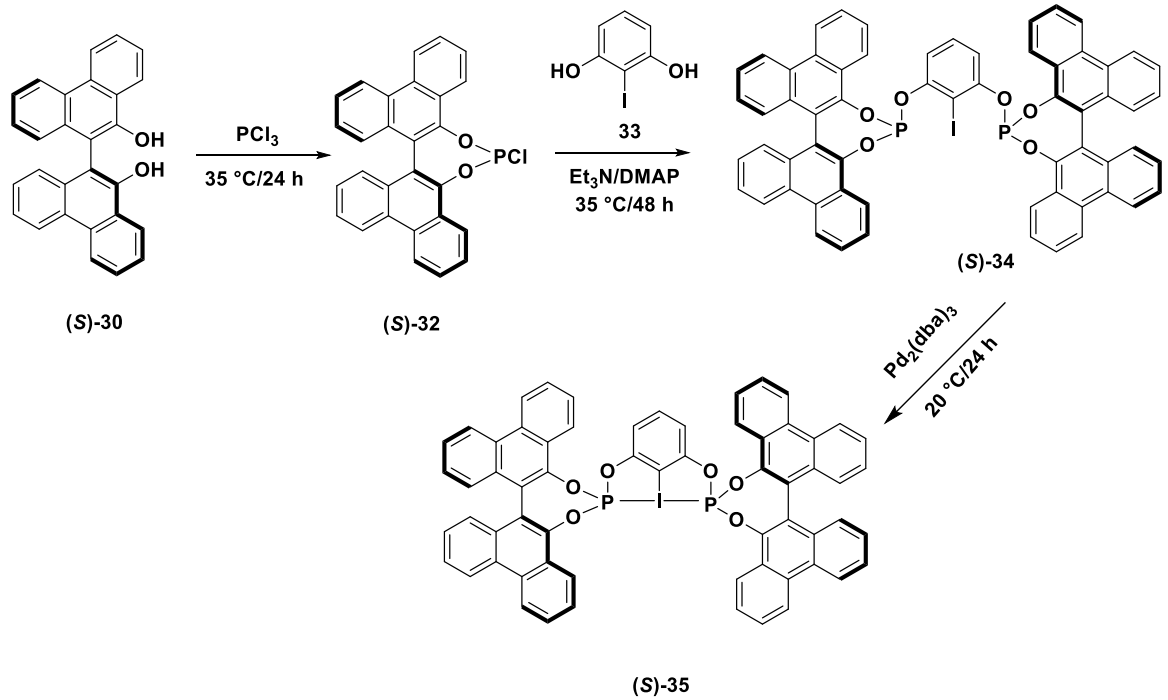
The chiral capacity of nonracemic 10,10'-dihydroxy-9,9'-biphenanthryl is low; therefore, various structural modifications of the substrate have been made. Yamamoto et al.[62] published the synthesis of modified hydride reagent (*S*)-**31** prepared *in situ* at room temperature reacting $LiA1H_4$, (*S*)-**30** and ethanol (1 : 1 : 1 molar ratio, Scheme 9).



Scheme 9. The preparation of (*S*)-**31**

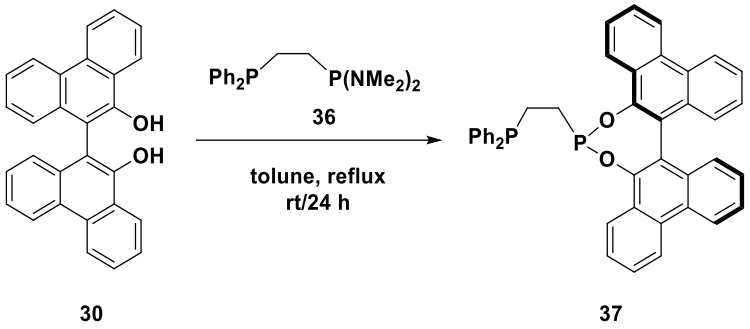
This reagent combination gave excellent enantioselectivity in the reduction of aromatic ketones. For example, acetophenone is reduced in 75% yield with 97% *ee*. It was concluded that the Noyori reagent with *S* configuration gave (*S*)-alcohols. It was also established that aliphatic ketones were reduced with low enantioselectivity. Both enantiomers of this auxiliary could be readily prepared and were recovered for reuse at the end of the reduction.

Szabó et al.[63] reported the synthesis of chiral ligand **35** starting from optically pure biphenanthrol (*S*)-**30**. The first step was the formation of the (*S*)-**32** derivative in the presence of phosphorus trichloride with stirring at 35 °C for 24 hours. Then the product was further transformed to **34** by the addition of resorcinol iodide **33**. The resulting chiral proligand [(*S*)-**34**)] was found to be extremely sensitive to hydrolysis and, therefore, its purification was a major problem. Namely, purification by column chromatography resulted in a large loss of the chiral proligand. However, it was found during process optimisation, that under mild conditions (20 °C, 4 h), in the presence of tris(dibenzylideneacetone)dipalladium(0) (Pd (dba)$_3$), the final product was obtained with sufficient purity and with an acceptable yield of 60% (Scheme 10).



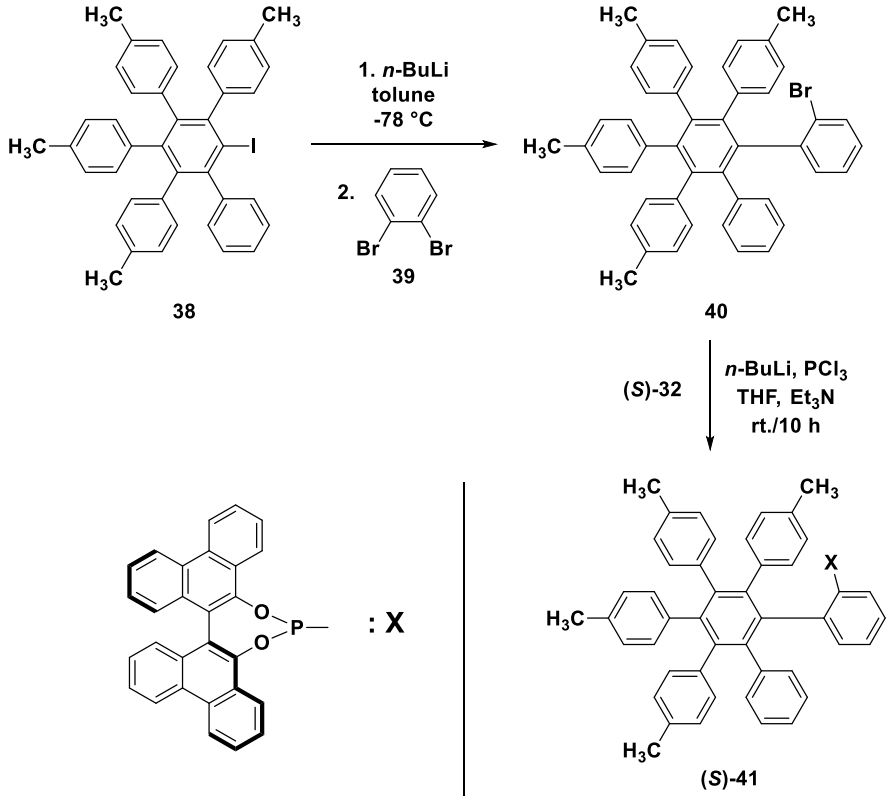
Scheme 10. The synthesis of the product **(*S*)-35**

Pringle et al. reported the synthesis of **37** starting from racemic biphenanthrol **30** and commercially available aminophosphane precursor $Ph_2P(CH_2)_2P(NMe_2)_2$ (**36**). The reaction was performed by treating the starting compounds in toluene under reflux conditions for 16 hours (Scheme 11).[64] The resulting racemic mixture was then resolved by the Toda method.[65] The resolution process involved the complexation of the racemic mixture with *trans*-(*R*,*R*)-(+)-*N*,*N*,*N*',*N*'-tetramethyl-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxamide. It should be mentioned that the method was successfully applied for the resolution of **37** in a higher quantity as well.



Scheme 11. The synthesis of **37**

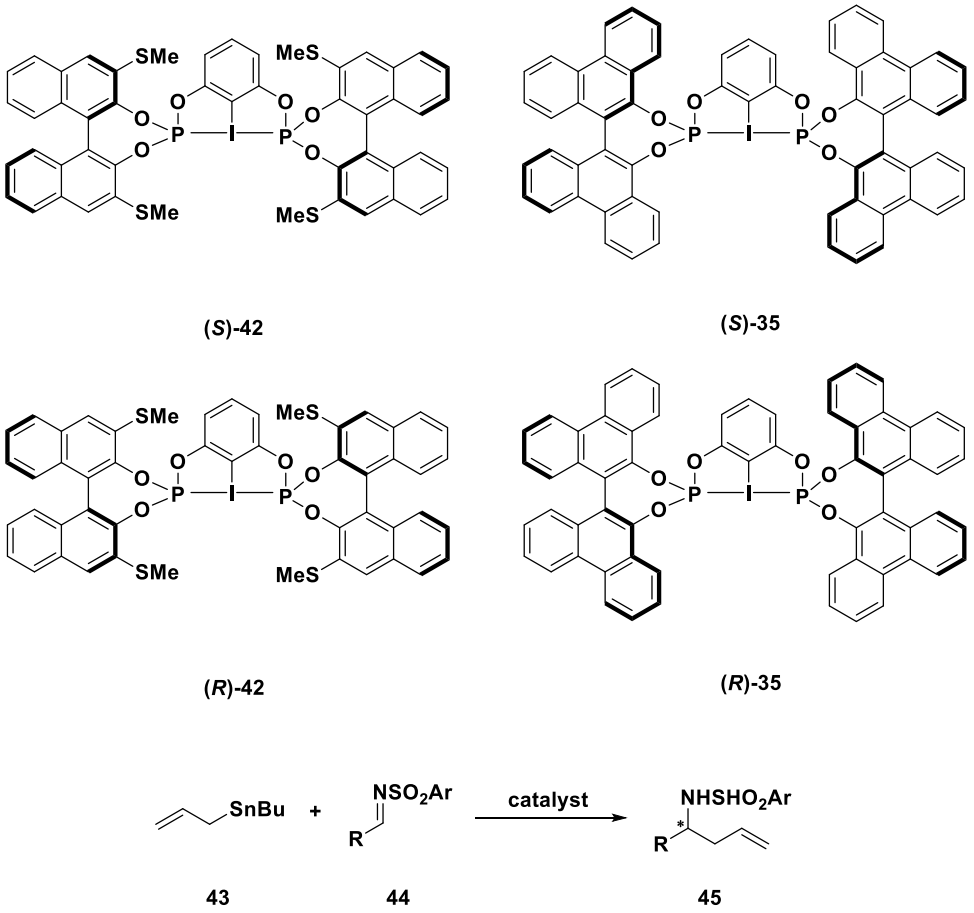
Iwasawa et al. synthesised new phosphonite-type chiral ligands.[66] In the first step, polyaryl-substituted benzene **38** was reacted with 1,2-dibromobenzene (**39**) to deliver bromo derivative **40**. Subsequent coupling of phosphonite (*S*)-**32** with **40** led to the formation of desired chiral ligand (*S*)-**41** (Scheme 12).



Scheme 12. The preparation of product **41**

2.2.3. Applications of BANOL-type catalysts

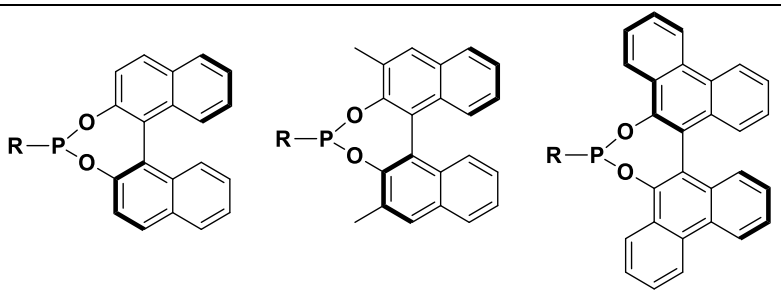
A literature survey on the application of BANOL-type derivatives revealed that their catalytic applicability has so far been tested only in a few model reactions. Although the number of publications on the topic is low, it can be concluded from their results that this field is still under development, thus opening up new and interesting research fields in the future.

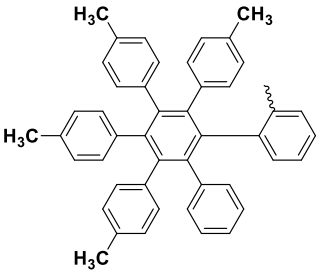
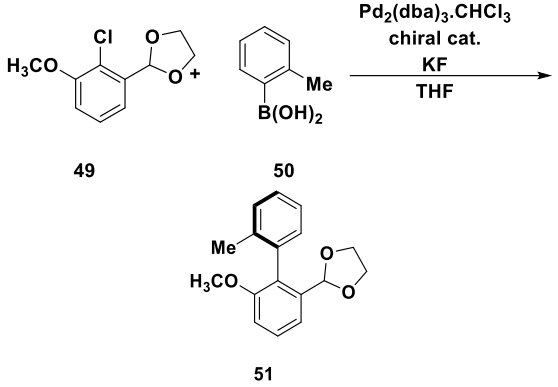
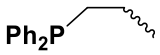
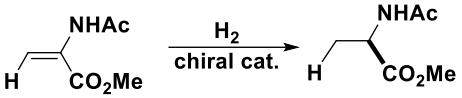


Scheme 13. Enantioselective allylation of sulfonylimine **44**

Szabó et al.[63] developed the allylation of sulfonylimine **44** in the presence of allyl stannate **43** to synthesise homoallyl-type sulfonamine **45** (Scheme 13). Palladium-catalysed asymmetric allylation of sulfonimines is of great importance, because chiral bis (allyl)-palladium complexes do not induce this type of reaction in a selective manner.[67] According to their protocol, first BINOL-type catalysts (*S*)-**42** and (*R*)-**42** were tested under mild conditions (6–20 °C, 66–96 h). The reaction resulted in products with 71–74% enantioselectivity. The model reaction was repeated by using biphenanthrol-type catalysts (*S*)-**35** and (*R*)-**35**. In this case, higher enantioselectivities (80–85%) were achieved under similar conditions (20 ° C, 68–94 h) in DMF.[63]

Table 2. Use of biphenanthrol ((***S***)-**37**, (***S***)-**41**) and BINOL ((***S***)-**46**–(***S***)-**48**) derivatives in various model reactions



R	Catalyst	Reaction	*ee* (%)	Lit.
	**46**		69	[66]
	47		74	
	41		78	
	**48**		74	[64]
	37		94	

Iwasawa et al. investigated the effect of chiral catalysts based on BINOL and biphenanthrol in the asymmetric Suzuki–Miyaura reaction.[66] The enantioinduction of chiral ligands (*S*)-**46**, (*S*)-**47** and (*S*)-**41** was tested and compared (Table 2). In the model reaction, halide **49** was reacted with boronic acid **50** in THF by using potassium fluoride (KF). In this case moderate *ee* values (60–65%) were observed. The role of the base and/or solvent was also investigated. The best results were found when reactions were conducted in toluene by using caesium fluoride (CsF) at 90 °C. The *ee* values determined are listed in Table 2. It is seen that the highest *ee* value (78%) was found when phenanthrol-type phosphonite ligand (*S*)-**41** was applied as catalyst.[66]

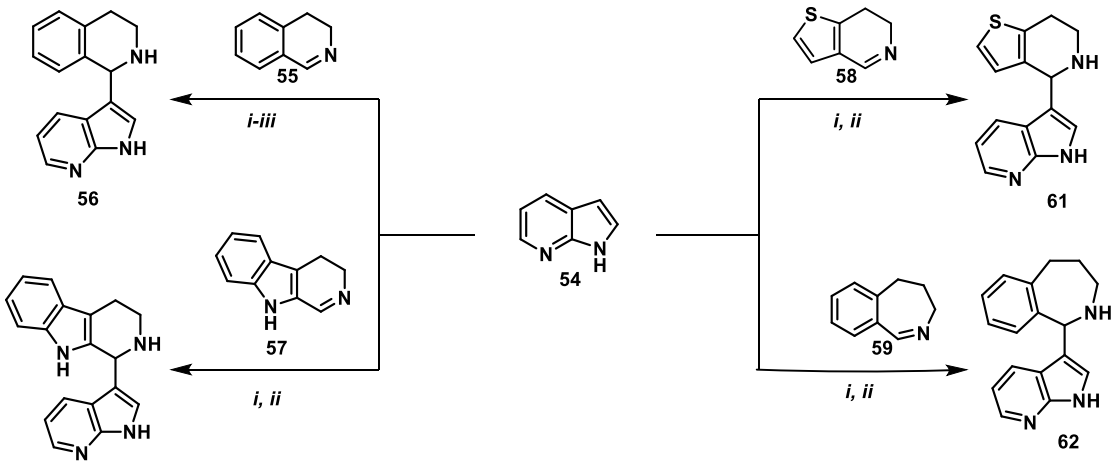
Pringle et al. inestigated the enantioselective double bond saturation of substrate **52** in the presence of molecular hydrogen (H_2) and chiral BANOL ligands (*S*)-**37**) or BINOL (*S*)-**48**. During the hydrogenation of acrylate **52** in CH_2Cl_2 as solvent, in a reaction time of 1 h, (*S*)-**48** gave 74% *ee*, while applying (*S*)-**37** the *ee* value was found to be 94%. Based on these results, it can be concluded that chiral ligand (*S*)-**37** is more selective in comparison with the enantioinduction of (*S*)-**48** (Table 2).[64]

3. RESULTS AND DISCUSSION

3.1. *aza*-Friedel–Crafts reaction of novel electron-rich aromatic compounds

3.1.1. Application of azaindole derivatives in the modified *aza*-Friedel–Crafts reaction

In our first experiments, 7-azaindole **54** was reacted with 1.5 equiv. of 3,4-dihydroisoquinoline (**55**), synthesised according to a literature method (Scheme 14).[68] The reaction between **54** and **55** was performed in solvent-free conditions by classical heating at 60 °C (*i*). Based on TLC, the reaction in a time of 18 h resulted in the formation of a multi-spot reaction mixture and the desired 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)-7-azaindole product (**56**) was isolated by chromatography in a yield of 31%. Since the yield was not satisfactory, the reaction was repeated at 80 °C (*ii*). A 10-h reaction led to the formation of **56** in a yield of 49%. Despite increasing the temperature further [100 °C, (*iii*)], the relatively long reaction led to **56** only in a poor yield of 28%. When the reaction was repeated under microwave irradiation by testing three different reaction conditions (Table 3), **56** was isolated in a yield of 81% after 120 min at 100 °C (Table 3). Note that in microwave reactions, 2 equiv. of **55** were needed to provide the homogeneity of the reaction mixture.



Scheme 14. Synthesis of 7-azaindole derivatives starting from different cyclic imines

The reaction was extended by using other cyclic imines such as 3,4-dihydro-*β*-carboline (**57**),[69] 6,7-dihydrothieno[3,2-*c*]pyridine (**58**)[70] and 4,5-dihydro-*3H*-benz[*c*]azepine (**59**).[20,71] Reactions were performed by using both oil-bath heating and microwave irradiation (Scheme 14). Table 3 shows that the corresponding products (**60**–**62**) were isolated in higher yields when microwave conditions were applied. It can be concluded that 6,7-dihydrothieno[3,2- *c*]pyridine **58** was found to

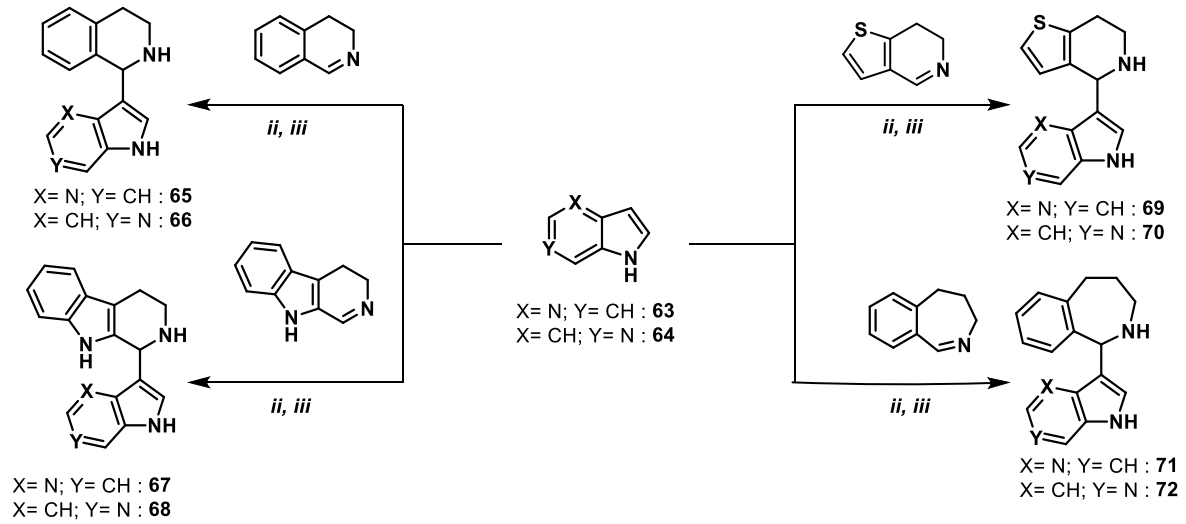
be the most reactive cyclic imine. Yields and the applied reaction conditions are summarised in Table 3.

Table 3. Reaction conditions for the synthesis of the azaindoles **56** and **60**–**62**

Product	Reaction time[a]	Temperature[a]	Yield[a] (%)	Reaction time[b]	Temperature[b]	Yield[b] (%)
56	18 h 10 h 6 h	60 °C (*i*) 80 °C (*ii*) 100 °C (*iii*)	31 ***49*** 28	2 h 4 h 2 h	80 °C (*ii*) 80 °C (*ii*) 100 °C (*iii*)	55 63 ***81***
60	10 h	80 °C (*ii*)	56	2.5 h	100 °C (*iii*)	75
61	6 h	80 °C (*ii*)	76	2 h	100 °C (*iii*)	89
62	20 h	80 °C (*ii*)	63	3 h	100 °C (*iii*)	78

[a] classical heating, [b] microwave irradiation

With the optimal reaction conditions in hand, we focused on extending the series of electron-rich aromatic compounds in the modified *aza*-Friedel–Crafts reaction. Accordingly, 4-azaindole **63** and 6-azaindole **64** were also reacted with cyclic imines **55**, **57–59** (Scheme 15).



Scheme 15. The extension of modified *aza*-Friedel–Crafts reaction starting from 4-azaindole **63** and 6-azaindole **64**

Reactions were performed under solvent-free conditions under both classical heating and using microwave irradiation. The reaction conditions for the synthesis of new azaindole derivatives are summarised in Table 4. The isolation method for azaindole derivatives **65–72** differed. In the case of **65**, **67**, **69** and **71,** a single crystallisation process from Et_2O was satisfactory to achieve the desired products with acceptable purity. In contrast, **66**, **68**, **70** and **72** had to be purified by column

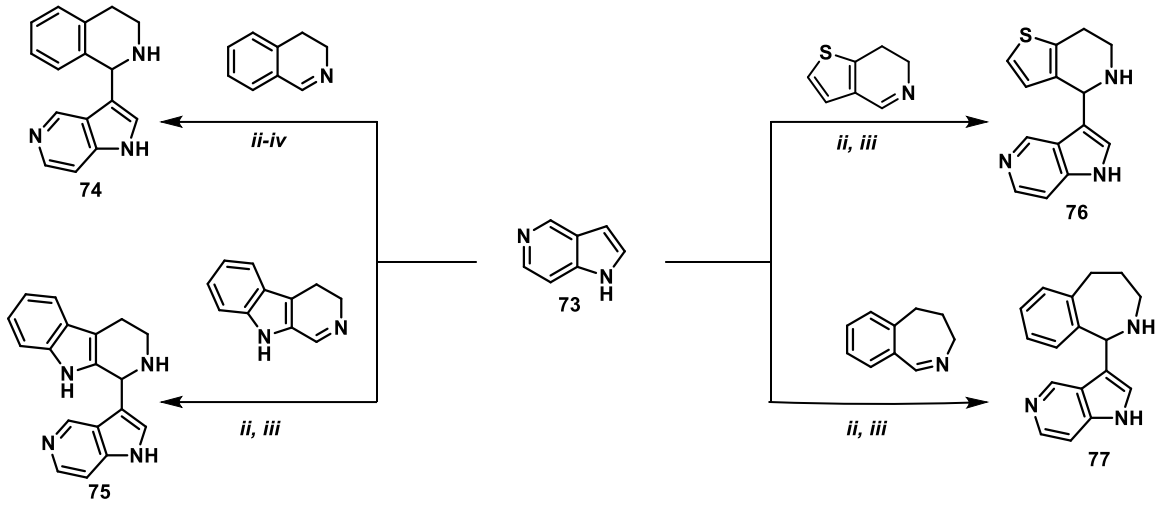
chromatography. It can be concluded that the use of microwave irradiation afforded the desired products (**65-72**) in higher yields and in significantly shorter reactions compared with those found with oil-bath heating (Table 4).

Table 4. Reaction conditions for the synthesis of the azaindoles **65**–**72**

Product	Reaction time[a]	Temperature[a]	Yield[a] (%)	Reaction time[b]	Temperature[b]	Yield[b] (%)
65	20 h	80 °C (*ii*)	49	2.5 h	100 °C (*iii*)	70
66	22 h	80 °C (*ii*)	39	2.5 h	100 °C (*iii*)	65
67	16 h	80 °C (*ii*)	52	2.5 h	100 °C (*iii*)	69
68	20 h	80 °C (*ii*)	48	2.5 h	100 °C (*iii*)	62
69	7 h	80 °C (*ii*)	63	2.5 h	100 °C (*iii*)	85
70	8 h	80 °C (*ii*)	62	2.5 h	100 °C (*iii*)	75
71	21 h	80 °C (*ii*)	57	3 h	100 °C (*ii*)	68
72	25 h	80 °C (*ii*)	55	3 h	100 °C (*iii*)	64

[a] classical heating, [b] microwave irradiation

Since the catalyst-free coupling of 7-, 6- and 4-azaindoles gave the desired C-3 aminoalkylated derivatives, we focussed our attention on the *aza*-Friedel–Crafts reaction of 5-azaindole **73**. In our first experiment, **73** was reacted with 3,4-dihydroisoquinoline as a representative cyclic imine (Scheme 16). However, even applying varied reaction conditions (classical heating, microwave irradiation) and different temperatures (80 °C, 100 °C, 120 °C), target compound **74** did not form. There was no conversion at lower temperature (80 °C, 100 °C), while higher temperature (120 °C) resulted in a multi-spot reaction mixture. Since *p*-toluenesulfonic acid (*p*-TSA), an acid catalyst, is applied frequently in the modified three-component Mannich reaction,[72–74] we decided to examine its effect on the reaction between **73** and 3,4-dihydroisoquinoline. First, 10 mol% of *p*-TSA was tested using oil-bath heating. In this case TLC showed the formation of a new compound that after isolation (30%) proved to be the desired 5-azaindole derivative **74**. Since the reaction needed a relatively long reaction time (19 h) and resulted in poor yield, it was repeated by using microwave irradiation. In this case, 100 °C was found to be optimal and 5-azaindole **74** was isolated in a yield of 72% (Table 5).



Scheme 16. Synthesis of **74**–**77** from 5-azaindole **73**

Table 5. Reaction conditions for the synthesis of the products **74**–**77**

Product	Reaction time[a]	Temperature[a]	Yield[a] (%)	Reaction time[b]	Temperature[b]	Yield[b] (%)
74	24 h 21 h 8 h 19 h[c]	80°C (*ii*) 100°C (*iii*) 120°C (*iv*) 80°C (*ii*)	- - - 30	2.5 h 2.5 h 2 h 2.5 h[c]	80°C (*ii*) 100°C (*ii*) 120°C (*iv*) 100°C (*iii*)	- - - 72
75	15 h[c]	80°C (*ii*)	44	2 h[c]	100°C (*iii*)	69
76	7 h[c]	80°C (*ii*)	62	2 h[c]	100°C (*iii*)	80
77	15 h[c]	80°C (*ii*)	52	3.5 h[c]	100°C (*iii*)	65

[a] classical heating, [b] microwave irradiation, [c] *p*-TSA

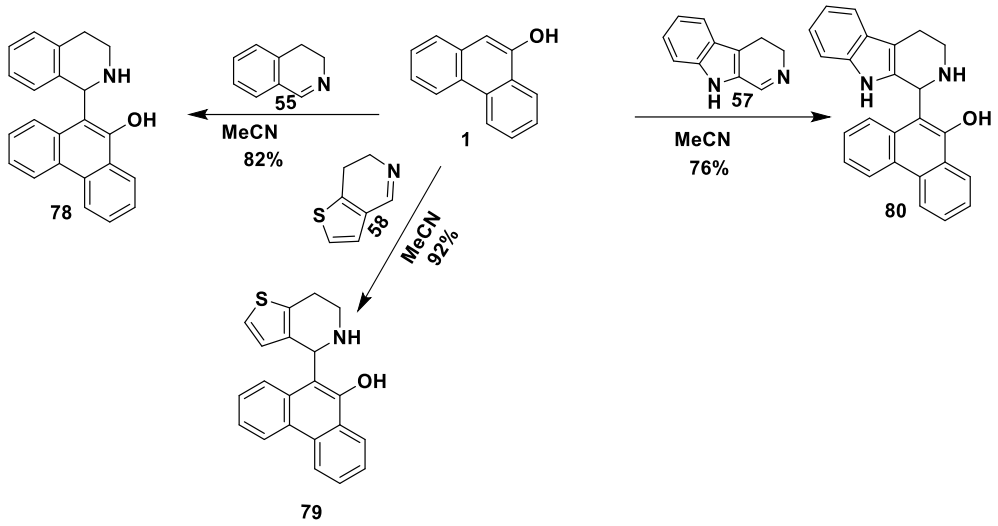
By applying 10 mol% of *p*-TSA catalyst, C-3 aminoalkylation of 5-azaindole **73** was extended with additional cyclic imines such as 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-*β*-carboline and 4,5-dihydro-*3H*-benz[*c*]azepine (Scheme 16). Reaction conditions and yields are summarised in Table 5. As data show, there is a difference between the reactivity of 7-, 6-, 4-azaindoles and 5-azaindole; namely, for C-3 aminoalkylation of 5-azaindole an acid catalyst was needed. The lower reactivity of 5-azaindole can be accounted for by its highest pKa value (8.42) compared with those of 6-azaindole (5.61), 4-azaindole (4.85) and 7-azaindole (3.67). The given pKa values were calculated by using the Marwin Sketch software (version 16.12.12.0, calculation module developed by ChemAxon).[75] The pKa values of azaindoles depend on the resonance stabilisation of their protonated forms. The reason, why the *aza*-Friedel–Crafts reaction of 5-azaindole undergoes only under acidic conditions, is that it has the highest basicity in the series of 4-, 5-, 6- and 7-azaindoles.

It is interesting to note that the fastest reactions were achieved with the electron-rich aromatic compound 7-azaindole. This is in complete agreement with its calculated pKa value (3.67) indicating that it is the most acidic compound among the azaindoles studied.

3.1.2. Application of 9-phenanthrol in the modified *aza*-Friedel–Crafts reaction

3.1.2.1. *α*-Arylation of 9-phenanthrol with cyclic imines

To examine the extension possibility of 9-phenanthrol (**1**) in the modified *aza*-Friedel–Crafts reaction, **1** was reacted with 1.5 equiv. of 3,4-dihydroisoquinoline (Scheme 17) under neat conditions at 80 °C. After a reaction time of 120 min, 1-(9-phenanthrol-10-yl)-isoquinoline **78** was isolated only with a yield of 10%. By increasing the temperature to 100 °C the yield of **78** was slightly increased to 19%. Since not only the yield was unsatisfactory under these conditions, but the appearance of side-products could also be identified, acetonitrile as solvent was tested The transformation at reflux temperature in acetonitrile (90 °C) gave **78** in an isolated yield of 49%. Note that the solid product separated out from the recation mixture; therefore, acetonitrile proved to be an optimal solvent. To improve the yield, the reaction was repeated under microwave conditions. In this case the reaction was driven at 100 °C and after a short reaction time (10 min) **78** was isolated in a yield of 67%, that could be improved to 82% by increasing the reaction time to 20 min (Table 6). It should be noted that the optimal workup procedure remained the same, that is filtration of the formed product from the cold reaction mixture. Subsequently, with the satisfactory optimal reaction conditions in hand, the extension possibility of the reaction was tested by using various cyclic imines, including 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-*β*-carboline. The reactions afforded new 1-(9-phenanthrol-10-yl)-thieonopyridine **79** and 1-(9-phenanthrol-10-yl)-*β*-carboline **80** in yields of 92% and 76%, respectively (Table 6).



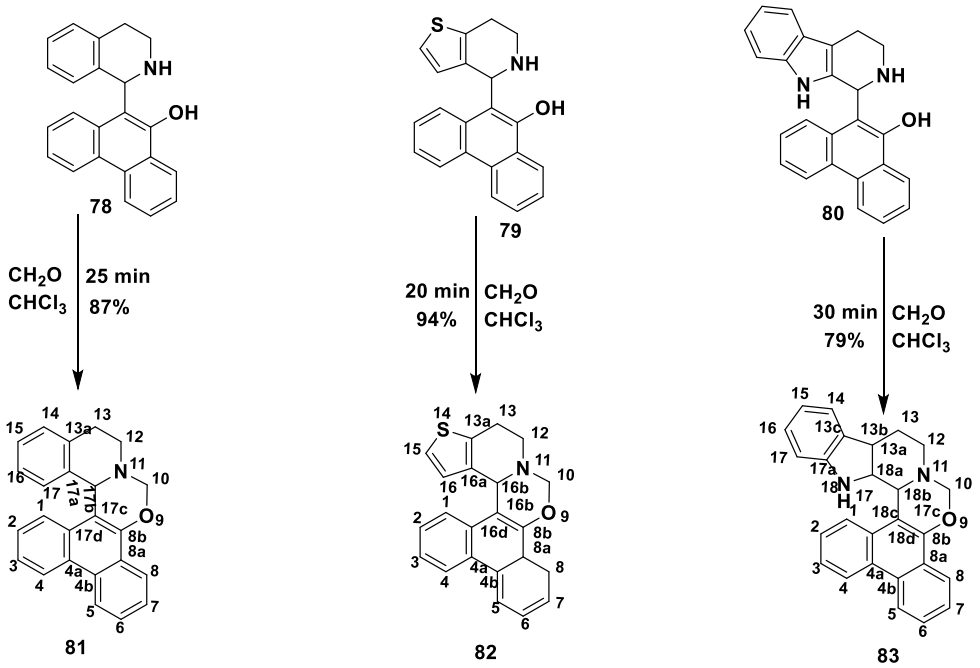
Scheme 17. Synthesis of bifunctional compounds **78**, **79** and **80**

Table 6. Reaction conditions for the synthesis of aminophenanthrols **78**,**79** and **80**

Product	Type of heating	Solvent	Reaction time	Temperature	Yield (%)
78	Oil bath	-	120 min	80 °C	10
	Oil bath	-	60 min	100 °C	19
	Oil bath	Acetonitrile	60 min	100 °C	49
	MW	Acetonitrile	10 min	100 °C	67
	MW	Acetonitrile	20 min	100 °C	82
79	MW	Acetonitrile	20 min	100 °C	72
	MW	Acetonitrile	35 min	100 °C	92
80	MW	Acetonitrile	20 min	100 °C	63
	MW	Acetonitrile	40 min	100 °C	76

3.1.2.2. Ring-closure reactions of secondary aminophenanthrols

The ring closures of aminophenanthrols **78**, **79** and **80** were performed with 35% aqueous formaldehyde in $CHCl_3$ at room temperature. Reactions completed in relatively short reactions and phenanthr[9,10-*e*][1,3]oxazino[4,3-*a*]isoquinoline **81**, phenanthr[9,10-*e*][1,3]oxazino[3,4-*e*] thieno[4,3-*a*]pyridine **82** and phenanthr[9,10-*e*][1,3]oxazino[4,3-*a*]-*β*-carboline **83** were isolated in excellent yields by simple crystallisation from *n*-hexane.

