Syntheses and transformations of carbamatoalkylnaphthols prepared via modified Mannich reactions

Ph.D. Thesis

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"We learn wisdom from failure much more than from success. We often discover what will do, by finding out what will not do; and probably he who never made a mistake never made a discovery."

(*Samuel Smiles*)

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PUBLICATIONS

Papers related to the thesis

I. **Renáta Csütörtöki**, István Szatmári, Attila Mándi, Tibor Kurtán, Ferenc Fülöp
Synthesis of hydroxynaphthyl-substituted α-amino acid derivatives via a modified Mannich reaction
Synlett **2011**, 1940-1946. **IF: 2.447**

II. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of new naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives
Tetrahedron **2011**, *67*, 8564-8571. **IF: 3.011**

III. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Syntheses and conformational analyses of new naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
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IV. **Renáta Csütörtöki**, István Szatmári, Matthias Heydenreich, Andreas Koch, Ines Starke, Ferenc Fülöp, Erich Kleinpeter
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Current Organic Synthesis, submitted.

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VI. **Csütörtöki Renáta**
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XXXII. Kémiai Előadói Napok
Szeged, 2009. október 26-28. Absztr.: 105.

VII. **Csütörtöki Renáta**
Módosított Mannich-reakció alkalmazása α-aminosav-származékok szintézisére
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány 10. tudományos előadóülése
Szeged, 2010. május 5.

VIII. István Szatmári, **Renáta Csütörtöki**, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
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IX. Ines Starke, **Renáta Csütörtöki**, Andreas Koch, Erich Kleinpeter, István Szatmári, Ferenc Fülöp
Mass spectrometric behaviour of new naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
Joint Conference of Polish Mass Spectrometry Society and German Mass Spectrometry Society
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X. **Renáta Csütörtöki**, István Szatmári, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Ferenc Fülöp
Synthesis and conformational analysis of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones
XIIth Eurasia Conference on Chemical Sciences
Corfu, Greece, April 16-21, 2012. Abstr.: S_3-PP5.

XI. **Csütörtöki Renáta**, Szatmári István, Fülöp Ferenc
Naftoxazinnal kondenzált kinazolin-származékok szintézise és konformáció-analízise
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése
Balatonszemes, 2012. június 6-8.

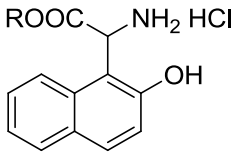
List of abbreviations

$[Bmim]HSO_4$	=	1-Butyl-3-methylimidazolium hydrogensulfate
[Bmim]Br	=	1-Butyl-3-methylimidazolium bromide
DAIL	=	Dicationic acidic ionic liquid
DCE	=	1,2-Dichloroethane
[Dsim]Cl	=	1,3-Disulfonic acid imidazolium chloride
[FemSILP]	=	Ferrocene labelled-supported ionic liquid phase
$Hf(NPf_2)_4$	=	Hafnium(IV) bis(perfluorooctanesulfonyl)imide
HMDS	=	Hexamethyldisiloxane
$[Hmim]HSO_4$	=	Methylimidazolium hydrogensulfate
IL	=	Ionic liquid
$[MIMPS][HSO_4]$	=	1-Methyl-3-propanesulfonic acid imidazolium hydrogensulfate
mMR	=	Modified Mannich reaction
$[Msim]AlCl_4$	=	3-Methyl-1-sulfonic acid imidazolium tetrachloroaluminate
[Msim]Cl	=	3-Methyl-1-sulfonic acid imidazolium chloride
$[NMP]^+HSO_4^-$	=	*N*-Methyl-2-pyrrolidone hydrogensulfate
Nph	=	Naphthyl
PEG	=	Poly(ethylene glycol)
Ph	=	Phenyl
PPA/SiO_2	=	Silica-supported polyphosphoric acid
PS	=	Polystyrene
TCT	=	2,4,6-Trichloro-1,3,5-triazine
$[TEBSA][HSO_4]$	=	*N*-(4-Sulfonic acid)butyl-triethylammonium hydrogensulfate
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TMSCl	=	Chlorotrimethylsilane
p-TSA	=	*para*-Toluenesulfonic acid

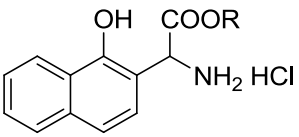
1. INTRODUCTION AND AIMS

More than one hundred years ago, Mario Betti reported a straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base),[1-5] starting from 2-naphthol, benzaldehyde and NH_3. The Betti procedure can be interpreted as a modified Mannich reaction (mMR). The formaldehyde in the formal Mannich procedure is replaced by an aromatic aldehyde, the secondary amine by NH_3 and the C-H acid by an electron-rich aromatic compound such as 2-naphthol. Thanks to the variability of this reaction through the use of different electron-rich aromatic compounds (2- or 1-naphthol, quinolinols, isoquinolinols, etc.), aldehydes and a number of nitrogen sources (NH_3 or amines), it has become a hot topic in organic chemistry. The reaction conditions and the method for the isolation of the synthetized Mannich products are determined to a considerable extent by the character of the nitrogen source used (NH_3 or amine).[6]

Since one of the most important areas of application of aminonaphthols prepared via mMRs is the synthesis of new heterocycles,[7] my Ph.D. work focused on the synthesis of novel trifunctional aminonaphthol derivatives. I therefore set out to prepare hydroxynaphthyl-substituted glycines (**I** and **II**) as new α-amino acid derivatives by starting from 1- or 2-naphthol. As aminononaphthol derivatives **I** and **II** contain one chiral centre, the separation of their enantiomers by a chiral HPLC technique was a further aim.



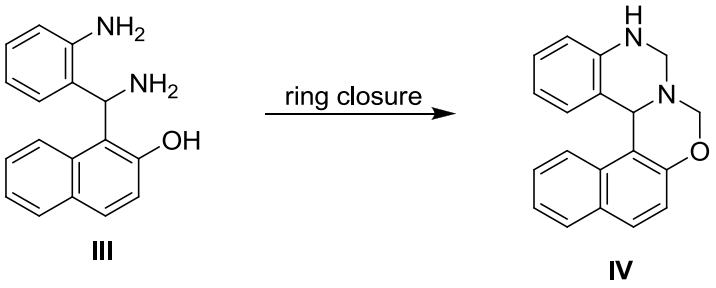
I



II

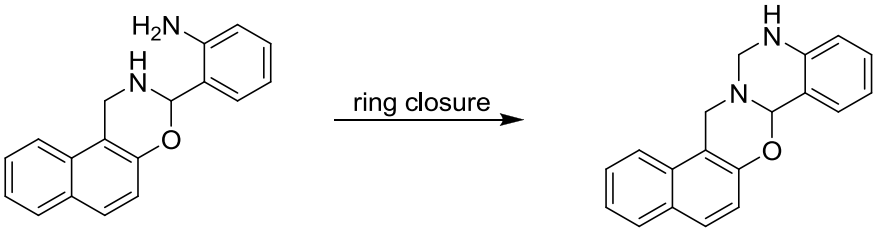
In previous studies, naphth[1,2-*e*][1,3]oxazino[1,3]benzoxazines were prepared through the ring closure of hydroxylated aminonaphthol or naphthoxazine derivatives with oxo compounds.[8,9] The syntheses of naphth[1,2-*e*][1,3]oxazinoisoquinolines were achieved via the cyclization of 1-(β-hydroxynaphthyl)-1,2,3,4-tetrahydroisoquinoline or through the unexpected reactions between 1-aminobenzyl-2-naphthols and 3,4-dihydroisoquinolines.[10,11]

In order to extend the series of naphthoxazino-fused heterocyclic ring systems during my Ph.D. work, the syntheses of naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline derivatives (**IV**) via the ring closure of diaminonaphthol **III** were planned.



III **IV**

In order to compare the naphthoxazine-fused quinazolines from the aspect of their conformational behaviour, I additionally set out to prepare naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolines (**VI**) through the cyclization of anilinonaphthoxazine **V** with oxo compounds.



V **VI**

Another goal was the conformational analysis of the newly prepared naphth[1,2-*e*][1,3]oxazinoquinazolines (**IV** and **VI**) by means of NMR spectroscopy and accompanying molecular modelling.

In order to capitalize on all three functional groups in 1-(amino(2-aminophenyl)methyl)-2-naphthol and 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol[9] at the same time, it was decided to investigate their reactions with dialdehydes, with a view to obtaining new hetero- and polycyclic compounds (**VII** and **VIII**). The heterocyclic moieties in **VII** and **VIII** are flexible, and their detailed conformational analysis by NMR spectroscopy and accompanying molecular modelling therefore appeared necessary.

VII n = 1, 2, 3 **VIII**

2. LITERATURE BACKGROUND

Syntheses of amido-, carbamido- and carbamatoalkylnaphthols

The application of amides or their derivatives instead of NH_3 or amines in the mMR can be interpreted as a special alteration. The research group of Möhrle successfully introduced the use of amides to synthetize 2-acetamidoalkyl-1-naphthol[12] and 7-benzamidoalkyl-8-quinolinol.[13] The desired products were isolated in low yields (7% and 48%) and it was found that an indirect synthetic pathway (the aminoalkylation of 8-quinolinol with benzaldehyde in the presence of NH_3, followed by acylation of the intermediate Schiff base with benzoyl chloride) was more efficient for the synthesis of 7-benzamidoalkyl-8-quinolinol, *e.g.* milder conditions were needed and the yields could be improved.[13]

Since 2006, attention has again focused on the preparation of amido-, carbamido- and carbamatoalkylnaphthol derivatives, since the reaction can be accelerated dramatically by the use of various heterogeneous Lewis and Brønsted acid catalysts.[14-16]

The importance of these compounds is that they can easily be converted by hydrolysis of the amide and carbamide moieties to aminoalkylnaphthols with potential hypotensive and bradycardiac properties,[17] they can also be transformed to 1,3-oxazine derivatives, and at higher temperatures they yield 1,3-oxazine derivatives with potentially valuable biological activities, *e.g.* antibiotic, antitumour, analgesic, anticonvulsant, antipsychotic, antimalarial, antianginal, antihypertensive and antirheumatic activities.[16] On the other hand, following deprotection, carbamatoalkylnaphthols can serve as important starting materials for the synthesis of new building blocks with potential pharmacological activities.[18]

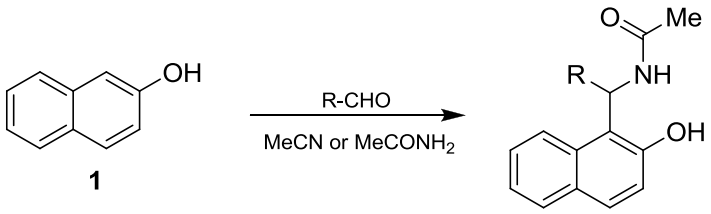
The literature on the syntheses of amido-, carbamido- and carbamatoalkylnaphthol derivatives will be reviewed. With regard to the appreciable number of publications (over 110) that have appeared in the past 6 years, the various reactions will be classified according to the types of nitrogen sources used (nitriles, amides, thioamide, ureas, thioureas or carbamates). A detailed description of the processes reported in the literature can be found in the review submitted to Current Organic Synthesis.

2.1. Syntheses of amidoalkylnaphthols

2.1.1. Syntheses of amidoalkylnaphthols from nitriles

The preparation of a 1-amidoalkyl-2-naphthol can be interpreted as a Ritter reaction. It is suggested that the aryl aldehyde first reacts with 2-naphthol to give 1-(hydroxy(aryl)methyl)-2-naphthol, which then reacts with acetonitrile (MeCN; both reactant and solvent) to produce *N*-((2-hydroxynaphthalen-1-yl)(aryl)methyl)ethanaminium as intermediate, hydrolysis of which gives the desired 1-amidoalkyl-2-naphthol.

Shaterian *et al.* reported the syntheses of a series of amidoalkylnaphthols from 2-naphthol, aryl aldehydes and MeCN, successfully applying different heterogeneous acid catalysts. For example, with $Fe(HSO_4)_3$ as catalyst at 85 ºC, amidonaphthols **2a-q** were isolated in moderate yields (47-74%) after 20 h,[17] while in the presence of SiO_2-supported $FeCl_3$ ($FeCl_3/SiO_2$),[19] $HClO_4/SiO_2$[20] or $NaHSO_4{\cdot}H_2O$[21] under the same conditions, the yields were improved (60-88%). Furthermore, they achieved the syntheses of **2a-l** and **2n-r** by using Al_2O_3-supported sulfonic acid (HSO_3/Al_2O_3) as a solid heterogeneous acid catalyst; **2h**,**q**,**r**, aromatic aldehydes bearing electron-donating groups, were obtained in relatively low yields (25-33%) (Scheme 1).[22]



R = Ph: **a**; 4-F-Ph: **b**; 4-Cl-Ph: **c**; 4-Br-Ph: **d**; 4-NO_2-Ph: **e**; 4-Me-Ph: **f**; 4-OMe-Ph: **g**; 4-NMe_2-Ph: **h**; 3-F-Ph: **i**; 3-NO_2-Ph: **j**; 3-OMe-Ph: **k**; 2-Cl-Ph: **l**; 2-NO_2-Ph: **m**; 2-Me-Ph: **n**; 2,4-Cl_2-Ph: **o**; 2,5-$(OMe)_2$-Ph: **p**; 3,4-$(OMe)_2$-Ph: **q**; 3,4,5-$(OMe)_3$-Ph: **r**; 4-OH-Ph: **s**; 2-OMe-Ph: **t**; 2-OH-Ph: **u**; 2-Br-Ph: **v**; 1-Nph: **w**; 2-Nph: **x**; Et: **y**; 4-CN-Ph: **z**; 2-furyl: **aa**; styryl: **ab**; 3,4-(OCH_2O)-Ph: **ac**; 2-NO_2,4,5-$(OMe)_2$-Ph: **ad**; 2-pyrimidyl: **ae**; 3-Me,4-OH-Ph: **af**; 3,4-Cl_2-Ph: **ag**; 2-F-Ph: **ah**; 9-phenanthryl: **ai**; 2-pyrrolyl: **aj**; 3-Cl-Ph: **ak**; 2-pyridyl: **al**; Et: **am**; *i*Pr: **an**; *n*-pentyl: **ao**; undecyl: **ap**; *n*Pr: **aq**; *n*Bu: **ar**; *i*Bu: **as**; cyclohexyl: **at**; 2,6-Cl_2-Ph: **au**; 4-COOMe-Ph: **av**; 3-Br-Ph: **aw**

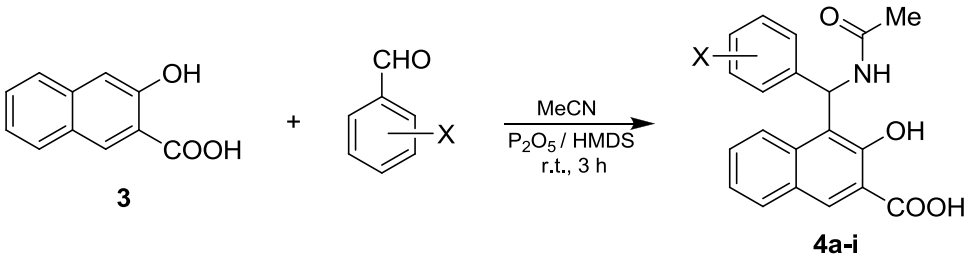
Scheme 1

A series of 1-(acetylamino(aryl)methyl)-2-naphthols were synthetized in excellent yields in the presence of HSO_3Cl.[23]

SiO_2-supported Preyssler nanoparticles were found to be an effective catalyst for the preparation of acetamidonaphthols **2a-c**,**e-g**,**j**,**m** (86-92%) in a short reaction time (3-8 min).[24] Liu *et al.* reported the syntheses of **2a-c**,**e-g**,**j**,**l**,**m**,**o**,**s** in moderate yields (42-77%) by the application of a sulfonic ionic liquid (IL), methylimidazolium hydrogensulfate ([MIMPS][HSO_4]), in a reaction time of 25 h,[25] while

Zolfigol *et al.* described a highly efficient and simple procedure for the preparation of **2a-h**,**j-o**,**q** in the presence of a catalytic amount of trityl chloride (Ph_3CCl) at room temperature (r.t.; Scheme 1); the reactions proceeded with high yields (83-94%) and in relatively short reaction times (0.75-3.5 h).[26]

The research group of Anary-Abbasinejad carried out the syntheses of acetamidonaphthols **2a-d**,**f**,**j-l**,**n**,**t** at r.t. in MeCN, induced by a mixture of P_2O_5 and hexamethyldisiloxane (HMDS; Scheme 1). To develop the above method, they also conducted the reaction with other 2-naphthol analogues, such as 3-hydroxy-2-naphthoic acid (**3**), aryl aldehydes and MeCN, which afforded the corresponding 4-(acetamido(aryl)methyl)-3-hydroxy-2-naphthoic acids (**4a-i**, Scheme 2) in excellent yields (90-97%).[27]



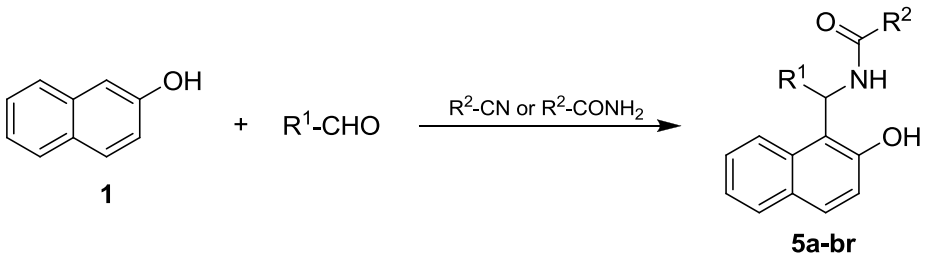
X = 4-Cl-Ph: **a**; 3-Cl-Ph: **b**; 2-Cl-Ph: **c**; 4-Me-Ph: **d**; 4-NO_2-Ph: **e**; 3-Cl-Ph: **f**; 4-Br-Ph: **g**; 3-OMe-Ph: **h**; 2-OMe-Ph: **i**

Scheme 2

$Ce(SO)_4$ was applied as catalyst by Perumal *et al.* to synthetize **2a-c**,**g**,**h**,**j**,**m**,**o**,**q**. The catalyst proved to be efficient enough to extend the series of aldehydes to aliphatic aldehydes and naphthaldehydes, leading to **2w**,**y** in moderate yields (42-74%).[14] The process was later optimized for **2a-c**,**g**,**h**,**j**,**m**,**o**,**q**,**u**,**w**,**y**, when, instead of heating of the reaction in MeCN, a mixture of acetyl chloride and 4 mol% I_2 was applied as catalyst (Scheme 1).[28]

To demonstrate the versatility of this reaction procedure, they examined the reactions with α-substituted nitriles (2-phenylacetonitrile and valeronitrile) and substituted aldehydes, obtaining the corresponding amidoalkylnaphthols **5a-i** (Scheme 3) in yields of 45-70% within 8-14 h.[28]

The research group of Tammadon found that $ZnCl_2/SiO_2$ is an efficient catalyst for the synthesis of *N*-*tert*-butyl amides via the Ritter reaction, and as an extension of their study they synthetized *N*-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)benzamide (**5j**, Scheme 3) from **1**, benzonitrile and benzaldehyde.[29] They additionally accomplished the syntheses of **5j-q** in good yields (84-91%) in the presence of $[MeC(OH)_2]^+ClO_4^-$ as a super-acidic IL (Scheme 3).[30]



1 **5a-br**

R^1 / R^2 = 2,4-Cl-Ph, Bn: **a**; 4-Cl-Ph, Bn: **b**; 3-NO_2-Ph, Bn: **c**; 4-NO_2-Ph, Bn: **d**; 2,4-Cl_2-Ph, *n*Bu: **e**; 3-NO_2-Ph, *n*Bu; **f**; 4-NO_2-Ph, *n*Bu: **g**; 4-OMe-Ph, *n*Bu: **h**; 4-Cl-Ph, *n*Bu: **i**; Ph, Ph: **j**; Ph, 4-NO_2-Ph: **k**; Ph, 4-Me-Ph: **l**; 4-Br-Ph, Ph: **m**; 4-Br-Ph, 4-NO_2-Ph: **n**; 4-Cl-Ph, Ph: **o**; Ph, *n*Pr: **p**; 4-Br-Ph, 2-furyl: **q**; 4-Cl-Ph, acryl: **r**; 2,4-Cl_2-Ph, acryl: **s**; 3-NO_2-Ph, acryl: **t**; 4-Me-Ph, Ph: **u**; 4-F-Ph, Ph: **v**; 3-OMe-Ph, Ph: **w**; 3-NO_2-Ph, Ph: **x**; 3,4,5-$(OMe)_3$-Ph, Ph: **y**; 4-CN-Ph, Ph: **z**; 4-NO_2-Ph, Ph: **aa**; 4-OMe-Ph, Ph: **ab**; 2,5-$(OMe)_2$-Ph, Ph: **ac**; 4-NMe_2-Ph, Ph: **ad**; 3-OMe,4-OH-Ph, Ph: **ae**; 2-Cl-Ph, Ph: **af**; 2-Br-Ph, C_6H_5: **ag**; 4-Cl-Ph, 3-pyridyl: **ah**; Ph, acryl: **ai**; 4-OMe-Ph, acryl: **aj**; 4-Me-Ph, acryl: **ak**; 3-Br-Ph, acryl: **al**; 2-F-Ph, Ph: **am**; 2-F-Ph, acryl: **an**; 2-NO_2-Ph, Ph: **ao**; 2,4-Cl_2-Ph, Ph: **ap**; 2-Cl-Ph, acryl: **aq**; 4-F-Ph, acryl: **ar**; 2-NO_2-Ph, acryl: **as**; 4-NO_2-Ph, acryl: **at**; 4-OH-Ph, acryl: **au**; 2-OMe-Ph, Ph: **av**; 4-NO_2-Ph, CH_2Cl: **aw**; 4-Cl-Ph, CH_2Cl: **ax**; 4-Me-Ph, CH_2Cl: **ay**; 4-OMe-Ph, CH_2Cl: **az**; Ph, CH_2Cl: **ba**; 1-Nph, Ph: **bb**; 4-*i*Pr-Ph, Ph: **bc**; 2-Nph, Ph: **bd**; 9-phenanthryl, Ph: **be**; 1-pyrenyl, Ph: **bf**; styryl, Ph: **bg**; Et, Ph: **bh**; undecyl, Ph: **bi**; Ph, 4-Br-Ph: **bj**; 4-NO_2-Ph, 4-Br-Ph: **bk**; 2-furyl, Ph: **bl**; 2-pyrrolyl, Ph: **bm**; *n*Pr, Ph: **bn**; 4-Br-Ph: acryl: **bo**; *n*Pr, acryl: **bp**; *i*Pr, Ph: **bq**; 4-pyridyl, Ph: **br**

Scheme 3

Das *et al.* achieved the three-component condensation of **1**, aryl aldehydes and alkyl nitriles in the presence of triflic acid (TfOH) at 85 ºC to obtain the corresponding amidoalkylnaphthols **2a**,**c**,**e**,**g**,**j**,**o**,**s**,**v**,**x** and **5r-t** (Schemes 1 and 3). It should be mentioned that, when MeCN was used, the reaction was complete within 1.5-5 h and the yields were good to excellent (50-91%), while with acrylonitrile the reaction time was somewhat longer (4.5-6 h) and the yield somewhat lower (60-67%).[15]

