Diastereoselective synthesis of novel tetrahydroquinoline derivatives *via tert*-amino effect

Doctoral thesis

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List of abbreviations

ACN	Acetonitrile
Ac_2O	Acetic anhydride
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
2-BEA	2-Bromoethylamine
Boc	*tert*-Butyloxycarbonyl
Boc_2O	Di-*tert*-butyl dicarbonate
(-)-CSA	(-)-Camphorsulfonic acid
CuAOs	Copper-containing amine oxidases
DBFox	4,6-Dibenzofurandiyl-2,2'-bisoxazoline
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DEPTQ	Distortionless Enhancement by Polarisation Transfer with retention of Quaternaries
DMB	*N*,*N*-Dimethylbarbituric acid
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DSC	Differential Scanning Calorimetry
E	Electrophile
EtOAc	Ethyl acetate
EWG	Electron Withdrawing Group
$Gd(OTf)_3$	Gadolinium triflate
IC_{50}	Concentration causing 50% inhibition of a given activity *vs*. killing treated cells
ID	Indane-1,3-dione
LA	Lewis acid
NBS	*N*-Bromosuccinimide

MS	Molecular sieves
MW	Microwave
4-PBA	4-Phenylbutylamine
ORTEP	Oak Ridge Thermal Ellipsoid Plot
PCET	Proton-coupled electron transfer
rfx	reflux
TCE	1,1,2-Trichloroethane
TES	Triethylsilyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TFA	Trifluoroacetic acid
TPQ	2,4,5-Trihydroxyphenylalanine quinone
TPQ_{AMQ}	aminoquinol
TPQ_{ox}	oxidised
TPQ_{PSB}	product Schiff base
TPQ_{SSB}	substrate Schiff base
$Yb(tfc)_3$	Ytterbium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]

1. Introduction and literature review

The functionalization of nitrogen heterocycles plays an important role in drug research. This is clearly illustrated by the structures of several top emerging blockbusters as well as the best-selling drugs of 2013, all of which contain nitrogen heterocycles (Figure 1 and Figure 2) [1].

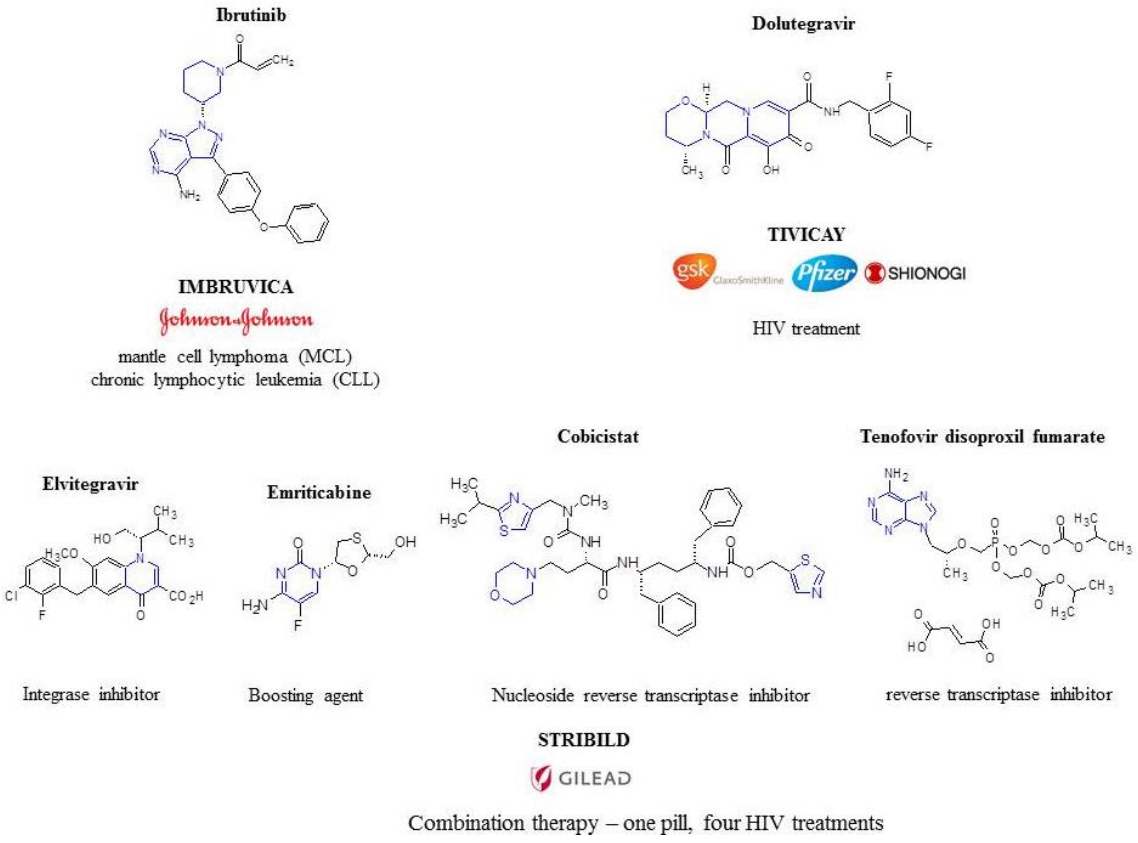


Figure 1: Top emerging blockbusters: drugs recently approved with $1 billion plus potential

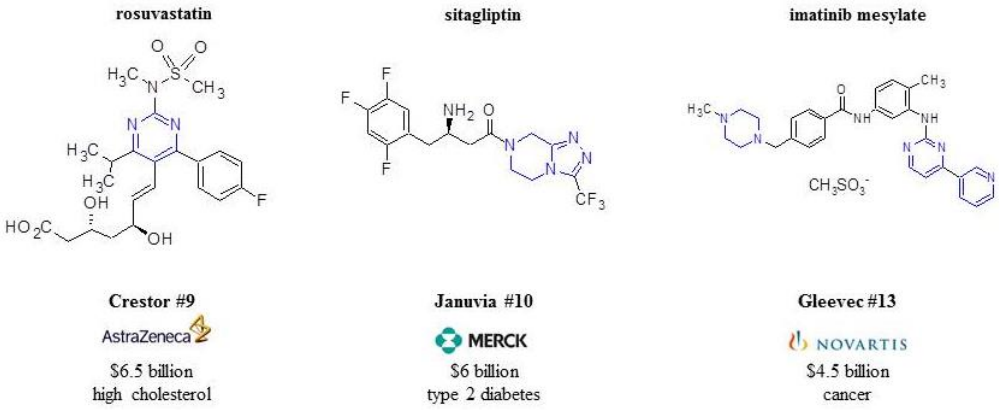


Figure 2: Top-selling drugs on the market in 2013

Several methods exist for the synthesis of heterocycles functionalized next to nitrogen. One of the most efficient way, beside many others, is the direct functionalization of sp^3 C-H bonds adjacent to nitrogen in heterocycles, including α-lithiation with alkyllithium/diamine complexes, α-amino radical formation, metal-catalyzed direct C-H activation, C-H oxidations and oxidative couplings and metal-catalyzed carbene insertions, respectively [2-4]. All of the previous methods require to use of external reagents and harsh conditions (Figure 3).

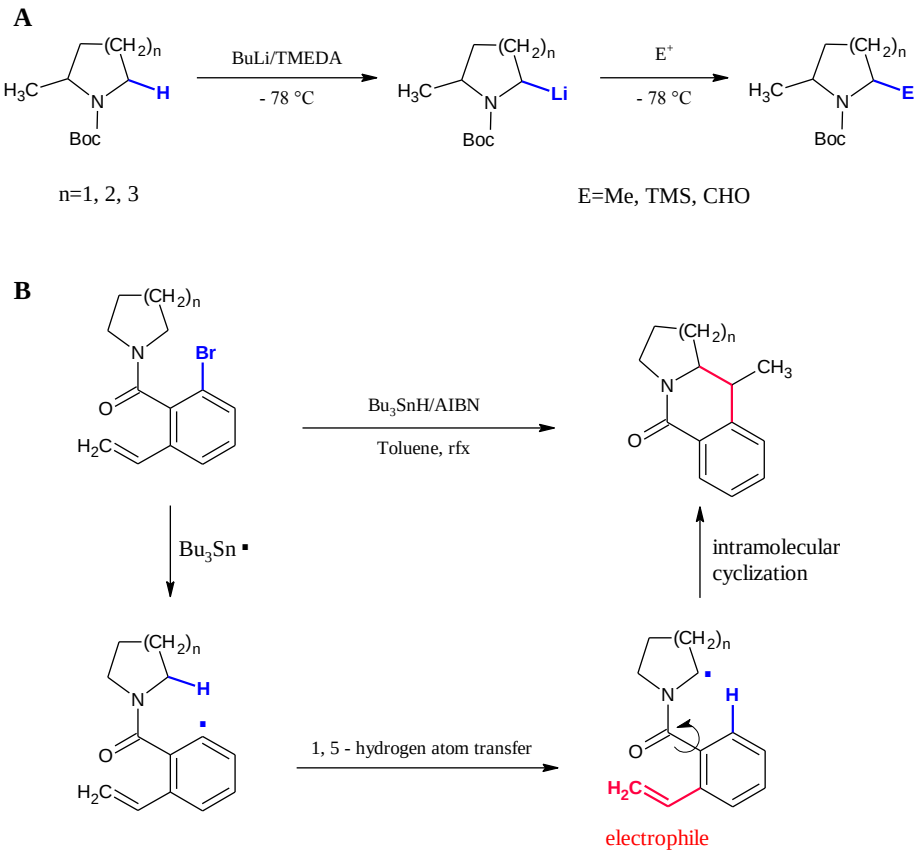


Figure 3: Functionalization of sp^3 C-H bonds adjacent to nitrogen: **A** α-lithiation/electrophile substitution, **B** radical-based C-H activation

The *tert*-amino effect is an internal redox process in the formation of nitrogen heterocycles with no other reagents required (Figure 4). The cyclization starts off with the cleavage of the migrating hydrogen (red H) from the α carbon atom of the secondary amino group, identical to sp^3 C-H bond activation *via* 1,5-H transfer, affording a dipolar chiral intermediate and a subsequent stereocenter-generating C-C bond formation ($R^1 = CH_3$, 4-$C_6H_4CH_3$; $R^2 = CH_3$, CH_2CH_3) [5]. Furthermore, the stereoselectivity of the *tert*-amino effect might provide information on the reaction mechanism.

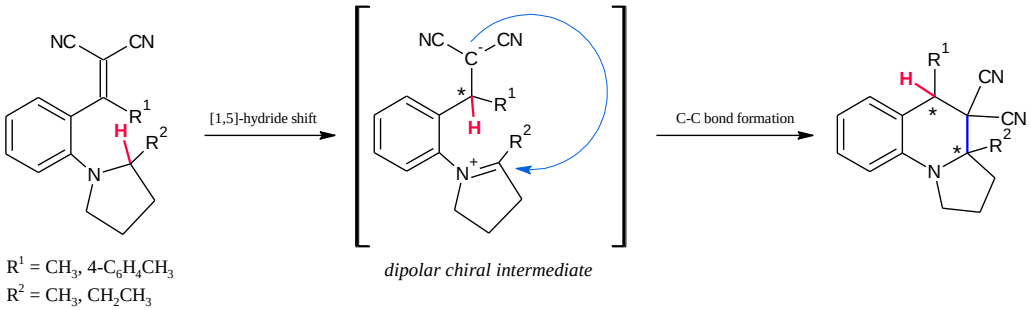


Figure 4: *tert*-Amino effect: formation of six-membered ring from type 2 reaction

1.1. The tert-amino effect

The *tert*-amino effect has been known for more than forty years as a ring closure method of the *ortho*-substituted *tert*-anilines. The term *tert*-amino effect was first used by Meth-Cohn and Suschitzky [6]. However the first *tert*-amino effect transformation was reported by Pinnow in 1895 [7]. During the experiment, an unexpected cyclization was observed, giving rise to the formation of the 1,2-dimethylbenzimidazole (**3**), instead of the desired product acetyl derivative of *o*-aminodimethylaniline (**2**) (Figure 5).

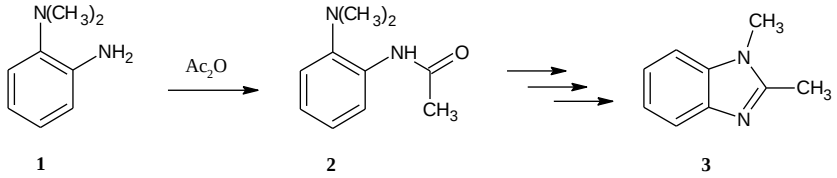
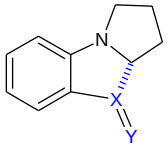


Figure 5: Unexpected cyclization in the course of the Pinnow-reaction

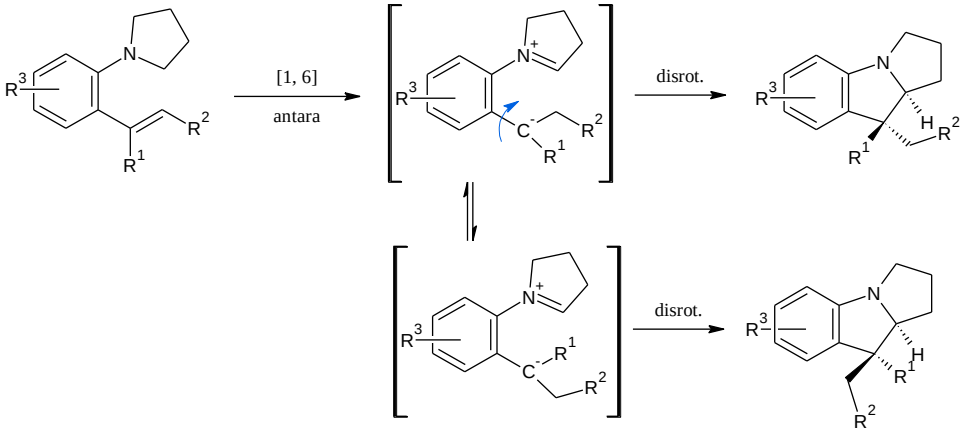
1.1.1. The types of the tert-amino effect

Seven types of the *tert*-amino effect have been distinguished so far, based on the ring size and the mode of its formation. Meth-Cohn summarized five types of the *tert*-amino effect in 1996 [8], and Quintela subsequently published two more types in 2003 [9]. The seven types of the *tert*-amino effect are displayed in Figure 6.

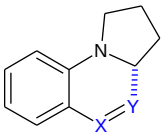
Type 1



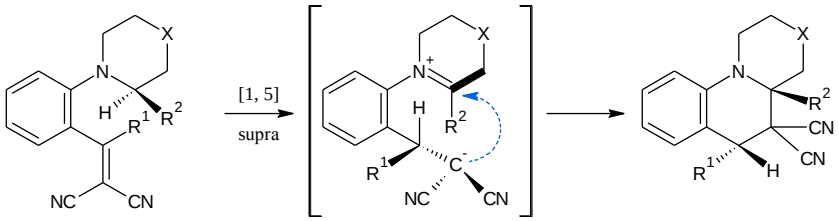
Example: X=Y is C=C



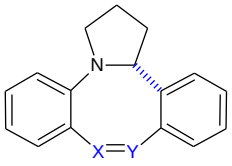
Type 2



Example: X=Y is C=C



Type 3



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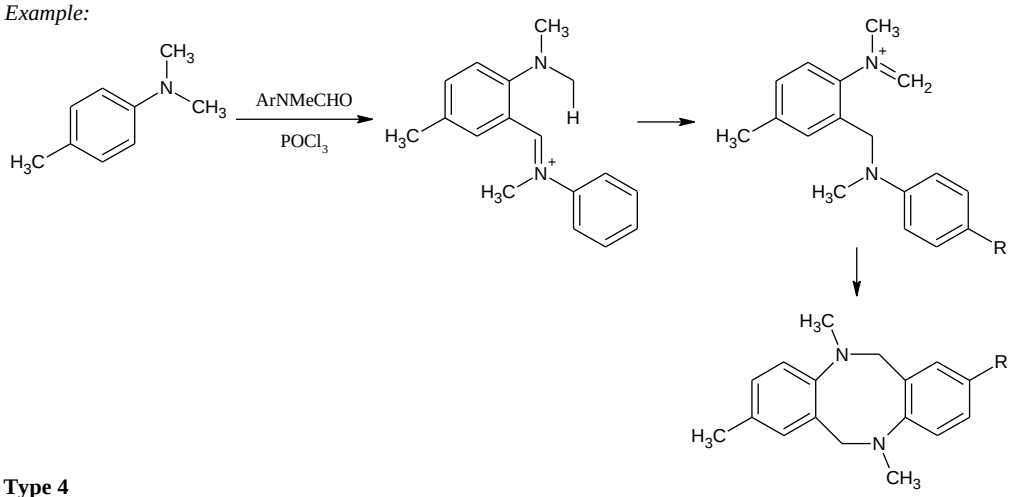
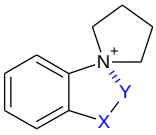


Type 4



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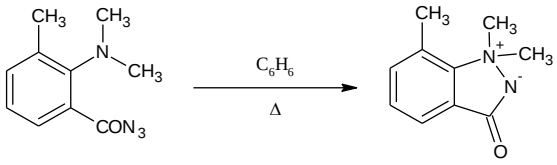
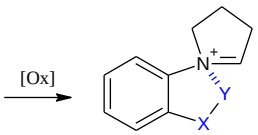


Type 5



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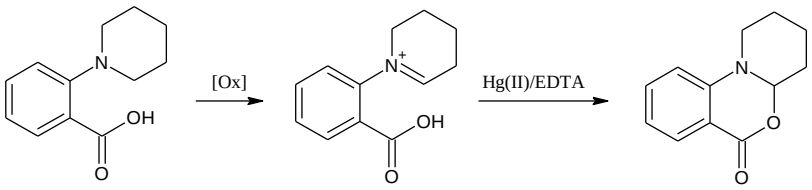


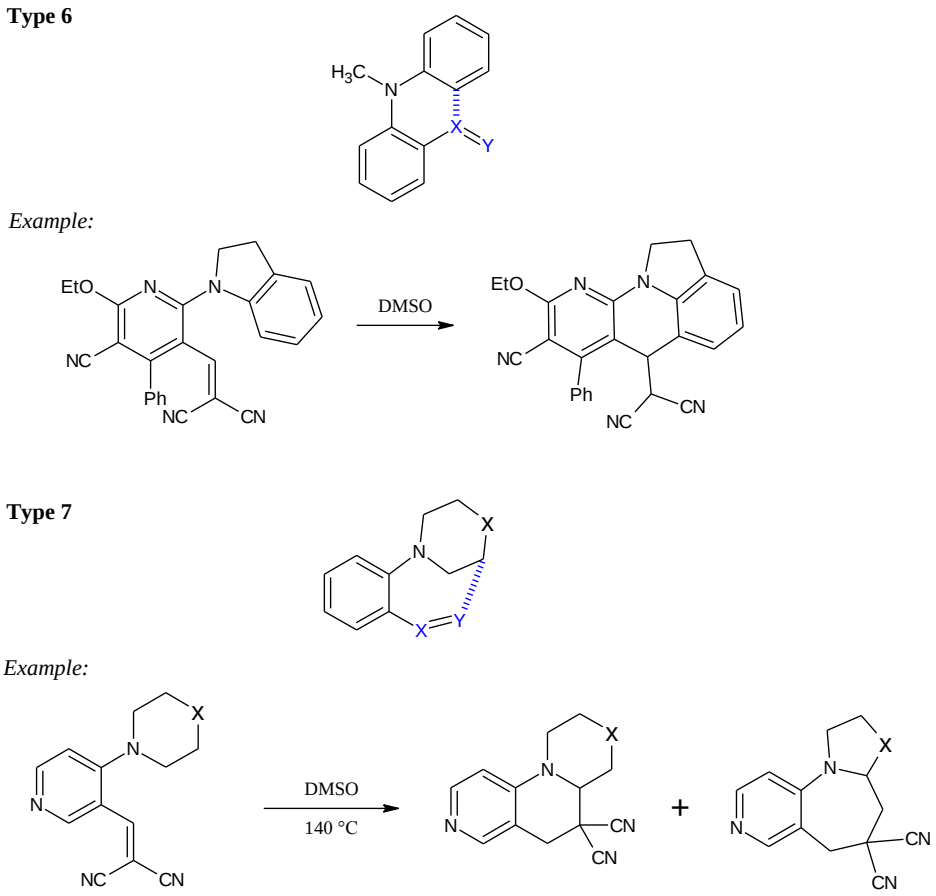
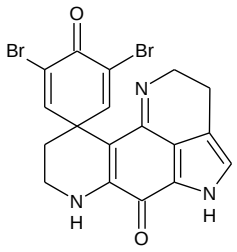


Figure 6: The seven types of the *tert*-amino effect with examples

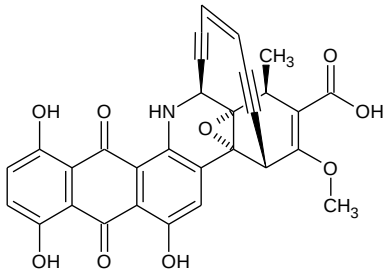
1.1.2. Application of the type 2 for the synthesis of tetrahydroquinolines

Tetrahydroquinolines have attracted attention due to their biological activities, some of them are presented in Figure 7 [10]. Beside pharmaceutical applications, tetrahydroquinoline derivatives have other widespread applications as well: pesticides [11], antioxidants [12], corrosion inhibitors, active components in various types of dyes [13], widely used in modern recording technologies [14], etc. According to the latest publications, remarkable biological effects of tetrahydroquinolines were described, such as anticancer activity and bromodomain inhibition [15, 16]. Furtheremore, treatment of arteriosclerotic diseases, hyperlipidemia, diabetes and insulin resistance were published as well [17, 18].

Natural products:

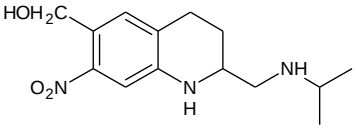


Discohabdin C
(sponge of Latrunculia du Bocage)
antitumor effect

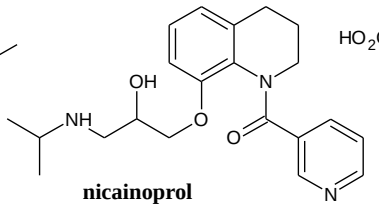


Dynemycin A
(bacteria Micromonospora chersina)
antitumor antibiotic

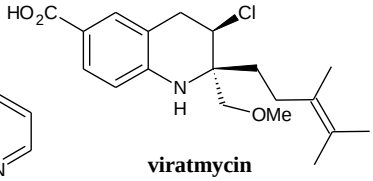
Pharmaceutical products:



oxamniquine
schistosomicide



nicainoprol
antiarrhythmic drug



viratmycin
antibiotic

Figure 7: Biologically active tetrahydroquinolines

One of the most plausible methods to synthesize a wide range of tetrahydroquinolines is the type 2 *tert*-amino effect. Several methods have been published from the 1980s, some of which are shown in Figure 8 (thermal isomerization [19], microwave acceleration[20, 21] and Lewis acid catalysis [22]).

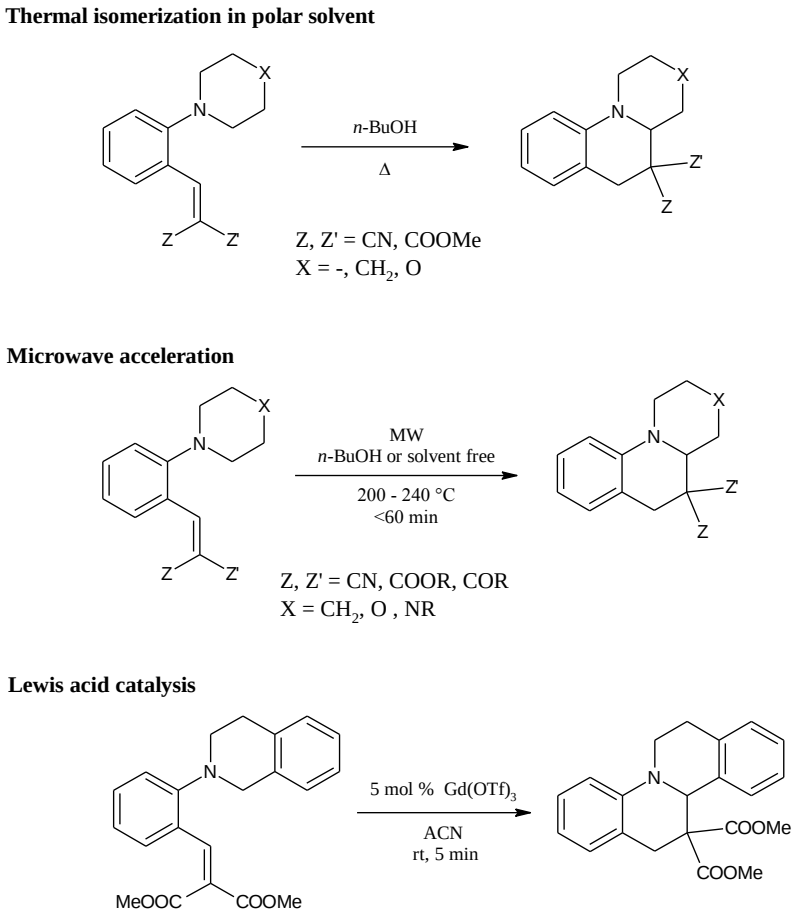


Figure 8: Synthesis of tetrahydroquinolines *via* the *tert*-amino effect

1.1.3. Stereo- and regiochemical aspects of type 2 reactions

Reinhoudt and co-workers thoroughly investigated the influence of the steric and electronic effects of various substituents on the regio-, enantio- and diastereoselectivity of the ring closure reaction of 2-vinyl-*N*,*N*-dialkylanilines [23-25] [5].

Because the diastereoselectivity aspects of *tert*-amino effect have been central to my investigations, the related literature is reviewed in-depth herein. Furthermore, in order to provide a more thorough summary of the mechanism of the *tert*-amino effect, regio- and enantioselectivity phenomena are analysed, as well.

1.1.3.1. Factors affecting the regioselectivity

The cyclization was carried out from compound **4** in refluxing *n*-BuOH to afford cyclized structures (**5-10**) [5], which were elucidated by ^{1}H NOE spectroscopy (Figure 9). In case of the cyclization of compounds **4b, e, f** (R^1 = H and R^2 = CH_3 or CH_2CH_3), compounds **5b, e, f** were formed exclusively. However, when R^2 = CH_2OCH_3 both regioisomers (**6c, g** and **7c, g**) were formed besides the formation of compounds **5c, g**. Similar results were obtained when R^1 = CH_3 (**6j, n**) or 4-$C_6H_4CH_3$ (**6p, q**), but the ratio of the regioisomers formed was not 1:1.

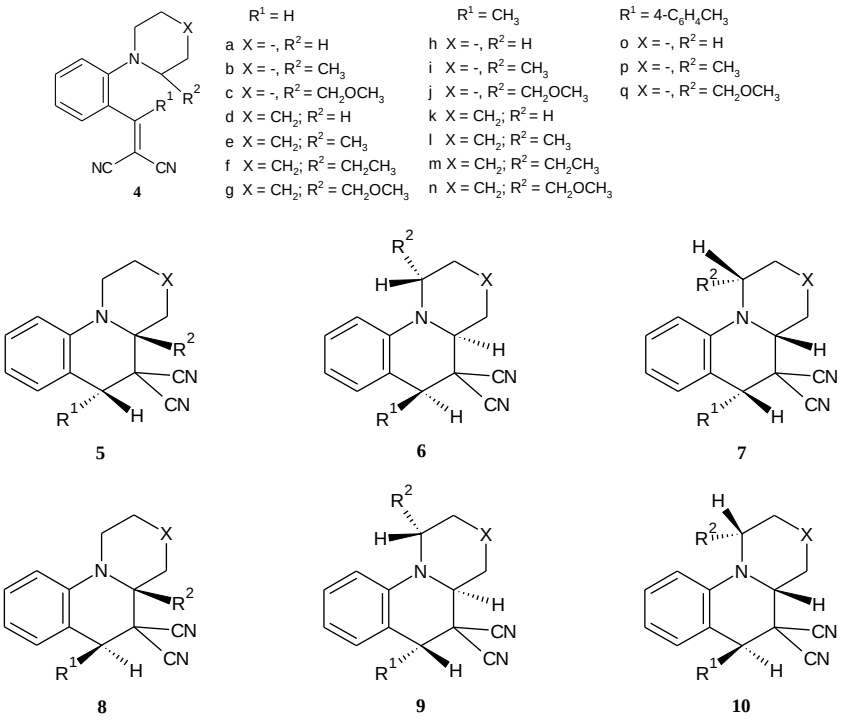


Figure 9: Vinyl compounds with various R^1 and R^2 substituents and their cyclized products

Table 1: Yields and reaction times of cyclizations

compound **4**	reaction time	yield % compound **5**	compound **6**	compound **7**
a	2 h	82	-	-
b	2 h	85	-	-
c	1.5 h	46	19	17
d	2 h	78	-	-
e	1.5 h	79	-	-
f	1.5 h	80	-	-
g	2.5 h	71	12.5	12.5
h	5 h	79	-	-
i	5 h	79	-	-
j	5 h	33	35	6
k	2 h	88	-	-
l	2 h	88	-	-
m	2.5 h	86	-	-
n	3 h	56	28	8
o	3 days	86	-	-
p	3 days	76	13	9
q	3 days	16	41	15

The formation of compound **5** took place predominantly or exclusively. This is due to a more effective stabilization of the tetrasubstituted iminium double bond in the dipolar intermediate over a trisubstituted double bond (Figure 10).

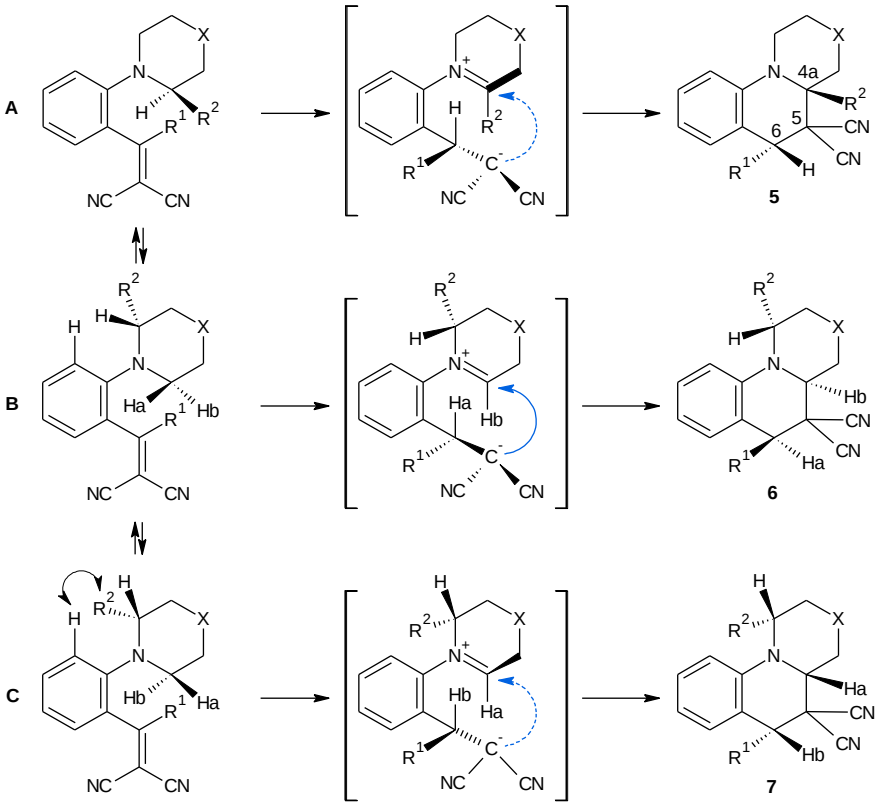


Figure 10: Formation of compounds **5**, **6**, **7**

Furthermore, the authors attributed the loss of regioselectivity to the sterical hindrance and inductive electron-withdrawing effect of the methoxymethyl group. If R^2 is a bulky substituent, the heterocyclic ring rotates along the C-N bond, with H_a and H_b acting as migrating hydrogens. The presence of oxygen destabilizes the iminium double bond in the dipolar intermediate, which serves the formation of the regioisomers, as well. Surprisingly, when R^2 was a methyl group, the formation of the regioisomers was still observed, explained by the presence of the bulky R^1 = 4-$C_6H_4CH_3$ (**4p**).