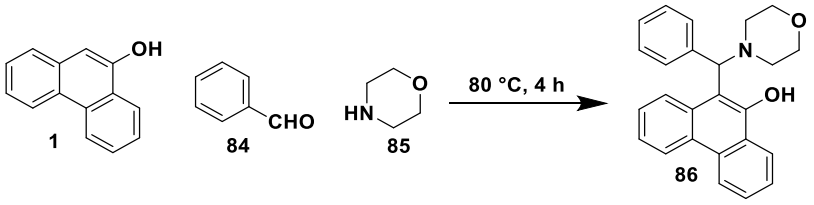


Scheme 18. Synthesis of phenanthroxazines **81–83**

3.2. Application of novel precursors in [4+2] cycloaddition reaction

3.2.1. Synthesis and transformations of new aminophananthrol precursor

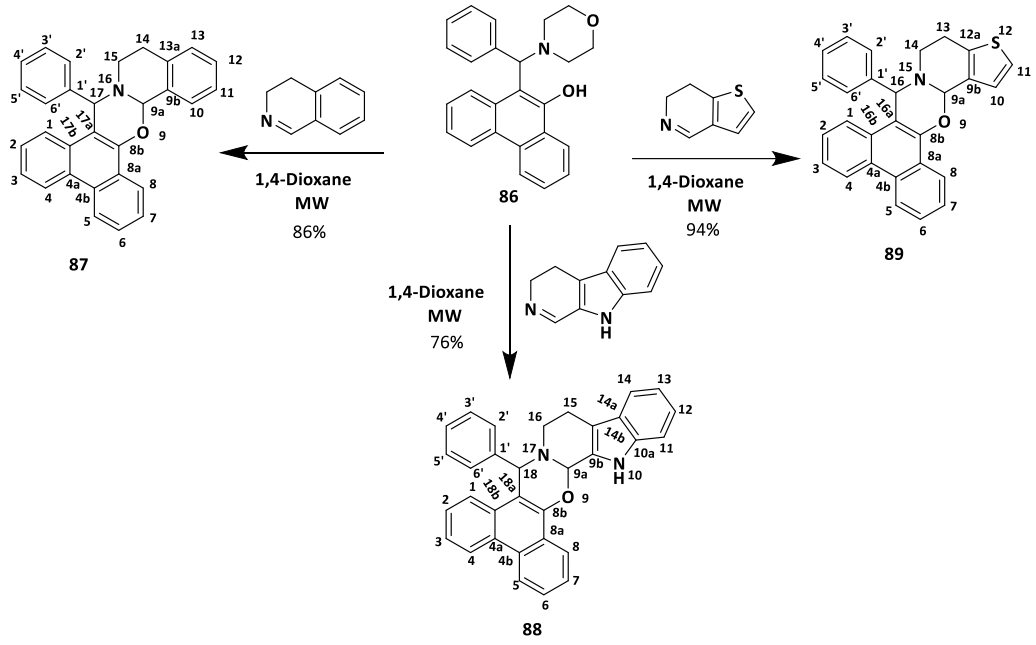
To test aminophenanthrols in the cycloaddition reaction, first the synthesis of precursor **86** was achieved by reacting 9-phenanthrol (**1**) with morpholine in the presence of benzaldehyde under solvent-free conditions at 80 °C. After a 4-h reaction the desired 10-morpholinobenzyl-9-phenanthrol (**86**) was isolated by crystallisation with *n*-hexane (Scheme 19).



Scheme 19. Synthesis of 10-morpholinobenzyl-9-phenanthrol **86**

Aminophenanthrol **86** was first reacted with 3,4-dihydroisoquinoline as dienophile. The reaction was performed in 1,4-dioxane under microwave irradiation at three different temperatures (60 °C, 80 °C and 100 °C). In our first experiment the reaction was performed at 60 °C and after a relatively short reaction time, the desired product (**87**) was isolated only in a low yield (47%). Since the yield was not satisfactory the reaction was repeated at 80 °C and 100 °C. As Table 7 shows, 80

°C and a reaction time of 15 min were found to be the optimal reaction condition. Other dienophiles tested included 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-β-carboline. The optimal conditions and related yields are listed in Table 7.



Scheme 20. Synthesis of phenanthr[9,10-*e*]oxazin derivatives **87**–**89**

Table 7. Results for the synthesis of phenanthr[9,10-*e*]oxazin derivatives **87**–**89**

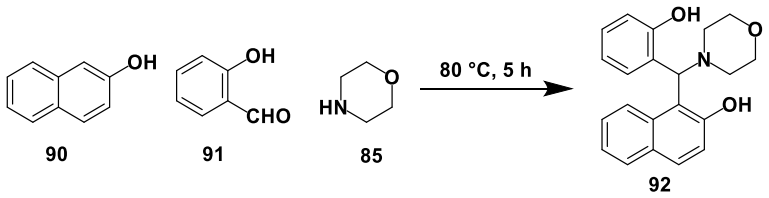
Product	Reaction time	Temperature (°C)	Yield (%)
87	15 min	60	47
		80	***86***
		100	29
88	15 min	60	21
		80	***76***
		100	37
89	15 min	60	52
		80	**94**
		100	32

Since two new stereogenic centres are generated during the reaction, two epimeric structures (**a** and **b**) can be obtained. The reaction was monitored by TLC and the compositions of the crude reaction mixtures were verified by ^{1}H-NMR analysis. On the basis of detailed NMR studies, all

reactions were found to be diastereoselective and the relative configuration of H-9a:H-17 (**87**), H-9a:H-16 (**89**) and H-9a:H-18 (**88**) proved to be *trans*.

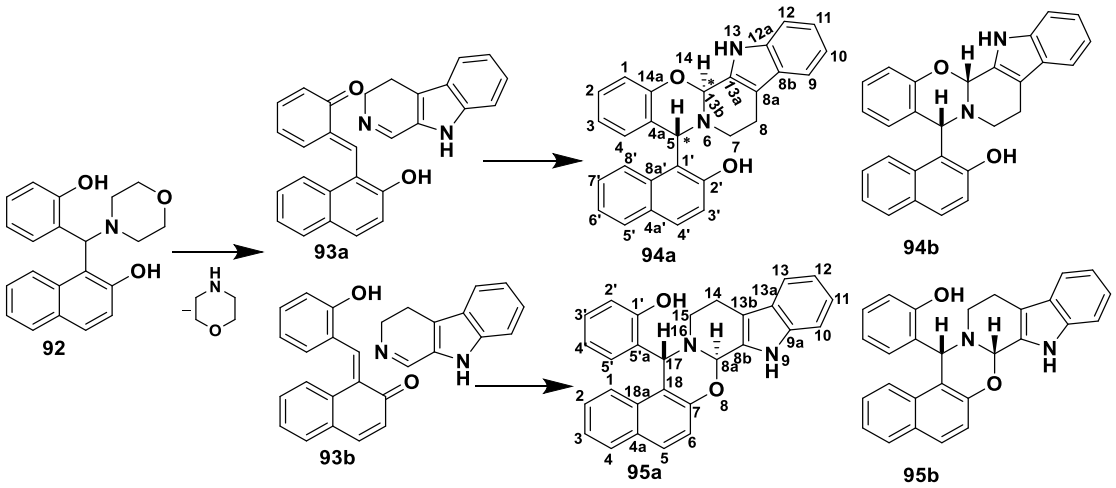
3.2.2. Synthesis and transformations of functionalised aminonaphthol derivatives

First, the synthesis of the starting functionalised aminonaphthol derivative was performed. 2-Naphthol (**90**) and salicylic aldehyde were reacted in the presence of morpholine as a cyclic secondary amine. The reaction was carried out under neat conditions at 80 °C in the optimal reaction time of 5 hours. The progress of the synthesis was followed by TLC that showed the formation of two main products. The workup procedure was based on the notion that we needed the product with the basic nitorgen atom. Therefore, dichloromethane was added to the mixture followed by extraction with 2% hydrochloric acid. Then, after alkalisation with sodium carbonate, the aqueous phase was extracted with dichloromethane. The collected organic layers were dried, evaporated and crystallised to isolate the expected bifunctional compound **92** (Scheme 21).



Scheme 21. The synthesis of the functionalised aminonaphthol **92**

To test the behaviour of this highly functionalised aminonaphthol **92** in [4+2] cycloaddition, it was first reacted with *β*-carboline. The reaction was performed in 1,4-dioxane using 1.5 equivalents of cyclic imine **57**. To accelerate the reaction, microwave irradiation was applied instead of conventional heating due to its well-known favourable effects. The thermal decomposition of starting material **92** affords two types of *o*-QM intermediates (**93a** and **93b**). The stabilisation of these reactive moieties with the dienophile (3,4-dihydro-*β*-carboline) can lead to the formation of two regioisomeric products: benzoxazino-*β*-carboline **94** and naphthoxazino-*β*-carboline **95** (Scheme 22). Since two new stereogenic centres are generated during the reaction, two regioisomers (**94** and **95**) and two epimeric structures (**a** and **b**) are obtained.



Scheme 22. [4+2] Cycloaddition between **92** and 3,4-dihydro-*β*-carboline

The reaction was monitored by TLC and the composition of the crude reaction mixture was verified by ^{1}H-NMR analysis. In our first experiment the reaction was performed at 60 °C. After a relatively short reaction time, the desired product was isolated in a yield of 47%. Since the yield was not satisfactory the reaction was repeated at 80 °C and 100 °C.

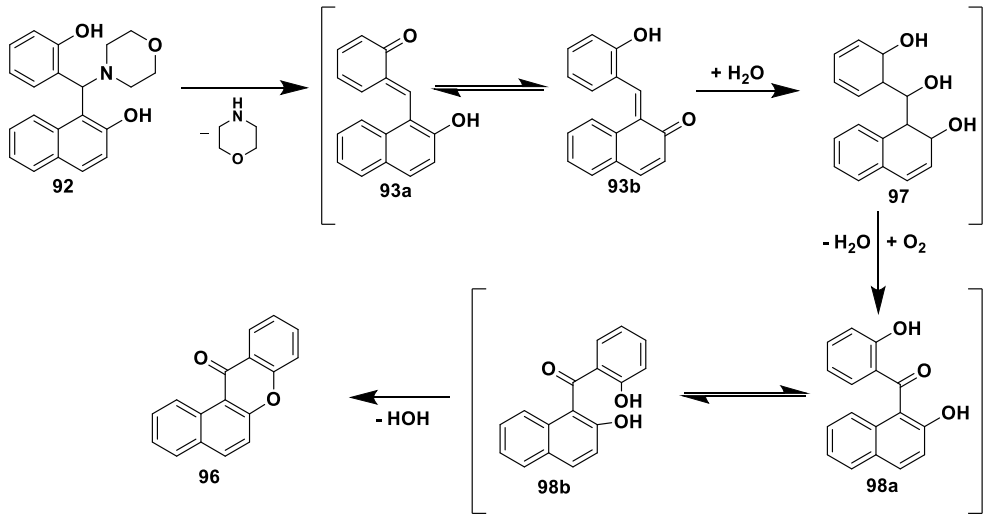
Table 8. Reaction conditions for preparation of compounds **94–95**, **99–102** and **106–107**

Product	Reaction time	Temperature (°C)	Yield (%)
94a,b **95a,b**	20 min	60 ***80*** 100	47 ***89*** 22
99a,b **100a,b**	20 min	60 ***80*** 100	55 ***87*** 27
101a,b **102a,b**	20min	60 ***80*** 100	36 ***92*** 21
106a,b **107a,b**	20 min	60	24
	40 min	80	36
	60 min	***100***	***90***
	40 min	*120*	67

According to results summarised in Table 8, 80 °C and a reaction time of 20 min were found to be optimal. The detailed NMR spectroscopic and computational stereochemistry analysis

confirmed that the formed regioisomer is a naphthoxazine derivative and the relative configuration of C-7a and C-16 is *trans* (**95a**, Scheme 22).

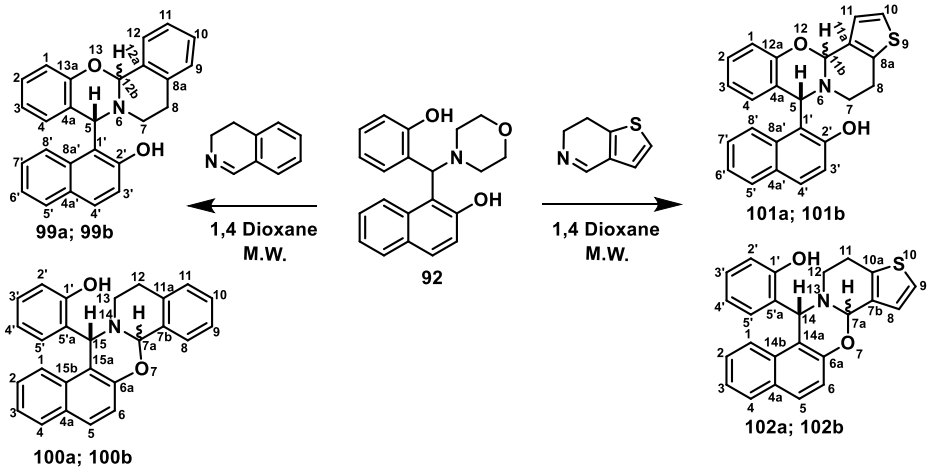
At higher temperature (100 °C) the desired product was isolated with a poor yield (22%), while the formation of a new spot in TLC was observed. After isolation in a yield of 37%, the side-product was identified to be 12*H*-benzo[*a*]xanthen-12-one **96**.[76] The xanthone moiety is found as the core structure of many natural compounds and pharmaceuticals. Furtermore, xanthone derivatives are versatile synthons to construct new heterocycles.[77–84] Most of the known methods for their synthesis require rather complicated and/or expensive starting materials or involve multistep transformations by using different catalysts.[85-88] In our case, the formation of **96** can be explained by the mechanism depicted in Scheme 23. Accordingly, the formed *o*-QMs (**93a** or **93b**) are stabilised by water addition to form triol **97**. The oxidation to dihydroxy keton **98a** followed by water elimination can lead to the formation of **96**. It was proposed that both the basicity of morpholine the leaving group and the presence of *β*-carboline are necessary for the formation of **96**. Therefore, the reaction was repeated starting from **92** by using Et_3N as base in 1,4-dioxane at 100 °C. The reaction performed under microwave irradiation gave desired xanthone derivative **96** in a yield of 71%. This method is the first synthesis of **96** via *o*-QM intermediates **93a** and **93b** starting from highly functionalised Mannich base **92**.



Scheme 23. Plausible mechanism for the formation of benzo[*a*]-xanthen-12-one **96**

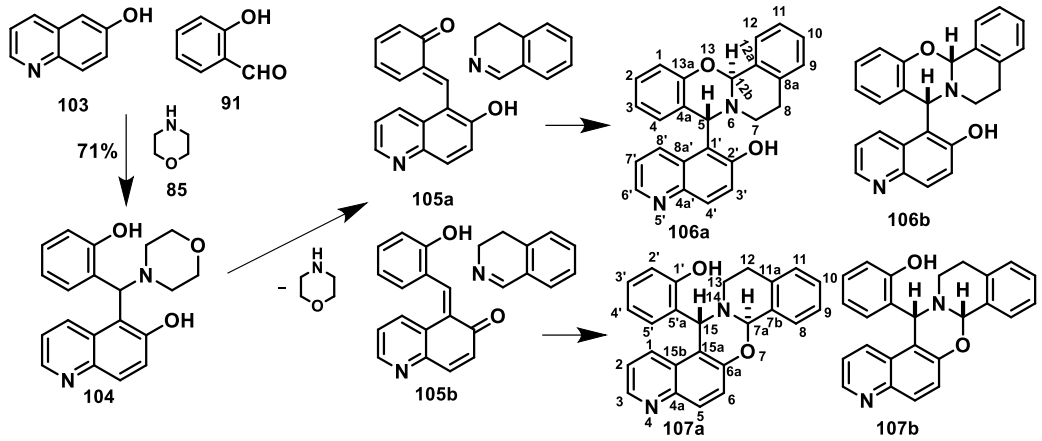
The extension of the reaction was investigated by using other cyclic imines as starting compounds. Therefore, 3,4-dihydroisoquinoline and 6,7-dihydrothieno[3,2-*c*]pyridine were selected as representative cyclic imines (Scheme 24). Reactions were performed at three different temperatures (60 °C, 80 °C and 100 °C) and yields obtained are summarised in Table 8. It can be seen that for these latter synthesis, the optimal reaction condition was 20 minutes at 80 °C. After

isolation of the desired polyheterocycles (**100a** and **102a**), both the diastereo- and regioselectivity of the reaction were confirmed. In all cases, the NMR spectra of the crude products showed the formation of a single product.



Scheme 24. Reaction of aminonaphthol **92** with cyclic imines

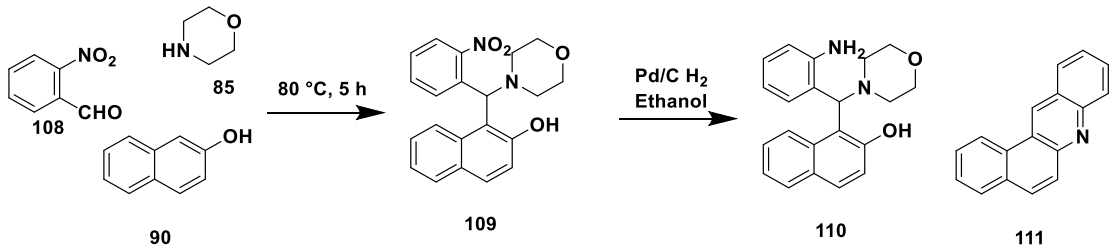
Our original idea was that the formation of the products is influenced by the relative stability of the *o*-QM intermediates. Consequently, our next aim was to investigate how an additional heteroatom (nitrogen) will modify the relative stability of the formed *o*-QMs and the composition of the product mixture. The synthesis of bifunctional quinolinol **104** was achieved by reacting 6-hydroxyquinoline **103** as *N*-containing 2-naphthol analogue with salicylic aldehyde in the presence of morpholine. The desired product was isolated and purified by crystallisation from *n*-hexane. The reactivity of **104** was tested in the [4+2] cycloaddition with 3,4-dihydroisoquinoline as representative cyclic imine. After a reaction time of 60 min at 100 °C, the TLC did not show the presence of the starting materials. The reaction mixture was cooled and product **107a** was isolated by treatment with MeOH (Scheme 25). Of the varied reaction temperatures (60 °C, 80 °C, 100 °C), 100 °C was found to be the optimal choice.



Scheme 25. Synthesis and transformation of aminoquinolinol **104**

The composition of the crude reaction mixtures was also checked and both the regio- and diastereoselectivity of the reaction were confirmed by the formation of a single product. The detailed NMR analysis proved that the isolated compound is *trans*-isoquinolino[1',2':2,3][1,3]oxazino[5,6-*f*]quinoline **107a**.

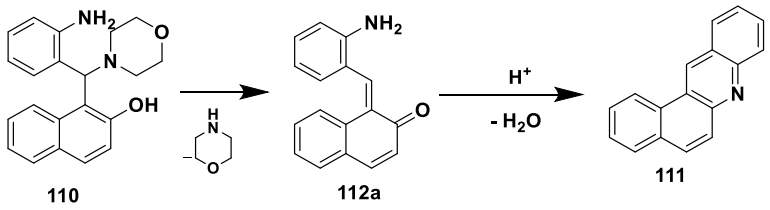
Our further aim was to synthesise a diaminonaphthol, which can lead to two types of *o*-QMs during the cycloaddition reaction. Furthermore, in this case, one of them is an *aza*-*o*-QM, where a special relative stability can be predicted. Accordingly, 2-naphthol was reacted with morpholine in the presence of 2-nitrobenzaldehyde. After a reaction time of 5 hours at 80 °C, aminonaphthol derivative **109** was isolated (Scheme 26). The next step was the hydrogenation of nitro compound **109** in the presence of Pd/C. The desired diaminonaphthol **110** was isolated after a 1-hour reaction time by crystallisation in a yield of 77%. According to TLC, however, the formation of a side-product was also observed. When the reaction was repeated in a longer reaction time of 5-h, it led almost completely to the formation of the side-product. The mixture was purified by column chromatography and the NMR and MS spectra together with the melting point proved that the isolated compound is benz[*a*]acridine **111**[89] (Scheme 27).



Scheme 26. The synthesis of the diaminonaphthol **110**

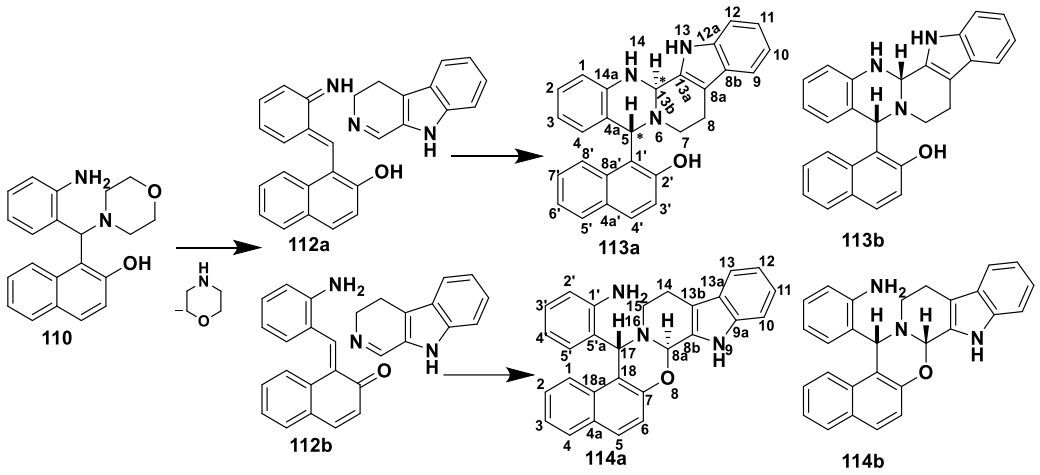
The possible reaction pathway to furnish **111** via formation of *o*-QM intermediate **112a** is depicted in Scheme 27. The synthesis of **111** has already been published starting from aniline and

1-*N*,*N*-dimethylaminomethyl-2-naphthol.[89] Accordingly, the *o*-QM-mediated synthesis of **111** can be considered as a new synthetic method to access benz[*a*]acridine derivatives.[90,91]



Scheme 27. Plausible mechanism for the formation of benz[*a*]acridine **111**

In our first experiment, bifunctional derivative **110** was reacted with *β*-carbolin as cyclic imine. The reaction was performed at three different temperatures, using microwave irradiation and 1,4-dioxane as solvent applied previously. Based on the crude product NMRs, the reaction again proved to be regio- and diastereoselective. Independently on the applied conditions (Table 9), quinazoline **113b** was isolated as a single product (Scheme 28). Note, that in this case the ring closure afforded the corresponding quinazoline. The relative configuration of H-5 and H-13b was determined from the detailed NMR spectra to be *cis*, supported by parallel DFT calculations.



Scheme 28. [4+2] Cycloaddition between **110** and 3,4-dihydro-*β*-carboline.

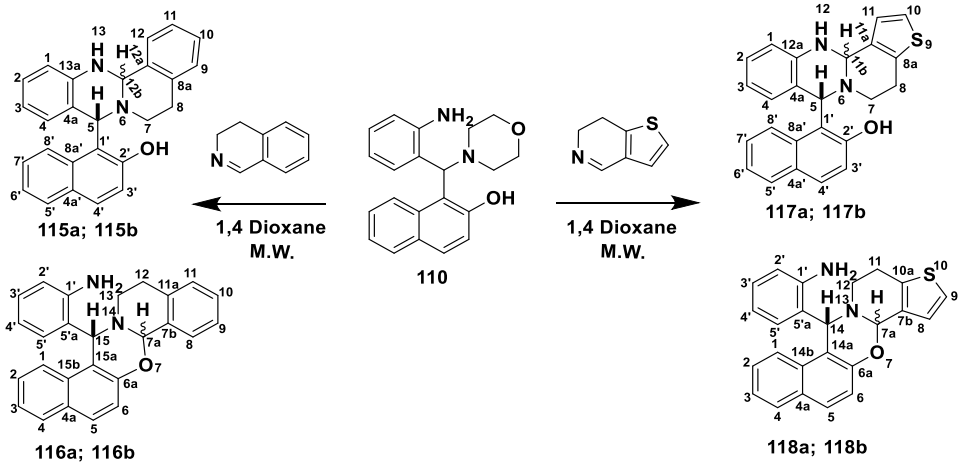
The reaction was then extended by testing 3,4-dihydroisoquinoline and 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imines (Scheme 29). The desired heterocycles were isolated after a reaction time of 20 min at 80 °C in good yields as depicted in Table 9. These optimal conditions were selected from the three different temperatures listed in Table 9. In all cases the regio- and diastereoselectivity of the reaction were verified by crude product NMR spectra. The

detailed NMR measurements unequivocally showed that the isolated products are the corresponding condensed quinazoline derivatives (**115b** and **117b**).

Table 9. Reaction conditions for preparation of compounds **113–118**

Product	Reaction time	Temperature (°C)	Yield (%)
113a,b **114a,b**	20 min	60 ***80*** 100	40 ***91*** 20
115a,b **116a,b**	20 min	60 ***80*** 100	40 ***89*** 19
117a,b **118a,b**	20 min	60 ***80*** 100	36 ***92*** 21

As it was proved experimentally and verified by theoretical calculations, the regioselectivity of the [4+2] cycloaddition is influenced by the structure of the starting bifunctional compounds. Namely, starting from aminodiols **92**, *trans*-naphthoxazines **95a**, **100a** and **102a** were formed, while diaminonaphthol **110** led to the formation of *cis*-quinazolines **113b**, **115b** and **117b**. It was surmised that these undesired selectivity resulted from the relative stability of the *o*-QM intermediates. Therefore, the relative energy for *o*-QMs pairs **93a**, **93b** and **112a**, **112b** were calculated.



Scheme 29. Reaction of diaminonaphthol **110** with cyclic imines

In the case of *o*-QMs **93a** and **93b**, the latter was found to have an energy about 10 kcal/mol lower compared with that of **93a**. This finding is in complete agreement with our experimental observation that the naphtholic hydroxy group participates in the cycloaddition reaction leading to the formation of naphthoxazines.

Comparing the energy values calculated for **112a** and **112b**, *o*-QM **112b** was found to have a lower energy by about 9 kcal/mol than *aza*-*o*-QM **112a**. This result cannot explain the fact that quinazolines were found experimentally to be the single products. It means that in this case the higher nucleophilicity of the amino group compared with that of the naphtholic hydroxy group overwrites the theory that it is only the relative stability of *o*-QMs that affects the outcome of the cycloaddition reaction.

To get the preferred regio- and stereoisomers of **101a,b** or **102a,b** and **117a,b** or **118a,b**, the structure and energy of *trans*/*cis* diastereomers (*RS*/*SR* and *RR*/*SS*) of the regioisomers were calculated by the DFT method.[92] The most stable structures and the corresponding energy differences are given in Figure 3. According to data, **102a** and **117b** can be identified to be the most stable structures. Energy differences around 1 kcal/mol to the next coming structure are rather unequivocal. Consequently, structures of *trans*-isomer **102a** and *cis*-isomer **117b** were compared with available experimental NMR [δ(1H)/ppm, δ(13C)/ppm, nJH,H/Hz)] and spatial NMR information (NOEs). The calculated (DFT modelling) and experimental (NMR analysis) data were in complate agrrement.

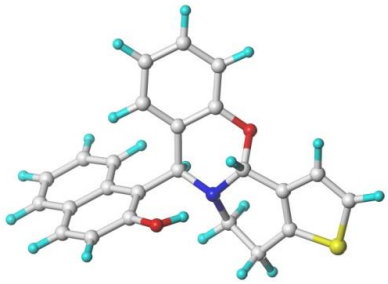
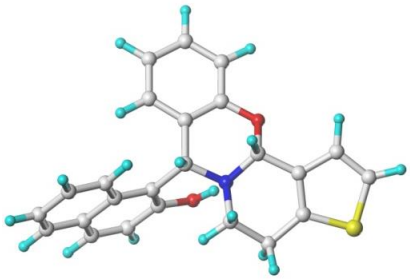
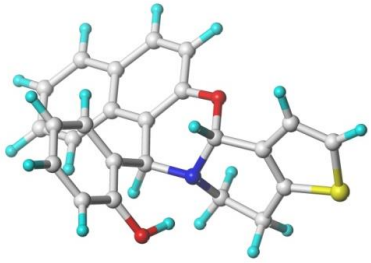
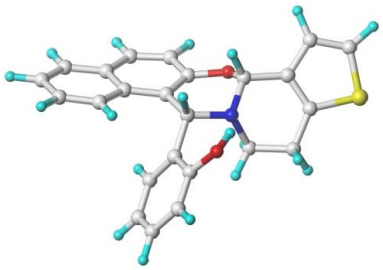
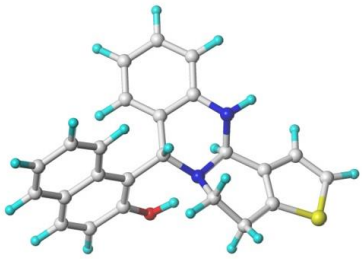
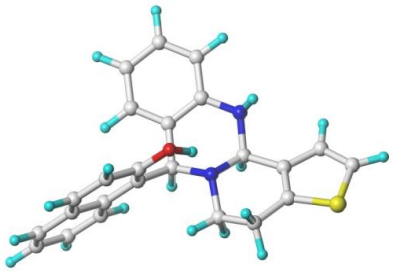
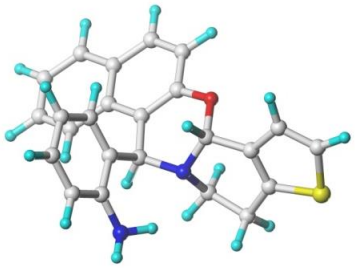
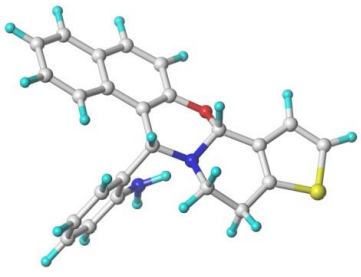
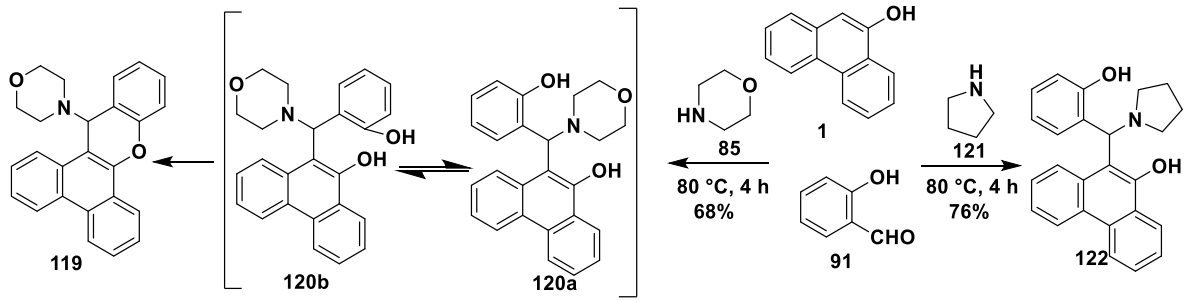
	
101a (3.95 kcal/mol)	**101b** (1.60 kcal/mol)
	
102a (0.00 kcal/mol)	**102b** (4.04 kcal/mol)
	
117a (2.80 kcal/mol)	**117b** (0.00 kcal/mol)
	
118a (1.12 kcal/mol)	**118b** (5.31 kcal/mol)

Figure 3

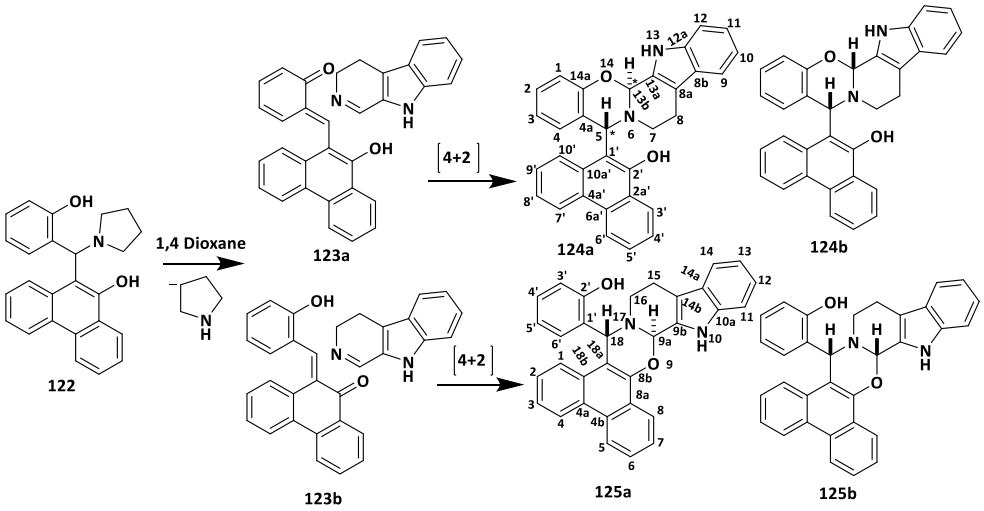
3.2.3. Synthesis and transformations of functionalised aminophenanthrol precursor

We wanted to investigate how *o*-QMs generated from functionalised aminophenanthrol derivatives can influence the [4+2] cycloaddition reaction. Accordingly, 9-phenanthrol **1** and salicylic aldehyde **91** were reacted in the presence of morpholine, carried out under neat conditions at 80 °C. The characteristic spot detected by TLC was isolated and found to be dibenzo[*a*,*c*]xanthen **119** by the NMR spectra. The formation of this side-product can be accounted for by the elimination of water from diol **120**. In this modified Mannich reaction the role of morpholine as the nucleophile was postulated. When it was replaced by pyrrolidine, after a reaction time of 4 h (80 °C, neat conditions), the desired functionalised phenanthrol derivative **122** was isolated in a yield of 76% (Scheme 30).



Scheme 30. Synthesis of compounds **119** and **122**

To test the scope and limitations of the [4+2] cycloaddition, precursor **122** was first reacted with 3,4-dihydro-β-carboline as a dienophile. The reaction was performed in 1,4-dioxane at three different temperatures (60 °C, 80 °C and 100 °C) under microwave irradiation (Table 10). After the thermal decomposition of starting material **122**, two types of *o*-QMs (**123a** and **123b**) were formed. Their further transformation can deliver two regioisomers and two diastereomers (Scheme 31). The composition of the crude reaction mixture was verified by ^{1}H-NMR analysis. As depicted in Table 10, various reaction conditions were applied. In all cases, reactions were found to be regio- and diastereoselective. The detailed NMR analysis indicated that the formed/isolated product is phenanthroxazine **125a** with a *trans* stereochemistry (relative configuration of H-9a:H-18).