2.1.2. Syntheses of amidoalkylnaphthols from amides

The syntheses of acetamidoalkylnaphthols can also be achieved by the reaction of 2-naphthol, aryl aldehydes and acetamide. In the presence of $Fe(HSO_4)_3$,[17] $HClO_4/SiO_2$[20] or $NaHSO_4 \cdot H_2O$[21] as catalyst under thermal (85/110/120 ºC) solvent-free conditions, **2a-q** were formed in good yields (73-97%) within a short reaction time (7-80 min). Under microwave (450/800 W) solvent-free conditions, the yields of the synthetized compounds were higher (84-97%) within very short reaction times (3-20 min). In the presence of HSO_3/Al_2O_3, **2a-l**,**n-r** (Scheme 1) were successfully prepared, but in the case of aryl aldehydes bearing electron-donating groups, the yields were moderate, even under microwave agitation (37-41%).[22]

$FeCl_3/SiO_2$[19] and $NaHSO_4$[31] were used as catalysts only under thermal (120 or 125 ºC) solvent-free conditions, resulting in amidoalkylnaphthols **2a-q** and **2a-l**,**n-q**, respectively, in high yields (73-94%) within 7-40 min (Scheme 1). The series of catalysts was extended by using $Sr(OTf)_2$, LiBr and $POCl_3/Na_2B_4O_7$.[32-34]

1,3-Dibromo-5,5-dimethylhydantoin was used as catalyst in the absence of organic solvent under thermal conditions (100 ºC) or with microwave irradiation (160 W), affording **2a-h**,**j-o**,**q** in good yields (89-96%) in reaction times of 17-28 min and 4-9 min, respectively (Scheme 1).[35]

The research group of Heravi applied SiO_2-supported Preyssler nanoparticles under thermal (90 ºC) solvent-free conditions for the preparation of acetamidonaphthols **2a-c**,**e-g**,**j**,**m**. The desired compounds were formed in high yields (84-96%) after a very short reaction time (3-8 min).[24] This group later investigated the efficiency of Brønsted acidic ILs in the one-pot three-component synthesis of acetamidonaphthols, both in CH_2Cl_2 and under neat conditions (90 ºC). Aromatic aldehydes underwent facile conversions (76-97%), yielding **2a**,**c-g**,**j**,**l**, but aliphatic aldehydes (ethanal and *n*-octanal) afforded the products in very poor yields (traces, Scheme 1).[36]

The Amberlite IR-120-catalysed syntheses of **2a-h**,**j-o**,**q** (Scheme 1) were found to proceed efficiently within 3-6 min in the absence of any organic solvent under microwave irradiation.[37]

Zare *et al.* reported an efficient and simple new method for the preparation of 1-amidoalkyl-2-naphthols as biologically interesting compounds. The one-pot multicomponent condensation of **1**, aromatic aldehydes and acetamide in the IL 1-butyl-3-methylimidazolium bromide ([Bmim]Br) under microwave and catalyst-free conditions afforded **2a-f**,**j**,**l**,**n**,**o** in high yields (78-94%) and in short reaction times (25-35 min).[38] They subsequently developed a clean and efficient solvent-free method for the synthesis of acetamidonaphthols **2a-g**,**j-l**,**n**,**q**,**z** (Scheme 1) in the presence of a catalytic amount of silphox $[POCl_{3-n}(SiO_2)_n]$ or silphos $[PCl_{3-n}(SiO_2)_n]$ as inexpensive, green and heterogeneous SiO_2-supported P-containing reagents.[39]

Nano-sulfated ZrO_2 at 120 ºC under neat conditions proved to be an efficient, recyclable and environmentally benign catalyst, leading to **2a**,**c-g**,**j**,**l**,**z** (Scheme 1) in yields of 87-93% within 30-90 min.[40]

Montazeri *et. al* investigated the effect of a SiO_2-supported Caro's acid (H_2SO_5/SiO_2) as catalyst under thermal (140 ºC) and solvent-free conditions: **2a**,**c**,**e-g**,**j**,**l**,**n** (Scheme 1) were formed in yields of 85-95% within 2-4 min.[41]

It is interesting that the syntheses of amidoalkylnaphthols **2a-g**,**j-l**,**aa** (Scheme 1) in the presence of $KHSO_4$ at 100 ºC under neat conditions were reported in three different publications[42-44] and the yields of the products were the same.

Amidoalkylnaphthols **2a**,**c-g**,**j** (Scheme 1) were prepared in the presence of mixed-addenda vanadium(V)-substituted polyoxomolybdates, including the heteropolyacids $H_{3+x}PMo_{12-x}V_xO_{40}$ (x=1-3) as recyclable catalysts under solvent-free conditions. In all cases, the heteropolyacid with x = 3 gave the highest yield (84-92%) under solvent-free conditions at 130 ºC.[45]

12-Tungstophosphoric acid ($H_3PW_{12}O_{40}$) was successfully applied as a heterogeneous catalyst for the syntheses of **2a**,**c**,**e**,**f**,**j**,**l**,**n**,**o** (Scheme 1). The reaction mixture was heated to 100 ºC in the presence of 2 mol% of catalyst for 80 min in 1 equivalent of molten Et_4NCl, furnishing the desired compounds in yields of 65-95%.[46]

The research group of Maheria successfully applied zeolite H-Beta as catalyst in refluxing toluene or under solvent-free conditions (120 ºC). The reactions starting from aryl aldehydes led efficiently to the formation of **2a-h**,**k-m**,**o**,**ab** (Scheme 1).[47]

$InCl_3$ was found to be a very efficient catalyst for the synthesis of amidoalkylnaphthols **2c**,**e**,**g**,**q**,**s**,**ac** (Scheme 1) from **1**, aromatic aldehydes and acetamide under solvent-free conditions with the use of microwave irradiation (800 W).[48]

Shingare *et al.* extended the series of aldehydes to heteroaromatic and aliphatic aldehydes. The reaction conditions were solvent-free heating at 60 ºC in the presence of $[Bmim]HSO_4$, leading to **2a-c**,**h**,**j**,**l**,**n**,**q**,**aa**,**am-ao** and **5j**,**u**,**v**;[49] when sodium 1-hexasulfonate was applied under solvent-free heating and microwave irradiation,[50] **2a**,**c**,**d**,**am** and **5j**,**o**,**v** were obtained (Schemes 1 and 3).

Potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}{\cdot}3H_2O$) was found to be an efficient heterogeneous catalyst for the syntheses of **2a**,**c**,**d**,**j-l**,**o** and **5j**,**o**,**u**,**w** (Schemes 1 and 3), both at r.t. in 1,2-dichloroethane (DCE) and under neat conditions at 125 ºC. Aryl aldehydes underwent facile conversions (86-92%), but aliphatic aldehydes afforded **2am**,**an** (Scheme 1) in only trace amounts.[51]

The montmorillonite K10-catalysed preparation of 1-amidoalkyl-2-naphthols **2a**,**d**,**j**,**k**,**o**,**q**,**r**,**ad** and **5j**,**x**,**y** (Schemes 1 and 3) was carried out under neat conditions at 125 ºC to furnish good yields (65-96%) within 0.5-2 h.[52]

The research group of Mahdavinia applied $HClO_4/SiO_2$ at reflux temperature in DCE and under solvent-free conditions at 125 ºC,[53] or used wet cyanuric chloride at 100 ºC[54] to synthetize **2a-d**,**j-l**,**z** and **5j**,**o**,**u**,**v**,**z** (Schemes 1 and 3). The conversions were high (85-96%) and reaction times of 6-14 h were usually needed.

Shinde *et al.* achieved the synthesis of **2j** and **5x** in the presence of $ZrOCl_2$,[55] H_3NSO_3 (sulfamic acid)[56] and I_2[57] at r.t. in DCE: I_2 was found to be the most effective. They also investigated oxalic acid as catalyst at 125 ºC under solvent-free conditions in order to prepare amidoalkylnaphthols **2a**,**c**,**e-h**,**p**,**q** and **5j**,**o**,**u**,**aa**,[58] while the catalytic activity of $H_3PMo_{12}O_{40}$ (phosphomolybdic acid) in CCl_4 at reflux

temperature proved to be appropriate for the preparation of **2a**,**c**,**f**,**g**,**j**,**ae** and **5j**,**m**,**u**,**x**,**ab** (Schemes 1 and 3).[59]

Shaterian *et al.* applied $Al(H_2PO_4)_3$ as catalyst under solvent-free conditions by using classical heating or by microwave irradiation to isolate amidoalkylnaphthols **2a-c**,**e**,**f**,**h-j**,**l**,**n-r** and **5j**,**o**,**u**,**v**,**x**,**y** in yields of 63-93%.[60] $HClO_4/Al_2O_3$ as catalyst under neat conditions at 125 ºC resulted in **2a-c**,**e**,**f**,**h-l**,**n-r** and **5j**,**o**,**u**,**v**,**x**,**y** in from moderate to good yields (Schemes 1 and 3).[61] On SiO_2-supported polyphosphoric acid (PPA/SiO_2) at 120 ºC, not only **2a**,**c-g**,**i**,**j**,**l**,**n-r** and **5j**,**x**,**y**,**aa**, but also **2am** could be obtained, in a yield of 49% (Schemes 1 and 3).[62]

A series of 1-amidoalkyl-2-naphthols **2a**,**c**,**e-g**,**j**,**l**,**n**,**o** and **5j**,**o**,**u**,**x** were synthetized in the presence of Cu-exchanged heteropolyacids $Cu_{1-5}PMo_{12}O_{40}$ and $Cu_{1-5}PW_{12}O_{40}$ in molten Bu_4NBr as an IL (Schemes 1 and 3).[63]

A Ferrocene labelled-supported ionic liquid phase ([FemSILP]) catalyst containing *L*-prolinate anion has been successfully applied under neat conditions to prepare **2a**,**f**,**g**,**j**,**aa** and **5j**,**o**,**u**,**x**,**ab** in moderate yields (62-87%; Schemes 1 and 3).[64]

Gokavi *et al.* prepared amidoalkylnaphthols **2a**,**e**,**g**,**j**,**k** and **5j**,**w**,**x**,**aa**,**ab** (Schemes 1 and 3) in the presence of silicotungstic acid ($H_4SiW_{12}O_{40}$) under solvent-free conditions at 110 ºC in high yields (80-95%) within a short reaction time (15-40 min).[65]

The combination of glycerol (solvent) and a polystyrene-poly(ethylene glycol) (PS-PEG) resin-supported sulfonic acid (catalyst) was found to be an environmentally friendly system with which to obtain **2a**,**c**,**e-g** and **5u**,**x** in yields of 80-89% within 6 h at 100 ºC (Schemes 1 and 3).[66]

Methylimidazolium hydrogensulfate ($[Hmim]HSO_4$) as a Brønsted acidic IL was efficiently employed as catalyst for the syntheses of **2a**,**c-g**,**j-l**,**p**,**t**,**z**,**au**,**av** and **5j**,**m**,**o**,**u**,**w**,**x**,**ac** within 15 min under solvent-free conditions at 115 ºC,[67] while the research group of Pasha prepared **2a**,**c**,**e**,**g**,**h**,**j-l**,**o**,**q-s**,**af** and **5j**,**o**,**w-y**,**aa**,**ab**,**ad**,**ae** in excellent yields (90-98%) within 9-36 min in the presence of SiO_2Cl, accelerated by ultrasound at r.t. (Schemes 1 and 3).[68]

The research group of Cai used the complex hafnium(IV) bis(perfluorooctanesulfonyl)imide ($Hf(NPf_2)_4$) as catalyst in perfluorodecalin at 110 °C, when amidoalkylnaphthols **2a**,**c-e**,**g**,**h**,**j**,**l**,**o** and **5j**,**o**,**ab** were formed in 75-95% yields within 4-8 h (Schemes 1 and 3).[69]

With $Cu(ClO_4)_2 \cdot 6H_2O$ at 35 kHz under ultrasonic irradiation, **2a-c**,**j**,**m**,**aw** and **5j**,**o**,**v** were formed in high yields (84-90%) within 30-75 min (Schemes 1 and 3).[70]

Srivastava *et al.* applied seven different Brønsted acidic ILs functionalized with imidazole and benzimidazole-based sulfonic acid groups at r.t. in DCE as catalysts for the synthesis of *N*-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)benzamide (**5j**).[71] They later described the synthesis of **5j** in the presence of dual metal (Zn^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+} and Fe^{2+}) cyanide catalysts, of which

Fe-Fe-PEG at 80 °C in DCE was found to be the most efficient, and was therefore utilized for the synthesis of **5o**,**u** (Scheme 3).[72]

1-Amidoalkyl-2-naphthols **2a**,**c**,**e**,**g**,**h**,**j**,**l**,**r**,**s** and **5j**,**o**,**x**,**aa**,**ab**,**af** were synthetized with a sulfonic acid-functionalized benzimidazolium-based supported IL catalyst as a mild and effective catalyst under solvent-free conditions,[73] while Bhanage *et al.* described the syntheses of **2a**,**c**,**e**,**f**,**l-n** and **5j**,**u**,**x**,**ag** under solvent-free conditions, *N*-methyl-2-pyrrolidone hydrogensulfate ($[NMP]^+HSO_4^-$) being used as Brønsted acidic IL. This methodology has several advantages: good yields (82-94%, except for **2m** 68%), short reaction times (4-22 min), easy work-up procedures, and a reusable catalyst (Schemes 1 and 3).[74]

The research group of Hajipour developed a facile, convenient and solvent-free method to obtain **2a**,**c-f**,**j-l**,**p**,**z**,**au**,**av** and **5j**,**m**,**o**,**u**,**w**,**x**,**ac** (Schemes 1 and 3) by coupling various aromatic aldehydes with amides and 2-naphthol, using *N*-(4-sulfonic acid)butyl-triethylammonium hydrogensulfate ([TEBSA][HSO_4]) as catalyst,[75] while MoO_3–ZrO_2 served as an efficient catalyst for the synthesis of **5j**,**aa**,**ab**,**af** (Scheme 3) under solvent-free conditions with conventional or microwave heating.[76]

Compounds **2a-f**,**j-l**,**n**,**q** and **5j**,**o**,**u**,**x**,**ag**,**ah** (Schemes 1 and 3) were produced in excellent yields (81-96%) by Zolfigol *et al.* through the use of different sulfonic acid-functionalized imidazolium salts, including 3-methyl-1-sulfonic acid imidazolium chloride ([Msim]Cl), 1,3-disulfonic acid imidazolium chloride ([Dsim]Cl) and 3-methyl-1-sulfonic acid imidazolium tetrachloroaluminate ([Msim]$AlCl_4$) under solvent-free conditions (120 °C).[77] Furthermore, in the presence of a catalytic amount of $H_3PMo_{12}O_{40}{\cdot}H_2O/SiO_2$ under neat conditions at 120 °C, **2a-g**,**j-n**,**q** and **5j**,**x**,**ah** (Schemes 1 and 3) were produced in high to excellent yields.[78]

A series of amidoalkylnaphthols **2a-g**,**j**,**l**,**m**,**o**,**ag**,**aw** and **5j**,**o**,**r**,**t-v**,**x**,**ai**,**aj** (Schemes 1 and 3) were successfully prepared by the condensation of **1**, amides (acetamide, benzamide and acrylamide) and aldehydes, with 2,4,6-trichloro-1,3,5-triazine (TCT) as catalyst.[79]

In the presence of *para*-toluenesulfonic acid (*p*-TSA) the syntheses of **2a**,**c**,**j** and **5j**,**o**,**r**,**t**,**u**,**x** (Schemes 1 and 3) were performed both in DCE at r.t. and under solvent-free conditions at 125 °C. The yield of the reaction was found to depend on the nature of the starting aldehyde (*e.g.* 65% for **2l** and 20% for **2aa**).[80]

Das *et al.* successfully prepared **2a**,**c**,**j** and **5o**,**r**,**t**,**u**,**ak** (Schemes 1 and 3) by applying I_2 as catalyst at r.t. in DCE, and also under neat conditions at 125 °C.[81]

The research group of Samant achieved the syntheses of **2a-c**,**j**,**l**,**n**,**aa** and **5j**,**o**,**r**,**t**,**u**,**v**,**x**,**ag**,**al** (Schemes 1 and 3) in the presence of H_3NSO_3, accelerated by ultrasound at r.t.[82] These products were resynthetized by applying different cation-exchange resins, of which Indion-130 was the best under neat conditions at 110 °C.[83]

$H_3PMo_{12}O_{40}$ catalysed the formation of **2a**,**f**,**g**,**ab**,**ah** and **5j**,**o**,**ab**,**ai**,**aj**,**ak**,**am**,**an** via the three-component condensation of **1**, aldehydes and amides in EtOAc at 65 °C (Schemes 1 and 3).[84]

Polymer-supported sulfonic acid NKC-9 was investigated as catalyst under reflux conditions in $CHCl_3$. Compounds **2a**,**f**,**ab** and **5j**,**o**,**v**,**x**,**aa**,**ab**,**ai** were obtained in good yields, except from formamide, which did not lead to any product, even after 10 h (Schemes 1 and 3).[85]

The syntheses of 1-amidoalkyl-2-naphthol derivatives **2a-c**,**e-g**,**j**,**l**,**m**,**o**,**s** and **5j**,**o**,**r**,**s**,**t**,**v**,**x**,**aa**,**ab**, **af**,**ai-ak**,**ao-au** were promoted by [MIMPS][HSO_4] under neat conditions at 125 °C. The expected products were formed in excellent yields (86-97%) within 5-40 min (Schemes 1 and 3).[25]

The amidoalkylation of **1** with aldehyde and amide, with P_2O_5 as catalyst at 60 °C, resulted in **2c**,**e-g**,**j**,**l**,**m**,**t** and **5j**,**o**,**u**,**x**,**aa**,**ab**,**ad**,**af**,**ao**,**ap**,**av**,**aw-ba** in high yields (84-97%) within 5-15 min,[86] while in the presence of $HClO_4/SiO_2$ under thermal (100 °C) solvent-free conditions, **2a**,**s** and **5o**,**r**,**u**,**ak**,**bb** were produced in yields of 68-82% (Schemes 1 and 3).[87]

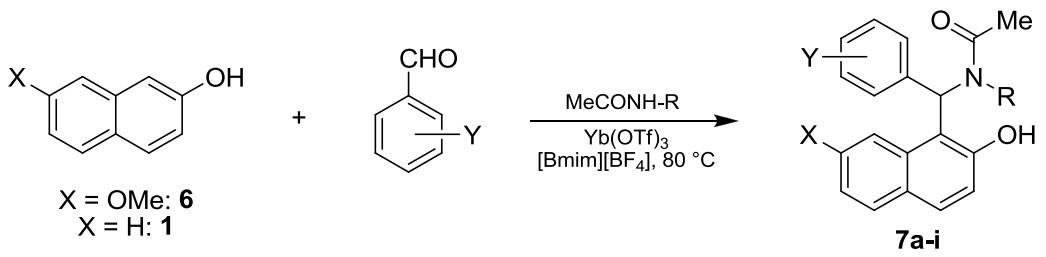
Sardarian *et al.* reported a convenient, mild and efficient procedure for the syntheses of **2a**,**v**,**ab**,**ai**,**ap** and **5j**,**x**,**aa**,**ab**,**ag**,**bc**,**bd-bi** (Schemes 1 and 3) from various aryl and alkyl aldehydes, 2-naphthol (**1**) and different amides in the presence of dodecylphosphonic acid under solvent-free conditions at 90° C. It was noteworthy that hindered aromatic aldehydes such as 2-naphthaldehyde, phenantherene-9-carbaldehyde and pyrene-1-carbaldehyde also gave the corresponding products in good yields (81-90%).[88]

A super-acidic IL ($[MeC(OH)_2]^+ClO_4^-$) proved to be a new and highly efficient catalyst in the syntheses of **2a**,**aj**,**aq** and **5j**,**u**,**aa**,**bj-bn** via the condensation of **1**, aldehydes (aryl, heteroaryl or alkyl) and amides at r.t. or at 80 °C under-solvent free conditions (Schemes 1 and 3).[30]

An eco-friendly procedure for the syntheses of **2a**,**c-g**,**j**,**k**,**o**,**aq** and **5j**,**m**,**o**,**u**,**x**,**ab**,**ac**,**bn** in the presence of silica gel-supported dual acidic IL at 85 °C in yields of 85-94% within 5-15 min (Schemes 1 and 3) was reported by the research group of Zhang.[89] They later investigated the efficiency of PEG-based dicationic acidic ionic liquid (DAIL) under thermal (80 °C) solvent-free conditions. This procedure was uniformly effective for both aliphatic and aromatic aldehydes, yielding **2a**,**c-g**,**j**,**k**,**ak**,**aq-as** and **5m**,**u**,**x**,**aa**,**ak**,**at**,**bn-bp** (Schemes 1 and 3). Aliphatic aldehydes such as *n*-butyraldehyde, valeraldehyde, and isovaleraldehyde were all converted to the corresponding products in yields of 80-98%.[90]

The research team of Kumar prepared **2a**,**c**,**e**,**f**,**j**,**k**,**ak** (Scheme 1) by using $Yb(OTf)_3$ as a mild Lewis acid catalyst in the IL [Bmim][BF_4] at 80 °C. When acetamide was replaced by benzamide, **5j** was isolated in a yield of only 35% (Scheme 3). When their method was applied to 7-methoxynaphthalen-2-ol (**6**), **7a-h** were produced in yields of 85-90% (Scheme 4). The reaction from *N*-methylacetamide under the same conditions also took place, but the transformation was slower than

that from acetamide, and **7i** was obtained in a yield of only 61% after 12 h (Scheme 4).[91] Murthy *et al.* applied H_2SO_4/SiO_2 successfully to obtain **2a**,**c**,**ab**,**al-ao**,**at** and **5w**,**bh**,**bq**,**br** (Schemes 1 and 3) in high yields (84-92%).[92]



X = OMe, R = H: **7a-h**; Y = H: **a**; 4-Cl: **b**; 4-Me: **c**; 4-OMe: **d**, 3-NO_2: **e**; 4-NO_2: **f**; 3-Cl: **g**; 3-OMe: **h**
X = H, R = Me, Y = 4-Cl: **7i**

Scheme 4

1-Amidoalkyl-2-naphthols **2a**,**c**,**e**,**g**,**p** and **5j**,**o**,**aa**,**ab** were prepared in high yields (85-94%) within surprisingly short reaction times (1-2 min) in the presence of $MeSO_3H$ at r.t. In the case of furfural, the desired **5bl** could be isolated in a yield of only 60% after a reaction time of 5 min (Schemes 1 and 3).[93]