The ratio of the two regioisomers (compounds **6** and **7**) depends on the size of the R^1 substituent. Bulkier methyl group allows a more intensive rotation from the plane of the aromatic ring than R^1 = H. Hence, the ring closure reaction (compound **6**) is more preferred starting from conformer **B**, because of the steric hindrance between the methoxymethyl group and the aromatic hydrogen in conformer **C** (Figure 10). When R^1 = 4-$C_6H_4CH_3$, the heterocyclic ring rotates much further from the plane of the aromatic ring, thus the steric hindrance between the methoxymethyl group and the aromatic

hydrogen prevails less (Table 1). Because of the bulky 4-methylphenyl group, the molecule rotates along the phenyl and vinyl bonds affording diastereomers. The results of these reactions are discussed further in the 2.1.3.2. Chapter.

The authors concluded that the regioselectivity depends on the size of the R^1 and R^2 substituents, as well as on the electronic effect of R^2.

1.1.3.2. Factors affecting the enantio- and diastereoselectivity

Regarding the diastereoselectivity, Reinhoudt and co-workers have published the following results starting from the racemic vinyl compound: i) if the migrating hydrogen and the hydrogen in the annulation are at the same face of the molecule only for $R^1 = CH_3$ and R^2 = H, CH_3, CH_2CH_3 or CH_2OCH_3 (compound **5**). ii) When R^1 = 4-$C_6H_4CH_3$ the diastereomers are formed, as well (compound **8** in addition to compound **5**, Figure 12).

The mechanism of the formation of the *cis* isomers (the relative configuration of the substituent at the bridgehead carbon atom and at the benzylic position) is displayed in Figure 10. When H_a or H_b is a migrating hydrogen, the ring closed products (compound **6** and **7**) are enantiomers regarding the C-6 and C-4a positions, whilst compound **5** is represented as an enantiomer. Therefore it is concluded that the carbanion is added to the iminium double bond in the dipolar intermediates from the direction of the original location of the hydrogen atom.

The authors ascribe the formation of the diastereomers to the rotation of the vinyl moiety, which is influenced by the size of the substituent on the α-carbon atom of the vinyl moiety. Furthermore, the X-ray analysis of the vinyl compound [24] showed that the β-carbon atom of the vinyl moiety is pointed away from the heterocyclic ring (Figure 11). Important for the hydrogen shift to take place is the proximity of the migrating hydrogen of the α-carbon atom of *sec* amino group to the α-carbon atom of the vinyl moiety. When the migrating hydrogen atom (H_a or H_b) is attached to the carbon atom, it takes place from the conformer in which the β-carbon atom of the vinyl moiety is below the plane of the aromatic ring. It seems likely that the hydrogen migration takes place suprafacially.

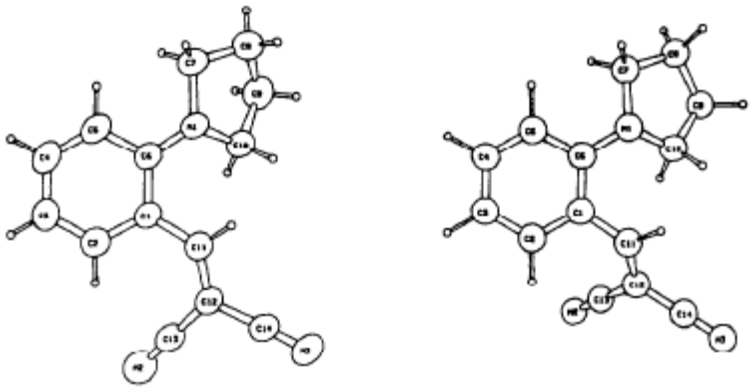


Figure 11: ORTEP drawings of the crystal structure (the left) and the calculated structure (the right) of the compound **4a**

However, the cyclization of the compound when R^1 is a 4-methylphenyl group gives rise to compounds **8-10** in addition to compounds **5-7**, which have the opposite configuration at C-5 (Figure 12). They explain this result by assuming that there is an interchange of the position of the vinyl group, because of the steric hindrance caused by the substituent R^1 at the α-position of the amine ring. In this situation, hydrogen migration leads to the formation of an intermediate with a new asymmetric center that has the opposite configuration compared with the previous intermediates (Figure 10).

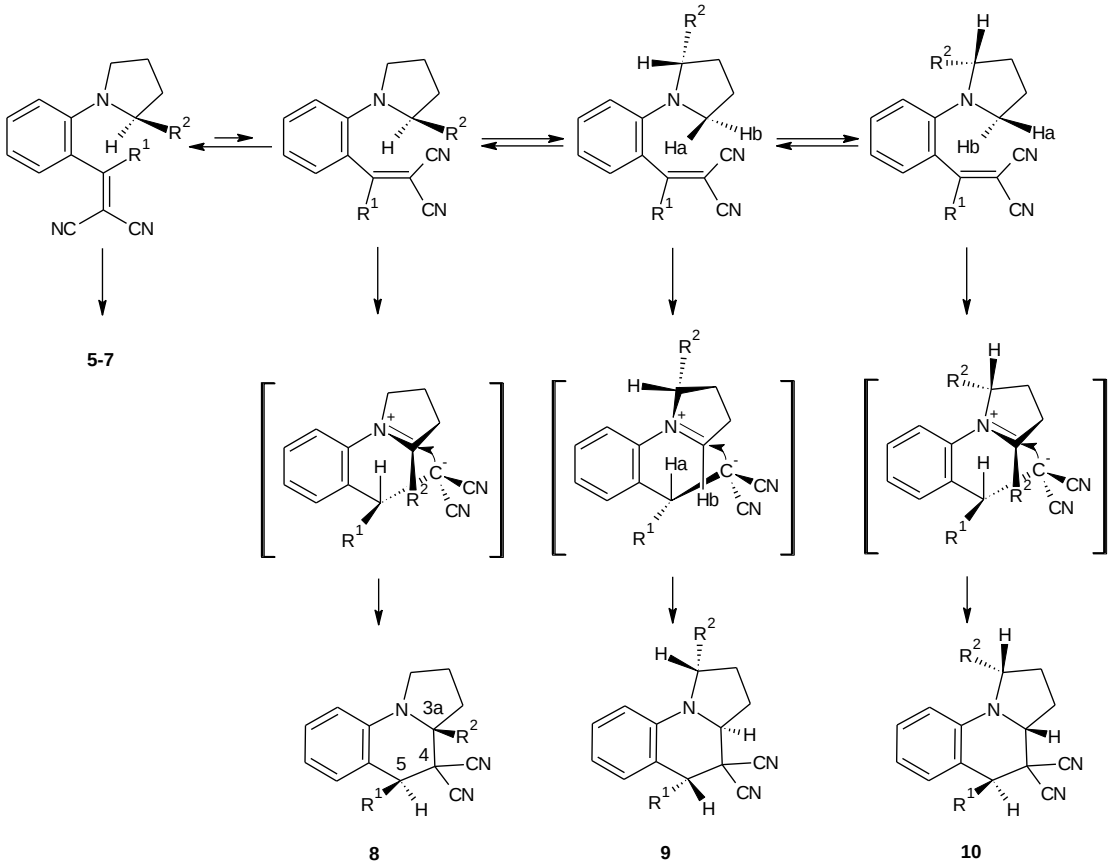


Figure 12: Formation of compounds **8-10**

They concluded that the size of the substituent R^1 determines the relative configuration of the substituent at the bridgehead carbon atom and at the benzylic position in the product because it directs the position of the vinyl moiety in the starting material.

The ratio of compounds **6p**, **q** and **7p**, **q** is determined by the sterical hindrance between the R^2 substituent and aromatic hydrogen, as well. The difference among the previous results (when $R^1 = CH_3$) and these results is that the ratio of the regioisomers is lesser. They provided the explanation that the more bulky 4-methylphenyl group turns much more easily over the heterocyclic ring from the plane of the aromatic ring, thus this position is more favorable for the formation of compounds **7p**, **q**, than the formation of compounds **7j**, **n** (Table 1).

1.1.3.3. Proposed mechanism based on the stereochemical results

In order to gain more understanding of the mechanism of the *tert*-amino effect, Reinhoudt and co-workers carried out the ring closure reaction from the pure enantiomer [25], as well. During the reaction, the formation and the alteration of the new and the preexistent stereogenic centers can provide a more extensive explanation for the mechanism.

Ring closure of the S configuration of the vinyl compound ($R^1 = CH_3$ and $R^2 = CH_2OCH_3$) resulted in the formation of compound **5j, 6j, 7j** [23] (Figure 13). In addition to the required product (**5j**) the two regioisomers are formed, as well, because of the steric and electronic effect of the methoxymethyl group. The compound **5j** was obtained as one enantiomer. ^{1}H NMR spectroscopy of compound **5j** in the presence of the chiral shift reagent ($Yb(tfc)_3$), proved an enantiomeric excess of >98%.

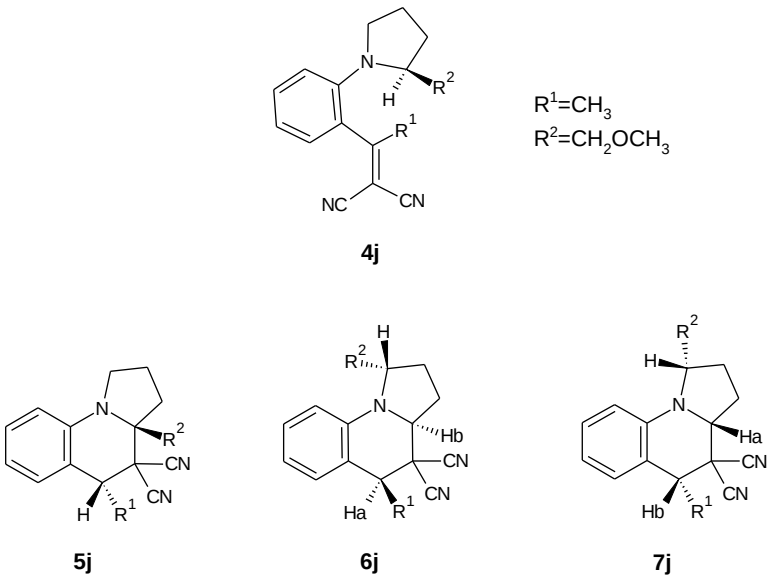


Figure 13: Chiral vinyl compound with S configuration and its ring closed products

In order to determine the absolute configuration of compound **5j**, it was brominated with NBS. X-ray analysis showed that the methoxymethyl group at the bridgehead carbon atom and the methyl group at the new chiral center are in the *trans* position (Figure 14).

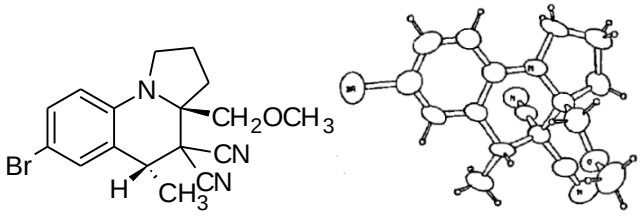


Figure 14: Crystal structure of the brominated compound

From these results the authors have given the following explanations: i) the 1,5-hydrogen shift proceeds enantioselectively; ii) the cyclization takes place with the retention of the configuration in the chiral center; iii) in the dipolar intermediate the carbanion is forced to add to the iminium double bound from below, namely from the *α*-position, because the *β*-position is shielded by the methoxymethyl group. In other words, the carbanion adds to the iminium double bond from the same face of the molecule where the migrating hydrogen originally was located. iv) The original chiral center was memorized in the form of a „unique chiral anticlockwise helical dipolar intermediate".

The authors completed the above results with further investigations. They have assumed that the thermal isomerization proceeds *via* a concerted suprafacial 1,5-hydrogen shift followed by subsequent cyclization, which explains the discrete chirality in the product molecule and the primary isotope effect and solvent effect are supporting this [24]. In order to justify that the hydrogen atom migrates in the rate-determining step, some papers have been presented the investigation of the reaction with deuterated derivatives [24, 26, 27]. The group of Reinhoudt determined the deuterium kinetic isotope effect (3.0±0.3 at 91.5 °C in DMSO-d_6) of the reaction, after the synthesis of the tetradeuterated vinyl compound (Figure 15). According to the ^{1}H-NMR and mass spectra of the ring closed compound it was clear that during the cyclization of deuterated vinyl compound there was no deuterium lost. Furtheremore, they mentioned too that the hydrogen transfer could be an intramolecular variant of a Meerwein-Ponndorf-Verley reaction.

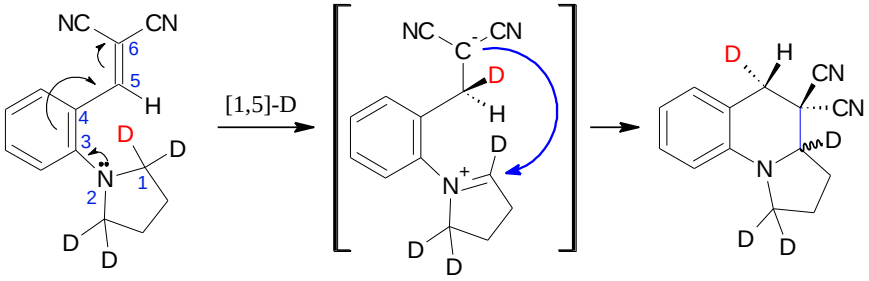


Figure 15: Deuterium migration in the rate-determining step

Further investigation of the stereochemical outcome of *tert*-amino effect was published in 1991 by Kelderman *et al.* [28]. They studied the Lewis-acid-catalyzed ($ZnCl_2$) cycloreversion of cyclic dicyano and ethyl ester cyano derivatives (Figure 16). From the results they concluded that 1) in the case of $R^1 = CH_3$ and R^2 = H, CH_3 after cycloreversion, interconversion of helical dipolar intermediate takes place with epimerization at C(3a) upon subsequent cyclization; 2) the stereochemistry at C(5) is retained after cycloreversion and cyclization, therefore the 1,5 hydrogen shift is irreversible; 3) the epimerization at C(3a) is influenced by the difference between the steric energy of the *cis* and *trans* diastereomers.

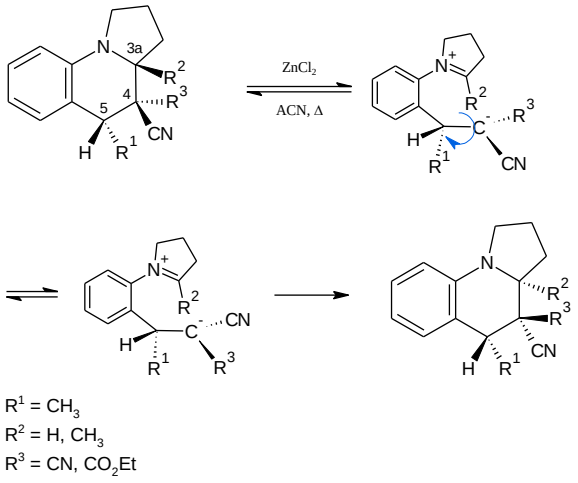


Figure 16: Epimerization at C(3a) upon subsequent cyclization

In summary, regarding the mechanism of the type 2 *tert*-amino effect we can conclude that the 1,5-hydrogen migration takes place irreversible with suprafacially manner following by subsequent cyclization with configuration retention. The hydrogen

transfer is the rate-determining step, which enable to formation of chiral helical dipolar intermediate. The negative end of this intermediate is forced to add to the positive end of this molecule to affording ring closed product with a discrete stereochemistry.

1.2. Application of the tert-amino effect for the synthesis of medium-sized rings

In our extensive studies on the new extension of the *tert*-amino effect to biaryls and fused bicyclic systems, incorporating the interacting amino and vinyl groups in the two *ortho* or *ortho* and *peri* positions, respectively, have been developed to provide easy accesses to medium or macrocyclic rings [29-31] (Figure 17).

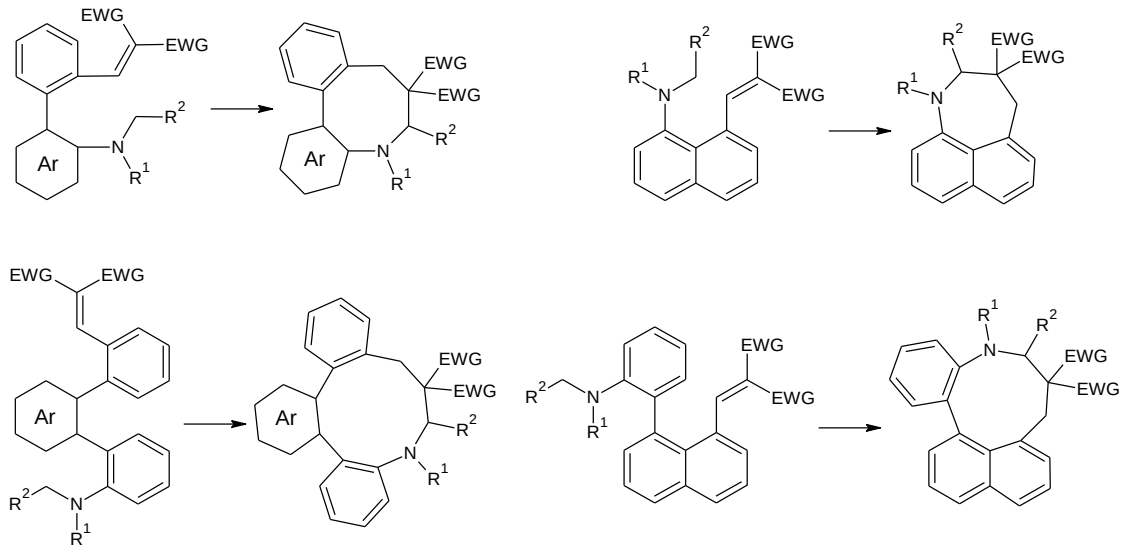


Figure 17: Synthesis of medium and macrocyclic ring systems *via* the *tert*-amino effect

Polonka-Bálint *et al.* investigated extensions of *tert*-amino effect to *ortho,ortho'*-fuctionalized biphenyl or phenylpyridazine derivatives [29]. They proposed to synthesize three types of vinyl derivatives (**11**), one with malononitrile and two other with indane-1,3-dione (ID) and *N*,*N*-dimethylbarbituric acid (DMB), respectively (Figure 18).

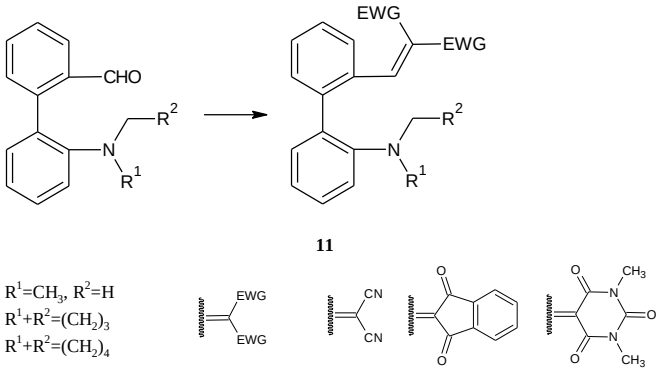


Figure 18: Synthesis of 2-(2-vinylphenyl)-*tert*-aniline derivatives

Surprisingly, the Knoevenagel condensation of biphenyl carbaldehydes with ID and DMB in ethanol at room temperature furnished an unexpected phenantridinium product (**12**) (Figure 19), except in the case of $R^1+R^2 = (CH_2)_4$ with ID, which allowed the isolation of the expected vinyl compound (**11**). The formation of the phenantridinium compound can be explained by a ring closure between the positively polarized carbon of the vinyl group formed in the condensation reaction and the *tert*-amino nitrogen *via* a new type of *tert*-amino effect. The biphenylvinyl carbaldehyde condensed product with malononitrile as well as the phenantridinium derivatives could be isomerized (in DMSO at 110 °C or 160 °C under argon) to dibenzazocines (**13**) *via* another type of the *tert*-amino effect, namely antarafacial [1,7]-hydrogen shift.

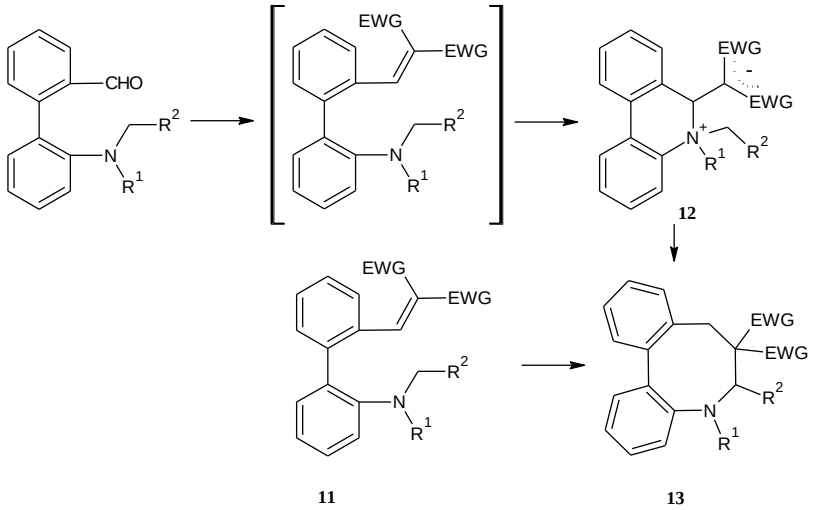


Figure 19: Formation of the phenantridinium compound (**12**) and the dibenzazocine (**13**)

Földi *et al*. studied the extensions of the *tert*-amino effect to 1-dialkylamino- and 1-(2-dialkylaminophenyl)-8-vinylnaphthalenes (compound **15** and **16**), respectively, to form *ortho*- and *peri*-fused naphthazepine (**17**) and naphthazonine (**18**) ring systems [32] (Figure 20).

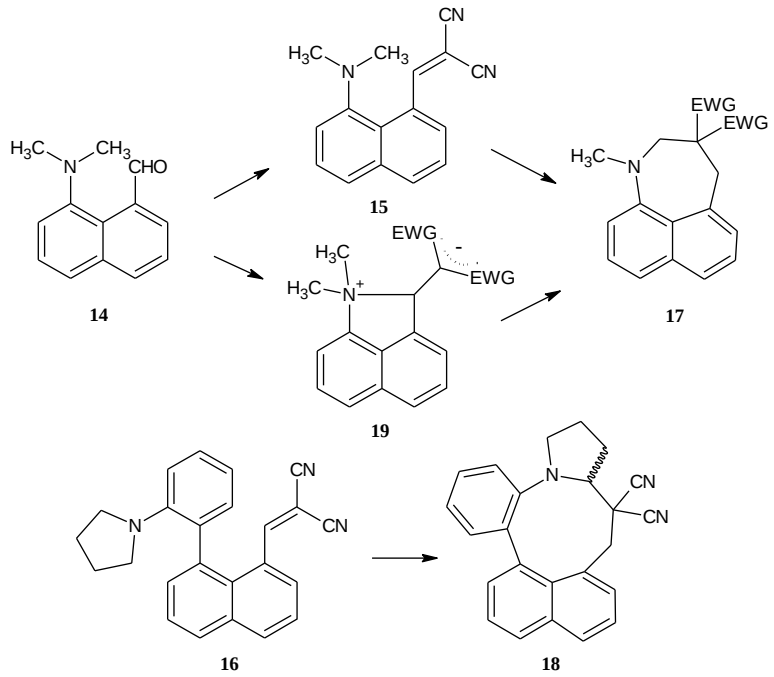


Figure 20: Formation of benzo[*c,d*]indolium (**19**), azepine (**17**) and azonine (**18**) ring systems

The Knoevenagel condensation of 8-dimethylaminonaphthalene-1-carbaldehyde (**14**) with malononitrile in ethanol at room temperature resulted the expected vinyl compound. However, treatment of carbaldehyde with ID and DMB led to zwitterionic benzo[*c,d*]indolium derivatives (**19**) *via* the *tert*-amino effect. From vinyl derivative (**15**), only the azepine (**17**) could be isolated in a good yield. The reactions were carried out in DMSO and solvent free condition at different temperatures with traditional and microwave heating. Transformation of zwitterionic compounds to azepines, could also be rationalized.

Dunkel *et al.* opened a new route to the formation of macrocycles *via* the *tert*-amino effect, to synthesize novel fused azecine ring systems by the microwave-assisted thermal isomerization of terphenyl (**20**) or biphenyl-pyridazine (**21**) compounds [31] (Figure 21).

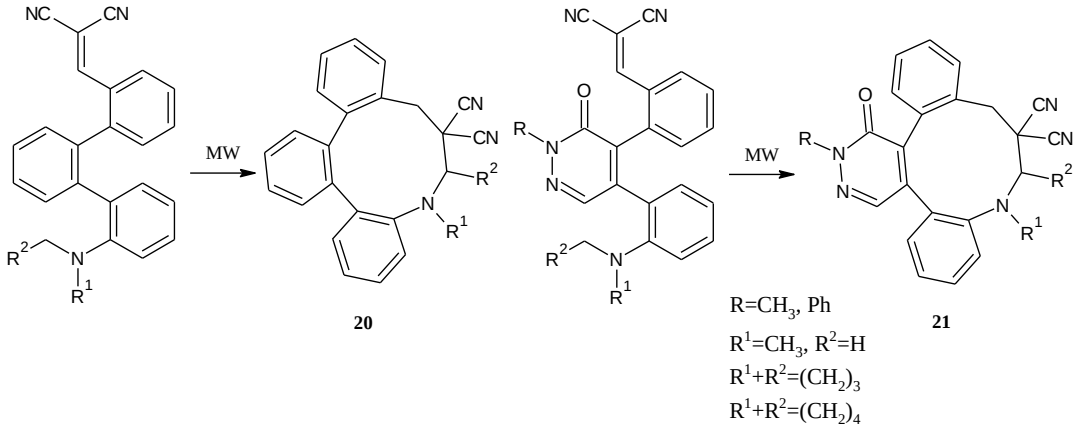


Figure 21: Extension of *tert*-amino effect to triphenyl compounds and their pyridazinone analogues

The formation of the azecine ring could be explained by two consecutive reactions: i) the rate-limiting step involving [1,9]-hydrogen shift, resulting a dipolar intermediate, and ii) intramolecular C-C bond formation between the oppositely charged carbons.

Previously, Meth-Cohn and co-workers published the synthesis of dibenzo[*b*,*f*][1,5]diazocines *via* type 3 of the *tert*-amino effect [33-36]. The interaction of *para*-substituted *tert*-aniline (**22**) with *N*-formyl-*N*-substituted arylamides in $POCl_3$ gives dibenzo[1,5]diazocines (**24**) (Figure 22).

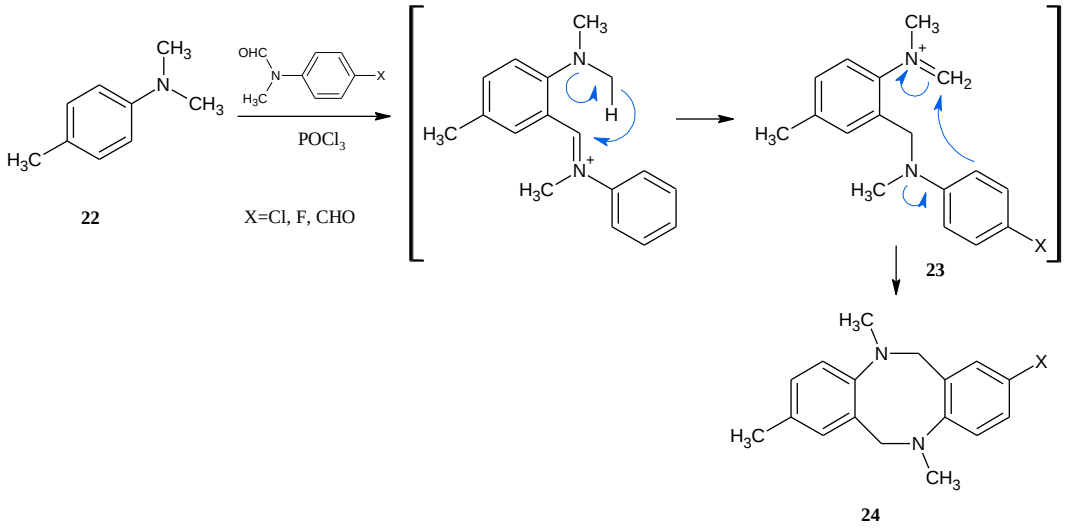
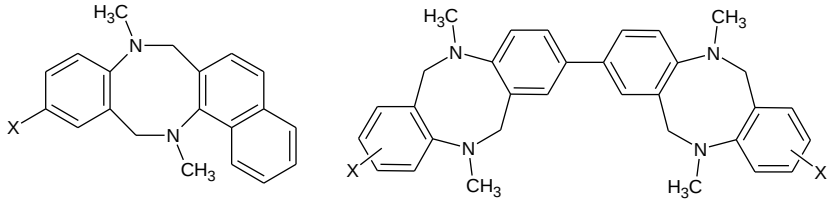


Figure 22: Synthesis of dibenzo[1,5]diazocines (**24**) *via* type 3 of the *tert*-amino effect

The reaction pathway could be rationalized by Vilsmeier formylation *ortho* to the dimethylamino group followed by [1,5]-hydrogen migration resulting new iminium ion (**23**). Subsequently, the C-C bond formation takes place between the iminium ion and the aromatic ring, affording diazocine derivatives.

The authors extended this methodology to the synthesis of benzo[*b*]naphtha[*1,2-f*][1,5]diazocines (**25**), as tetracyclic heterocycles and bis-dibenzo[*b,f*][1,5]diazocines (**26**), which could be novel macrocycles with flexible ring system [36, 37] (Figure 23).

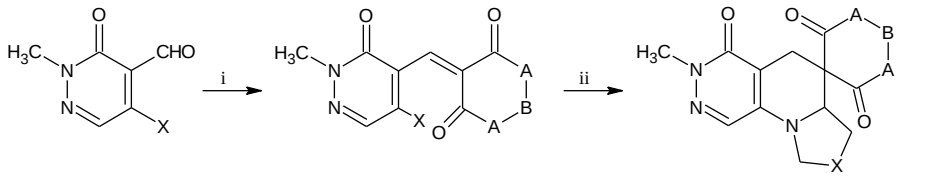


25 X = F, Cl, Br, CH_3, OCH_3 **26**

Figure 23: Formation of macrocyclic ring systems using Vilsmeier reagent *via tert*-amino effect

1.3. Synthesis of spirocyclic ring system *via* the *tert*-amino effect

The group of Mátyus has revealed that the incorporation of the terminal vinylic carbon into a trioxopyrimidine ring of an *ortho*-vinyl-*tert*-aniline (**27**) accelerates the cyclization to the resulting spiro-substituted pyrido-fused diazines (**28**) (Figure 24) [26, 27, 38].



X = morpholino, pyrrolidino

27a: A = NCH_3, B = C=O
27b: A = O, B = $C(CH_3)_2$

28a: A = NCH_3, B = C=O, X = CH_2
28b: A = O, B = $C(CH_3)_2$, X = CH_2O

Figure 24: *Reagents and conditions*: i) DMB or Meldrum's acid, toluene, AcOH, piperidine, r.t., 45 min or DMB, EtOH; ii) xylene, $AlCl_3$, 150 °C, 8 h.

The Knoevenagel condensation was performed with DMB or Meldrum's acid. Surprisingly easy transformation of the vinyl compounds affords the corresponding tetrahydropyridines with spirocyclic substituents. For the cyclization of dicyanovinyl derivatives longer reaction times were required (Figure 25).

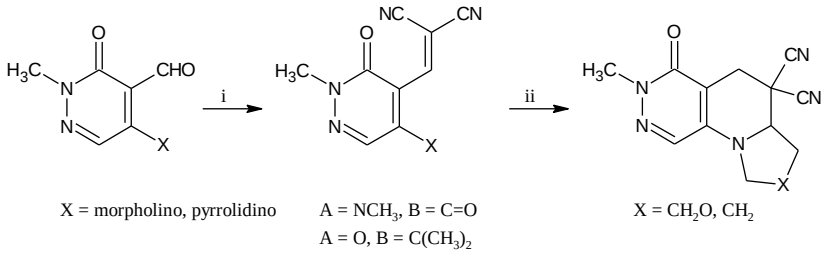


Figure 25: *Reagents and conditions*: i) $CH_2(CN)_2$, EtOH, r.t.; ii) DMSO, 150 °C, 44 h for morpholino derivative and 39 h for pyrrolidino derivative.