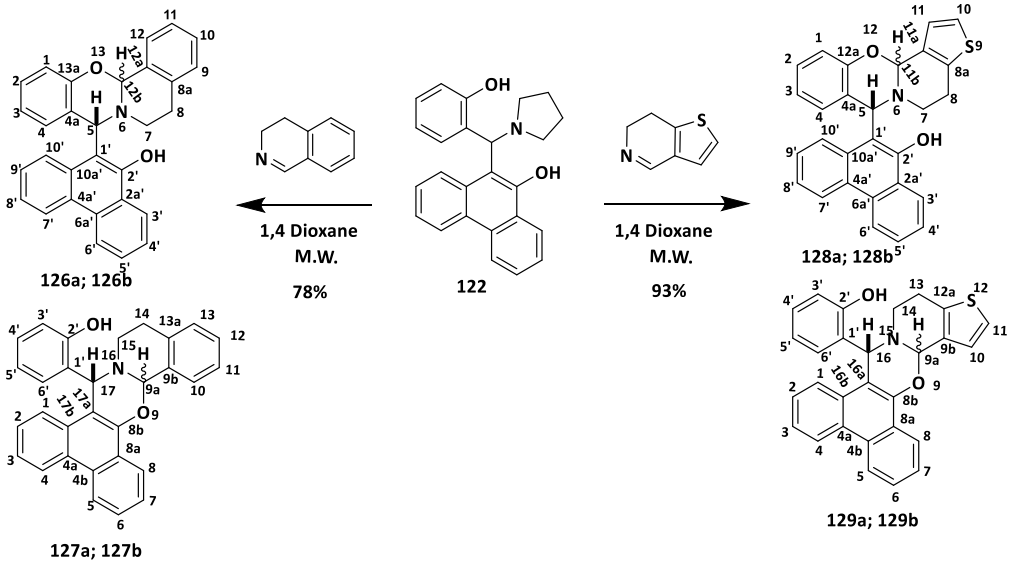
Scheme 31. [4+2] Cycloaddition between **122** and 3,4-dihydro-*β*-carboline

The reaction was then extended by using 3,4-dihydroisoquinoline and 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imines (Scheme 32).

Table 10. Optimizing of the reaction conditions for the synthesis of products **124–129**

Product	Reaction time	Temperature (°C)	Yield (%)
124a,**b** **125a**,**b**	15 min	60	48
		80	***85***
		100	33
126a,**b** **127a**,**b**	15 min	60	28
		80	***78***
		100	19
128a,**b** **129a**,**b**	15 min	60	51
		80	***93***
		100	38

In all cases the regio- and diastereoselectivity of the reactions were also explored and the detailed NMR analysis adequately supported that the isolated products are *trans* phenanthroxazines **127a** and **129a** (Scheme 32). The optimal reaction conditions together with the yields are summarised in Table 10.



Scheme 32. Reaction of functionalised aminophenanthrol **122** with cyclic imines

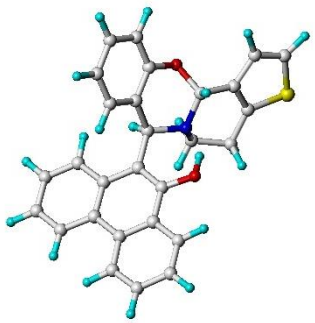
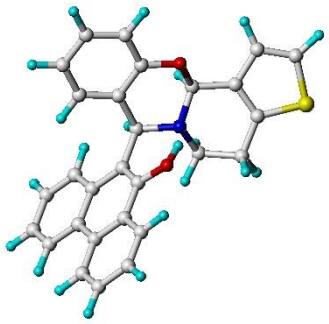
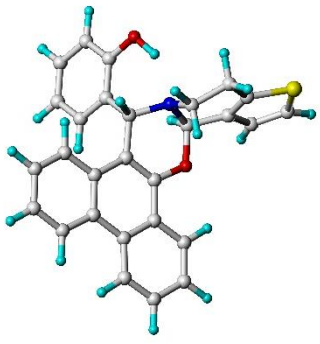
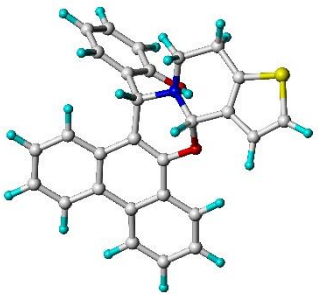
	
128a (3.98 kcal/mol)	**128b** (1.85kcal/mol)
	
129a (0.00 kcal/mol)	**129b** (4.33 kcal/mol)

Figure 4

To get the preferred stereoisomers of **129a**,**b**, the *trans*/*cis* diastereomers of the regioisomers were calculated by the DFT method. Both the most stable structures and the corresponding energy differences are given in Figure 4. On the basis of these data, **129a** could be confirmed to be the most stable structure. Energy differences around 1 kcal/mol to the next coming structure are rather unequivocal. Consequently, this structure of *trans* isomer **129a** will be adjusted with the available experimental NMR [$\delta(^{1}H)$/ppm, $\delta(^{13}C)$/ppm, $^{n}J_{H,H}$/Hz)] and spatial NMR information (qualitative NOE's).

4. SUMMARY

1. The modified *aza*-Friedel–Crafts reaction was applied for C-3 substitution of azaindoles. The reactions were carried out by using 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-*β*-carboline and 4,5-dihydro-3*H*-benz[*c*]azepine as imine substrates. The transformations of 7-azaindole, 4-azaindole and 6-azaindole led to the formation of new 3-isoquinolyl-, 3-thieno[3,2-*c*]pyridyl-, 3-*β*-carbolinyl- and 3-benz[*c*]azepinyl-azaindole derivatives. Starting from 5-azaindole, the modified *aza*-Friedel–Crafts reaction could only be performed by using 10 mol% of *p*-TSA as catalyst. Systematic correlation was found between the reactivity of azaindoles and their pKa values. This observation allowed to explain why the direct coupling of 5-azaindole underwent only under acidic conditions. Namely, 5-azaindole (pKa=8.42) has the highest basicity in the series of 4-, 5-, 6- and 7-azaindoles. It is important to note that all reactions could be accelerated by using microwave irradiation.

2. 9-Phenanthrol as a unique electron-rich aromatic compound was tested in the modified *aza*-Friedel–Crafts reaction. The application of 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*] pyridine or 3,4-dihydro-*β*-carboline as cyclic imines led to the formation of the corresponding bifunctional phenanthrol derivatives that were further transformed to new phenanthr[9,10-*e*][1,3]oxazines.

3. 9-Phenanthrol was aminoalkylated by using morpholine in the presence of benzaldehyde. Aminophenanthrol **86** prepared in this way was reacted with 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine and 3,4-dihydro-*β*-carboline as dienophiles. The reaction was performed in 1,4-dioxane under microwave irradiation at three different temperatures (60°C, 80°C and 100°C). Since two new stereogenic centres are generated during the transformation, two epimeric structures (**a** and **b**) can be obtained. The reactions were monitored by TLC and the compositions of the crude reaction mixtures were verified by ^{1}H-NMR analysis. All reactions were diastereoselective and, on the basis of detailed NMR studies, relative configurations were found to be *trans*.

4. Starting from salicylaldehyde and 2-naphthol or 6-hydroxyquinoline, functionalised Mannich bases could be synthesised in the presence of morpholine affording two types of *o*-QM intermediates. While the relative stability of the formed *o*-QM intermediates was postulated to influence the formation of the products in subsequent [4+2] cycloaddition, the highly functionalised aminodiols were reacted

under heating with different cyclic imines such us 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-c]pyridine and 3,4-dihydro-*β*-carboline. The latter reactions were found to be diastereo- and regioselective leading to *trans*-naphthoxazines. Its structure was proved by DFT computed structures in comparison with the experimental $^{1}H/^{13}C$-NMR spectra and a detailed analysis of the spatial magnetic properties of the preferred diastereomers.

5. Mannich base **110** was synthesised as a unique substrate that can form *o*-QM and *aza*-*o*-QM after thermal elimination. The functionalised diaminonaphthol was tested in [4+2] cycloaddition with cyclic imines. The regio- and diastereoselectivity of the reactions were examined by computational and $^{1}H/^{13}C$ NMR analysis indicating the formation of *cis*-quinazolines as single products.

6. The relative stabilities of *o*-QMs/*aza*-*o*-QM were examined by calculating their relative energies. The obtained results (**93b** is more stable than **93a**) supported completely the experimental findings, that naphthoxazines are formed during the cycloaddition reactions when aminodiol **92** was the starting compound. When diaminonaphthol **110** was applied as precursor, the regioselectivity of the reaction was found to be driven by the higher nucleophilicity of the amino group compared with that of the hydroxy group. During the synthesis and/or transformation of functionalised aminonaphthols, unexpected heterocycles (benzo[*a*]xanthen-12-one and benz[*a*]acridine) were obtained. Their formation was explained through formed *o*-QMs and/or *aza*-*o*-QM intermediates and the processes can be recommended as useful methods for the synthesis of benzo[*a*]xanthen-12-ones and benz[*a*]acridines, respectively.

7. The synthesis of functionalised aminophenanthrol **122** could only be achieved by using salicylic aldehyde in the presence of pyrrolidine. Applying morpholine in this modified Mannich reaction led to the formation of 14-morpholinyl-dibenzo[*a*,*c*]xanthene. Phenanthrol-based bifunctional Mannich products were further tested in [4+2] cycloaddition by using 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine or 3,4-dihydro-*β*-carboline as dienophiles. The regio- and diastereoselectivity of the reactions were supported by NMR spectroscopy and DFT calculations.

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6. REFERENCES

1. Bur, S. K.; Martin, S. F. *Tetrahedron,* **2001**, *57,* 3221.
2. Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron,* **2000**, *56,* 3817.
3. Lian, X.; Lin, L.; Fu, K.; Ma, B.; Liu, X.; Feng, X. *Chem. Sci.* **2017**, *8,* 1238.
4. Liras, S.; Davoren, J. E.; Bordner, J. *Org. Lett.* **2001**, *3,* 703.
5. Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123,* 8003.
6. Filho, J. F. A.; Lemos, B. C.; de Souza, A. S.; Pinheiro, S.; Greco, S. J. *Tetrahedron,* **2017**, *73,* 6977.
7. Szatmári, I.; Fülöp, F. *Curr. Org. Synth.* **2004**, *1*, 155.
8. Betti, M. *Gazz. Chim. Ital.* **1900**, *30 II*, 310.
9. Betti, M. *Gazz. Chim. Ital.* **1901**, *31 II*, 377.
10. Betti, M. *Gazz. Chim. Ital.* **1901**, *31 II*, 170.
11. Betti, M. Gazz. *Chim. Ital.* **1901**, *31 II*, 191.
12. Betti, M. *Org. Synth. Coll. Vol.* **1941**, *1*, 381.
13. Karmakar, B.; Banerji, J. *Tetrahedron Lett.* **2011**, *52*, 4957.
14. MacLeod, P. D.; Li, Z.; Feng, J.; Li, C. J. *Tetrahedron Lett.* **2006**; *47*, 6791.
15. Heydenreich, M.; Koch, A.; Klod, S.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. *Tetrahedron* **2006**; *62*, 11081.
16. Heydenreich, M.; Koch, A.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. *Tetrahedron*, **2008**; *64*, 7378.
17. Szatmári, I.; Barta, P.; Tóth, G.; Balázs, A.; Halász, J.; Fülöp, F. *Eur. J. Org. Chem*, **2017**; 5537.
18. Barta, P.; Szatmári, I.; Fülöp, F.; Heydenreich, M.; Koch, A.; Kleinpeter, E. *Tetrahedron*, **2016**; *72*, 2402.
19. Szatmári, I.; Sas, J.; Fülöp, F. *Tetrahedron Lett*. **2013**, *54*, 5069.
20. Sas, J.; Szatmári, I.; Fülöp, F. *Curr. Org. Synth*. **2016**, *13*, 611.
21. Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schmürch, M. *Chem. Commun*. **2010**, *46*, 8836.
22. Ghobrial, M.; Schmürch, M.; Mihovilovic, M. D. *J. Org. Chem*. **2011**, *76*, 8781.
23. Barta, P.; Fülöp, F.; Szatmári, I. *Beilstein J. Org. Chem.* **2018**; 14, 560.
24. Van De Water, R. W.; Petus, T. R. R. *Tetrahedron*, **2002**, *58*, 5367.
25. Szatmári, I.; Fülöp, I. *Tetrahedron Lett.* **2011**, *52*, 4440.

26. Szatmári, I.; Barta, P.; Csámpai, A.; Fülöp, I. *Tetrahedron*, **2017**, *73*, 4790.
27. Crandall, J. K.; Zucco, M.; Kirsch, R. S.; Coppert, D. M. *Tetrahedron Lett*. **1991**, *32*, 5441.
28. Matsumoto, J.; Ishizu, M.; Kawano, R. I.; Hesaka, D.; Shiragami, T.; Hayashi, Y.; Yasuda, M. *Tetrahedron*, **2005**, *61*, 5735.
29. Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369.
30. Jacob, A.; Roy, T.; Kaicharla, T.; Biju, A. T. *J. Org. Chem.*, **2017**, *82*, 11269.
31. Choi, Y.W.; Takamatsu, S.; Khan, S. I.; Srinivas, P. V.; Ferreira, D.; Zhao, J. *J. Nat. Prod.* **2006**, *69*, 356.
32. Xia, Y.; Yang, Z.Y.; Xia, P.; Bastow, K. F.; Kuo, S. C.; Li, K. H. *J. Med. Chem.* **1998**, *41*, 1155.
33. Gupta, S.; Das, L.; Datta, A. B.; Poddar, A.; Janik, M. E.; Bhattacharrya, B. *Biochemistry* **2006**, *45*, 6467.
34. Wei, L.; Shi, Q.; Bastow, K. F.; Brossi, A.; Morris-Natschke, S. L.; Nakagawa-Goto, K.; Wu, T. S.; Pan, S. L.; Teng, C. H.; Lee, K. H. *J. Med. Chem*. **2007**, *50*, 3674.
35. Wu, X. S.; Lin, S. Z.; Li, M. Z.; You, T. P. *Synlett*, **2009**, 1501.
36. Gao, Q.; Wu, X.; Liu, S.; Wu, A. *Org. Lett.* **2014**, *16*, 1732.
37. Tempesti, T. C.; Pierini, A. B.; Baumgartner, M. T. *J. Org. Chem.* **2005,** *70*, 6508.
38. Amand, S.; Vallet, M.; Guedon, L.; Genta-Jouve, G.; Wien, F.; Mann, S.; Dupont, J.; Prado, S.; Nay, B. *Org. Lett*. **2017**, *19*, 4038.
39. Eiji, Y.; Takashi, A.; Hiroki, K.; Tomoya, K. Japan Patent JP 2015218291. **2015**.
40. Xu, Z. R.; Wang, Q.; Zhu, J. P. *J. Am. Chem. Soc.* **2015**, *137*, 6712.
41. Reddy, R. R; Gudup, S. S.; Ghoria, P. *Angew. Chem. Int. Ed.* **2016**, *55*, 15115.
42. Jin, M.; Ren, W.; Qian, D. W.; Yang, S. D. *Org. lett*. **2018**, *20*, 7015.
43. Middleton, J. E.; Kandaswami, C.; Theoharides, T. C. *Pharm. Rev.* **2000**, *52*, 673.
44. Boots, A. W.; Haenen, G. R.; Bast, A. *Eur. J. Pharmacol*. **2008**, *585*, 325.
45. Lee, H.; Yi, C. S. *Eur.J. Org. Chem*. **2015**, *9*, 1899.
46. Noyori, R.; Tomino, I.; Nishizawa, M. *J. Am. Chem. Soc*. **1979**, *101*, 5843.
47. Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev*. **2003**, *103*, 3155.
48. Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev*. **2003**, *103*, 3213.
49. Heumann, L. V.; Keck, G. E. *J. Org. Chem.* **2008**, *73*, 4725.
50. Brunel, J. M. *Chem. Rev*. **2007**, *107*, PR1.
51. Osakama, K.; Nakajima, M. *Org. lett.* **2016**, *18*, 236.
52. Kim, H. Y.; Takizawa, S.; Sasai, H.; Oh, K. *Org. Lett.*, **2017**, *19*, 3867.

53. Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534.
54. Li, X.; Hewgley, J. B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *14*, 5500.
55. Takizawa, S.; Rajesh, D.; Katayama, T.; Sasai, H. *Synlett*, **2009**, *10*, 1667.
56. Takizawa, S.; Kodera, J.; Yoshida, Y,;Sako, M.; Breukers, S.; Enders, D.; Sasai, H. *Tetrahedron*, **2014**, *70.* 1786.
57. Takizawa, S.; Gröger, H.; Sasai, H. *Chem. Eur. J.* **2015**, *21*, 8992.
58. Shaikh, M.; Sahu, A.; Kumar, A. K.; Sahu, M.; Singh, S. K.; Ranganath, K. V. *Green Chem*, **2017**, *19*, 4533.
59. Tada, M.; Iwasawa, Y. *Chem. Comm.* **2006**, 2833.
60. Guo, Q. X.; Wu, Z. J.; Luo, Z. B.; Liu, Q. Z.; Ye, J. L.; Luo, S. W.; Cun, L. F.; Gong, L. Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927.
61. Chu, C. Y.; Uang, B. J. *Tetrahedron Asymmety*, **2003**, *14*, 53.
62. Yamamoto, K.; Fukushima, H.; Nakazaki, M. *Chem. Comm.* **1984**, 1490.
63. Aydin, J.; Kumar, K.; Sayah, M. J.; Wallner, O. A.; Szabó. J. *J. Org. Chem.* **2007**, *72*, 4689.
64. Norman, D. W.; Carraz, C. H.; Hyett, D. J.; Pringle, P. G.; Sweeney, J. B.; Orpen, A. G.; Phetmung, H.; Wingand, R. L. *J. Am. Chem. Soc.* **2008,** *130,* 6840.
65. Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607.
66. Kamei, I.; Sato H. A.; Iwasawa T.; *Tetrahedron Lett.* **2011**, *21*, 2638.
67. Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.
68. Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. *Bioorg. Med. Chem.* **2009**, *17*, 2351.
69. Herz, W.; Tsai, L. *J. Chem. Soc.* **1955**, *77*, 3529.
70. Meyers, A. I.; Hutchings, R. H. *Tetrahedron*, **1993**, *49*, 1807.
71. Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267.
72. Khodaei, M.M.; Khosropour, A.R.; Moghanian, H. *Synlett*, **2006**, 916.
73. Khosropour, A. R.; Khodaei, M. M.; Moghanian, H. *Synlett*, **2005**, 955.
74. Csütörtöki, R.; Szatmári, I.; Mándi, A.; Kurtán, T.; Fülöp, F. *Synlett*, **2011**, 1940.
75. Marvin was used for calculating pKa values of azaindoles, Marvin 16.12.12.0, 2016, ChemAxon (http://www.chemaxon.com)
76. Tang, J.; Zhao, S.; Wei, Y.; Quan, Z. Huo, C. *Org. Biomol. Chem.* **2017**, *15*, 1589.
77. Sultanbawa, M.U.S. *Tetrahedron*, **1980**, *36*, 1465.
78. Peres, V.; Nagem, T.J. *Phytochemistry*, **1997**, *44*, 191.
79. Bennett, G.J.; Lee, H.H. *Phytochemistry*, **1989**, *28*, 967.

80. Mandal, S.; Das, P.C.; Joshi, P.C. *J. Indian Chem. Soc.*, **1992**, *69*, 611.
81. Finnegan, R.A.; Stephani G.M.; Ganguli G.; Bhattacharya S.K. *J. Pharm. Sci.*, **1968**, *57*, 1039.
82. Shagufta, I. A. *Eur. J. Med. Chem*., **2016**, *116*, 267.
83. Pinto, M.M.M.; Sousa, M.E.; Nascimento, M.S.J., *Curr. Med. Chem*., **2005**, *12*, 2517.
84. Na, Y. *J. Pharm. Pharmacol*., **2009** *61*, 707.
85. Okuma, K.; Nojima, A.; Matsunaga N.; Shioji, K. *Org. Lett*. **2009**, *11*, 169.
86. Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4273.
87. Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
88. Wang, S.; Xie, K.; Tan, Z.; An, X.; Zhou, X.; Guo, C. C.; Peng, Z. *ChemComm*. **2009**, *42*, 6469.
89. Bilgic, O.; Young, D.W. *J. Chem. Soc. Perkin Trans.* **1980**, *1*, 1233.
90. Alajarín, M.; Vidal, Á.; Ortín, M. M. *Tetrahedron*, **2005**, *61*, 7613.
91. Karthikeyan, P.; Rani, A. M.; Saiganesh, R.; Balasubramanian, K. K.; Kabilan, S. *Tetrahedron*, **2009**, *65*, 811.
92. Szatmári, I.; Heydenreich, M.; Koch, A.; Fülöp, F.; Kleinpeter, E. *Tetrahedron*, **2013**, *69*, 4755.

ANNEX

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Ortho-Quinone Methide Driven Synthesis of New *O,N*- or *N,N*-Heterocycles

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To synthesize functionalized Mannich bases that can serve two different types of *ortho*-quinone methide (*o*-QM) intermediates, 2-naphthol and 6-hydroxyquinoline were reacted with salicylic aldehyde in the presence of morpholine. The Mannich bases that can form *o*-QM and *aza*-*o*-QM were also synthesized by mixing 2-naphthol, 2-nitrobenzaldehyde, and morpholine followed by reduction of the nitro group. The highly functionalized aminonaphthol derivatives were then tested in [4+2] cycloaddition with different cyclic imines. The reaction proved to be both regio- and diastereoselective. In all cases, only one reaction product was obtained. Detailed structural analyses of the new polyheterocycles as well as conformational studies including DFT modelling were performed. The relative stability of *o*-QMs/*aza*-*o*-QM were also calculated, and the regioselectivity of the reactions could be explained only when the cycloaddition started from aminodiol **4**. It was summarized that starting from diaminonaphthol **25**, the regioselectivity of the reaction is driven by the higher nucleophilicity of the amino group compared with the hydroxy group. 12H-benzo[a]xanthen-12-one (**11**), formed via *o*-QM formation, was isolated as a side product. The proton NMR spectrum of **11** proved to be very unique from NMR point of view. The reason for the extreme low-field position of proton H-1 could be accounted for by theoretical calculation of structure and spatial magnetic properties of the compound in combination of ring current effects of the aromatic moieties and steric compression within the heavily hindered H(1)-C(1)-C(12b)-C(12a)-C(12)=O structural fragment.

1. Introduction

The Mannich reaction is one of the most important basic reaction types in organic chemistry for C–C and C–N bond formation.[1–3] The classical Mannich product arises from the condensation reaction of a compound containing at least one active hydrogen atom with formaldehyde and a secondary amine.[4] A special variation of this latter reaction when formaldehyde is replaced by benzaldehyde, the secondary amine by ammonia, and the C–H acid by an electron-rich aromatic compound such as 2-naphthol. The reaction was first developed by Mario Betti and the aminonaphthol synthesized in this way became as Betti base.[5] This modified three-component Mannich reaction (mMR) was then extended to apply 1-naphthol, quinolinol or isoquinolinol as electron-rich aromatic compounds.[5–6] Mechanistically, the bifunctional product is formed by the nucleophilic addition of the electron-rich aromatic compound on the C=N bond formed by in situ condensation of the aldehyde and amine. As a consequence of the two or more functional groups in the structures of the Mannich bases prepared via such modified reactions, one of the most important areas of application is the synthesis of new heterocycles.[5,7]

Another proposed mechanism for the synthesis of modified Mannich bases is via formation of an *ortho*-quinone methide (*o*-QMs) intermediate that is generated from the aldehyde and the electron-rich aromatic compound such as 2-naphthol. This intermediate reacts with the nucleophile to form the final Mannich products.[8] Accordingly, *o*-QMs can also be generated from the Mannich bases after thermal elimination of the amine. This reactive moiety can be stabilized by reacting with different dienophiles.[5,9,10] One of the possibilities is when the formed *o*-QMs reacts with electron-rich aromatic compounds. Accordingly, Rueping et al.[11] recently published reactions between aza-*o*-QMs generated in situ from α-substituted *ortho*-aminobenzyl alcohols and substituted indoles catalyzed by *N*-triflylphosphoramides (NTPAs). The process provided new C-2- and C-3-functionalized indole polyheterocycles in good yields with 90–99% ee.[11]

The preparation of novel condensed polyheterocycles is a relatively new area of the chemistry of *o*-QMs generated from Mannich bases. In this case, the [4+2] cycloaddition take place between the *o*-QMs and cyclic imines (containing C=N bond). Our research group developed for the first time the reaction of 1-aminoalkyl-2-naphthols with 3,4-dihydroisoquinoline as cyclic imine.[12] The reaction was then extended starting from 2-

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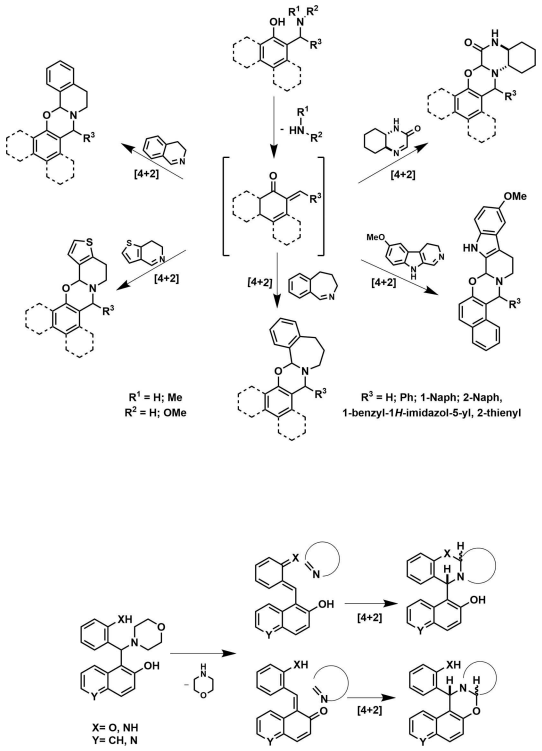


Figure 1. Summary of previous work and the results of this study.

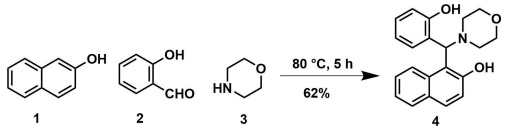
aminoalkyl-1-naphthols and other C=N dienophiles (cyclic imines) preparing new naphthoxazino-isoquinoline, -benzazepine and -thienopyridine derivatives.[13] At the same time, Osyanin *et al.*[14] reported the same reaction extended by various substituted aminonaphthols achieving the syntheses in ethanol at 78 °C (Figure 1).

To the best of our knowledge, the transformation of bifunctional Mannich bases, which can serve two different types of *o*-QMs has not been investigated. According to this, our first aim was to synthesize new functionalized aminonaphthol derivatives. Our further aim was to study the scope and limitations of the applicability of these aminonaphthols in [4+2] cycloaddition. Furthermore, we wanted to investigate the influence of the relative stability of the formed *o*-QMs and/or the dienophile on the structure of the final product. Finally, both structure and conformational behavior of the novel polyheterocycles was studied by NMR spectroscopy and accompanying theoretical quantum chemical (QC) calculations.

2. Results and Discussion

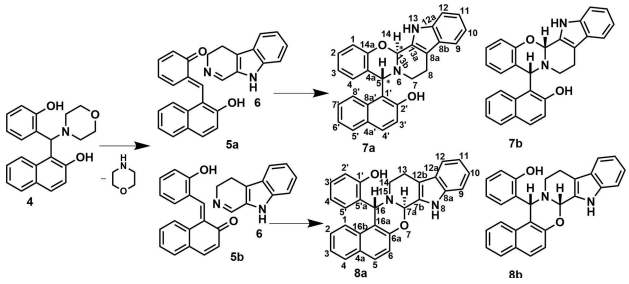
2.1. Synthesis

First, the synthesis of the functionalized precursor aminonaphthol derivative was achieved. Accordingly, 2-naphthol and salicylic aldehyde were reacted in the presence of morpholine as a cyclic secondary amine. The reaction was carried out under neat conditions at 80 °C. The optimal reaction time was 5 hours. The progress of the synthesis was followed by TLC that showed the formation of two main products. The separation of the desired aminonaphthol from the side product was achieved based on the concept that the derivative we want to produce contains basic nitrogen. Therefore, the work-up procedure was optimized by adding dichloromethane to the mixture and then extracting with 2% hydrochloric acid. Then the aqueous phase was alkalized with sodium carbonate and extracted with dichloromethane. The collected organic layers were dried, evaporated, and crystallized to isolate the expected bifunctional compound **4** (Scheme 1).



Scheme 1. The synthesis of the functionalized aminonaphthol **4**.

To test the behavior of this highly functionalized aminonaphthol **4** in [4+2] cycloaddition, it was first reacted with β-carboline **6**.[15] The reaction was performed in 1,4-dioxane by using 1.5 equivalents of the cyclic imine **6**. To accelerate the reaction, microwave irradiation was. applied instead of conventional heating due to its positive effects (shorter reaction, improved yields). Because of the thermal decomposition of starting material **4**, two types of *o*-QM intermediate (**5a** and **5b**) can be formed. The stabilization of these reactive moieties with the dienophile (3,4-dihydro-β-carboline) can lead to the formation of two regioisomeric products: benzoxazino-β-carboline **7** and naphthoxazino-β-carboline **8** (Scheme 2). Since



Scheme 2. [4+2] cycloaddition between **4** and 3,4-dihydro-β-carboline.

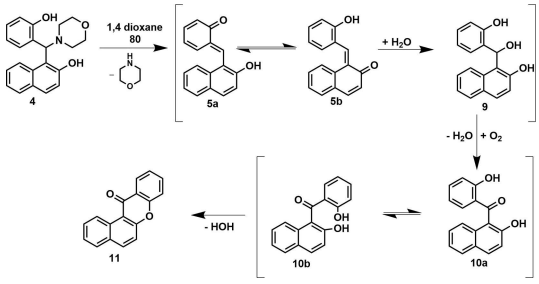
during the reaction two new stereogenic centers are generated, two regioisomers (**7** and **8**) and two epimeric structures (**a** and **b**) can be obtained.

The reaction was monitored by TLC, and the composition of the crude reaction mixture was verified by ^{1}H-NMR analysis. In our first experiment the reaction was performed at 60 °C. After a relatively short reaction time, the desired product was isolated in a yield of 47%; since the yield was not satisfactory, the reaction was repeated at 80 °C and 100 °C. Results are summarized in Table 1. 80 °C and 20 minutes reaction time was found to be the optimal reaction conditions. The detailed NMR spectroscopic and computational stereochemistry analysis (see

Table 1. Reaction Conditions for Preparation of Compounds **8a**, **14a**, **16a** and **22a**

Product	Time	Temperature (°C)	Yield (%)
8a	20 min	60	47
		80	*89*
		100	22
14a	20 min	60	55
		80	*87*
		100	27
17a	20 min	60	36
		80	*92*
		100	21
22a	20 min	60	24
	40 min	80	36
	60 min	*100*	*90*
	40 min	*120*	67

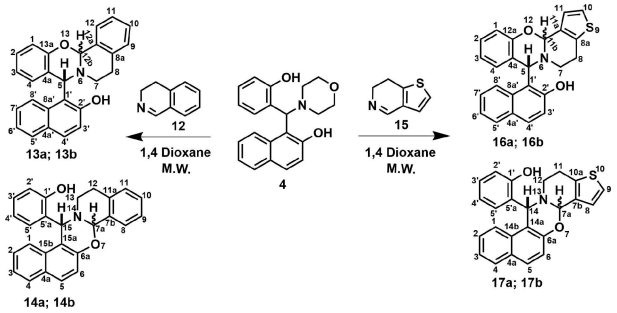
2.2.) proved that the formed regioisomer is a naphthoxazine and the relative configuration of C-7a and C-16 is *trans* (**8a**, Scheme 2). By using higher temperatures (*e.g.* 100 °C) the desired product was isolated with only a poor yield (22%), while the formation of a new spot in TLC was observed. After isolation, the side product was identified (see **2.3.**) to be 12*H*-benzo[*a*]xanthen-12-one **11**.[16] that was isolated in a yield of 37%. The xanthone derivatives are the core structure of many natural compounds and pharmaceuticals and, at the same time, they are versatile synthons to achieve new heterocycles. Most of the known methods for their synthesis either require rather complicated and/or expensive starting materials or involve multistep transformations by using different catalysts.[17–20] In our case the formation of **11** can be explained by the mechanism depicted in Scheme 3. Accordingly, the formed *o*-



Scheme 3. Plausible mechanism for the formation of benzo[*a*]-xanthen-12-one

QMs (**5a** or **5b**) are stabilized by water addition to form triole **9**. The oxidation to dihydroxy keton **10a** followed by water elimination can led to the formation of **11**. It was proposed that both the basicity of the leaving morpholine and the presence of β-carboline are necessary for the formation of **11**. Therefore, the reaction was repeated starting from **4** by using Et_3N as a base in 1,4-dioxane at 100 °C. The reaction was performed under microwave irradiation, and the desired xanthone derivative **11** was obtained in a yield of 71%. This method is the first synthesis of **11** via *o*-QM intermediates **5a** and **5b** starting from a highly functionalized Mannich base **4**. The ^{1}H NMR spectrum of 12*H*-benzo[*a*]xanthen-12-one (**11**) is very interesting and will be discussed below (*see* **2.3.**).

The extension of the reaction was investigated by using other cyclic imines as starting compounds. Therefore, 3,4-dihydroisoquinoline[21] and 6,7-dihydrothieno[3,2-*c*]pyridine[22] were selected as representative cyclic imines (Scheme 4). The



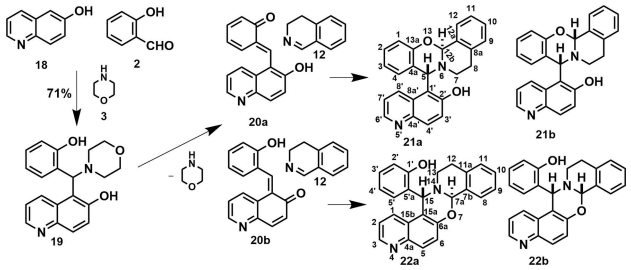
Scheme 4. Reaction of aminonaphthol **4** with cyclic imines.

reactions were performed at three different temperatures (60 °C, 80 °C, and 100 °C). The yields obtained are summarized in Table 1. It can be concluded that for these latter synthesis, the optimal reaction condition was 20 minutes at 80 °C. After isolation of the desired polyheterocycles (**14a** and **17a**), both the diastereo- and regioselectivity of the reaction were confirmed. In all cases, the NMR spectra of the crude products show the formation of single product.

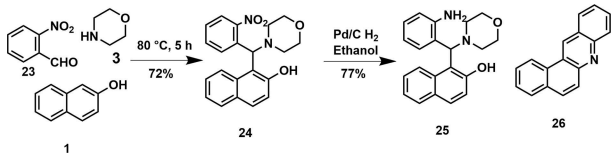
Our original idea was that the formation of the products is influenced by the relative stability of the *o*-QM intermediates. Consequently, our next aim was to investigate how an additional heteroatom (nitrogen) will modify the relative stability of the formed *o*-QMs, and how it will influence the composition of the product mixture. The synthesis of bifunctional quinolinol **19** was achieved by reacting 6-hydroxyquinoline **18** as *N*-containing 2-naphthol analogue with salicylic aldehyde in the presence of morpholine. The desired product was isolated and purified by crystallization from *n*-hexane (see *Experimental Part*). The reactivity of **19** was tested in the [4+2] cycloaddition reaction with 3,4-dihydroisoquinoline as representative cyclic imine. After a reaction time of 60 min. at 100 °C, TLC did not show the presence of the starting materials. The reaction mixture was cooled and product **22a** was isolated by treatment with MeOH (Scheme 5). From the varied reaction temperature (60 °C, 80 °C, 100 °C), 100 °C was found to be the optimal one.

The composition of the crude reaction mixtures was also checked, and both the regio- and the diastereoselectivity of the reaction were confirmed by the formation of a single product. The detailed NMR analysis proved that the isolated compound is the *trans* isoquinolino[1′,2′:2,3][1,3]oxazino[5,6-*f*]quinolin (**22a**, see **2.2.**).

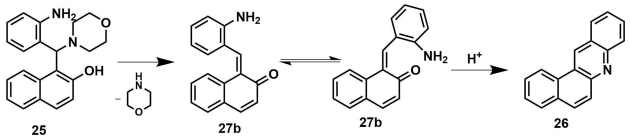
Our further aim was to synthesize diaminonaphthol, which can lead to two types of *o*-QMs during the cycloaddition reaction. Furthermore, in this case, one of them is an *aza*-*o*-QM, where a special relative stability can be predicted. Accordingly, 2-naphthol was reacted with morpholine in the presence of 2-



Scheme 5. Synthesis and transformation of aminoquinolinol **19**.



Scheme 6. The synthesis of the diaminonaphthol **25**.



Scheme 7. Plausible mechanism for the formation of benz[a]acridine **26**.