When Cu *p*-toluenesulfonate was applied under thermal (80 °C) solvent-free conditions, the corresponding products **2a**,**c**,**j**,**l** and **5j**,**o**,**u**,**x**,**aa**,**ab**,**af**,**ao**,**ap**,**bh**,**bn** (Schemes 1 and 3) were formed in good yields (72-96%). Aromatic aldehydes bearing electron-donating groups reacted more slowly (**2f**,**g** and **5ad**) and the yields were lower (65, 16 and 31%). It should be mentioned that the reactions of aliphatic aldehydes (propionaldehyde and butyraldehyde) also led to the desired products (**2am** and **2aq**, Scheme 1) in moderate to good yields.[94] In the presence of Cu *o*-tolunesulfonate, the amidoalkylation of **1** with alkyl or aryl aldehydes and benzamide led to the formation of **5j**,**o**,**u**,**x**,**aa**,**af**,**ao**,**ap**,**bh**,**bn** (Scheme 3) in excellent yields (90-97%; except for **5ab**: 65%), and from acetamide compounds, **2a**,**c**,**f**,**j**,**l**,**am**,**aq** (Scheme 1) were isolated in yields of 51-76 %.[95]

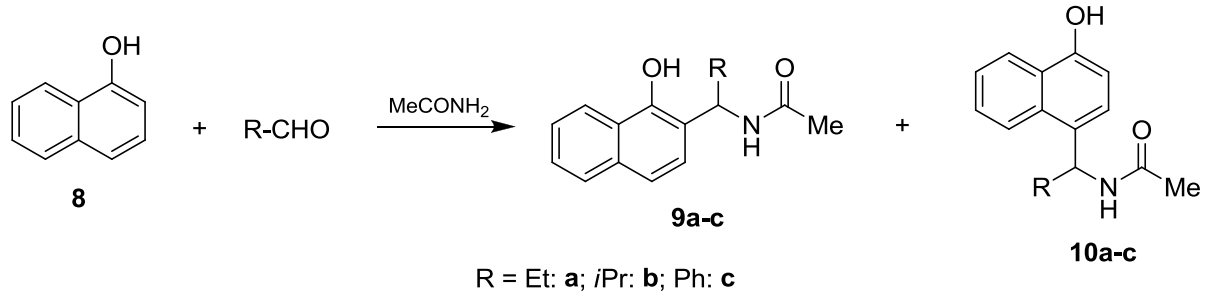
The research group of Wang used $MeSO_3H/SiO_2$ under solvent-free conditions at 80 °C for the synthesis of **2a**,**c**,**e-g**,**j**,**l**,**m**,**o** and **5j**,**o**,**u**,**x**,**ab**,**af**,**ao**,**ap**,**bh**,**bn** (Schemes 1 and 3), this method affording the corresponding products in from moderate to good yields (70-96%). Aromatic aldehydes containing a strong electron-donating group, such as 4-dimethylaminobenzaldehyde, generally failed to yield any product, and **2am** was isolated in a yield of only 34% (Scheme 1).[96] The efficiency of $Bi(NO_3)_3{\cdot}5H_2O$ in the preparation of **2a-e**,**g**,**j**,**am**,**aq** and **5j**,**o**,**u**,**x**,**aa**,**ab**,**af**,**ao**,**ap**,**bh**,**bn** was investigated under the same conditions (Schemes 1 and 3).[97]

A zwitterionic-type molten salt was successfully applied as mild organocatalyst under neat conditions at 80 °C to furnish **2a-e**,**g**,**j**,**aq**,**ar** and **5j**,**o**,**u**,**x**,**bq** (Schemes 1 and 3) in yields of 74-90%, even from aliphatic aldehydes such as *n*-butyraldehyde, isobutyraldehyde, and valeraldehyde.[98]

The application of thiamine hydrochloride as catalyst in the condensations of **1** and acetamide/acrylamide/benzamide with aromatic aldehydes gave the desired products (**2a**,**f**,**j** and **5j**,**u**,**x**,**ab**,**ai-ak**,**as**; Schemes 1 and 3) in excellent yields (88-93%). It was reported that this methodology failed when *N*-methylbenzamide and caprolactam were utilized as nitrogen sources.[99]

The research team of Murthy investigated the use of 1-naphthol (**8**) to afford amidoalkylated products. As catalyst, H_2SO_4/SiO_2 was used and the reaction was carried out at r.t. under solvent-free conditions, during which mixtures of regioisomers **9a-c** (30-32%) and **10a-c** (38-42%) were formed (Scheme 5).[92]

The catalytic activity of $Hf(NPf_2)_4$ was studied in the three-component condensation of 1-naphthol, benzaldehyde and acetamide at 110 °C in perfluorodecalin, yielding **9c** and **10c** in yields of 41% and 59%, respectively (Scheme 5).[69]



Scheme 5

2.2. Syntheses of carbamidoalkylnaphthols

1-Carbamidoalkyl-2-naphthols can be prepared successfully through the condensation of 2-naphthol (**1**), aromatic aldehydes and urea in the presence of various catalysts.

Mahdavinia *et al.* produced **11a-e** (Scheme 6) in the presence of $HClO_4/SiO_2$[53] under both thermal (refluxing in DCE) and neat conditions (125 °C), and also with wet cyanuric chloride (100 °C).[54]

11a,**e-g** (Scheme 6) were synthetized in good yields when either conventional heating in DCE or microwave irradiation (125 °C) was utilized in the presence of $K_5CoW_{12}O_{40}\cdot 3H_2O$ as catalyst.[51]

Montmorillonite K10 effectively catalysed the formation of **11a**,**g-i** under neat conditions (125 °C) within 1.5 h,[52] while the syntheses of **11b**,**e**,**j** could be carried out with TCT as catalyst under solvent-free conditions at 100 °C (Scheme 6).[79]

When thiamine hydrochloride[99] at 80 °C in EtOH and Brønsted acidic IL [TEBSA][HSO_4][75] were employed as catalysts under thermal (120 °C) solvent-free conditions, **11a**,**e** were formed in moderate yields (Scheme 6).

Khabazzadeh *et al.* applied $Cu_{1-5}PMo_{12}O_{40}$ and $Cu_{1-5}PW_{12}O_{40}$ as catalysts in molten Bu_4NBr as an IL for the synthesis of **11a**,**b**,**e** (Scheme 6).[63]

1-Carbamidoalkyl-2-naphthols **11a**,**j** were produced in yields of 83% and 74% in the presence of [FemSILP]*L*-prolinate as catalyst at 100 °C[64] and Zhang *et al.* efficiently used silica gel-supported dual acidic IL as catalyst for the preparation of **12a**,**e**,**g**.[89] They later tested $PEG_{1,000}$-DAIL as catalyst at 80 °C, which resulted in **11a**,**b**,**e** in yields of 80-84% within 5-10 min (Scheme 6).[90]

1,2-Dihydro-1-(4-chlorophenyl)naphth[1,2-*e*][1,3]oxazin-3-one (**12b**) was prepared from 2-naphthol, 4-chlorobenzaldehyde, urea and AcOH, and its structure was elucidated by means of X-ray diffraction (Scheme 6).[100]

$MeSO_3H$ was demonstrated to be an effective catalyst in water at r.t. for the synthesis of carbamidoalkylnaphthols **11a**,**b**,**k-m**,[93] while the syntheses of **11e**,**f**,**l**,**n** in yields of 85-89% were carried out by applying [MIMPS][HSO_4] at 125 °C (Scheme 6).[25]

Heravi *et al.* prepared **11a-c**,**e**,**f**,**j** (Scheme 6) in the presence of two Brønsted acidic ILs, 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogensulfate [$(CH_2)_4SO_3HMIM$][HSO_4] (IL_1) and *N*-(4-sulfonic acid)butylpyridinium hydrogensulfate [$(CH_2)_4SO_3HPY$][HSO_4] (IL_2). The reactions promoted by IL_2 gave higher yields of the products within shorter reaction times.[36]

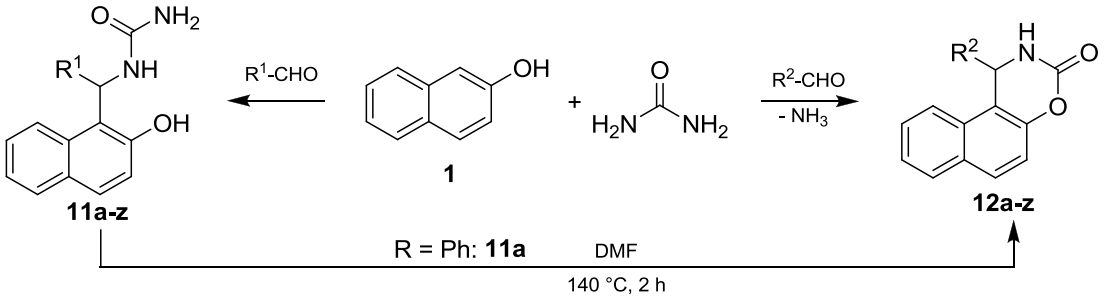
The oxalic acid-catalysed solvent-free condensations of **1**, aromatic aldehydes and urea afforded **11a**,**b**,**e**,**j** in yields of 88-98% within 8-24 min,[58] and the group of Gokavi investigated the effectiveness of $H_4SiW_{12}O_{40}$ as catalyst under thermal (110 °C) solvent-free conditions, obtaining **11a**,**e**,**g**,**k**,**l** in good yields (Scheme 6).[65]

Hosseini *et al.* achieved the synthesis of **11a**,**b**,**k** (Scheme 6) by using $H_3PW_{12}O_{40}$ as catalyst, and their corrosion inhibition ability in 0.5 M H_2SO_4 solution was additionally investigated.[101] These compounds were also prepared by Cai *et al.* in yields of 76-89%, in the presence of $Hf(NPf_2)_4$ in perfluorodecalin at 110 °C.[69]

When the combination chlorotrimethylsilane (TMSCl)/NaI was applied as catalyst in MeCN at r.t. the reactions of **1**, aromatic aldehydes and urea gave the corresponding carbamidoalkylnaphthols (**11a**,**b**,**j**,**k**,**o**) in 78-81% yields. When **11a** was heated in DMF at 140 °C for 2 h, cyclization occurred to produce the naphth[1,2-*e*][1,3]oxazinone (**12a**). The syntheses of naphth[1,2-*e*][1,3]oxazinones (**12b-m**) were achieved directly through the reactions of **1**, aromatic aldehydes and urea.[102] Compounds **12a**,**b**,**d-g**,**n** were also prepared in excellent yields (90-96%) within 5 min in the presence of I_2 as catalyst at 80 °C,[103] while Chaskar *et al.* accomplished the syntheses of **12a-d**,**h**,**n-r** in the presence of

$H_3PMo_{12}O_{40}$ in DMF at 100 °C (Scheme 6).[104] For the syntheses of 1-carbamidoalkyl-2-naphthols, $Sr(OTf)_2$ and $POCl_3/Na_2B_4O_7$ were also stated to be convenient and efficient catalysts.[32,34]

On the addition of aromatic aldehydes, 2-naphthol, urea and ZnO nanoparticles in an inappropriate sequence, a xanthene derivative was observed as major product and no naphthoxazinone derivative was formed. The correct sequential addition of aryl aldehydes, urea and catalyst followed by **1** played a crucial role and influenced the reaction in the direction of the desired naphthoxazinone **12b-d,f,s-x** (Scheme 6).[105]



R^1 = Ph: **a**; 4-Cl-Ph: **b**; 4-Br-Ph: **c**; 4-CN-Ph: **d**; 3-NO_2-Ph: **e**; 2-Cl-Ph: **f**; 3-OMe-Ph: **g**; 3,4-$(OMe)_2$-Ph: **h**; 3,4,5-$(OMe)_3$-Ph: **i**; 4-Me-Ph: **j**; 4-OMe-Ph: **k**; 4-NO_2-Ph: **l**; 2,5-$(OMe)_2$-Ph: **m**; 2-NO_2-Ph: **n**; 4-OH-Ph: **o**; 2-Br-Ph: **p**; 2,4-Cl_2-Ph: **q**; 1-Nph: **r**; Et: **s**; *i*Bu: **t**; 2-pyridyl: **u**; 2-thienyl: **v**; 3-pyridyl: **w**; 2-furyl: **x**; 4-NMe_2-Ph: **y**; 3,4-(OCH_2O)-Ph: **z**

R^2 = Ph: **a**; 4-Cl-Ph: **b**; 4-Me-Ph: **c**; 4-OMe-Ph: **d**; 4-OH-Ph: **e**; 4-F-Ph: **f**; 4-Br-Ph: **g**; 2-Cl-Ph: **h**; 3-Br-Ph: **i**; 3-OMe-Ph: **j**; 3-OH-Ph: **k**; 4-*i*Pr-Ph: **l**; 4-*t*Bu-Ph: **m**; 3-NO_2-Ph: **n**; 4-NO_2-Ph: **o**; 2-OH-Ph: **p**; 2,5-$(OH)_2$-Ph: **q**; 2-OH,5-OMe-Ph: **r**; 3-F-Ph: **s**; 3-Cl-Ph: **t**; 4-OEt-Ph: **u**; 4-CF_3-Ph: **v**; 4-OCF_3-Ph: **w**; 4-*t*Bu-Ph: **x**; 3-OMe,4-OH-Ph: **y**; 2-furyl: **z**; 3,4-(OCH_2O)-Ph: **aa**

Scheme 6

The research group of Srivastava investigated the efficiency of different dual metal (Zn^{2+}, Mn^{2+}, Ni^{2+}, Co^{2+} and Fe^{2+}) cyanide complexes at reaction temperatures of 25 °C, 50 °C and 80 °C. Fe-Fe-PEG at 80 °C was found to be best for the synthesis of **11a,b,k** (Scheme 6).[72]

Composite oxides MoO_3–ZrO_2 were successfully applied as catalysts for the preparation of **11a,b,e,f,k,l,o** through conventional or microwave heating (Scheme 6). The products were formed in yields of 76-86% within 3-6 min under microwave irradiation.[76]

The preparation of **11a,b,e** (Scheme 6) proceeded satisfactorily in a very short reaction time (4-7 min) in the presence of $[Hmim]HSO_4$ at 125°C[67] or on the use of sodium 1-hexasulfonate under solvent-free and microwave irradiation.[50]

The formation of **11a,e** through thermal (80 °C) solvent-free condensation in the presence of Cu *p*-toluenesulfonate has been described.[94] When Cu *o*-toluenesulfonate was used as catalyst, **11a,e** were formed in yields of 86%, whereas that of **11b** was only 59%.[95] In the presence of $MeSO_3H/SiO_2$, the yield of **11a** was 77%, and that of **11e** was 30%, while **11j** was formed in merely trace amounts (Scheme 6).[96]

Compound **11a** was prepared both in the presence of $Bi(NO_3)_3 \cdot 5H_2O$ at 80 °C[97] and by using $[MeC(OH)_2]^+ClO_4^-$ as a super-acidic IL.[30] When $Fe(HSO_4)_3$ was applied as catalyst in DCE at 60 °C, carbamidoalkylnaphthols **11a**,**b**,**k**,**l** were formed in yields of 84-94% (Scheme 6).[106]

11a,**b**,**e** (Scheme 6) have been prepared independently by different research groups with the use of different catalysts as follows: [Bmim]Br under microwave irradiation;[38] silphox and silphos at 120 °C;[39] a sulfonic acid-functionalized benzimidazolium-based supported IL catalyst at 100 °C;[73] $[NMP]^+HSO_4^-$ as a reusable Brønsted acidic IL at 125 °C;[74] and $Cu(ClO_4)_2 \cdot 6H_2O$ accelerated by ultrasound irradiation.[70]

11a,**e** were prepared in the presence of the imidazolium salts [Msim]Cl, [Dsim]Cl and $[Msim]AlCl_4$ as catalysts,[77] while Das *et al.* isolated **11a**,**b**,**e**,**j**,**p**,**q**,**r** in yields of 71-93% under solvent-free conditions by using $HClO_4/SiO_2$ as heterogeneous catalyst.[87] The series of compounds was extended by starting from propionaldehyde in the presence of I_2 in DCE at r.t. and under solvent-free conditions at 125 °C to lead to **11s** (Scheme 6).[81]

Under mild conditions (60 °C) in $[Bmim]HSO_4$, **11a**,**b**,**t-v** (Scheme 6) were prepared in 80-92% yields within 35-47 min,[49] while Chaskar *et al.* applied $H_3PMo_{12}O_{40}$ as catalyst in CCl_4 under reflux conditions to afford **11a**,**c**,**e**,**h**,**j**,**k**,**w**.[59] The team of Cai and Almahy achieved the $KHSO_4$-catalysed syntheses of **11a-c**,**e**,**l**,**x** (Scheme 6) in good yields.[42-44]

Aryl aldehydes containing both electron-withdrawing and electron-donating groups, and also propionaldehyde, gave high yields of the desired products (**11a**,**b**,**e**,**f**,**i**,**k**,**l**,**o**,**s**,**y**) in the presence of *N*,*N*,*N*,'*N*'-tetrabromobenzene-1,3-disulfonamide under neat conditions at r.t. (Scheme 6).[107]

The syntheses of derivatives **11a**,**b**,**e**,**f**,**q**,**r** through the use of $H_3PW_{12}O_{40}$ in a molten salt (Et_4NCl) were described by Saidi *et al.*,[46] while $InCl_3$ was found to be an efficient catalyst in furnishing **11b**,**h**,**k**,**l**,**o**,**z** under solvent-free microwave conditions (800 W; Scheme 6).[48]

Khavasi *et al.* carried out the synthesis of **13a** (Scheme 7) in the presence of *p*-TSA at 100 °C under solvent-free conditions, with a yield of 54% in 3 h, and studied the intermolecular and intramolecular hydrogen-bonds in the stabilization of the crystal structure.[108]

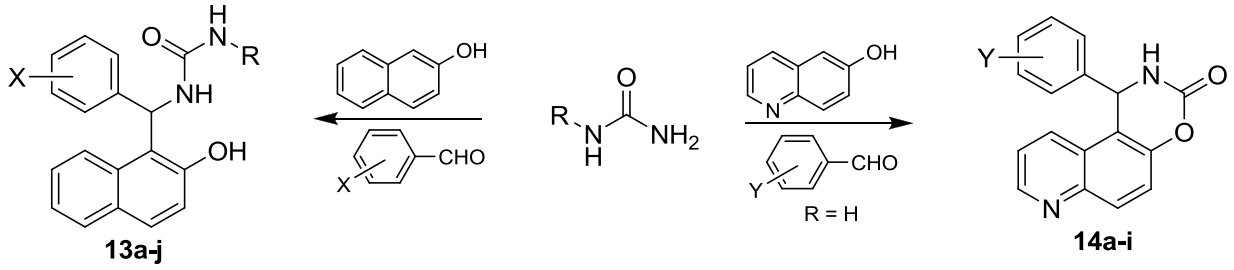
Zali *et al.* produced **11a**,**b**,**e**,**g**,**j**,**l**,**r** in yields of 83-93% within 30-90 min by applying nano-sulfated ZrO_2 under thermal (120 °C) conditions.[40] The preparations of **11a-c**,**e**,**j** and **13a-e** (Schemes 6 and 7) were achieved with excellent yields in DCE at r.t. and under solvent-free conditions at 125 °C in the presence of *p*-TSA.[80]

The ultrasound-promoted H_3NSO_3-catalysed three-component condensations of **1**, ureas and aldehydes gave **11a-c**,**e** and **13a-g** in good yields (82-94%; Schemes 6 and 7).[82] In the presence of Indion-130 as catalyst at 110 °C, these compounds were prepared within shorter reaction times, and in somewhat higher yields.[83]

The group of Shinde also investigated the catalytic effect of H_3NSO_3, but applied it in DCE at r.t., which led to the formation of **11a**,**b**,**e**,**f**,**k**,**x** and **13b** in yields of 55-86% within 7-23 h (Schemes 6 and 7).[56] They carried out the syntheses of these compounds in the presence of $ZrOCl_2$ in DCE at r.t. too, which afforded the products in higher yields, but in longer reaction times.[55] When I_2 was applied under the same conditions, the yields of all the above-mentioned compounds were improved.[57] From propionaldehyde, **11s** was isolated in yields of only 23-30%, and longer reaction times were needed in comparison with aromatic aldehydes.

PPA/SiO_2 was demonstrated to be an efficient catalyst for the synthesis of **11a**,**b**,**e** and **13a-c**,**e** in $CHCl_3$ at 50 °C (Schemes 6 and 7). The products were formed in high yields within 4-10 min.[62] Jiang *et al.* carried out the synthesis of **13h-j** in the presence of $H_3PMo_{12}O_{40}$ in EtOAc at 65 °C[84] and of polymer-supported sulfonic acid NKC-9 in $CHCl_3$ under reflux conditions (Scheme 7).[85]

Efficient methodology was developed for the preparation of 2-naphthol-condensed 1,3-oxazinone derivatives, involving a one-pot condensation in the presence of K_2CO_3 and Cu nanoparticles in PEG-400. With this method, 1,3-oxazinones **12a**,**b**,**d-g**,**o**,**y**,**z** were formed in yields of 74-93% within 45-60 min (Scheme 6).[109]



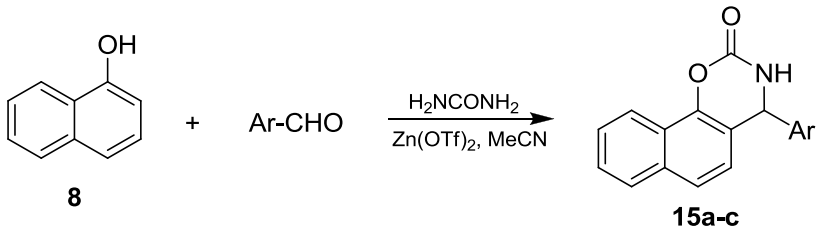
R = Me: **13a-f**, X = H: **a**; 3-NO_2: **b**; 4-Cl: **c**; 4-Br: **d**; 4-Me: **e**; 4-F: **f**;
R = Et, X = H: 13**g**;
R = Ph: **13h-j**; X = H: **h**; 2-F: **i**; 4-F: **j**

Y = H: **a**; 4-Cl: **b**; 4-F: **c**; 4-Br: **d**; 2-Cl: **e**; 3-Br: **f**; 2-OMe: **g**; 4-OMe: **h**; 4-Me: **i**

Scheme 7

The team of Bazgir isolated 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-ones (**12a-g**, Scheme 6) in moderate to high yields by using *p*-TSA under microwave-assisted (900 W) and thermal (160 °C) solvent-free conditions.[110] They also extended this reaction to 6-quinolinol as starting compound, and prepared oxazino[5,6-*f*]quinolin-3-ones (**14a-i**, Scheme 7).[111]

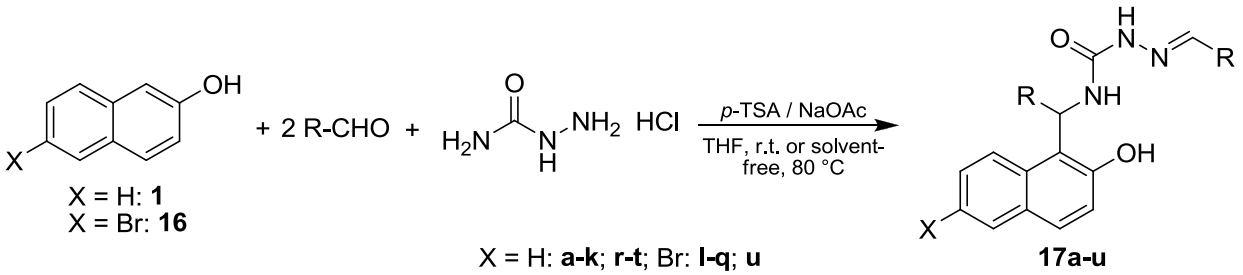
The syntheses of naphthoxazinones **12a-g**,**aa** were achieved with good yields in the presence of $Zn(OTf)_2$ in MeCN at reflux temperature. This method was additionally utilized for the preparation of 4-aryl-3,4-dihydronaphth[2,1-*e*][1,3]oxazin-2-ones from 1-naphthol, which afforded **15a-c** in yields of 64-69% (Scheme 8).[112]



Ar = Ph: **a**; 4-Me-Ph: **b**; 3,4,5-$(OMe)_3$-Ph: **c**

Scheme 8

A further procedure for condensation of 2-naphthol, aldehydes and urea as nitrogen source involves the application of semicarbazide. When 2-naphthol (**1**) or 6-bromo-2-naphthol (**16**), aldehydes and semicarbazide hydrochloride were reacted in tetrahydrofuran (THF) at r.t. or under solvent-free conditions at 80 °C, catalysed by the *p*-TSA/NaOAc system, **17a-u** were isolated in moderate to good yields, as presented in Scheme 9. The reaction was carried out with 2 equivalents of aldehyde, since the carbamidoalkylnaphthol formed immediately reacts with a second equivalent of aldehyde to form the isolated products.[113]



X = H: **a-k**; **r-t**; Br: **l-q**; **u**

R = Ph: **a**; 4-Cl-Ph: **b**; 2-Cl-Ph: **c**; 4-NO_2-Ph: **d**; 3-NO_2-Ph: **e**; 4-Me-Ph: **f**; 4-OMe-Ph: **g**; 3-OMe-Ph: **h**; 2-F,6-Cl-Ph: **i**; 2-furyl: **j**; 5-Me-2-thienyl: **k**; Ph: **l**; 4-NO_2-Ph: **m**; 4-Cl-Ph: **n**; 4-Me-Ph: **o**; 3-OMe-Ph: **p**; 5-Me-2-thienyl: **q**; *i*Pr: **r**; Et: **s**; *n*Pr: **t**; Et: **u**

Scheme 9

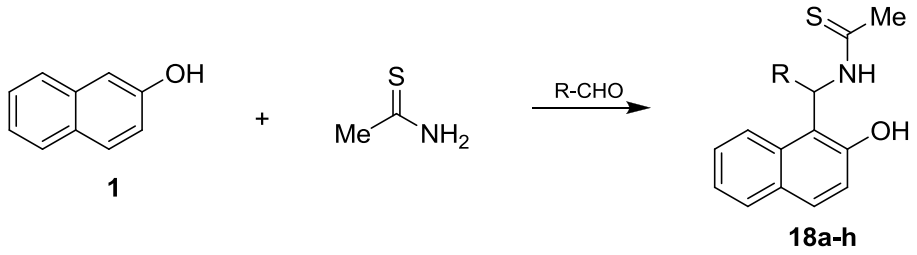
2.3. Syntheses of thioamido- and thiocarbamidoalkylnaphthols

In consequence of the lower reactivity of the thio analogues of acetamide and urea, comparatively few publications have appeared on this field.