The increased reactivity of the vinyl compounds substituted with DMB or Meldrum's acid was interpreted by Mátyus and his group as follows. I) The crystal structure of the vinyl compound (**27a**) showed that the NCH_2 group and the vinylic moiety are in a favorable position for the reaction. The distances between the migrating hydrogen and the acceptor carbon atom, as well as between the carbon atoms participating in the ring formation are well below the sums of their van der Waals radii (2.626 Å and 3.057 Å, respectively) (Figure 26). II) The electronic interaction between the lone pair of the *tert*-amino nitrogen and an unfilled orbital of the vinyl moiety, facilitated by an electron-withdrawing substituent on the vinyl group, might also increase the rate of the cyclization.

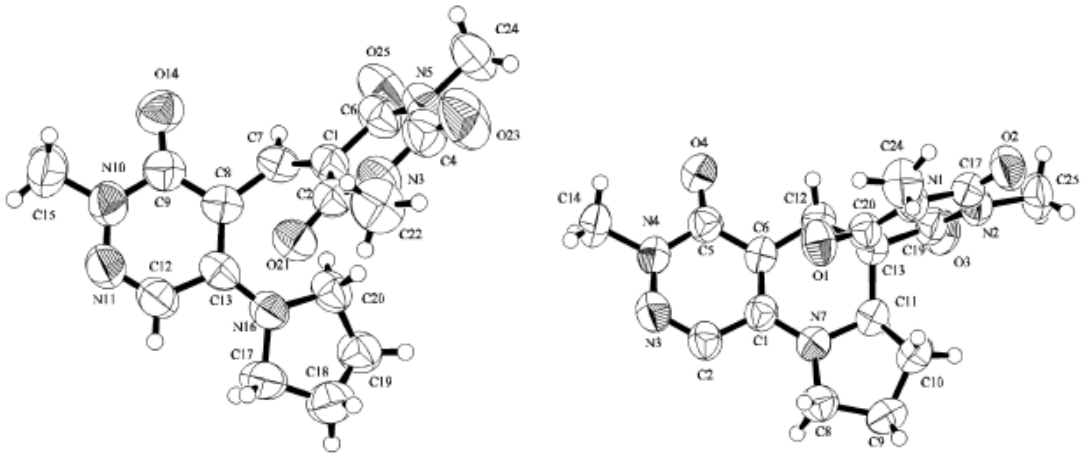


Figure 26: ORTEP plots of vinyl (**27a**) (the left) and ring closed (**28a**) (the right) product with crystallographic numbering Figure

The reactions of *tert*-anilines substituted with DMB were studied to compare with cyclization of pyridazine derivatives. In the former case, the thermal isomerization was performed under milder conditions (Figure 27).

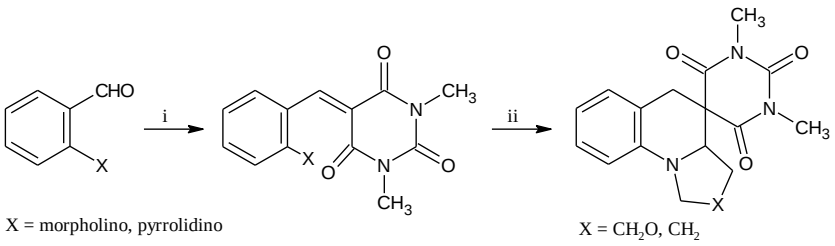


Figure 27: *Reagents and conditions*: i) DMB, EtOH, r.t., 15 min for morpholine derivative, 10 min for pyrrolidine derivative; ii) toluene, $AlCl_3$, 70 °C, 3 h for morpholine derivative, the vinyl compound substituted with pyrrolidino group could not be isolated in pure from since ring closed product was also formed.

Interestingly, PNU-286607, a compound displaying structural similarity, exerts an antibacterial activity due to its DNA gyrase inhibitory effect (Figure 28) [39, 40]. The synthesis of the active enantiomer of PNU-286607 by asymmetric cyclization of alkylidene barbiturate using the *tert*-amino effect was performed by Ruble *et al*. [41].

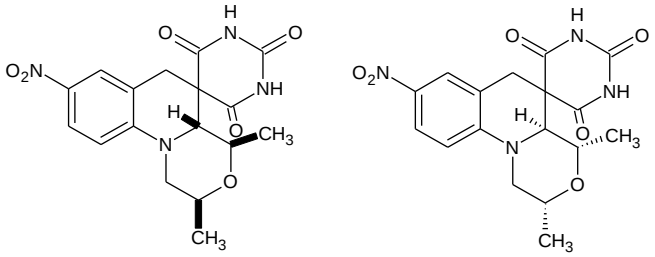


Figure 28: Structure of PNU-286607 (±) and its active enantiomer (-)

The synthetic advantages provided by the *tert*-amino effect are widely employed for the synthesis of structurally related spiro compounds with an antibacterial potential, e.g. benzisoxazole (**29**) and tetrahydronaphthyridine (**30**) derivatives (Figure 29) [42, 43].

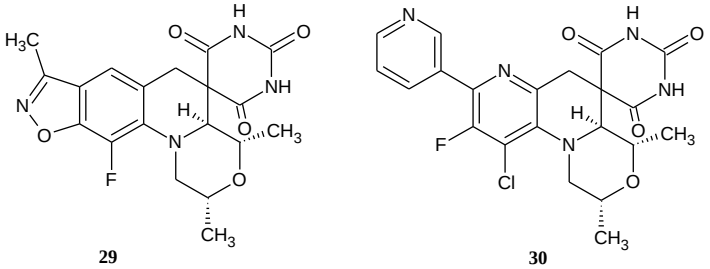


Figure 29: Biologically active benzisoxazole (**29**) and tetrahydronaphthyridine derivatives (**30**)

Other research groups have also studied the stereodirection of *tert*-amino effect in the course of the synthesis of spiroheterocyclic systems. Krasnov *et al*. have shown by X-ray diffraction analysis that the diastereoselectivity of the *tert*-amino effect can be related to the structure of the Knoevenagel products whose conformations are stabilized by the strong intramolecular C-H···π interaction [44, 45]. The group of Morzherin has provided further demonstration of the stereoselective synthesis of spiro-joined fused quinolines in several papers [46-48].

1.4. Microwave-assisted cyclizations *via* the *tert*-amino effect

Kaval *et al*. have studied the cyclization of two series of vinylpiridazines (**27, 31**) and one series of vinylbenzenes (**4** and **32**) by application of microwave irradiation (Figure 30) [20].

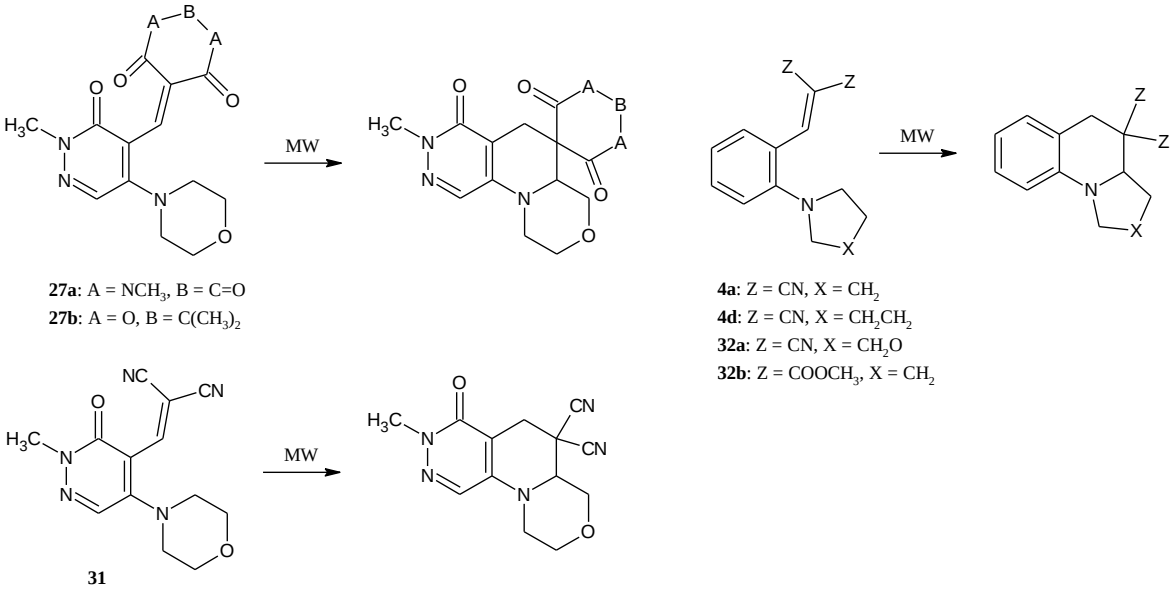


Figure: 30: Microwave-assisted cyclization of vinylpiridazine (**27, 31**) and vinylbenzene (**4**, **32**) derivatives *via tert*-amino effect

They systematically compared the results of the ring closure reactions using the traditional heating method and microwave irradiation. In the latter case, the reaction times significantly decreased, while the yields obtained were similar or even better (Table 2).

Table 2: Traditional heating method *vs.* the microwave irradiation

Compound	Method of activation	Solvent	Temp. (°C)	Time	Yield (%)
4a	Δ	*n*-BuOH	117	2 h	82
	MW	*n*-BuOH	200	3 min	84
4d	Δ	*n*-BuOH	117	2 h	78
	MW	*n*-BuOH	200	3 min	80
32a	Δ	*n*-BuOH	117	35 h	84
	MW	*n*-BuOH	220	30 min	96
32b	Δ	*n*-BuOH	117	22 h	67
	MW	*n*-BuOH	220	15 min	73
31	Δ	DMSO	150	44 h	35
	MW	DMSO	210	42 min	29
27a	Δ	Xylene	138	2 h	45
	MW	*n*-BuOH	230	5 min	63
27b	Δ	DMF	100	5 h	79
	MW	DMF	200	30 min	73

Moreover, the authors applied an environmentally safe and economic way for the synthesis of tetrahydroquinolines: the Knoevenagel condensation was performed in water at 100 °C for 10 minutes, then catalytic amount of TFA was added to the mixture continued the reaction at 200 °C for 3 minutes, affording the cyclized product in an overall yield of 50%.

Kaval *et al.* investigated the cyclization under microwave-assisted solvent-free conditions as well, in order to develop enviromentally safe protocols [21]. The results of the conventional heating and the microwave method are listed in Table 3. The authors

proved that the use of the solvent-free method for the cyclization reaction *via* the *tert*-amino effect is effective in improving the yields and purities of the products.

Table 3: Solvent-free thermal *vs.* microwave cyclization

Compound	Method of activation	Temp (°C)	Time (min)	Yield (%)
4d	Δ	150	5	99
	MW	150	5	99
32a	Δ	180	22	94
	Δ	180	5	<2
	MW	180	22	94
	MW	180	5	58
32b	Δ	170	17	87
	MW	170	17	86
31	Δ	200	18	57
	Δ	200	20	78
	MW	200	18	75
	MW	200	20	67
27a	Δ	210	1	97
	MW	210	1	96
27b	Δ	216	1	0
	Δ	175	7	31
	MW	216	1	0
	MW	175	7	55

Dunkel *et al*. have investigated novel fused azecine ring systems, synthesised *via* microwave-assisted thermal isomerization of terphenyl or biphenyl-pyridazine compounds through the application of a new extension of the *tert*-amino effect (Figure 21) [31]. They observed that the solution phase experiment, performed in DMSO, was more productive than the solvent-free method regarding the conversion and the rate of decomposition.

The latest example of performing microwave-assisted synthesis making use of the *tert*-amino effect was reported by Platonova *et al*. [49]. They showed that the reaction of 2-dialkylaminobenzaldehydes with cyanothioacetamide led to Knoevenagel condensation products and their cyclized derivatives (Figure 31).

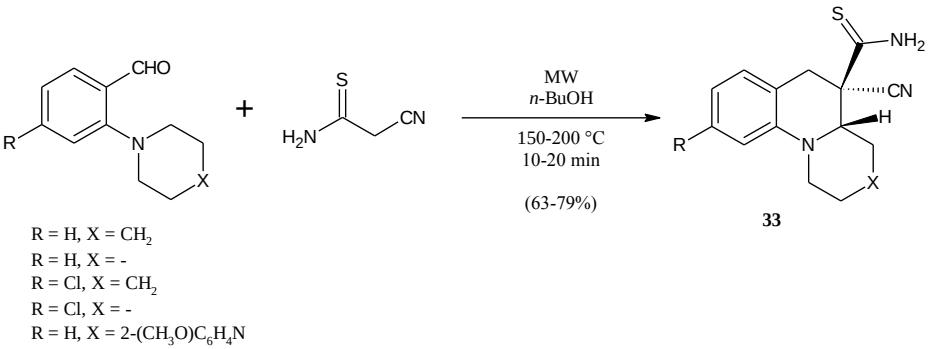


Figure 31: Microwave-assisted synthesis of fused 3-thiocarbamoylquinolines (**33**) *via* the *tert*-amino effect

1.5. Recent applications of the *tert*-amino effect - enantioselective *tert*-aminocyclization

A revision of the recent applications of cyclizations *via* the *tert*-amino effect allows the conclusion that the synthetic potential of this reaction is unfailing. Some of the general structure of the final products are presented in Figure 32 (*Aminals* [50], *Benzoxazines, Benzothiazines* [51], *Diaminoadenines* [52], *tetrahidropirido[4,5-b] piridazin* [26], *Tetrahydroquinolines* [5], *Benzimidazoles, Dihydropurines* [53]).

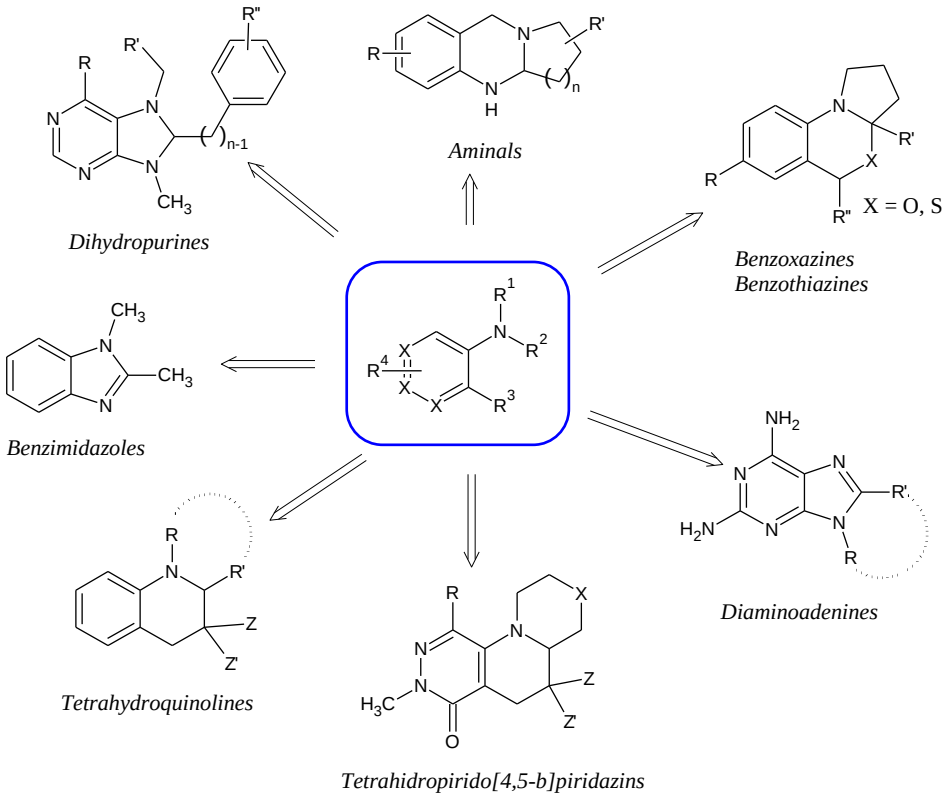


Figure 32: Potential applicability of the *tert*-amino effect

Recently, particular consideration was devoted to the development of catalysts, which can control the enantioselectivity of the ring closure reaction.

Siedel and co-workers reported the first catalytic enantioselective *tert*-aminocyclization reaction using a chiral magnesium complex [54]. They investigated substrates bearing an acyl oxazolidinone (**34**) as an alternative acceptor moiety capable of chelating to a chiral metal complex (Figure 33). The reactions were carried out using various metal salts (e.g., $Sc(OTf)_3$, $Gd(OTf)_3$, $Mg(ClO_4)_2$ x $6H_2O$, $Mg(OTf)_2$) and ligands. The best result was obtained with magnesium triflate and DBFox/Ph ligand (IIIa) in 1,2-dichloroethane at 84 °C. One example of the synthesis of the tetrahydroquinoline derivative by enantioselective *tert*-amino cyclization is presented in Figure 33. The enantioselectivity was explained by the trigonal bipyramidal coordination geometry of the substrate-magnesium-DBFox complex in the transition-state (Figure 34).

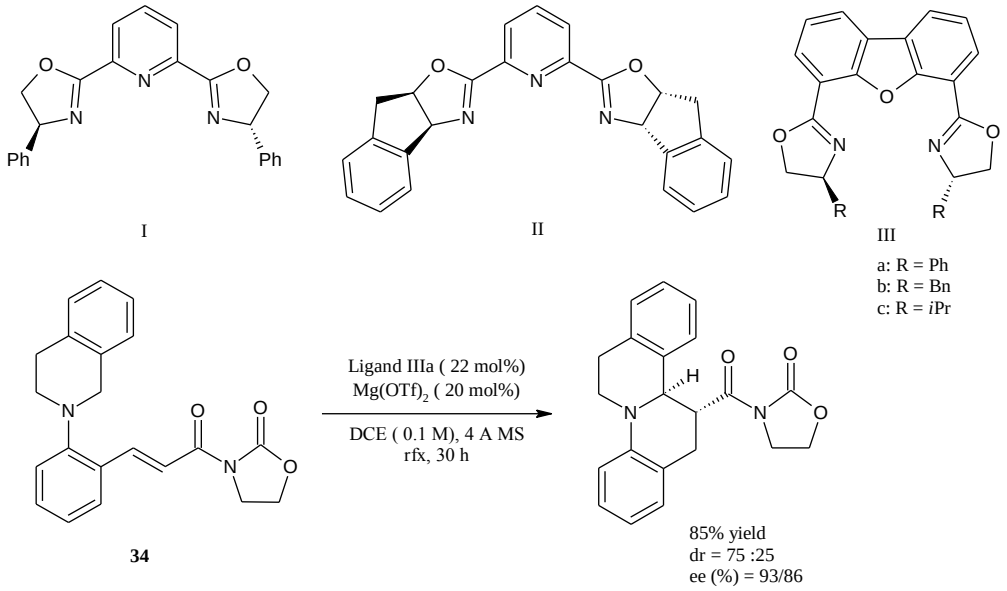


Figure 33: Chiral ligands and enantioselective synthesis of tetrahydroquinoline derivative *via tert*-amino effect

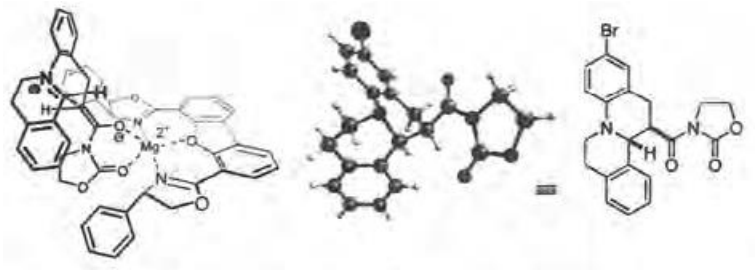


Figure 34: Proposed transition-state leading to major diastereomer. Absolute configuration of brominated compound (X-ray)

Following this report, several chiral metal complexes were developed for this transformation including cobalt (eq. **1**) [55] and gold (eq. **2**) [56]. In addition, a number of organocatalysts (eq. **3**) [57] and chiral phosphoric acid (eq. **4**) [58] were employed (Figure 35).

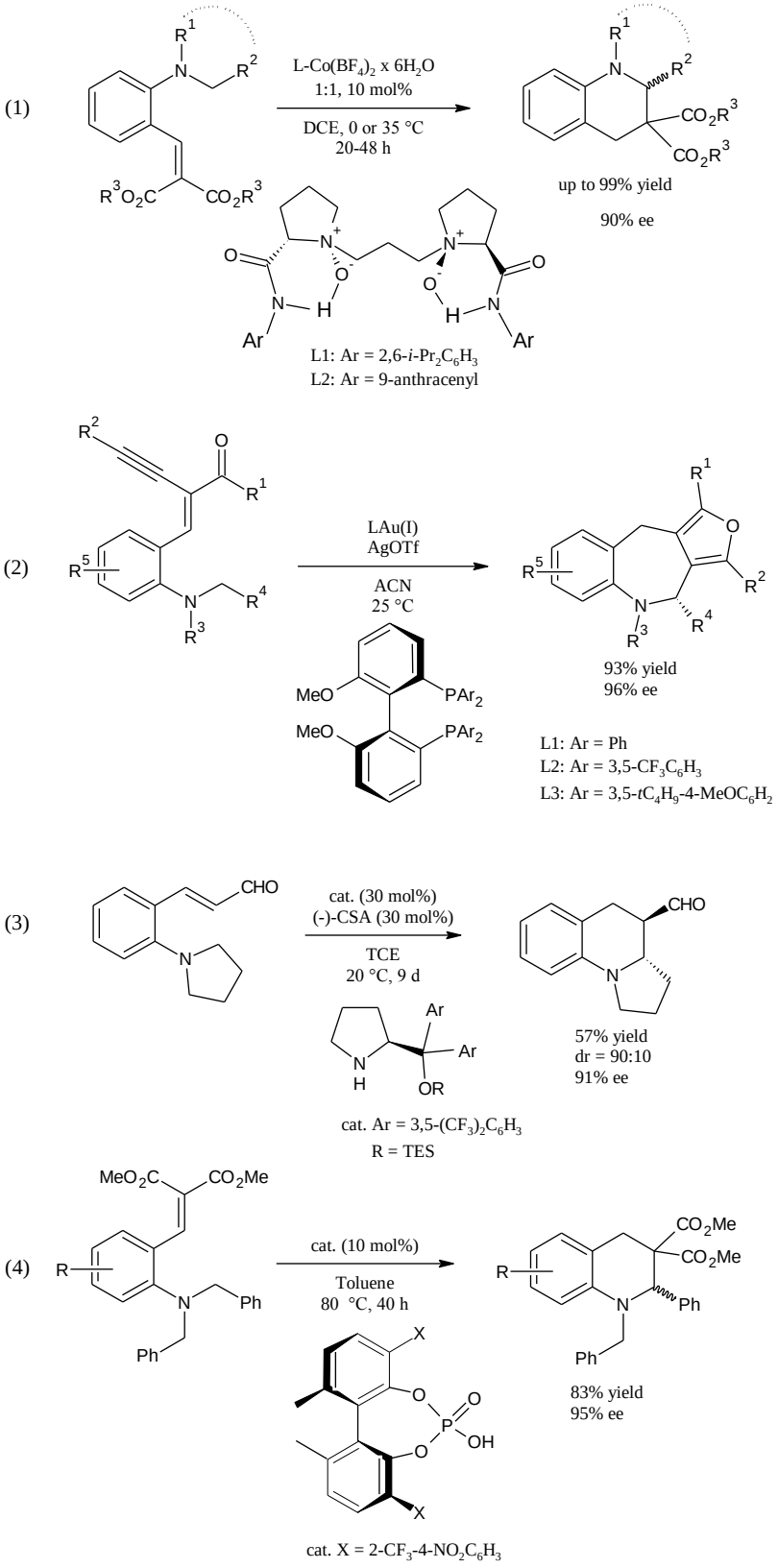


Figure 35: Enantioselective synthesis *via tert*-amino effect

Previously, Brønsted (TFA, EtOH, rfx., 3 h) [50, 59] and Lewis ($Gd(OTf)_3$, ACN, rt, 5 min) [22] acid-catalyzed *tert*-amino effect were employed for the synthesis of aminals and malonate substituted tetrahydroquinolines under mild conditions (Figure 36).

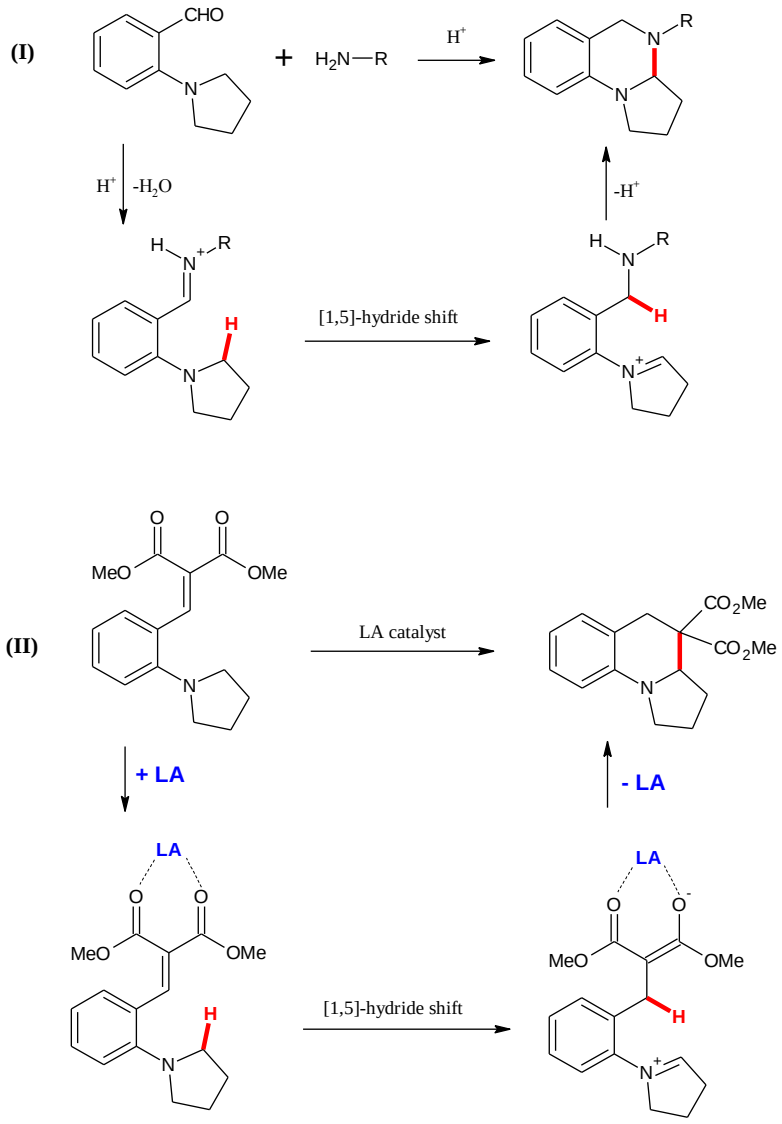


Figure 36: Proposed Brönsted (**I**) and Lewis acid (**II**) catalyzed processes

1.6. Brief overview of semicarbazide-sensitive amine oxidase

Semicarbazide-sensitive amine oxidase (SSAO), also known as vascular adhesion protein-1 (VAP-1) belonging to the family of copper-containing amine oxidases (CuAOs), with its name derived from its sensitivity to inhibition by semicarbazides

[60]. SSAO is identical to primary amine oxidase (SSAO/PrAO) [61], as well as circulating benzylamine amine oxidase (BzAO) [62]. SSAO performs the oxidative deamination of primary aliphatic and aromatic amines, producing a corresponding aldehyde metabolite, hydrogen peroxide and ammonia. The major sources of SSAO include endothelial cells, smooth muscle cells and adipocytes, furthermore it plays an important role in the inflammation and leukocyte trafficking. Recently, numerous types of small molecules with a VAP-1 inhibiting potential have been published [63-65].

The pharmacological significance of SSAO/VAP-1 inhibitors are demonstrated by several studies: pathological angiogenesis [66], ocular diseases [67-69], neuroprotective effect [70-72] and anti-inflammatory effect [73-76]. Furthermore, SSAO substrates might also be of therapeutic value in the treatment of diabetes due to their insulin-like effects (e.g., glucose uptake, lipogenesis stimulation and antilipolysis). Therefore, several potent substrates were investigated in human adipocytes compared with benzylamine as the reference substrate (Figure 37) [77, 78].

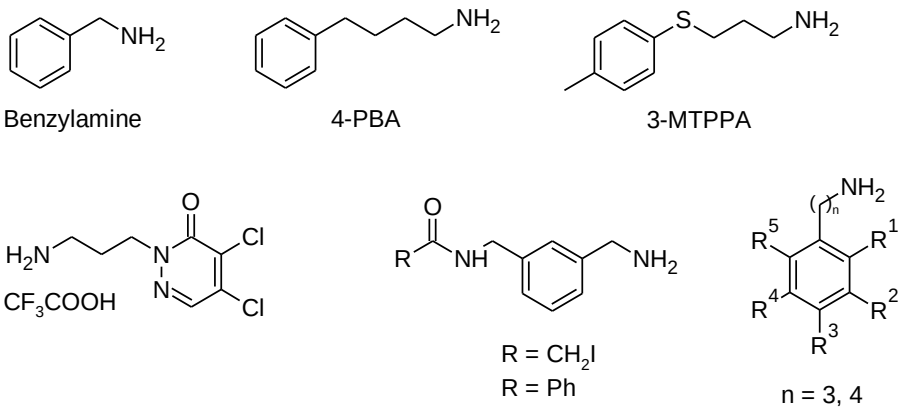


Figure 37: SSAO substrates

According to the experiments, 4-phenylbutylamine (4-PBA), 3-(4-methylthiophenyl)propylamine (3-MTPPA) and 2-(3-aminopropyl)-4,5-dichloro-3(2*H*)-pyridazinone were able to increase hydrogen peroxide production in human white adipose tissue homogenates, therefore they behaved as substrates (Figure 37). On the other hand, efficient glucose-transport activation of these compounds should be mentioned as well, compared with the effect of benzylamine.

Several works have been published that SSAO/VAP-1 has potential as an anti-inflammatory therapeutic target, therefore numerous efforts were made towards the

design of novel inhibitors. Some of them are presented in Figure 38, such as hydrazines, allylamines, propargylamines and further miscellaneous structures. Since, SSAO/VAP-1 is a protein which can facilitate cell-cell interaction and can oxidize a family of primary amines, there are in effect two targets for drug design: antagonize the adhesion binding site or inhibit the amine oxidase activity.