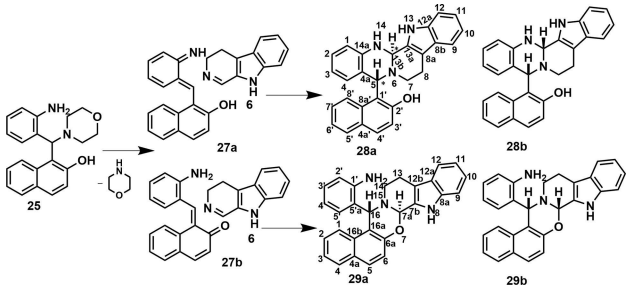
nitrobenzaldehyde. After a reaction time of 5 hours at 80 °C, aminonaphtol derivative **24** was isolated (Scheme 6). The next step was the reduction of nitro compound **24** via hydrogenation in the presence of Pd/C. The desired diaminonaphthol **25** was isolated after 1 hour reaction time, by crystallization in a yield of 77 %. According to TLC, the reaction proved to be sensitive to the reaction time. After 1 hour, the formation of a side product was observed. When the reaction was repeated by using longer reaction time (5 hours), it led almost completely to the formation of the side product. The mixture was purified by column chromatography and the NMR and MS spectra together with the melting point proved that the isolated compound is benz[*a*]acridine (**26**).[23]

The possible reaction pathway to furnish **26** via formation of the *o*-QM intermediate **27** is depicted in Scheme 7. The synthesis of **26** has already been published starting from aniline and 1-*N*,*N*-dimethylaminomethyl-2-naphthol.[23] Accordingly, the *o*-QM mediated synthesis of **26** can be interpreted as a new synthetic method to prepare benz[*a*]acridine derivatives.

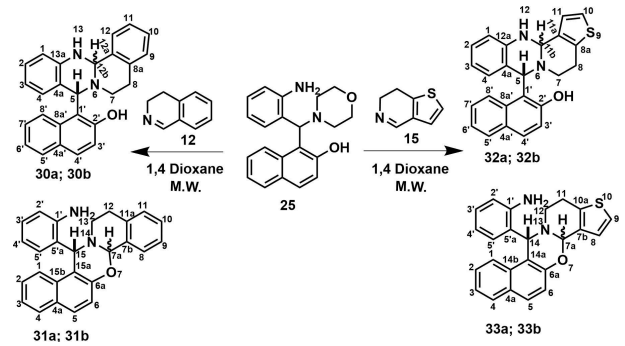
In our first experiment, bifunctional derivative **25** was reacted with β-carbolin as cyclic imine. The reaction was performed by applying three different temperatures, using microwave irradiation, leaving the previously applied solvent (1,4-dioxane) unchanged. Based on the crude product NMRs, the reaction again proved to be regio- and diastereoselective, and independently of the applied conditions (Table 2), quinazoline **28 b** was also isolated as a single product (Scheme 8). Note, that in this case the ring closure went to the direction of forming quinazoline, and the relative configuration of H-5 and

Table 2. Reaction Conditions for Preparation of Compounds **28 b, 30 b and 32 b**

Product	Time	Temperature (°C)	Yield (%)
28 b	20 min	60	40
		80	*91*
		100	20
30 b	20 min	60	40
		80	*89*
		100	19
32 b	20 min	60	36
		80	*92*
		100	21



Scheme 8. [4 + 2] cycloaddition between **25** and 3,4-dihydro-β-carboline.



Scheme 9. Reaction of diaminonaphthol **25** with cyclic imines.

H-13b was found from the detailed NMR spectra to be cis, supported by the parallel DFT calculations (see **2.2.**).

The reaction was extended by testing 3,4-dihydroisoquinoline and 6,7-dihydrothieno[3,2-*c*]pyridine as cyclic imines (Scheme 9). After a reaction time of 20 min at 80 °C, the desired heterocycles were isolated in good yields as depicted in (Table 2). These optimal conditions were selected from three different temperatures listed in Table 2. In all cases, the regio- and diastereoselectivity of the reaction were proved by the crude product NMR spectra. The detailed NMR measurements adequately showed that the isolated products are the corresponding condensed quinazoline derivatives **30 b** and **32 b**.

As it was proved experimentally and supported by theoretical calculations, the regioselectivity of the [4 + 2] cycloaddition is influenced by the structure of the starting bifunctional compounds. Namely, starting from aminodiols (**4**), *trans*-naphthoxazines (**8 a, 14 a and 17 a**) were formed, while diaminonaphthol (**25**) led to the formation of *cis*-quinazolines (**28 b,**

30b, and **32b**). It was surmised that this undesired selectivity resulted from the relative stability of the *o*-QM intermediates. Therefore, the relative energy for the pair of *o*-QMs (**5a**, **5b**) and (**27a**, **27b**) were calculated.

In the case of o-QMs **5a** and **5b**, **5b** was found to have about 10 kcal/mol lower energy compared with **5a**. This finding is in complete agreement with our experimental result that the naphtholic hydroxyl group is participating in the cycloaddition reaction, *i.e.*, the reaction leads to the formation of the naphthoxazines.

Comparing the energy values calculated for **27a** and **27b**: *o*-QM **27b** was found to have lower energy (about 9 kcal/mol) than the *aza*-*o*-QM **27a**. This result cannot explain the fact that quinazolines were found experimentally to be the single products. It means that in this case the higher nucleophilicity of the amino group compared with naphtholic hydroxyl group overwrite the theory that only the relative stability of *o*-QMs is influencing the outcome of the cycloaddition reaction.

2.2. Structural and Conformational Analysis

The complete NMR of the educts shows different structures with different ring formations depending on the starting material **4**, with an OH group, or **25** with an NH_2 group at *ortho* position. All products starting from **4** showed the same regioselectivity and stereochemistry while those starting from **25** were found to have different regio- and stereoselectivity, but the same within the series. This will be shown by compounds **16a,b** or **17a,b** and **32a,b** or **33a,b**, selected as examples. For the corresponding structure elucidation, both the NMR spectra (chemical shift, coupling constants, NOE's) and quantum chemical calculations are examined.

To get the preferred regio- and stereoisomers of **16a,b** or **17a,b** and **32a,b** or **33a,b** the *trans/cis* diastereomers (RS/SR and RR/SS) of the regioisomers were calculated by the DFT method. Both the most stable structures and the corresponding energy differences are given in Figure 2; hereby, **17a** and **32b**, respectively, could be identified to be the most stable structures. Energy differences around 1 kcal / mol to the next coming structure are rather unequivocal. Consequently, structures of *trans*-isomer **17a** and of *cis*-isomer **32b** were compared with available experimental NMR [$\delta(^1H)$/ppm, $\delta(^{13}C)$/ppm, $^nJ_{H,H}$/Hz)] and spatial NMR information (NOEs).

First, all ^1H and ^{13}C NMR chemical shifts for **17** could be unequivocally assigned. Hereby, the OH-bearing positions 6a and 1′ are crucial, and the AX spin system of H-5 and H-6 protons can serve as useful starting point. It is the only spin system of aromatic protons with two doublets and the characteristic *ortho*-coupling constant of *ca.* 9 Hz.[7,24] The low-field doublet (at 7.72 ppm) was assigned to the H-5 proton. The long-range coupling constant of the H-5 proton to the ^{13}C signal of C-6a (at 151.0 ppm) unequivocally assigns this carbon atom and can serve as entry into the sequence of ^{13}C signals: Thus, the other OH-bearing carbon atom C-1′ must have the chemical shift of 156.7 ppm. Based on this entry, assignment of the other aromatic carbon atoms using direct and long-range connectivities can be easily realized.

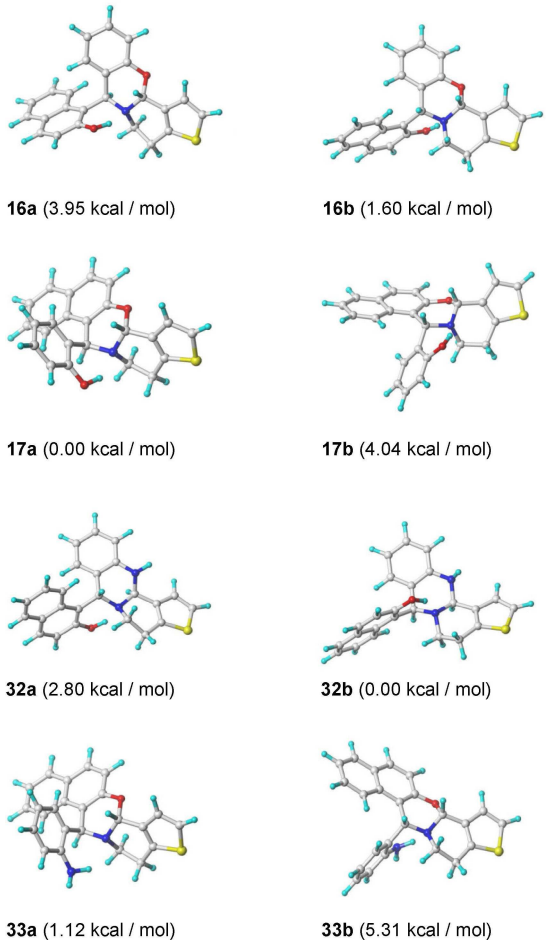


Figure 2. The most stable structures of the regioisomeric (**16** or **17**; **32** or **33**) heterocycles including their *trans* (**a**) and *cis* (**b**) diastereomeric possibilities.

Another ^1H NMR and the HMBC spectrum were recorded in [D_6]DMSO as solvent to stabilize the OH-group. Along the analysis, long-range connectivities between OH and the carbons at positions 1′, 2′, and 5′a, respectively, together with a medium NOE between H-7a and H-8 (2.85 Å from quantum chemical calculations) unambiguously lead to the regioisomer **17**. Some more representative long-range connectivities corroborate this structure: From H-14 to carbons C-1′, C-5′a, C-6a, C-14a, and C-14b; from H-5 to C-4, C-6a, and C-14b, and from H-8 to C-7a, C-7b and C-10a, respectively. In addition, the obtained NOE's agree only with the stereochemistry of **17a**: the protons H-7a and H-14 are in *trans* position. The corresponding NOE's do support this conclusion: strong NOE between H-1 and H-14 (2.17 Å), medium NOE between H-1 and H-5′ (3.14 Å) and the weak NOE between H-7a and H-11eq (4.52 Å), respectively (*cf.* Table 3).

Starting from aniline derivative **25**, instead of the phenol analogue **4**, another type of ring closure was observed. Again, for exemplary purposes, the stereochemical analysis is described for compound **32**. The two low-field ^{13}C NMR signals at 155.5 and 142.2 ppm, respectively, can be easily assigned to the

Table 3. Computed distances and measured NOE's for **32b**.

Positions	computed distances (Å)	NOE
H-11/H-12	2.81	Medium
H-11/H-11b	3.14	Medium
H-8ax/H-12	4.42	Weak
H-7eq/H-5	2.78	Medium
H-7ax/H-5	2.51	Strong
H-7eq/H-12	4.89	Weak
H-7ax/H-11b	2.54	Strong
H-5/H-4	2.97	Medium
H-5/H-12	4.28	Weak
H-5/H-11b	2.44	Strong
H-5/H-8′	1.92	Strong
H-4/H-8′	2.89	Medium
H-12/H-11b	2.91	Medium

two heteroatom bearing aromatic carbons: 155.5 ppm is assigned to the C-2′ signal due to the higher electronegativity of oxygen in comparison with nitrogen (C-12a: 142.2 ppm). This is corroborated by long-range connectivities between H-4′ and C-2′, and between H-5 and C-12a. A $^{3}J_{H\text{-}16b,H\text{-}12}$ coupling constant of 5.8 Hz and long-range connectivities of the OH proton to C-2′, C-3′ and C-4′ (weak), respectively, support only the presence of regioisomer **32**. A strong NOE between H-5 and H-11b (calculated distance: 2.44 Å) confirms additionally the *cis* configuration of H-5 and H-11b. Actually, **32b** proves to be the only possible configuration, where the calculated distances fit with the experimentally determined NOE's (see Table 3).

Interestingly, in both compounds a large difference in the ^{1}H NMR chemical shifts between H-1 and H-5′ (in **17a**) and between H-8′ and H-4 (in **32b**) was observed. These extremely large chemical shift differences of $\Delta\delta = 1.04$ ppm in the first and $\Delta\delta = 1.62$ ppm in the latter case correspond to their computed different distances of 3.14 Å and 2.89 Å, respectively. This points to strong steric compression within the corresponding fragments. In addition, the influence of ring current effects of the present aromatic moieties in **17a** and **32b** can be expected (see **2.4.**).

The same *trans* configuration as in **17a** was found in the stereochemically analogous β-carboline **8a** and isoquinoline derivatives **14a**, and the *cis* configuration as in **32b** was also found in the structurally analogous new *N,N*-heterocyclic compounds **30b** and **28b**, respectively.

2.3. ^{1}H and ^{13}C NMR Spectra of 12*H*-Benzo[*a*]xanthen-12-one (11)

The ^{13}C chemical shifts of the carbon atoms in 12*H*-benzo[*a*]xanthen-12-one (**11**)[25] (*cf.* Figure 3) were found as expected. That is, the aromatic *C*-H carbon atoms resonate in the common range for this kind of carbons ($\delta = 117.8$ to 136.9 ppm) and do so the quaternary carbon atoms at $\delta = 114.7$ to 131.4 ppm. Out of this absorption range are only the carbons bound directly to oxygen ($\delta = 155.0$ and 157.9 ppm, respectively), and the carbonyl carbon itself ($\delta = 178.5$ ppm). In contrast, a similar general conclusion cannot be drawn from the analysis of the corresponding ^{1}H NMR spectrum of **11**. The aromatic protons

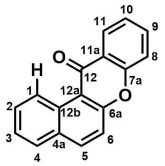


Figure 3. 12H-benzo[*a*]xanthen-12-one **11**

resonate in a completely normal way ($\delta = 7.47$ to 8.41 ppm) [with expected H,H-coupling values ($J_{ortho} = 7.5$ to 8.5 Hz, J_{meta} and $J_{para} < 1.5$ Hz)] except for H-1 ($\delta = 10.06$ ppm). This proton chemical shift of H-1 is widely outside of the resonance range of aromatic protons; usually only aldehyde protons can be expected so far low-field shifted. Therefore, the structure elucidation of **11** was far from ordinary. Finally, the DFT/GIAO calculation of this shift values ($\delta_{calc} = 10.9$ ppm) and reference 25 cleared up the present structure.

There are two reasonable but controversial reasons for this low-field position of H-1 in 12*H*-benzo[*a*]xanthen-12-one **11** out of the resonance range for aromatic protons:

(i) The combined ring current effect of the C-7a to 11a phenyl residue and the anisotropy effect of the carbonyl moiety.
(ii) *Steric compression* within the heavily hindered H(1)-C(1)-C(12b)-C(12a)-C(12)=O structural fragment. In this latter case, consequences on both the involved bond lengths and bond angles can be expected.

For this reason, the structure, the NMR chemical shifts (*vide supra*), and the spatial magnetic properties of 12*H*-benzo[*a*]xanthen-12-one **11** have been calculated (*cf.* Figure 4). We

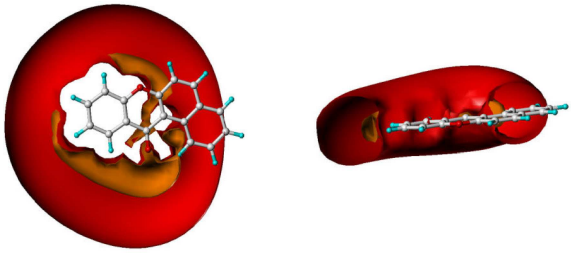


Figure 4. Visualization[26–28] of the in-plane spatial magnetic properties (TS NMRS) of 12*H*-benzo[*a*]xanthen-12-one (**11**) by the ICSS of −0.5 ppm (orange) and −0.1 ppm (red) *deshielding*.

employed our through-space NMR shielding concept (TS NMRS)[26–28] to qualify and quantify the spatial magnetic properties (actually, the familiar concept of anisotropy/ring current effect in ^{1}H NMR spectroscopy) of the studied conjugated species. Along this concept,[26–28] the TS NMRS are calculated as NICS values[29–30] for a grid of ghost atoms surrounding the molecules in order to locate diatropic and paratropic regions around the molecules. The TS NMRS values are visualized as iso-chemical-shielding surfaces (ICSS) of resulting NICS and were already employed to visualize and quantify the anisotropic effects of functional groups and the ring current effect of aromatic species and, hereby, present

(anti)aromaticity.[26–28] Specifications normally employed from magnetic point of view to quantify, *e.g.*, (anti)aromaticity, are theoretical non-measurable items:[31] single NICS values or components of the latter, or traces of NICS or components of the latter starting from the centre of the (anti)aromatic compound up to 10 Å outwards. Experimental $\Delta\delta$/ppm in proton NMR spectra, in turn, are the molecular response property of our TS NMRS values.[32–34] For this latter reason, the spatial magnetic properties (TS NMRS values) of 12*H*-benzo[*a*]xanthen-12-one **11** (and, *vide infra*, of the preferred conformers/diastereomers of the new *O,N*- and *N,N*-heterocycles) have been calculated and examined with respect to (i) the combined ring current effect of the C-7a to 11a phenyl residues and the anisotropy effect of the carbonyl moiety on the chemical shift of H-1 in **11** (*cf.* Figure 4). Proton H-1 is positioned within the deshielding belt [(ICSS) of −0.5 ppm (orange) and −0.1 ppm (red) deshielding] of this completely planar molecule; the exact value is −0.51 ppm deshielding.

Thus, the combined ring current effect of the C-7a to C-11a phenyl residue together with the anisotropy effect of the carbonyl moiety deshields the H-1 proton by about 0.5 ppm only. It remains a deshielding effect at least of *ca.* 1.5 ppm which must come from other resources, and this can be only (ii) *steric compression* within the heavily hindered H(1)-C(1)-C(12b)-C(12a)-C(12)=O structural fragment. From NMR spectra we have no direct access but the calculation of the structure of **11** indicates the corresponding consequences on both involved bond lengths and bond angles in **11**. The C(1)-H(1) bond length is shortened (normally 1.085 to 1.082 Å) and bond angles $<$C(12a,C(12b),C(1)=123.3°, $<$C(12),C(12a),C(12b)=123.6° and $<$O,C(12),C(12a)=124.7° are widened and document hereby, the steric hindrance in the studied H(1)-C(1)-C(12b)-C(12a)-C(12)=O structural fragment. Because ring current/anisotropy effects on H-1 is quantified to *ca.* −0.5 ppm deshielding for the present steric compression effect on $\delta(^1H)$/ppm at least *ca.* 1.5 ppm deshielding can be concluded. It is no surprise that for *steric compression* in **11** the value obtained was about the same as that in 11-ethynylphenanthrene.[35] The 11-ethynylphenanthrene molecule was employed to quantify the anisotropic effect of the –C≡C– triple bond, which should be −1.57 ppm deshielding around the triple bond. However, when employing our TS NMRS approach[26–28] we found that this effect is rather pretty showing only −0.06 ppm deshielding. The difference to −1.57 ppm deshielding results from *steric compression* within the 11-ethynylphenanthrene molecule.

2.4. Spatial Magnetic Properties (TS NMRS) of Preferred Regioisomers/diastereomers of the New *O,N*- and *N,N*-Heterocycles

The result of the NMR spectroscopic stereochemistry analysis of the reaction products of the studied [4+2] cycloaddition of the highly functionalized aminonaphthol derivatives (**4**, **19**, and **25**, respectively) *via* the *o*-QM intermediates (**5**, **20**, and **27**, respectively) proved to be unequivocal. Namely, in each case, when reacting various representative cyclic imines (**6**, **12**, and **15**, respectively) with **4** and **9**, the formation of one single product could be reported, which was unequivocally assigned to be the *trans* diastereomer for **8a**, **14a**, **17a** and **22a**. Furthermore, in the case of heterocycles formed starting from **25**, the relative *cis* configurations (**28b**, **30b** and **32b**) were assumed. As examples, both *O,N*-heterocycles **14a** and **17a** and *N,N*-heterocycles **30b** and **32b** were studied by our TS NMRS approach[26–28] (i) to prove the assigned diastereomers (*vide supra*) from the spatial magnetic point of view, and (ii) to find a simple NMR spectroscopic tool to readily differentiate the diastereomers.

In Figure 5, TS NMRSs of the preferred *trans* diastereomer **17a** are visualized by ICSS of 1 ppm (greenblue) and 0.5 ppm

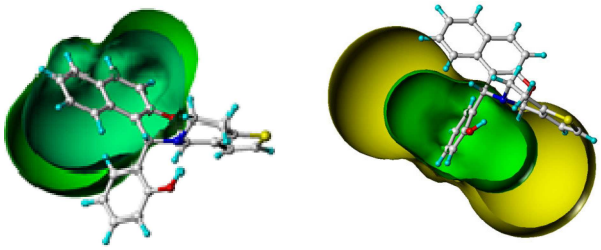


Figure 5. Visualization[26–28] of the spatial magnetic properties (TS NMRS) of both the naphthyl moiety (left) and of the phenol moiety of polyheterocycle **17a** by different ICSS of 1 ppm (greenblue), 0.5 ppm (green) and 0.1 ppm (yellow) *shielding*.

(green) *shielding* (for the ring current effect of the naphthyl moiety) and by ICSS of 0.5 ppm (green) and 0.1 ppm (yellow) *shielding* (for the ring current effect of the phenol moiety). In Figure 6, the corresponding TS NMRSs of the preferred *cis* diastereomer **32b** are visualized. In this case, because of additional influence, TS NMRS of the phenyl moiety are visualized by ICSS of −0.1 ppm (red) *deshielding*. Identical TS NMRS visualizations were obtained for **14a** and **30b** (*cf.* Table 4).

In **17a**, the naphthyl ring current effect on the phenoxy protons H-4′/5′ is *shielding* and it is extraordinarily large on the adjacent proton H-5′. The corresponding naphthyl protons H-1/2 are less affected (0.28 and 0.12 ppm *shielding*). The reversed effect is observed on the chemical shifts of the corresponding *trans* diastereomer protons: *shielding* on the protons of the phenyl moiety (H-3/4). The naphthoxy protons are less effected

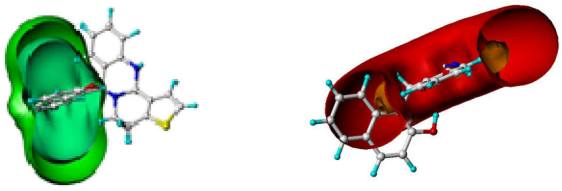


Figure 6. Visualization[26–28] of the spatial magnetic properties (TS NMRS) of both the naphthyl moiety (left) and of the phenol moiety of polyheterocycle **32b** by different ICSS of 1 ppm (greenblue) and 0.5 ppm (green) *shielding*, and −0.1 ppm (red) *deshielding*.

Table 4. Ring current effects of the phenyl/naphthyl moieties on protons H-1/2 and H-4′/5′ in **17 a**, and of the naphthyl/phenyl moieties on H-3/4 and H-7′/8′ in **32 b** as compared with the chemical shifts δ/ppm of the corresponding protons (in brackets).

Compd.	Ring current effects Δδ/ppm on				Ring current effects Δδ/ppm on			
	H-5′	H-4′	H-1	H-2	H-4	H-3	H-8′	H-7′
14 a	1.33 (6.51)	0.35 (6.65)	0.28 (7.41)	0.12 (7.37)				
17 a	1.34 (6.38)	0.35 (6.55)	0.28 (7.42)	0.12 (7.33)				
30 b					0.98 (6.54)	0.37 (6.57)	-0.24 (8.16)	-0.08 (7.57)
32 b					1.00 (6.45)	0.37 (6.48)	-0.23 (8.07)	-0.08 (7.48)

and it is even *deshielding* (−0.24 to −0.08 ppm). Identical results have been obtained for **14 a** and **30 b**, respectively (*cf.* Table 4).

The differences in the ring current effects [as calculated from TS NMRS values (*cf.* Table 4)], as being active in the diastereomers, are reproduced by the chemical shifts in the compounds studied. This is in no case remarkable. The experimental proton chemical shift δ(^{1}H)/ppm is the molecular response property of the spatial magnetic properties TS NMRS (*e.g.*, the anisotropy/ring current effect).[33–34] Both the chemical shift difference between the phenyl protons in the *cis* (**17 a**) and the *trans* diastereomer (**32 b**) [Δδ(H-5′-H-4) = 0.07 ppm, Δδ(H-4′-H-3 = −0.07 ppm] and the calculated ring current effects [Δδ(H-5′-H-4) = -0.34 ppm, Δδ(H-4′-H-3 = + 0.02 ppm] are comparable. In turn, the corresponding differences in Δδ(^{1}H)/ppm of the naphthyl protons are fairly different [Δδ(H-1-H-8′) = 0.65 ppm, Δδ(H-2-H-7′) = 0.15 ppm] in complete agreement with the calculated ring current effects [Δδ(H-1-H-8′) = 0.52 ppm, Δδ(H-2-H-7′) = 0.20 ppm]. Thus, the proton chemical shifts of the naphthyl protons can readily serve as simple indication of the present diastereomerism: H-7′ and H-8′ in the *cis* diastereomer are low field shifted with respect to H-1 and H-2 in the *trans* analogue. Thanks to TS NMRS (the ring current effects), the *cis*/*trans* diastereomers of the new *O*,*N*- and *N*,*N*-heterocycles can be simply differentiated.

3. Conclusions

Starting from salicylaldehyde and 2-naphthol or 6-hydroxyquinoline in the presence of morpholine, functionalized Mannich bases could be synthesized that served two different types of *o*-QM intermediates. While the relative stability of the formed *o*-QM intermediates was postulated to influence the formation of the products in the subsequent [4 + 2] cycloaddition, the highly functionalized aminodioles were reacted under heating with different cyclic imines such us 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, and 3,4-dihydro-β-carboline. The latter reactions were found to be diastereo- and regioselective leading to *trans* naphthoxazine. Its structure was proved by DFT computed structures in comparison with the experimental ^{1}H/^{13}C-NMR spectra, and a detailed analysis of the spatial magnetic properties of the preferred diastereomers.

Mannich base **25** was synthesized as a unique substrate that was formed after thermal elimination *o*-QM and *aza*-*o*-QM. The functionalized diaminonaphthol was tested in [4 + 2] cycloaddition with cyclic imines **6**, **12**, and **15**. The regio- and diastereoselectivity of the reactions were proved by the same computational and ^{1}H/^{13}C NMR analysis; *cis*-quinazolines were isolated as single products.

The relative stability of *o*-QMs/*aza*-*o*-QM was examined by calculating their relative energies. The obtained results (**5 b** is more stable than **5 a**) supported completely the experimental findings, that naphthoxazines are formed during the cycloaddition reactions when aminodiole **4** was the starting compound. When diaminonaphthol **25** was applied as precursor, the regioselectivity of the reaction was found to be driven by the higher nucleophilicity of the amino group compared with the hydroxyl group.

During the synthesis and/or transformation of the functionalized aminonaphthols, unexpected heterocycles were achieved. Their formations were explained by the aim of the formed *o*-QMs and/or *aza*-*o*-QM and can be recommended as useful synthetic methods for benzo[*a*]xanthen-12-ones and benz[*a*]acridines, respectively.

Along the reaction of the *o*-QM intermediates **5 a,b** with dienophile 3,4-dihydro-β-carboline at higher temperatures (*e.g.*, 100 °C), 12*H*-benzo[*a*]xanthen-12-one **11** could be isolated as side product. The extreme low-field position of proton H-1 [δ(^{1}H) = 9.97 ppm] in **11** proved to be unusual and could be verified and quantified to be a combination of the paramagnetic ring current effect of the aromatic residues (together with the anisotropy effect of the carbonyl group, respectively) and steric compression within the heavily hindered H(1)-C(1)-C(12b)-H(12a)-C(12) = O structural fragment.

Experimental Section

Melting points were determined on a Hinotek X-4 melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor.

The used starting cyclic imines 4,9-dihydro-β-carboline[15] (**6**), 3,4-dihydroisoquinoline[21] (**12**), and 6,7-dihydrothieno[3,2-*c*]pyridine[22] (**15**) were synthesized according to the process known from the literature.

Quantum chemical calculations were performed using the Gaussian 09 program package[36] and carried out on LINUX clusters. The various different conformations and configurations of the studied compounds were optimized.[36] The B3LYP density functional method was selected for all calculations. The method is based on Becke's three-parameter hybrid functionals[37] and the correlation functional of Lee, Yang and Parr.[38] All optimizations were carried out without any restriction at this B3LYP/6-311G(d,p) level of theory.[39–40] NICS values[41] were computed using the gauge-including atomic orbital (GIAO) method[42–43] at the B3LYP/6-311G (d,p) theory level. Visualization was carried out with the modelling software SYBYL-X.[44]

The ^{1}H and ^{13}C NMR spectra were recorded in CD_2Cl_2 or [D_6]DMSO solution in 5 mm tubes at room temperature, on a Bruker Avance III

spectrometer at 600.13 (^{1}H) and 150.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. All spectra (^{1}H, ^{13}C, gs-H, H-COSY, edited HSQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER software.

1-[(2-Hydroxyphenyl)-morpholin-4-yl-methyl]-2-naphthol (4)

2-Naphthol (2.0 g, 13.88 mmol), salicylic aldehyde (1.7 g, 13.90 mmol) and morpholine (1.21 g, 13.90 mmol) were stirred and heated at 80 °C under neat conditions for 5 h. Dichloromethane (100 ml) and water (100 ml) were added to the mixture that was then extracted with 2% hydrochloric acid. After separation of the fractions, the aqueous phase was alkalized with Na_2CO_3 and extracted with dichloromethane (2×70 ml). The organic fractions were collected, dried with anhydrous Na_2SO_4, filtered and then the solvent was removed under reduced pressure. The residue was crystallised with *n*-hexane (15 mL) and recrystallized from *i*Pr_2O (10 mL) R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 2.89 g (62%).

Beige crystals; m.p. 107–109 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.57 (m, 1H, H-2″), 3.09 (m, 1H, H-2″), 3.62 (m, 1H, H-3″), 3.84 (m, 1H, H-3″), 5.84 (br s, 1H, H-8b), 6.80 (t, 7.7 Hz, 1H, H-5′), 6.82 (d, 8.1 Hz, 1H, H-3′), 7.10 (t, 7.8 Hz, 1H, H-4′), 7.13 (d, 8.9 Hz, 1H, H-3), 7.23 (t, 7.6 Hz, 1H, H-6), 7.35 (t, 7.9 Hz, 1H, H-7), 7.44 (dd, 7.8, 1.6 Hz, 1H, H-6′), 7.69 (d, 9.0 Hz, 1H, H-4), 7.71 (d, 8.7 Hz, 1H, H-5), 7.92 (d, 8.5 Hz, 1H, H-8), 13.50 (br s, 1H, 2-OH);^{13}C NMR (CD_2Cl_2): δ = 54.0 (br, C-2″), 62.8 (br, C-8b), 66.9 (C-3″),115.7 (2 C, br, C-1, C-3′), 119.9 (C-3), 121.6 (br, C-5′), 121.7 (C-8), 122.9 (C-6), 125.2 (br, C-1′), 126.8 (C-7), 128.9 (C-5), 129.0 (C-4a), 129.5 (C-4′), 129.6 (C-4), 130.5 (br, C-6′), 133.1 (C-8a), 154.0 (C-2′), 155.8 (C-2); elemental analysis calcd (%) for $C_{21}H_{21}NO_3$ (335.40) : C 75.20, H 6.31, N 4.18; found: C 75.16, H 6.34, N 4.13.

General Procedure for the Synthesis of Naphthoxazines (8 a, 14 a, and 17 a)

A mixture of the appropriate aminonaphthol **4** (40 mg 0.12 mmol), 4,5-dihydro-3*H*-benz[*c*]azepine **12** (26 mg, 0.18 mmol), 6,7- dihydrothieno[3,2-*c*]pyridine **15** (24 mg, 0.18 mmol), 3,4-dihydro-β-carboline **6** (30 mg, 0.18 mmol) in 1,4-dioxane (5 mL) was placed in a 10 mL pressurized reaction vial and heated in a CEM SP microwave reactor under the conditions given in Table 1. The solvent was removed *in vacuo,* and the residue was isolated by crystallization with MeOH (5 mL).

7a*R**,16*S**-17-(2-Hydroxyphenyl)-naphth[1,2-*e*]oxazino-[2,3-*a*]-β-carboline (8 a)

Recrystallized from *i*Pr_2O (5 mL); R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 44 mg (89%). Light brown crystals; m.p. 216–217 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.97 (dd, *J* = 15.8, 3.5 Hz, 1H, H-13), 3.19 (ddd, *J* = 15.6, 12.1, 5.7 Hz, 1H, H-13), 3.35 (m, 2H, H-14), 5.84 (s, 1H, H-16), 5.99 (s, 1H, H-7a), 6.48 (d, *J* = 7.5 Hz, 1H, H-5′), 6.65 (t, *J* = 7.3 Hz, 1H, H-4′), 6.90 (d, *J* = 7.9 Hz, 1H H-2′), 7.08 (d, *J* = 8.9 Hz, 1H, H-6), 7.14 (t, *J* = 7.5 Hz, 1H, H-11), 7.18 (t, *J* = 7.2 Hz, 1H, H-3′), 7.23 (t, *J* = 7.6 Hz, 1H, H-10), 7.39 (m, 2H, H-3, H-9), 7.44 (t, *J* = 7.5 Hz, 1H, H-2), 7.54 (d, *J* = 8.3 Hz, 1H, H-1), 7.57 (m, 1H, H-12), 7.81 (d, *J* = 8.9 Hz, 1H, H-5), 7.85 (d, *J* = 7.9 Hz, 1H, H-4), 8.23 (br s, 1H, H-8), 9.52 (br s, 1H, H-1′);^{13}C (CD_2Cl_2): δ = 22.3(C-13), 45.3(C-14), 60.4(C-16), 77.3(C-7a), 109.4(C-16a), 110.8(C-12b), 111.7(C-9), 117.5(C-2′), 118.6(C-6), 119.3(C-12), 119.9(C-4′), 120.1(C-11), 122.5(C-1), 123.3(C-10), 124.0(C-3), 125.5(C-5a′), 126.2(C-12a), 127.3(C-2), 128.9(C-4),129.2(C-4a), 129.7(C-3′), 129.8(C-7b), 130.1(C-5), 130.7(C-5′), 132.8(C-16b), 150.8(C-6a), 156.9(C-1′); elemental analysis calcd (%) for $C_{28}H_{22}N_2O_2$ (418.50): C 80.36, H 5.30, N 6.69; found: C 80.41, H 5.27, N 6.74.

7a*R**,15*S**-15-(2-Hydroxyphenyl)-naphth[1,2-*e*]oxazino[2,3-*a*]-isoquinoline (14 a)

Recrystallized from *i*Pr_2O (6 mL); R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 40 mg (87%). White crystals; m.p. 206–207 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.96 (m, 1H, H-12), 3.17 (m, 1H, H-13), 3.31 (m, 2H, H-12, H-13), 5.74 (s, 1H, H-15), 5.80 (s, 1H, H-7a), 6.51 (d, *J* = 7.6 Hz, 1H, H-5′), 6.65 (t, *J* = 7.4 Hz, 1H, H-4′), 6.89 (t, *J* = 8.0 Hz, 1H, H-2′), 7.08 (d, *J* = 8.9 Hz, 1H, H-6), 7.17 (t, *J* = 7.3 Hz, 1H, H-3′), 7.25 and 7.37 (2xm, 2x2H, H-8, H-9, H-10, H-11), 7.37 (m, 1H, H-3), 7.41 (t, *J* = 7.1 Hz, 1H, H-2), 7.50 (d, *J* = 8.3 Hz, 1H, H-1), 7.80 (d, *J* = 8.9 Hz, 1H, H-5), 7.83 (d, *J* = 7.9 Hz, 1H, H-4), 9.56 (br s, 1H, H-1′);^{13}C NMR (CD_2Cl_2): δ = 29.3(C-12), 43.9(C-13), 60.8(C-15), 81.5(C-7a), 109.1(C-15a), 117.4(C-2′), 118.8(C-6), 119.9(C-4′), 122.7(C-1), 123.9(C-3), 125.7(C-5a′), 126.6(C-10 or C-9), 127.2(C-2), 128.8(C-4), 129.1(C-8), 129.1(C-11), 129.2(C-4a), 129.5(C-9 or C-10), 129.6(C-3′), 130.1(C-5), 130.8(C-5′), 132.5(C-7b), 132.9(C-15b), 134.4(C-11a), 151.2(C-6a), 156.8(C-1′), elemental analysis calcd (%) for $C_{26}H_{21}NO_2$ (379.46):C 82.30, H 5.58, N 3.69; found: C 82.26, H 5.60, N 3.74.