2.3.1. Syntheses of thioamidoalkylnaphthols

The research group of Murthy synthetized thioamidoalkylnaphthols from thioacetamide, benzaldehyde/pyridine-4-carbaldehyde and 2-naphthol in the presence of H_2SO_4/SiO_2, obtaining **18a** and **18b** in yields of 79% and 82%, respectively, within 2.2 and 2.5 h (Scheme 10).[92]

Derivatives **18a**,**c-h** were prepared in yields of 78-88% in the presence of $Fe(HSO_4)_3$ in DCE at 60 °C (Scheme 10).[106]



R = Ph: **a**; 4-pyridyl: **b**; 4-Cl-Ph: **c**; 4-NO_2-Ph: **d**;
4-OMe-Ph: **e**; 2-OH,3-OMe-Ph: **f**; 2-OH-Ph: **g**; 2-furyl: **h**

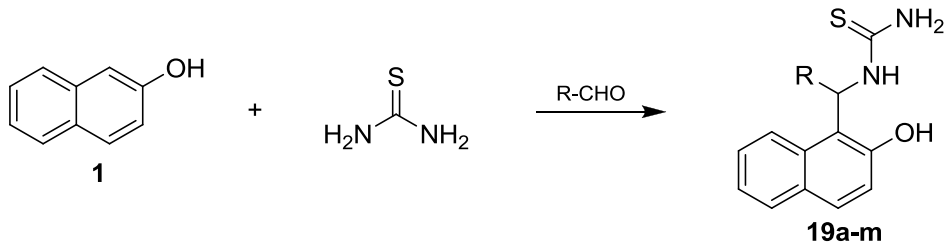
Scheme 10

2.3.2. Syntheses of thiocarbamidoalkylnaphthols

H_2SO_4/SiO_2 was successfully applied under solvent-free conditions at r.t. in the three-component condensation of **1**, aldehydes and thiourea. The expected products (**19a-f**) were formed in yields of 80-85% within 1.5-2.5 h (Scheme 11).[92] It is worthy of note that this reaction did not lead to the desired thiocarbamidoalkylnaphthols from **1**, thiocarbamide and the appropriate aldehyde in the presence of K_2CO_3 and Cu nanoparticles in PEG-400.[109]

Hossein *et al.* prepared thiocarbamidoalkylnaphthols **19g-m** by using $Fe(HSO_4)_3$ at 60 °C in DCE (Scheme 11). The desired products were formed in yields of 75-91% within 5-8 h, whereas with furfural as starting compound, **19m** was obtained in a yield of only 35%.[106]

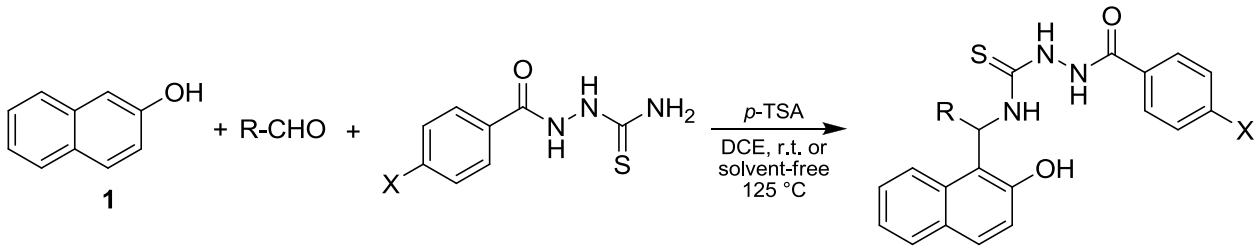
A series of 1-thiocarbamidoalkyl-2-naphthols were prepared by Zhang *et al*. from aromatic aldehydes, 2-naphthol and *N*-phenylthiourea or thiourea in the presence of *p*-TSA at r.t. This inexpensive and mild method furnished the corresponding products in high yields.[114]



R = Et: **a**; *i*Pr: **b**; CH=CH-Ph: **c**; pentyl: **d**; cyclohexyl: **e**; 4-pyridyl: **f**; Ph: **g**; 4-Cl-Ph: **h**; 4-NO_2-Ph: **i**; 4-OMe-Ph: **j**; 2-OH,3-OMe-Ph: **k**; 2-Nph: **l**; 2-furyl: **m**

Scheme 11

It is of interest that 4-substituted 1-acylthiosemicarbazides **20a-r** (Scheme 12) could be prepared in moderate to good yields in the presence of *p*-TSA via the three-component condensation of 2-naphthol, aldehydes and 1-acylthiosemicarbazides.[115]



X = H: **a-j**; 4-NO_2: **k-r**

R = Ph: **a**; 4-Me-Ph: **b**; 4-NO_2-Ph: **c**; 4-OMe-Ph: **d**; 4-Cl-Ph: **e**; 2-Cl-Ph: **f**; 2-furyl: **g**; 2-pyridyl: **h**; Et: **i**; *n*Pr: **j**; Ph: **k**; 4-OMe-Ph: **l**; 3-NO_2-Ph: **m**; 4-Cl-Ph: **n**; 4-Me-Ph: **o**; 2-pyridyl: **p**; Et: **q**; *n*Pr: **r**

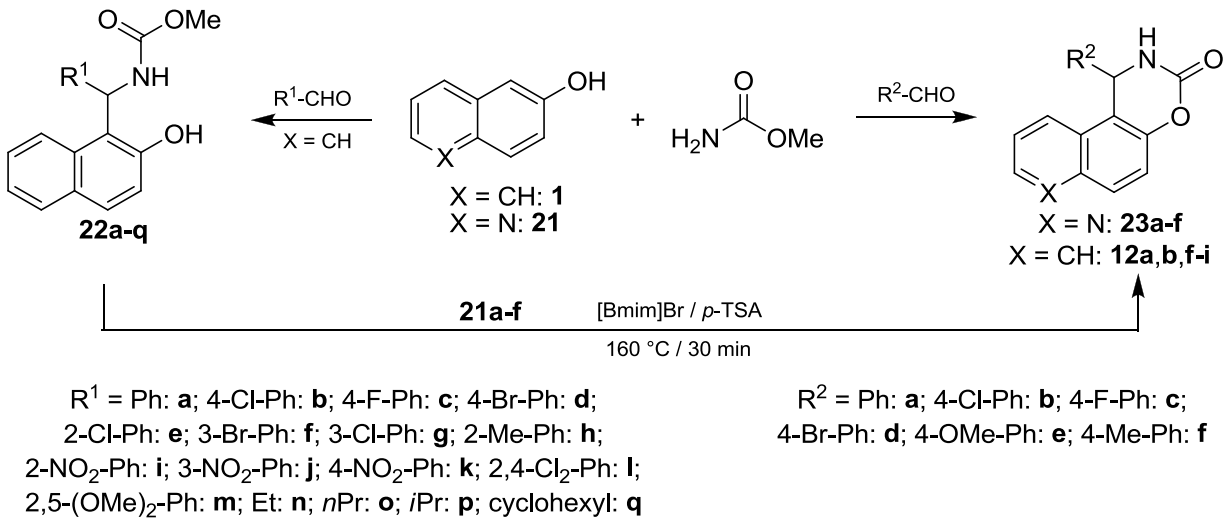
Scheme 12

2.4. Syntheses of carbamatoalkylnaphthols

In the presence of a catalytic amount of *p*-TSA in a [Bmim]Br medium at 60 ºC, **22a-f** were synthetized in yields of 75-88% within a reaction time of 35-60 min. It emerged that **22a-f** can be converted into 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-ones (**12a**,**b**,**f-i**) by heating in [Bmim]Br in the absence of catalyst at 160 ºC for 30 min (Schemes 6 and 13). Naphthoxazinone derivatives were obtained in yields of 58-79%.[116]

Carbamatoalkylnaphthols **22a**,**b**,**g-l** were also prepared in high yields when SiO_2-supported Preyssler nanoparticles were used as catalyst at 90 ºC under solvent-free conditions (Scheme 13).[117]

Methyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate (**22a**, Scheme 13) was prepared in a yield of 85% in the presence of $[MeC(OH)_2]^+ClO_4^-$, either at 80 ºC under solvent-free conditions or in EtOAc at r.t.[30]



Scheme 13

Efficient syntheses of 1,2-dihydro-1-arylnaphth[1,2-*e*][1,3]oxazin-3-ones (**12a-d**,**f**,**g**) and 1,2-dihydro-1-aryl[1,3]oxazino[5,6-*f*]quinolin-3-ones (**23a-f**) were accomplished in good yields (78-85%) via reactions between 2-naphthol (**1**) or 6-quinolinol (**21**), aryl aldehydes and methyl carbamate in aqueous medium, catalysed by triethylbenzylammonium chloride (Schemes 6 and 13).[118]

Shaterian *et al.* achieved the $NaHSO_4/SiO_2$[119] and PPA/SiO_2-catalysed[120] syntheses of **22a**,**b**,**g**,**j-m** and **24a-e** at 100 ºC. In the presence of $HClO_4/SiO_2$ at 85 °C, carbamatoalkylnaphthols **22a**,**b**,**g**,**j-m** and **24a-e** were obtained in good yields (78-93%) within 2.5-8.5 min (Schemes 13 and 14).[121] The methods examined led to the formation of the desired compounds in good yields in the case of substituted benzaldehydes.

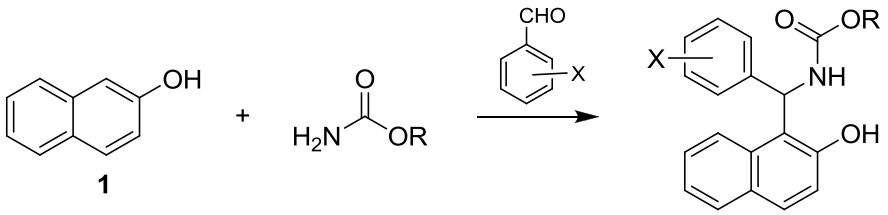
The research team of Hajra used a zwitterionic salt at 80 ºC, this method furnishing **22a**,**b**,**j**,**k**,**n-q** and **24a**,**b** in yields of 72-88% (Schemes 13 and 14). With aliphatic aldehydes, the reactions were complete within shorter reaction times.[98]

Brønsted acidic ILs (IL_1 and IL_2) were revealed to be efficient catalysts for the preparation of **22a**,**b**,**f-l** and **24a**,**e-g** at 90 ºC under neat conditions (Schemes 13 and 14). In both cases, high yields were attained, but no product could be detected when aliphatic aldehydes were used.[122]

Multicomponent condensation of aldehydes, 2-naphthol and methyl/benzyl carbamate was accomplished by using $Mg(OCOCF_3)_2$ as an efficient catalyst. This method resulted in the formation of a variety of methyl(2-hydroxynaphthalen-1-yl)(aryl)methyl/benzyl-carbamate derivatives in high yields.[123]

The IL $[NMP]^+HSO_4^-$ was applied as catalyst at 125 ºC for the preparation of **24d**,**g**,**h**,**j-l** in moderate to good yields (Scheme 14).[74]

The three-component aza-Friedel-Crafts reactions of 2-naphthol, 4-chlorobenzaldehyde and benzyl or *tert*-butyl carbamate in the presence of I_2 as catalyst in toluene at r.t. led to the formation of carbamatoalkylnaphthols **24i**,**m** in yields of 74% and 62%, respectively (Schemes 14).[124]



X = H: **a**; 2-Cl: **b**; 3-Cl: **c**; 3-OMe: **d**; 4-F: **e**; 3-Br: **f**; 3-NO_2: **g**; 4-COOH: **h**; 4-Cl: **i**; H: **j**; 4-OMe: **k**; 3-NO_2: **l**; 4-Cl: **m**

Scheme 14

The high number of publications that have appeared on the synthesis of amido-, carbamido- and carbamatoalkylnaphthol derivatives reflect the importance of this area of organic chemistry. It is clear that the synthetic procedures generally demand the application of a heterogenous catalyst, and the reactions can usually be accelerated by applying additional irradiation techniques such as microwave irradiation or ultrasound. It may be concluded that the reactivity of 2-naphthol is higher than those of 1-naphthol or *N*-containing naphthol analogues. Benzaldehyde or substituted benzaldehydes generally react smoothly, and lower reactivity is observed for heteroaryl aldehydes. With aliphatic aldehydes as starting compounds, the desired products are not formed or can be isolated only in trace amounts.

3. RESULTS AND DISCUSSION

3.1. Syntheses of hydroxynaphthyl-substituted α-amino acid derivatives

When the synthesis of the desired hydroxynaphthyl-substituted glycine derivatives was designed, a rather cumbersome synthesis of 2-amino-2-(2'-hydroxynaphthalen-1'-yl)acetic acid was found.[125] The intermediate 5-(2-methoxynaphthalen-1-yl)hydantoin was prepared from 2-hydroxy-1-naphthaldehyde in two steps, and then treated with aq. NaOH solution under reflux for 1 day. The resulting product (2-amino-2-(2-methoxynaphthalen-1-yl)acetic acid) in THF was treated with Et_3N and di-*tert*-butyl dicarbonate at r.t. for 1 day to give 2-amino-2-(2'-hydroxynaphthalen-1'-yl)acetic acid hydrochloride.

In our first experiment, we attempted to prepare our target compound through the aminoalkylation of 2-naphthol with 2 equivalents of ethyl glyoxalate in the presence of NH_3, followed by hydrolysis of the intermediate naphthoxazine. However, the basicity of the medium due to the NH_3[126] led to the formation of ethyl 2-hydroxy-2-(2'-hydroxynaphthalen-1'-yl)acetate by the direct addition of 2-naphthol to ethyl glyoxalate. To decrease the basic character of the reaction mixture, the NH_3 was replaced by *tert*-butyl carbamate,[127] but even on the use of different reaction conditions (solvent-free or MeOH, 60-100 ºC; microwave irradiation, solvent-free or MeOH, 60-130 °C), the target compound could not be isolated, *e.g.* at low temperature there was no conversion, while higher temperature resulted in the formation of a multi-spot reaction mixture.

At this point, our attention was drawn to benzyl carbamate as another protected NH_3 source.[128] A mixture of 2-naphthol, glyoxylic acid monohydrate and benzyl carbamate was refluxed in MeOH for 70 h, and the product was then isolated by column chromatographic purification (*n*-hexane–EtOAc 2/1), in a yield of 13%. The NMR data supported the structure of methyl 2-(benzyloxycarbonylamino)-2-(2'-hydroxynaphthalen-1'-yl)acetate (**25a**, Scheme 15). It is interesting to note that in this reaction MeOH simultaneously played roles both as a solvent and as an esterification reagent. Since *p*-TSA is frequently applied as a catalyst in the mMR,[80,129] its effect was examined in this reaction. In the presence of 10 mol% *p*-TSA, the reaction yield rose to 21%. In an effort to achieve a higher conversion, the amount of *p*-TSA was systematically increased, as presented in Table 1.

With 1 equivalent of *p*-TSA under reflux conditions, the product started to separate out as white crystals from the reaction mixture after a few hours; further refluxing for 24 h gave the product in 69% yield. The benzyloxycarbonyl group was then removed by catalytic (Pd/C) hydrogenation to afford compound **26a** (Scheme 15). For the hydrolysis of **26a**, different concentrations of aq. HCl solution

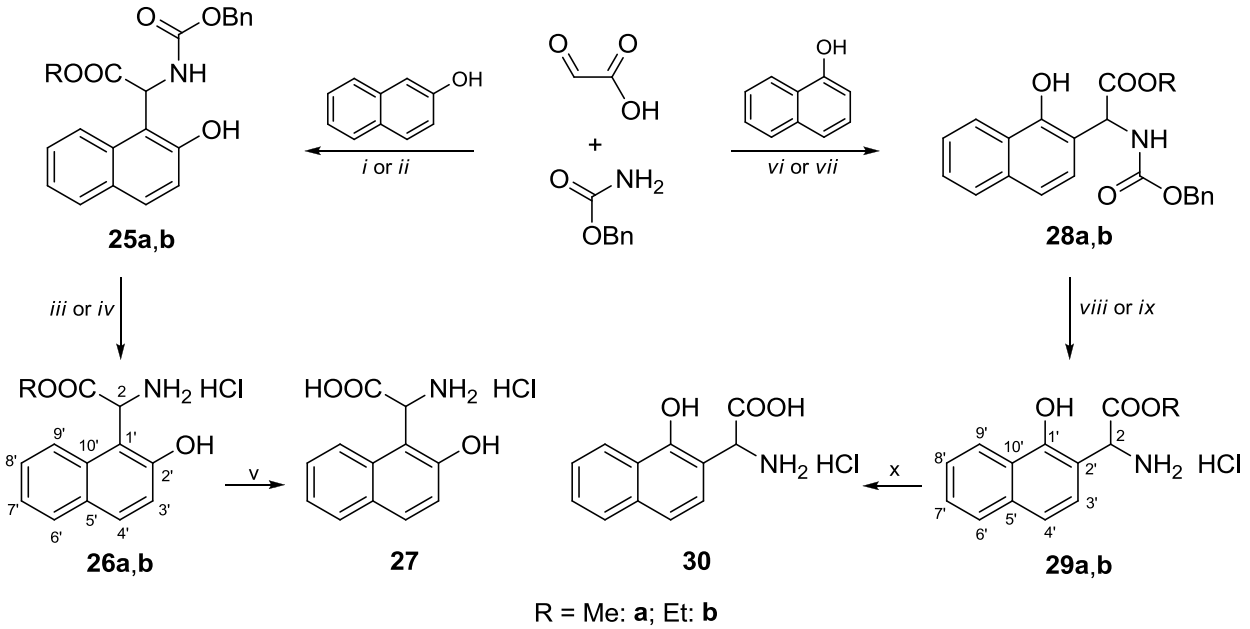
were tested; refluxing for 2 h in 5% aq. HCl solution was found to be optimum for the formation of **27** (Scheme 15)**.**

Table 1. Effect of the amount of *p*-TSA on the isolated yield of **25a** by using benzyl carbamate in MeOH under reflux conditions

Catalyst (mol%)	Time (h)	Yield (%)[a]
0	70	13
10	62	21
20	51	44
30	37	50
100	26	69

[a] Isolated yields.

The optimized reaction conditions were then extended to 1-naphthol. Its reactions with glyoxylic acid monohydrate, benzyl carbamate and *p*-TSA in MeOH at reflux temperature led to the formation of **28a** as white crystals that started to separate out from the reaction mixture after a few hours; further refluxing for 31 h gave the product **28a** in 53% yield. The protecting group of **28a** was removed by catalytic (Pd/C) hydrogenation to yield **29a**, which was then hydrolysed with 10% aq. HCl solution to furnish **30** in 88% yield (Scheme 15).

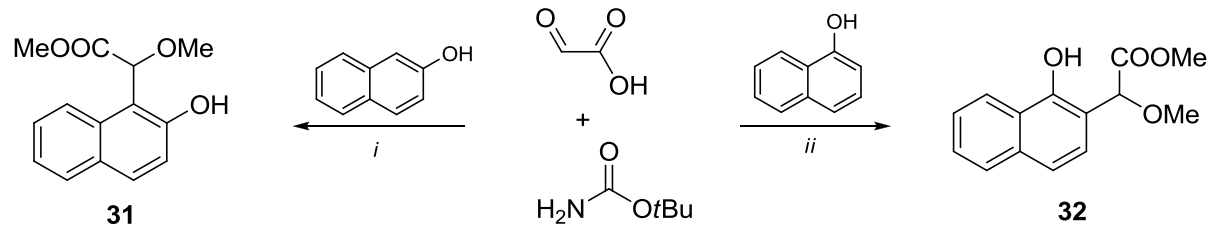


Reagent, conditions and yields: (*i*) *p*-TSA, MeOH, reflux, 26 h, 69%; *(ii) p*-TSA, EtOH, reflux, 94 h, 34%; *(iii)* Pd/C, H_2, MeOH, r.t., 1 h, HCl-EtOH, 75%; (*iv*) Pd/C, H_2, EtOH, r.t., 1.5 h, HCl-EtOH, 72%; *(v)* R = Me, 5% aq. HCl, reflux, 2 h, 82%; (*vi*) MeOH, reflux, 36 h, 53%; *(vii)* EtOH, reflux, 97 h, 27%; *(viii)* Pd/C, H_2, MeOH, r.t., 1 h, HCl-EtOH, 84%; *(ix)* Pd/C, H_2, EtOH, r.t., 1.5 h, HCl-EtOH, 69%; *(x)* R = Me, 10% aq. HCl, reflux, 4 h, 88%.