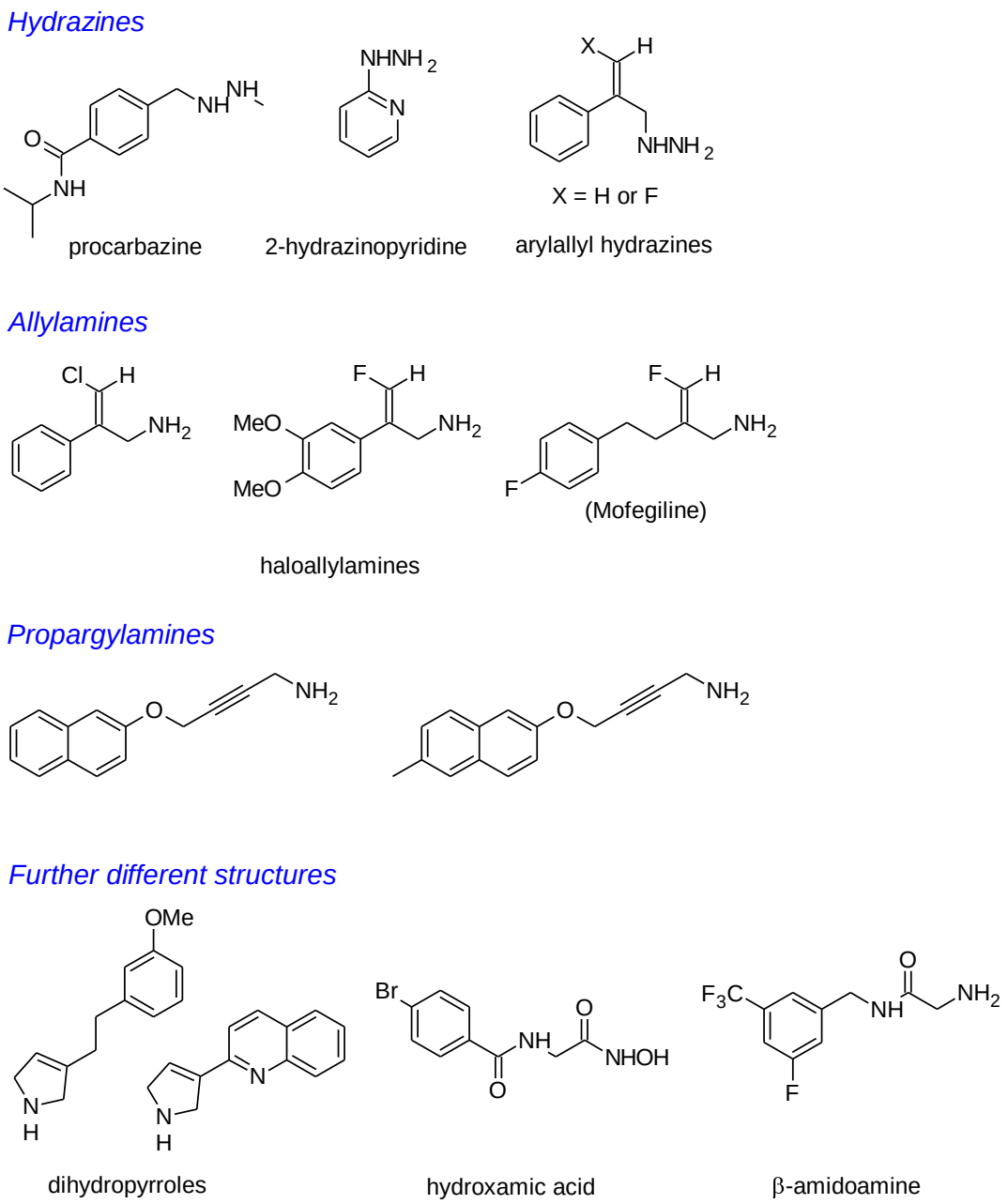


Figure 38: SSAO inhibitors

Recently, new therapeutic aspects of SSAO inhibitors have been published associated with preventing the progress of cerebral amyloid angiopathy in Alzheimer's disease [79]; analgesic effects in traumatic neuropathy and neurogenic inflammation [80] and expression of glucose transporters in chronic liver disease [81]. Furtheremore, the role of SSAO/VAP-1 in physiopathology of several diseases and application as a biomarker [82] have been highlighted as well (e.g. ischemic stroke [83], renal dysfunction and vascular inflammation in type 1 diabetes [84]). In addition to, new therapeutic targets were reported by Payrits *et al.* namely, they have described a dual antagonistic action of a known SSAO inhibitor on transient receptor potential ankyrin 1 and vanilloid 1 ion channels on primary sensory neurons [85].

In order to understand the role of substrate and inhibitor selectivity and efficacy in CuAOs, Shepard and Dooley have summarized the factors which may play the role of these. The authors described in detail the proposed mechanism of reductive half-reaction as well as oxidative half-reaction. Furtheremore, the significance of copper in the biogenesis of topaquinone and in the catalytic cycle were highlighted too (Figure 39) [86]. In summary, they have proven, that the extensive characterization of these mechanisms may be exploited to develop selective mechanism-based inhibitors.

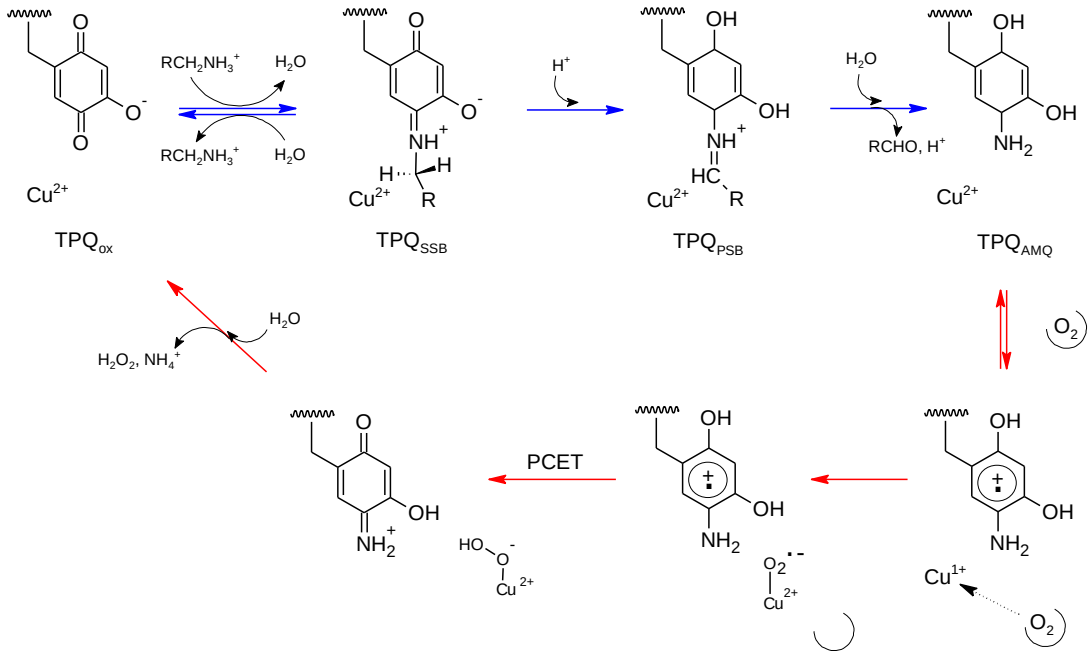


Figure 39: Proposed mechanism of reductive (TPQ_{ox}→TPQ_{AMQ}) and oxidative (inner-sphere) (TPQ_{AMQ}→TPQ_{ox}) half-reactions

Regarding the importance of the field of SSAO in our days, the phase 1 clinical trial of PXS-4728A should be mentioned as well, which is a very potent (IC_{50} <10 nM) and selective (more than 500-fold selective for SSAO over all the related human amine oxidase) inhibitor for the treatment of liver-related disease Nonalcoholic Steatohepatitis (NASH) (Figure 40) [76].

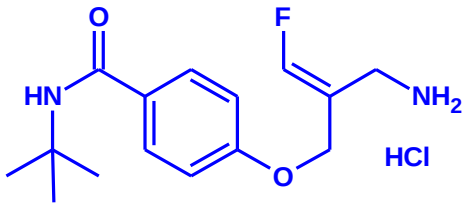


Figure 40: Structure of PXS-4728A

Until now, only few reversible inhibitors of that enzyme were reported in the literature [87-89], however, none of them based on tetrahydroquinoline scaffold. In the present work, we aimed to develop a facile, short synthesis for a novel, small presumably reversible inhibitor library designed for SSAO, represented by few relevant examples.

2. Aims of the work

During my Ph.D. work, three main goals were settled.

1) The primary aim of my research was to investigate the *tert*-amino effect with respect to the synthesis of condensed heterocycles containing nitrogen:

a) the investigation of the ring-closure reactions of 2-vinyl-*N,N*-dialkylanilines supported by microwaves from the aspect of diastereoselectivity, and to study the diastereomers formed including their ratios, giving an accurate description of the experimental findings.

b) studying the stereochemical outcome of the cyclized products obtained in the chemical reactions performed (Figure 41), in the respect of the relationship between the substituent size and the diastereomeric ratios. While a substantial discussion is available on this topic in the literature, the mechanism of the ring closure, isomer ratio of the crude products, the range of reaction selectivities and the differences in activation energies have not been elucidated satisfactorily.

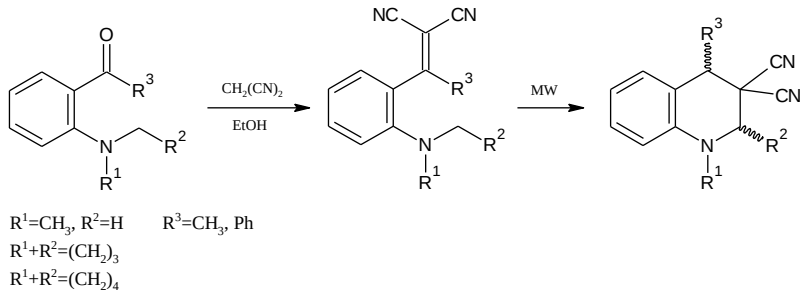


Figure 41: *tert*-Amino effect: formation of the new stereogenic centers *via* the formation of six-membered ring

c) comparing ring closure reactions in terms of reaction time and yield performed in solvent as well as in solvent-free media with the support of microwaves,

d) the confirmation and/or amendment of the earlier descriptions of the mechanism of the *tert*-amino effect,

e) studying the reactions accomplished in the presence of highly electron withdrawing groups (1,3-indanedione and Meldrum's acid) (Figure 42) in order to understand the impact of these compounds on the rate of ring formation.

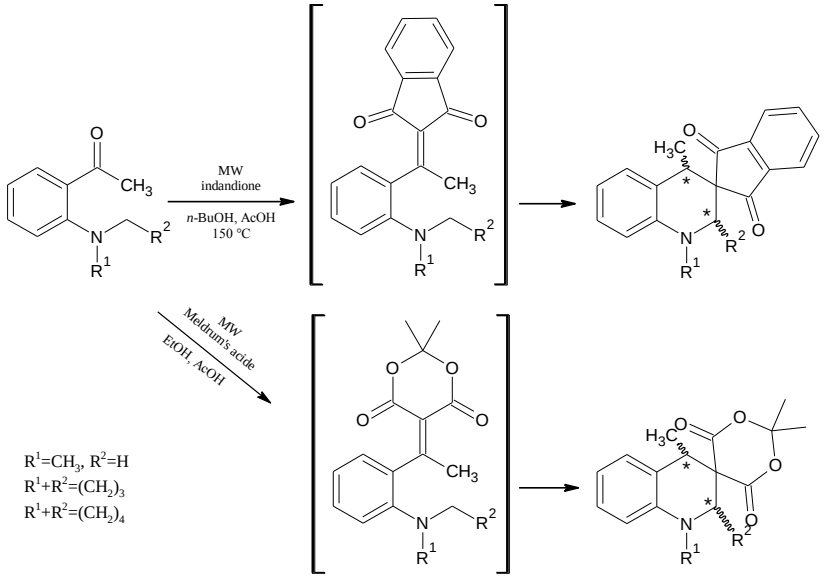


Figure 42: Synthesis of new spirocyclic compounds *via* the *tert*-amino effect

2) Several substances exerting semicarbazide sensitive aminooxidase (SSAO) activity have been synthesized at the Department by Mátyus *et al*. There is still intensive research relates to amine oxidase enzyme activity with a special emphasis on the role of monoamine oxidase (MAO). Some aminomethyl derivatives were also planned by Péter Mátyus as potentially SSAO inhibitors/substrates in a part of the SSAO project. My role was to synthesize the target compounds from dinitriles applying the previously described method (Földi et al) (Figure 43).

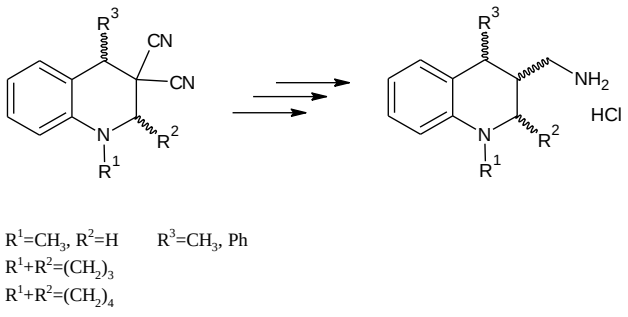


Figure 43: Synthesis of potential SSAO active aminomethyl derivatives

3) My third aim was to investigate the extension of the *tert*-amino effect to, and study its contribution to the regioselectivity in, biaryl systems bridged with methylamino-*N*-methyl groups. Performing ring closure reactions on these skeletons may give rise to medium-sized or macrocyclic entities (Figure 44).

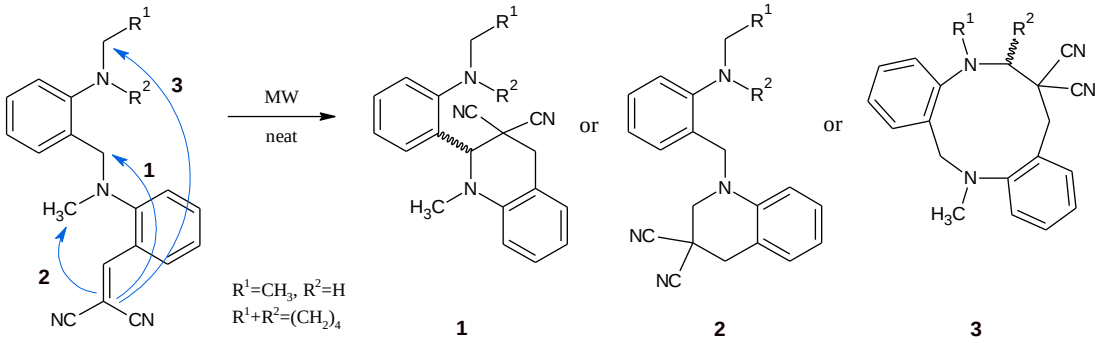


Figure 44: Extension of the *tert*-amino effect to the bridged biaryl systems

3. Materials and methods

3.1. General

All reaction solvents were purified in accordance with Purification of Laboratory Chemicals (Fourth Edition) prior to use. All reagents were used as purchased without further purification. The solvents were removed under reduced pressure using standard rotary evaporators. All of the reactions were monitored by TLC using Merck's silica gel 60 F_{254}-precoated aluminum sheets. Visualization was accomplished with UV light (254 or 365 nm). Solvent mixtures used for chromatography are always given in a vol/vol ratio. Flash column chromatography was generally performed using Silica Gel 60 (Merck, spherical, 40-63 μm). Melting points were determined on a Büchi-540 capillary melting point apparatus and are uncorrected. The high-resolution accurate masses (HRMS) were determined with an Agilent 6230 time-of-flight mass spectrometer. Samples were introduced by the Agilent 1260 Infinity LC system. The mass spectrometer was operated in conjunction with a Jet Stream electrospray ion source in positive ion mode. Reference masses of *m/z* 121.050873 and 922.009798 were used to calibrate the mass axis during analysis. Mass spectra were processed using Agilent MassHunter B.02.00 software. High-performance liquid chromatography (HPLC) was performed on a Jasco 2080 Plus isocratic binary pump, using a Jasco 2075 Plus variable wavelength absorbance detector and Jasco ChromPass v.1.8.6.1 software. All samples were dissolved in the mobile phase used for the assay at a level of approximately 1 mg/mL. Stock solutions were diluted 1:20 using the mobile phase, resulting in a concentration of approximately 50 μg/mL. The diluted samples were injected without further manipulation. Stock solutions were kept at -20 °C overnight. Diluted solutions were prepared on each day of the analysis and were not stored. Chromatographic runs lasted 30 min typically. When all peaks were recovered, runs were terminated manually regardless of the time that had passed. Two stationary phases were employed with the following parameters: 1) Chiralcel® „OJ-H" cellulose tris-4-methylbenzoate, 250 mm x 4.6 mm, 5 μm d_p. 2) Chiralpak® „AD-H" amylose tris-(3,5-dimethylphenyl-carbamate), 250 mm x 4.6 mm, 5 μm d_p. The mobile phase was a *n*-hexane/ethanol mixture in all cases. The ratio of the components is provided in the prescription of the exact compound. The differential scanning calorimetry (DSC) examinations were carried out with a Pyris 6 DSC (Perkin Elmer) instrument. The DSC

curves were evaluated with Pyris Software. The starting and final temperatures were 30 °C and 300 °C, respectively. Heating rate was 5 and 10 °C/min. Nitrogen atmosphere was always used. Samples from 0.79 to 3.20 mg were used (in aluminium sample pans). Three parallel examinations were made in every case. The instrument was calibrated by using indium. Elemental analyses were performed on an Elementar VarioEL III apparatus. MW irradiation experiments were carried out in a monomode CEM-Discover MW reactor, using the standard configuration as delivered, including proprietary software. The experiments were executed in 10 or 80 mL MW process vials with control of the temperature by infrared detection. After completion of the reaction, the vial was cooled to 50 °C by air jet cooling. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature, in the solvent indicated, on a Varian Mercury Plus 400 spectrometer at a frequency of 400 and 100 MHz or on a Varian Unity 600 spectrometer at a frequency of 600 and 150 MHz or on a Bruker Avance III 500 spectrometer at a frequency of 500 and 125 MHz respectively. Chemical shifts are given using the δ-scale (in ppm) relative to tetramethylsilane or the residual solvent signal as an internal reference. Coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, ovl. m=overlapping multiplet, br=broad, dd = doublet doublet, dm = doublet multiplet and tm = triplet multiplet. The signification of the stars in the ^{13}C NMR means tentative assignments.

Computational chemistry 1: semiempirical PM3 and density functional theory (DFT) calculations were carried out by using Schrödinger's Jaguar program package (Jaguar, version 7.8, Schrödinger, LLC, New York, NY, USA, 2011) on HP (Z800) workstation. Starting geometries were obtained with ConfGen Advanced module (with standard settings), followed by PM3 level optimization. For DFT, gradient-corrected functional BP86 model and hybrid functional [90-94] with a 6-31G** basis set in vacuum were used. Computational chemistry 2: All computations were carried out using the Gaussian09 program package (G09) [95]. Geometry optimizations and subsequent frequency analyses were carried out at B3LYP/6-31G(d,p) level of theory [96] in order to properly confirm all structures as residing at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions U, H, G and S were computed at 398.15 K. To model the experimental media, the default IEF-PCM (integral equation

formalism polarizable continuum medium) method was applied as implicit solvent model, choosing the parameters of DMSO as a good compromise. According to our estimation, the error of this solvent model was around 1–2 kJ mol^{-1}.

Unpublished (**36d-f** [102], **37d-f** [29], **37a, 5h *trans*, 5k *trans*, 41, 42a-c** [20]) and published (**5h *cis*, 5k *cis*** [5]**, 35a-f** [20]**, 36a, 4h-k** [27]**, 45a-b, 46a-b, 47a-b** [101]) compounds were prepared according to the literature procedures cited.

Own compounds:

a) are going to be published (under review): **36d-f, 37a, 5h *trans*, 5k *trans*, 37d-f, 42a-c, 41, 44a-c, 43, 38a-f, 39a-f, 40a-f;**
b) published: **48a-b, 49a-b, 50a-b, 51a-b** [97].

3.2. Biology

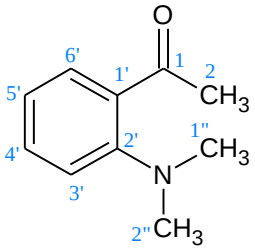
Rat SSAO activity was measured using the microsomal fraction of rat aorta purified by means of differential centrifugation. The enzymatic activity was measured in a fluorescent coupled reaction. SSAO oxidizes its substrates (benzylamine in 1 mM concentration) to produce hydrogen peroxide which produces the oxidized form of Amplex® UltraRed (Invitrogen) that can be readily measured in a fluorimetric plate reader at Ex/Em 540/590 nm. Measurements were conducted in a 384-well format in the final volume of 40 µl. The tested products were incubated 10 minutes at room temperature with the enzyme, and then the substrate was added to initialize the reaction at 30 °C. Fluorescence was read at one hour of reaction and corrected with the value read before substrate addition. Single concentration measurements were conducted at 100 and 10 µM concentration of the compounds using duplicates. The dose response curves of the inhibitors were measured using at least 7 dilution points with 5-fold dilution steps. Duplicate points were determined for each concentration. IC_{50} values were calculated from the remaining activity, the graphs were fitted using Origin 5.0 software.

3.3. Chemistry

3.3.1. General procedure for the synthesis of 2-(dialkylamino)acetophenone and benzophenone derivetives (method A)

A mixture of 2-fluoroacetophenone or 2-fluorobenzophenone (1.0 eq), the appropriate secondary amine (pyrrolidine or piperidine purified by redistillation (760 mmHg, 85-110 °C) or dimethylamine (40 wt.% in water) (1.0 eq) and K_2CO_3 (1.0 eq) in water was irradiated in a pressurized vessel in microwave reactor for the time and the temperature indicated below (at a maximum power level of 200 W). The vessel was subsequently cooled to ambient temperature. To the reaction mixture distilled water was added and it was extracted with diethyl ether. The organic layer was washed with saturated solution of NH_4Cl, then with distilled water and then dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was used for the one-pot reaction without further purification. The melting points and/or spectral data of compounds **35b** [98], **35c** [5] and **35d** [99], **35e** [100], **35f** [98] are identical with the published values. The boiling point of compound **35a** is given in the literature [101], but we characterized by NMR spectroscopy.

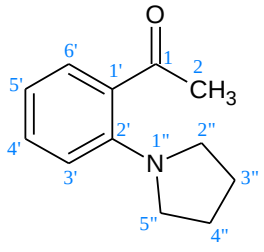
1-[2'-(Dimethylamino)phenyl]ethan-1-one (35a)



Following **method A**, the title compound was isolated. A mixture of 2-fluoroacetophenone (5.00 g, 36.20 mmol, 4.40 mL), dimethylamine (1.63 g, 36.20 mmol, 4.08 mL) and K_2CO_3 (5.00 g, 36.20 mmol) in 20 mL of water was irradiated at 130 °C for 35 minutes. Dark oil (5.49 g, 92%). ^{1}H NMR: (400 MHz, methanol-d_4): 7.38 (2H, m, H – 4', 6'), 7.08 (1H, dm, J = 6.8 Hz, H – 3'), 6.93 (1H, m, H – 5'), 6.93 (1H, tm, J = 7.6 Hz, H - 5'), 2.77 (6H, s, H - 1'', 2"), 2.58 (3H, s, H – 2). ^{13}C NMR: (100 MHz, methanol-d_4): 204.9 (C-1), 152.2 (C-2'), 132.4 (C-1'), 131.9 (C-4'), 129.0 (C-6'), 120.1 (C-5'), 117.0 (C-3'), 43.4 (C-1", 2"), 27.5 (C-2).

Before using for the synthesis of the vinyl compound (**method B1**) the crude product was purified by column chromatography (*n*-hexane/EtOAc 8:1). Yellow oil (66%).

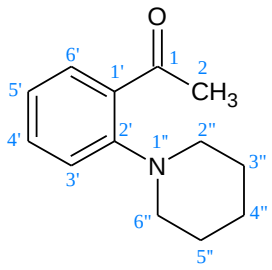
1-[2'-(Pyrrolidin-1"-yl)phenyl]ethan-1-one (35b)



Following **method A**, the title compound was isolated. A mixture of 2-fluoroacetophenone (5.00 g, 36.20 mmol, 4.40 mL), pyrrolidine (2.57 g, 36.20 mmol, 3.02 mL) and K_2CO_3 (5.00 g, 36.20 mmol) in 20 mL of water was irradiated at 130 °C for 40 minutes. Brown oil (6.05 g, 88%). ^{1}H NMR: (400 MHz, chloroform-*d*): 7.51 (1H, dd, *J* = 7.8, 1.6 Hz, H – 6'), 7.32 (1H, tm, *J* = 8.6 Hz, H – 4'), 6.82 (1H, d, *J* = 8.5 Hz, H – 3'), 6.74 (1H, tm, *J* = 7.8 Hz, H – 5'), 3.15 – 3.11 (4H, m, H – 2", 5"), 2.60 (3H, s, H – 2), 1.97 – 1.93 (4H, m, H – 3", 4").

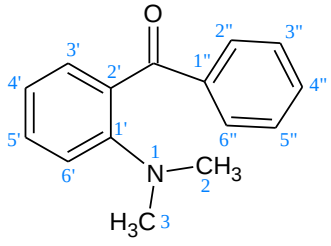
Before using for the synthesis of the vinyl compound (**method B1**) the crude product was purified by column chromatography (*n*-hexane/EtOAc 8:1). Yellow oil (76%).

1-[2'-(Piperidin-1"-yl)phenyl]ethan-1-one (35c)



Following **method A**, the title compound was isolated. A mixture of 2-fluoroacetophenone (5.00 g, 36.20 mmol, 4.40 mL), piperidine (2.98 g, 36.20 mmol, 3.46 mL) and K_2CO_3 (5.00 g, 36.20 mmol) in 30 mL of water was irradiated at 130 °C for 30 minutes. Yellow oil (6.53 g, 92%). ^{1}H NMR: (500 MHz, chloroform-*d*): 7.41 – 7.39 (1H, dm, *J* = 7.5 Hz, H – 6'), 7.39 – 7.36 (1H, m, H – 4'), 7.06 – 7.05 (1H, dm, *J* = 7.5 Hz, H – 3'), 7.03 – 7.00 (1H, m, H – 5'), 2.95 – 2.93 (4H, m, H – 2", 6"), 2.67 (3H, s, H - 2), 1.73 – 1.69 (4H, m, H – 3", 5"), 1.57 - 1.56 (2H, m, H – 4").

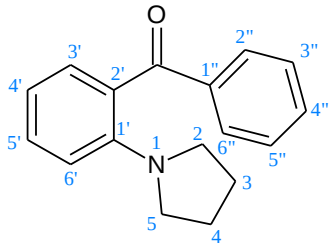
2'-Benzoyl-*N*,*N*-dimethylaniline (35d)



Following **method A**, the title compound was isolated. A mixture of 2-fluorobenzophenone (5.00 g, 24.97 mmol, 4.22 mL), dimethylamine (40 wt. % in water) (1.13 g, 24.97 mmol, 2.8 mL) and K_2CO_3 (3.45 g, 24.97 mmol) in 30 mL of water was irradiated at 130 °C for 2 hours. Yellow dense oil (5.35 g, 95%). ^{1}H NMR: (400 MHz, chloroform-*d*): 7.83 (2H, d, *J* = 7.2 Hz, H – 2", 6"), 7.56 – 7.37 (4H, m, H – 5', 3", 4", 5"), 7.33 – 7.31 (1H, dm, *J* =

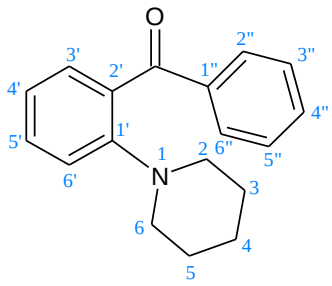
7.6 Hz, H – 3'), 7.00 (1H, d, *J* = 8.3 Hz, H – 6'), 6.90 (1H, m, H – 4'), 2.70 (6H, s, H – 2, 3).

1-(2'-Benzoylphenyl)pyrrolidine (35e)



Following **method A**, the title compound was isolated. A mixture of 2-fluorobenzophenone (3.00 g, 14.98 mmol, 2.50 mL), pyrrolidine (1.07 g, 14.98 mmol, 1.24 mL) and K_2CO_3 (2.07 g, 14.98 mmol) in 30 mL of water was irradiated at 150 °C for 2.5 hours. Yellow solid (2.51 g, 67%). Mp.: 58-60 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.95 – 7.93 (2H, m, H – 2", 6"), 7.59 – 7.56 (1H, m, H – 4"), 7.47 – 7.43 (2H, m, H – 3", 5"), 7.39 – 7.36 (1H, m, H – 5'), 7.27 – 7.25 (1H, dm, *J* = 7.7 Hz, H – 3'), 6.85 – 6.85 (1H, dm, *J* = 8.5 Hz, H – 6'), 6.69 – 6.67 (1H, m, H – 4'), 3.15 – 3.12 (4H, m, H – 2, 5), 1.90 – 1, 87 (4H, m, H – 3, 4).

1-(2'-Benzoylphenyl)piperidine (35f)



Following **method A**, the title compound was isolated. A mixture of 2-fluorobenzophenone (5.00 g, 24.97 mmol, 4.22 mL), piperidine (2.10 g, 24.97 mmol, 2.5 mL) and K_2CO_3 (3.45 g, 24.97 mmol) in 30 mL of water was irradiated at 150 °C for 1.5 hours. Yellow solid (6.52 g, 98%). Mp.: 90.1-91.0 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.77 – 7.75 (2H, m, H – 2", 6"), 7.53 – 7.37 (5H, m, H – 3', 5', 3", 4", 5") 7.09 – 7.03 (2H, m, H – 4', 6'), 2.83 (4H, m, H – 2, 6), 1.27 (2H, m, H – 4), 1.15 (4H, m, H – 3, 5).

3.3.2. General procedure for the synthesis of 2-vinyl-N,N-dialkylanilines from acetophenone derivatives (method B1)

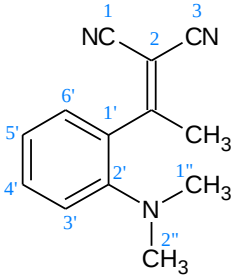
To a mixture of the appropriate acetophenone derivative (1.0 eq) in EtOH, malononitrile (1.0 eq) and 2 drops of piperidine were added. After several hours at room temperature,

the yellow solution turned to orange. When the reaction was completed as followed by TLC, the solvent was removed under reduced pressure. The residue was purified by column chromatography to give the pure product. The melting points and/or spectral data of compounds **36a, 4h**, **4k** [5] are corresponding with the literature data.

3.3.3. General procedure for the synthesis of 2-vinyl-N,N-dialkylanilines from benzophenone derivatives (method B2)

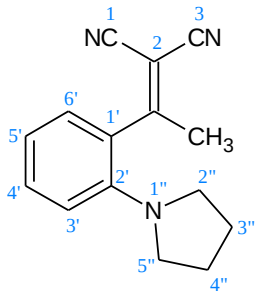
Malononitrile (1 eq) and *i*-PrOH (distilled from CaO, dried over 4 Å molecular sieves) were placed in a sealed tube under argon atmosphere. To this colorless solution, the appropriate benzophenone (1 eq) and Ti(O-*i*-Pr)$_4$ (1 eq) were added and the mixture was heated at 70-80 °C. After completion of the reaction, the dark brown reaction mixture was poured into 1N HCl and it was vigorously stirred at 0-5 °C for 0.5 hours. Then, it was extracted by EtOAc and the organic phase was washed with sodium bicarbonate solution and brine, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography and washed with diethyl ether to afford the pure product.

2-{1'-[2'-(Dimethylamino)phenyl]ethylidene}propanedinitrile (36a)



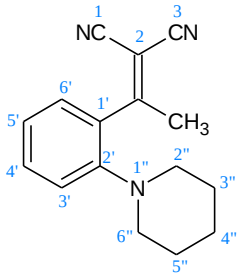
Following **method B1**, the title compound was isolated. To a mixture of 1-[2-(dimethylamino)phenyl]ethanone (4.86 g, 29.80 mmol) in 50 mL of EtOH, malononitrile (2.36 g, 35.76 mmol, 1.2 eq) and 2 drops piperidine were added. The orange reaction mixture was stirred at room temperature for 15 hours. The crude product was purified by column chromatography (*n*-hexane/EtOAc 10:1). Orange dense oil (5.52 g, 88%). ^{1}H NMR (500 MHz, chloroform-*d*): 7.43-7.47 (1H, m, H-4'), 7.19 (1H, dm, *J* = 7.7 Hz, H-3'), 7.09 (1H, dm, *J* = 8.3 Hz, H-6'), 7.05-6.99 (1H, m, H-5'), 2.75 (6H, s, H-1", 2"), 2.63 (3H, s, C*H*$_3$); ^{13}C NMR (125 MHz, chloroform-*d*): 179.2 (=*C*$_q$CH$_3$), 151.3 (C-2'), 132.2 (C-4'), 129.1 (C-1'), 128.9 (C-6'), 121.5 (C-5'), 118.8 (C-3'), 112.7* (C-1), 112.6* (C-3), 85.5 (C-2), 43.7 (C-1", 2"), 22.8 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{13}H_{14}N_3$ $[M+H]^+$ 212.1182, found 212.1190.