7a*R**,14*S**-14-(2-Hydroxyphenyl)-naphth[1,2-*e*]oxazino[2,3-*a*]-thieno[3,2-*c*]pyridine (17 a)

Recrystallized from *i*Pr_2O (5 mL); R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 43 mg (92%). Light brown crystals; m.p. 186–187 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.93 (m, 1H, H-11), 3.20 (m, 3H, H-11, H12), 5.69 (s, 1H, H-14), 5.74 (s, 1H, H-7a), 6.38 (d, *J* = 7.6 Hz, 1H, H-5′), 6.55 (t, *J* = 7.4 Hz, 1H, H-4′), 6.81 (t, *J* = 7.9 Hz, 1H, H-2′), 6.89 (d, *J* = 5.1 Hz, 1H, H-8), 7.00 (d, *J* = 8.9 Hz, 1H, H-6), 7.09 (t, *J* = 7.6 Hz, 1H, H-3′), 7.12 (d, *J* = 5.1 Hz, 1H; H-9), 7.28 (t, *J* = 7.3 Hz, 1H, H-3), 7.33 (t, *J* = 7.2 Hz, 1H, H-2), 7.42 (d, *J* = 8.2 Hz, 1H, H-1), 7.72 (d, *J* = 9.0 Hz, 1H, H-5), 7.75 (d, *J* = 7.9 Hz, 1H, H-4), 9.42 (br s, 1H, H-1′);^{13}C NMR (CD_2Cl_2): δ = 26.1(C-11), 44.6(C-12), 60.4(C-14), 78.3(C-7a), 109.1(C-14a), 117.5(C-2′); 118.7(C-6), 119.9(C-4′), 122.5(C-1), 123.9(C-3), 124.3(C-9), 125.6(C-5a′), 126.0(C-8), 127.3(C-2), 128.8(C-4), 129.2(C-4a), 129.7(C-3′), 130.1(C-5), 130.8(C-5′), 133.0(C-7b), 132.8(C-14b), 137.7(C-10a), 151.0(C-6a), 156.7(C-1′), elemental analysis calcd (%) for $C_{24}H_{19}NO_2S$ (385.48): C 74.78, H 4.94, N 3.63; found: C 74.82, H 4.92, N 3.69.

12*H*-Benzo[*a*]xanthen-12-one (11)

Aminonaphthol **4** (40 mg, 0.12 mmol), was heated with 2 equivalent of Et_3N (24.2 mg, 0.24 mmol) in 1,4-dioxane (5 mL) at 100 °C for 2 hour under microwave irradiation. The residue was purified by column chromatography (n-hexane: EtOAc, 3:1); 21 mg (71%); White solid; mp 144–146 °C (Lit.:[16] mp 145–146 °C).

5-[(2-Hydroxyphenyl)-morpholin-4-yl-methyl]-quinolin-6-ol (19)

6-Hydroxyquinoline (1.0 g, 6.88 mmol) was reacted with salicylic aldehyde (0,84 g. 6,88 mmol) in the presence of morpholine (0,60 g, 6.88 mmol). The reaction was stirred for 6 h at 80 °C, under neat conditions. The desired product was isolated by crystallization with *n*-hexane (10 ml) and recrystallized from *i*Pr_2O (8 mL). R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 1.64 g (71%). Brown crystals; m.p. 196–197 °C. ^{1}H NMR ([D_6]DMSO): δ = 2.44 (br s, 2H, H-2″), 3.67 (br s, 2H, H-3″), 5.71 (s, 1H, H-8b), 6.70 (t, 7.4 Hz, 1H, H-5′), 6.90 (d, 8.0 Hz, 1H, H-3′), 7.06 (t, 7.8 Hz, 1H, H-4′), 7.26 (d, 7.6 Hz, 1H, H-6′), 7.32 (d, 9.1 Hz, 1H, H-3), 7.38 (dd, 8.6, 4.1 Hz, 1H, H-7), 7.81 (d, 9.1 Hz, 1H, H-4), 8.26 (d, 8.4 Hz, 1H, H-8), 8.62 (d, 4.2 Hz, 1H, H-6), 10.20 (s, 1H, OH), 13.45 (s, 1H, OH); ^{13}C NMR ([D_6]DMSO): δ = 50.7 (br, C-2″), 61.7 (C-8b), 66.2 (C-3″),115.6 (C-3′), 115.9 (C-1), 120.0 (C-5′), 121.4 (C-7), 123.0 (C-3), 124.5 (C-1′), 127.4 (C-8a), 128.8 (C-6′), 129.2 (C-3′), 129.4 (C-8), 130.0 (C-4), 143.3 (C-4a), 146.7 (C-6), 154.7 (C-2′), 155.2 (C-2); elemental

analysis calcd (%) for $C_{20}H_{20}N_2O_3$ (336.39): C 71.41, H 5.99, N 8.33; found: C 71.48, H 5.96, N 8.37.

7a*R**,15*S**-15-(2-Hydroxyphenyl)-isoquinolino[1′,2′:2,3][1,3]-oxazin-o[5,6-f]quinolin (22 a)

Aminoquinolinol **19** (40 mg, 0.12 mmol), dihydroisoquinoline **12** (23 mg, 0.18 mmol) and 1,4-dioxane (5 mL) were placed in a 10 mL reaction vial and heated in a CEM microwave reactor under the conditions given in Table 1. The solvent was removed *in vacuo,* and the residue was isolated by crystallisation from MeOH (5 mL) and recrystallized from iPr_2O (10 mL). R_f = 0.38 (*n*-hexane/ EtOAc, 2:1); 34 mg (90%). Light brown crystals; m.p. 208–209 °C; ^{1}H NMR ([D_6] DMSO): δ = 2.84 (br d, *J* = 16.0 Hz, 1H, H-12), 3.05 (ddd, *J* = 16.7, 8.6, 8.6 Hz, 1H, H-12), 3.16 (m, 2H, H-13), 5.78 (s, 2H, H-7a, H-15), 6.61 (t, *J* = 7.0 Hz, 1H, H-4′), 6.66 (m, 1H, H-5′), 6.93 (d, *J* = 7.7 Hz, 1H, H-2′), 7.09 (t, *J* = 8.0 Hz, 1H, H-3′), 7.24 and 7.33 (2 x m, 2H and 1H, H-9, H-10, H-11), 7.34 (d, *J* = 9.2 Hz, 1H, H-6), 7.36 (dd, *J* = 8.5, 4.1 Hz, 1H, H-2), 7.41 (br d, *J* = 7.6 Hz, 1H, H-8), 7.63 (br d, *J* = 7.9 Hz, 1H, H-1), 7.89 (d, *J* = 9.2 Hz, 1H, H-5), 8.68 (dd, *J* = 4.2-1.6 Hz, 1H, H-3), 9.84 (br s, 1H, H-1′); ^{13}C NMR ([D_6]DMSO): δ = 28.5(C-12), 44.5(C-13), 55.9(C-15), 82.0(C-7a), 111.3(C-15a), 115.6(C-2′), 118.4(C-4′), 121.5(C-2 or C-6), 121.9(C-6 or C-2), 125.9(C-9), 126.5(C-15b), 128.5(C-10 or C-11), 128.7(C-3′), 128.8(C-5a′), 128.9(C-8), 128.9(C-11 or C-10), 129.5(C-5′), 129.8(C-5), 130.4(C-1), 132.2(C-7b), 134.9 (C-11a), 143.9(C-4a), 147.3(C-3), 151.8(C-6a), 155.1(C-1′); elemental analysis calcd (%) for $C_{25}H_{20}N_2O_2$ (380.45): C 78.93, H 5.30, N 7.36; found: C 78.89, H 5.36, N 7.71.

1-[(2-Nitrophenyl)-morpholin-4-yl-methyl]-naphthalen-2-ol (24)

50 ml round-bottom flask was charged with 2-naphthol (0.72 g, 5 mmol), morpholine (0.48 g, 5.5 mmol) and 2-nitrobenzaldehyde (0.79 g, 5.25 mmol). The mixture was stirred and heated under solvent-free conditions at 70 °C for 6 hours. The mixture was purified by column chromatography (*n*-hexane: EtOAc, 2:1); 1.31 g (72%). Yellow crystals; m.p. 148–149 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.63 (dt, 11.8, 3.0 Hz, 1H, H-2″), 3.09 (d, 11.7 Hz, 1H, H-2″), 3.74 (dt, 11.7, 1.7 Hz, 1H, H-3″), 3.85 (t, 12.5 Hz, 1H, H-3″), 6.11 (s, 1H, H-8b), 7.13 (d, 8.9 Hz, 1H, H-3), 7.24 (ddd, 8.0, 6.9, 1.1 Hz, 1H, H-6), 7.36 (ddd, 8.6, 7.1, 1.5 Hz, 1H, H-7), 7.40 (dt, 7.8, 1.4 Hz, 1H, H-4′), 7.49 (dt, 7.7, 1.3 Hz, 1H, H-5′), 7.68 (d, 8.6 Hz, 1H, H-8), 7.71 (d, 8.1 Hz, 1H, H-5), 7.72 (d, 8.9 Hz, 1H, H-4), 7.85 (dd, 8.2, 1.3 Hz, 1H, H-3′), 7.88 (dd, 8.1, 1.5 Hz, 1H, H-6′), 13.46 (br s, 1H, 2-OH); ^{13}C NMR (CD_2Cl_2): δ = 54.0 (C-2″), 64.1 (C-8b), 66.9 (C-3″), 114.5 (C-1), 120.3 (C-3), 120.8 (C-8), 123.1 (C-6), 124.7 (C-3′), 127.3 (C-7), 129.0 (C-4a), 129.1 (C-5), 129.6 (C-4′), 130.6 (C-4), 131.5 (C-6′), 132.8 (C-8a), 133.0 (C-1′), 134.1 (C-5′), 150.6 (C-2′), 156.5 (C-2); elemental analysis calcd (%) for $C_{21}H_{20}N_2O_4$ (364.40): C 69.22, H 5.53, N 7.69; found: C 69.30, H 5.50, N 7.72.

1-[(2-Aminophenyl)-morpholin-4-yl-methyl]-naphthalen-2-ol (25)

(0.73 g, 2 mmol) of **24** was dissolved in 50 ml of EtOH and 0.2 g of 5% Pd/C catalyst was added. The mixture was hydrogenated at atmospheric pressure for 1 hour. After filtration of the catalyst, the solvent was removed and the residue was crystallized from Et_2O (30 mL) and recrystallized from iPr_2O (18 mL); 0.5 g (77%). Beige crystals; m.p. 133–134 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.51 (ddd, 12.1, 9.3, 3.1 Hz, 1H, H-2″), 2.97 (m, 1H, H-2″), 3.76 (t, 9.2 Hz, 1H, H-3″), 3.82 (m, 1H, H-3″), 4.12 (br s, 2H, 2′-NH_2), 5.28 (s, 1H, H-8b), 6.66 (t, 7.5 Hz, 1H, H-5′), 6.71 (d, 7.9 Hz, 1H, H-3′), 7.03 (t, 7.6 Hz, 1H, H-4′), 7.10 (d, 8.9 Hz, 1H, H-3), 7.23 (t, 7.5 Hz, 1H, H-6), 7.33 (d, 7.7 Hz, 1H, H-6′), 7.36 (ddd, 8.5, 7.0, 1.4 Hz, 1H, H-7), 7.68 (d, 9.0 Hz, 1H, H-4), 7.71 (,d, 8.2 Hz, 1H, H-5), 7.76 (d, 8.6 Hz, 1H, H-8), 13.37 (br s, 1H, 2-OH); ^{13}C NMR (CD_2Cl_2): δ = 53.9 (br, C-2″), 67.0 (C-3″),114.7 (br, C-1), 117.1 (C-3′), 119.7 (br, C-5′), 120.0 (C-3), 121.8 (C-8), 122.9 (C-6), 123.0 (br, C-1′), 126.8 (C-7), 129.0 (C-5), 129.0 (C-4a), 129.3 (C-4′), 129.8 (C-4), 130.6 (br, C-6′), 133.0 (C-8a), 145.0 (C-2′), 155.7 (C-2), C-8b could not be detected (very broad line); elemental analysis calcd (%) for $C_{21}H_{22}N_2O_2$ (334.17): C 75.42, H 6.63, N 8.38; found: C 75.45, H 6.60, N 8.37.

Benz[*a*]acridine (26)

The synthetic protocol applied to achieve **25** was repeated, and the reaction was driven till the formation of **26** (5 hours). After removal of the catalyst, the filtrate was concentrated under reduced pressure and the crude reaction mixture was purified by column chromatography (*n*-hexane:EtOAc, 2:1) resulting in **26** (0.32 g, (69%); Beige crystals; m.p. 129–130 °C (Lit.:[24] mp 130–131 °C).

General Procedure for the Synthesis of Quinazolines (28 b, 30 b and 32 b)

A mixture of diaminonaphtol **25** (67 mg 0.2 mmol) and 3,4-dihydro-β-carboline **6** (50 mg, 0.3 mmol), or 3,4-dihydroisoquinoline **12** (39.4 mg, 0.3 mmol) or 6,7-dihydrothieno[3,2-*c*]pyridine **15** (41.2 mg, 0.3 mmol), in 1,4-dioxane (5 mL) was placed in a 10 mL pressurized reaction vial and heated in a CEM SP microwave reactor under the conditions given in Table 2. The solvent was removed under reduced pressure and the residue was isolated by crystallization from MeOH and recrystallized.

5S,13bS**-7-(2-Hydroxynaphth-1-yl)-[2,3-*a*]-β-carbolino[2,1-*b*]-quinazoline (28 b)

Recrystallized from iPr_2O (6 mL); R_f = 0.38 (*n*-hexane/EtOAc 2:1); 76 mg (91%). Beige crystals; m.p 182–183 °C; ^{1}H NMR ([D_6]DMSO): δ = 2.71 (m, 1H, H-8), 2.79 (m, 1H, H-8), 2.80 (m, 1H, H-7), 3.09 (m, 1H, H-7), 5.27 (br s, 1H, H-13b), 6.10 (s, 1H, H-5), 6.41 (d, *J* = 8.0 Hz 1H, H-4), 6.48 (m, 1H, H-14), 6.49 (m, 1H, H-3), 6.80 (d, *J* = 7.5 Hz, 1H, H-1), 7.01 (m, 2H, H-11, H-3′), 7.02 (m, 1H, H-2′), 7.14 (d, *J* = 8.4 Hz, 1H, H-9), 7.38 (t, *J* = 7.4 Hz, 1H, H-6′), 7.45 (m, 2H, H-10, H-12), 7.59 (t, *J* = 7.6 Hz, 1H, H-7′), 7.79 (d, *J* = 8.8 Hz, 1H, H-4′), 7.89 (d, *J* = 7.8 Hz, 1H, H-5′), 8.29 (d, *J* = 8.6 Hz, 1H, H-8′), 11.09 (s, 1H, H-13), 11.82 (br s, 1H, H-2′); ^{13}C ([D_6]DMSO): δ = 21.0(C-8), 47.7(C-7), 61.0(C-5), 68.2(C-13b), 108.2(C-8b), 111.5(C-12), 116.5(C-1), 117.8(C-1′), 118.2(C-10), 119.0(C-3 or C3′), 119.4(C-3′ or C-3), 119.4(C-11), 121.5(C-9), 121.8(C-8′), 122.6(C-6′), 123.8(C-4a), 125.8(C-8a), 127.1(C-7′ or C-2), 127.2(C-2 or C-7), 127.3(C-4), 128.0(C-4a′), 128.7(C-5′), 129.3(C-4′), 131.5(C-13a), 134.1(C-8a′), 136.3(C-12a), 143.0(C-14a), 155.5(C-2′), elemental analysis calcd (%) for $C_{26}H_{22}N_3O$ (417.51): C 80.55, H 5.55, N 10.06; Found: C 80.48, H 5.57, N 10.04.

5S,12bS**-7-(2-Hydroxynaphth-1-yl)-[2,3-*a*]isoquinolino-[2,1-*b*]-quinazoline (30 b)

Recrystallized from iPr_2O (7 mL); R_f = 0.38 (*n*-hexane/EtOAc 2:1); 67 mg (89%). White crystals; m.p. 191–192 °C; ^{1}H NMR (CD_2Cl_2): δ = 2.61 (ψt, *J* = 13.8 Hz, 1H, H-7), 2.71 (d, *J* = 14.7 Hz, 1H, H-8), 3.19 (m, 2H, H-7, H-8), 4.36 (d, *J* = 5.6 Hz, 1H, H-13), 5.14 (d, *J* = 5.9 Hz, 1H, H-12b), 5.83 (s, 1H, H-5), 6.54 (m, 1H, H-4), 6.57 (m, 1H, H-3), 6.87 (d, *J* = 7.9 Hz, 1H, H-1), 7.06 (m, 2H, H-2, H-3′), 7.19 (d, *J* = 7.2 Hz, 1H, H-9), 7.31 (m, 1H, H-10), 7.35 (m, 1H, H-11), 7.38 (m, 1H, H-6′), 7.57 (t, *J* = 7.5 Hz, 1H, H-7′), 7.65 (d, *J* = 7.4 Hz, 1H, H-12), 7.76 (d, *J* = 8.7 Hz, 1H, H-4′), 7.85 (d, *J* = 8.0 Hz, 1H, H-5′), 8.16 (d, *J* = 8.5 Hz, 1H, H-8′), 11.38 (br s, 1H, H-2′);^{13}C (CD_2Cl_2): δ = 29.3(C-8), 47.3(C-7), 63.0(C-5),

72.7(C-12b), 117.5(C-1′), 118.0(C-1), 120.0(C-3′), 120.6(C-3), 121.7(C-8′), 122.9(C-6′), 124.8(C-4a), 125.4(C-12), 127.0(C-11), 127.3(C-7′), 127.9(C-2), 128.2(C-10), 128.2 (C-4), 128.8(C-4a′), 129.1(C-9), 129.1(C-5′), 129.8 (C-4′), 134.6(C-8a′), 135.0(C-12a), 135.4(C-8a), 142.5(C-13a), 155.5(C-2′); elemental analysis calcd (%) for $C_{26}H_{22}N_2O$ (378.48): C 82.51, H 5.86, N 7.40; found: C 82.67, H 5.88, N 7.38.

5S,11bS**-7-(2-Hydroxynaphth-1-yl)-thieno[3,2-c]pyrido-[2,1-*b*]quinazoline (32 b)

Recrystallized from iPr_2O (6 mL); $R_f = 0.38$ (*n*-hexane/EtOAc 2:1); 71 mg (92%). White crystals; m.p. 198–199 °C; ^1H NMR (CD_2Cl_2): δ 2.62 (td, $J = 11.8$, 3.7 Hz, 1H, H-7), 2.70 (br d, $J = 16.4$ Hz, 1H, H-8), 3.02 (br t, $J = 14.0$ Hz, 1H, H-8), 3.16 (ddd, $J = 11.8$, 5.3, 1.4 Hz, 1H, H-7), 4.24 (d, $J = 5.8$ Hz, 1H, H-12), 4.93 (d, $J = 5.8$ Hz 1H, H-11b), 5.75 (s, 1H, H-5), 6.45 (m, 1H, H-4), 6.48 (ddd, $J = 7.9$, 6.9, 1.1 Hz, 1H, H-3), 6.74 (dd, $J = 8.0$, 0.8 Hz, 1H, H-1), 6.95 (d, $J = 6.95$ Hz, 1H, H-3′), 6.97 (br t, $J = 7.5$ Hz, 1H, H-2), 7.08 (d, $J = 5.2$ Hz, 1H, H-11), 7.19 (dd, $J = 5.2$, 0.6 Hz, 1H, H-10), 7.29 (ddd, $J = 8.5$, 6.9, 1.5 Hz, 1H, H-6′), 7.48 (ddd, $J = 8.5$, 6.9, 1.5 Hz, 1H, H-7′), 7.66 (d, $J = 8.8$ Hz, 1H, H-4′), 7.75 (d, $J = 8.0$ Hz, 1H, 5′), 8.07 (d, $J = 8.6$ Hz, 1H, H-8′), 11.18 (br s, 1H, H-2′); ^{13}C (CD_2Cl_2): δ = 25.5(C-8), 48.1(C-7), 62.1(C-5), 71.3(C-11b), 117.7(C-1′), 117.8(C-1), 120.0(C-3′), 120.7(C-3), 121.7(C-8′), 123.0(C-6′), 123.9(C-11), 124.7(C-10), 124.8(C-4a), 127.3(C-7′), 127.9(C-2), 128.2(C-4), 128.9(C-4a′), 129.2(C-5′), 129.8(C-4′), 134.3(C-8a′), 134.5(C-11a), 136.7(C-8a), 142.2(C-12a), 155.5(C-2′); elemental analysis calcd (%) for $C_{24}H_{20}N_2OS$ (384.50): C 74.97, H 5.24, N 7.29; Found: C 74.95, H 5.26, N 7.34.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: *ortho*-quinone methide (*o*-QMs) · modified Mannich reaction · cycloaddition · NMR spectroscopy · conformational analysis · DFT calculations

[1] S. K. Bur, S. F. Martin, *Tetrahedron* **2001**, *57*, 3221–3242.
[2] W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856.
[3] X. Lian, L. Lin, K. Fu, B. Ma, X. Liu, X. Feng, *Chem. Sci.* **2017**, *8*, 1238–1242.
[4] J. F. A. Filho, B. C. Lemos, A. S. de Souza, S. Pinheiro, S. J. Greco, *Tetrahedron* **2017**, *73*, 6977–7004.
[5] I. Szatmári, F. Fülöp, *Tetrahedron* **2013**, *69*, 1255–1278.
[6] B. Karmakar, J. Banerji, *Tetrahedron Lett.* **2011**, *52*, 4957–4960.
[7] P. Barta, I. Szatmári, F. Fülöp, M. Heydenreich, A. Koch, E. Kleinpeter, *Tetrahedron* **2016**, *72*, 2402–2410.
[8] P. Barta, F. Fülöp, I. Szatmári, *Beilstein J. Org. Chem.* **2018**, *14*, 560–575.
[9] V. A. Osyanin, D. V. Osipov, Y. N. Klimochkin, *Tetrahedron* **2012**, *68*, 5612–5618.
[10] J. D. Pettigrew, R. P. Freeman, P. D. Wilson, *Can. J. Chem.* **2004**, *82*, 1640–1648.
[11] H. H. Liao, A. Chatupheeraphat, C. C. Hsiao, I. Atodiresei, M. Rueping, *Angew. Chemie, Int. Ed.* **2015**, *54*, 15540–15544.
[12] I. Szatmári, F. Fülöp, *Tetrahedron Lett.* **2011**, *52*, 4440–4442.
[13] I. Szatmári, P. Barta, A. Csámpai, F. Fülöp, *Tetrahedron* **2017**, *73*, 4790–4804.
[14] V. A. Osyanin, E. A. Lvleva, Y. N. Klimochkin, *Chem. Heterocycl. Compd.* **2012**, *48*, 795–798.
[15] Z. Chen, G. Hu, D. Li, J. Chen, Y. Li, H. Zhou, Y. Xie, *Bioorg. Med. Chem.* **2009**, *17*, 2351–2359.
[16] J. Tang, S. Zhao, Y. Wei, Z. Quan, C. Huo, *Org. Biomol. Chem.* **2017**, *15*, 1589–1592.
[17] K. Okuma, A. Nojima, N. Matsunaga, K. Shioji, *Org. Lett.* **2009**, *11*, 169–171.
[18] J. Zhao, R. C. Larock, *Org. Lett.* **2005**, *7*, 4273–4275.
[19] J. Zhao, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 583–588.
[20] S. Wang, K. Xie, Z. Tan, X. An, X. Zhou, C. C. Guo, Z. Peng , *Chem. Commun.* **2009**, *42*, 6469–6471.
[21] I. Szatmári, J. Sas, F. Fülöp, *Tetrahedron Lett.* **2013**, *54*, 5096–5071.
[22] W. Herz, L. Tsai, *J. Chem. Soc.* **1955**, 77, 3529–3533.
[23] O. Bilgic, D. W. Young, *J. Chem. Soc. Perkin Trans. 1* **1980**, *1*, 1233–1239.
[24] I. Szatmári, M. Heydenreich, A. Koch, F. Fülöp, E. Kleinpeter, *Tetrahedron* **2013**, *69*, 4755–7465.
[25] A. M. S. Silva, D. C. G. A. Pinto, H. R. Travares, J. A. S. Cavaleiro, M. L. Jimeno, J. Elguero, *Eur. J. Org. Chem.* **1998**, 2031–2039.
[26] S. Klod, E. Kleinpeter, *J. Chem. Soc. Perkin Trans. 2* **2001**, 1893–1898.
[27] E. Kleinpeter, S. Klod, A. Koch, *J. Mol. Struct. (THEOCHEM)* **2007**, *811*, 45-60 and references cited therein.
[28] Kleinpeter, *Annual Reports on NMR Spectroscopy (edited by Graham A. Webb), ELSEVIER, Vol. 82 (2014) - Chapter 3:* Quantification and Visualization of the Anisotropy Effect in NMR Spectroscopy by Through-Space NMR Shieldings.
[29] P. v. R. Schleyer, C. Maerker, A. Dransfield, H. Jiao, H. N. J. Van Eikema Hommes, *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318.
[30] Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R. Schleyer, *Chem. Rev.* **2005**, *105*, 3842–3888.
[31] A. Stanger, *Chem. Commun.* **2009**, 1939–1947.
[32] A. Lämmermann, H. Kühn, E. Kleinpeter, *Org. Biomol. Chem.* **2011**, *9*, 1098–1111.
[33] E. Kleinpeter, A. Koch, *J. Phys. Chem. A* **2012**, *116*, 5674–5680.
[34] E. Kleinpeter, A. Koch, *Phys. Chem. Chem. Phys.* **2012**, *14*, 8742–8746.
[35] E. Kleinpeter, S. Klod, *J. Am. Chem. Soc.* **2004**, *126*, 2231–2236.
[36] M. J. Frisch Gaussian 09, Revision A.02. Wallingford, CT: Gaussian, Inc. **2009**
[37] A. D. Becke *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[38] C. Lee, W. Yang, R. G. Parr *Phys. Rev. B* **1988**, *37*, 785–789.
[39] W. J. Hehre L. Radom, P. von Rague Schleyer *J. Pople Ab Initio Molecular Orbital Theory*; Wiley: New York, NY, **1986**.
[40] A. D. Becke *J. Chem. Phys.* **1993**, *98*, 1372–1492.
[41] P. von Rague Schleyer, C. Maerker, A. Dransfeld, H. Jiao, N. J. R. van E. Hommes *J. Am. Chem. Soc.* **1996**, *118*, 6317–6318.
[42] R. Ditchfield *Mol. Phys.* **1974**, *27*, 789–807.
[43] G. W. Cheeseman, T. A. Trucks, M. J. Keith *J. Chem. Phys.* **1996**, *104*, 5497–5509.
[44] SYBYL-X 2.1.1. Tripos, 2013, 1699 South Hanley Road, St. Louis, MO 63144, USA.

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Solvent-Free C-3 Coupling of Azaindoles with Cyclic Imines

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Abstract: By direct coupling 7-azaindole and cyclic imines, such as 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine, 3,4-dihydro-β-carboline, and 4,5-dihydro-*3H*-benz[*c*]azepine, new 3-substituted 7-azaindole derivatives have been synthesized. The reaction was extended to 4-azaindoles and 6-azaindoles, as electron-rich aromatic compounds. The lowest reactivity was observed in the case of C-3 substitution of 5-azaindole. In this case, the aza-Friedel-Crafts reaction took place by using 10 mol % of *p*-toluenesulfonic acid (*p*-TSA) as the catalyst. The role of the acid catalyst can be explained by the different pKa values of the azaindoles. All reactions were performed in solvent-free conditions by using both classical heating and microwave irradiation. In all cases, microwave heating proved to be more convenient to synthesize new C-3-substituted azaindole derivatives.

Keywords: cyclic imines; 7-azaindole; 6-azaindole; 4-azaindole; 5-azaindole; *aza*-Friedel-Crafts reaction; microwave reaction

1. Introduction

7-Azaindole is a well-known hinge-binding element in kinase inhibition [1–5]. The N atom of the pyridine ring and the NH group of the pyrrole moiety of 7-azaindole serve as the hydrogen bond acceptor and donor, respectively, to make bidentate hydrogen bonds with the hinge region of the kinase. 7-Azaindole has five modification sites where various substituents can be readily attached to obtain 7-azaindole derivatives with improved activity. Among them, vemurafenib [6], a B-RAF kinase (serine –threonine kinase (STK)) inhibitor, is the first U.S. Food and Drug Administration (FDA)-approved, 7-azaindole-based kinase drug for the treatment of melanoma [7]. Vemurafenib was discovered through lead optimization, starting from a small 7-azaindole fragment, and now it is recognized as the first successful example of a "fragment-based" drug discovery approach [8]. Some derivatives have been developed that target various kinds of kinases, including Janus kinase 3 (JAK3; a cytoplasmic tyrosine kinase (TK)) [9]; colony stimulating factor 1 receptor (CSF1R; a TK receptor) [10]; aurora kinases (STKs) [11]; and Rho-associated, coiled coil-containing protein kinase 1 (ROCK1; STK) [12].

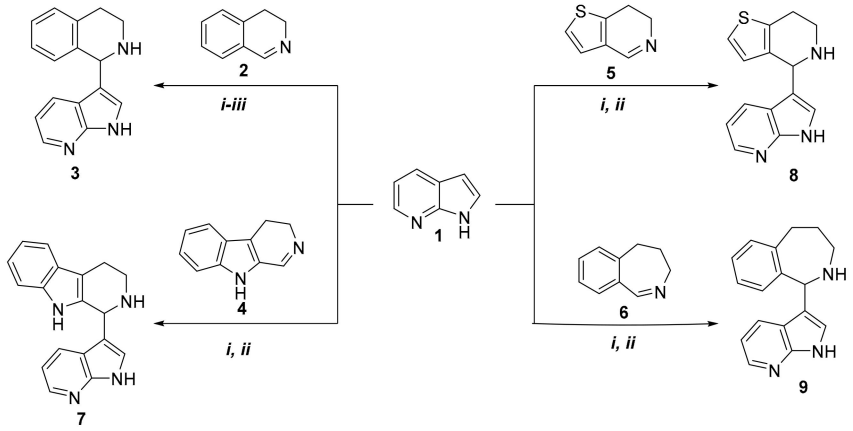
Thanks to the close similarity of azaindoles to the indole skeleton, C-3 functionalization of these compounds has been postulated [13,14]. Most of the methods known already for the synthesis of 3-functionalized 7-azaindole derivatives have applied multistep transformations. Particular efforts have been made to insert another biologically active moiety, such as tetrahydroisoquinoline, into position three. In this case, the synthesis of 1-(7-azaindol-3-yl)-1,2,3,4-tetrahydroisoquinoline involves the coupling of 7-azaindole with N-protected tetrahydroisoquinoline under iron and copper catalysis [15,16].

The catalyst-free direct coupling of partially-saturated cyclic amines and indole as an electron-rich aromatic compound, via a modified *aza*-Friedel-Crafts reaction, has recently been published by our research group [17,18]. The reaction has been extended by using indole-2-carboxylic acid as a substrate, leading to the formation of γ-amino acid derivatives [17].

Our aim was to perform a systematic study of the synthesis of azaindole derivatives (7-, 4-, 5-, and 6-azaindoles), applying the modified aza-Friedel–Crafts reaction using cyclic imine substrates, such as 3,4-dihydroisoquinoline; 6,7-dihydrothieno[3,2-*c*]pyridine; 3,4-dihydro-β-carboline; and 4,5-dihydro-*3H*-benz[*c*]azepine.

2. Results

In our initial experiments, 7-azaindole (compound **1**) was reacted with 1.5 equivalent of 3,4-dihydroisoquinoline (compound **2**), which was synthesized using a method from the literature (Scheme 1) [18]. The reaction between compounds **1** and **2** was performed in solvent-free conditions by classical heating (oil bath) at 60 °C (*i*). Based on thin-layer chromatography (TLC), the reaction over a time of 18 h resulted in the formation of a multi-spot reaction mixture; the desired product (compound **3**) was isolated by chromatography, with a yield of 31%. Since the yield was not satisfactory, the reaction was repeated at 80 °C (*ii*). A 10 h reaction led to the formation of compound **3**, with a yield of 49%. Despite increasing the temperature further (100 °C, (*iii*)), the relatively long reaction led to compound **3** only with a poor yield (28%). When the reaction was repeated under microwave irradiation by testing three different reaction conditions (Table 1), 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)-7-azaindole (**3**) was isolated with a yield of 81% after 120 min at 100 °C (Table 1). It is interesting to note that for microwave reactions, 2 equivalents of 3,4-dihydroisoquinoline was applied to provide homogeneity for the reaction mixture.



Scheme 1. Synthesis of 7-azaindole derivatives, starting from different cyclic imines.

Table 1. Reaction conditions for the synthesis of the azaindole compounds **3** and **7–9.**

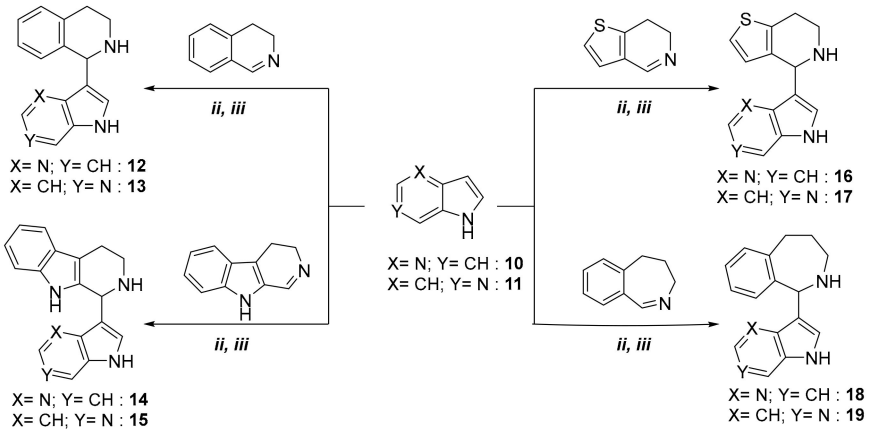
Products	Reaction Time [a]	Temperature [a]	Yield [a](%)	Reaction Time [b]	Temperature [b]	Yield [b] (%)
	18 h	60 °C (*i*)	31	2 h	80 °C (*ii*)	55
3	10 h	80 °C (*ii*)	49	4 h	80 °C (*ii*)	63
	6 h	100 °C (*iii*)	28	2 h	100 °C (*iii*)	81
7	10 h	80 °C (*ii*)	56	2.5 h	100 °C (*iii*)	75
8	6 h	80 °C (*ii*)	76	2 h	100 °C (*iii*)	89
9	20 h	80 °C (*ii*)	63	3 h	100 °C (*iii*)	78

[a] classical heating, [b] microwave irradiation.

The reaction was extended by using other cyclic imines, such as 3,4-dihydro-β-carboline (compound **4**) [19]; 6,7-dihydrothieno[3,2-*c*]pyridine (compound **5**) [20]; and 4,5-dihydro-*3H*-benz[*c*]azepine (compound **6**) [21,22]. Reactions were performed by using both oil-bath heating

and microwave irradiation (Scheme 1). Table 1 shows that the corresponding products—compounds **7**, **8**, and **9**—were isolated in higher yields when microwave conditions were applied. It can be concluded that 6,7-dihydrothieno[3,2-*c*]pyridine (**5**) was found to be the most reactive cyclic imine. Yields and the applied reaction conditions are summarized in Table 1.