Scheme 15

As a new extension of the synthetic protocol, MeOH was successfully replaced by EtOH, starting either from 2-naphthol or from 1-naphthol (Scheme 15). It should be mentioned that longer reaction times were needed for the formation of the protected ethyl ester derivatives (**25b** and **28b**), and the products were isolated in lower yields. Removal of the benzyloxycarbonyl group furnished **26b** and **29b**, respectively (Scheme 15).

Our attention next focused on the application of other carbamates, such as *tert*-butyl carbamate. In the reaction of 2-naphthol, glyoxylic acid and *tert*-butyl carbamate in the presence of 1 equivalent of *p*-TSA, the desired protected ester derivative was not formed. The NMR spectra of the isolated product adequately supported the structure of **31**, which is a known product of the reaction between 2-naphthol and glyoxylic acid, followed by reflux in MeOH in acidic media.[126] The previous reaction was tested by starting from 1-naphthol, glyoxylic acid and *tert*-butyl carbamate, which led to the formation of methyl 2-(1'-hydroxynaphthalen-2'-yl)-2-methoxyacetate (**32**), in a yield of 39% (Scheme 16).



Reagent, conditions and yields: (*i*) *p*-TSA, MeOH, reflux, 93 h, 38%, (*ii*) *p*-TSA, MeOH, reflux, 98 h, 39%.

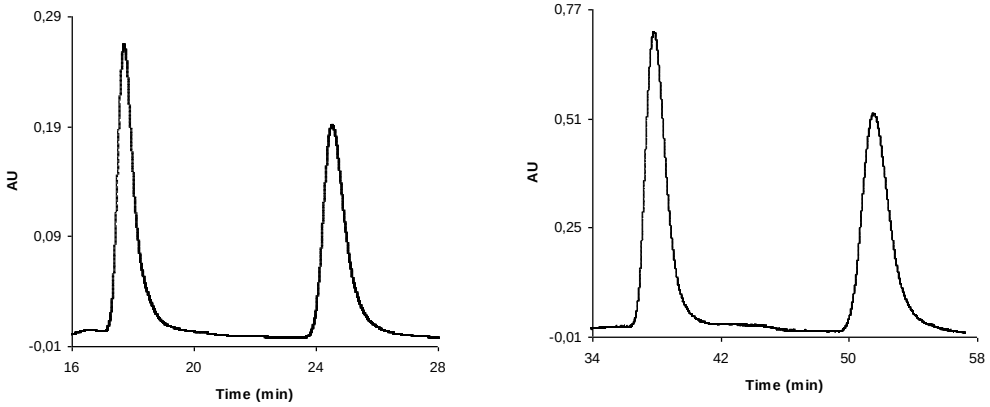
Scheme 16

HPLC enantioseparation of aminonaphthol derivatives is frequently carried out on a cellulose *tris*(3,5-dimethylphenylcarbamate)-based chiral stationary phase (Chiralcel OD-H), with *n*-hexane–2-PrOH as mobile phase.[130] 1.1 equivalents of Et_3N were used for the liberation of compounds **26a** and **29a**, and the enantioseparation of their substituted glycine esters was then started with this column. Different mobile phase compositions were tested and the best resolution for **26a** and **29a** was found under the conditions described in Figure 1.

The enantioseparation was scaled up to milligram quantities by using a Lux^{TM} Cellulose-1 semi-preparative column. The chromatographic conditions applied were: *n*-hexane–2-PrOH (80/20 (v/v) for **26a**, and 85/15 (v/v) for **29a**) with a flow rate of 2 mL/min.

For the configurational assignment of the separated enantiomers of **26a** and **29a**, their CD analysis was performed. An MMFF conformational search for the second-eluting enantiomer of **26a** followed by B3LYP/6-31G(d) optimization afforded the lowest-energy conformer with high population (96.5%) and its torsional angle $\omega_{2H,C2,C1',C10'}$ was found to be –12.04°. The CD spectra were

then calculated for the lowest-energy conformer of **26a** with various functionals (B3LYP, BH&HLYP and CAM-B3LYP) and the TZVP basis set.



a **b**

Figure 1. a) Chromatogram of **26a**. Conditions: Chiralcel OD-H; *n*-hexane–2-PrOH = 70/30 (v/v); detection at 230 nm; flow rate 0.5 mL/min.

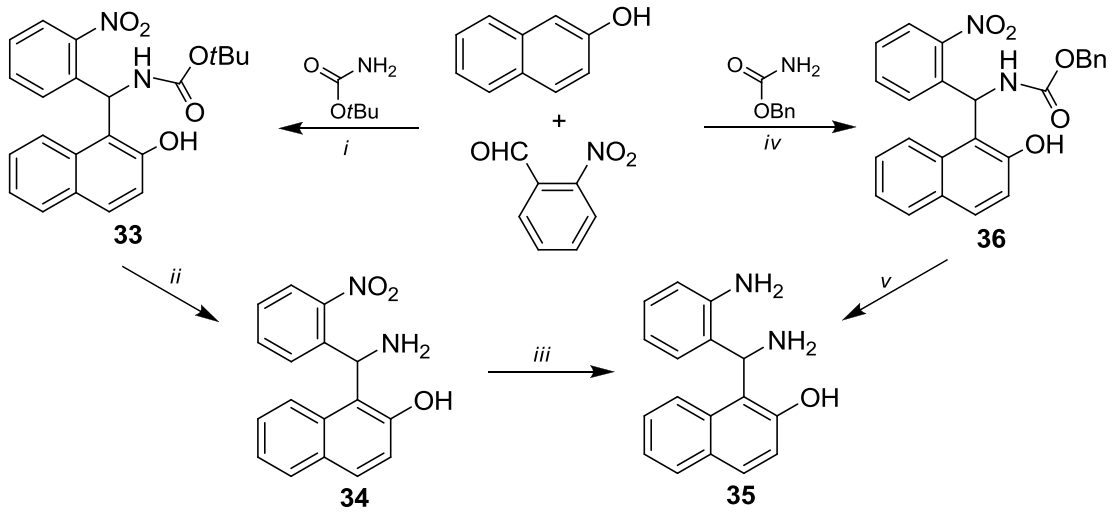
b) Chromatogram of **29a**. Conditions: Chiralcel OD-H; *n*-hexane–2-PrOH = 85/15 (v/v); detection at 230 nm; flow rate 0.5 mL/min.

All the calculated CD spectra reproduced the experimental CD of the second-eluting enantiomer of **26a** well, with BH&HLYP/TZVP giving the best agreement. Thus, the absolute configuration of the second-eluting enantiomer was determined unambiguously as *S*. A similar CD calculation protocol was carried out on the first-eluting enantiomer of **29a** to determine its absolute configuration. The lowest-energy calculated conformer had a population of 96.2% and its torsional angle $\omega_{2H,C2,C2',C3'}$ was found to be –10.91°. All three computed CD spectra of **29a** reproduced the experimental CD of the first-eluting enantiomer well with the CAM-B3LYP/TZVP method, which showed negative CEs in the ^1L_b and ^1L_a regions and a negative couplet centred around 221 nm. Thus, the absolute configuration of the first-eluting enantiomer of **29a** was determined as *S*.

3.2. Syntheses and conformational analyses of naphthoxazine-fused quinazoline derivatives

3.2.1. Syntheses of naphthoxazinoquinazoline derivatives

For the synthesis of the proposed naphthoxazinoquinazoline derivatives, the preparation of 1-(amino(2-aminophenyl)methyl)-2-naphthol (**35**) as starting material was planned. In our initial experiment, we attempted the aminoalkylation of 2-naphthol with 2 equivalents of 2-nitrobenzaldehyde in the presence of NH_3, followed by hydrolysis of the intermediate naphthoxazine. This reaction resulted in the formation of a multi-spot reaction mixture (based on the TLC). In the following experiment, NH_3 was replaced by *tert*-butyl carbamate as a protected NH_3 source, and a mixture of 2-naphthol, 2-nitrobenzaldehyde and *tert*-butyl carbamate was therefore heated under solvent-free conditions for 55 h at 60 ºC. This furnished nitro derivative **33** in a yield of 46%. When the reaction was repeated at 80 ºC, **33** was isolated in 53% yield after 47 h. The *tert*-butoxycarbonyl group was removed with TFA, resulting in **34**. This step was followed by reduction of the NO_2 group by means of catalytic (Pd/C) hydrogenation, yielding **35** (Scheme 17).



Reagents, conditions and yields: (*i*) 80 ºC, 47 h, 53%; (*ii*) 99% TFA, r.t., 10 min, 10% Na_2CO_3, 90%; (*iii*) Pd/C, H_2, MeOH, r.t., 1.5 h, 68%; (*iv*) 80 ºC, 32 h, 76%; (*v*) Pd/C, H_2, MeOH, r.t., 2 h, 69%.

Scheme 17

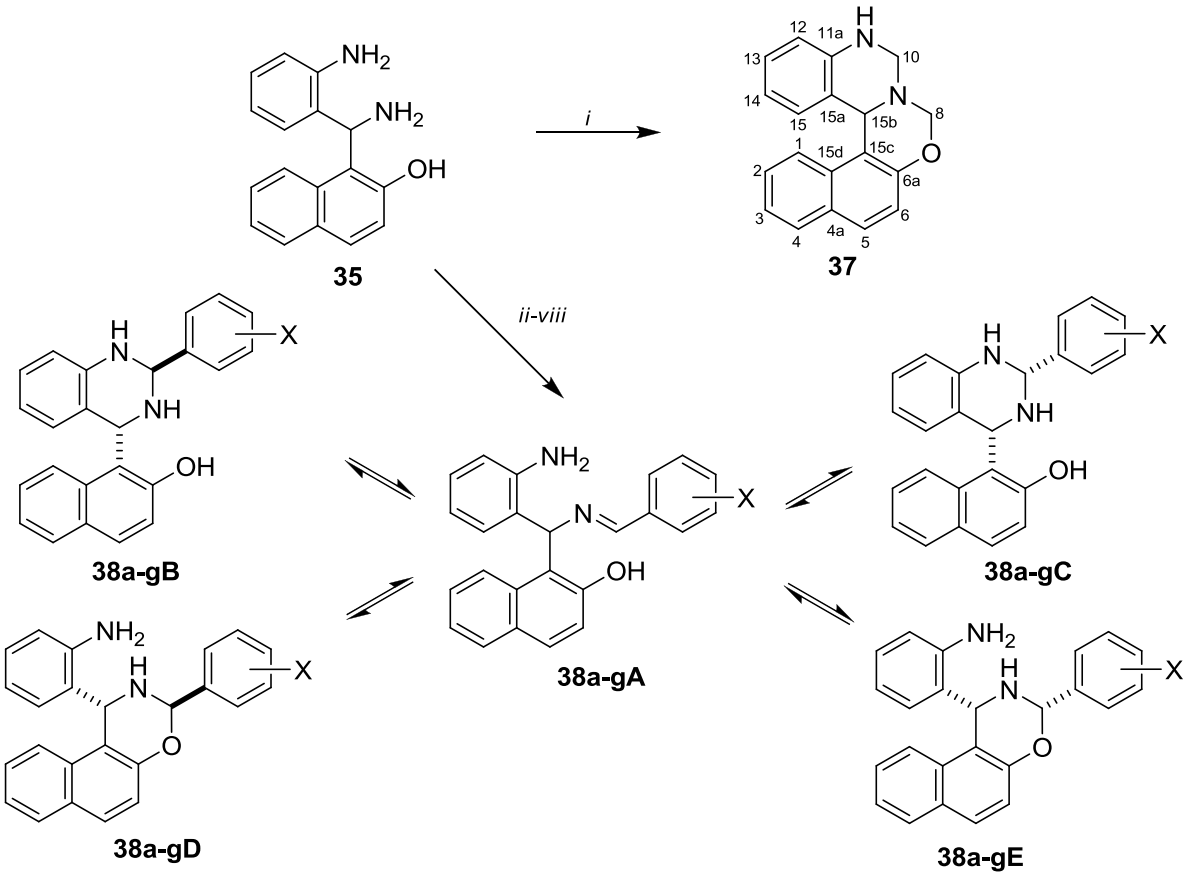
Since **33** was formed in only 53% yield on starting from *tert*-butyl carbamate, our attention focused on another protected NH_3 source, benzyl carbamate. From 2-naphthol, 2-nitrobenzaldehyde and benzyl carbamate under solvent-free conditions, **36** was synthetized in 71% yield at 60 ºC after

46 h, whereas at 80 ºC, in a shorter reaction time (32 h), the yield was 76%. Removal of the protecting group and reduction of the NO_2 group were accomplished in one step by catalytic (Pd/C) hydrogenation, yielding **35** (Scheme 17).

In the first stage of the transformations of **35** to heterocyclic derivatives, an sp^3 carbon was inserted between the OH and NH_2 groups (in position C-8 or C-10). Compound **35** was stirred with 2 equivalents of aqueous formaldehyde in $CHCl_3$ at r.t. After 1.5 h, when TLC showed no presence of the starting material, the reaction was stopped and 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline (**37**) was isolated by column chromatographic purification (Scheme 18). Since **37** was formed from aqueous formaldehyde in $CHCl_3$ in a yield of only 40%, another solvent (MeOH) and the use of paraformaldehyde were also examined, but these reactions were found by TLC to result in the formation of a multi-spot reaction mixture.

In order to extend the number of aldehyde reagents, we set out to examine the reactions of diamine **35** with benzaldehyde. Aminonaphthol derivative **35** was dissolved in MeOH, 1.1 equivalents of benzaldehyde was added and the mixture was left to stand at r.t. for 1 day. After a few hours, the product **38d** (X=H) started to separate out from the reaction mixture. Due to the presence of two NH_2 and one phenolic OH group in the starting diamine **35**, two different ring systems can be formed via its condensation with benzaldehyde. In solution at 300 K, compound **38d** is potentially present as a five-component tautomeric mixture of the chain tautomer (**A**), two epimers of quinazoline (**38B** and **38C**) and two epimers of naphthoxazine (**38D** and **38E**) derivatives (Scheme 18).

In the NMR spectra of **38d** in CD_2Cl_2 at 300 K, only three tautomeric forms were detected and identified. The *major* ring form was found to be 2-phenyl-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazoline (**38dB** or **38dC**); the NOESY spectrum proved that the *major* ring-closed tautomer in the equilibria contains H-2 and H-4 in the *trans* position (**38dB**). Formation of the quinazoline derivative as the *major* product can be explained by the stabilization caused by the strong intramolecular hydrogen-bonds between the lone pair of the N atom and the OH group, and the higher nucleophilic character of NH_2 than that of OH. The *minor* ring forms were found to be 8-phenyl-10-(2-aminophenyl)-8,9-dihydro-7*H*-naphth[1,2-*e*][1,3]oxazine (**38dD** and **38dE**). The NOE interaction observed between H-8 and H-10 showed that the relative configuration of the *major* naphthoxazine epimer attains the *cis* arrangement (**38dE**), while for the *minor* epimer the lack of the cross-peak for H-8 and H-10 proves their *trans* arrangement (**38dD**). The chain tautomer (**A**) and the *cis* quinazoline (**C**) were not detected in the NMR spectra.



Reagents, conditions and yields: (*i*) 2 equiv. 30% aq. CH_2O, $CHCl_3$, r.t., 1.5 h, 40%; (*ii*) *p*-NO_2-PhCHO, MeOH, r.t., 24 h, **38a**: 77%; (*iii*) *m*-Cl-PhCHO, MeOH, r.t., 24 h, **38b**: 52%; (*iv*) *p*-Cl-PhCHO, MeOH, r.t., 24 h, **38c**: 63%; (*v*) PhCHO, MeOH, r.t., 24 h, **38d**: 88%; (*vi*) *p*-Me-PhCHO, MeOH, r.t., 24 h, **38e**: 66%; (*vii*) *p*-OMe-PhCHO, MeOH, r.t., 24 h, **38f**: 90%; (*viii*) *p*-NMe_2-PhCHO, MeOH, r.t., 24 h, **38g**: 57%.

Scheme 18

To characterize the effects of the aryl substituents on the tautomeric equilibria of this ring system, 2-(aryl-substituted)-4-(2-hydroxynaphthalen-1-yl)-1,2,3,4-tetrahydroquinazolines (**38a-c** and **38e-g**) were also prepared (Scheme 18). The proportions of the ring tautomers (**B**, **D** and **E**) in the tautomeric equilibria of **38a-g** (Table 2) were determined by integration of the quinazoline and naphthoxazine proton singlets or doublets in the ^{1}H NMR spectra.

The tautomeric composition (*e.g.* the proportions of the ring-closed forms) demonstrated a small, but systematic dependence on the Hammett-Brown parameter[131,132] (σ^+) of the aryl substituent, which characterizes the electronic character of the substituent in question (Table 2).

The plots of the proportions of the tautomeric forms (**B**, **D** and **E**) for **41a-g** *vs.* σ^+ (Figure 2) gave good correlations for all three forms (0.951 for **B**, 0.938 for **D** and 0.978 for **E**). It can be concluded that electron-donating substituents increase the proportions of the quinazoline form (**B**), while electron-withdrawing substituents prefer the naphthoxazine forms (**D** and **E**). As concerns the slopes, the

dependence for **B** seems to be the most characteristic; for **E**, only small changes were observed for the various substitutions (Figure 2).

Table 2. Proportions (%) of the tautomeric forms (**A**, **B**, **C**, **D** and **E**) in tautomeric equilibrium for compounds **38a-g** (CD_2Cl_2, 300 K)

X	σ^+	**A** (%)	**B** (%)	**C** (%)	**D** (%)	**E** (%)
p-NO_2	0.79	-	79.1	-	5.8	15.1
m-Cl	0.40	-	80.6	-	5.5	13.9
p-Cl	0.11	-	82.0	-	5.3	12.7
H	0.00	-	84.5	-	4.8	10.7
p-Me	-0.31	-	85.2	-	4.5	10.3
p-OMe	-0.78	-	87.0	-	4.1	8.9
p-NMe_2	-1.70	-	88.6	-	3.5	7.9

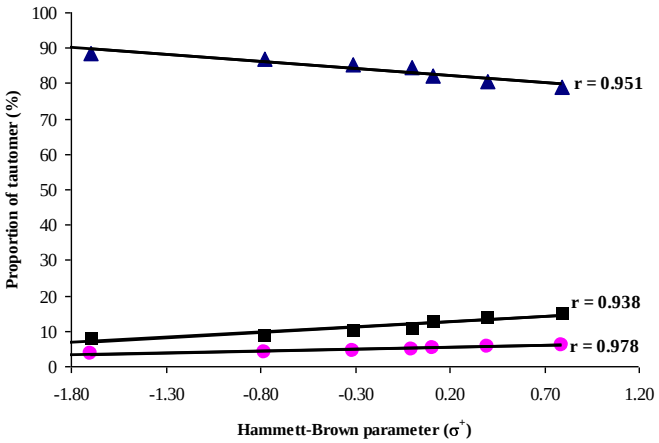
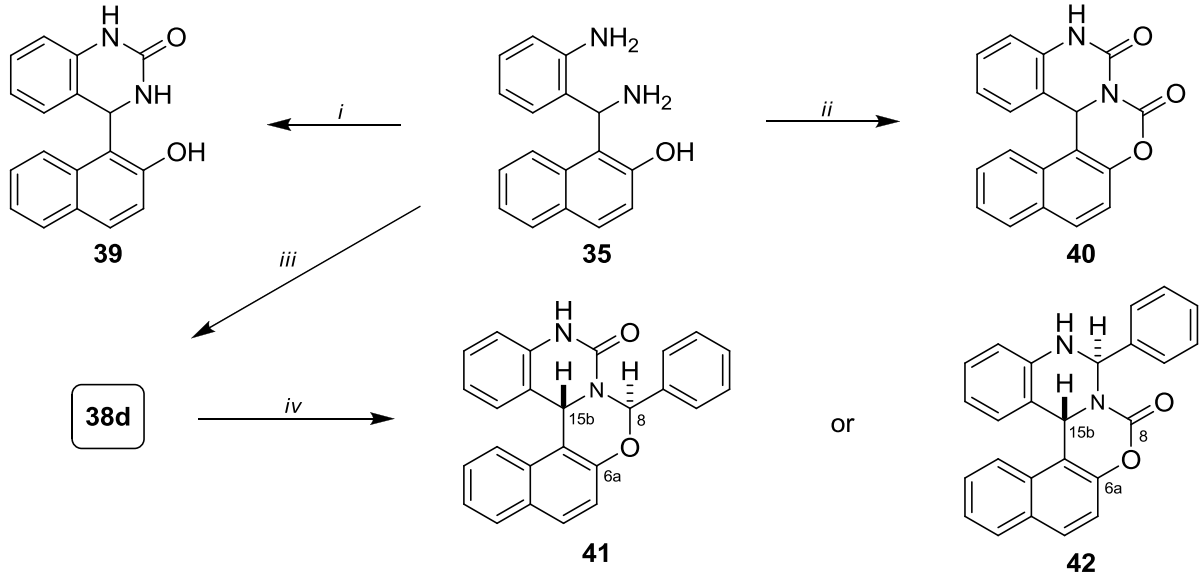


Figure 2. Plots of proportions of the tautomers (in CD_2Cl_2), **B (▲)**, **D (■)**, **E (●)** for **38a-g** *vs.* Hammett-Brown parameter (σ^+)

A further aim was the insertion of an sp^2 carbon in position C-8 or C-10 or both. For the direct ring closure reaction of diamine **35** with phosgene, it was stirred with 0.5 equivalents of triphosgene in toluene in the presence of Na_2CO_3 (Scheme 19). The appearance of two new TLC spots was observed. The products formed were separated by column chromatography and the mass spectra confirmed that one was the oxo compound **39** and the other was the corresponding 8,10-dione (**40**). The 2D NMR measurements on the single ring-closed compound supported the structure of the quinazolin-2-one derivative (**39**). For its preparation, a reaction time of 45 h was found to be optimum, but it should be mentioned that **39** was separated in only 40% yield, which can be explained in terms of the parallel formation of 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-8,10-dione (**40**).

To isolate **40** in higher yield, and to avoid the formation of **39**, the reaction of **35** was repeated but with 4 equivalents of triphosgene. After a reaction time of 8.5 h, **40** was isolated in 67% yield (Scheme 19).

To examine the ring closure ability of **39**, it was reacted with benzaldehyde. In consequence of the decreased nucleophilic character of the carbamide NH (PhCH*N*H), despite a long reaction time (refluxing in toluene for 51 h), the presumed oxo derivative **41** was not formed.



Reagents, conditions and yields: (*i*) 0.5 equiv. $(COCl_2)_3$, 5 equiv. Na_2CO_3, toluene, r.t., 45 h, 40%; (*ii*) 4 equiv. $(COCl_2)_3$, 10 equiv. Na_2CO_3, toluene, r.t., 6.5 h, 31%; (*iii*) 1.1 equiv. PhCHO, MeOH, r.t., 24 h, 88%; (iv) 4 equiv. $(COCl_2)_3$, 10 equiv. Na_2CO_3, toluene, r.t., 8.5 h, 67%.