2-{1'-[2'-(Pyrrolidin-1"-yl)phenyl]ethylidene}propanedinitrile (4h)



Following **method B1**, the title compound was isolated. To a mixture of 2-(pyrrolidin-1-yl)acetophenone (1.00 g, 5.28 mmol) in 10 mL of EtOH, malononitrile (0.35 g, 5.28 mmol) and 2 drops piperidine were added. The orange reaction mixture was stirred at room temperature for 24 hours. The crude product was purified by column chromatography (toluene) and washed with diethyl ether to afford the pure product. Orange crystals (0.94 g, 75%). Mp.: 106.0-107.9 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.36 – 7.29 (1H, m, H-4'), 7.14 (1H, dm, *J* = 7.9 Hz, H-3'), 6.90 (1H, dm, *J* = 8.5 Hz, H-6'), 6.87 – 6.80 (1H, m, H-5'), 3.22-3.05 (4H, m, H-2", 5"), 2.59 (3H, s, C*H*$_3$), 2.03 - 1.94 (4H, m, H-3", 4"); ^{13}C NMR: (100 MHz, chloroform-*d*): 178.6 (=*C*$_q$CH$_3$), 147.4 (C-2'), 132.0 (C-4'), 129.0 (C-1'), 123.4 (C-6'), 117.8 (C-5'), 115.0 (C-3'), 113.1* (C-1), 112.4* (C-3), 84.1 (C-2), 51.1 (C-2", 5"), 25.8 (C-3", 4"), 23.7 (*C*H$_3$). Anal. calcd. for $C_{15}H_{15}N_3$ (237.29): C, 75.92%; H, 6.37%; N, 17.71%. Found: C, 75.59%; H, 6.18%; N, 17.30%. HRMS (ESI+) *m/z* calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1339, found 238.1343.

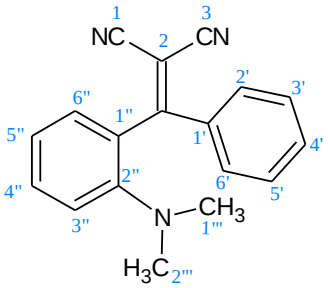
2-{1'-[2'-(Piperidin-1"-yl)phenyl]ethylidene}propanedinitrile (4k)



Following **method B1**, the title compound was isolated. To a mixture of 2-(piperidin-1-yl)acetophenone (0.80 g, 3.94 mmol) in 10 mL of EtOH, malononitrile (0.26 g, 3.94 mmol) and 2 drops piperidine were added. The yellow reaction mixture was stirred at room temperature for 21 hours. The crude product was purified by column chromatography (*n*-hexane/EtOAc 4:1). Yellow crystals (0.76 g, 77%). Mp.: 100.6-101.9 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.45 – 7.41 (1H, m, H-4'), 7.20 – 7.18 (1H, m, H-6'), 7.16 – 7.14 (1H, m, H-3'), 7.10 – 7.08 (1H, m, H-5'), 2.87 (4H, t, *J* = 8.0 Hz, H-2", 6"), 2.68 (3H, s, C*H*$_3$), 1.73 - 1.69 (4H, m, H-3", 5"), 1.59 – 1.57 (2H, m, H-4"); ^{13}C NMR: (100 MHz, chloroform-*d*): 178.9 (=*C*$_q$CH$_3$), 151.9 (C-2'), 132.2 (C-4'), 131.2 (C-1'), 128.6 (C-6'), 122.8 (C-5'), 120.2 (C-3'), 112.7* (C-1), 112.6* (C-3), 86.1 (C-2), 53.8 (C-2", 6"), 26.2 (C-3", 5"), 23.9 (C-4"), 23.4 (*C*H$_3$). Anal. calcd. for

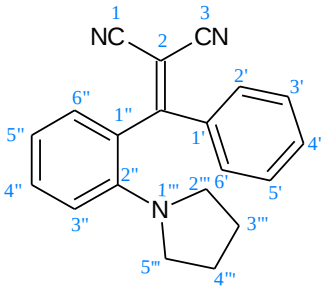
$C_{16}H_{17}N_3$ (251.33): C, 76.46%; H, 6.82%; N, 16.72%. Found: C, 76.05%; H, 6.62%; N, 16.37%. HRMS (ESI+) *m/z* calcd. for $C_{15}H_{18}N_3$ $[M+H]^+$ 252.1495, found 252.1504.

2-{[2”-(Dimethylamino)phenyl](phenyl)methylidene}propanedinitrile (36d)



Following **method B2**, the title compound was isolated. To a mixture of malononitrile (0.55 g, 8.40 mmol) in *i*-PrOH (20 mL), [2-(dimethylamino)phenyl](phenyl)methanone (1.90 g, 8.40 mmol) and Ti(O-*i*-Pr)$_4$ (2.39 g, 8.40 mmol, 2.50 mL) were added. The dark red reaction mixture was stirred at 70 °C for 71 hours. The crude product was purified by column chromatography (toluene). Red crystals (1.66 g, 75%). Mp.: 116-119 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.52 -7.49 (1H, m, H-4’), 7.48 - 7.46 (2H, m, H-2’, 6’), 7.44 – 7.42 (3H, m, H-3’, 5’, 4”), 7.17 (1H, dd, *J* = 7.7 and 1.4 Hz, H-6”), 7.05 (1H, d, *J* = 8.2 Hz, H-3”), 6.99 (1H, t, *J* = 7.7 Hz, H-5”), 2.66 (6H, s, H-1”’, 2”’); ^{13}C NMR: (100 MHz, chloroform-*d*): 175.2 (=C_qPh) 152.8 (C-2”), 135.9 (C-1’), 132.9 (C-4”), 132.4 (C-4’), 132.3 (C-6”), 129.6 (C-3’, 5’), 128.6 (C-2’, 6’), 127.6 (C-1”), 120.6 (C-5”), 118.6 (C-3”), 114.4* (C-3), 114.1* (C-1), 81.4 (C-2), 43.1 (C-1”’, 2”’). Anal. calcd. for $C_{18}H_{15}N_3$ (273.33): C, 79.10%; H, 5.53%; N, 15.37%. Found: C, 78.95%; H, 5.49%; N, 15.21%. HRMS (ESI+) *m/z* calcd. for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1345.

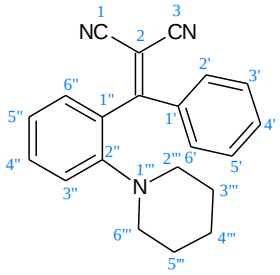
2-{Phenyl[2”-(pyrrolidin-1”’-yl)phenyl]methylidene}propanedinitrile (36e)



Following **method B2**, the title compound was isolated, however the major product was the cyclized derivative (see below compound **6b**). To a mixture of malononitrile (1.31 g, 19.89 mmol) in *i*-PrOH (70 mL), phenyl[2-(pyrrolidin-1-yl)phenyl]methanon (5.00 g, 19.89 mmol) and Ti(O-*i*-Pr)$_4$ (5.65 g, 19.89 mmol, 5.88 mL) were added. The dark red reaction mixture was stirred at 80 °C for 96 hours. Dark red crystals (0.36 g, 6%). Mp.: 148.2-151.1 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.64 – 7.52 (3H, m, H-2’, 4’, 6’), 7.51 – 7.41 (2H, m, H-3’, 5’), 7.40 – 7.33 (1H, m, H-4”), 6.93 (1H, dm, *J* =

8.5 Hz, H-3”), 6.87 (1H, dm, *J* = 8.1 Hz, H-6”), 6.73 (1H, m, H-5”), 3.48 – 2.92 (4H, brm, H-2”’, 5”’), 2.13 - 1.81 (4H, brm, H-3”’, 4”’); ^{13}C NMR: (100 MHz, chloroform-*d*): 174.7 (=C_qPh), 148.8 (C-2”), 136.6 (C-1’), 133.0 (C-4”), 132.8 (C-4’), 132.5 (C-6”), 130.7 (C-1”), 129.0 (C-2’, 6’), 128.7 (C-3’, 5’), 121.4 (C-5”), 116.9 (C-3”), 114.9* (C-1), 113.7* (C-3), 78.7 (C-2), 51.0 (C-2”’, 5”’), 25.9 (C-3”’, 4”’). HRMS (ESI+) *m/z* calcd. for $C_{20}H_{18}N_3$ $[M+H]^+$ 300.1495, found 300.1497.

2-{Phenyl[2”-(piperidin-1”’-yl)phenyl]methylidene}propanedinitrile (36f)



Following **method B2**, the title compound was isolated. To a mixture of malononitrile (2.50 g, 37.68 mmol) in *i*-PrOH (70 mL), 1-(2’-benzoylphenyl)piperidine (10.00 g, 37.68 mmol) and Ti(O-*i*-Pr)$_4$ (10.72 g, 37.68 mmol, 11.2 mL) were added. The dark orange reaction mixture was stirred at 80 °C for 7 hours. The crude product was purified by column chromatography (*n*-hexane/EtOAc 9:1). Orange crystals (46%). Mp.: 166-168 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.57 – 7.36 (5H, m, H-2’, 3’, 4’, 5’, 6’), 7.48 (1H, m, H-4”), 7.25 (1H, dm, *J* = 6.5 Hz, H-6”), 7.13 (1H, dm, *J* = 1.0 Hz, H-3”), 7.11 (1H, m, H-5”), 2.77 (4H, brs, H-2”’, 6”’), 1.50 – 1.25 (6H, brm, H-3”’, 4”’, 5”’); ^{13}C NMR: (125 MHz, chloroform-*d*): 174.9 (=C_qPh), 153.7 (C-2”), 136.0 (C-1’), 133.0 (C-4”), 132.4 (C-4’), 131.9 (C-6”), 131.1 (C-1”), 129.7 (C-2’, 6’), 128.5 (C-3’, 5’), 122.6 (C-5”), 120.8 (C-3”), 114.3* (C-1), 114.2* (C-3), 82.1 (C-2), 53.4 (C-2”’, 6”’), 25.9 (C-3”’, 5”’), 23.8 (C-4”’). Anal. calcd. for $C_{21}H_{19}N_3$ (313.40): C, 80.48%; H, 6.11%; N, 13.41%. Found: C, 80.74%; H, 6.18%; N, 13.33%. HRMS (ESI+) *m/z* calcd. for $C_{21}H_{19}N_3$ $[M+H]^+$ 314.1652, found 314.1640.

3.3.4. General procedure for the synthesis of pyrido-fused ring system

3.3.4.1. One-pot microwave reaction (method C1)

1. step: To a mixture of the appropriate acetophenone (1.0 eq) in 30 mL of water, malononitrile (1.0 eq) was added. The reaction mixture was irradiated in a pressurized vessel for the time and the temperature indicated below (at a maximum power level of

200 W). The vessel was subsequently cooled to ambient temperature, monitoring the completion of the reaction by TLC. The reaction mixture was used for the next step without work-up and purification.

2. step: To the reaction mixture trifluoroacetic acid was added in catalytic amount (3 drops). The vinyl precursor was irradiated in a pressurized vessel for the time and the temperature indicated below (at a maximum power level of 200 W). The vessel was subsequently cooled to ambient temperature, the crude product was taken for the analysis of the ratio of the diastereomers by NMR. After transferring from the vial, the reaction mixture was extracted with DCM (3x30 mL). The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by crystallization or filtration. The melting points and/or spectral data of compounds **5h *cis*** and **5k *cis*** [5] are corresponding with the literature data.

3.3.4.2. Solvent free microwave reaction (method C2)

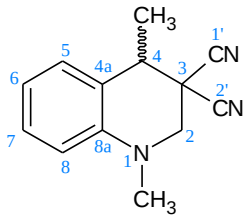
The vinyl precursor was irradiated in a sealed vessel without solvent. When the reaction was completed as followed by TLC, the vessel was subsequently cooled to ambient temperature. The crude product was taken for the analysis of the ratio of the diastereomers by NMR. After transferring from the *via*l, to the reaction mixture DCM (20 mL) and water (20 mL) were added, then the water phase was extracted with DCM (2x30 mL). The organic layer was washed with saturated solution of NH_4Cl (60 mL), then dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography and/or crystallization.

3.3.4.3. *Synthesis of spirocyclic ring systems (method C3)*

To the appropriate 2-(dialkylamino)acetophenone (1 eq) in *n*-BuOH (distilled from Na, dried over 4 Å molecular sieves) or EtOH indane-1,3-dione (ID) (1.2 eq) or Meldrum's acid (3 eq) and acetic acid (2 drops) were added. The reaction mixture was irradiated in a pressurized vessel for the time and the temperature indicated below (at a maximum power level of 200 W). The vessel was subsequently cooled to ambient temperature, an aliquot was taken for the analysis of the ratio of the diastereomers by NMR. After

transferring from the vial, the reaction mixture (dark brown solution) was extracted with DCM. The organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography and crystallization.

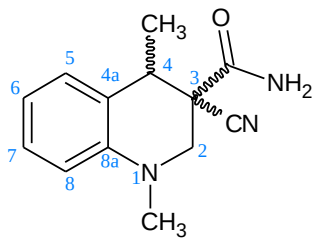
(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinoline-3,3-dicarbonitrile (37a)



Following **method C1**, the title compound was isolated. (1. step) To a mixture of 2-(dimethylamino)acetophenone (5.50 g, 33.70 mmol) in 30 mL of water, malononitrile (2.22 g, 33.70 mmol) was added. The reaction mixture was irradiated at 100 °C for 35 min, then (2. step) to the reaction mixture trifluoroacetic acid was added and it was irradiated at 165 °C for 10 min. The crude product was purified by column chromatography (toluene), then was washed with *n*-hexane (in the reaction 10% **side product** was formed, see below). Pale yellow crystals (0.44 g, 6%). Mp.: 86.0-86.8 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.22 – 7.21 (1H, m, H-7), 7.12 (1H, dm, *J*= 8.0 Hz, H-6), 6.83 – 6.80 (1H, m, H-5), 6.71 (1H, dm, *J* = 8.5 Hz, H-8), 3.78 (1H, dm, *J* = 12.0 Hz, H_x-2), 3.74 (1H, dm, *J* = 12.0 Hz, H_y-2), 3.49 (1H, q, *J* =7.0 Hz, H-4), 3.06 (3H, s, NCH_3), 1.64 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 142.9 (C-8a), 129.0 (C-7), 128.1 (C-5), 120.2 (C-4a), 118.6 (C-6), 114.8* (C-2'), 113.3* (C-1'), 112.3 (C-8), 54.1 (C-2), 39.6 (C-4), 39.4 (N*C*H$_3$), 36.7 (C-3), 19.0 (*C*H$_3$). Anal. calcd. for $C_{13}H_{13}N_3$ (211.26): C, 73.91%; H, 6.20%; N, 19.89%. Found: C, 73.53%; H, 6.15%; N, 19.86%. HRMS (ESI+) *m/z* calcd. for $C_{13}H_{14}N_3$ $[M+H]^+$ 212.1182, found 212.1188.

Following **method C2**, the title compound was isolated. The vinyl precursor (0.98 g, 4.62 mmol) was irradiated at 180 °C for 20 minutes. The crude product was washed with *n*-hexane. Pale yellow crystals (0.73 g, 74%).

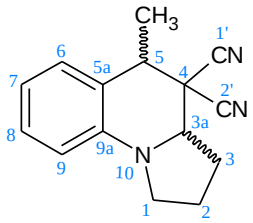
3-Cyano-1,4-dimethyl-1,2,3,4-tetrahydroquinoline-3-carboxamide (side product)



Following **method C1**, the title compound was isolated. Cream powder (0.69 g, 10%), mp 160.3-161.1 °C. According to the NMR analysis the diastereomer ratio is 80:20 *cis*/*trans*. ^{1}H NMR (500 MHz, chloroform-*d*): 7.20 - 7.17 (1H, m, H-7), 7.08 (1H, dm, *J* = 8.5 Hz, H-5), 6.75 (1H, dm, *J* = 7.5 Hz, H-

6), 6.72 (1H, dm, J = 8.0 Hz, H-8), 6.35 (1H, brs, NH_2), 5.75 (1H, brs, NH_2) 3.73 (1H, d, J = 17.5 Hz, H_x-2), 3.46 (1H, d, J = 14.0 Hz, H_y-2), 3.41 (1H, q, J = 7.0 Hz, H-4), 3.03 (3H, s, H-NCH_3), 1.32 (3H, d, J = 7.5 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 167.3 (*C*=O), 143.5 (C-8a), 128.9 (C-5), 128.5 (C-7), 122.8 (C-4a), 120.2 (*C*N), 117.8 (C-6), 111.9 (C-8), 50.1 (C-2), 45.8 (C-3), 40.1 (C-4), 39.1 (N*C*H$_3$), 20.0 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{14}H_{16}N_2O$ $[M+H]^+$ 229.1335, found: 229.1342.

cis-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (5h _cis_)
trans-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (5h _trans_)

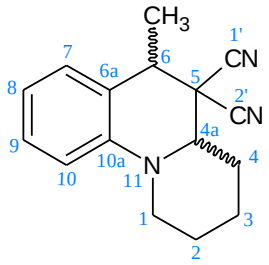


Following **method C1**, the title compound (**5h *cis***) was isolated. (1. step) To a mixture of 2-(pyrrolidino)acetophenone (6.58 g, 34.80 mmol) in 40 mL water, malononitrile (2.30 g, 34.80 mmol) was added. The reaction mixture was irradiated at 100 °C for 15 minutes, then (2. step) to the reaction mixture trifluoroacetic acid was added and it was irradiated at 150 °C for 6 min. The ratio of the diastereomers in the crude product by NMR: only *cis* isomer was formed. The crude solid product was washed with Et_2O and crystallized from EtOH (anhydrous, dried over 3 Å molecular sieves). White crystals (4.12 g, 50%). Mp.: 134.0 – 134.5 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.25 – 7.16 (2H, m, H-6, 8), 6.82 – 6.75 (1H, m, H-7), 6.57 (1H, dm, J = 8.0 Hz, H-9), 3.92 (1H, dd, J = 9.0 and 6.0 Hz, H-3a), 3.56 – 3.40 (2H, m, H-1) 3.48 (1H, q, J = 7.0 Hz, H-5), 2.60 – 2.50 (1H, m, H_x-3), 2.27 – 2.06 (3H, m, $H_{x,y}$-2, H_y-3), 1.77 (3H, d, J = 7.0 Hz, H-CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 141.9 (C-9a), 129.1 (C-8), 126.8 (C-6), 118.7 (C-5a), 117.6 (C-7), 115.3* (C-1'), 112.0* (C-2'), 111.9 (C-9), 63.0 (C-3a), 48.1 (C-1), 42.3 (C-4), 41.1 (C-5), 30.3 (C-3), 22.7 (C-2), 16.1 (C-*C*H$_3$). Anal. calcd. for $C_{15}H_{15}N_3$ (237.30): C, 75.92%; H, 6.37%; N, 17.71%. Found: C, 75.90%; H, 6.41%; N, 17.87%. HRMS (ESI+) *m/z* calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1339, found 238.1334.

Following **method C2**, the title compound (**5h** *trans*) was isolated. The vinyl precursor (0.20 g, 0.84 mmol) was irradiated at 180 °C for 10 minutes. The ratio of the diastereomers in the crude product by NMR: *cis*/*trans* 85:15. The crude product was

purified by column chromatography (toluene). Pale yellow crystals (0.13 g, 65%). The two diastereomers were separated by HPLC. **5h *trans*** isomer. Mp.: 125.1 – 125.8 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.21 – 7.18 (1H, m, H-8), 7.09 (1H, dm, *J* = 8.0 Hz, H-6), 6.76 – 6.73 (1H, m, H-7), 6.60 (1H, dm, *J* = 8.0 Hz, H-9), 3.85 (1H, dd, *J* = 9.0 and 6.0 Hz, H-3a), 3.60 (1H, m, H_x-1), 3.59 (1H, m, H-5), 3.42 (1H, m, H_y-1), 2.52 (1H, m, H_x-3), 2.28 (1H, m, H_x-2), 2.18 (1H, m, H_y-3), 2.10 (1H, m, H_y-2), 1.50 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, chloroform-*d*):140.9 (C-9a), 129.1 (C-6, 8), 119.5 (C-5a), 117.5 (C-7), 114.3* (C-2'), 113.8* (C-1'), 112.3 (C-9), 56.9 (C-3a), 48.2 (C-1), 40.6 (C-5), 39.1 (C-4), 30.1 (C-3), 23.0 (C-2), 21.7 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{15}H_{16}N_3$ $[M+H]^+$ 238.1339, found 238.1349.

cis-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5,5-dicarbonitrile (5k *cis*)

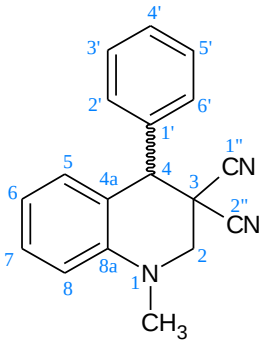


Following **method C1**, the title compound was isolated. (1. step) To a mixture of 2-(piperidino)acetophenone (6.55 g, 32.30 mmol) in 40 mL of water, malononitrile (2.13 g, 32.30 mmol) was added. The reaction mixture was irradiated at 100 °C for 12 minutes, then (2. step) to the reaction mixture trifluoroacetic acid was added and it was irradiated at 170 °C for 5 min. The ratio of the diastereomers in the crude product by NMR: only *cis* isomer was formed. The crude product was crystallized from MeOH (distilled from Na and P_2O_5, dried over 3 Å molecular sieves). White crystals (4.88 g, 60%). Mp.: 141.0 – 141.6 °C (MeOH). ^{1}H NMR: (600 MHz, chloroform-*d*): 7.23 – 7.18 (2H, m, H-7, 9), 6.93 (1H, dm, *J* = 8 Hz, H-10), 6.87 – 6.85 (1H, m, H-8), 4.01-3.95 (1H, m, H_x-1), 3.53 – 3.52 (1H, m, H-6), 3.35 (1H, dm, *J* = 11.5 and 3.0 Hz, H-4a), 2.70 – 2.68 (1H, m, H_y-1), 2.39 – 2.36 (1H, m, H_x-4), 2.02 – 2.00 (1H, m, H_x-3), 1.91 – 1.88 (1H, m, H_x-2), 1.81 – 1.79 (1H, m, H_y-4), 1.77 (3H, d, *J* = 7.0 Hz, C*H*$_3$), 1.75 – 1.73 (1H, m, H_y-2), 1.47 – 1.46 (1H, m, H_y-3); ^{13}C NMR: (150 MHz, chloroform-*d*): 144.6 (C-10a), 128.9 (C-9), 127.0 (C-7), 121.4 (C-6a), 119.6 (C-8), 115.1* (C-1'), 114.0 (C-10), 112.3* (C-2'), 60.2 (C-4a), 48.1 (C-1), 46.2 (C-5), 40.0 (C-6), 30.0 (C-4), 24.8 (C-2), 22.8 (C-3), 16.6 (*C*H$_3$). Anal. calcd. for $C_{16}H_{17}N_3$ (251.33): C, 76.46%; H, 6.82%; N, 16.72%. Found: C,

76.11%; H, 7.01%; N, 16.36%. HRMS (ESI+) *m/z* calcd. for $C_{16}H_{18}N_3$ $[M+H]^+$ 252.1495, found 252.1505.

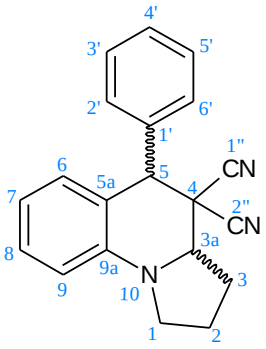
Following **method C2**, the title compound was isolated. The vinyl precursor (0.20 g, 0.80 mmol) was irradiated at 180 °C for 10 minutes. The ratio of the diastereomers in the crude product by NMR: *cis*/*trans* 92:8. The crude product was purified by column chromatography (toluene). Pale yellow crystals (0.14 g, 70%). Mp.: 131.3 – 133.1 °C. We were not able to isolate the *trans* isomer.

(±)-1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3,3-dicarbonitrile (37d)



Following **method C2**, the title compound was isolated. The vinyl precursor (1.33 g, 4.86 mmol) was irradiated at 180 °C for 1.5 hours. After transferring from the vial, to the reaction mixture EtOAc (20 mL) and water (20 mL) were added, then the water phase was extracted with EtOAc (2x20 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by column chromatography (*n*-hexane/EtOAc 8:1). Yellow crystals (0.87 g, 67%). Mp.: 120.8-121.4 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.40-7.38 (3H, m, H-3', 4', 5'), 7.29 – 7.22 (3H, m, 2', 6', 7), 6.84 – 6.79 (2H, m, H-5, 8), 6.74 – 6.70 (1H, m, H-6), 4.65 (1H, s, H-4), 3.81 (1H, d, J = 11.5 Hz, H_x-2), 3.80 (1H, d, J = 11.5 Hz, H_y-2), 3.14 (3H, s, NCH_3); ^{13}C NMR: (100 MHz, chloroform-*d*): 144.0 (C-8a), 137.4 (C-1'), 130.3 (C-5), 130.2 (C-2', 6'), 129.3 (C-7), 129.0 (C-4'), 128.8 (C-3', 5'), 118.6 (C-6), 118.4 (C-4a), 114.5 (C-1"), 113.4 (C-2"), 112.4 (C-8), 54.6 (C-2), 51.3 (C-4), 39.7 (*C*H_3), 37.5 (C-3). Anal. calcd. for $C_{18}H_{15}N_3$ (273.33): C, 79.10%; H, 5.53%; N, 15.37%. Found: C, 78.71%; H, 5.52%; N, 15.17%. HRMS: calcd for $C_{18}H_{16}N_3$ $[M+H]^+$ 274.1339, found 274.1333.

cis-(±)-5-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-_a_]quinoline-4,4-dicarbonitrile (37e _cis_)
trans-(±)-5-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-_a_]quinoline-4,4-dicarbonitrile (37e _trans_)

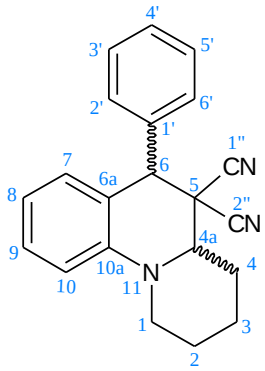


Following **method B2**, the title compound (**37e _cis_**) was isolated. To a mixture of malononitrile (1.31 g, 19.89 mmol) in *i*-PrOH (70 mL), phenyl[2-(pyrrolidin-1-yl)phenyl]methanone (5.00 g, 19.89 mmol) and Ti(O-*i*-Pr)$_4$ (5.65 g, 19.89 mmol, 5.88 mL) were added. The dark red reaction mixture was stirred at 110-120 °C for 87 hours. The ratio of the diastereomers in the crude product was determined by NMR: *cis*/*trans* 92:8. The crude product was purified by column chromatography (toluene) and washed with diethyl ether to afford the pure *cis* isomer. Beige crystals (1.36 g, 35%). Mp.: 164.7-167.2 °C. ^{1}H NMR: (600 MHz, chloroform-*d*): 7.48 – 7.41 (5H, m, H-2', 3', 4', 5', 6'), 7.25 – 7.25 (1H, m, H-8), 6.71 (1H, dm, *J* = 8.1 Hz, H-6), 6.63 (1H, dm, *J* = 7.8 Hz, H-7), 6.63 (1H, m, H-9), 4.59 (1H, s, H-5), 4.08 (1H, dd, *J* = 8.3, 6.2 Hz, H-3a), 3.58 (1H, m, H_x-1) 3.52 (1H, m, H_y-1), 2.55 (1H, m, H_x-3), 2.31 (1H, m, H_x-2), 2.28 (1H, m, H_y-3), 2.10 (1H, m, H_y-2); ^{13}C NMR: (150 MHz, chloroform-*d*): 142.7 (C-9a), 136.2 (C-1'), 129.6 (C-6), 129.3 (C-8), 129.2 (C-2', 6'), 128.9 (C-4'), 128.5 (C-3', 5'), 118.1 (C-5a), 117.3 (C-7), 114.5* (C-2"), 112.6* (C-1"), 112.2 (C-9), 63.7 (C-3a), 53.5 (C-5), 47.9 (C-1), 43.3 (C-4), 30.2 (C-3), 22.7 (C-2). Anal. calcd. for $C_{20}H_{17}N_3$ (299.37): C, 80.24%; H, 5.72%; N, 14.04%. Found: C, 80.40%; H, 5.68%; N, 14.16%. HRMS (ESI+) *m/z* calcd. for $C_{20}H_{18}N_3$ $[M+H]^+$ 300.1494, found 300.1501.

Following **method C2**, the title compound (**37e _trans_**) was isolated. The vinyl precursor (0.20 g, 0.67 mmol) was irradiated at 150 °C for 30 minutes. The ratio of the diastereomers in the crude product was determined by NMR: *cis*/*trans* 82:18. Beige crystals (0.16 g, 82% overall yield of the crude product). The two diastereomers were separated by preparative HPLC (Teknokroma Nucleosil 100 C18 10 µm 25 cm×1 mm; mobile phase composition: A/B 50:50 (A = methanol/water 3:7, B = acetonitrile); flow rate: 3 mL/min). Beige crystals (*trans* isomer). Mp.: 130.7 – 131.7 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.38 – 7.11 (5H, m, H-2', 3', 4', 5', 6'), 7.28 – 7.25 (1H, m,

H-8), 7.02 (1H, dm, *J* = 7.5 Hz, H-6), 6.74 – 6.72 (1H, m, H-7), 6.73 (1H, dm, *J* = 6.5 Hz, H-9), 4.74 (1H, s, H-5), 3.77 (1H, dd, *J* = 9.0 and 5.5 Hz, H-3a), 3.73 (1H, m, H_x-1), 3.46 (1H, m, H_y-1), 2.37 (1H, m, H_x-3), 2.28 (1H, m, H_x-2), 2.16 (1H, m, H_y-3), 2.08 (1H, m, H_y-2); ^{13}C NMR: (125 MHz, chloroform-*d*): 142.2 (C-9a), 137.9 (C-1'), 130.3 (C-2', 6'), 130.2 (C-6), 129.6 (C-8), 128.7 (C-4'), 128.6 (C-3', 5'), 117.7 (C-7), 116.7 (C-5a), 114.0 (C-2"), 113.9 (C-1"), 112.2 (C-9), 57.1 (C-3a), 51.1 (C-5), 48.7 (C-1), 39.7 (C-4), 30.0 (C-3), 23.1 (C-2). HRMS (ESI+) *m/z* calcd. for $C_{20}H_{18}N_3$ $[M+H]^+$ 300.1494, found 300.1503.

cis-(±)-6-Phenyl-1_H_-2,3,4,4a,5,6-hexahydropyrido[1,2-_a_]quinoline-5,5-dicarbonitrile (37f _cis_)
trans-(±)-6-Phenyl-1_H_-2,3,4,4a,5,6-hexahydropyrido[1,2-_a_]quinoline-5,5-dicarbonitrile (37f _trans_)



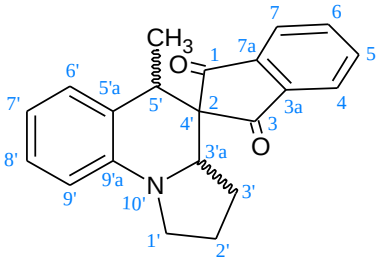
Following **method C2**, the title compound (**37f _cis_**) was isolated. The vinyl precursor (0.20 g, 0.64 mmol) was irradiated at 190 °C for 10 minutes. Beige crystals (0.19 g, 95% overall yield of the crude product). The ratio of the diastereomers in the crude product was determined by NMR: *cis*/*trans* 71:29 and by HPLC: CH_3CN/H_2O 65:35, t_R: 19.7 and 18.8 min, 70% and 30%. The two diastereomers were separated by preparative HPLC (Teknokroma Nucleosil 100 C18 10 µm 25 cm×1 mm; mobile phase composition: A/B 40:60 (A = methanol/water 3:7, B = acetonitrile); flow rate: 3 mL/min).