With the optimal reaction conditions in hand, we focused on extending the series of electron-rich aromatic compounds in a modified aza-Friedel-Crafts reaction. Accordingly, 4-azaindole (compound **10**) and 6-azaindole (compound **11**) were also reacted with cyclic imines **2**, **4**, **5**, and **6** (Scheme 2).



Scheme 2. The extension of a modified aza-Friedel–Crafts reaction, starting from 4-azaindole and 6-azaindole.

Reactions were performed under solvent-free conditions by both classical heating and using microwave irradiation. The new azaindole derivatives, formed in reaction times indicated in Table 2, were isolated and purified by crystallization or column chromatography (see Material and Methods). It can be concluded that the use of microwave irradiation afforded the desired products (compounds **12**–**19**) in higher yields and with significantly shorter reactions, compared with those using oil-bath heating (Table 2).

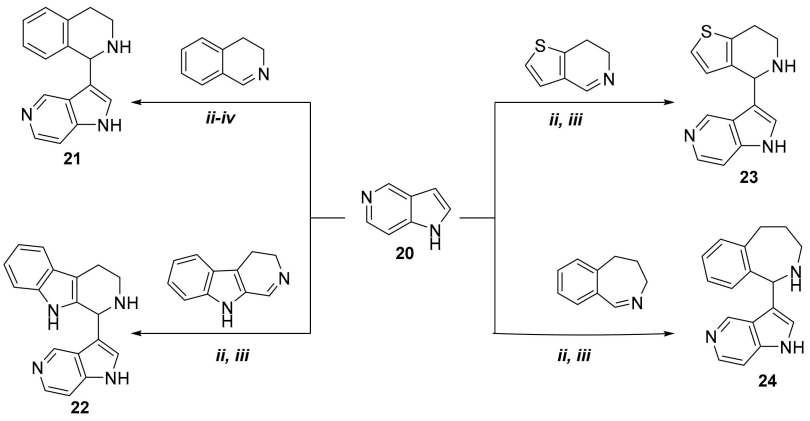
Table 2. Reaction conditions for the synthesis of the azaindoles **12**–**19.**

Products	Reaction Time [a]	Temperature [a]	Yield [a] (%)	Reaction Time [b]	Temperature [b]	Yield [b] (%)
12	20 h	80 °C (*ii*)	49	2.5 h	100 °C (*iii*)	70
13	22 h	80 °C (*ii*)	39	2.5 h	100 °C (*iii*)	65
14	16 h	80 °C (*ii*)	52	2.5 h	100 °C (*iii*)	69
15	20 h	80 °C (*ii*)	48	2.5 h	100 °C (*iii*)	62
16	7 h	80 °C (*ii*)	63	2.5 h	100 °C (*iii*)	85
17	8 h	80 °C (*ii*)	62	2.5 h	100 °C (*iii*)	75
18	21 h	80 °C (*ii*)	57	3 h	100 °C (*ii*)	68
19	25 h	80 °C (*ii*)	55	3 h	100 °C (*iii*)	64

[a] classical heating, [b] microwave irradiation.

Since the catalyst-free coupling of 7-, 6-, and 4-azaindoles resulted in the desired C-3 aminoalkylated derivatives, we focused our attention on the aza-Friedel-Crafts reaction of 5-azaindole (compound **20**). In our first experiment, **20** was reacted with 3,4-dihydroisoquinoline (**2**) as representative cyclic imine (Scheme 3). However, even when applying different reaction conditions (classical heating, microwave irradiation) and different temperatures (80 °C (*ii*), 100 °C (*iii*), 120 °C (*iv*)), target compound **21** did not form. There was no conversion at lower temperature (80 °C, 100 °C), while higher temperature (120 °C) resulted in the formation of a multi-spot reaction mixture. Since *p*-toluenesulfonic acid (*p*-TSA) is a frequently applied acid catalyst in the modified three-component Mannich reaction [23–25], we decided to examine its effect on the reaction between **20** and 3,4-dihydroisoquinoline. First,

10 mol % of *p*-TSA was tested by using oil-bath conditions. In this case, TLC showed the formation of a new compound, which after isolation (30%) proved to be the desired 5-azaindole derivative **21**. Since the reaction needed a relatively long reaction time (19 h) and resulted in a poor yield, it was repeated by using microwave irradiation. In this case, 100 °C proved to be optimal, and 3-(1,2,3,4-tetrahydroisoquinolin-1-yl)-5-azaindole (**21**) was isolated with a yield of 72% (Table 3).



Scheme 3. Synthesis of compounds **21**–**24** from 5-azaindole.

Table 3. Reaction conditions for the synthesis of the products **21**–**24.**

Products	Reaction Time [a]	Temperature [a]	Yield [a] (%)	Reaction Time [b]	Temperature [b]	Yield [b] (%)
21	24 h	80 °C (*ii*)	-	2.5 h	80 °C (*ii*)	-
	21 h	100 °C (*iii*)	-	2.5 h	100 °C (*iii*)	-
	8 h	120 °C (*iv*)	-	2 h	120 °C (*iv*)	-
22	19 h [c]	80 °C (*ii*)	30	2.5 h [c]	100 °C (*iii*)	72
23	15 h [c]	80 °C (*ii*)	44	2 h [c]	100 °C (*iii*)	69
24	7 h [c]	80 °C (*ii*)	62	2 h [c]	100 °C (*iii*)	80
	15 h [c]	80 °C (*ii*)	52	3.5 h [c]	100 °C (*iii*)	65

[a] classical heating, [b] microwave irradiation, [c] *p*-TSA.

By applying 10 mol % of *p*-TSA catalyst, C-3 aminoalkylation of 5-azaindole was extended with additional cyclic imines, such as 6,7-dihydrothieno[3,2-*c*]pyridine; 3,4-dihydro-β-carboline; and 4,5-dihydro-*3H*-benz[*c*]azepine (Scheme 3). Reaction conditions and yields are summarized in Table 3. As the data show, there is a difference between the reactivity of 7-, 6-, and 4-azaindoles and that of 5-azaindole—that is, for C-3 aminoalkylation of 5-azaindole an acid catalyst was needed. The lower reactivity of 5-azaindole can be accounted for by its higher pKa value (8.42), compared with those of 6-azaindole (5.61), 4-azaindole (4.85), and 7-azaindole (3.67). The given pKa values were calculated by using the Marvin Sketch software (version 16.12.12.0, calculation module developed by ChemAxon) [26]. The pKa values of azaindoles depend on the resonance stabilization of their protonated forms. The reason why the aza-Friedel-Crafts reaction of 5-azaindole occurs only under acidic conditions is that 5-azaindole has the highest basicity in the series of 4-, 5, 6-, and 7-azaindoles. It is interesting to note that the fastest reactions were achieved with the electron-rich aromatic compound 7-azaindole. This is in complete agreement with its calculated pKa value (3.67), indicating that it is the most acidic compound among the azaindoles studied.

3. Materials and Methods

3.1. General Methods

Melting points were determined on a Hinotek X-4 (Hinotek Technology Co., Ltd., Ningbo, China) melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS

elemental analyzer (Perkin-Elmer, Waltham, MA, USA) in the Institute of Pharmaceutical Chemistry, University of Szeged. Merck Kieselgel 60F254 plates (Merck Hungary, Budapest, Hungary) were used for the TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor (CEM, Matthwes, NC, USA).

The starting cyclic imines 3,4-dihydroisoquinoline (**2**) [18]; 3,4-dihydro-β-carboline (**4**) [19]; 6,7-dihydrothieno[3,2-*c*]pyridine (**5**) [20]; and 4,5-dihydro-*3H*-benz[*c*]azepine (**6**) [21,22] were synthesized according to the literature.

The ^{1}H-and ^{13}C-NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO solution in 5 mm tubes at room temperature, on a Bruker Avance II spectrometer (Bruker, Karlsruhe, Germany) at 500 (^{1}H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as the internal standard. All spectra (^{1}H, ^{13}C) were acquired and processed with the standard BRUKER software.

Procedures

For method A, the cyclic imine 3,4-dihydroisoquinoline (66 mg, 0.50 mmol); 6,7-dihydrothieno[3,2-*c*]pyridine (51 mg, 0.38 mmol); 3,4-dihydro-β-carboline (63 mg, 0.38 mmol) or 4,5-dihydro-*3H*-benz[*c*]azepine (55 mg, 0.38 mmol); and the azaindoles (7-, 6- or 4-azaindole, (30 mg, 0.25 mmol)) were mixed in a 25 mL round bottom flask. The mixture was heated in an oil bath. Reaction conditions are shown in Tables 1–3. In the case of 5-azaindole, 10 mol % (4.3 mg, 0.025 mmol) of *p*-TSA as a catalyst was also added.

For method B, the mixture of the cyclic imine 3,4-dihydroisoquinoline (66 mg, 0.50 mmol); 6,7-dihydrothieno[3,2-*c*]pyridine (51 mg, 0.38 mmol); 3,4-dihydro-β-carboline (63 mg, 0.38 mmol) or 4,5-dihydro-*3H*-benz[*c*]azepine (55.3 mg, 0.38 mmol); and the electron-rich aromatic compound (7-, 6-, 4-, or 5-azaindole (30 mg, 0.25 mmol)) were placed in a 10 mL pressurized reaction vial and heated in a microwave reactor, under the conditions given in Tables 1–3. In the case of 5-azaindole, 10 mol % of *p*-TSA (4.3 mg, 0.025 mmol) as a catalyst was also added.

3.2. Synthesis of New Compounds

3.2.1. Synthesis of 3-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-7-azaindole

Compound **3** (Figures S1 and S2) was crystallized from Et_2O, recrystallized from *i*-Pr_2O. It was a white solid, with mp: 178–180 °C (Lit.: [16] mp: 172–174°C); yield: 81% (51 mg); ^{1}H-NMR ([D_6] DMSO): δ = 2.73–2.81 (1H, m), 2.91–3.00 (2H, m), 3.10–3.17 (1H, m), 5.29 (1H, s), 6.79 (1H, d, *J* = 7.9 Hz), 6.87 (1H, t, *J* = 7.6 Hz), 6.88–6.93 (1H, m), 6.97 (1H, t, *J* = 5.2 Hz), 7.07–7.16 (2H, m), 7.24 (1H, s), 7.65 (1H, d, *J* = 7.7 Hz), 8.14 (1H, d, *J* = 5.1 Hz), and 11.40 (1H, s); ^{13}C-NMR ([D_6]DMSO): δ = 29.7, 42.3, 54.5, 115.3, 117.5, 118.9, 125.3, 125.8, 126.3, 127.6, 128.6, 129.3, 135.6, 139.2, 142.9, and 149.4. The analysis calculated for $C_{16}H_{15}N_3$ found C: 77.08; H: 6.06; and N: 16.85; found values were C: 77.10; H: 5.98, and N: 16.88.

3.2.2. Synthesis of 3-(1,2,3,4-Tetrahydro-β-carboline-1-yl)-7-azaindole

Product **7** (Figures S3 and S4) was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a white solid, with mp: 219–220 °C; yield: 75% (55 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.64–2.73 (1H, m), 2.75–2.84 (1H, m), 2.93–3.01 (1H, m), 3.13–3.21 (1H, m), 5.38 (1H, s), 6.87–7.00 (3H, m), 7.15 (1H, d, *J* = 7.8 Hz), 7.30 (1H, s), 7.42 (1H, d, *J* = 7.6 Hz), 7.63 (1H, d, *J* = 8.4 Hz), 8.14 (1H, d, *J* = 4.4 Hz), 10.38 (1H, s,), and 11.50 (1H, s, brs); ^{13}C-NMR ([D_6]DMSO): δ = 22.0, 42.1, 49.7, 107.4, 107.9, 111.6, 118.1, 118.8, 121.3, 123.8, 126.6, 127.2, 135.0, 136.4, 140.3, 140.4, and 143.1. The analysis calculated for $C_{18}H_{16}N_4$ found C: 74.98, H: 5.59, and N: 19.43; the found values were C: 74.91, H: 5.60, and N: 19.45.

3.2.3. Synthesis of 3-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-4-yl)-7-azaindole

Product **8** (Figures S5 and S6) was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a white solid, with mp: 191–195 °C; yield: 89% (58 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.74–2.81 (1H, m),

2.85–3.01 (2H, m), 3.12–3.20 (1H, m), 5.25 (1H, s), 6.49 (1H, d, *J* = 6.1 Hz), 6.92–6.98 (1H, m), 7.14 (1H, d, *J* = 5.3 Hz), 7.20–7.24 (1H, m), 7.71 (1H, d, *J* = 9.6 Hz), 8.15 (1H, d, *J* =7.2 Hz), 7.42 (1H, d, *J* = 7.9 Hz), and 11.14 (1H, s,); ^{13}C-NMR ($CDCl_3$): δ = 26.1, 42.2, 52.3, 115.8, 117.0, 119.0, 121.8, 123.8, 126.4, 128.2, 134.7, 136.6, 143.0, and 149.1 The analysis calculated for $C_{14}H_{13}N_3S$ was C: 65.85, H: 5.13, and N: 16.46; found values were C: 65.83, H: 5.15, and N: 16.50.

3.2.4. Synthesis of 3-(2,3,4,5-Tetrahydro-1H-benz[*c*]azepin-1-yl)-7-azaindole

Product **9** (Figures S7 and S8)was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a white solid, with mp: 192–194 °C; yield: 78% (52 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.87–2.96 (1H, m), 2.97–3.14 (3H, m), 3.30 (2H, s), 5.40 (1H, s), 6.80 (1H, d, *J* = 8.1 Hz), 6.95–7.07 (3H, m), 7.11 (1H, t, *J* = 7.2 Hz), 7.19 (1H, d, *J* = 7.4 Hz), 7.84 (1H, d, *J* = 8.4 Hz), 8.19 (1H, d, *J* = 5.5 Hz), and 11.45 (1H, s); ^{13}C-NMR ([D_6]DMSO): δ = 29.9, 35.5, 49.6, 59.7, 115.2, 115.5, 119.1, 124.5, 126.1, 127.1, 128.0, 128.6, 130.1, 142.5, 143.0, 144.8, 149.8, The analysis calculated for $C_{17}H_{17}N_3$ was C: 77.54, H: 6.51, and N: 15.96; found values were C: 77.60, H: 6.52, and N: 15.98.

3.2.5. Synthesis of 3-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-4-azaindole

Product **12** (Figures S9 and S10) was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a light beige solid, with mp: 166–168 °C; yield: 70% (44 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.74–2.84 (1H, m), 2.85–2.93 (2H, m), 3.04–3.11 (1H, m), 5.50 (1H, s), 6.94–7.02 (2H, m), 7.06–7.15 (4H, m), 7.74 (1H, d, *J* = 8.1 Hz), 8.32 (1H, d, *J* = 4.6 Hz), and 11.12 (1H, s); ^{13}C-NMR ([D_6]DMSO): δ = 29.7, 41.4, 52.6, 116.8, 119.0, 119.4, 125.6, 126.2, 127.8, 127.9, 129.2, 129.3, 135.6, 139.6, 142.3, and 144.9; The analysis calculated for $C_{16}H_{15}N_3$ was C: 77.08, H: 6.06, and N: 16.85; found values were C: 77.09, H: 5.99, and N: 16.89.

3.2.6. Synthesis of 3-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-6-azaindole

Product **13** (Figures S11 and S12) was purified by column chromatography (Dichloro-methane(DCM)/MeOH 9:1) and crystallized from *n*-hexane. It was a light beige solid, with mp: 152–154 °C; yield: 65% (41 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.72–2.79 (1H, m), 2.89–2.98 (2H, m), 3.08–3.14 (1H, m), 5.29 (1H, s), 6.76 (1H, d, *J* = 8.1 Hz), 6.96 (1H, t, *J* = 5.6 Hz), 7.05–7.15 (2H, m), 7.25 (1H, d, *J* = 7.5 Hz), 7.36 (1H,s), 7.94 (1H, d, *J* = 6.1 Hz), 8.68 (1H, s), and 11.36 (1H, s); ^{13}C-NMR ([D_6]DMSO): δ = 29.8, 42.4, 54.01, 115.0, 118.8, 125.8, 126.3, 127.5, 128.7, 129.3, 130.9, 134.3, 134.8, 135.7, 137.5, and 139.5 The analysis calculated for $C_{16}H_{15}N_3$ was C: 77.08, H: 6.06, and N: 16.85; found values were C: 77.12, H: 5.98, and N: 16.87.

3.2.7. Synthesis of 3-(1,2,3,4-Tetrahydro-β-carboline-1-yl)-4-azaindole

Product **14** (Figures S13 and S14) was crystallized from Et_2O, recrystallized from *i*-Pr_2O. It was a light brown solid, with mp: 157–160 °C; yield: 69% (50 mg); ^{1}H-NMR (500 MHz, ([D_6]DMSO): δ = 2.86–3.06 (2H, m); 3.37–3.54 (1H, m), 6.04 (1H, s), 6.94–7.09 (2H, m), 7.14–7.29 (2H, m), 7.43–7.58 (2H, m), 7.85 (1H, d, *J* =8.6 Hz), 8.34–8.45 (1H, m), 10.81 (1H, s,), and 11.60 (1H, s, brs). ^{13}C-NMR ($CDCl_3$): δ = 22.4, 42.1, 49.0, 107.78, 111.4, 117.1, 118.0, 118.9, 119.0, 121.3, 125.6, 127.2, 129.6, 135.4, 135.6, 142.6, 143.0, and 144.0. The analysis calculated for $C_{18}H_{16}N_4$ was C: 74.98, H: 5.59, and N: 19.43; found values were C: 74.97, H: 5.62, N: 19.43.

3.2.8. Synthesis of 3-(1,2,3,4-Tetrahydro-β-carboline-1-yl)-6-azaindole

Product **15** (Figures S15 and S16) was purified by column chromatography (DCM/MeOH 3:1) and crystallized from *n*-hexane. It was a light brown solid, with mp: 217–219 °C; yield: 62% (45 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.65–2.84 (2H, m), 2.93–3.02 (1H, m), 3.11–3.19 (1H, m), 6.92–6.99 (2H, m), 5.43 (1H, s), 7.18 (1H, d, *J* =7.6 Hz), 7.24(1H, d, *J* = 5.4 Hz), 7.38–4.44 (1H, m), 7.94 (1H, d, *J* = 5.6 Hz), 8.70 (1H, s), 10.37 (1H, s,), and 11.44 (1H, s, brs); ^{13}C-NMR ([D_6]DMSO): δ = 22.6, 42.4, 49.8, 108.4, 111.52, 114.62, 118.02, 118.60,

120.8, 127.3, 128.9, 131.1, 134.3, 134.9, 136.0, 136.2, and 137.7. The analysis calculated for $C_{18}H_{16}N_4$ was C: 74.98, H: 5.59, and N: 19.43; found values were C: 74.96, H: 5.61, and N: 19.44.

3.2.9. Synthesis of 3-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-4-yl)-4-azaindole

Product **16** (Figures S17 and S18) was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a white solid, with mp: 179–182 °C; yield: 85% (55 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.73–2.82 (2H, m), 2.90–2.98 (1H, m), 3.11–3.15 (1H, m), 5.25 (1H, s), 6.50 (1H, d, *J* = 4.9 Hz), 6.91 (1H, t, *J* = 7.4 Hz), 7.05 (1H, t, *J* = 7.6 Hz), 7.07 (1H, s), 7.13 (1H, d, *J* = 5.1 Hz), 7.34 (1H, t, *J* = 7.9 Hz), 7.42 (1H, d, *J* = 7.9 Hz), 10.85 (1H, s), 8.19 (1H, s, brs), 11.52 (1H, s,), and 16.78 (1H, s, brs); ^{13}C-NMR ($CDCl_3$): δ = 25.6, 41.3, 50.6, 117.1, 118.0, 118.5, 121.9, 126.3, 126.7, 129.3, 134.7, 135.8, 143.0, and 144.4. The analysis calculated for $C_{14}H_{13}N_3S$ was C: 65.85, H: 5.13, N: 16.46; found values were C: 65.82, H: 5.12, and N: 16.48.

3.2.10. Synthesis of 3-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-4-yl)-6-azaindole

Product **17** (Figures S19 and S20) was purified by column chromatography (DCM/MeOH 9:1) and crystallized from *n*-hexane. It was a white solid, with mp: 167–169 °C; yield: 75% (49 mg); ^{1}H-NMR ([D_6]DMSO): δ = 2.71–2.80 (1H, m), 2.82–2.99 (2H, m), 3.09–3.16 (1H, m), 5.23 (1H, s), 6.46 (1H, d, *J* = 5.1 Hz), 7.13 (1H, d, *J* =5.6 Hz), 7.25–7.40 (2H, m), 7.98 (1H, d, *J* = 5.4 Hz), 8.68 (1H, s), and 11.35 (1H, s); ^{13}C-NMR ($CDCl_3$): δ = 26.0, 42.2, 51.8, 114.2, 118.3, 122.0, 126.1, 127.4, 131.3, 133.8, 134.1, 134.8, 136.4, and 138.2. The analysis calculated for $C_{14}H_{13}N_3S$ was C: 65.85, H: 5.13, and N: 16.46; found values were C: 65.83, H: 5.15, and N: 16.45.

3.2.11. Synthesis of 3-(2,3,4,5-Tetrahydro-*1H*-benzo[*c*]azepin-1-yl)-4-azaindole

Product **18** (Figures S21 and S22) was crystallized from Et_2O and recrystallized from *i*-Pr_2O. It was a light beige solid, with mp: 162–165 °C; yield: 68% (45 mg); ^{1}H-NMR (500 MHz, ([D_6]DMSO): δ = 2.95–3.03 (1H, m), 3.18–3.29 (3H, m), 3.30–3.40 (2H, m), 6.06 (1H, s), 6.85 (1H, d, *J* = 7.4 Hz), 7.06 (1H, t, *J* = 7.9 Hz), 7.18–7.25 (2H, m), 7.29 (1H, d, *J* = 7.4 Hz), 7.60 (1H, s), 7.90 (1H, d, *J* = 8.4 Hz), 8.35 (1H, d, *J* = 4.6 Hz), and 11.76 (1H, s); ^{13}C-NMR (100 MHz, [D6]DMSO): δ = 25.9, 34.0, 49.4, 57.5, 111.4, 117.6, 119.8, 126.6, 128.7, 128.8, 129.3, 129.4, 130.0, 138.0, 142.5, 142.9, and 144.1. The analysis calculated for $C_{17}H_{17}N_3$ was C: 77.54, H: 6.51, and N: 15.96; found values were C: 77.53, H: 6.53, and N: 15.99.

3.2.12. Synthesis of 3-(2,3,4,5-Tetrahydro-*1H*-benzo[*c*]azepin-1-yl)-6-azaindole

Product **19** (Figures S23 and S24) was purified by column chromatography (DCM/MeOH 9:1) and crystallized from *n*-hexane. It was a light beige solid, with mp: 154–156 °C; yield: 64% (42 mg); ^{1}H-NMR (500 MHz, ([D_6]DMSO): δ = 2.91–2.29 (1H, m), 3.13–3.30 (2H, m), 5.89 (1H, s), 6.86 (1H, d, *J* = 7.9 Hz), 7.08 (1H, t, *J* = 7.4 Hz), 7.17–7.30 (3H, m), 7.48 (1H, d, *J* = 5.3 Hz), 7.53 (1H,s), 8.07 (1H, d, *J* = 5.3 Hz), 8.81 (1H, s), and 11.86 (1H, s); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 33.8, 34.3, 49.0, 50.1, 50.8, 58.2, 114.6, 126.7, 126.9, 128.6, 128.9, 129.4, 129.7, 130.3, 130.5, 131.0, 134.2, 135.4, 138.2, and 142.6. The analysis calculated for $C_{17}H_{17}N_3$ was C: 77.54, H: 6.51, and N: 15.96; found values were C: 77.56, H: 6.50, and N: 15.94.

3.2.13. Synthesis of 3-(1,2,3,4-Tetrahydroisoquinolin-1-yl)-5-azaindole

Product **20** (Figures S25 and S26) was purified by column chromatography (DCM/MeOH 9:1) and crystallized from *n*-hexane. It was a light beige solid, with mp: 118–119 °C; yield: 72% (46 mg); ^{1}H-NMR (500 MHz, ([D_6]DMSO): δ = 2.88–3.39 (4H, m), 6.35 (1H, s), 6.92 (1H, d, *J* = 7.8 Hz), 7.27–7.49(3H, m), 7.80–7.92 (1H, m), 8.03 (1H, d, *J* = 7.1 Hz), 8.45 (1H, d, *J* = 7.1 Hz), 9.14(1H, s), and 13.25 (1H, s); ^{13}C-NMR (100 MHz, [D_6]DMSO): δ = 29.7, 42.3, 54.1, 107.3, 118.8, 123.5, 125.8, 125.9, 126.4, 127.6, 129.3, 135.6, 139.3, 140.3, 140.5, and 143.6. The analysis calculated for $C_{16}H_{15}N_3$ was C: 77.08, H: 6.06, and N: 16.85; found values were C: 77.02, H: 5.98, and N: 16.88.

3.2.14. Synthesis of 3-(1,2,3,4-Tetrahydro-β-carboline-1-yl)-5-azaindole

Product **22** (Figures S27 and S28) was purified by column chromatography (DCM/MeOH 3:1) and crystallized from *n*-hexane. It was a light brown solid, with mp: 187–189 °C; yield: 69% (50 mg); ^{1}H-NMR (500 MHz, ([D$_6$]DMSO): δ = 2.75–2.82 (1H, m), 2.84–2.91 (1H, m), 3.07–3.13 (1H, m), 3.22–3.27 (1H, m), 5.63 (1H, s), 6.97–7.03 (2H, m), 7.18 (1H, d, *J* = 6.6 Hz), 7.32–7.38 (2H, m), 7.47 (1H, d, *J* = 5.4 Hz), 8.11 (1H, d, *J* = 4.5 Hz), 8.49 (1H, s,), 10.53 (1H, s,), and 11.50 (1H, s); ^{13}C-NMR (100 MHz, [D$_6$]DMSO): δ = 22.0, 42.1, 49.6, 107.3, 107.9, 111.6, 115.2, 118.1, 118.8, 121.3, 123.8, 126.6, 127.2, 135.0, 136.4, 140.3, 140.4, and 143.1. The analysis calculated for $C_{18}H_{16}N_4$ was C: 74.98, H: 5.59, and N: 19.43; found values were C: 74.93, H: 5.58, and N: 19.46.

3.2.15. Synthesis of 3-(4,5,6,7-Tetrahydrothieno[3,2-*c*]pyridin-4-yl)-5-azaindole

Product **23** (Figures S29 and S30) was purified by column chromatography (DCM/MeOH 9:1) and crystallized from *n*-hexane. It was a light beige solid, with mp: 113–115 °C; yield: 80% (52 mg); ^{1}H-NMR ([D$_6$]DMSO): δ = 2.80–3.23 (4H, m), 5.26 (1H, s), 6.48 (1H, d, *J* = 5.1 Hz), 6.98–7.40 (3H, m), 8.08 (1H, d, *J* = 5.5 Hz), 8.16 (1H, s), and 11.24 (1H, s); ^{13}C-NMR ([D$_6$]DMSO): δ = 25.8, 42.4, 52.0, 107.3, 117.7, 122.4, 123.6, 125.3, 126.7, 134.4, 137.9, 140.3, 140.4, and 143.3. The analysis calculated for $C_{14}H_{13}N_3S$ was C: 65.85, H: 5.13, and N: 16.46; found values were C: 65.84, H: 5.14, and N: 16.49.

3.2.16. Synthesis of 3-(2,3,4,5-Tetrahydro-*1H*-benzo[*c*]azepin-1-yl)-5-azaindole

Product **24** (Figures S31 and S32) was purified by column chromatography (DCM/MeOH 9:1) and crystallized from *n*-hexane. It was a light beige solid, with mp: 142–145 °C; yield: 65% (43 mg); ^{1}H-NMR ([D$_6$]DMSO): δ = 2.82–3.09 (6H, m), 5.40 (1H, s), 6.81 (1H, d, *J* = 6.7 Hz), 6.93–7.02 (1H, m), 7.07–7.14 (3H, m), 7.19 (1H, d, *J* = 7.3 Hz), 7.35 (1H, d, *J* = 7.3 Hz), 8.12 (1H, d, *J* = 5.7 Hz), 8.72 (1H, s), 11.27 (1H, brs); ^{13}C-NMR ($CDCl_3$): δ = 30.2, 35.8, 53.4, 106.8, 117.8, 123.6, 124.3, 126.1, 127.2, 127.7, 129.3, 130.0, 140.3, 140.7, 142.2, 143.2, and 144.0. The analysis calculated for $C_{17}H_{17}N_3$ was C: 77.54, H: 6.51, and N: 15.96; found values were C: 77.57, H: 6.52, and N: 15.94.

4. Conclusions

To conclude, the modified aza-Friedel–Crafts reaction was applied for the C-3 substitution of azaindoles. The reactions were achieved by using 3,4-dihydroisoquinoline; 6,7-dihydrothieno[3,2-*c*]pyridine; 3,4-dihydro-β-carboline; and 4,5-dihydro-*3H*-benz[*c*]azepine as imine substrates. The reactions of 4-azaindole and 6-azaindole with similar reactivity led to the formation of new 3-isoquinolyl-, 3-thieno[3,2-*c*]pyridyl-, 3-β-carbolinyl-, and 3-benz[*c*]azepinyl-azaindole derivatives. Starting from 5-azaindole, the modified aza-Friedel–Crafts reaction could only be performed by using 10 mol % of *p*-TSA as a catalyst. Systematic correlation was found between the reactivity of azaindoles and their pKa values. This latter observation allows us to explain why the direct coupling of 5-azaindole works only under acidic conditions. Namely, 5-azaindole (pKa = 8.42) has the highest basicity in the series of 4-, 5-, 6-, and 7-azaindoles. It is important to note that all reactions could be accelerated by using microwave irradiation.

Supplementary Materials: Supplementary materials are available online.

Author Contributions: F.F., K.B., and I.S. planned and designed the project. I.S. and K.B. performed the syntheses and characterized the synthesized compounds. K.B., F.F., and I.S. prepared the manuscript for publication. All authors discussed the results and commented on the manuscript.

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References

1. Ghose, A. K.; Herbertz, T.; Pippin, D. A.; Salvino, J. M.; Mallamo, J. P. Knowledge Based Prediction of Ligand Binding Modes and Rational Inhibitor Design for Kinase Grug Discovery. *J. Med. Chem.* **2008**, *51*, 5149–5155. [CrossRef] [PubMed]
2. Tang, J.; Hamajima, T.; Nakano, M.; Sato, H.; Dickerson, S.H.; Lackey, K.E. Knowledge-Based Design of 7-azaindoles as Selective B-Raf Inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4610–4614. [CrossRef] [PubMed]
3. Mérour, J.Y.; Buron, F.; Plé, K.; Bonnet, P.; Routier, S. The Azaindole Framework in the Design of Kinase Inhibitors. *Molecules* **2014**, *19*, 19935–19979. [CrossRef] [PubMed]
4. Pires, M.J.; Poeira, D.L.; Purificacao, S.I.; Marques, M.M.B. Synthesis of Substituted 4-, 5-, 6-, and 7-Azaindoles from Aminopyridines via a Cascade C–N Cross-Coupling/Heck Reaction. *Org. Lett.* **2016**, *18*, 3250–3253. [CrossRef] [PubMed]
5. Irie, T.; Sawa, M. 7-Azaindole: A Versatile Scaffold for Developing Kinase Inhibitors. *Chem. Pharm. Bull.* **2018**, *66*, 29–36. [CrossRef] [PubMed]
6. Manning, G.; Whyte, D.B.; Martinez, R.; Hunter, T.; Sudarsanam, S. The Protein Kinase Complement of the Human Genome. *Science* **2002**, *298*, 1912–1934. [CrossRef]
7. Bollag, G.; Tsai, J.; Zhang, J.; Zhang, C.; Ibrahim, P.; Nolop, K.; Hirth, P. Vemurafenib: The First Drug Approved for BRAF-Mutant Cancer. *Nature* **2012**, *11*, 873–886. [CrossRef] [PubMed]
8. Tsai, J.; Lee, J.T.; Wang, W.; Zhang, J.; Cho, H.; Mamo, S.; Bremer, R.; Gillette, S.; Kong, J.; Haass, N.K.; et al. Discovery of a Selective Inhibitor of Oncogenic B-Raf Kinase with Potent Antimelanoma Activity. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3041–3046. [CrossRef]
9. Ito, M.; Yamazaki, S.; Yamagami, K.; Kuno, M.; Morita, Y.; Okuma, K.; Nakamura, K.; Chida, N.; Inami, M.; Inoue, T.; et al. A Novel JAK Inhibitor, Peficitinib, Demonstrates Potent Efficacy in a Rat Adjuvant-Induced Arthritis Model. *J. Pharmacol. Sci.* **2017**, *133*, 25–33. [CrossRef]
10. Tap, W.D.; Wainberg, Z.A.; Anthony, S.P.; Ibrahim, P.N.; Zhang, C.; Healey, J.H.; Chmielowski, B.; Staddon, A.P.; Cohn, A.L.; Shapiro, G.I.; et al. Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor. *Engl. J. Med.* **2015**, *373*, 428–437. [CrossRef]
11. Adams, N.D.; Adams, J.L.; Burgess, J.L.; Chaudhari, A.M.; Copeland, R.A.; Donatelli, C.A.; Drewry, D.H.; Fisher, K.E.; Hamajima, T.; Hardwicke, M.A.; et al. Discovery of GSK1070916, A Potent and Selective Inhibitor of Aurora B/C Kinase. *J. Med. Chem.* **2010**, *53*, 3973–4001. [CrossRef] [PubMed]
12. Tokushige, H.; Inatani, M.; Nemoto, S.; Sakaki, H.; Katayama, K.; Uehata, M.; Tanihara, H. Effects of Topical Administration of Y-39983, a Selective Rho-Associated Protein Kinase Inhibitor, on Ocular Tissues in Rabbits and Monkeys. *Invest. Ophthalmol. Vis. Sci.* **2007**, *48*, 3216–3222. [CrossRef] [PubMed]
13. Szatmári, I.; Sas, J.; Fülöp, F. C-3 Functionalization of Indole Derivatives with Isoquinolines. *Curr. Org. Chem.* **2016**, *20*, 2036–2038. [CrossRef]
14. Santos, A.; Mortinho, A.; Marques, M. Metal-Catalyzed Cross-Coupling Reactions on Azaindole Synthesis and Functionalization. *Molecules* **2018**, *23*, 2673. [CrossRef] [PubMed]
15. Ghobrial, M.; Harhammer, K.; Mihovilovic, M.D.; Schmürch, M. Facile, Solvent and Ligand Free Iron Catalyzed Direct Functionalization of N-Protected Tetrahydroisoquinolines and Isochroman. *Chem. Commun.* **2010**, *46*, 8836. [CrossRef] [PubMed]
16. Ghobrial, M.; Schmürch, M.; Mihovilovic, M.D. Direct Functionalization of (Un)protected Tetrahydroisoquinoline and Isochroman under Iron and Copper Catalysis: Two Metals, Two Mechanisms. *J. Org. Chem.* **2011**, *76*, 8781–8793. [CrossRef] [PubMed]
17. Szatmári, I.; Sas, J.; Fülöp, F. Catalyst-Free Coupling of Indole Derivatives with 3,4-dihydroisoquinoline and Related Compounds. *Tetrahedron Lett.* **2013**, *54*, 5069–5071. [CrossRef]
18. Sas, J.; Szatmári, I.; Fülöp, F. One-Pot α-Arylation of β-Carboline with Indole and Naphthol Derivatives. *Curr. Org. Synth.* **2016**, *13*, 611–616. [CrossRef]
19. Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. Synthesis and Vasodilator Effects of Rutaecarpine Analogues which Might be Involved Transient Receptor Potential Vanilloid Subfamily, Member 1 (TRPV1). *Bioorg. Med. Chem.* **2009**, *17*, 2351–2359. [CrossRef]
20. Herz, W.; Tsai, L. Sulfur Analogs of Isoquinolines. IV. The Pictet-Gams Reaction and Attempts to Prepare Analogs of Papaverine1,2. *J. Chem. Soc.* **1955**, *77*, 3529–3533. [CrossRef]

21. Meyers, A.I.; Hutchings, R.H. The Asymmetric Synthesis of 1-alkyl-2,3,4,5-tetrahydro-benzazepines and Benzo[β]-1-azabicyclo[5,3,1]decanes. *Tetrahedron* **1993**, *49*, 1807–1820. [CrossRef]
22. Jakubec, P.; Helliwell, M.; Dixon, D.J. Cyclic Imine Nitro-Mannich/ Lactamization Cascades: A Direct Stereoselective Synthesis of Multicyclic Piperidinone Derivatives. *D. J. Org. Lett.* **2008**, *10*, 4267–4270. [CrossRef] [PubMed]
23. Khodaei, M.M.; Khosropour, A.R.; Moghanian, H. A Simple and Efficient Procedure for the Synthesis of Amidoalkyl Naphthols by *p*-TSA in Solution or under Solvent-Free Conditions. *Synlett* **2006**, *6*, 916–920. [CrossRef]
24. Khosropour, A.R.; Khodaei, M.M.; Moghanian, H. A Facile, Simple and Convenient Method for the Synthesis of 14-Alkyl or Aryl-14-H-Dibenzo[a,j]xanthenes Catalyzed by *p*TSA in Solution and Solvent-Free Conditions. *Synlett* **2005**, *6*, 955–958. [CrossRef]
25. Csütörtöki, R.; Szatmári, I.; Mándi, A.; Kurtán, T.; Fülöp, F. Synthesis of Hydroxynaphthyl-Substituted α-Amino Acid Derivatives via a Modified Mannich Reaction. *Synlett* **2011**, *13*, 1940–1946.
26. Marvin was used for calculating pKa values of azaindoles, Marvin 16.12.12.0, ChemAxon. 2016. Available online: http://www.chemaxon.com.