Scheme 19

The ability of **38d** to undergo transformation was further tested by its reaction with phosgene. When **38d** was reacted with 4 equivalents of triphosgene in the presence of Na_2CO_3 in toluene for 6.5 h at r.t., the product (**41** or **42**) was isolated after column chromatographic purification in a yield of 31%. Full assignment of the NMR signals in DMSO supported the formation of the quinazolinone derivative (**41**). The two possible ring systems have very similar chemical environments; the cross-peak between C-6a (150.5 ppm) and H-8 (7.04 ppm) in the HMBC spectrum should be the only difference supporting the presence of 8-phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-10-one (**41**) instead of 10-phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-8-one (**42**). To support the structure found by NMR measurement, crystalline product **41** was examined with electron impact ionization in MeOH. The electron ionization (EI) mass spectrum of naphthoxazinoquinazolinone **41** is characterized by the fragment ion $[M\text{-}CONH]^+$ at *m/z* 335. This ion is probably formed by direct loss of this fragment from the molecular ion at *m/z* 378, which proves that the newly inserted oxo group is at position 10. This unexpected structure can be explained through the

tautomeric equilibrium present for **38d** in solution and, probably because of the stronger nucleophilic character of NH_2 (**38dD**, Scheme 18) than that of OH (**38dB**, Scheme 18), this minor tautomeric form reacts with triphosgene to give **41**. During the reaction, the formation of two diastereomers is possible; the diastereomeric ratio was therefore checked by NMR spectroscopy on the crude product. It was found that only one diastereomer is present. The NOE measurements on purified **41** indirectly proved the *trans* arrangement of H-8 and H-15b (Scheme 19).

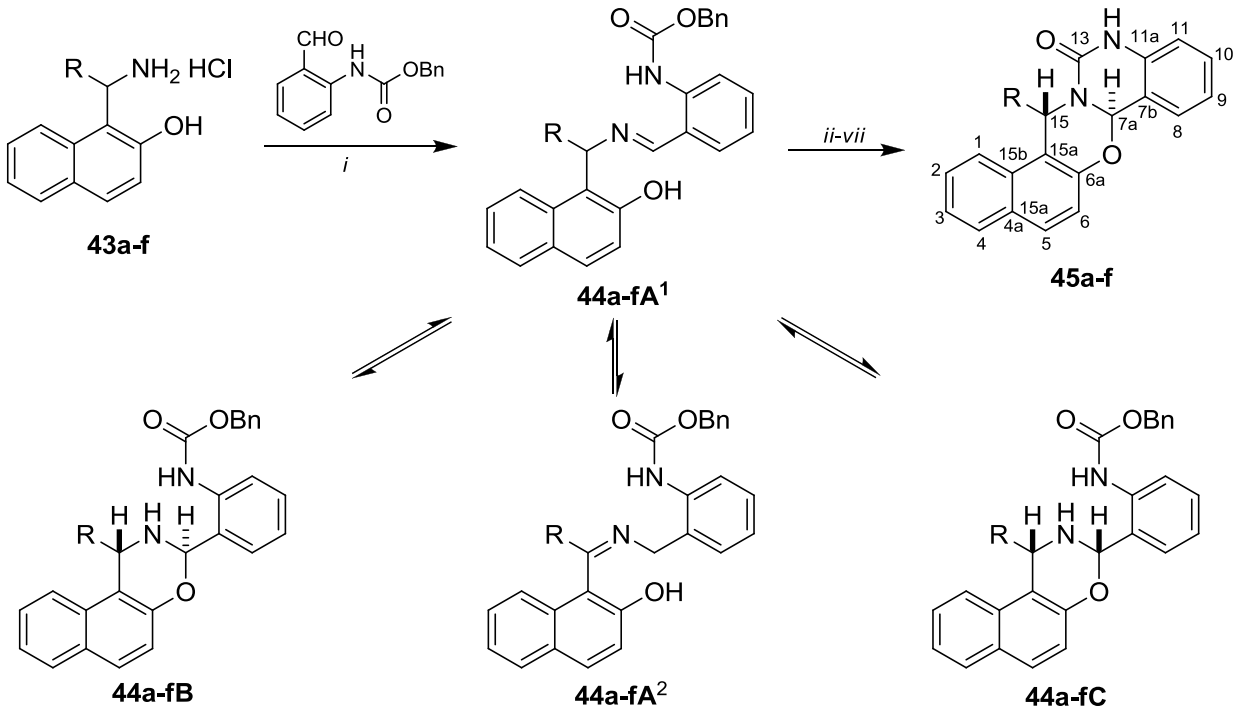
In order to investigate the influence of the anellation on the conformation of naphth[1,2-*e*][1,3]oxazinoquinazolines, our aims were to synthetize new naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazoline derivatives, and to achieve the conformational analyses of these polycyclic compounds by NMR spectroscopy and accompanying molecular modelling.

For the synthesis of the proposed naphthoxazinoquinazolines, the preparations of 2-(2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-yl)aniline and 2-(1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-yl)aniline as starting materials were planned. In our initial experiments, we attempted to prepare the target compounds through the condensations of 1-aminomethyl-2-naphthol or 1-aminobenzyl-2-naphthol with 1.1 equivalents of 2-aminobenzaldehyde.[133] However, because of the low reactivity of 2-aminobenzaldehyde (which can be explained by the presence of its imino mesomer structure),[134] there was no conversion. An attempt was made to shift the equilibrium towards the aldehyde function by using 1.5 equivalents of Et_3N or HCl–EtOH, but even on the use of different reaction conditions (in EtOH at r.t., or the application of microwave irradiation in EtOH at 60-90 ºC), the target compounds could not be isolated, *e.g.* at r.t. there was no conversion, while the higher temperatures led to decomposition of the starting aminonaphthol.

In further experiments, the condensations of 1-aminomethyl-2-naphthol or 1-aminobenzyl-2-naphthol with 1.1 equivalents of 2-nitrobenzaldehyde were attempted in MeOH in order to synthetize 2-(2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-yl)aniline and 2-(1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-yl)aniline. These reactions did lead to the formation of the expected NO_2 derivatives. However, although the transformation of the NO_2 function to an NH_2 group should have been achieved for the syntheses of 2-aminophenyl-substituted naphthoxazines, neither catalytic (Pd/C) hydrogenation nor reduction with Fe powder in the presence of concentrated HCl resulted in isolation of the desired amino derivatives, and after even a short reaction time decomposition of the starting naphthoxazines was observed on TLC.

As a new synthetic strategy, aminonaphthols **43a** and **43c** were reacted with benzyl *N*-(2-formyl-phenyl)carbamate[135] to afford the corresponding benzyloxycarbonyl-protected intermediates (**44a** and

44c, Scheme 20). The mixtures were stirred for 2-4 days at r.t., during which white crystals separated out. The crystalline products (**44a** and **44c**) were filtered off and washed with cold EtOH.



R = H: **a**; *p*-Cl-Ph: **b**; Ph: **c**; *p*-OMe-Ph: **d**; 1-Nph: **e**; 2-Nph: **f**

Reagents, conditions and yields: (*i*) Et_3N, EtOH, r.t., 2-4 days; (*ii*) MeONa, 174 °C, 10 min, **45a**: 70%; (*iii*) MeONa, 179 °C, 20 min, **45b**: 61%; (*iv*) MeONa, 152 °C, 30 min, **45c**: 54%; (*v*) MeONa, 154 °C, 40 min, **45d**: 60%; (*vi*) MeONa, 203 °C, 15 min, **45e**: 74%; (*vii*) MeONa, 165 °C, 20 min, **45f**: 51%;

Scheme 20

Our efforts to remove the protecting group, either by catalytic (Pd/C) hydrogenation at atmospheric pressure or with 33% HBr–AcOH at r.t., led to the decomposition of **44a** and **44c** instead of the formation of the desired amino derivatives. In additional experiments, the benzyloxycarbonyl-protected intermediates (**44a** and **44c**) were heated with MeONa (30 mol%) under solvent-free conditions at their melting temperatures. After reaction times of 10-65 min, when TLC showed no presence of the starting materials, the reaction mixtures were cooled down and the products (**45a** and **45c**) were isolated by treatment with EtOH. This synthetic pathway was extended to the preparation of naphthoxazinoquinazolinones containing different aryl substituents at position 15 (*p*-Cl-Ph: **45b**, *p*-OMe-Ph: **45d**, 1-Nph: **45e**, and 2-Nph: **45f**) (Scheme 20). It should be mentioned that in the cases of **45d** and **45f** a doubled amount of MeONa (60 mol%) increased the yields (from 31% to 60% for **45d**, and from 37% to 51% for **45f**). For **45f**, a different work-up procedure was applied; the solid residue was extracted with

EtOAc and dried (Na_2SO_4), and after evaporation of the solvent the residue was crystallized from a mixture of *n*-hexane–EtOAc.

During the ring closure reaction of **44b-f** with MeONa, the formation of two diastereomers is possible; the diastereomeric ratio was therefore checked by NMR spectroscopy on the crude products. It was found that only one diastereomer was present in all five cases. The preliminary NOE check on purified **45b-f** adequately proved the *trans* arrangement of H-15 and H-7a (Scheme 20), similarly to the ring-anellation analogue phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-10-one (**41**; Scheme 19).

In solvent at 300 K, **44a-f** can be present in three-component tautomeric mixtures containing diastereomeric ring forms (**B** and **C**) besides the chain form (**A**). Because of the low solubility of intermediates **44a-f** in $CDCl_3$, the NMR spectra were recorded in DMSO. The total assignment of **44c** revealed the presence of a new tautomeric chain form ($\mathbf{A^2}$) besides the *trans* ring form **B** and chain form $\mathbf{A^1}$. Through the use of 2D NMR techniques, the structure of $\mathbf{A^2}$ was identified as a new chain form, in which the imine double bond is in an α position relative to the naphthyl ring, as depicted in Scheme 20. To establish whether this unexpected rearrangement is influenced by the nature of substituent R, the NMR spectra of **44a**,**b** and **44d-f** (Table 3, entries 1, 4, 14, 19 and 24) were recorded on solutions of 15 mg of crystals in 700 μL of deuterated DMSO. The ratio of $\mathbf{A^1}$ to $\mathbf{A^2}$ did differ, but our attention then focused on the influence of time. Thus, the spectra of **44b-f** were recorded after the solutions had been allowed to stand for 4 h or 3, 4 or 7 days. In the case of **44a**, form $\mathbf{A^2}$ could not be detected even after 12 days (Table 3, entry 3). The reason for this is that, in the lack of an aromatic ring system, there is no possibility of conjugation with the C=N double bond in $\mathbf{A^2}$. Further proof of the presence of conjugation in form $\mathbf{A^2}$ is that, in the case of **44e**, containing a 1-naphthyl (1-Nph) ring, the newly formed $\mathbf{A^2}$ could not be detected even after 7 days. This can be explained by the hindered rotation of the naphthyl ring, which restricts conjugation of the aromatic system with the C=N double bond.

Table 3 demonstrates that the standing time has a characteristic influence on the tautomeric ratios. In all cases (**44b-d**,**f**), the amount of $\mathbf{A^2}$ increases, while those of **B** and $\mathbf{A^1}$ decrease as time passes. It can also be concluded from Table 3 that the formation of $\mathbf{A^2}$ (after standing for 7 days) is the highest for the electron-donating substituent *p*-OMe.

To prove the reversibility of the process in DMSO (the presence of a tautomeric equilibrium), 40 mg of **44c** was dissolved in DMSO (2 mL, corresponding to the concentration used for the NMR measurements) and the solution was left to stand at r.t. for 7 days. A sample from this mixture was then evaporated to dryness, and dissolved again in deuterated DMSO, after which its NMR spectrum was run. The tautomeric composition observed was similar to that after the dissolution of crystalline **44c**.

Table 3. Tautomeric ratios for **44a-f** in DMSO at 300 K

Entries	R	Time[a]	A^1 (%)	A^2 (%)	B (%)
1	H **44a**	0	100	-	-
2		7 days	82.2	-	17.8
3		12 days	76.9	-	23.1
4	*p*-Cl-Ph **44b**	0	91.7	-	8.3
5		4 h	81.1	11.1	7.8
6		3 days	40.5	54.1	5.4
7		4 days	30.4	67.2	2.4
8		7 days	18.6	80.1	1.3
9	Ph **44c**	0	82.6	10.5	6.9
10		4 h	65.3	28.8	5.9
11		3 days	38.3	57.7	4.0
12		4 days	34.2	63.2	2.6
13		7 days	27.6	70.2	2.2
14	*p*-OMe-Ph **44d**	0	89.4	-	10.6
15		4 h	76.7	14.0	9.3
16		3 days	12.4	86.3	1.3
17		4 days	5.9	93.1	1.0
18		7 days	2.8	97.2	-
19	1-Nph **44e**	0	66.7	-	33.3
20		4 h	67.4	-	32.6
21		3 days	66.4	-	33.6
22		4 days	67.4	-	32.6
23		7 days	67.0	-	33.0
24	2-Nph **44f**	0	90.9	0.5	8.6
25		4 h	53.9	38.9	7.2
26		3 days	19.4	76.2	4.4
27		4 days	16.3	83.7	-
28		7 days	14.8	85.2	-

[a] The duration of standing after dissolution of the samples.

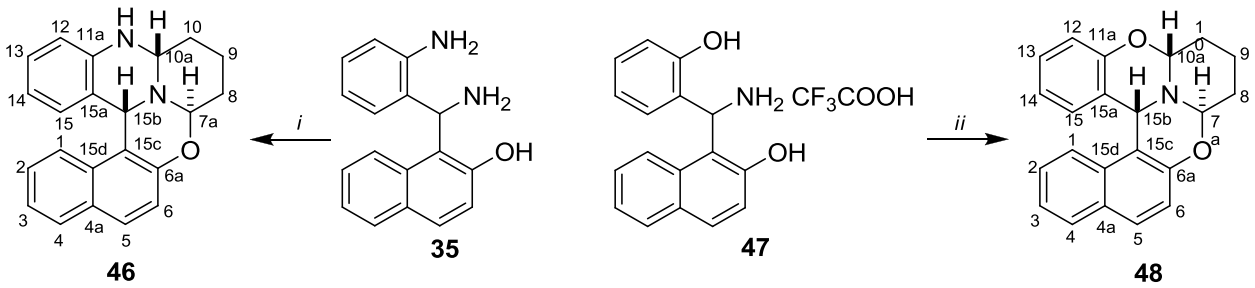
The mMR was successfully applied for the synthesis of highly functionalized aminonaphthols such as 1-(amino(2-aminophenyl)methyl)-2-naphthol (**35**) and 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol (**46**).[9]

In order to capitalize on all three functional groups in compounds **35** and **47** at the same time, our aim was to investigate their reactions with dialdehydes, with a view to obtaining new hetero- and polycyclic compounds (Scheme 21).

The synthesis of piperidine-fused quinazolinonaphthoxazine derivative **46** was planned from 1-(amino(2-aminophenyl)methyl)-2-naphthol (**35**). A mixture of diamine **35** and 1.1 equivalents of aqueous glutardialdehyde solution was dissolved in EtOH and the solution was stirred at r.t. After 3 h, when TLC indicated no more starting material, the reaction mixture was concentrated to dryness and

the product was isolated by column chromatography and crystallized from *n*-hexane. The 2D NMR spectra of the isolated compound proved the structure of **46**.

The starting aminodiol (**47**) was synthetized according to the literature procedure[9] by the aminoalkylation of 2-naphthol with 2 equivalents of salicylaldehyde in the presence of NH_3, followed by acidic hydrolysis of the intermediate napthoxazine with TFA.



Reagents, conditions and yields: (*i*) 25% aq. $OHC(CH_2)_3CHO$, EtOH, r.t., 3 h, 43%; (*ii*) Et_3N, 25% aq. $OHC(CH_2)_3CHO$, EtOH, r.t., 24 h, 81%.

Scheme 21

For the synthesis of the analogous piperidine-fused benzoxazinonaphthoxazine derivative **48**, aminodiol **47** was dissolved in EtOH and 1.1 equivalents of aqueous glutardialdehyde solution was added. The mixture was stirred for 1 day at r.t., during which white crystals separated out. Preliminary 2D NMR measurements on the precipitated crystals supported the expected structure of **48** (Scheme 21).

In the course of the ring closure reactions of **35** and **47** with glutardialdehyde, two new asymmetric centres are introduced, and the formation of four diastereomers is therefore theoretically possible. However, the NMR spectra of the crude products indicated that only a single diastereomer was formed. In the NOESY spectra of the purified **46** and **48**, the weak interactions between H-7a and H-15b and between H-7a and H-10a proved their *trans* arrangement, while the presence of a strong cross-peak between H-10a and H-15b demonstrated their *cis* arrangement.

In order to extend the series of newly synthetized hexacyclic ring systems, *e.g.* to the syntheses of pyrrollidine- and azepane-fused naphthoxazine derivatives, our attention focused on the reactions of diamine **35** and aminodiol **47** with succindialdehyde and adipic dialdehyde. However, these reactions did not result in the desired polycyclic compounds either at r.t. or at higher temperature (80-90 ºC, classical heating or MW), *e.g.* at r.t. there was no conversion, while the higher temperature led to decomposition of the starting **35** and **47**.

3.2.2. Conformational study of naphthoxazinoquinazoline derivatives

3.2.2.1. Conformational analysis of naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolines

In the case of the naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline ring system, theoretical calculations were performed on compounds **37**, **41** and **42**, and their global minimum-energy structures were determined.

While **37** can be accepted as the basic ring system (unsubstituted 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline), full geometry optimization was performed by using DFT calculations. The unsaturated ring system **37** contains invertible N atoms. Both the *R* and the *S* configurations of the N atoms and of C-15b must be considered. All isomers/enantiomers were studied by means of DFT calculations with regard to the conformational equilibria. The preferred conformers thus obtained, together with other proximate conformers with similar energy, were collected and studied with respect to ring puckering as the second variable beside the *N*-interconversion. The energy difference values (ΔE) obtained for the lowest-energy conformers for each configuration are listed in Table 4.

Table 4. Calculated energy differences for **37**

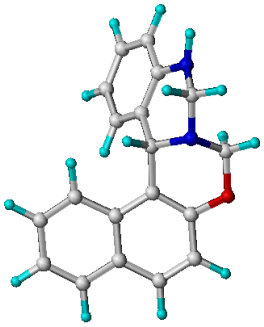
Optimized geometry	C-15b	N-9	N-11	ΔE^a (kcal/mol)	ΔE^b (kcal/mol)
*G*_I	*S**	*R**	*R**	0	0
*G*_II	*S**	*R**	*S**	0.41	0.26
*G*_III	*S**	*S**	*R**	13.12	12.66
*G*_IV	*S**	*S**	*S**	13.27	13.80

[a] In the gas phase.
[b] In CH_2Cl_2 as solvent.

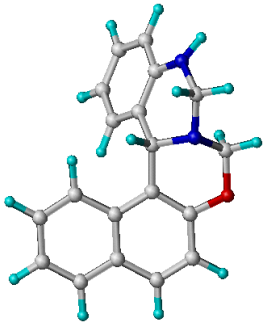
It can be concluded that the relative configurations of C-15b and N-9 exert characteristic effects on the ΔE values (Table 4, geometries *G*_I, *G*_II *vs.* *G*_III, *G*_IV). As the NMR measurements were recorded in CD_2Cl_2, the energies of the participating conformers were calculated with consideration of the effect of the solvent too (CH_2Cl_2). Table 4 shows the same tendency for the ΔE values. Unfortunately, the conformations obtained are not characteristic in a stereochemical frame, especially because of the nearly planar -NH- structures. Thus, general conclusions concerning the conformers of compound **37** could not be drawn.

To distinguish between structures *G*_I and *G*_II (Figure 3), low-temperature NMR measurements were recorded. The dynamic process in which conformers *G*_I and *G*_II are equilibrated, *N*-inversion,

is still fast on the NMR time-scale, even at the lowest temperatures. Thus, it was not possible experimentally to differentiate between the two conformers.



*G*_I
Δ*E* = 0 kcal/mol



*G*_I I
Δ*E* = 0.26 kcal/mol

Figure 3. Minimum-energy conformers of **37**

Since the formation of **41** *vs.* **42** was experimentally proved, our further aim was to support this finding by using DFT calculations. For the studied compounds (**41** and **42**), theoretical calculations were performed for all of the stereoisomers as regards the inversion possibilities for **41** (C-15b and C-8) and for **42** (C-15b, N-11 and C-10). It was found that the geometry of the N atoms (N-9 and N-11 for **41** and N-9 for **42**) are parts of planar amide bonds. Calculations were performed for all *cis* and *trans* isomers of **41** and **42**. The results of the optimization are given in Table 5 for **41** and in Table 6 for **42**.

Table 5. Calculated energy differences for **41**

Optimized geometry	C-15b	C-8	Δ*E* (kcal/mol)
G_t [a]	*S**	*R**	0
G_c [b]	*S**	*S**	1.33

[a] G_t = *trans* isomer.
[b] G_c = *cis* isomer.

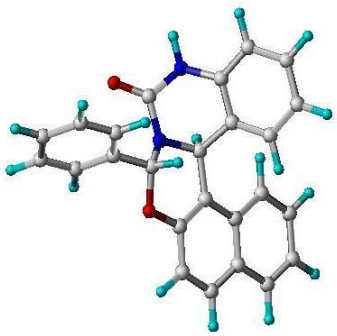
It can be concluded that the *trans* arrangement of H-15b and H-8 is favourable for **41**, while for **42**, the *trans* orientation of H-15b and H-10 is favourable (Tables 5 and 6).

Table 6. Calculated energy differences for **42**

Optimized geometry	C-15b	N-11	C-10	ΔE (kcal/mol)
G_t_I[a]	*S**	*S**	*R**	0
G_t_II	*S**	*R**	*R**	0.48
G_c_I[b]	*S**	*S**	*S**	3.81
G_c_II	*S**	*R**	*S**	5.45

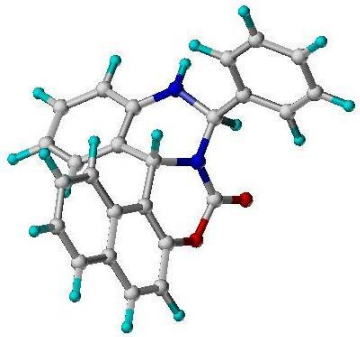
[a] G_t = *trans* isomer.
[b] G_c = *cis* isomer.

Figure 4 depicts the global minimum-energy structures of **41** and **42**. Since our original aim was to explain the formation of **41** instead of **42**, we calculated the energy difference between the global minimum-energy structures, G_t geometry for **41** and G_t_I for **42**. It was found to be 0.74 kcal/mol, which clearly supports our experimental results, *i.e.* **41** is the preferred product, corresponding to the MS results.



G_t for **41**

ΔE = 0 kcal/mol



G_t_I for **42**

ΔE = 0.74 kcal/mol

Figure 4. Global minimum-energy structures of **41** and **42**

3.2.2.2. Conformational analysis of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolinones

As the NMR measurements on naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives were recorded in DMSO, the energies of the participating conformers were calculated with consideration of the effect of the solvent via the dielectric constant ε = 46.7. All configurations of **45a-f** were studied at the DFT level of theory with respect to the preferred conformers or conformational equilibria. In 7a*H*,12*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one (**45a**), only one chiral centre is present. Figure 5 shows the global minimum-energy structure of **45a**.