Beige powder (**_cis_ isomer**). Mp.: 199-202 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.44 – 7.43 (5H, m, H-2', 3', 4', 5', 6'), 7.26 – 7.21 (1H, m, H-9), 6.99 (1H, dm, *J* = 8.5 Hz, H-10), 6.74 – 6.72 (2H, m, H-7, 8), 4.68 (1H, s, H-6), 4.03 (1H, dm, *J* = 11.9 Hz, H_x-1), 3.50 (1H, dd, *J* = 11.5 and 3.4 Hz, H-4a), 2.71 (1H, td, *J* = 12.4 and 3.3 Hz, H_y-1), 2.44 – 2.41 (1H, m, H_x-4), 2.01 – 1.90 (1H, m, H_x-3), 1.89 – 1.81 (1H, m, H_y-4), 1.79 – 1.76 (1H, m, H_x-2), 1.46 – 1.36 (2H, m, H_y-2, 3); ^{13}C NMR: (100 MHz, chloroform-*d*): 145.9 (C-10a), 136.7 (C-1'), 130.3 (C-3', 5'), 130.0 (C-7), 129.2 (C-4'), 129.1 (C-9), 128.8 (C-2', 6'), 120.7 (C-6a), 119.4 (C-8), 114.3 (C-10), 114.0* (C-2"), 112.9* (C-1"), 60.7 (C-4a), 52.7 (C-6), 48.0 (C-1), 47.2 (C-5), 30.0 (C-4), 24.9 (C-2), 22.4 (C-3). Anal.

calcd. for $C_{21}H_{19}N_3$ (313.40): C, 80.48%; H, 6.11%; N, 13.41%. Found: C, 80.47%; H, 6.16%; N, 13.19%. HRMS (ESI+) *m/z* calcd. for $C_{21}H_{20}N_3$ $[M+H]^+$ 314.1652, found 314.1645.

Beige crystals (***trans* isomer**). Mp.: 54.6 – 61.9 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.42 – 7.14 (5H, m, H-2', 3', 4', 5', 6'), 7.25 (1H, m, H-9), 7.04 (1H, dm, *J* = 8.5 Hz, H-10), 6.89 (1H, dm, *J* = 7.5 Hz, H-7), 6.76 (1H, m, H-8), 4.64 (1H, s, H-6), 4.20 (1H, m, H_x-1), 3.29 (1H, dd, *J* = 11.0 and 2.5 Hz, H-4a), 2.86 (1H, m, H_y-1), 2.14 - 1.42 (6H, m, $H_{x,y}$-2, 3, 4); ^{13}C NMR: (125 MHz, chloroform-*d*): 144.3 (C-10a), 138.0 (C-1'), 130.8 (C-7), 130.6 (C-2', 6'), 129.5 (C-9), 128.8 (C-4'), 128.6 (C-3', 5'), 119.4 (C-8), 118.8 (C-6a), 114.3* (C-2"), 114.2 (C-10), 113.7* (C-1"), 55.7 (C-4a), 49.8 (C-6), 48.8 (C-1), 43.5 (C-5), 28.8 (C-4), 24.5 (C-2), 23.5 (C-3). HRMS (ESI+) *m/z* calcd. for $C_{21}H_{20}N_3$ $[M+H]^+$ 314.1652, found 314.1657.

cis-(±)-5'-Methyl-1,2',3,3',3'a,5'-hexahydro-1'*H*-spiro[indene-2,4'-pyrrolo[1,2-*a*]quinoline]-1,3-dione (42a *cis*)
trans-(±)-5'-Methyl-1,2',3,3',3'a,5'-hexahydro-1'*H*-spiro[indene-2,4'-pyrrolo[1,2-*a*]quinoline]-1,3-dione (42a *trans*)

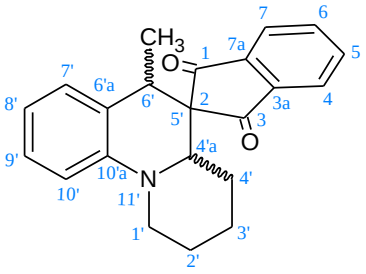


Following **method C3**, the title compound was isolated. To the mixture of the 2-pyrrolidinoacetophenone (0.99 g, 5.25 mmol) in 5 mL of *n*-BuOH ID (1.15 g, 7.88 mmol, 1.5 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 150 °C for 20 minutes. The crude product was purified by column chromatography (*n*-hexane/EtOAc 7:1). Orange crystals (0.82 g, 49% overall yield of the diastereomers). Mp.: 133.5 – 134.5 °C (*n*-Hexane). The ratio of the diastereomers in the crude product was determined by NMR: cis/trans 75:25. ^{1}H NMR (500 MHz, chloroform-*d*, ***cis* isomer**): 8.04-7.77 (4H, m, H-4, 5, 6, 7), 7.20 (1H, m, H-8'), 7.16 (1H, dm, *J* = 8 Hz, H-6'), 6.69 (1H, m, H-7'), 6.58 (1H, dm, *J* = 8 Hz, H-9'), 3.92 (1H, dd *J* = 10, 6 Hz, H-3'a), 3.58 (1H, m, H_x-1'), 3.48 (1H, q, *J* = 7 Hz, H-5'), 3.27 (1H, m, H_y-1'), 2.00-1.82 (2H, m, H-2'), 1.78 (1H, m, H_x-3'), 1.23 (1H, m, H_y-3'), 1.11 (3H, d, *J* = 7 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 204.0* (C-3), 199.7* (C-1), 143.8** (C-7a), 143.7 (C-9'a), 142.6** (C-3a), 135.8, 135.3 (C-4, 5), 127.5 (C-8'), 125.7 (C-6'), 122.7, 122.6 (C-6, 7), 122.5 (C-5'a), 115.6 (C-7'), 110.2 (C-9'), 62.1 (C-

3’a), 56.5 (C-2≡C-4’), 47.7 (C-1’), 37.7 (C-5’), 28.3 (C-3’), 23.6 (C-2’), 14.5 (*C*H$_3$). Anal. calcd. for $C_{21}H_{19}NO_2$ (317.36): C, 79.47%; H, 6.04%; N, 4.42%. Found: C, 79.55%; H, 6.04%; N, 4.09%.

The two diastereomers were separated by preparative HPLC („AD-H”, *n*-hexane/ethanol 50:50, flow rate 0.5 mL/min). (***trans* isomer**) Light yellow solid. Mp.: 157.0 – 159.8 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 8.02-7.76 (4H, m, H-4, 5, 6, 7); 7.19 (1H, m, H-8’), 6.94 (1H, dm, *J* = 7.5 Hz, H-6’), 6.62 (1H, m, H-9’), 6.62 (1H, m, H-7’), 4.18 (1H, dd, *J* = 11, 6 Hz, H-3’a), 3.64 (1H, m, H$_x$-1’), 3.28 (1H, m, H$_y$-1’), 3.03 (1H, q, *J* = 7.5 Hz, H-5’), 2.07-1.95 (2H, m, H-2’), 1.86 (1H, m, H$_x$-3’), 1.37 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.31 (1H, m, H-3’); ^{13}C NMR (125 MHz, chloroform-*d*): 201.8* (C-1), 199.1* (C-3), 143.6 (C-9’a), 141.8** (C-7a), 141.8** (C-3a), 135.7, 135.3 (C-4, 5), 128.1 (C-6’), 127.8 (C-8’), 123.8 (C-5’a), 123.3, 123.1 (C-6, 7), 115.5 (C-7’), 110.7 (C-9’), 55.6 (C-3’a), 54.9 (C-2≡C-4’), 48.2 (C-1’), 39.3 (C-5’), 28.0 (C-3’), 24.1 (C-2’), 20.6 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{21}H_{20}NO_2$ $[M+H]^+$ 318.1489, found 318.1496.

cis-(±)-(6'-Methyl-1,1',2',3,3',4',4'a,6'-octahydrospiro[indene-2,5'-pyrido[1,2-*a*]quinoline]-1,3-dione (42b _cis_)
trans-(±)-(6'-Methyl-1,1',2',3,3',4',4'a,6'-octahydrospiro[indene-2,5'-pyrido[1,2-*a*]quinoline]-1,3-dione (42b _trans_)

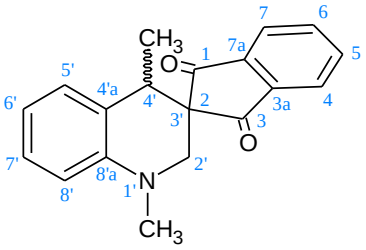


Following **method C3**, the title compound was isolated. To the mixture of the 2-piperidinoacetophenone (1.00 g, 4.92 mmol) in 5 mL of *n*-BuOH ID (1.08 g, 7.38 mmol, 1.5 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 150 °C for 30 minutes. The crude product was purified by column chromatography (*n*-hexane/EtOAc 10:1). Light yellow powder (1.19 g, 72% overall yield of the diastereomers). Mp.: 158.5 – 159.5 °C (*n*-Hexane). The ratio of the diastereomers in the crude product was determined by NMR: cis/trans 62:38. ^{1}H NMR (500 MHz, chloroform-*d*, ***cis* isomer**): 8.08-7.74 (4H, m, H-4, 5, 6, 7), 7.19 (1H, m, H-9’), 7.11 (1H, dm *J* = 8 Hz, H-7’), 6.97 (1H, dm, *J* = 8.5 Hz, H-10’), 6.75 (1H, m, H-8’), 4.14 (1H, m, H$_x$-1’), 3.52 (1H, q, *J* = 7 Hz, H-6’), 3.45 (1H, dd, *J* = 12 and 2 Hz, H-4’a), 2.83 (1H, m, H$_y$-1’), 1.04 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.78-0.98 (6H, m, H-2’, 3’, 4’); ^{13}C NMR

(125 MHz, chloroform-*d*): 204.1* (C-3), 199.7* (C-1), 146.0 (C-10'a), 143.8** (C-7a), 142.7** (C-3a), 136.0, 135.4 (C-4, 5), 127.4 (C-9'), 125.7 (C-7'), 125.4 (C-6'a), 122.8, 122.7 (C-6, 7), 117.7 (C-8'), 113.2 (C-10'), 61.1 (C-4'a), 60.4 (C-2≡C-5'), 49.3 (C-1'), 36.7 (C-6'), 29.0, 25.3, 24.2 (C-2', 3', 4'), 14.4 (*C*H_3). Anal. calcd. for $C_{22}H_{21}NO_2$ (331.39): C, 79.73%; H, 6.39%; N, 4.23%. Found: C, 80.15%; H, 6.40%; N, 3.93%. HRMS (ESI+) *m/z* calcd. for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645, found 332.1651.

The two diastereomers were separated by preparative HPLC („OJ-H", *n*-hexane/ethanol 50:50, flow rate 0.5 mL/min). (***cis* isomer**) Pale yellow crystals. Mp.: 184.0-185.1 °C (***trans* isomer**) Pale yellow powder. Mp.: 145.6-147.6 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.99-7.79 (4H, m, H-4, 5, 6, 7), 7.18 (1H, m, H-9'), 6.98 (1H, dm *J* = 7.5 Hz, H-7'), 6.93 (1H, dm *J* = 8 Hz, H-10'), 6.71 (1H, m, H-8'), 4.15 (1H, m, H_x-1'), 3.12 (1H, q, *J* = 7 Hz, H-6'), 3.44 (1H, dd, *J* = 10, 3 Hz, H-4'a), 2.88 (1H, m, H_y-1'), 1.26 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.86-1.36 (6H, m, H-2', 3', 4'); ^{13}C NMR 125 MHz, chloroform-*d*): 200.7* (C-3), 199.8* (C-1), 144.7 (C-10'a), 141.7** (C-7a), 141.7** (C-3a), 135.6, 135.5 (C-4, 5), 127.7 (C-7'), 127.5 (C-9'), 126.5 (C-6'a), 123.4, 123.3 (C-6, 7), 117.3 (C-8'), 112.7 (C-10'), 59.5 (C-2≡C-5'), 56.9 (C-4'a), 49.2 (C-1'), 35.8 (C-6'), 27.8, 25.0, 24.6 (C-2', 3', 4'), 18.8 (*C*H_3). HRMS (ESI+) *m/z* calcd. for $C_{22}H_{22}NO_2$ $[M+H]^+$ 332.1645, found 332.1655.

1',4'-Dimethyl-1,2',3,4'-tetrahydro-1'*H*-spiro[indene-2,3'-quinoline]-1,3-dione (42c)

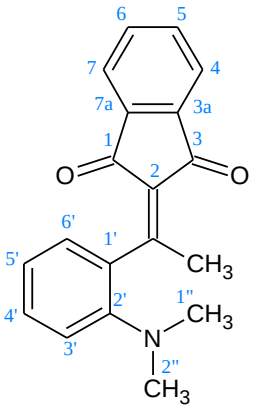


Following **method C3**, the title compound was isolated. To the mixture of the 2-dimethylacetophenone (1.00 g, 6.13 mmol) in 6 mL of *n*-BuOH ID (1.34 g, 9.19 mmol, 1.5 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 150 °C for 25 minutes. After the column chromatography (*n*-hexane/EtOAc 9:1) two different fractions were obtained.

The first fraction was the ring-closured compound by the NMR analysis, as light yellow crystals (0.62 g, 35%). Mp.: 114.5 – 115.5 °C (2-propanol). ^{1}H NMR (500 MHz, chloroform-*d*): 8.02-7.80 (4H, m, H-4, 5, 6, 7), 7.20 (1H, m, H-7'), 7.12 (1H, dm, *J* = 7.5 Hz, H-5'), 6.74 (1H, m, H-6'), 6.72 (1H, dm, *J* = 6 Hz, H-8'), 3.55 (1H, d, *J* = 12 Hz, H_x-2'), 3.40 (1H, q, *J* = 7 Hz, H-4'), 3.26 (1H, d, *J* = 12 Hz, H_y-2'), 2.98

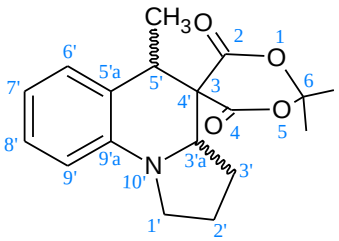
(3H, s, NCH_3), 1.16 (3H, d, J = 7 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 202.0* (C-3), 199.7* (C-1), 145.2 (C-8'a), 142.2** (C-7a), 141.2** (C-3a), 135.9***, 135.5*** (C-4, 7), 127.4 (C-7'), 126.0 (C-5'), 124.6 (C-4'a), 123.2****, 123.1**** (C-5, 6), 116.8 (C-6'), 110.7 (C-8'), 55.8 (C-2≡C-3'), 53.6 (C-2'), 39.3 (N*C*H_3), 36.1 (C-4'), 15.3 (*C*H_3). Anal. calcd. for $C_{19}H_{17}NO_2$ (291.34): C, 78.33%; H, 5.88%; N, 4.80%. Found: C, 78.77%; H, 5.93%; N, 4.58%. HRMS (ESI+) *m/z* calcd. for $C_{19}H_{17}NO_2$ $[M+H]^+$ 292.1332 found 292.1335.

2-{1'-[2'-(Dimethylamino)phenyl]ethylidene}-2,3-dihydro-1*H*-indene-1,3-dione (41)



The second fraction was the vinyl compound by the NMR analysis, as a red crystals (0.01g, 1%). Mp.: 110.5 – 114.0 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 8.00-7.69 (4H, m, H-4, 5, 6, 7), 7.35 (1H, m, H-4'), 7.10 (1H, dm, J = 7.5 Hz, H-3'), 7.02 (1H, dm, J = 5.5 Hz, H-6'), 6.96 (1H, m, H-5'), 2.86 (3H, s, CH_3), 2.71 (6H, s, N(CH_3)$_2$); ^{13}C NMR 125 MHz, chloroform-*d*): 192.1* (C-3), 188.8* (C-1), 169.7 (*C*=C), 150.6 (C-2'), 141.3** (C-7a), 140.8** (C-3a), 134.8***, 134.8*** (C-4, 7), 133.8 (C-1'), 130.0 (C-4'), 129.3 (C-6'), 126.7 (C-2), 123.0****, 122.7**** (C-5, 6), 120.7 (C-5'), 118.0 (C-3'), 43.8 N(*C*H_3)$_2$), 22.1 (*C*H_3). HRMS (ESI+) *m/z* calcd. for $C_{19}H_{17}NO_2$ $[M+H]^+$ 292.1332, found 292.1337.

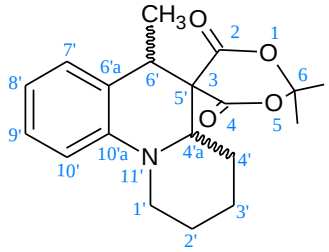
5',6,6-Trimethyl-2',3',3'a,5'-tetrahydro-1'*H*-spiro[1,5-dioxane-3,4'-pyrrolo[1,2-*a*]quinoline]-2,4-dione (44a *cis*)



Following **method C3**, the title compound was isolated. To the mixture of the 2-pyrrolidinoacetophenone (1.00 g, 5.25 mmol) in 8 mL of EtOH Meldrum's acid (3.03 g, 21.02 mmol, 4 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 50 °C for 10 hours. The crude product was purified by column chromatography (*n*-hexane/EtOAc 8:1). Yellow crystals (0.53 g, 31%, overall yield of the diastereomers). Mp.: 160.0 – 161.5 °C

(*n*-Hexane). The ratio of the diastereomers in the crude product was determined by NMR: cis/trans 83:17. ^{1}H NMR (500 MHz, chloroform-*d*, ***cis* isomer**): 7.18 (1H, m, H-8'), 7.17 (1H, dm, *J* = 8 Hz, H-6'), 6.71 (1H, m, H-7'), 6.56 (1H, dm, J = 7.5 Hz, H-9'), 4.07 (1H, dd, *J* = 9.5, 5.5 Hz, H-3'a), 3.66 (1H, q, *J* = 7 Hz, H-5'), 3.62 (1H, m, H_x-1'), 3.29 (1H, m, H_y-1'), 2.19 (1H, m, H_x- 3'), 2.07 (1H, m, H_x-2'), 1.98 (1H, m, H_y-2'), 1.77 (3H, s, OO(C-6)(CH_3)$_x$), 1.76 (3H, s, OO(C-6)(CH_3)$_y$), 1.71 (1H, m, H_y-2'), 1.44 (3H, d *J* = 7 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 169.5* (C-2), 162.3* (C-4), 143.1 (C-9'a), 127.6 (C-8'), 125.4 (C-6'), 121.9 (C-5'a), 116.0 (C-7'), 110.6 (C-9'), 105.6 (C-6), 64.4 (3'a), 53.6 (C-3≡C-4'), 47.9 (C-1'), 40.4 (C-5'), 30.1** (OO(C-6)*C*H$_3$), 29.4** (OO(C-6)*C*H$_3$), 29.1 (C-3'), 23.1 (C-2'), 15.4 (*C*H$_3$). Anal. calcd. for $C_{18}H_{21}NO_4$ (315.35): C, 68.55%; H, 6.71%; N, 4.44%. Found: C, 68.92%; H, 6.84%; N, 4.20%. HRMS (ESI+) *m/z* calcd. for $C_{18}H_{21}NO_4$ $[M+Na]^+$ 338.1363, found 338.1366.
We were not able to separated the two diastereomers, thus the *trans* isomer was not characterized.

6,6,6'-Trimethyl-1',2',3',4',4'a,6'-hexahydrospiro[1,5-dioxane-3,5'-pyrido[1,2-*a*]quinoline]-2,4-dione (44b *cis*)

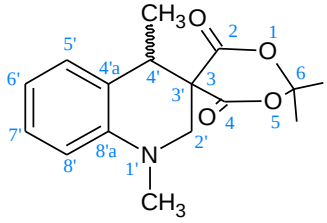


Following **method C3**, the title compound was isolated. To the mixture of the 2-piperidinoacetophenone (1.00 g, 4.89 mmol) in 8 mL of EtOH Meldrum's acid (2.82 g, 19.57 mmol, 4 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 50 °C for 2.5 hours. The crude product was purified by column chromatography (*n*-hexane/EtOAc 8:1). White crystals (0.24 g, 15%, overall yield of the diastereomers). Mp.: 121.5 – 122.5 °C (*n*-Hexane). The ratio of the diastereomers in the crude product was determined by NMR: cis/trans 63:37. ^{1}H NMR (500 MHz, chloroform-*d*, ***cis* isomer**): 7.17 (1H, m, H-9'), 7.12 (1H, dm, *J* = 7.5 Hz, H-7'), 6.94 (1H, dm, *J* = 8.5 Hz, H-10'), 6.78 (1H, m, H-8'), 4.12 (1H, m, H_x-1'), 3.73 (1H, q, *J* = 7 Hz, H-6'), 3.58 (1H, dd, *J* = 11.5, 2.5 Hz, H-4'a), 2.83 (1H, m, H_y-1'), 1.77 (3H, s, OO(C-6)(CH_3)$_x$), 1.77 (3H, s, OO(C-6)(CH_3)$_y$), 1.98-1.37 (6H, m, H-2', 3', 4'), 1.41 (3H, d, *J* = 7 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 169.2* (C-4), 162.5* (C-2), 145.5 (C-10'a), 127.4 (C-9'), 125.4 (C-7'), 124.7 (C-6'a), 118.2 (C-8'), 113.3 (C-10'), 105.9 (C-6), 62.5 (C-4'a), 58.6 (C-3≡C-5'),

49.1 (C-1'), 39.4 (C-6'), 30.3** (OOC*C*H$_3$), 29.9** (OOC*C*H$_3$), 29.3 (C-4'), 25.0 (C-2'), 24.0 (C-3'), 15.4 (*C*H$_3$). Anal. calcd. for $C_{19}H_{23}NO_4$ (329.37): C, 69.28%; H, 7.04%; N, 4.25%. Found: C, 68.99%; H, 7.06%; N, 3.94%.

We were not able to separate the two diastereomers, thus the *trans* isomer was not characterized.

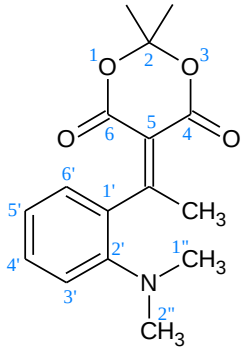
1',4',6,6-Tetramethyl-2',4'-dihydro-1'*H*-spiro[1,5-dioxane-3,3'-quinoline]-2,4-dione (44c)



Following **method C3**, the title compound was isolated. To the mixture of the 2-dimethylacetophenone (0.50 g, 3.06 mmol) in 4 mL of EtOH Meldrum's acid (1.32 g, 9.18 mmol, 3 eq) and 2 drops of acetic acid were added. The reaction mixture was irradiated at 45 °C for 9 hours. After the column chromatography (*n*-hexane/EtOAc 8:1) two different fractions were obtained.

The first fraction was the ring-closured compound by the NMR analysis, as a white powder (0.16 g, 18%). Mp.: 66 - 67 °C (*n*-Hexane). ^{1}H NMR (500 MHz, chloroform-*d*): 7.20 (1H, m, H-7'), 7.13 (1H, dm, *J* = 8 Hz, H-5'), 6.79 (1H, m, H-6'), 6.72 (1H, dm, *J* = 8 Hz, H-8'), 3.74 (1H, d, *J* = 12 Hz, H$_x$-2'), 3.63 (1H, q, *J* = 7 Hz, H-4'), 3.51 (1H, d, *J* = 12 Hz, H$_y$-2'), 2.99 (3H, s, NC*H*$_3$), 1.78 (3H, s, OO(C-6)(C*H*$_3$)$_x$), 1.76 (3H, s, OO(C-6)(C*H*$_3$)$_y$), 1.39 (3H, d, *J* = 7 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, chloroform-*d*): 169.2* (C-4), 165.2* (C-2), 145.0 (C-8'a), 127.6 (C-7'), 125.6 (C-5'), 124.6 (C-4'a), 117.9 (C-6'), 111.4 (C-8'), 105.1 (C-6), 56.7 (C-2'), 53.7 (C-3≡C-3'), 39.7 (C-4'), 39.4 (N*C*H$_3$), 29.9** (OOC*C*H$_3$), 28.7** (OOC*C*H$_3$), 15.0 (*C*H$_3$). Anal. calcd. for $C_{16}H_{19}NO_4$ (289.31): C, 66.42%; H, 6.62%; N, 4.84%. Found: C, 66.02%; H, 6.61%; N, 4.47%.

5-{1-[2-(Dimethylamino)phenyl]ethylidene}-2,2-dimethyl-1,3-dioxane-4,6-dione (43)



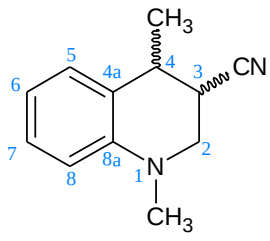
The second fraction was the vinyl compound by the NMR analysis, as red crystals (0.11 g, 13%). Mp.: 100 – 105°C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.32 (1H, m, H-4'), 7.10 (1H, dm, *J* = 8 Hz, H-3'), 7.00 (1H, m, H-5'), 6.91 (1H, dm, *J* = 8 Hz, H-6'), 2.74 (3H, s, C*H*$_3$), 2.70 (6H, s, N(C*H*$_3$)$_2$), 1.86 (3H, s, OO(C-2)(C*H*$_3$)$_x$), 1.80 (3H, s, OO(C-2)(C*H*$_3$)$_y$); ^{13}C NMR (125 MHz, chloroform-*d*): 175.2 (CH$_3$*C*=(C-5)), 161.6* (C-4), 160.6* (C-6), 149.8 (C-2'), 136.5 (C-1'), 130.1 (C-4'), 126.8 (C-3'), 122.1 (C-5'), 119.0 (C-3'), 116.0 (C-5), 103.7 (C-2), 44.0 (N(*C*H$_3$)$_2$), 27.5** (OO*C*CH$_3$), 27.3** (OO*C*CH$_3$), 25.1 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{16}H_{19}NO_4$ $[M+Na]^+$ 312.1206, found 312.1209.

3.3.5. General procedure for the radical decyanation (method D)

The dinitrile compound (pure diastereomer) (1 eq) was dissolved in dry toluene (80 mL) (distilled from $LiAlH_4$ prior to use), a pale yellow solution was formed. After addition of azobisisobutyronitrile (AIBN) (0.2 eq) and tributyltinhydride (2 eq) at 0 °C, the mixture was stirred for the time indicated below at 80 °C (oil bath). After cooling, an aliquot was taken for the analysis of the diastereomers. To the pale yellow or colorless reaction mixture 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.3 eq) was added and stirred for 30 min. The mixture was filtered through a silica gel plug and the solvent was evaporated in vacuum. The crude product was purified as described below.

The ratio of the diastereomers in the crude product was determined by HPLC (Gemini NX C18 RP 25 cm×4.6 mm 5 µm column, CH_3CN/H_2O 80:20) or ^{1}H NMR.

***cis*-(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile (38a *cis*)**

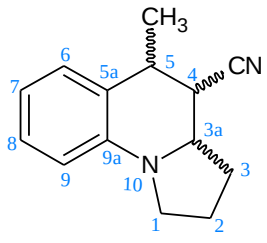


Following **method D**, the title compound was isolated. To a solution of the dinitrile derivative (0.77 g, 3.63 mmol) in 20 mL of toluene, AIBN (0.12 g, 0.73 mmol, 0.2 eq) and tributyltinhydride (2.9 mL, 3.17 g, 10.87 mmol, 3 eq) were

added at 0 °C, the reaction mixture was stirred at 90-100 °C for 1.5 hours. Diastereomeric ratio in the crude product (HPLC): 67:33 *cis*/*trans*. Overall yield of the diastereomers is 85%. The diastereomers were separated by preparative HPLC (see Appendix). The determination of the relative configuration in these compounds was not possible, due to overlap of the relevant aliphatic protons. However, the Boc derivative (**39a**) proved to be *cis* diastereoisomer, based on NOE interactions and analysis of the vicinal coupling constants. Since under the reaction conditions of Boc formation the configuration of the carbon atoms does not change, the relative configuration in this compound is also *cis*. White crystals. Mp.: 88.0-89.5 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.15 – 7.14 (1H, m, H-7), 7.06 - 7.04 (1H, m, H-5), 6.73 – 6.71 (1H, m, H-6), 6.64 (1H, dm, *J* = 7.5 Hz, H-8), 3.49 – 3.45 (2H, m, $H_{x,y}$-2), 3.22 – 3.22 – 3.19 (2H, m, H-3, 4), 2.95 (3H, s, NCH_3), 1.45 (3H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, chloroform-*d*): 144.9 (C-8a), 128.9 (C-5), 128.8 (C-7), 124.6 (C-4a), 120.1 (*C*N), 118.0 (C-6), 112.2 (C-8), 49.6 (C-2), 39.6 (N*C*H$_3$), 33.7 (C-4), 31.7 (C-3), 20.6 (*C*H$_3$). Anal. calcd (%) for $C_{12}H_{14}N_2$ (186.25): C, 77.38; H, 7.58; N, 15.04. Found: C, 77.33; H, 7.67; N, 15.14. HRMS (ESI+) *m/z* calcd. for $C_{12}H_{15}N_2$ $[M+H]^+$ 187.1230, found 187.1225.

cis-cis-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-carbonitrile (38b _cis-cis_)

cis-trans-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-carbonitrile (38b _cis-trans_)



Following **method D**, the title compounds were isolated. To a mixture of the dinitrile derivative (*cis* isomer) (4.04 g, 17.04 mmol) in 70 mL of toluene AIBN (0.56 g, 34.10 mmol, 0.2 eq) and tributyltinhydride (9.18 mL, 34.08 mmol, 2 eq) were added at 0 °C, the reaction mixture was stirred at 90 °C for 24 hours. Diastereomeric ratio in the crude product (HPLC): 58:42 *cis-cis*/*cis-trans*. The two diastereomers were separated by column chromatography (*n*-hexane/EtOAc 4:1).

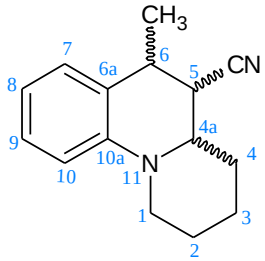
(**38b _cis-cis_**) Off-white crystals (1.10 g, 31%). Mp.: 136.4-137.4 °C (*n*-hexane/EtOAc 6.5:1). ^{1}H NMR (500 MHz, chloroform-*d*): 7.14 – 7.12 (2H, m, H-6, 8), 6.68 – 6.67

(1H, m, H-7), 6.47 (1H, dm, *J* = 8.5 Hz, H-9), 3.73 – 3.70 (1H, m, H-3a), 3.40 – 3.38 (1H, m, H_x-1), 3.34 – 3.33 (1H, m, H_y-1), 3.24 – 3.23 (1H, m, H-5), 3.13 (1H, dd, *J* = 4.8 and 3.0 Hz, H-4), 2.19 - 2.17 (2H, m, H_x-2, 3), 2.00 – 1.97 (2H, m, H_y-2, 3), 1.57 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, chloroform-*d*): 143.9 (C-9a), 128.9 (C-8), 127.0 (C-6), 121.9 (C-5a), 118.4 (*C*N), 116.8 (C-7), 111.4 (C-9), 59.0 (C-3a), 47.9 (C-1), 37.7 (C-4), 34.8 (C-5), 31.3 (C-3), 24.0 (C-2), 18.4 (*C*H$_3$). Anal. calcd (%) for $C_{14}H_{16}N_2$ (212.29): C, 79.21; H, 7.60; N, 13.20. Found: C, 79.35; H, 7.64; N, 13.24. HRMS (ESI+) *m/z* calcd. for $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1386, found 213.1392.