Sample Availability: Samples of the compounds are not available from the authors.

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Synthesis and conformational analysis of naphthoxazine-fused phenanthrene derivatives

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Abstract: Synthesis of new phenanthr[9,10-*e*][1,3]oxazines was achieved by direct coupling of 9-phenanthrol with cyclic imines in the modified *aza*-Friedel-Crafts reaction followed by the ring closure of the bifunctional aminophenanthrols with formaldehyde. Aminophenanthrol type Mannich bases were synthesized and transformed to phenanthr[9,10-*e*][1,3]oxazines via [4+2] cycloaddition. Detailed NMR structural analyses of the new polyheterocycles as well as conformational studies including DFT modelling were performed. The relative stability of *o*-QMs was calculated, the geometries obtained compared with the experimentally determined NMR structures and, hereby, the regioselectivity of the reactions has been assigned.

Keywords: Modified Mannich reaction - Cyclic imines - [4+2] cycloaddition - NMR spectroscopy - Conformational analysis - DFT calculations.

1. Introduction

9-Phenanthrol is one of the most attractive structural units present in a large number of biologically active compounds. It is the identified inhibitor of the transient receptor potential melastatin (TRPM) 4 channels, a Ca^{2+} activated non-selective cation channel whose mechanism of action remains to be determined [1-4]. Subsequent studies proved that it modulates smooth muscle contraction in bladder and cerebral arteries, affects spontaneous activity in neurons and in the heart, and reduces the lipopolysaccharide-induced cell death [5-7].

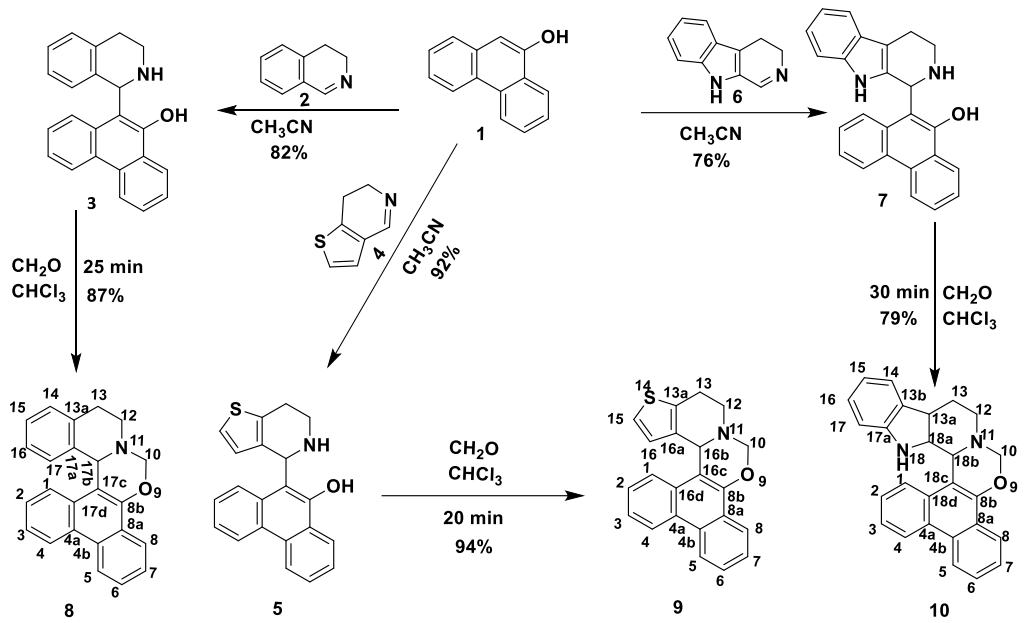
The Mannich reaction is one of the most important C–C bond forming reaction in organic synthesis [8-10]. This synthetic pathway is widely used in the formation of secondary and tertiary amine derivatives and it is a key step in the syntheses of numerous bioactive molecules and complex natural products [11,12]. In one of the special variations of the modified Mannich reaction (*m*MR), 1- and 2 naphthol were applied as electron-rich aromatic compounds [13,14]. Mechanistically, the modified *aza*-Friedel-Crafts reaction can be interpreted as a special *m*MR where electron-rich aromatic compounds such as 1- and 2-naphthol and their *N*-containing analogues were reacted with a wide range of cyclic imines to furnish aminonaphthols [15,18] aminoquinolinols [16] or aminoisoquinolinols [16,19]. Accordingly, our first aim was to examine the reactivity of 9-phenanthrol with different cyclic imines in the modified *aza*-Friedel-Crafts reaction.

Recent publications pointed out that *ortho*-quinone methides (*o*-QMs) can also be generated from the Mannich bases after thermal elimination of the amine [20]. This reactive moiety can be stabilized by reacting with different dienophiles [14,22] or can participate in a [4+2] cycloaddition with cyclic imines to form new heterocycles [18,23,24]. Very recently the transformations of functionalized 1-aminobenzyl-2-naphthols via [4+2] cycloaddition has been examined. It was found that the regio- and diastereoselectivity of the cycloaddition depends on the functional group on the phenyl substituent [25]. Based on this, our aim was to synthesize aminobenzylphenanthrols or functionalized aminobenzylphenanthrols and to study their reactivity with cyclic imines as novel precursor Mannich bases in [4+2] cycloaddition. Finally, both structure and conformational behavior of the novel polyheterocycles was planned to be studied by NMR spectroscopy and accompanying theoretical quantum chemical (QC) calculations.

2. Results

2.1. Synthesis

To examine the extension possibility of 9-phenanthrol (**1**) in the modified *aza*-Friedel-Crafts reaction, **1** was reacted with 1.5 equiv of 3,4-dihydroisoquinoline (**2**) [26] (Scheme 1) under neat conditions at 80 °C. After a reaction time of 120 min, the desired product **3** was isolated only with a yield of 10%. By increasing the temperature to 100 °C the yield of **3** was slightly increased to 19%. Under these conditions the yield was not yet satisfactory and the appearance of side products was found, thus, acetonitrile was tried as solvent. Now, at the reflux temperature of acetonitrile (90 °C) **3** was isolated in a yield of 49%. The product was readily separated out from the solvent; therefore, acetonitrile proved to be an optimal solvent. To further improve the yield, the reaction was repeated under microwave conditions. In this case the reaction was driven at 100 °C and after a short reaction time (10 min.) **3** was isolated in a yield of 67%, that could be improved to 82% by increasing the reaction time to 20 min (Table 1). It should be noted that the optimal workup procedure remained the filtration of the formed product from the cooled down reaction mixture. Subsequently, with the satisfactory optimal reaction conditions in hand, the extension possibility of the reaction was tested by using various cyclic imines, including 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) [27] or 3,4-dihydro-*β*-carboline (**6**) [28]. The reactions afforded the new 1-(9-phenanthrol-10-yl)-thieonopyridine (**5**) and 1-(9-phenanthrol-10-yl)-*β*-carboline (**7**) in a yield of 92% and 76%, respectively (Table 1).



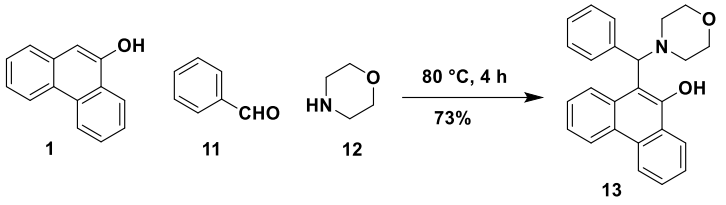
Scheme 1 Synthesis and ring closures of the bifunctional compounds **3**, **5** and **7**

The ring closures of aminophenanthrols **3**, **5** and **7** were performed with 35% aqueous formaldehyde in $CHCl_3$ at room temperature. The reactions proved to be complete after relatively short reaction times and phenanthrooxazines **8**-**10** were isolated in excellent yields by simple crystallization from *n*-hexane.

Table 1. Reaction conditions for the synthesis of aminophenanthrols **3**, **5** and **7**

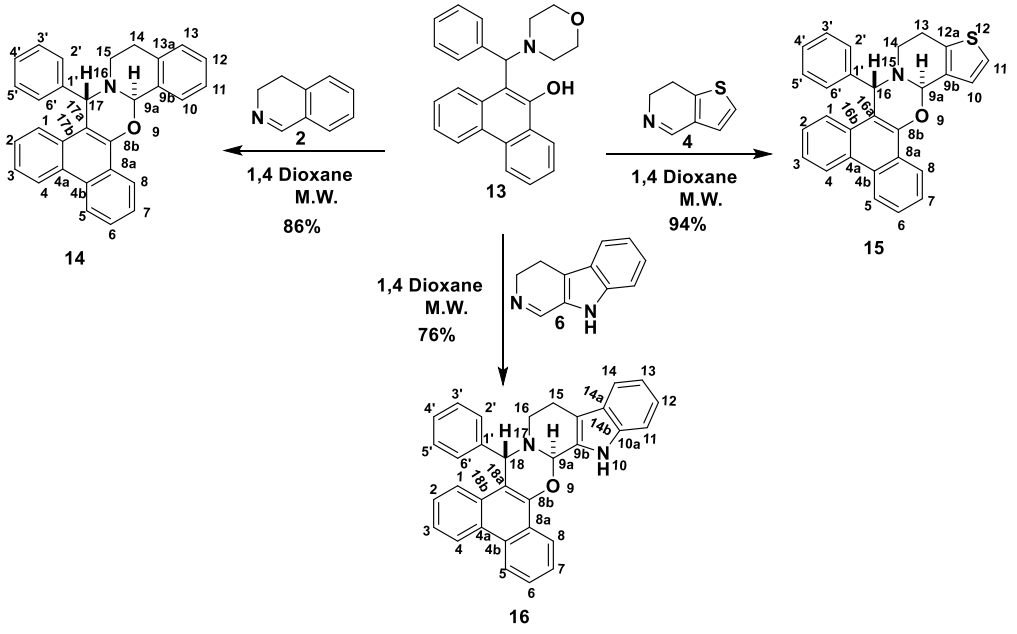
Products	Type of heating	Solvent	Reaction Time	Temperature	Yield (%)
3	Oil bath	-	120 min	80 °C	10
	Oil bath	-	60 min	100 °C	19
	Oil bath	Acetonitrile	60 min	90 °C	49
	M.W	Acetonitrile	10 min	100 °C	67
	M.W	Acetonitrile	20 min	100 °C	**82**
5	M.W	Acetonitrile	20 min	100 °C	72
	M.W	Acetonitrile	35 min	100 °C	**92**
7	M.W	Acetonitrile	20 min	100 °C	63
	M.W	Acetonitrile	40 min	100 °C	**76**

To test aminophenanthrols in cycloaddition reaction, first the synthesis of the precursor **13** was achieved. Accordingly, 9-phenanthrol (**1**) was reacted with morpholine in the presence of benzaldehyde. The reaction was carried out under solvent-free conditions at 80 °C. After 4 hours reaction time the desired 10-morpholinobenzyl-9-phenanthrol (**13**) was isolated by crystallization with *n*-hexane (Scheme 2).



Scheme 2. Synthesis of 10-morpholinobenzyl-9-phenanthrol (**13**)

First, the aminophenanthrol **13** was reacted with 3,4-dihydroisoquinoline **2** as dienophile. The reaction was performed in 1,4-dioxane under microwave irradiation and three different temperatures (60 °C, 80 °C and 100 °C) were tested. In our first experiment the reaction was performed at 60 °C, after a relatively short reaction time, the desired product (**14**) was isolated only in a low yield (47%). Since the yield was not satisfactory the reaction was repeated at 80 °C and 100 °C. As Table 2 shows, 80 °C and 15 min. reaction time was found to be the optimal reaction condition. The series of dienophiles was extended by using 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) and 3,4-dihydro-*β*-carboline (**6**) respectively. The optimal conditions together with the yields are listed in Table 2. Since during the reaction two new stereogenic centres are generated, two epimeric structures (**a** and **b**) can be obtained. The reaction was monitored by TLC, and the compositions of the crude reaction mixtures were verified by ^{1}H-NMR analysis. All the reactions were found to be diastereoselective, and the relative configuration of H-9a:H-17 (**14**); H-9a:H-16 (**15**); H-9a:H-18 (**16**) proved to be *trans*, based on the detailed NMR analysis (*vide infra*).

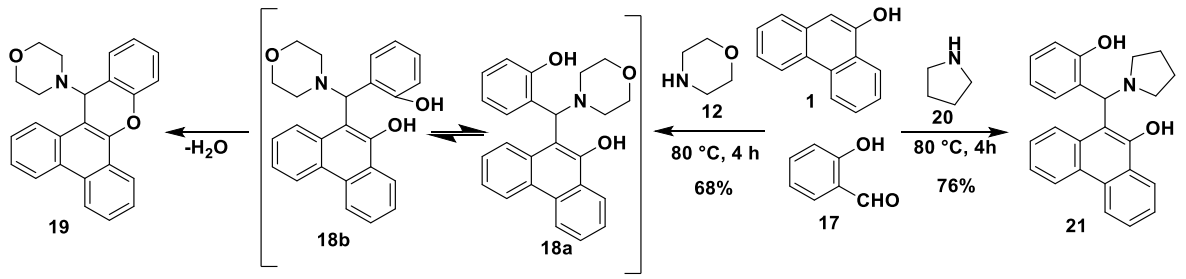


Scheme 3. Synthesis of phenanthr[9,10-*e*]oxazine derivatives (**14** - **16**)

Table 2. Reaction conditions for the synthesis of phenanthr[9,10-*e*]oxazine derivatives (**14** - **16**)

Product	Reaction Time	Temperature (°C)	Yield (%)
14	15 min	60	47
		80	**86**
		100	29
15	15 min	60	52
		80	**94**
		100	37
16	15 min	60	21
		80	**76**
		100	32

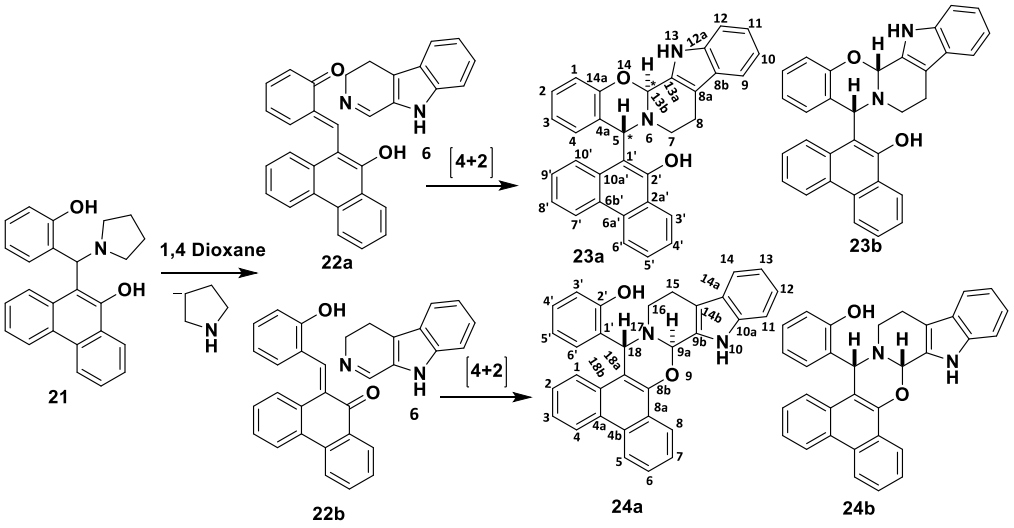
Next, we wanted to investigate how *o*-QMs generated from functionalized aminophenanthrol derivatives can influence on the [4+2] cycloaddition reaction. Accordingly, 9-phenanthrol and salicylic aldehyde were reacted in the presence of morpholine. The reaction was carried out under neat conditions at 80 °C. The characteristic spot that formed according to the TLC was isolated. The NMR spectra of the formed compound confirmed the structure of **19**; the formation of the dibenzo[*a*,*c*]xanthen (**19**) side-product can be explained by the water elimination from the diole **18**. In this latter modified Mannich reaction the availability of the nucleophile (morpholine) was postulated, therefore it was replaced by pyrrolidine. The starting materials were heated at 80 °C under neat conditions. After a reaction time of 4 h the perused phenanthrol derivative **21** was isolated in a yield of 76% (Scheme 4).



Scheme 4. Synthesis of the products **19** and **21**

To test the scope and limitations of the [4+2] cycloaddition, the precursor **21** was first reacted with 3,4-dihydro-*β*-carboline as dienophile. The reaction was performed in 1,4-dioxane at three different temperatures (60 °C, 80 °C and 100 °C) under microwave irradiation (Table 3). Since after the thermal decomposition of the starting material **21** two types of *o*-QMs (**22a** and **22b**) can be formed that can lead to the formation of two regioisomers and two diastereomers (Scheme 5), the composition

of the crude reaction mixture was verified by ^{1}H-NMR analysis. Different reaction conditions were applied as depicted in Table 3. In all cases the reaction was found to be regio- and diastereoselective. The detailed NMR analysis (*vide infra*) confirmed that the formed/isolated product of **22** is a phenanthroxazine and the relative configuration of H-9a:H-18 (**24a**) is *trans*.

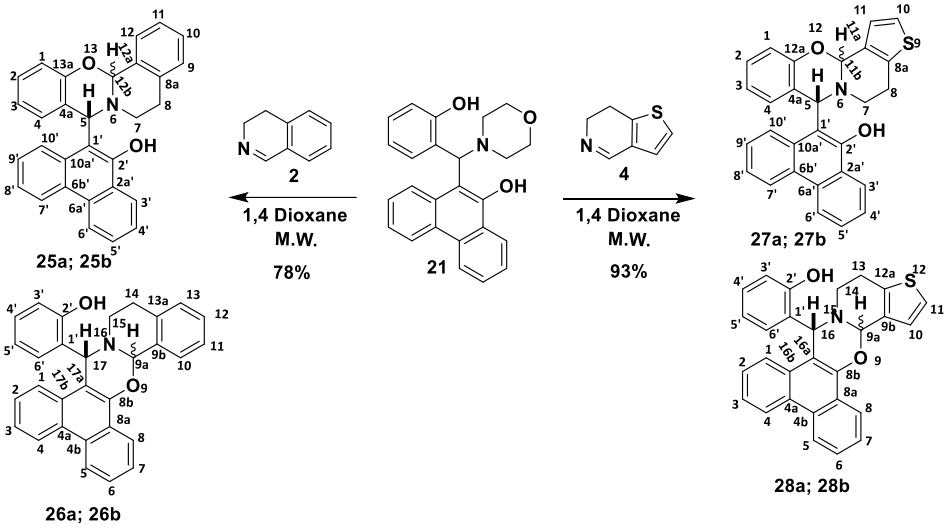


Scheme 5. [4+2] cycloaddition between **21** and 3,4-dihydro-*β*-carboline

Table 3. Optimizing of the reaction conditions for the synthesis of products **24b**, **26b** and **28b**

Products	Reaction Time	Temperature (°C)	Yield (%)
23a,b **24a,b**	15 min	60	48
		80	**85**
		100	33
25a,b **26a,b**	15 min	60	28
		80	**78**
		100	19
27a,b **28a,b**	15 min	60	51
		80	**93**
		100	38

The reaction was then extended by using 3,4-dihydroisoquinoline (**2**) and 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) as cyclic imines (Scheme 6). Also in these cases, the regio- and diastereoselectivity of the reaction was proved: the detailed NMR analysis (*vide infra*) adequately supported that the isolated products are the *trans* phenanthroxazines (**26a**, **28a**, Scheme 6). The optimal reaction conditions together with the yields are summarized in Table 3.



Scheme 6. Reaction of functionalyzed aminophenanthrol **21** with cyclic imines

2.2. Structural and conformational analysis.

The complete ^{1}H and ^{13}C NMR study of both the diastereomeric phenanthr[9,10-*e*]oxazine derivatives **14** - **16**, and the regioisomeric/diastereotopic phenanthroxazine derivatives **24a**, **26a**, and **28a** showed the identical stereoisomerism (only one set of NMR spectra obtained); the NMR analyses of the *β*-carboline derivative **16** and the thiophene compound **28a** were exemplarily utilized. The same stereoisomeric results were obtained for **14**, **15**, **24a**, and **26a**, respectively. For the corresponding structure elucidation, in addition to the NMR spectra (chemical shift, coupling constants, NOE's) also the quantum chemical calculations are examined.

*Detailed NMR analysis of the new phenanthr[9,10-e]oxazine **16.***

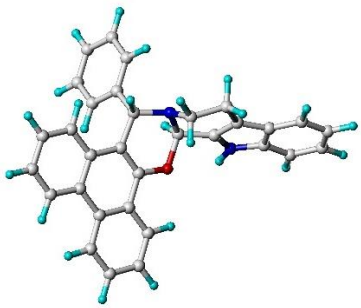
The determination of the relative configuration of **14 – 16** is based mainly on NOE interactions and their comparison with the corresponding calculated QC structures (exemplary, the *β*-carboline derivative **16** was examined; see Figure 1). Only one of the two possible diastereomers fits the experimental results: the position of the two methine hydrogens H-9a and H-18 was always found to be *trans*. The complete spatial information, exemplarily found in **16**, is collected in Table 4; the NOE's found are compared with the calculated distances from QM calculations.

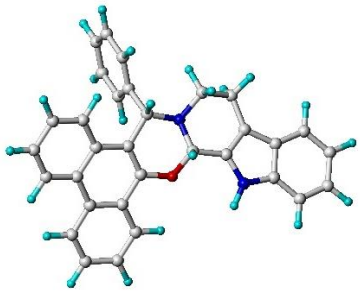
Table 4**. Experimental NOE's and calculated distances in** 16**.**

positions	1/18	9a/18	18/16(ψ-eq)	9a/16(ψ-eq)	9a/16(ψ-ax)	9a/10	14/15(ψ-ax)	14/15(ψ-eq)
measured NOE	strong	medium	strong	weak	weak	medium	weak	medium
Calculated distances d [Å]	2.2	3.6	2.2	4.1	3.8	2.8	4.3	2.9
	2.2(*cis*)	2.7(*cis*)	2.7(*cis*)	3.8(*cis*)	2.7(*cis*)	3.0(*cis*)	3.4(*cis*)	2.9(*cis*)

NOE-estimated distances d [Å]	2.2	3.4	2.3	4.4	4.3	2.8	3.5	3.0

ψ-eq (smaller signal at higher field); ψ-ax (the corresponding broadened signal at lower field).





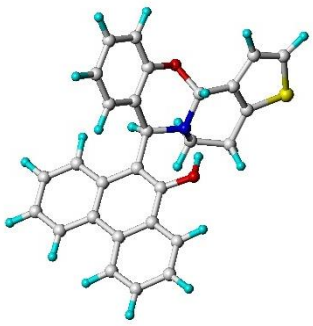
16a *trans* (0.00 kcal/mol) **16b** *cis* (3.34 kcal/mol)

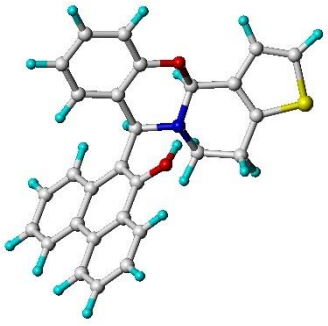
Figure 1. The most stable structures of the diastereotopic heterocycle **16**

Detailed NMR analysis of the new phenanthr[9,10-e]oxazine ***27a,b–28a,b***.

In analogy to previous investigations [25] and to the results of the structural analyses of **14** – **16** (*vide supra*) the reaction products starting from **21** yielded in all cases the *trans*-isomers **24a**, **26a**, and **28a**. Their NMR spectra are akin to the corresponding spectra of the compounds without an OH group at position 2′ (**14** – **16**) and to the compounds having a naphthalene moiety instead of phenanthrene [25].

To get the preferred stereoisomers of **28a**,**b** the *trans*/*cis* diastereomers of the regioisomers were calculated by the DFT method. Both the most stable structures and the corresponding energy differences are given in Figure 2; hereby, **28a** could be confirmed to be the most stable structure. Energy differences around 1 kcal/mol to the next coming structure are rather unequivocal. Consequently, this structure of the *trans*-isomer **28a** will be adjusted with the available experimental NMR [$\delta(^1H)$/ppm, $\delta(^{13}C)$/ppm, $^nJ_{H,H}$/Hz)] and spatial NMR information (qualitative NOE's).





27a *trans* (3.98 kcal/mol) **27b** *cis* (1.85kcal/mol)

28a *trans* (0.00 kcal/mol) **28b** *cis* (4.33 kcal/mol)

Figure 2. The most stable structures of the regioisomeric heterocycle **27a**,**b** and **28a**,**b** including their *trans* (**a**) and *cis* (**b**) diastereomeric possibilities.

First, all ^{1}H and ^{13}C NMR chemical shifts for **28a** could be unequivocally assigned. Hereby, the two singlets of the protons H-16 and H-9a, and the AX spin system of thiophene protons H-10 and H-11 can serve as useful starting points. The latter is the only spin system of aromatic protons with two doublets and the characteristic *ortho*-coupling constant of ca. 5.2 Hz. The high-field doublet (at 7.09 ppm) was assigned to the H-10 proton due to the substantial NOE to the tertiary proton H-9a. On the other hand, no NOE between H-10 and the second tertiary proton (H-16) could be measured: The *trans* position of these two protons and, hereby, the *trans* stereochemistry of **28a** can be proved. Further, the HMBC connectivity of same proton singlet (H-16) established the access to both the ^{1}H and ^{13}C assignments of the present aromatic moieties [(i) to H-6′, C-1′, and C-2′ of the phenolic, and (ii) to H-16a and H-8b of the phenanthryl parts of the molecule], and to the piperidyl moiety via C-14. The *trans* stereochemistry of **28a** could be proved additionally by strong NOEs of H-16 to one of the H-14 protons and to the aromatic proton H-6′ and to one of the H-14 protons whereby H-12a did not show any NOE to protons of the piperidyl ring.

The excellent agreement between the proton, proton distances, as calculated, and the existence of strong NOEs in **28a** can serve as further excellent proof of the present regio- and diastereoselectivity. Identical ^{1}H/^{13}C NMR studies of the isoquinoline (**25a**,**b**-**26a**,**b**) and the *β*-carboline analogues (**23a**,**b**-**24a**,**b**) came to the same result: also these compounds prefer the same regioisomerism in *trans*-configuration **24a** and **26a**, respectively.

3. Materials and Methods

3.1. General Methods

Melting points were determined on a Hinotek X-4 melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F254 plates were used for TLC. The microwave reactions were performed with a CEM Discover SP microwave reactor.

The used starting cyclic imines 3,4-dihydroisoquinoline (**2**) [26], 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) [27] and 4,9-dihydro-*β*-carboline (**6**) [28] were synthesized according to the process known from the literature.

Quantum chemical calculations were performed using the Gaussian 09 program package [29] and carried out on LINUX clusters. The various different conformations and configurations of the studied compounds were optimized [30]. The B3LYP density functional method was selected for all calculations. The method is based on Becke's three-parameter hybrid functionals [31] and the correlation functional of Lee, Yang and Parr [32]. All optimizations were carried out without any restriction at this B3LYP/6-311G(d,p) level of theory [33-35].

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, CD_2Cl_2, or [D6]DMSO solution in 5 mm tubes at room temperature on a Bruker Avance NEO spectrometer at 400.18 (^{1}H) MHz, or on a Bruker Avance spectrometer at 500.17 (^{1}H) and 125.77 (^{13}C) MHz, or on a Bruker Avance III spectrometer at 600.13 (^{1}H) and 150.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. All spectra (^{1}H, ^{13}C, gs-H, H COSY, edited HSQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER software.

3.2. Procedures

General procedure for the synthesis of hydroxyphenanthryl-isoquinoline, -thienopyridine and -*β*-carboline (3, 5 and 7)

The mixture of the cyclic imine (3,4-dihydroisoquinoline (**2**), 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) or 4,9-dihydro-*β*-carboline (**6**) 0.51 mmol) and 9-phenanthrol (**1**: 100 mg, 0.51 mmol) in acetonitrile (5 mL) was placed in a 10 mL pressurized reaction vial and heated under microwave conditions at 100 ^{o}C. After the reaction completed the mixture was cooled down and the formed crystals was filtered and washed with could acetonitrile (2x 5 mL).

*3.2.1. 1-(9-Hydroxyphenanthr-10-yl)-1,2,3,4-tetrahydroisoquinoline (**3**)*

Reaction time: 20 min; Recrystallized from *i*Pr$_2$O (5 mL); R_f=0.38 (*n*-hexane/ EtOAc, 2:1); 135 mg (82%); withe crystals; *Mp*. 147-149 °C; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 8.80 (1H, d, *J* = 8.3 Hz, H-4 or H-5), 8.80 (1H, d, *J* = 8.3 Hz, H-4 or H-5), 8.23 (1H, d, *J* = 8.3 Hz, H-8), 8.17 (1H, d, *J* = 8.2 Hz, H-1), 7.67 (1H, m, H-6), 7.66 (1H, m, H-2), 7.60 (1H, t, *J* = 7.5 Hz, H-7), 7.52 (1H, t, *J* = 7.7 Hz, H-3), 7.18 (1H, d, *J* = 7.5 Hz, H-5'), 7.09 (1H, t, *J* = 7.4 Hz, H-6'), 6.86 (1H, t, *J* = 7.4 Hz, H-7'), 6.58 (1H, d, *J* = 7.9 Hz, H-8'), 6.10 (1H, s, H-1'), 3.44 (1H, m, H-3'), 3.20 (2H, m, H-3', H-4'), 2.90 (1H, d, *J* = 14.1 Hz, H-4'); elemental analysis calcd (%) for $C_{23}H_{19}NO$ (323.41): C 84.89, H 5.89, N 4.30; found: C 84.82, H 5.90, N 4.26.

3.2.2. *4-(9-Hydroxyphenanthr-10-yl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (**5**).*

Reaction time: 35 min; Recrystallized from *i*Pr$_2$O (4 mL); R_f=0.38 (*n*-hexane/ EtOAc, 2:1); 155 mg (92%); Light biege crystals; Mp. 191-188 °C; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 14.33 (1H, d, *J* = 7.7 Hz, H-4 or H-5), 8.78 (1H, d, *J* = 7.9 Hz, H-4 or H-5), 8.19 (1H, d, *J* = 8.7 Hz, H-1), 8.17 (1H, dd, *J* = 8.2, 1.2 Hz, H-8), 7.66 (1H, m, H-6), 7.65 (1H, m, H-2), 7.60 (1H, t, *J* = 7.5 Hz, H-7), 7.51 (1H, t, *J* = 7.7 Hz, H-3), 7.06 (1H, d, *J* = 5.2 Hz, H-6'), 6.16 (1H, d, *J* = 5.2 Hz, H-7'), 6.01 (1H, s, H-1'), 4.74 (1H, br s, H-2'), 3.53 (1H, m, H-3'), 3:13 (2H, m, H-3', H-4'), 2.94 (1H, m, H-4'); elemental analysis calcd (%) for $C_{21}H_{17}NOS$ (331.43): C 76.10, H 5.17, N 4.23; found: C 76.25, H 5.17, N 4.13.

*3.2.3. 1-(9-Hydroxyphenanthr-10-yl)-1,2,3,4-tetrahydro-β-carboline (**7**)*

Reaction time: 40 min; Recrystallized from *i*Pr$_2$O (6 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 146 mg (76%); brown crystals; Mp. 205-207 °C; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 9.76 (1H, s, 9-OH), 8.83 (1H, d, *J* = 8.2 Hz, H-4 or H-5), 8.81 (1H, d, *J* = 8.2 Hz, H-4 or H-5), 8.29 (1H, d, *J* = 8.3 Hz, H-8), 8.17 (1H, dd, *J* = 8.1, 0.9 Hz, H-1), 7.68 (2H, m, H-6, H-7), 7.59 (1H, t, *J* = 7.6 Hz, H-2), 7.55 (1H, t, *J* = 7.5 Hz, H-3), 7.44 (1H, m, H-5′); 7.15 (1H; m; H-8′), 6.95 (2H, m, H-6′, H-7′), 6.24 (1H, s, H-1′), 3.55 (1H, dd, *J* = 11.5, 5.1 Hz, H-3′), 3.18 (1H, ddd, *J* = 11.6, 11.6, 5.1 Hz, H-3′), 3.02 (1H, m, H-4′); 2:87 (1H, dd, *J* = 15.4 Hz, H-4′); elemental analysis calcd (%) for C$_{25}$H$_{20}$N$_2$O (364.45): C 82.39, H 5.53, N 7.69; found: C 82.25, H 5.49, N 7.72.

General procedure for the synthesis of phenanthr[9,10-*e*][1,3]oxazinoisoquinoline,-thienopyridine and -*β*-carboline (8-10)

Aminophenanthrols (**3**, **5** and **7**; 0.25 mmol) was dissolved in 10 mL CHCl$_3$, aqueous solution of formaldehyde (20 mg, 0.66 mmol, 35%) was then added and the mixture was stirred at room temperature. The mixture was next extracted with 10 mL distillated water. The organic phase was collected, and then dried on Na$_2$SO$_4$. The solvent was evaporated off and the residue was crystallized from *n*-hexane (10 mL).

*3.2.4. Phenanthr[9,10-e][1,3]oxazino[4,3-a]isoquinoline (**8**)*

Reaction time: 25 min; Recrystallized from *n*-hexane: *i*Pr$_2$O (4:1, 5 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 73 mg (87%); Purple crystals. Mp: 139-141 °C ^{1}H NMR (CD$_2$Cl$_2$, 500 MHz): δ 8.71 (2H, m, H-4, H-5), 8.28 (1H, d, *J* = 8.1 Hz, H-8), 7.73 (1H, m, H-1), 7.70 (1H, m, H-6), 7.63 (1H, t, *J* = 7.5 Hz, H-7), 7.54 (2H, m, H-2, H-3), 7.24 (1H, d, *J* = 7.3 Hz, H-14), 7.20 (1H, t, *J* = 7.3 Hz, H-15), 6.97 (1H, t, *J* = 7.4 Hz, H-16), 6.85 (1H, d, *J* = 7.7 Hz, H-17), 5.54 (1H, s, H-17b), 4.76 (1H, d, *J* = 7.0 Hz, H-10), 4.68 (1H, d, *J* = 6.9 Hz, H-10), 3.87 (1H, m H-12), 2.99 (3H, m, H-12, H-13); elemental analysis calcd (%) for C$_{24}$H$_{19}$NO (337.42): C 85.43, H 5.68, N 4.15; found: C 85.35, H 5.56, N 4.20.