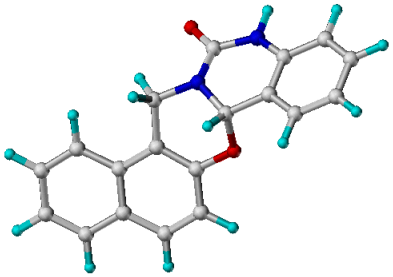


Figure 5. Global minimum-energy structure of **45a**

In consequence of the presence of the aryl substituents at position 15, the other five compounds (**45b-f**) contain two chiral centres. Theoretical calculations were performed for all of the stereoisomers as regards both the configurations of C-15 and C-7a and the ring interconversions of the two non-aromatic ring moieties. The results of optimization for **45b-d** are listed in Table 7. It can be concluded from the relative energy values that the *trans* arrangement of H-15 and H-7a is favourable for **45b-d** (Table 7).

Table 7. Calculated energy differences for **45b-d**

	Optimized geometry	C-15	C-7a	ΔE^a (kcal/mol)	ΔE^b (kcal/mol)
48b	G_t [c]	*S**	*R**	0	0
	G_c [d]	*S**	*S**	5.27	5.10
48c	G_t [c]	*S**	*R**	0	0
	G_c [d]	*S**	*S**	5.56	5.32
48d	G_t [c]	*S**	*R**	0	0
	G_c [d]	*S**	*S**	5.79	5.57

[a] In the gas phase. [b] In DMSO as solvent.
[c] G_t = *trans* isomer. [d] G_c = *cis* isomer.

The lack of NOESY interaction between H-15 and H-7a indirectly proved the *trans* arrangement, which is indicated by the theoretical calculations at the DFT level. Figure 6 depicts the global minimum-energy structures (G_t) of **45b-d**.

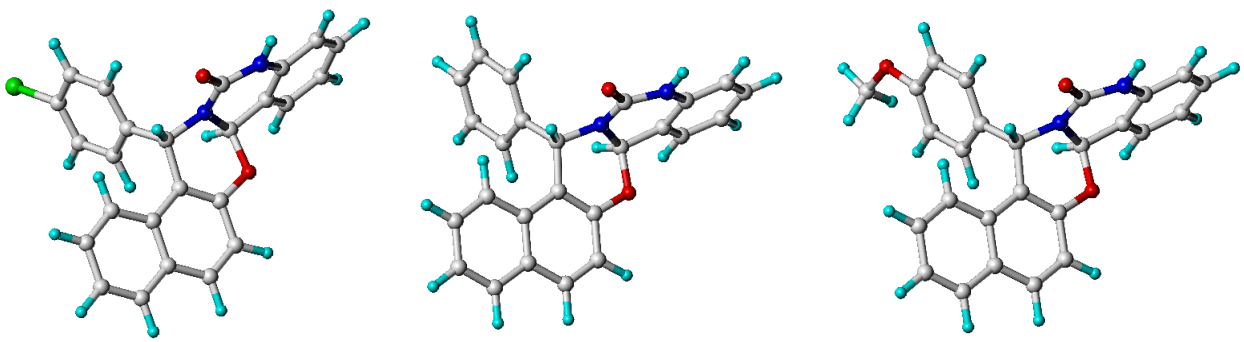


Figure 6. Global minimum-energy structures of **45b-d**

As a result of the restricted rotation of the Nph substituents at position 15 around the C-15–C-1' bond in **45e**, and around the C-15–C-2' bond in **45f**, four conformers were obtained after the geometry optimization, *i.e.* structures with *syn* and *anti* positions of H-15 and C-2' in **45e** and of H-15 and C-1' in **45f** (Table 8).

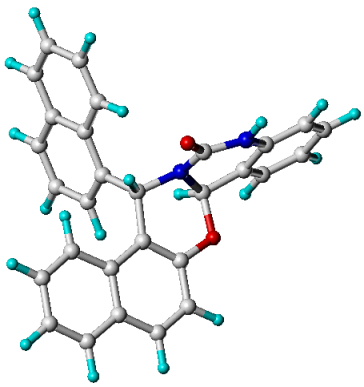
The theoretical results in Table 8 demonstrate that the *trans* arrangement of H-15 and H-7a is favourable for both **45e** and **45f**. This is the case in both the *trans* and the *cis* diastereomers of **45e** (*anti* position of H-15 and C-2'). In the G_t_I and G_c_II geometries of **45e**, N-14 is not planar and its relative configuration is *R**, while in both the G_t_II and the G_c_I geometries of **45e**, N-14 was found to be planar, as in the cases of **45a-d** and **48f**.

Table 8. Calculated energy differences for **45e** and **45f**

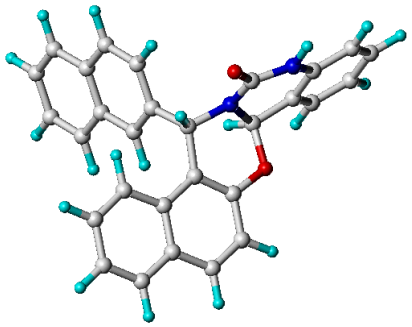
	H-15–C-2'/ H-15–C-1'	Optimized geometry	C-15	C-7a	ΔE^a (kcal/mol)	ΔE^b (kcal/mol)
45e	*anti*[c]	G_t_I[d]	*S**	*R**	0	0
	syn	G_t_II	*S**	*R**	4.88	4.92
	anti	G_c_I[e]	*S**	*S**	8.27	8.09
	syn[c]	G_c_II	*S**	*S**	9.21	8.78
45f	*anti*	G_t_I[d]	*S**	*R**	0	0
	syn	G_t_II	*S**	*R**	0.79	0.78
	syn	G_c_I[e]	*S**	*S**	5.66	5.40
	anti	G_c_II	*S**	*S**	6.25	5.98

[a] In the gas phase. [b] In DMSO as solvent.
[c] In these structures, N-14 was found to be not planar and its relative configuration was *R**.
[d] G_t = *trans* isomer. [e] G_c = *cis* isomer.

The sterically hindered rotation of the 1-Nph substituent around the C-15–C-1' bond led to the energy difference between the G_t_I and G_t_II geometries of **45e** being relatively high: 4.92 kcal/mol (Table 8). Figure 7 illustrates the global minimum-energy structures (G_t_I) of **45e** and **45f**.



G_t_I for **45e**



G_t_I for **45f**

Figure 7. Global minimum-energy structures of **45e** and **45f**

In order to demonstrate the stereochemistry of the naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolinone derivatives (obtained by means of DFT calculations and proved only indirectly through the lack of NOE (H-7a-H-15) information), the ring current effects of the 15-aryl substituents on H-1 in **45c**,**e** and **45f** were computed. For this purpose, the spatial NICS approach[136] was employed. The through-space NMR shieldings (TSNMRSs) can be visualized[136] as iso-chemical-shielding surfaces (ICSSs) and employed to quantify the anisotropic effects of functional groups on proton chemical shifts (to determine the stereochemistry of nuclei proximal to the functional group),[137] in order to separate the anisotropic effects of functional groups from the influence of steric hindrance on the same proton chemical shifts,[138] and to visualize and quantify planar or spherical (anti)aromaticity and chelatoaromaticity.

From the optimized geometries of **45c**,**e** and **45f**, the TSNMRSs of the aryl moieties on C-15 were calculated, visualized by ICCSs of various sizes and directions (Figure 8 for **45c** (Ph) and **45e** (Nph ring system), respectively) and finally the corresponding anisotropic effect of the 15-aryl moiety on H-1 was computed quantitatively. The corresponding values (as shielding values, negative for deshielding and positive for the shielding of H-1) are given in Table 9, together with the H-1 chemical shift in **45a** as reference.

Table 9. Experimental differences in the chemical shifts δ/ppm of H-1 and the anisotropic effects of 15-aryl in **45c**,**e**,**f** σ/ppm

Compound	δ_{exp} (H-1)	$\Delta\delta_{exp}$/ppm	σ_{calc}/ppm
45a	7.84	0	-
45c	7.39	0.45	0.56
45e	7.22	0.62	0.55
45f	7.45	0.39	0.49

The coincidence is very good: the anisotropic effect of the 15-aryl moiety proves to be ~ 0.5 ppm, in complete agreement with the experiment, and proves the stereochemistry of the naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolinone derivatives **45c**,**e** and **45f**.

Figure 8. Ring current effects of the Ph ring in **45c** and the 1-Nph ring in **45e** on H-1

The conformational study of phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazolin-10-one (**41**, Figure 4) revealed that the oxazine ring proved to prefer an *envelope*, and the quinazolone ring a *twisted boat* conformation; while in naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones (**45a-f**) the oxazine ring prefers a *twisted chair* conformation and the quinazolone ring is almost planar (Figures 5, 6 and 7).

3.2.2.3. Conformational analysis of piperidine-fused quinazolino- and benzoxazino-naphthoxazines

As the NMR measurements of piperidine-fused quinazolino- and benzoxazinonaphthoxazines were recorded in CD_2Cl_2, the energies of the participating conformers were calculated with consideration of the effect of the solvent too (CH_2Cl_2). Compounds **46** and **48** were studied in all the configurations at the DFT level of theory with respect to the preferred conformers and conformational equilibria. Theoretical calculations were performed for all of the stereoisomers of **46** and **48** as regards the *R*/*S* stereochemistry of the involved chiral centres C-7a, C-10a C-15b and N-16. The results of the optimization are given in Table 10 for **46** and in Table 11 for **48**.

Table 10. Calculated energy differences for **46**

Optimized geometry	H-7a–H-15b	H-10a–H-15b	H-7a–H-10a	Δ*E* (kcal/mol) (in the gas phase)	Δ*E* (kcal/mol) (in CH_2Cl_2)
G_{tct}_I[a]	*trans*	*cis*	*trans*	0	0
G_{ccc}_I[b]	*cis*	*cis*	*cis*	4.13	3.77
G_{ctt}_I[c]	*cis*	*trans*	*trans*	5.61	5.46
G_{ttc}_I[d]	*trans*	*trans*	*cis*	8.19	7.67
G_{ccc}_II[e]	*cis*	*cis*	*cis*	8.20	7.99
G_{ctt}_II[f]	*cis*	*trans*	*trans*	10.22	9.88
G_{ttc}_II[g]	*trans*	*trans*	*cis*	10.48	10.73
G_{tct}_II[h]	*trans*	*cis*	*trans*	17.61	17.32

The numbers correspond to the following relative configurations:
[a] C-15b (*S**), N-16 (*R**), C-7a (*R**), C-10 (*S**).
[b] C-15b (*S**), N-16 (*S**), C-7a (*S**), C-10 (*S**).
[c] C-15b (*S**), N-16 (*R**), C-7a (*S**), C-10 (*R**).
[d] C-15b (*S**), N-16 (*S**), C-7a (*R**), C-10 (*R**).
[e] C-15b (*S**), N-16 (*R**), C-7a (*S**), C-10 (*S**).
[f] C-15b (*S**), N-16 (*S**), C-7a (*S**), C-10 (*R**).
[g] C-15b (*S**), N-16 (*R**), C-7a (*R**), C10 (*R**).
[h] C-15b (*S**), N-16 (*S**), C-7a (*R**), C-10 (*S**).

It can be concluded from the relative energies of the stereoisomers that the *trans* arrangement of H-7a and H-15b, the *cis* arrangement of H-10a and H-15b and the *trans* arrangement of H-7a and H-10a were preferred for both **46** and **48** (Tables 10 and 11); on the energy hypersurface, the *cis/cis/cis* and *cis/trans/trans* isomers display energies of 6.1 kcal/mol and 3.8 kcal/mol, respectively. These computational results were corroborated by the NOE measurements on **46** and **48** (*vide supra*).

Table 11. Calculated energy differences for **48**

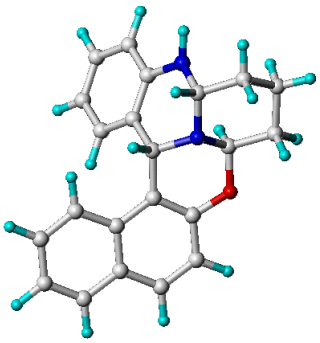
Optimized geometry	H-7a–H-15b	H-10a–H-15b	H-7a–H-10a	Δ*E* (kcal/mol) (in the gas phase)	Δ*E* (kcal/mol) (in CH_2Cl_2)
G_{tct}_I[a]	*trans*	*cis*	*trans*	0	0
G_{ccc}_I[b]	*cis*	*cis*	*cis*	6.39	6.10
G_{ccc}_II[c]	*cis*	*cis*	*cis*	6.44	5.97
G_{ctt}_I[d]	*cis*	*trans*	*trans*	7.62	7.63
G_{ttc}_I[e]	*trans*	*trans*	*cis*	11.24	11.38
G_{ttc}_II[f]	*trans*	*trans*	*cis*	11.34	10.84
G_{ctt}_II[g]	*cis*	*trans*	*trans*	13.15	12.89
G_{tct}_II[h]	*trans*	*cis*	*trans*	18.33	18.08

The numbers correspond to the following relative configurations:
[a] C-15b (*S**), N-16 (*R**), C-7a (*R**), C-10 (*R**).
[b] C-15b (*S**), N-16 (*R**), C-7a (*S**), C-10 (*R**).
[c] C-15b (*S**), N-16 (*S**), C-7a (*S**), C-10 (*R**).
[d] C-15b (*S**), N-16 (*R**), C-7a (*S**), C-10 (*S**).
[e] C-15b (*S**), N-16 (*R**), C-7a (*R**), C-10 (*S**).
[f] C-15b (*S**), N-16 (*S**), C-7a (*R**), C-10 (*S**).
[g] C-15b (*S**), N-16 (*S**), C-7a (*S**), C-10 (*S**).
[h] C-15b (*S**), N-16 (*S**), C-7a (*R**), C-10 (*R**).

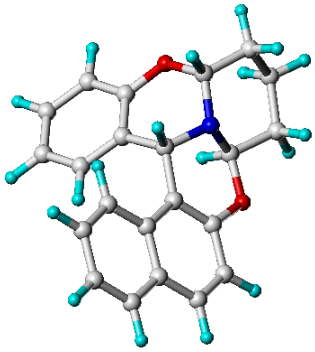
No really preferred conformation of the three flexible saturated/partly saturated heterocyclic ring moieties (benzoxazine *bo* and quinazoline *q*, respectively, naphthoxazine *no* and piperidine *p*) was found. The lowest-energy conformers, G_{tct}_I for **46** and G_{tct}_I for **48**, of the two *trans*/*cis*/*trans* isomers are conformationally identical: *bo*, *q* (*half-chair*), *no* (*twist*) and *p* (*chair*). The chair conformation of the piperidine moiety was proved by proton spectrum simulation/iteration of the frozen $–C_{10a}H–C_{10}H_2–C_9H_2–C_8H_2–C_{7a}H–$ unit delivering the expected large coupling constants ^3J(ax,ax) and ^2J(ax,eq) and the much smaller ^3J(ax,eq) and ^3J(eq,eq). As the two G_{tct}_I minimum-energy conformers of **46** and **48** are the experimentally available ones, the congruence of the experimental NMR and the computational study can be concluded. For the same reasons, experimental information concerning the energetically next-lowest conformers is not available: G_{ccc}_I of **46** occurs as the *q* (*twisted boat*), *no* (*half-chair*), *p* (*chair*) conformers and G_{ctt}_I of **46** as the *q* (*half-chair*), *no* (*boat*), *p* (*twisted chair*) conformers, and the *O*-analogue G_{ccc}_I of **48** occurs as the *bo* (*twist*), *no* (*boat*), *p* (*twist-boat*) conformer and G_{ccc}_II of **48** as the *bo* (*half-chair*), *no* (*twisted boat*), *p* (*chair*) conformers (Figure 9).

The most stable stereoisomers, G_{tct}_I for **46** and G_{tct}_I for **48**, were identified by theoretical calculations at the DFT level of theory, considering the solvent, corroborated by spatial NOE information between H-7a/H-10a/H-15b and the H,H coupling pattern of the protons in the flexible part of the piperidine ring moiety.

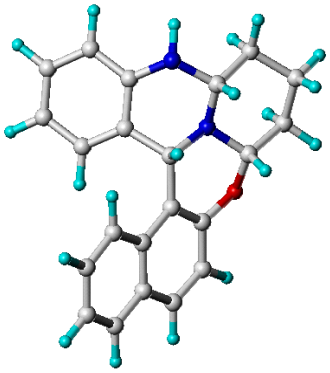
The fragmentations of **46** and **48** were investigated by positive ESI. The corresponding ions $[M+H]^+$ and the fragment ions resulting from "in source CID" experiments were used as precursor ions and their CID fragmentations were studied. The similar intensities of the typical fragment ions, together with the NMR results (*vide supra*), corroborate the conformations of the two heterocyclic ring systems in **46** and **48**: the *twisted chair* and the G_{tct}_I configuration, as obtained from DFT calculations and depicted in Figure 9.



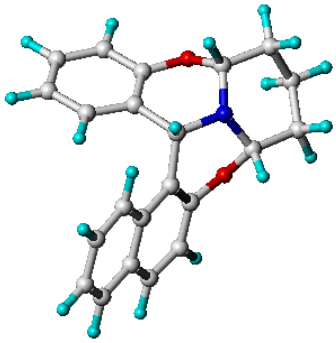
G_{tct}_I for **46**



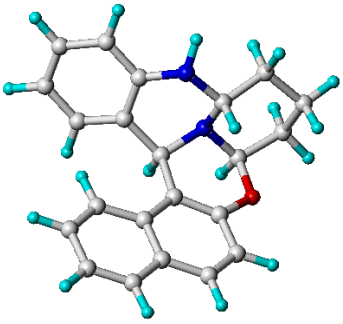
G_{tct}_I for **48**



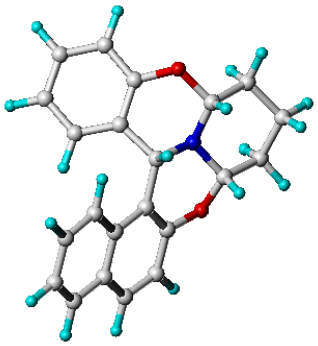
G_{ccc}_I for **46**



G_{ccc}_I for **48**



G_{ctt}_I for **46**



G_{ccc}_II for **48**

Figure 9. Minimum-energy conformers of **46** and **48**

3.3. Methods

Melting points and elemental analysis:

For compounds **25-31** and **33-41**, melting points were determined on a Kofler micro melting point apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser.

For compounds **44-46** and **48**, melting points were determined on a Hinotek X-4 melting point apparatus and are uncorrected. The HRMS EI spectra were recorded with a GC/MS instrument with a time-of-flight mass analyser (Micromass/Waters, Manchester, UK) in positive ion mode. The elemental compositions of the ions were determined by accurate mass measurements with standard deviation < 5 ppm. Perfluorokerosene was used as reference compound and the mass resolution was 5000.

NMR measurements:

For compounds **25-31**, the ^{1}H and ^{13}C NMR spectra were recorded in DMSO solution in 5 mm tubes, at r.t., on a Bruker Avance DRX400 spectrometer at 400.13 (^{1}H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard.

For compounds **33-36**, **39-41**, **44** and **45**, the ^{1}H and ^{13}C NMR spectra were recorded in DMSO solution, and for compounds **37**, **38**, **46** and **48** in CD_2Cl_2 solution, in 5 mm tubes, at r.t., 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, gs-HMQC, gs-1D-HMQC, gs-HMBC and NOESY) were acquired and processed with the standard BRUKER software. For the equilibria to be established in tautomeric mixtures (**38a-g**), the samples were dissolved in CD_2Cl_2 and the solutions were allowed to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 24.

Quantum chemical calculations:

Conformational searches for **26a** and **29a** were carried out by means of the Macromodel 9.7.211[139] software, using the Merck Molecular Force Field (MMFF) with the implicit solvent model for H_2O. In each conformational search, the maximum number of steps was set to 30 000. Geometry reoptimizations at the B3LYP/6-31G(d) level of theory, followed by TDDFT calculations using various functionals (B3LYP, BH&HLYP and CAM-B3LYP) and the TZVP basis set, were performed with the Gaussian 03[140] and the Gaussian 09[141] packages. Boltzman distributions were estimated from the ZPVE corrected B3LYP/6-31G(d) energies. CD spectra were generated as the sum of Gaussians[142] with 3000 cm^{-1} half-height width (corresponding to *ca.* 15 nm at 225 nm), using dipole-velocity computed rotational strengths. The MOLEKEL[143] software package was used for visualization of the

results.

Geometry optimizations for compounds **37**, **41**, **42**, **45a-f**, **46** and **48** were performed without restrictions, using the Gaussian 09[141] program package. Different conformations and configurations of all studied compounds were preoptimized by using the PM3 Hamiltonian[144,145] Density functional theory calculations were carried out at the B3LYP/6-31G**[146,147] level of theory. Different starting conformations were created and the results were analysed and displayed by using the molecular modelling program SYBYL 7.3[148] and the program GaussView 2.0.[149] The self-consistent reaction field method and the integral equation formalism variant of the polarizable continuum model were applied to take solvent effects (CD_2Cl_2 and DMSO) into account.[150] Different local minimum-energy conformations were selected to analyse the relative stability and the geometrical parameter.

Mass spectrometric measurements:

The low-resolution EI mass spectra for compounds **37**, **41**, **44-46** and **48** were obtained by using a GC-MS TRACE DSQ II mass spectrometer (Thermo Fisher Scientific Dreieich, Germany), with an electron energy of 70 eV and a source temperature of 180 °C, using a direct insertion probe with a DEP (Direct Desorption Probe) filament in positive ion mode.

The ESI mass spectra for compounds **39** and **40** were recorded (in the interval 200-2200 a.m.u.) by using the AGILENT 1100 LC/MSD TRAP instrument in positive ion mode.

4. SUMMARY

1. Hydroxynaphthyl-substituted glycine derivatives **26a** and **29a** were successfully prepared from 2- or 1-naphthol, glyoxylic acid and benzyl carbamate in MeOH via a mMR in the presence of *p*-TSA, followed by removal of the protecting group. Acidic hydrolysis of **26a** and **29a** resulted in the expected α-amino acids **27** and **30**. The optimized reaction conditions were extended by starting from EtOH. Benzyloxycarbonyl-protected ethyl esters **25b** and **28b** were isolated in lower yields as compared with those of methyl esters **25a** and **28a**.

2. The enantiomers of **26a** and **29a** were successfully separated on analytical and semi-preparative HPLC columns. Their absolute configurations were determined by CD analysis supported by TDDFT CD calculations, which revealed that the absolute configuration of the second-eluting enantiomer of **26a** was *S*, and that of the first-eluting enantiomer of **29a** was *S*.

3. A new, highly functionalized aminonaphthol derivative, 1-(amino(2-aminophenyl)methyl)-2-naphthol (**35**), was synthetized by the reaction of 2-naphthol, 2-nitrobenzaldehyde and *tert*-butyl carbamate or benzyl carbamate, followed by reduction and/or removal of the protecting group. The aminonaphthol derivative thus obtained was converted in a ring closure reaction with formaldehyde to 10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*]quinazoline (**37**). The ring closure reaction of the starting diamine with phosgene and/or benzaldehyde led to the formation of new naphthoxazinoquinazolinone derivatives (**39-41**).