(**38b *cis-trans***) White crystals (0.82 g, 22%). Mp.: 142.8-143.5 °C (*n*-hexane). ^{1}H NMR (500 MHz, chloroform-*d*): 7.17 (1H, dm, *J* = 7.5 Hz, H-6), 7.14 - 7.13 (1H, m, H-8), 6.70 - 6.69 (1H, m, H-7), 6.45 (1H, dm, *J* = 9.0 Hz, H-9), 3.63 – 3.62 (1H, m, H-3a), 3.40 -3.39 (1H, m, H_x-1), 3.29 – 3.27 (1H, m, H_y-1), 3.17 – 3.16 (1H, m, H-5), 2.47 – 2.44 (1H, m, H_x-3), 2.35 (1H, dd, *J* = 11.5 and 10.4 Hz, H-4), 2.14 - 2.11 (1H, m, H_x-2), 1.99 -1.97 (1H, m, H_y-2), 1.70 -1.67 (1H, m, H_y-3), 1.58 (3H, d, *J* = 6.5 Hz, C*H*$_3$); ^{13}C NMR (125 MHz, chloroform-*d*): 143.9 (C-9a), 128.8 (C-8), 127.1 (C-6), 123.3 (C-5a), 121.3 (*C*N), 117.0 (C-7), 111.6 (C-9), 59.8 (C-3a), 48.4 (C-1), 40.3 (C-4), 35.9 (C-5), 33.1 (C-3), 23.8 (C-2), 18.9 (*C*H$_3$). Anal. calcd (%) for $C_{14}H_{16}N_2$ (212.29): C, 79.21; H, 7.60; N, 13.20. Found: C, 79.45; H, 7.64; N, 13.25. HRMS (ESI+) *m/z* calcd. for $C_{14}H_{17}N_2$ $[M+H]^+$ 213.1386, found 213.1390.

cis-cis-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5-carbonitrile (38c _cis-cis_)

cis-trans-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5-carbonitrile (38c _cis-trans_)



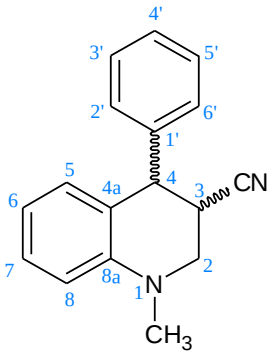
Following **method D**, the title compounds were isolated. To a mixture of the dinitrile derivative (*cis* isomer) (4.86 g, 19.37 mmol) in 80 mL of toluene AIBN (0.63 g, 3.87 mmol, 0.2 eq) and tributyltinhydride (10.43 mL, 11.27 g, 38.74 mmol, 2 eq) were added at 0 °C, the reaction mixture was stirred for 24 hours at 90 °C. Diastereomeric product ratio in the crude

product (HPLC): 72:28 *cis-cis*/*cis-trans*. The two diastereomers were separated by column chromatography (*n*-hexane/EtOAc 4:1).

(**38c *cis-cis***) White crystals (2.50 g, 55%). Mp.: 181.6-183.0 °C (*n*-hexane/EtOAc 1:1.1). ^{1}H NMR: (500 MHz, chloroform-*d*): 7.15 – 7.11 (2H, m, H-7, 9), 6.89-6.87 (1H, dm, *J* = 10.5 Hz, H-10), 6.76 – 6.74 (1H, m, H-8), 3.98 (1H, dm, *J*= 15.5 Hz, H_x-1), 3.30 – 3.25 (1H, m, H-6), 3.13 – 3.09 (1H, m, H-4a), 3.04 - 3.02 (1H, m, H-5), 2.65 – 2.59 (1H, m, H_y-1), 1.91 – 1.89 (1H, m, H_x-3), 1.84 – 1.71 (4H, m, $H_{x,y}$-2, 4), 1.52 (3H, d, *J* = 12 Hz, CH_3), 1.41 - 1.39 (1H, m, H_y-3); ^{13}C NMR: (125 MHz, chloroform-*d*): 146.5 (C-10a), 128.6* (C-9), 127.5* (C-7), 125.4 (C-6a), 119.3 (C-8), 119.0 (*C*N), 114.4 (C-10), 57.9 (C-4a), 48.9 (C-1), 41.7 (C-5), 34.1 (C-6), 32.2 (C-4), 26.1 (C-2), 24.2 (C-3), 18.6 (*C*H_3). Anal. calcd (%) for $C_{15}H_{18}N_2$ (226.32): C, 79.61; H, 8.02; N, 12.38. Found: C, 79.75; H, 8.12; N, 11.98. HRMS (ESI+) *m/z* calcd. for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1543, found 227.1538.

(**38c *cis-trans***) White crystals (0.768 g, 17%). Mp.: 144.0 – 144.5 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.16 (1H, m, H-7), 7.16-7.13 (1H, m, H-9), 6.85 (1H, dm, *J* = 8.5 Hz, H-10), 6.80-6.77 (1H, m, H-8), 3.89 (1H, dm, *J* = 8.4 Hz, H_x-1), 3.15 (1H, m, H-6), 3.10 (1H, m, H-4a), 2.67 (1H, m, H_y-1), 2.58 (1H, m, H-5), 2.28 (1H, m, H_x-4), 1.90 (1H, m, H_x-3), 1.82 (1H, m, H_x-2), 1.62 (1H, m, H_y-2), 1.54 (3H, d, *J* = 4.8 Hz, CH_3), 1.44 (1H, m, H_y-3), 1.38 (1H, m, H_y-4); ^{13}C NMR: (125 MHz, chloroform-*d*): 146.4 (C-10a), 128.5 (C-9), 127.4 (C-7), 126.6 (C-6a), 121.1 (*C*N), 119.3 (C-8), 114.2 (C-10), 58.3 (C-4a), 49.0 (C-1), 42.9 (C-5), 35.2 (C-6), 32.9 (C-4), 25.9 (C-2), 24.2 (C-3), 19.7 (*C*H_3). Anal. calcd (%) for $C_{15}H_{18}N_2$ (226.32): C, 79.61; H, 8.02; N, 12.38. Found: C, 79.29; H, 7.99; N, 12.00. HRMS (ESI+) *m/z* calcd. for $C_{15}H_{19}N_2$ $[M+H]^+$ 227.1543, found 227.1532.

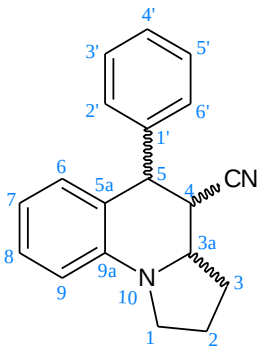
cis-(±)-1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile (38d *cis*)



Following **method D**, the title compound was isolated. To a mixture of the dinitrile derivative (1.03 g, 3.73 mmol) in 25 mL of toluene AIBN (0.11 g, 0.70 mmol, 0.2 eq) and tributyltinhydride (3.0 mL, 3.26 g, 11.20 mmol, 3 eq) were added at 0 °C, the reaction mixture was stirred at 90 °C for 2

hours. Only *cis* isomer was formed as determined form the crude product by NMR. After the crystallisation white, bright crystals were obtained (0.28 g, 30%). Mp.: 117.3 – 120.0 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.39 – 7.08 (6H, m, H-7, 2', 3', 4', 5', 6'), 6.90 – 6.82 (1H, dm, *J* = 7.3 Hz, H-5), 6.78 – 6.70 (1H, dm, *J* = 8.1 Hz, H-8), 6.69 – 6.61 (1H, m, H-6), 4.45 – 4.37 (1H, m, H-4), 3.51 – 3.31 (3H, m, $H_{x,y}$-2, H-3), 3.02 (3H, s, C*H*$_3$); ^{13}C NMR: (100 MHz, chloroform-*d*): 145.1 (C-8a), 140.6 (C-1'), 130.0 (C-5), 129.7 (C-2', 6'), 128.6 (C-7), 128.4 (C-3', 5'), 127.6 (C-4'), 121.0 (C-4a), 119.0 (*C*N), 117.3 (C-6), 111.5 (C-8), 49.0 (C-2), 45.0 (C-4), 39.1 (*C*H$_3$), 31.9 (C-3). Anal. calcd. for $C_{17}H_{16}N_2$ (248.33): C, 82.22%; H, 6.49%; N, 11.28%. Found: C, 81.89%; H, 6.50%; N, 11.11%. HRMS (ESI+) *m/z* calcd. for $C_{17}H_{17}N_2$ $[M+H]^+$ 249.1386, found 249.1382.

cis-cis-(±)-5-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-carbonitrile (38e _cis-cis_)
cis-trans-(±)-5-Phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4-carbonitrile (38e _cis-trans_)

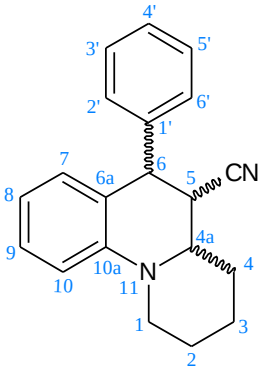


Following **method D**, the title compound (**38e *cis-trans***) was isolated. To a mixture of the dinitrile derivative (*cis* isomer) (2.28 g, 7.61 mmol) in 50 mL of toluene AIBN (0.25 g, 1.52 mmol, 0.2 eq) and tributyltinhydride (6.1 mL, 6.64 g, 22.82 mmol, 3 eq) were added at 0 °C, the reaction mixture was stirred at 90 °C for 8 hours. Diastereomeric product ratio in the crude product (NMR): *cis-cis*/*cis-trans* 50:50. The two diastereomers were separated by column chromatography (*n*-hexane/EtOAc 8:1). The pure ***cis-trans*** isomer was obtained. White crystals (0.34 g, 16%). Mp.: 205.3-205.6 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.39 – 7.30 (3H, m, H-3', 4', 5'), 7.26 – 7.21 (2H, m, H-2', 6'), 7.13 – 7.10 (1H, m, H-8), 6.58 – 6.49 (3H, m, H-6, 7, 9), 4.28 (1H, d, *J* = 11.8 Hz, H-5), 3.77 – 3.70 (1H, m, H-3a), 3.47 – 3.35 (2H, m, $H_{x,y}$-1), 2.81 (1H, dd, *J* = 11.8 and 10.4 Hz, H-4), 2.50 – 2.44 (1H, m, H_x-3), 2.19 – 2.15 (1H, m, H_x-2), 2.07 – 1.99 (1H, m, H_y-2), 1.79 – 1.73 (1H, m, H_y-3); ^{13}C NMR: (100 MHz, chloroform-*d*): 143.7 (C-9a), 141.2 (C-1'), 129.7 (C-6), 129.03 (C-3', 5'), 128.96 (C-2', 6'), 128.3 (C-8), 127.8 (C-4'), 122.3 (C-5a), 119.8 (*C*N), 116.4

(C-7), 111.1 (C-9), 59.4 (C-3a), 48.5 (C-5), 47.6 (C-1), 40.7 (C-4), 32.3 (C-3), 23.0 (C-2). HRMS (ESI+) *m/z* calcd. for $C_{19}H_{19}N_2$ $[M+H]^+$ 275.1543, found 275.1541.

(**38e *cis-cis*** isomer) Beige powder. Mp.: 175.0 – 178.5 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.44 – 7.31 (5H, m, H-2', 3', 4', 5', 6'), 7.17 – 7.14 (1H, m, H-8), 6.72 (1H, dm, *J* = 2.7 Hz, H-6), 6.57 – 6.56 (1H, m, H-7), 6.56 – 6.54 (1H, m, H-9), 4.45 (1H, d, *J* = 5.0 Hz, H-5), 3.90 – 3.87 (1H, m, H-3a), 3.50 – 3.39 (2H, m, $H_{x,y}$-1), 3.29 (1H, dd, *J* = 4.9 and 2.7 Hz, H-4), 2.22 – 2.20 (2H, m, H_x-2, 3), 2.09 – 2.07 (1H, m, H_y-3), 2.05 – 2.00 (1H, m, H_y-2); ^{13}C NMR: (125 MHz, chloroform-*d*): 144.0 (C- 9a), 140.2 (C-1'), 129.5 (C-2', 6'), 129.1 (C-6), 128.7 (C-4'), 128.5 (C-8), 127.9 (C-3', 5'), 119.9 (C-5a), 118.2 (*C*N), 116.0 (C-7), 111.2 (C-9), 58.9 (C-3a), 47.6 (C-5), 47.1 (C-1), 38.2 (C-4), 30.5 (C-3), 23.2 (C-2). HRMS (ESI+) *m/z* calcd. for $C_{19}H_{19}N_2$ $[M+H]^+$ 275.1543, found 275.1545.

cis-cis-(±)-6-Phenyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5-carbonitrile (38f *cis-cis*)



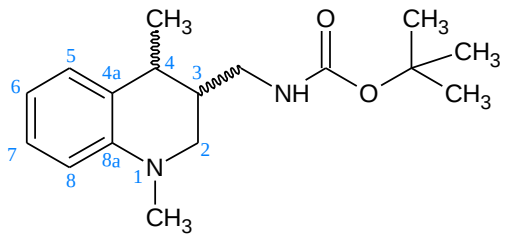
Following **method D**, the title compound was isolated. To a mixture of the dinitrile derivative (*cis* isomer) (3.00 g, 9.57 mmol) in 60 mL of toluene AIBN (0.31 g, 1.91 mmol, 0.2 eq) and tributyltinhydride (7.7 mL, 8.36 g, 28.72 mmol, 3 eq) were added at 0 °C, the reaction mixture was stirred at 90 °C for 3 hours. Diastereomeric product ratio in the crude product by NMR: *cis-cis*/*cis-trans* 95:5. The crude product was washed with diethyl ether to obtain the pure *cis-cis* isomer product. The *cis-trans* isomer was not isolated. White crystals (1.92 g, 71%). Mp.: 162.1-167.3 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.40 – 7.29 (5H, m, H-2', 3', 4', 5', 6'), 7.20 – 7.11 (1H, m, H-9), 6.99 – 6.90 (1H, m, H-10), 6.79 – 6.71 (1H, m, H-7), 6.69 – 6.59 (1H, m, H-8), 4.51 (1H, d, *J* = 5.5 Hz, H-6), 4.05 – 3.99 (1H, m, H_x-1), 3.31 – 3.25 (1H, m, H-4a), 3.17 (1H, dd, *J* = 5.5 and 2.0 Hz, H-5), 2.67 – 2.58 (1H, m, H_y-1), 1.94 – 1.70 (5H, m, $H_{x,y}$-2,3, H_x-4), 1.45 – 1.33 (1H, m, H_y-4); ^{13}C NMR: (100 MHz, chloroform-*d*): 147.0 (C-10a), 140.2 (C-1'), 129.7 (C-7), 129.6 (C-2', 6'), 128.6 (C-3', 5'), 128.3 (C-9), 127.8 (C-4'), 123.2 (C-6a), 118.6 (*C*N), 118.4 (C-8), 113.9 (C-10), 57.7 (C-4a), 48.1 (C-1), 46.9 (C-6), 42.2 (C-5), 31.5 (C-2), 25.5 (C-3), 23.2 (C-4). Anal. calcd. for $C_{20}H_{20}N_2$

(288.39): C, 83.30%; H, 6.99%; N, 9.71%. Found: C, 82.84%; H, 6.97%; N, 9.49%. HRMS (ESI+) *m/z* calcd. for $C_{20}H_{20}N_2$ $[M+Na]^+$ 311.1519, found 311.1527.

3.3.6. General procedure for the reduction of the mononitrile derivatives (method E)

The precursor mononitrile compound (1 eq) was dissolved in dry MeOH (distilled from Mg/I_2 prior use) (50 mL). At 0 °C di-*tert*-butyl dicarbonate (Boc_2O) (2 eq) and $NiCl_2 \times 6H_2O$ (0.4 eq) were added under argon atmosphere. Subsequently $NaBH_4$ (10 eq) was added in small portions (within 45-55 min), keeping the temperature below 5 °C (the reaction is strongly effervescent, while adding $NaBH_4$ and the reaction mixture turns black). The mixture was allowed to warm up and was stirred for 1 hour at ambient temperature, followed by adding of 25% aq. NH_3 (100 mL) and the mixture was stirred for a further 1 h. After evaporation to dryness, the residue was taken up in 300 mL of H_2O/EtOAc 2:1 and the phases were separated. The inorganic layer was extracted with EtOAc (4×50 mL) and washed with saturated $NaHCO_3$ solution (2×50 mL). The organic phase was dried over $MgSO_4$, filtered, evaporated to dryness and purified by column chromatography.

tert-Butyl _N_-{[_cis_-(±)-1,4-dimethyl-1,2,3,4-tetrahydroquinolin-3-yl]methyl} carbamate (39a _cis_)
tert-Butyl _N_-{[_trans_-(±)-1,4-dimethyl-1,2,3,4-tetrahydroquinolin-3-yl]methyl}carbamate (39a _trans_)



Following **method E**, the title compounds were isolated. To the suspension of mononitrile compound (mixture of *cis*/*trans*) (0.40 g, 2.16 mmol, 1 eq) in dry MeOH (20 mL) di-*tert*-butyl dicarbonate (0.96 g, 4.38 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.21 g, 0.86 mmol, 0.4 eq) and $NaBH_4$ (0.82 g, 21.6 mmol, 10 eq) were added. The ratio of the diastereomers in the crude product by NMR: 66:34 *cis*/*trans*. After purification of the crude product by column chromatography (DCM/*n*-hexane 4:1) white crystals were obtained (0.50 g, 81%).

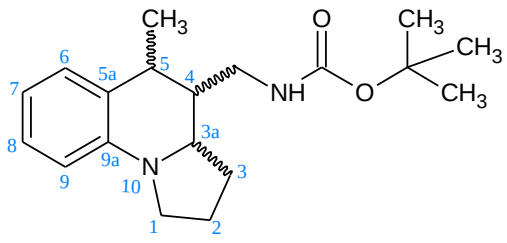
Diastereomers were separated by HPLC (Chiralpak® „AD-H" amylose tris-(3,5-dimethylphenyl-carbamate), 250 mm x 4.6 mm, 5 µm d_p. The mobile phase was a *n*-hexane/ethanol 50:50 mixture and the flow rate was 0.5 mL/min).

(**39a *cis***) Mp.: 67.0-73.5 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.08 (1H, m, H-7), 7.00 (1H, dm, *J* = 6.0 Hz, H-5), 6.62 (1H, m, H-6), 6.58 (1H, dm, *J* = 8.0 Hz, H-8), 4.60 (1H, brt, NH), 3.16 (2H, m, C*H*$_2$-NH), 3.13 (2H, m, H$_{x,y}$-2), 2.94 (1H, m, H-4), 2.90 (3H, s, N-C*H*$_3$), 2.18 (1H, m, H-3), 1.46 (9H, s, C(C*H*$_3$)$_3$), 1.13 (3H, d, *J* = 7.5 Hz, C*H*$_3$); ^{13}C NMR: (125 MHz, chloroform-*d*): 156.0 (*C*=O), 145.3 (C-8a), 128.4 (C-5), 127.6 (C-4a), 127.3 (C-7), 116.1 (C-6), 110.7 (C-8), 79.4 (*C*(CH$_3$)$_3$), 50.0 (C-2), 41.1 (*C*H$_2$-NH), 38.9 (N-*C*H$_3$), 37.1 (C-3), 33.8 (C-4), 28.4 (C(*C*H$_3$)$_3$), 17.8 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{17}H_{26}N_2O_2$ $[M+H]^+$ 291.2067, found 291.2079.

(**39a *trans***) Mp.: 92.0-98.8 °C. ^{1}H NMR: (500 MHz, chloroform-*d*): 7.08 (1H, m, H-7), 7.03 (1H, dm, *J* = 6.5 Hz, H-5), 6.65 (1H, m, H-6), 6.60 (1H, dm, *J*= 8.5 Hz, H-8), 4.73 (1H, brt, NH), 3.31 (1H, dd, *J* = 11.5 and 3.5 Hz, H$_x$-2), 3.11 – 3.00 (2H, m, C*H*$_2$-NH), 2.98 (1H, m, H$_y$-2), 2.90 (3H, s, N-C*H*$_3$), 2.65 (1H, m, H-4), 1.94 (1H, s, H-3), 1.44 (9H, s, C(C*H*$_3$)$_3$), 1.27 (3H, d, *J* = 7.0 Hz, C*H*$_3$); ^{13}C NMR: (125 MHz, chloroform-*d*): 156.2 (*C*=O), 145.4 (C-8a), 129.6 (C-5), 127.1 (C-7), 126.0 (C-4a), 116.6 (C-6), 111.1 (C-8), 79.2 (*C*(CH$_3$)$_3$), 49.0 (C-2), 42.9 (*C*H$_2$-NH), 39.3 (N-*C*H$_3$), 38.5 (C-3), 33.9 (C-4), 28.4 (C(*C*H$_3$)$_3$), 24.9 (C*H*$_3$). HRMS (ESI+) *m/z* calcd. for $C_{17}H_{26}N_2O_2$ $[M+H]^+$ 291.2067, found 291.2080.

tert-Butyl _N_-{[_cis-cis_-(±)-5-methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-_a_]quinolin-4-yl]methyl}carbamate (39b _cis-cis_)

tert-Butyl _N_-{[_cis-trans_-(±)-5-methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-_a_]quinolin-4-yl]methyl}carbamate (39b _cis-trans_)

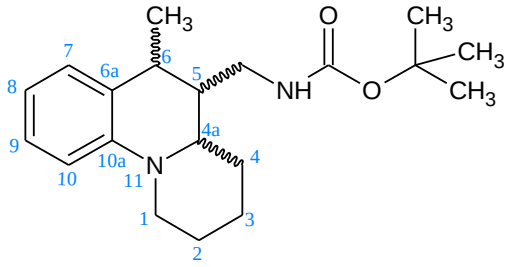


Following **method E**, the title compound (*cis-cis*) was isolated. To the suspension of mononitrile compound (*cis-cis*) (0.20 g, 0.96 mmol, 1 eq) in dry MeOH (20 mL), di-*tert*-butyl dicarbonate (0.43 g, 1.95 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.09 g, 0.38 mmol, 0.4 eq) and $NaBH_4$ (0.36 g, 9.6 mmol, 10 eq)

were added. After purification of the crude product by column chromatography (DCM/*n*-hexane 4:1) a beige powder was obtained (0.05 g, 18%). Mp.: 103.4 – 109.9 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.06 – 7.04 (2H, m, H-6, 8), 6.59 – 6.58 (1H, m, H-7), 6.33 (1H, dm, *J* = 8.5 Hz, H-9), 4.46 (1H, brs, NH), 3.77 – 3.75 (1H, m, H-3a), 3.28 – 3.22 (2H, m, $H_{x,y}$-1), 3.16 – 3.15 (1H, m, H-5), 3.05 - 3.04 (1H, m, C*H*$_2$-NH), 2.88 – 2.70 (1H, m, C*H*$_2$-NH), 2.07 – 2.06 (1H, m, H_x-2), 2.00 – 1.95 (2H, m, H_x-3, H-4), 1.90 – 1.87 (2H, m, H_y-2, 3), 1.45 (3H, d, *J* = 7.5 Hz, C*H*$_3$), 1.38 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, chloroform-*d*): 155.5 (*C*=O), 144.3 (C-9a), 127.3 (C-8), 126.0 (C-6), 123.7 (C-5a), 115.3 (C-7), 109.1 (C-9), 78.9 (*C*(CH$_3$)$_3$), 61.9 (C-3a), 47.0 (C-1), 39.9 (C-4), 36.1 (*C*H$_2$-NH), 35.8 (C-5), 29.0 (C-3), 28.4 (C(*C*H$_3$)$_3$), 23.7 (C-2), 17.1 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{19}H_{29}N_2O_2$ $[M+H]^+$ 317.2224, found 317.2236.

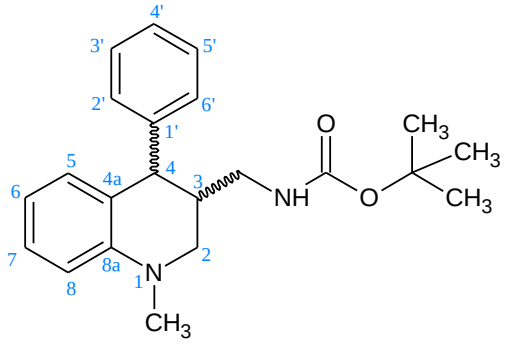
Following **method E**, the title compound (**39b *cis-trans***) was isolated. To the suspension of mononitrile compound (*cis-trans*) (0.30 g, 1.41 mmol, 1 eq) in dry MeOH (20 mL), di-*tert*-butyl dicarbonate (0.63 g, 2.86 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.13 g, 0.56 mmol, 0.4 eq) and $NaBH_4$ (0.53 g, 14.1 mmol, 10 eq) were added. After the work up, pale yellow crystals were obtained (0.41 g, 91%). Mp.: 80.7 – 82.9 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.19 (1H, dm, *J*= 7.5 Hz, H-6), 7.08 (1H, m, H-8), 6.65 (1H, m, H-7), 6.44 (1H, dm, *J*= 8.0 Hz, H-9), 4.57 (1H, brt, NH), 3.51 - 3.39 (2H, m, C*H*$_2$-NH), 3.34-3.33 (1H, m, H_x-1), 3.19 – 3.18 (1H, m, H_y-1), 3.07 – 3.06 (1H, m, H-3a), 2.76 - 2.73 (1H, m, H-5), 2.32 – 2.30 (1H, m, H_x-3), 2.09 – 2.07 (1H, m, H_x-2), 1.91 – 1.89 (1H, m, H_y-2), 1.59 – 1.56 (1H, m, H_y-3), 1.44 (9H, m, C(C*H*$_3$)$_3$), 1.37 (H, d, *J* = 7.0 Hz, C*H*$_3$), 1.35 – 1.33 (1H, m, H-4); ^{13}C NMR (125 MHz, chloroform-*d*): 156.2 (*C*=O), 144.7 (C-9a), 127.0 (C-6), 127.0 (C-8), 126.8 (C-5a), 115.9 (C-7), 110.6 (C-9), 79.3 (*C*(CH$_3$)$_3$), 59.9 (C-3a), 47.3 (C-1), 45.7 (C-4), 40.6 (*C*H$_2$-NH), 33.0 (C-5), 32.1 (C-3), 28.4 (C(*C*H$_3$)$_3$), 23.1 (C-2), 18.8 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{19}H_{29}N_2O_2$ $[M+H]^+$ 317.2224, found 317.2237.

tert-Butyl _N_-{[_cis-cis_-(±)-6-methyl-1_H_-2,3,4,4a,5,6-hexahydropyrido[1,2-_a_]quinolin-5-yl]methyl}carbamate (39c _cis-cis_)



Following **method E**, the title compound was isolated. To the suspension of mononitrile compound (*cis-cis*) (1.01 g, 3.47 mmol, 1 eq) in dry MeOH (50 mL), di-*tert*-butyl dicarbonate (1.52 g, 6.94 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.49 g, 2.08 mmol, 0.6 eq) and $NaBH_4$ (1.18 g, 31.21 mmol, 9 eq) were added. The crude product was purified by column chromatography (DCM/MeOH 100:1). White powder (0.36 g, 27%). Mp.: 111-113 °C. ^{1}H NMR: (500 MHz, dimethyl sulfoxide-d_6): 7.03 (1H, m, H-9), 7.03 (1H, dm, J = 7.0 Hz, H-7), 6.85 (1H, brd, H-10), 6.67 (1H, m, H-8), 6.64 (1H, brs, N*H*), 3.98 (1H, dm, J = 12.5 Hz, H_y-1), 3.16 (1H, m, H-4a), 3.10 (1H, m, CH_2-NH), 2.99 (1H, m, H-6), 2.90 (1H, m, CH_2-NH), 2.72 (1H, m, H_x-1), 2.09 (1H, m, H-5), 1.87 – 1.29 (6H, m, $H_{x,y}$-2, 3, 4), 1.38 (9H, s, C(CH_3)$_3$), 1.24 (3H, d, J = 7.5 Hz, CH_3); ^{13}C NMR: (125 MHz, dimethyl sulfoxide-d_6): 156.0 (*C*=O), 144.1 (C-10a), 128.9 (C-6a), 127.4 (C-7), 126.7 (C-9), 117.7 (C-8), 113.0 (C-10), 77.2 (*C*(CH$_3$)$_3$), 60.1 (C-4a), 48.5 (C-1), 41.0 (C-5), 37.8 (*C*H$_2$-NH), 34.0 (C-6), 28.1 (C(*C*H$_3$)$_3$), 28.1, 25.1, 24.9 (C-2, 3, 4), 17.0 (*C*H$_3$). HRMS (ESI+) *m/z* calcd. for $C_{20}H_{31}N_2O_2$ $[M+H]^+$ 331.2380, found 331.2391.

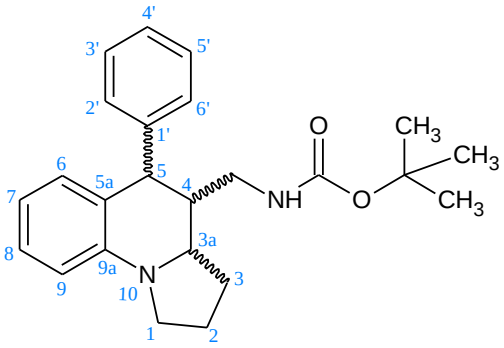
tert-Butyl _N_-{[_cis_-(±)-1-methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]methyl} carbamate (39d _cis_)



Following **method E**, the title compound was isolated. To the suspension of the mononitrile compound (*cis*) (0.48 g, 1.95 mmol, 1 eq) in dry MeOH (25 mL), di-*tert*-butyl dicarbonate (0.86 g, 3.96 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.19 g, 0.78 mmol, 0.4 eq) and $NaBH_4$ (0.74 g, 19.45 mmol, 10 eq) were added. After washing the crude product with diethyl ether, white crystals were obtained (0.67 g, 98%). Mp.: 162.3 – 163.0 °C. ^{1}H NMR:

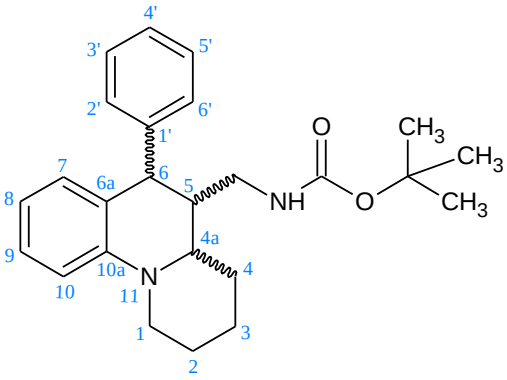
(600 MHz, chloroform-*d*): 7.28 – 7.09 (4H, m, H-7, 3', 4', 5'), 7.05 – 6.98 (2H, m, H-2', 6'), 6.90 – 6.85 (1H, dm, *J* = 7.6 Hz, H-5), 6-72 – 6.67 (1H, dm, *J* = 8.5 Hz, H-8), 6.59 – 6.53 (1H, m, H-6), 4.47 (1H, brs, NH), 4.14 (1H, d, *J* = 4.9 Hz, H-4), 3.19 – 3.09 (2H, m, CH_2-NH), 3.08 – 3.02 (1H, m, H_x-2), 3.00 (3H, s, CH_3), 2.79 – 2.68 (1H, m, H_y-2), 2.48 – 2.37 (1H, m, H-3), 1.42 (9H, s, C(CH_3)$_3$). ^{13}C NMR: (150 MHz, chloroform-*d*): 155.9 (*C*=O), 145.9 (C-8a), 142.2 (C-1'), 130.2 (C-5), 129.5 (C-2', 6'), 128.1 (C-3', 5'), 127.8 (C-7), 126.5 (C-4'), 124.3 (C-4a), 117.2 (C-6), 110.7 (C-8), 79.4 (*C*(CH$_3$)$_3$), 49.8 (*C*H$_2$-NH), 46.3 (C-4), 41.9 (C-2), 39.0 (*C*H$_3$), 37.5 (C-3), 28.4 (C(*C*H$_3$)$_3$). HRMS: (ESI+) *m/z* calcd. for $C_{22}H_{29}N_2O_2$ $[M+H]^+$ 353.2224; found. 353.2221.

tert-Butyl _N_-{[_cis-trans_-(±)-5-phenyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-_a_]quinolin-4-yl]methyl} carbamate (39e _cis-trans_)



Following **method E**, the title compound was isolated. To the suspension of the mononitrile compound (*cis-trans*) (0.30 g, 1.09 mmol, 1 eq) in dry MeOH (20 mL), di-*tert*-butyl dicarbonate (0.48 g, 2.21 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.10 g, 0.44 mmol, 0.4 eq) and $NaBH_4$ (0.41 g, 10.93 mmol, 10 eq) were added. After purification of the crude product by column chromatography (DCM) white crystals were obtained (0.11 g, 27%). Mp.: 187.5 – 189.0 °C (dec.). ^{1}H NMR: (400 MHz, chloroform-*d*): 7.39 – 7.14 (5H, m, H-2', 3', 4', 5', 6'), 7.07 – 7.03 (1H, m, H-8), 6.49 – 6.40 (3H, m, H-6, 7, 9), 4.19 (1H, brt, NH), 3.84 (1H, d, *J* = 11.4 Hz, H-5), 3.40 – 3.30 (3H, m, H_x-1, H_y-1, H-3a), 3.24 – 3.18 (1H, m, CH_2-NH), 3.12 – 3.09 (1H, m, CH_2-NH), 2.43 – 2.42 (1H, m, H_x-3), 2.13 – 2.10 (1H, m, H_x-2), 1.99 – 1.93 (1H, m, H_y-2), 1.89 – 1.83 (1H, m, H-4), 1.65 – 1.60 (1H, m, H_y-3), 1.40 (9H, s, C(CH_3)$_3$); ^{13}C NMR: (100 MHz, chloroform-*d*): 155.9 (*C*=O), 144.5 (C-9a), 144.0 (C-1'), 129.5 (C-6), 129.4 (C-2', 6'), 128.8 (C-4'), 127.4 (C-8), 126.8 (C-3', 5'), 125.5 (C-5a), 115.3 (C-7), 110.0 (C-9), 79.1 (*C*(CH$_3$)$_3$), 60.1 (3a), 48.2 (C-5), 47.2 (C-1), 45.1 (C-4), 41.1 (*C*H$_2$-NH), 32.3 (C-3), 28.4 (C(*C*H$_3$)$_3$), 23.4 (C-2). HRMS: (ESI+) *m/z* calcd. for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2380; found: 379.2374.

tert-Butyl _N_-({_cis-cis_-(±)-6-phenyl-1,2,3,4,4a,5,6-hexahydropyrido[1,2-_a_]quinolin-5-yl}methyl)carbamate (39f _cis-cis_)

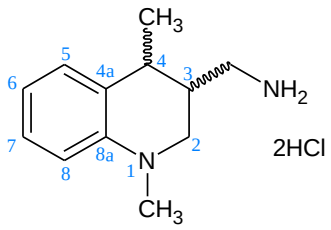


Following **method E**, the title compound was isolated. To the suspension of the mononitrile compound (*cis-cis*) (1.01 g, 3.47 mmol, 1 eq) in dry MeOH (50 mL), di-*tert*-butyl dicarbonate (1.52 g, 6.94 mmol, 2 eq), $NiCl_2 \times 6H_2O$ (0.49 g, 2.00 mmol, 0.6 eq) and $NaBH_4$ (1.18 g, 31.21 mmol, 9 eq) were added. After the column chromatography (DCM/MeOH 100:1) the product was washed with *n*-hexane. White crystals (0.36 g, 27%). Mp.: 111.0 – 113.0 °C. ^{1}H NMR: (400 MHz, chloroform-*d*): 7.36 – 7.15 (5H, m, H-2', 3', 4', 5', 6'), 7.16 – 7.13 (1H, m, H-9), 6.99 (1H, dm, *J* = 7.5 Hz, H-7), 6.89 (1H, dm, *J* = 8.2 Hz, H-10), 6.68 – 6.65 (1H, m, H-8), 4.51 (1H, d, *J* = 5.4 Hz, H-6), 3.93 – 3.90 (1H, m, H_x-1), 3.80 (1H, brt, NH), 3.51 – 3.46 (1H, m, C*H*$_2$-NH), 3.21 – 3.16 (1H, m, H-4a), 3.04 – 2.98 (1H, m, C*H*$_2$-NH), 2.59 – 2.52 (1H, m, H_y-1), 2.11 – 2.02 (1H, m, H-5), 1.90 – 1.28 (6H, m, $H_{x,y}$-2, 3, 4), 1.34 (9H, s, C(C*H*$_3$)$_3$); ^{13}C NMR: (100 MHz, chloroform-*d*): 155.5 (*C*=O), 148.4 (C-10a), 142.6 (C-1'), 130.2 (C-7), 129.2 (C-2', 6'), 128.8 (C-3', 5'), 127.6 (C-9), 126.5 (C-4'), 125.7 (C-6a), 117.7 (C-8), 113.4 (C-10), 78.6 (*C*(CH$_3$)$_3$), 60.1 (C-4a), 48.5 (C-1), 48.5 (C-6), 45.4 (C-5), 38.3 (*C*H$_2$-NH), 28.0 (C-2), 27.3 (C(*C*H$_3$)$_3$), 25.8 (C-3), 23.9 (C-4). Anal. calcd. for $C_{25}H_{32}N_2O_2$ (392.53): C, 76.49%; H, 8.22%; N, 7.14%. Found: C, 76.35%; H, 8.45%; N, 7.09%. HRMS: (ESI+) *m/z* calcd. for $C_{25}H_{33}N_2O_2$ $[M+H]^+$ 393.2537; found: 393.2532.