*3.2.5. Phenanthr[9,10-e][1,3]oxazino[4,3-a]thieno[3,2-c]pyridine (**9**)*

Reaction time: 20 min; Recrystallized from *n*-hexane: *i*Pr$_2$O (4:1, 4 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 80 mg (94%); Yelow crystals. Mp: 186-188 °C ^{1}H NMR (CD$_2$Cl$_2$, 500 MHz): δ 8.70 (1H, d, *J* = 8.1 Hz, H-4), 8.69 (1H, d, *J* = 8.2 Hz, H-5), 8.26 (1H, d, *J* = 8.1 Hz, H-8), 7.99 (1H, d, *J* = 8.1 Hz, H-1), 7.69 (1H, t, *J* = 7.5 Hz, H-6), 7.63 (2H, m, H-2, H-7), 7.58 (1H, t, *J* = 7.7 Hz, H-3), 6.95 (1H, d, *J* = 5.2 Hz, H-15), 6.66 (1H, d, *J* = 5.2 Hz, H-16), 5.67 (1H, s, H-16b), 4.96 (1H, d, *J* = 6.9 Hz, H-10), 4.93 (1H, d, *J* = 6.9 Hz, H-10), 3.75 (1H, ddd, *J* = 14.2, 12.2, 6.0 Hz, H-12), 3.66 (1H, dd, *J* = 14.3, 6.8 Hz, H-12), 3.03 (1H, m, H-13), 2.87 (1H, dd, *J* = 17.1, 5.7 Hz, H-13); elemental analysis calcd (%) for C$_{22}$H$_{17}$NOS (343.44): C 76.94, H 4.99, N 4.08; found: C 76.86, H 5.02, N 4.13.

*3.2.6. Phenanthr[9,10-e][1,3]oxazino[4,3-a]-β-carboline (**10**)*

Reaction time: 30 min; Recrystallized from *n*-hexane: *i*Pr$_2$O (4:1, 5 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 74 mg (79%); Dark pink crystals. Mp: 183-185 °C ^{1}H NMR (CD$_2$Cl$_2$, 500 MHz): δ 8.78 (1H, d, *J* = 8.2 Hz, H-4), 8.71 (1H, d, *J* = 8.3 Hz, H-5), 8.28 (1H, dd, *J* = 8.2, 0.7 Hz, H-8), 8.15 (1H, d, *J* = 8.1 Hz, H-1), 7.85 (1H, br s, H-18), 7.76 (1H, t, *J* = 7.5 Hz, H-2), 7.71 (1H, t, *J* = 7.6 Hz, H-6), 7.66 (1H, t, *J* = 7.5 Hz, H-3), 7.64 (1H, t, *J* = 7.6 Hz, H-7), 7.51 (1H, m, H-14), 7.11 (1H, m, H-17), 7.06 (2H, m, H-15, H-16), 5.92

(1H, s, H-18b), 5.01 (1H, d, *J* = 7.1 Hz, H-10), 4.95 (1H, d, *J* = 7.1 Hz, H-10), 3.77 (1H, ddd, *J* = 14.2, 12.0, 5.7 Hz, H-12), 3.71 (1H, dd, *J* = 14.3, 6.3 Hz, H-12), 2.99 (1H, dddd, *J* = 16.2, 11.9, 6.7, 2.4 Hz, H-13), 2.83 (1H, dd, *J* = 16.3, 5.1 Hz, H-13); elemental analysis calcd (%) for $C_{26}H_{20}N_2O$ (376.46): C 82.95, H 5.36, N 7.44; found: C 83.03, H 5.45, N 7.32.

*3.2.7. 10-[(Phenyl)-morpholin-4-yl-methyl]-9-phenanthrol (**13**)*

9-Phenanthrol (1.0 g, 5.13 mmol), benzaldehyde (0.54 g, 5.13 mmol) and morpholine (0.45 g, 5.13 mmol) were stirred and heated at 80 °C under neat conditions for 4 h.. The residue was crystallized with *n*-hexane (14 mL) and recrystallized from *i*Pr$_2$O (9 mL) R_f=0.38 (*n*-hexane/ EtOAc, 2:1); 1.38g (73%); Light biege crystals; m.p. 107-109 °C; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 14.37 (1H, s, 9-OH), 8.75 (1H, d, *J* = 7.6 Hz, H-5), 8.71 (1H, d, *J* = 7.8 Hz, H-4), 8.39 (1H, m, H-8), 8.07 (1H, d, *J* = 8.3 Hz, H-1), 7.69 (4H, m, H-6, H-7, H-2'), 7.51 (1H, t, *J* = 7.7 Hz, H-2), 7.42 (1H, t, *J* = 7.5 Hz, H-3), 7.31 (2H, t, *J* = 7.5 Hz, H-3'); 7.23 (1H, t, *J* = 7.3 Hz, H-4'), 5.45 (1H, s, H-11), 3.72 (4H, m, H-3''), 3.72 (1H, m, , H-2''); elemental analysis calcd (%) for $C_{25}H_{23}NO_2$ (369.46): C 81.27, H 6.28, N 3.79; found: C 81.31, H 6.12, N 3.71.

General procedure for the synthesis of phenanthr[9,10-*e*][1,3]oxazines (14, 15, and 16)

A mixture of the appropriate aminophenanthrol **13** (60 mg 0.16 mmol) and 0.13 mmol from the cyclic imine (3,4-dihydroisoquinoline (**2**), 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) or 4,9-dihydro-*β*-carboline (**6**) in 1,4-dioxane (5 mL) was placed in a 10 mL pressurized reaction vial and heated under microwave conditions at 80 °C for 20 min. The solvent was removed under reduced pressure and the residue was isolated by crystallization with MeOH (5 mL).

3.2.8. 9aR,17S*-15-(Phenyl)-phenanthr[9,10-e]oxazino[2,3-a]isoquinoline (**14**)*

Recrystallized from *n*-hexane: *i*Pr$_2$O (2:1, 4 mL); R_f=0.38 (*n*-hexane/ EtOAc, 2:1); 56 mg (86%); Light yellow crystals. Mp: 209-211 °C ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 8.72 (1H, d, *J* = 8.3 Hz, H-5), 8.69 (1H, d, *J* = 8.4 Hz, H-4), 8.28 (1H, dd, *J* = 8.2, 0.9 Hz, H-8), 7.70 (1H, ddd, *J* = 8.3, 7.0, 1.3 Hz, H-6), 7.61 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-7), 7.51-7.41 (6H, m, H-1, H-2, H-3, H-13, H-2'); 7:37-7:24 (6H, m, H-10, H-11, H-12, H-3', H-4'), 5.83 (1H, s, H-9a), 5.49 (1H, s, H-17), 3.40 (1H, m, H-15-ψ-ax), 3.31 (1H, m, H-14-ψ- ax), 3.18 (1H, dd, *J* = 10.4, 5.7 Hz, H-15-ψ-eq), 2.89 (1H, dd, *J* = 16.0, 2.8 Hz, H-14-ψ-eq);^{13}C NMR (CD_2Cl_2, 125 MHz): δ 148.1 (C-8b), 142.9 (C-1'), 135.7 (C-13a), 133.5 (C-9b), 131.8 (C-4a or 4b), 131.3 (C-4a or 4b), 129.8 (C-2'), 129.3 (C-10 or 12 or 13), 129.2 (C-10 or 12 or 13), 129.1 (C-10 or 12 or 13), 128.6 (C-3'), 127.8 (C-4'), 127.5 (C-6), 127.3 (C-2), 126.9 (C-7), 126.5 (C-8a), 126.4 (C-11), 125.9 (C-17b), 124.3 (C-3), 123.7 (C-1), 123.2 (C-4), 122.9 (C-5), 122.8 (C-8), 107.8 (C-17a), 82.9 (C-9a), 63.3 (C-17), 45.9 (C-15), 29.8 (C-14); elemental analysis calcd (%) for $C_{30}H_{23}NO$ (413.52): C 87.14, H 5.61, N 3.39; found: C 87.09, H 5.45, N 3.32.

3.2.9. 9aR,16S*-16-(Phenyl)-phenanthr[9,10-e]oxazino[2,3-a]thieno[3,2-c]pyridine (**15**)*

Recrystallized from *n*-hexane: *i*Pr$_2$O (2:1, 4 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 63 mg (94%); white crystals. Mp: 216-218 °C ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 8.71 (1H, d, *J* = 8.3 Hz, H-5), 8.67 (1H, d, *J* = 8.5 Hz, H-4), 8.29 (1H, dd, *J* = 8.1, 0.9 Hz, H-8), 7.70 (1H, ddd, *J* = 8.3, 7.0, 1.3 Hz, H-6), 7.62 (1H, ddd, *J* = 8.1, 7.0, 1.1 Hz, H-7), 7.47 (2H, m, H-1, H-3), 7.42 (1H, m, H-2), 7.37 (2H, m, H-2'), 7.29 (2H, m, H-3'), 7.25 (1H, m, H-4'), 7.21 (1H, d, *J* = 5.2 Hz, H-11), 7.11 (1H, d, *J* = 5.2 Hz, H-10), 5.83 (1H, s, H-9a), 5.51 (1H, s, H-16), 3.42 (1H, m, H-14-ψ-ax), 3.24 (2H, m, H-14-ψ-eq, H-13-ψ-ax), 2.94 (1H, m, H-13-ψ-eq);^{13}C NMR (CD_2Cl_2, 125 MHz): δ 147.9 (C-8b), 142.9 (C-1'), 138.7 (C-12a), 133.8 (C-9b), 131.7 (C-4a), 131.3 (C-4b), 129.8 (C-2'), 128.6 (C-3'), 127.9 (C-4'), 127.6 (C-6), 127.3 (C-2), 126.9 (C-7), 126.5 (C-8a), 126.3 (C-10), 125.8 (C-16b), 124.3 (C-3), 123.8 (C-1), 123.6 (C-11), 123.2 (C-4), 122.8 (C-5. 8), 107.8 (C-16a), 79.6 (C-9a), 62.9 (C-16), 46.7 (C-14), 26.5 (C-13); elemental analysis calcd (%) for $C_{28}H_{21}NOS$ (419.54): C 80.16, H 5.05, N 3.34; found: C 83.10, H 5.15, N 3.32.

3.2.10. 9aR,18S*-19-(Phenyl)-phenanthr[9,10-e]oxazino[2,3-a]-β-carboline (**16**).*

Recrystallized from *n*-hexane: *i*Pr$_2$O (2:1, 4 mL); R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 55 mg (76%); Light yellow crystals. Mp: 180-182 °C ^{1}H NMR (CD_2Cl_2, 500 MHz): δ 8.72 (1H, *J* = 8.3 Hz, H-5), 8.68 (1H, d, *J* = 7.9 Hz, H-4), 8.31 (1H, br s, H-10), 8.30 (1H, d, *J* = 8.3 Hz, H-8), 7.70 (1H, ddd, *J* = 8.3, 7.0, 1.3 Hz, H-6), 7.61 (1H, m, H-7), 7.58 (1H, d, *J* = 8.1 Hz, H-14), 7.51 (1H, m, H-1), 7.49 (1H, m, H-3), 7.45 (1H, m, H-2), 7.42 (1H, m, H-11), 7.41 (2H, m, H-2'), 7.30 (2H, m, H-3'), 7.27 (1H, m, H-4'), 7.23 (1H, ddd, *J* = 8.2, 7.1, 1.1 Hz, H-12), 7.14 (1H, t, *J* = 7.5 Hz, H-13), 5.98 (1H, s, H-9a), 5.58 (1H, s, H-18), 3.46 (1H, m, H-16-ψ-ax), 3.32 (1H, dd, *J* = 10.9, 5.5 Hz, H-16-ψ-eq), 3.13 (1H, ddd, *J* = 15.5, 11.8, 5.9 Hz, H-15-ψ-ax), 2.89 (1H, ddd, *J* = 15.4, 4.2, 1.3 Hz, H-15-ψ-eq); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ 47,6 (C-8b), 142,8 (C-1'), 136,9 (C-10a), 131,7 (C-4a), 131,3 (C-4b), 130,9 (C-9b), 129,8 (C-2'), 128,7 (C-3'), 128,0 (C-4'), 127,6 (C-6), 127,4 (C-2), 126,9 (C-7), 126,6 (C-8a or 14a), 126,5 (C-8a or 14a), 125,8 (C-18b), 124,4 (C-3), 123,6 (C-1), 123,3 (C-4), 123,1 (C-12), 122,8 (C-5), 122,7 (C-8), 120,0 (C-13), 119,4 (C-14), 111,8 (C-11), 111,5 (C-14b), 108,2 (C-18a), 78,7 (C-9a), 62,8 (C-18), 47,3 (C-16), 22,6 (C-15); elemental analysis calcd (%) for $C_{32}H_{26}N_2O$ (454.57): C 84.55, H 5.77, N 6.16; found: C 84.49, H 5.67, N 6.21.

*3.2.11. 14-Morpholin-4-yl-dibenzo[a,c]xanthene (**19**).*

9-Phenanthrol (100. mg, 0.51 mmol), salicylic aldehyde (62 mg, 0.51 mmol) and morpholine (44 mg, 0.51 mmol) were stirred and heated at 80 °C under neat conditions for 4 h.. The residue was crystallized with *n*-hexane (15 mL) and recrystallized from *i*Pr$_2$O (10 mL) R$_f$=0.38 (*n*-hexane/ EtOAc, 2:1); 127 mg (68%); Browne crystals; Mp. 176-178 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.68 (2H, m, H4, H-5), 8.58 (1H, m, H-1), 8.22 (1H, d, *J* = 7.5 Hz, H-8), 7.71 (1H, m, H-2), 7.66 (2H, m, H-3, H-7), 7.60 (1H, m, H-6), 7.40 (3H, m, H-11, H-12, H-14), 7.23 (1H, m, H-13), 5.52 (1H, s, H-15), 3.52 (4H, m, H-2'), 2.52 (2H, m H-3'), 2.40 (2H, m H-3'); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.0 (C-10a), 147.2 (C-9), 131.3 (C-4a or C-4b), 131.2 (C-4a or C-4b), 130.0 (C-14), 128.8 (C-12), 128.3 (C-15b), 127.7 (C-2 or C-3 or C-7), 127.2 (C-2 or C-3 or C-7), 127.0 (C-2 or C-3 or C-7), 125.2 (C-6), 124.6 (C-8a), 124.5 (C-8), 123.2 (C-13), 123.0 (C-1 or C-4 or C-5), 122.8 (C-1 or C-4 or C-5), 122.7 (C-1 or C-4 or C-5), 117.6 (C-14a), 116.5 (C-11), 110.5 (C-15a), 67.5 (C-3'), 57.7 (C-15), 48.7 (C-2');. elemental analysis calcd (%) for $C_{25}H_{21}NO_2$ (367.45): C 81.72, H 5.76, N 3.81; found: C 81.34, H 5.65, N 3.77.

401

402 *3.2.12. 10-[(2-Hydroxyphenyl)-pyrrolidin-1-yl-methyl]-9- phenanthrol (**21**).*

403 9-Phenanthrol (500 mg, 2.56 mmol), salicylic aldehyde (312 mg, 2.56 mmol) and pyrrolidine (182 mg,
404 2.56 mmol) were stirred and heated at 80 °C under neat conditions for 4 h. The residue was
405 crystallized with *n*-hexane (16 mL) and recrystallized from *i*Pr$_2$O (11 mL) R_f=0.38 (*n*-hexane/ EtOAc,
406 2:1); 718 mg (76%); Light beige crystals; Mp. 172-174 °C; ^{1}H NMR (DMSO-d$_6$, 500 MHz): δ 15.32 (1H,
407 br s, OH), 10.12 (1H, br s, OH), 8.74 (1H, d, *J* = 8.4 Hz, H-5), 8.68 (1H, d, *J* = 8.1 Hz, H-4), 8.38 (1H, d, *J*
408 = 8.5 Hz, H-8), 7.94 (1H, d, *J* = 8.3 Hz, H-1), 7.67 (2H, m, H-6, H-7), 7.45 (1H, t, *J* = 7.5 Hz, H-2), 7.38
409 (2H, m, H-3, H-6′), 7.04 (1H, t, *J* = 7.4 Hz, H-4′), 6.91 (1H, d, *J* = 8.1 Hz, H-3′), 6.66 (1H, t, *J* = 7.4 Hz, H-
410 5′), 5.82 (1H, s, H-11), 3.16 (2H, m, H-2″), 2.66 (2H, m, H-3″), 2.49 (2H, m, H-3″), 2.40 (2H, m, H-2″);
411 ^{13}C NMR (DMSO-d$_6$, 125 MHz): δ 154.3 (C-2'), 151.9 (C-9), 131.3 (C-4a), 130.3 (C-4b), 128.7 (2C, C-4',
412 C-6'), 126.9 (C-8a), 126.9 (2C, C-2, C-6), 126.2 (C-7), 124.9 (C-10a), 123.0 (C-4), 122.9 (C-3), 122.6 (C-8),
413 122.4 (C-5), 121.5 (C-1), 119.7 (C-5'), 115.5 (C-3'), 112.4 (C-10), 61.1 (C-11), 54.1 (C-2''), 49.6 (C-3'');
414 elemental analysis calcd (%) for $C_{25}H_{23}NO_2$ (369.46): C 81.27, H 6.28, N 3.79; found: C 81.31, H 6.15, N
415 3.76.
416

417 **General procedure for the synthesis of phenanthr[9,10-*e*][1,3]oxazines (24, 26, and 28)**

418 The mixture of aminophenanthrol **21** (50 mg 0.13 mmol) and 0.13 mmol from the correspondent cyclic
419 imine (3,4-dihydroisoquinoline (**2**), 6,7-dihydrothieno[3,2-*c*]pyridine (**4**) or 4,9-dihydro-*β*-carboline
420 (**6**) was dissolved in 1,4-dioxane (5 mL) and placed in a 10 mL pressurized reaction vial. The mixture
421 was heated at 80 °C for 15 min under microwave conditions. The solvent was removed in vacuo, and
422 the residue was isolated by crystallization with MeOH (5 mL).

423 *3.2.13. 9aR*,18S*-19-(2-Hydroxyphenyl)-phenanthr[9,10-e]oxazino[2,3-a]–β–carboline (**24**).*

424 Recrystallized from *i*Pr$_2$O (7 mL); R_f=0.38 (n-hexane/ EtOAc, 2:1); 47 mg (78%). brown crystals; Mp:
425 163-165 °C ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.69 (2H, br s, H-4 and H-5), 8.21 (2H, br s, H-8 and H-10),
426 7.69 (1H, t, *J* = 7.1 Hz, H-6), 7.57 7.54 (5H, m, H-1, H-2, H-3, H-7, and H-14), 7.41 (1H, d, *J* = 7.8 Hz, H-
427 11), 7.16 (2H, m, H-13 and H-4′), 6.95 (1H, d, *J* = 7.7 Hz, H-3′), 6.64 (2H, br s, H-5′ and H-6′), 6.12 (1H,
428 s, H-9a), 5.82 (1H, s, H-18), 3.44 (1H, m, H-16-ψ-ax), 3.31 (1H, m, H-16-ψ-eq), 3.21 (1H, m, H-15-ψ-ax),
429 2.97 (1H, dd, *J* = 15.7, 3.1 Hz, H-15-ψ-eq); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 156.8 (C-2'), 146.6 (C-8b),
430 136.8 (C-10a), 131.5 (C-4a or 4b), 131.4 (C-4a or 4b), 131.0 (C-6'), 129.9 (C-9b), 129.8 (C-4'), 127.8 (C-6
431 or C-2), 127.7 (C-6 or C-2), 126.8 (C-7), 126.4 (C-14a or C-8a), 126.3 (C-14a or C-8a), 125.5 (C-18b), 125.2
432 (C-1'), 124.7 (C-3), 123.4 (C-12), 123.2 (C-1. 5), 122.7 (C-8 or C-4), 122.6 (C-8 or C-4), 120.3 (C-13), 120.1
433 (C-5'), 119.4 (C-14), 117.7 (C-3'), 111.7 (C-11), 110.9 (C-14b), 106.0 (C-18a), 77.7 (C-9a), 60.7 (C-18), 45.4
434 (C-16), 22.4 (C-15);. elemental analysis calcd (%) for $C_{32}H_{24}N_2O_2$ (468.56): C 82.03, H 5.16, N 5.98; found:
435 C 82.12, H 5.09, N 5.82.
436

437 *3.2.14. 9aR*,17S*-15-(2-Hydroxyphenyl)-phenanthr[9,10-e]oxazino[2,3-a]isoquinoline (**26**)*

438 Recrystallized from *i*Pr$_2$O (5 mL); R_f=0.38 (-*n*-hexane/ EtOAc, 2:1); 47 mg (85%). Light biege crystals;
439 Mp: 194-196 °C ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.67 (1H, br s, 2′–OH), 8.68 (2H, m, H-4 and H-6), 8.22

(1H, d, *J* = 8.2 Hz, H-8), 7.68 (1H, d, *J* = 7.6 Hz, H-6), 7.53 (4H, m, H-1, H-2, H-3, and H-7), 7.41 (1H, d, *J* = 7.5 Hz, H-10), 7.37 (1H, t, *J* = 7.6 Hz, H-12), 7.31 (1H, t, *J* = 7.4 Hz, H-11), 7.24 (1H, m, H-13), 7.19 (1H, m, H-4′), 6.95 (1H, d, *J* = 8.1 Hz, H-3′), 6.66 (2H, m, H-5′ and H-6′), 5.96 (1H, s, H-9a), 5.73, (1H, s, H-17), 3.37 (1H, m, H-15-ψ-ax), 3.32 (1H, m, H-14-ψ-ax), 3.18 (1H, m, H-15-ψ-eq), 2.95 (1H, m, H-14-ψ-eq); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (C-147.1 (C-8b), 134.3 (C-13a), 132.7 (C-9b), 131.6 (C-4a or C-4b), 131.4 (C-4a or C-4b), 131.2 (C-6'), 129.7 (C-4'), 129.5 (C-12), 129.3 (C-10), 129.0 (C-13), 127.7 (C-6), 127.6 (C-2), 126.8 (C-7), 126.7 (C-11), 126.4 (C-8a), 125.7 (C-17b), 125.4 (C-1'), 124.5 (C-3), 123.3 (C-1), 123.2 (C-4 or C-5), 122.9 (C-8), 122.6 (C-4 or C-5), 120.1 (C-5'), 117.6 (C-3'), 105.6 (C-17a), 81.9 (C-9a), 61.1 (C-17), 44.0 (C-15), 29.4 (C-14); elemental analysis calcd (%) for $C_{30}H_{23}NO_2$ (429.52): C 83.89, H 5.40, N 3.26; found: C 83.78, H 5.35, N 3.29.

3.2.15. 9aR,16S*-16-(2-Hydroxyphenyl)-phenanthr[9,10-e]oxazino[2,3-a]thieno[3,2-c]pyridine (**28**).*

Recrystallized from *i*Pr_2O (4 mL); R_f=0.38 (*n*-hexane/ EtOAc, 2:1); 52 mg (93%). Light biege crystals; Mp: 181-183 °C ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.65 (1H, br s, 2′-OH), 8.69 (2H, m, H-4, H-5), 8.25 (1H, d, *J* = 8.1 Hz, H-8), 7.69 (1H, t, *J* = 7.5 Hz, H-6), 7.60 (1H, m, H-7), 7.55 (1H, m, H-1), 7.53 (1H, m, H-3), 7.50 (1H, m, H-2), 7.22 (1H, d, *J* = 5.3 Hz, H-11), 7.19 (1H, m, H-4′); 7:09 (1H, d, *J* = 5:1 Hz, H-10), 6:96 (1H, d, *J* = 8:0 Hz, H-3′), 6.65 (1H, m, H-5′), 6.63 (1H, m, H-6′), 5.98 (1H, s, H-9a), 5.77 (1H, s, H-16), 3.40 (1H, m, H-14-ψ-ax), 3.30 (1H, m, H-13-ψ-ax), 3.25 (1H, m, H-14-ψ-eq), 3.01 (1H, m, H-13-ψ-eq); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.6 (C- 2'), 146.9 (C- 8b), 137.4 (C- 12a), 133.2 (C- 9b), 131.6 (C- 4a or C-4b), 131.4 (C- 4a or C-4b), 131.1 (C- 6'), 129.7 (C- 4'), 127.7 (C- 6), 127.6 (C- 2), 126.8 (C- 7), 126.4 (C-8a), 126.2 (C- 10), 125.6 (C- 16b or C-1'), 125.3 (C- 16b or C-1'), 124.6 (C- 3), 124.2 (C- 11), 123.2 (C- 5), 123.2 (C- 10), 122.8 (C- 4 or C-8), 122.6 (C- 4 or C-8), 120.1 (C- 5'), 117.6 (C- 3'), 105.5 (C- 16a), 78.7 (C-9a), 60.7 (C- 16), 44.8 (C- 14), 26.2 (C- 13);. elemental analysis calcd (%) for $C_{28}H_{21}NO_2S$ (435.54): C 77.22, H 4.86, N 3.22; found: C 77.12, H 4.75, N 3.31.

4. Conclusions

9-Phenanthrol, a unique electron-rich aromatic compound, was tested along the modified *aza*-Friedel-Crafts reaction. The application of 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine or 3,4-dihydro-*β*-carboline as cyclic imines led to the formation of the corresponding bifunctional phenanthrol derivatives that were furthermore transformed to the new phenanthr[9,10-*e*][1,3]oxazines (**8–10**). Further, 9-phenanthrol was aminoalkylated by using morpholine in the presence of benzaldehyde: The functionalized aminophenanthrol (**21**) could only be achieved by using salicylic aldehyde in the presence of pyrrolidine. Morpholine in this latter modified Mannich reaction led to the formation of 14-morpholinyl-dibenzo[*a*,*c*]xanthene (**19**). Phenanthrol-based bifunctional Mannich products were further tested in [4+2] cycloaddition by using 3,4-dihydroisoquinoline, 6,7-dihydrothieno[3,2-*c*]pyridine or 3,4-dihydro-*β*-carboline as dienophiles. The regio- and diastereoselectivity of the reactions were proved by NMR spectroscopy and supported by DFT calculations: all reaction products were found in *trans*-configuration (**14–16**, **24a**, **26a** and **28a**). Applying functionalized aminophenanthrol precursor in [4+2] cycloaddition, the reactions regioselectively led to the formation of new phenanthr[9,10-*e*][1,3]oxazines (**24a**, **26a** and **28a**) in good yields.

Supplementary Materials: Supplementary materials are available online.

Author Contributions: I.S, K.B and F.F. planned and designed the project. K.B, L.T. and I.S. performed the syntheses. E.K., M.H. and A.K. characterized the synthesized compounds. KB., F.F. and I.S. prepared the manuscript for publication, all authors discussed the results and commented on the manuscript.

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References

1. Grand, T.; Demion, M.; Norez, C.; Mettey, Y.; Launay, P.; Becq, F.; Bois, P.; Guinamard, R. 9-Phenanthrol Inhibits Human TRPM4 but not TRPM5 Cationic Channels. *Br. J. Pharmacol.* **2008**, *153*, 1697-1705.
2. Guinamard, R.; Hof, T.; Del Negro, C. A. The TRPM4 Channel Inhibitor 9-Phenanthrol. *Br. J. Pharmacol.* **2014**, *171*, 1600-1613.
3. Cho, C. H.; Lee, Y. S.; Kim, E.; Hwang, E. M.; Park, J. Y. Physiological Functions of the TRPM4 Channels via Protein Interactions. *BMB Reports* **2015**, *48*, 1-5.
4. Gonzales, A. L.; Amberg, G. C.; Earley, S. Ca^{2+} Release from the Sarcoplasmic Reticulum is Required for Sustained TRPM4 Activity in Cerebral Artery Smooth Muscle Cells. *Am. J. Physiol. Cell. Physiol.* **2010**, *299*, C279-C288.
5. Parajuli, S. P.; Hristov, K. L.; Sullivan, M. N.; Xin, W.; Smith, A. C.; Earley, S.; Malysz, J.; Petkov, G. V. Control of Urinary Bladder Smooth Muscle Excitability by the TRPM4 Channel Modulator 9-Phenanthrol. *Channels* **2013**, *7*, 537-540.
6. Becerra, A.; Echeverría, C.; Varela, D.; Sarmiento, D.; Armisén, R.; Nuñez-Villena, F.; Montecinos, M.; Simon, F. Transient Receptor Potential Melastatin 4 Inhibition Prevents Lipopolysaccharide-Induced Endothelial Cell Death. *Cardiovasc. Res.* **2011**, *91*, 677-684.
7. Hou, J.; Fei, Y.; Li, W.; Chen, Y.; Wang, Q.; Xiao, Y.; Wang, Y.; Li, Y. The Transient Receptor Potential Melastatin 4 Channel Inhibitor 9-Phenanthrol Modulates Cardiac Sodium Channel. *Br. J. Pharmacol.* **2018**, *175*, 4325-4337.
8. Bur, S. K.; Martin, S. F. Vinylogous Mannich Reactions: Selectivity and Synthetic Utility. *Tetrahedron* **2001**; *57*, 3221-3242.
9. Speckamp, W. N.; Moolenaar, M.J. New Developments in the Chemistry of N-Acyliminium Ions and Related Intermediates. *Tetrahedron* **2000**; *56*, 3817-3856.
10. Arend, M.; Westermann, B.; Risch, N. Modern Variants of the Mannich Reaction. *Angew. Chem. Int. Ed. Engl.* **1998**; *37*, 1045-1070.

11. Liras, S.; Davoren, J. E.; Bordner, J. An Approach to the Skeleton of the Securinega Alkaloids. The Total Synthesis of (±)-Securinine. *Org. Lett*. **2001**; *3*, 703-706.
12. Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. Biogenetically Inspired Approach to the Strychnos Alkaloids. Concise Syntheses of (±)-Akuammicine and (±)-Strychnine. *J. Am. Chem. Soc.* **2001**; *123*, 8003-8010.
13. Szatmári, I.; Fülöp, F. Syntheses and Transformations of 1-(*α*-Aminobenzyl)-2-Naphthol Derivatives. *Curr. Org. Synth.* **2004**; *1*, 155-165.
14. Szatmári, I.; Fülöp, F. Syntheses, Transformations and Applications of Aminonaphthol Derivatives Prepared via Modified Mannich Reactions. *Tetrahedron* **2013**; *69*, 1255-1278.
15. MacLeod, P. D.; Li, Z.; Feng, J.; Li, C. J. Solvent-Free Direct *aza*-Friedel–Crafts Reactions between 3,4-Dihydroisoquinoline and 1- or 2-Naphthols. *Tetrahedron Lett.* **2006**; *47*, 6791-6794.
16. Heydenreich, M.; Koch, A.; Klod, S.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. Synthesis and Conformational Analysis of Naphth[1′,2′:5,6][1,3]oxazino[3,2-*c*][1,3]benzoxazine and Naphth[1′,2′:5,6][1,3]oxazino[3,4-*c*][1,3]benzoxazine Derivatives. *Tetrahedron* **2006**; *62*, 11081- 11089.
17. Heydenreich, M.; Koch, A.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. Synthesis and Conformational Analysis of Naphth[1,2-*e*][1,3]oxazino[4,3-*a*][1,3]isoquinoline and Naphth[2,1-*e*][1,3]oxazino[4,3-*a*]isoquinoline Derivatives. *Tetrahedron* **2008**; *64*, 7378-7385.
18. Szatmári, I.; Barta, P.; Tóth, G.; Balázs, A.; Halász, J.; Fülöp, F. Synthesis and Conformational Behaviour of Enantiomeric Naphthoxazinoquinoxalinone Derivatives. *Eur. J. Org. Chem*, **2017**; 5537-5545.
19. Barta, P.; Szatmári, I.; Fülöp, F Heydenreich, M.; Koch, A.; Kleinpeter, E. Synthesis and Stereochemistry of New Naphth[1,3]oxazino[3,2-*a*]benzazepine and Naphth[1,3]oxazino[3,2-*e*]thienopyridine Derivatives. *Tetrahedron*. **2016**; *72*, 2402-2410.
20. Barta, P.; Fülöp, F.; Szatmári, I. Mannich Base-Connected Syntheses Mediated by *Ortho*-Quinone Methides. *Beilstein J. Org. Chem.* **2018**; 14, 560-575.
21. Osyanin, V. A.; Osipov, D. V.; Klimochkin, Y. N. Convenient One-Step Synthesis of 4-Unsubstituted 2-Amino-4H-chromene-2-carbonitriles and 5-Unsubstituted 5H-chromeno[2,3-*b*]pyridine-3-carbonitriles From Quaternary Ammonium salts. *Tetrahedron* **2012**; *68*, 5612-5618.
22. Pettigrew, J. D.; Freeman, R. P.; Wilson, P. D. Total Synthesis of ()-Xyloketal D and its Enantiomer Confirmation of Absolute Stereochemistry. *Can. J. Chem*. **2004**; *82*, 1640-1648.

23. Szatmári, I.; Fülöp, F. Simple Access to Pentacyclic Oxazinoisoquinolines Via an Unexpected Transformation of Aminomethylnaphthols. *Tetrahedron Lett*. **2011**; *52*, 4440-4442.
24. Szatmári, I.; Barta, P.; Csámpai, A.; Fülöp, F. Synthesis and Detailed Conformational Analysis of New Naphthoxazino[2,3-*a*]benz[*c*]azepine and Naphthoxazino[2,3-*a*]thieno[3,2-*c*]pyridine Derivatives. *Tetrahedron* **2017**; *73*, 4790-4804.
25. Szatmári, I.; Belasri, K.; Heydenreich, M.; Koch, A.; Kleinpeter, E.; Fülöp, F. *Ortho*-Quinone Methide Driven Synthesis of New *O*,*N*- or *N*,*N*-Heterocycles. *ChemistryOpen*. **2019**; *8*, 961-971.
26. Szatmári, I.; Sas,I.; Fülöp, F. Catalyst-Free Coupling of Indole Derivatives with 3,4-Dihydroisoquinoline and Related Compounds. *Tetrahedron Lett*. **2013**; *54*, 5069-5071.
27. Herz, W.; Tsai, L. Sulfur analogs of isoquinolines. IV. The Pictet-Gams Reaction and Attempts to Prepare Analogs of Papaverine1,2. *J. Chem. Soc*. **1955**; *77*, 3529-3533.
28. Chen, Z.; Hu, G.; Li, D.; Chen, J.; Li, Y.; Zhou, H.; Xie, Y. Synthesis and Vasodilator Effects of Rutaecarpine Analogues which Might be Involved Transient Receptor Potential Vanilloid Subfamily, Member 1 (TRPV1) *Bioorg. Med. Chem.* **2009**; *17*, 2351-2359.
29. Frisch, M. J. et al.; *Gaussian 09* (Revision A.02); Gaussian, Inc.; Wallingford CT **2009**.
30. Becke, A. D. A. Density‐Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98*, 5648-5652.
31. Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37*, 785-789.
32. Hehre, W. J.; Radom, L. von Rague Schleyer, P.; Pople, J. Ab Initio Molecular Orbital Theory; Wiley: New York, NY, **1986**.
33. Becke, A. D. A New Mixing of Hartree–Fock and Local Density‐Functional Theories. *J. Chem. Phys.***1993**, *98*, 1372-1492.
34. Ditchfield, R. Self-Consistent Perturbation Theory of Diamagnetism. *Mol. Phys.* **1974**, *27*, 789-807.
35. Cheeseman, G. G. W.; Trucks, T. A.; Keith, M. J. A Comparison of Models for Calculating Nuclear Magnetic Resonance Shielding Tensors. *J. Chem. Phys.* **1996**, *104*, 5497-5509.

573 **Sample Availability:** Samples of the compounds ..... are available from the authors.

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