4. Products **38a-g** obtained via the condensation of **35** with substituted benzaldehydes can potentially furnish five-component tautomeric mixtures in CD_2Cl_2 at 300 K. We succeeded in detecting three of the five components: one epimeric quinazoline (**B**) and two epimeric naphthoxazines (**D** and **E**). The influence of aryl substituents on the tautomeric composition could be described in terms of the Hammett-Brown parameter (σ^+). It can be concluded that electron-donating substituents increase the proportion of the quinazoline form (**B**), while electron-withdrawing substituents prefer the naphthoxazine forms (**D** and **E**).

5. The syntheses of naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**45a** and **45c**) were achieved by the solvent-free heating of benzyloxycarbonyl-protected intermediates (**44a** and **44c**) with MeONa. Compounds **44a** and **44c** were synthetized by the reactions of substituted aminonaphthol derivatives (**43a** and **43c**) with benzyl *N*-(2-formylphenyl)carbamate. This synthetic pathway was extended to the preparation of naphthoxazinoquinazolinones containing different aryl substituents at position 15 (*p*-Cl-Ph: **45b**, *p*-OMe-Ph: **45d**,

1-Nph: **45e**, and 2-Nph: **45f**). The lack of a cross-peak between H-15 and H-7a in the NOESY NMR spectra of **45b-f** indirectly proved their *trans* arrangement.

6. In solution at 300 K, **44a-f** can furnish three-component tautomeric mixtures containing diastereomeric ring forms (**B** and **C**) besides the chain form (**A**). When the NMR spectra of **44a-f** were recorded in DMSO, the spectra of **44b-d**,**f** revealed the presence of a new tautomeric chain form ($\mathbf{A^2}$) besides the *trans* ring form **B** and the chain form $\mathbf{A^1}$. The reason for the formation of $\mathbf{A^2}$ may be the possibility of conjugation of substituent R (aryl) with the C=N double bond, which is supported by the lack of $\mathbf{A^2}$ in **44a** and **44e**. In **44a** there is no aromatic ring, while for **44e** the hindered rotation of the 1-Nph ring restricts the conjugation. The amount of $\mathbf{A^2}$ increases, while those of **B** and $\mathbf{A^1}$ decrease as the duration of standing in DMSO becomes longer.

7. Compounds **37**, **41** and **42** were studied in all the configurations at the DFT level of theory with respect to the preferred conformers and conformational equilibria. The experimental NMR parameters obtained were in general agreement with the theoretical findings. The conformational study of phenyl-10,11-dihydro-8*H*,15b*H*-naphth[1,2-*e*][1,3]oxazino[3,4-*c*] quinazolin-10-one (**41**) revealed that the oxazine ring proved to prefer an *envelope*, and the quinazolone ring a *twisted boat* conformation; while in naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-ones (**45a-f**) the oxazine ring prefers a *twisted chair* conformation and the quinazolone ring is almost planar.

8. The anisotropic effect of the 15-aryl ring on H-1 was calculated for **45b-f**: the excellent agreement of the computational and experimental results proved the stereochemistry of the naphth[1,2-*e*][1,3]oxazino[3,2-*c*]quinazolin-13-one derivatives (**45b-f**) deduced from the theoretical calculations.

9. The reactions of 1-(amino(2-aminophenyl)methyl)-2-naphthol (**35**) and 1-(amino(2-hydroxyphenyl)methyl)-2-naphthol (**47**) with glutardialdehyde resulted in the formation of piperidine-fused quinazolinonaphthoxazine **46** and benzoxazinonaphthoxazine **48**, respectively, both in diastereopure form.

   The NOESY measurements on **46** and **48** revealed the following relative arrangements of H-7a–H-15b–H-10a: $H-7a \overset{trans}{\longleftrightarrow} H-15b$; $H-10a \overset{cis}{\longleftrightarrow} H-15b$; $H-7a \overset{trans}{\longleftrightarrow} H-10a$. The experimental results were supported by theoretical calculations at the DFT level of theory. These calculations and the H,H coupling pattern of the protons in the flexible part of the piperidine ring moiety highlighted that the configuration with a *twisted chair* conformation is preferred for both **46** and **48.**

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6. REFERENCES

1. Betti, M. *Gazz. Chim. Ital.* **1900**, *30 II*, 310.
2. Betti, M. *Gazz. Chim. Ital.* **1901**, *31 II*, 377.
3. Betti, M. *Gazz. Chim. Ital.* **1901**, *31 II*, 170.
4. Betti, M. Gazz. *Chim. Ital.* **1901**, *31 II*, 191.
5. Betti, M. *Org. Synth. Coll. Vol.* **1941**, *1*, 381.
6. Szatmári, I.; Fülöp, F. *Tetrahedron*, submitted.
7. Szatmári, I.; Fülöp, F. *Curr. Org. Synth.* **2004**, *1*, 155.
8. Szatmári, I.; Hetényi, A.; Lázár, L.; Fülöp, F. *J. Heterocycl. Chem.* **2004**, *41*, 367.
9. Heydenreich, M.; Koch, A.; Klod, S.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. *Tetrahedron* **2006**, *62*, 11081.
10. Heydenreich, M.; Koch, A.; Szatmári, I.; Fülöp, F.; Kleinpeter, E. *Tetrahedron* **2008**, *64*, 7378.
11. Szatmári, I.; Fülöp, F. *Tetrahedron Lett.* **2011**, *52*, 4440.
12. Möhrle, H.; Tröster, K. *Arch. Pharm.* **1982**, *315*, 222.
13. Möhrle, H.; Miller, C.; Wendisch D. *Chem. Ber.* **1974,** *107*, 2675.
14. Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 7481.
15. Das, B.; Laxminarayana, K.; Thirupathi, P.; Ramarao, B. *Synlett* **2007**, 3103.
16. Damodiran, M.; Selvam, N. P.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 5474.
17. Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 788.
18. Green, W.; Wats, M. P. G. Protecting groups in organic synthesis; 2nd ed.; John Wiley and Sons: New York, **1999**.
19. Shaterian, H. R.; Yarahmadi, H. *Tetrahedron Lett.* **2008**, *49*, 1297.
20. Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Tetrahedron* **2008**, *64*, 1263.
21. Shaterian, H. R.; Yarahmadi, H. *Arkivoc* **2008**, *ii*, 105.
22. Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Lett. Org. Chem.* **2008**, *5*, 290.
23. Anary-Abbasinejad, M.; Hassanabadi, A.; Kamali-Gharamaleki, M.; Saidipoor, A.; Anaraki-Ardakani, H. *J. Chem. Res.* **2007**, 644.
24. Heravi, M. M.; Tavakoli-Hoseini, N.; Bamoharram, F. F. *Bulg. Chem. Commun.* **2011**, *3*, 423.
25. She, T-T.; Liu, Z-L., Gong, K. *Chin. J. Appl. Chem.* **2010**, *7*, 778.
26. Khazaei, A.; Zolfigol, M. A. Moosavi-Zare, A. R.; Zare, A.; Parhami, A.; Khalafi-Nezhad, A. *Appl. Catal. A: Gen.* **2010**, *386*, 179.

27. Anary-Abbasinejad, M.; Anaraki-Ardakani, H.; Hassanabadi, A. *Synth. Commun.* **2008**, *38*, 3706.
28. Selvam, N. P.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2972.
29. Tamaddon, F.; Tavakoli, F. *J. Mol. Cat. A: Chem.* **2011**, *337*, 52.
30. Tamaddon, F.; Bistgani, J. M. *Synlett* **2011**, 2947.
31. Shaterian, H. R.; Yarahmadi, H.; Ghashang, M. *Turk. J. Chem.* **2009**, *33*, 449.
32. Su, W.; Tang, W.; Li, J. *J. Chem. Res.* **2008**, 123.
33. Prasanna, T. S. R.; Raju, K. M. *Org. Chem.: An Indian Journal* **2011**, *7*, 332.
34. Jafari, H.; Moghanian, H. *Lett. Org. Chem.* **2012**, *9*, 273.
35. Habibzadeh, S.; Ghasemnejad-Bosra, H. *J. Chin. Chem. Soc.* **2011**, *6*, 1.
36. Heravi, M. M.; Tavakoli-Hoseini, N.; Bamoharram, F. F. *Synth. Commun.* **2011**, *41*, 298.
37. Forouzani, M.; Ghasemnejad-Bosra, H. *Arab. J. Chem.* **2011**, http://dx.doi.org/10.1016/j.arabjc.2011.08.002.
38. Zare, A.; Hasaninejad, A.; Salimi Beni, A.; Moosavi-Zare, A. R.; Merajoddina, M.; Kamali, E.; Akbari-Seddigh, M.; Parsaee, Z. *Scientia Iranica* **2011**, *18*, 433.
39. Zare, A. *Org. Prep. Proc. Int.* **2012**, *44*, 82.
40. Zali, A.; Shokrolahi, A. *Chin. Chem. Lett.* **2012**, *23*, 269.
41. Montazeri, N.; Pourshamsian, K.; Ghorchibeigi, M.; Fouladi, M. *Res. J. Pharm., Biol. Chem. Sci.* **2012**, 3, 867.
42. Cai, X-H.; Guo, H.; Xie, B. *Jordan J. Chem.* **2011**, *6*, 17.
43. Cai, X-H. *Int. J. Chem.* **2011**, *3*, 119.
44. Almahy, H. A. A. *Res. J. Appl. Sci.* **2011**, *6*, 464.
45. Bamoharram, F. F.; Heravi, M.; Roshani, M.; Mohammad, J.; Charkhi, S. *Eur. J. Chem.* **2011**, *8*, 523.
46. Dorehgiraee, A.; Khabazzadeh, H.; Saidi, K. *Arkivoc* **2009**, *vii*, 303.
47. Mistry, S. R.; Joshi, R. S.; Maheria, K. C. *J. Chem. Sci.* **2011**, *123*, 427.
48. Chavan, N. L.; Naik, P. N.; Nayak, S. K.; Kusurkar, R. S. *Synth. Commun.* **2010**, *40*, 2941.
49. Sapkal, S. B.; Shelke, K. F.; Madje, B. R.; Shingate, B. B.; Shingare, M. S. *Bull. Korean Chem. Soc.* **2009**, 30, 2887.
50. Niralwad, K. S.; Shingate, B. B.; Shingare, M. S. *Chin. Chem. Lett.* **2011**, *22*, 551.
51. Nagarapu, L.; Baseeruddin, M.; Apuri, S.; Kantevari, S. *Catal. Commun.* **2007**, *8*, 1729.
52. Kantevari, S.; Vuppalapati, S. V. N.; Nagarapu, L. *Catal. Commun.* **2007**, *8*, 1857.
53. Mahdavinia, G. H.; Bigdeli, M. A.; Heravi, M. M. *Chin. Chem. Lett.* **2008**, *19*, 1171.

54. Mahdavinia, G. H.; Bigdeli, M. A. *Chin. Chem. Lett.* **2009**, *20*, 383.
55. Nagawade, R. R.; Shinde, D. B. *Acta Chim. Slov.* **2007**, *54*, 642.
56. Nagawade, R. R.; Shinde, D. B. *Chin. J. Chem.* **2007**, *25*, 1710.
57. Nagawade, R. R.; Shinde, D. B. *Mendeleev Commun.* **2007**, *17*, 299.
58. Ansari, S. A. M. K.; Sangshetti, J. N.; Kokare, N. D.; Wakte, P. S., Shinde, D. B. *Indian J. Chem. Technol.* **2010**, *17*, 71.
59. Gawand, P.; Deokar, H.; Langi, B.; Yadav, A.; Chaskar, A. *Synth. Commun.* **2009**, *39*, 4171.
60. Shaterian, H. R.; Amirzadeh, A.; Khorami, F.; Ghashang, M. *Synth. Commun.* **2008**, *38*, 2983.
61. Shaterian, H. R.; Khorami, F.; Amirzadeh, A.; Ghashang, M. *Chin. J. Chem.* **2009**, *27*, 815.
62. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Synth. Commun.* **2008**, *38*, 3375.
63. Khabazzadeh, H.; Saidi, K.; Seyedi, N. *J. Chem. Sci.* **2009**, *121*, 429.
64. Rashinkar, G.; Salunkhe, R. *J. Mol. Cat. A: Chem.* **2010**, *316*, 146.
65. Supale, A. R.; Gokavi, G. S. *J. Chem. Sci.* **2010**, *122*, 189.
66. Quan, Z-J., Ren, R-G.; Da, Y-X.; Zhang, Z.; Wang, X-C. *Synth. Commun.* **2011**, *41*, 3106.
67. Khazdooz, L.; Zarei, A.; Hajipour, A. R.; Sheikhan, N. *Iranian J. Catal.* **2011**, *1*, 1.
68. Datta, B.; Pasha, M. A. *Ultrason. Sonochem.* **2011**, *18*, 624.
69. Hong, M.; Cai, C.; Yi, W. B. *Chin. Chem. Lett.* **2011**, *22*, 322.
70. Puri, S.; Kaur, B.; Parmar, A.; Kumar, H. *Org. Prep. Proced. Int.* **2012**, *44*, 91.
71. Kore, R.; Srivastava, R. *J. Mol. Cat. A: Chem.* **2011**, *345*, 117.
72. Ravindran, A.; Srivastava, R. *Chin. J. Catal.* **2011**, *32*, 1597.
73. Deepali, A.; Kotadia, D. A.; Soni, S. S. *J. Mol. Cat. A: Chem.* **2012**, *353-354*, 44.
74. Deshmukh, K. M.; Qureshi, Z. S.; Patil, Y. P.; Bhanage, B. M. *Synth. Commun.* **2012**, *42*, 93.
75. Hajipour, A. R.; Ghayeb, Y.; Sheikhan, N.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 5649.
76. Samantaray, S.; Hota, G.; Mishra, B. G. *Catal. Commun.* **2011**, *12*, 1255.
77. Zolfigol, M. A.; Khazaei, A.; Moosavi-Zare, A. R.; Zare, A.; Khakyzadeh, V. *Appl. Catal. A: Gen.* **2011**, *400*, 70.
78. Zare, A.; Hasaninejad, A.; Rostami, E.; Moosavi-Zare, A. R.; Pishahang, N.; Roshankar, M.; Khedri, F.; Khedr, M. *Eur. J. Chem.* **2010**, *7*, 1162.

79. Zhang, P.; Zhang, Z-H. *Monatsh. Chem.* **2009**, *140*, 199.
80. Khodaei, M. M.; Khosropour, A. R.; Moghanian, H. *Synlett* **2006**, 916.
81. Das, B.; Laxminarayana, K.; Ravikanth, B.; Rao, B. R. *J. Mol. Cat. A: Chem.* **2007**, *261*, 180.
82. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Ultrason. Sonochem.* **2007**, *14*, 515.
83. Patil, S. B.; Singh, P. R.; Surpur, M. P.; Samant, S. D. *Synth. Commun.* **2007**, *37*, 1659.
84. Jiang, W-Q.; An, L-T.; Zou, J-P. *Chin. J. Chem.* **2008**, *26*, 1697.
85. An, L-T.; Lu, X-H.; Ding, F-Q.; Jiang, W-Q.; Zou, J-P. *Chin. J. Chem.* **2008**, *26*, 2117.
86. Nandi, G. C.; Samai, S.; Kumar, R.; Singh, M. S. *Tetrahedron Lett.* **2009**, *50*, 7220.
87. Das, B.; Kumar, D. N.; Laxminarayana, K.; Ravikanth, B. *Helv. Chim. Acta* **2007**, *90*, 1330.
88. Zandi, M.; Sardarian, A. R. *C. R. Chimie* **2012**, 15, 365.
89. Zhang, Q.; Luo, J.; Wei, Y. *Green Chem.* **2010**, *12*, 2246.
90. Luo, J.; Zhang, Q. *Monatsh. Chem.* **2011**, *142*, 923.
91. Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. *Can. J. Chem.* **2009**, *87*, 714.
92. Srihari, G.; Nagaraju, M.; Murthy, M. M. *Helv. Chim. Acta* **2007**, *90*, 1497.
93. Rani, V. J.; Suresh, M.; Lavanya, P.; Vani, K. V.; Nagarjuna, B.; Rao, C. V. *Pharma Chemica* **2010**, *2*, 224.
94. Wang, M.; Liang, Y. *Monatsh. Chem.* **2011**, *142*, 153.
95. Song, Z.; Zhao, S.; Wan, X. *Chin. J. Org. Chem.* **2011**, *31*, 870.
96. Wang, M.; Liang, Y.; Zhang, T.; Gao, J. *Chin. J. Chem.* **2011**, *29*, 1656.
97. Wang, M.; Liang, Y.; Zhang, T. T.; Gao, J. J. *Chin. Chem. Lett.* **2012**, *23*, 65.
98. Kundu, D.; Majee, A.; Hajra, A. *Catal. Commun.* **2010**, *11*, 1157.
99. Lei, M.; Ma, L.; Hu, L. *Tetrahedron Lett.* **2009**, *50*, 6393.
100. Khavasi, H. R.; Bazgir, A.; Amani, V.; Rahimi, R. *J. Chem. Res.* **2008**, 450.
101. Bahrami, M. J.; Hosseini, S. M. A.; Pilvar, P. *Corros. Sci.* **2010**, *52*, 2793.
102. Sabitha, G.; Arundhathi, K.; Sudhakar, K.; Sastry, B. S.; Yadav, J. S. *J. Heterocycl. Chem.* **2010**, *47*, 272.
103. Nizam, A.; Päsha, M. A. *Synth. Commun.* **2010**, *40*, 2864.
104. Chaskar, A.; Vyavhare, V.; Padalkar, V.; Phatangare, K.; Deokar, H. *J. Serb. Chem. Soc.* **2011**, *76*, 21.
105. Rao, G. B. D.; Kaushik, M. P.; Halve, A. K. *Tetrahedron Lett.* **2012**, *53*, 2741.
106. Eshghi, H.; Zohuri, G. H.; Damavandi, S. *Synth. Commun.* **2012**, *42*, 516.

107. Ghorbani-Vaghei, R.; Malaekehpour, S. M. *Cent. Eur. J. Chem.* **2010**, *8*, 1086.

108. Bazgir, A.; Amani, V.; Khavasi, H. R. *Acta Cryst.* **2006**, *E62*, 3875.

109. Kumar, A.; Saxena, A.; Dewan, M.; De, A.; Mozumdar, S. *Tetrahedron Lett.* **2011**, *52*, 4835.

110. Dabiri, M.; Delbari, A. S., Bazgir, A. *Synlett* **2007**, 821.

111. Shakibaei, G. I.; Khavasi, H. R.; Mirzaei, P.; Bazgir, A. *J. Heterocycl. Chem.* **2008**, *45*, 1481.

112. Hajra, A.; Kundu, D.; Majee, A. *J. Heterocycl. Chem.* **2009**, *46*, 1019.

113. Foroughifar, N.; Mobinikhaledi, A.; Moghanian, H.; Ebrahimi, S.; Fard, M. A. B. *Synlett* **2008**, 821.

114. Zhang, Z-P.; Wen, J-M.; Li, J-H.; Hu, W-X. *J. Chem. Res.* **2009**, 162.

115. Foroughifar, N.; Mobinikhaledi, A.; Moghanian, H. *Synth. Commun.* **2009**, *39*, 3668.

116. Dabiri, M.; Delbari, A. S.; Bazgir, A. *Heterocycles* **2007**, *71*, 543.

117. Heravi, M. M.; Tavakoli-Hoseini, N., Bamoharram, F. F. *Green Chem. Lett. Rev.* **2010**, *3*, 263.

118. Mosslemin, M. H.; Nateghi, M. R.; Mohebat, R. *Monatsh. Chem.* **2008**, *139*, 1247.

119. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Tetrahedron Lett.* **2008**, *49*, 5804.

120. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Chin. J. Chem.* **2009**, *27*, 821.

121. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Synth. Commun.* **2009**, *39*, 2560.

122. Tavakoli-Hoseini, N.; Heravi, M. M.; Bamoharram, F. F.; Davoodnia, A. *Bull. Korean Chem. Soc.* **2011**, *32*, 787.

123. Shafiee, M. R. M.; Moloudi, R.; Ghashang, M. *J. Chem. Res.* **2011**, *35*, 622.

124. Jaratjaroonphong, J.; Krajangsri, S.; Reutrakul, V. *Tetrahedron Lett.* **2012**, *53*, 2476.

125. Sato, F.; Ikobe, A.; Koizumi, T.; Katsuno, K; Kobayashi, Y. *Jpn. Kokai Tokkyo Koho* JP 09059233, **1997**.

126. Okano, H.; Motoyanagi, Y.; Cho, N.; Yoshinaga, T.; Tsuru, T.; Mukae, K. *Synthesis* **2004**, 341.

127. Tsuzuki, Y.; Chiba, K.; Mizuno, K.; Tomita, K.; Suzuki, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2989.

128. Carter, H. E.; Frank, R. L.; Johnston, H. W. *Org. Synth. Coll. Vol.* **1955**, *3*, 167.

129. Khosropour, A. R.; Khodaei, M. M.; Moghanian, H. *Synlett* **2005**, 955.

130. Sztojkov-Ivanov, A.; Tóth, D.; Szatmári, I.; Fülöp, F.; Péter, A. *Chirality* **2007**, *19*, 374.

131. Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1-83.

132. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

133. Diedrich, C. L. *Eur. J. Org. Chem.* **2008**, *10*, 1811.

134. Sanz, P.; Mó, O.; Yáñez, M.; Elguero, J. *J. Phys. Chem. A* **2007**, *111*, 3585.

135. Waibel, M.; Hasserodt, J. *Tetrahedron Lett.* **2009**, *50*, 2767.

136. Klod, S.; Kleinpeter, E. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1893.

137. Klod, S.; Koch, A.; Kleinpeter, E. *J. Chem. Soc., Perkin Trans. 2*, **2002**, 1506.

138. Kleinpeter, E.; Koch, A.; Seidl, P. R. *J. Phys. Chem. A* **2008**, *112*, 4989.

139. (a) Mohamadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.; (b) MacroModel, Schrödinger LLC, 2009. http://www.schrodinger.com/Products/ macromodel .html.

140. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*, 2004, Gaussian Inc., Wallingford CT.

141. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E. Jr.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.;

Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision A.02*, 2009, Gaussian, Inc., Wallingford CT.

142. Stephens, P. J.; Harada, N. *Chirality* **2010**, *22*, 229.
143. Flükiger, P.; Lüthi, H. P.; Portmann, S.; Weber, J. MOLEKEL 5.4., 2000-2002, Swiss Center for Scientific Computing, Manno, Switzerland.
144. Stewart, J. J. P. *Comp. Chem.* **1989**, *10*, 209.
145. Stewart, J. J. P. *Comp. Chem.* **1989**, *10*, 221.
146. Hehre, W. J.; Radom, L.; Schleyer P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory* Wiley, New York, **1986**.
147. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
148. SYBYL 7.3, Tripos Inc., 1699 South Hanley Rd. St. Louis, MO 63144, USA **2006**.
149. GaussView 2.0, Gaussian Inc. Carnegie Office Park, Building 6, Pittsburgh, PA 15106, USA.
150. Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

7. ANNEX