3.3.7. General procedure for the preparation of aminomethyl derivatives (method F)

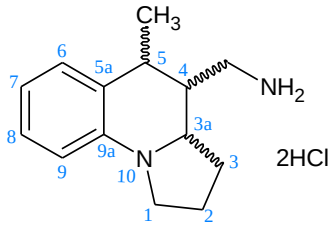
The Boc-protected amine precursor (1 eq) was dissolved in dry EtOAc (distilled from Na, dried over 4 Å molecular sieves). At 0 °C, 4M HCl/EtOAc was added dropwise, until pH = 1-2. The reaction mixture was stirred overnight at room temperature. The precipitated crystals were filtered off and washed with diethyl ether to afford the product.

(*cis*-(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinolin-3-yl)methanamine dihydrochloride (40a *cis*)



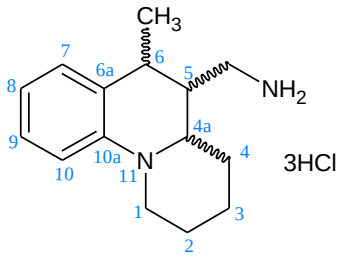
Following **method E**, the title compound was isolated. Hygroscopic off-white powder (0.08 g, 71%). Mp.: 205.3 – 207.9 °C (red foam). ^{1}H NMR (500 MHz, dimethyl sulfoxide-d_6): 8.26 (3H, brs, NH_3^+), 7.00 – 7.03 (1H, m, H-7), 6.97 (1H, dm, J = 7 Hz, H-5), 6.67 (1H, brd, H-8), 6.63 (1H, brm, H-6), 3.32 (1H, dd, J = 11.5 and 3.5 Hz, H$_x$-2), 3.10 (1H, t, J = 11 Hz, H$_y$-2), 2.99 – 2.97 (1H, m, H-4), 2.88 (3H, s. N-CH_3), 2.87 – 2.86 (1H, m, CH_2), 2.74 – 2.72 (1H, m, CH_2), 2.34 – 2.29 (1H, m, H-3), 1.05 (3H, d, J = 7 Hz, CH$_3$). ^{13}C NMR (125 MHz, dimethyl sulfoxide-d_6): 144.3 (C-8a), 128.8 (C-5), 128.2 (C-4a), 127.7 (C-7), 117.6 (C-6), 112.2 (C-8), 49.0 (C-2), 39.6 (N-*C*H$_3$), 39.2 (*C*H$_2$), 34.5 (C-3), 33.1 (C-4), 18.2 (*C*H$_3$). Anal. calcd. for C$_{12}$H$_{18}$N$_2$ × 2HCl (263.21): C, 54.76%; H, 7.66%; N, 10.64%. Found: C, 54.57%; H, 7.58%; N, 10.51%. HRMS: (ESI+) *m/z* calcd. for C$_{12}$H$_{19}$N$_2$ [M+H]$^+$ 191.1548; found: 191.1544.

[*cis-trans*-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (40b *cis-trans*)



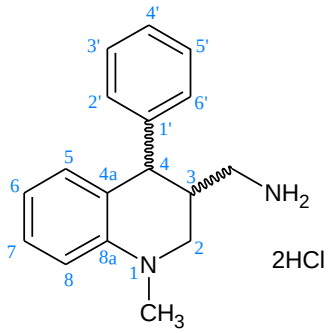
Following **method E**, the title compound was isolated. White powder (0.26 g, 95%). Mp.: 145.8 – 148.4 °C. ^{1}H NMR (500 MHz, dimethyl sulfoxide-d_6): 8.25 (3H, brs, NH_3^+), 7.15 (1H, dm, J = 7.5 Hz, H-6), 7.05 – 7.02 (1H, m, H-8), 6.67 – 6.64 (1H, m, H-7), 6.49 (1H, dm, J = 8.0 Hz, H-9), 3.30 – 3.28 (1H, m, H$_x$-1), 3.18 – 3.15 (2H, m, H$_y$-1, H-3a), 3.09 – 3.08 (1H, m, CH_2), 3.01 – 2.90 (1H, m, CH_2), 2.89 – 2.87 (1H, m, H-5), 2.35 – 2.33 (1H, m, H$_x$-3), 2.04 – 2.02 (1H, m, H$_x$-2), 1.86 – 1.84 (1H, m, H$_y$-2), 1.58 – 1.52 (2H, m, H$_y$-3, H-4), 1.27 (3H, d, J = 7.0 Hz, CH_3); ^{13}C NMR (125 MHz, dimethyl sulfoxide-d_6): 143.9 (C-9a), 127.4 (C-6), 127.3 (C-8), 127.3 (C-5a), 117.4 (C-7), 112.1 (C-9), 59.7 (C-3a), 48.1 (C-1), 43.2 (C-4), 39.4 (CH_2), 32.6 (C-5), 31.1 (C-3), 22.8 (C-2), 19.4 (CH_3). Anal. calcd. for C$_{14}$H$_{20}$N$_2$ × 2HCl (289.24): C, 58.13%; H, 7.67%; N, 9.69%. Found: C, 57.97%; H, 7.79%; N, 9.26%. HRMS: calcd. for C$_{14}$H$_{21}$N$_2$ [M+H]$^+$ 217.1699; found. 217.1710.

[*cis-trans*-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine trihydrochloride (40c *cis-trans*)



Following **method E**, the title compound was isolated. White powder (0.26 g, 29%). Mp.: 162 – 166 °C. ^{1}H NMR: (500 MHz, dimethyl sulfoxide-d_6): 8.19 (3H, brs, NH_3^+), 7.12 – 7.09 (2H, m, H-7, 9), 6.85 (1H, brd, H-10), 6.77 (1H, brt, H-8), 3.73 (1H, dm, J = 13.0 Hz, H_x-1), 2.87 – 2.85 (1H, m, H-4a), 2.85 – 2.84 (1H, m, H-6), 2.78 – 2.75 (1H, m, H_y-1), 2.67 – 2.62 (2H, m, CH_2), 2.03 – 2.01 (1H, m , H-5), 1.85 – 1.40 (6H, m, $H_{x,y}$-2, 3, 4), 1.31 (3H, d, J = 7.5 Hz, CH_3); ^{13}C NMR: (125 MHz, dimethyl sulfoxide-d_6): 144.0 (C-10a), 129.5 (C-6a), 127.9 (C-7), 127.0 (C-9), 118.8 (C-8), 112.9 (C-10), 59.0 (C-4a), 47.7 (C-1), 44.1 (C-5), 42.2 (*C*H$_2$), 33.0 (C-6), 32.0, 23.7, 23.7 (C-2, 3, 4), 20.4 (*C*H$_3$). Anal. calcd. for $C_{15}H_{22}N_2$ x 3HCl (339.73): C, 53.03%; H, 7.42%; N, 8.25%. Found: C, 52.93%; H, 7.53%; N, 7.99%. HRMS: (ESI+) *m/z* calcd. for $C_{15}H_{23}N_2$ $[M+H]^+$ 231.1856; found: 231.1851.

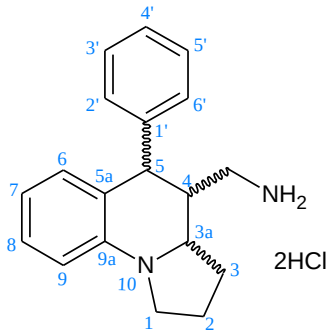
[*cis*-(±)-1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]methanamine dihydrochloride (40d *cis*)



Following **method E**, the title compound was isolated. Cream powder (0.37 g, 65%). Mp.: 177.3 – 181.3 °C. ^{1}H NMR: (400 MHz, dimethyl sulfoxide-d_6): 8.20 (3H, brs, H-NH_3^+), 7.28 – 7.27 (2H, m, H-3', 5'), 7.22 – 7.21 (1H, m, H-4'), 7.03 – 7.11 (3H, ovl. m, H-2', 6', 7), 6.76 - 6.75 (2H, m, H-5, 8), 6.51 (1H, t, J= 7.2 Hz, H-6), 4.27 (1H, d, J = 4.4 Hz, H-4), 3.37 (1H, dd, J = 11.7 and 2.8 Hz, H_x-2), 2.99 (1H, t, J = 11.7 Hz, H_y-2), 2.97 (3H, s, CH_3), 2.86 – 2.84 (1H, m, CH_2), 2.48 – 2.37 (1H, m, H-3), 2.09 – 2.07 (1H, m, CH_2). ^{13}C NMR: (100 MHz, dimethyl sulfoxide-d_6): 145.4 (C-8a), 142.2 (C-1'), 129.7 (C-5), 129.6 (C-2', 6'), 128.2 (C-3', 5'), 128.0 (C-7), 126.7 (C-4'), 123.9 (C-4a), 116.3 (C-6), 111.2 (C-8), 48.6 (C-2), 45.0 (C-4), 39.8 (*C*H$_2$), 38.9 (*C*H$_3$), 34.6 (C-3). Anal. calcd. for $C_{17}H_{20}N_2$ × 2HCl (325.28): C, 60.85%; H, 7.45%; N, 7.24%.

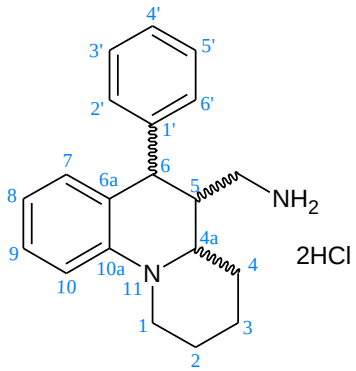
Found: C, 60.91%; H, 7.27%; N, 7.24%. HRMS: (ESI+) *m/z* calcd. for $C_{17}H_{21}N_2$ $[M+H]^+$ 253.1699; found. 253.1691.

[*cis-trans*-(±)-5-Phenyl-1,2,3,3a,4,5-pyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (40e *cis-trans*)



Following **method E**, the title compound was isolated. Brown shiny crystals (0.05 g, 54%). Mp.: 183.7 – 185.4 °C (foaming). ^{1}H NMR (600 MHz, dimethyl sulfoxide - d_6): 8.16 (3H, brt, NH_3^+), 7.43 – 7.19 (5H, m, H-2', 3', 4', 5', 6'), 7.02 - 6.98 (1H, m, H-8), 6.44 (1H, dm, *J* = 8.0 Hz, H-9), 6.39 – 6.36 (1H, m, H-7), 6.26 (1H, dm, *J* = 7.5 Hz, H-6), 4.17 (1H, d, *J* = 12.0 Hz, H-5), 3.36 – 3.33 (1H, m, H-3a), 3.31 - 3.29 (1H, m, H_x-1), 3.25 - 3.24 (1H, m, H_y-1), 2.83 - 2.80 (1H, m, CH_2), 2.57 -2.55 (1H, m, CH_2), 2.50 - 2.48 (1H, m, H_x-3), 2.08 -2.06 (1H, m, H_x-2), 2.06 (H-4), 1.90 – 1.88 (1H, m, H_y-2), 1.56 – 1.54 (1H, m, H_y-3); ^{13}C NMR (150 MHz, dimethyl sulfoxide-d_6): 144.0 (C-9a), 143.4 (C-1'), 129.3 (C-2', 6'), 129.1 (C-6), 128.8 (C-4'), 127.2 (C-8), 126.9 (C-3', 5'), 124.9 (C-5a), 115.3 (C-7), 110.4 (C-9), 58.8 (C-3a), 46.7 (C-1), 45.2 (C-5), 42.0 (C-4), 38.8 (*C*H_2), 30.9 (C-3), 22.8 (C-2). Anal. calcd. for $C_{19}H_{22}N_2 \times 2HCl$ (351.32): C, 64.96%; H, 6.89%; N, 7.97%. Found: C, 65.15%; H, 6.68%; N, 8.20%. HRMS: (ESI+) *m/z* calcd. for $C_{19}H_{23}N_2$ $[M+H]^+$ 279.1864; found. 279.1864.

[*cis-cis*-(±)-6-Phenyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine dihydrochloride (40f *cis-cis*)



Following **method E**, the title compound was isolated. White powder (0.12 g, 76%). Mp.: 215.8 – 221.0 °C (foaming). ^{1}H NMR: (600 MHz, dimethyl sulfoxide-d_6): 8.16 (3H, s, NH_3^+), 7.27 (2H, t, *J* = 7.2 Hz, H-3', 5'), 7.17 – 7.23 (3H, ovl. m, H-2', 4', 6'), 7.11 (1H, t, *J* = 7.7 Hz, H-9), 6.90 (1H, d, *J* = 8.2 Hz, H-10), 6.80 (1H, d, *J* = 7.2 Hz, H-7), 6.58 (1H, d, *J* = 7.7 Hz, H-8), 4.38 (1H, d, *J* = 4.7 Hz, H-6), 4.01 (1H, d, *J* = 12.5 Hz, H_x-1), 3.32 – 3.31 (1H, m, H-

4a), 3.02 – 3.00 (1H, m, CH_2), 2.85 – 2.83 (1H, m, CH_2), 2.72 (1H, t, J = 11.5 Hz, H_y-1), 2.55 – 2.56 (1H, m, H-5), 1.69 – 1.59 (2H, ovl. m, H_x-2, 3), 1.45 – 1.39 (1H, m, H_y-2), 1.36 – 1.30 (2H, m, H_y-3, 4), 1.01 – 0.98 (1H, m, H_x-4); ^{13}C NMR: (150 MHz, dimethyl sulfoxide-d_6): 145.8 (C-10a), 140.6 (C-1'), 130.3 (C-2', 6'), 129.2 (C-7), 128.2 (C-3', 5'), 128.2 (C-9), 126.9 (C-6a), 126.8 (C-4'), 117.0 (C-8), 112.5 (C-10), 58.1 (C-4a), 47.6 (C-1), 45.0 (C-6), 40.3 (C-5), 37.9 (*C*H_2), 26.1 (C-4), 25.1 (C-2), 24.7 (C-3). Anal. calcd. for $C_{20}H_{24}N_2 \times 2HCl$ (365.33): C, 65.70%; H, 7.12%; N, 7.66%. Found: C, 65.48%; H, 7.19%; N, 7.49%. HRMS: (ESI+) *m/z* calcd. for $C_{20}H_{25}N_2$ $[M+H]^+$ 293.2012; found. 293.2002.

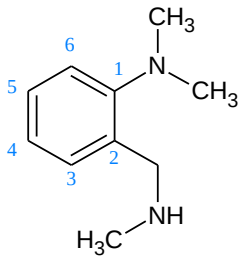
3.3.8. Extension of type 2 reaction to bridged biaryls

Compounds **45a**, **45b**, **46a**, **46b**, **47a**, and **47b** were prepared according to the literature procedures cited [102] and had melting points and/or spectral data identical with the published values.

3.3.8.1. Synthesis of N,N-dialkyl-2-[(methylamino)methyl]anilines

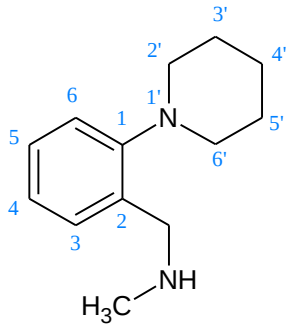
To 40 wt% aq. methylamine (776.00 mmol, 67 mL, 40 eq) at -10 °C, a solution of the 2-(chloromethyl)-*N*,*N*-dialkylanilines (19.42 mmol, for **48a**: 2-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride – 4.00 g, for **48b**: 1-[2-(chloromethyl)phenyl] piperidine hydrochloride – 4.78 g) in EtOH (70 mL) was added dropwise. The mixture was stirred at -10 °C for 2 h (monitored by TLC). The solvent was removed in vacuo, 30 mL of water was added, and the mixture was extracted with EtOAc (3x30 mL). The organic layer was discarded, and the pH of the aqueous phase was adjusted to 13 with 2M NaOH. The aqueous phase was extracted with EtOAc (5x30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness.

***N,N*-dimethyl-2-[(methylamino)methyl]aniline (48a)**



The crude product was purified by fractionary distillation under reduced pressure (102 °C, 5 mmHg). Colorless oil (1.28 g, 40%). ^{1}H NMR (500 MHz, chloroform-*d*): 7.31 (1H, dd, *J* = 7.5, 1.5 Hz, H-3), 7.25–7.20 (1H, m, H-5), 7.11 (1H, dd, *J* = 7.5, 1.5 Hz, H-6), 7.06–7.02 (1H, m, H-4), 3.83 (2H, s, C*H*$_2$), 2.70 (6H, s, N(C*H*$_3$)$_2$), 2.44 (3H, s, C*H*$_3$), 1.17 (N*H*). ^{13}C NMR (125 MHz, chloroform-*d*): 153.3 (C-1), 134.9 (C-2), 130.3 (C-3), 128.3 (C-5), 124.0 (C-4), 119.9 (C-6), 52.9 (*C*H$_2$), 45.7 (N(*C*H$_3$)$_2$), 36.8 (*C*H$_3$). For elemental analysis, HCl salt of the product was formed. Anal. calcd. for $C_{10}H_{16}N_2 \times 2.5HCl$ (255.40): C, 77.50%; H, 6.79%; N, 15.72%. Found: C, 77.49%; H, 6.89%; N, 15.90%.

Methyl({[2-(piperidin-1-yl)phenyl]methyl})amine (48b)



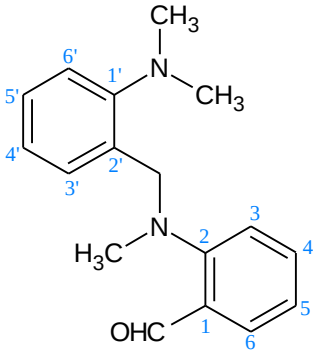
Colorless oil (2.42 g, 61%). ^{1}H NMR (500 MHz, dimethyl sulfoxide-d_6): 7.71-7.65 (1H, m, H-3), 7.44–7.35 (2H, m, H-5,6), 7.25–7.20 (1H, m, H-4), 3.66 (2H, s, C*H*$_2$), 2.85–2.75 (4H, m, C*H*$_2$), 2.30 (3H, s, C*H*$_3$), 1.68–1.60 (4H, m, C*H*$_2$), 1.55–1.45 (2H, m, C*H*$_2$). ^{13}C NMR (125 MHz, dimethyl sulfoxide-d_6): 152.3, 134.5, 129.1, 127.2, 122.8, 119.2, 53.5, 50.6, 36.1, 26.2, 23.9. For elemental analysis, HCl salt of the product was formed. Anal. calcd. for $C_{13}H_{20}N_2 \times 2HCl$ (277.23): C, 56.32%; H, 8.00%; N, 10.10%. Found: C, 55.91%; H, 8.11%; N, 9.80%.

3.3.8.2. Synthesis of 2-{[2'-(sec-amino)benzyl](methyl)amino}benzaldehydes

A suspension of the amine compound (4.29 mmol, for **49a**: **48a** – 0.71 g, for **49b**: **48b** – 0.88 g), 2-fluorobenzaldehyde (4.29 mmol, 0.45 mL, 1 eq), and K_2CO_3 (0.90 g, 6.54 mmol, 1.5 eq) in 12 mL of DMF was heated at 110 °C for 7 h (monitored by TLC). The mixture was then cooled down to room temperature and filtered. The solvent was

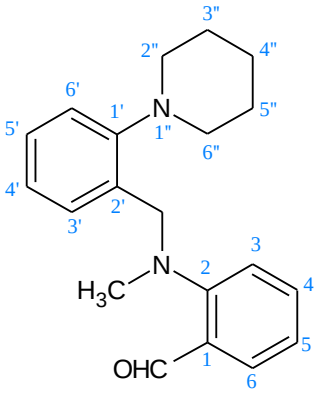
removed in vacuo, and the crude product obtained was purified by flash column chromatography on silica gel.

2-({[2'-(Dimethylamino)phenyl]methyl}(methyl)amino)benzaldehyde (**49a**)



Column chromatography: *n*-hexane/EtOAc 9:1, R_f = 0.16. Yellow oil (1.07 g, 93%). ^{1}H NMR (500 MHz, chloroform-*d*): 10.33 (1H, s, C*H*O), 7.80 (1H, dm, *J* = 7.5 Hz, H-6), 7.46–7.41 (2H, m, H-4, 3'), 7.26–7.21 (1H, m, H-5'), 7.12 (1H, dm, *J* = 8.0 Hz, H-6'), 7.11 (1H, dm, *J* = 8.0 Hz, H-3), 7.06–7.02 (1H, m, H-4'), 7.02–6.98 (1H, m, H-5), 4.46 (2H, s, CH_2), 2.86 (3H, s, CH_3), 2.63 (6H, s, N(CH_3)$_2$). ^{13}C NMR (125 MHz, chloroform-*d*): 192.0 (*C*HO), 156.6 (C-2), 153.5 (C-1'), 135.2 (C-4), 132.4 (C-2'), 130.7 (C-6), 129.2 (C-3'), 128.5 (C-5'), 128.1 (C-1), 124.0 (C-4'), 121.5 (C-5), 120.0 (C-6'), 119.6 (C-3), 58.1 (*C*H$_2$), 45.6 (N(*C*H$_3$)$_2$), 43.4 (*C*H$_3$). For elemental analysis, HCl salt of the product was formed. Anal. calcd. for $C_{17}H_{20}N_2O$ × 2HCl (341.28): C, 59.83%; H, 6.50%; N, 8.21%. Found: C, 60.03%; H, 6.61%; N, 8.25%.

2-[Methyl({[2'-(piperidin-1-yl)phenyl]methyl})amino]benzaldehyde (**49b**)



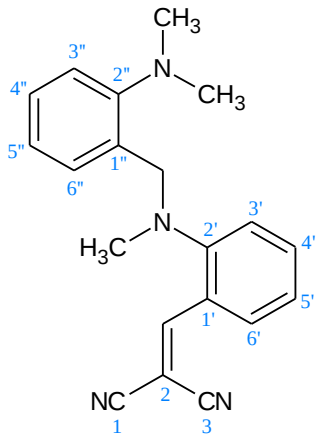
Column chromatography: *n*-hexane/EtOAc 4:1, R_f = 0.65. Yellow oil (1.26 g, 95%). ^{1}H NMR (500 MHz, chloroform-*d*): 10.30 (1H, s, C*H*O), 7.80-7.78 (1H, m, H-6), 7.45–7.40 (1H, m, H-4), 7.39 (1H, dm, *J* = 7.5 Hz, H-3'), 7.25–7.20 (1H, m, H-5'), 7.11 (1H, dm, H-3), 7.10 (1H, dm, *J* = 8.0 Hz, H-6'), 7.06–7.01 (1H, m, H-4'), 7.02–6.97 (1H, m, H-5), 4.44 (2H, s, CH_2), 2.88 (3H, s, CH_3), 2.85–2.75 (4H, m, C-2", 6"), 1.70–1.60 (4H, m, C-3", 5"), 1.60–1.50 (2H, m, C-4"). ^{13}C NMR (125 MHz, chloroform-*d*): 192.0 (*C*HO), 156.5 (C-2), 153.7 (C-1'), 135.2 (C-4), 132.9 (C-2'), 130.8 (C-6), 129.2 (C-3'), 128.6 (C-5'), 128.0 (C-1), 124.1 (C-4'), 121.2 (C-5), 120.7 (C-6'), 119.6 (C-3), 57.4 (*C*H$_2$), 55.0 (C-2", 6"), 43.7 (*C*H$_3$),

27.2 (C-3”, 5”), 24.9 (C-4”). Anal. calcd. for $C_{20}H_{24}N_2O$ (204.31): C, 77.89%; H, 7.84%; N, 9.08%. Found: C, 78.06%; H, 7.99%; N, 9.09%.

3.3.8.3. Synthesis of 2-(2’-{[2”-(sec-amino)benzyl](methyl)amino}benzylidene) malononitriles

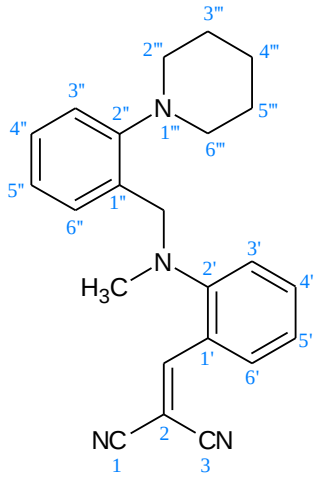
A mixture of the benzaldehyde compound (4.86 mmol, for **50a**: **49a** – 1.30 g, for **50b**: **49b** – 1.50 g) and malononitrile (4.86 mmol, 0.32 g) in 24 mL of EtOH was stirred for 3 h at room temperature.

2-{[2’-({[2”-(Dimethylamino)phenyl]methyl}(methyl)amino)phenyl]methylidene} propanedinitrile (**50a**)



After the reaction time the solvent was removed in vacuo, and the crude product was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc 4:1, R_f = 0.36). Orange oil (1.32 g, 86%). ^{1}H NMR (500 MHz, chloroform-*d*): 8.01 (1H, dm, *J* = 8.0 Hz, H-6’), 8.12 (1H, s, C*H*), 7.49–7.45 (1H, m, H-4’), 7.29–7.24 (2H, m, 4”, 6”), 7.15-7.13 (2H, dm, *J* = 8.5 Hz, H-3’, 3”), 7.11–7.03 (2H, m, H-5’, 5”), 4.29 (2H, s, CH_2), 2.82 (3H, s, CH_3), 2.61 (6H, s, N(CH_3)$_2$). ^{13}C NMR (125 MHz, chloroform-*d*): 159.0 (*C*H), 155.8 (C-2’), 153.5 (C-2”), 135.3 (C-4’), 132.0 (C-1”), 129.9 (C-6’), 129.6 (C-6”), 129.1 (C-4”), 125.0 (C-1’), 124.2 (C-5”), 122.9 (C-5’), 120.6 (C-3’, 3”), 115.0* (C-1), 113.7* (C-3), 80.7 (C-2), 58.4 (*C*H_2), 45.7 (N(*C*H_3)$_2$), 43.5 (*C*H_3). For elemental analysis, HCl salt of the product was formed. Anal. calcd. for $C_{20}H_{20}N_4$ × 2HCl (389.32): C, 61.70%; H, 5.70%; N, 14.39%. Found: C, 61.69%; H, 6.75%; N, 14.30%.

2-({2'-[Methyl({[2"-(piperidin-1-yl)phenyl]methyl})amino]phenyl}methylidene) propanedinitrile (**50b**)

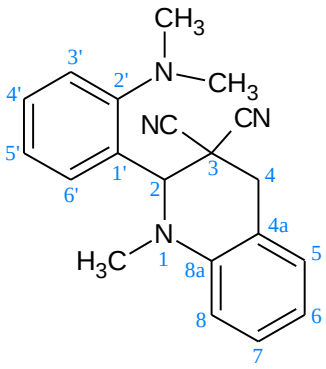


After the reaction time the precipitated crystals were filtered off and washed with EtOH. Orange crystals (1.56 g, 90%). Mp.: 95–96 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 8.03 (1H, s, C*H*), 8.00 (1H, dm, *J* = 8.0 Hz, H-6'), 7.50–7.45 (1H, m, H-4'), 7.28–7.22 (2H, m, H-6"), 7.19 (1H, dm, *J* = 8.5 Hz, H-3'), 7.14–7.03 (3H, m, 5', 3", 5"), 4.26 (2H, s, CH_2), 2.85 (3H, s, CH_3), 2.75–2.65 (4H, m, C-2"', 6"'), 1.70–1.65 (4H, m, C-3"', 5"'), 1.60–1.50 (2H, m, C-4"'). ^{13}C NMR (125 MHz, chloroform-*d*): 158.9 (*C*H), 155.7 (C-2'), 153.6 (C-2"), 135.3 (C-4'), 132.6 (C-1"), 129.9 (C-6'), 129.4 (C-6"), 129.1 (C-4"), 125.0 (C-1'), 124.4 (C-5"), 122.9 (C-5'), 121.0 (C-3"), 120.7 (C-3'), 115.0* (C-1), 113.7* (C-3), 80.6 (C-2), 57.5 (*C*H_2), 55.0 (C-2"', 6"'), 44.2 (*C*H_3), 27.3 (C-3"', 5"'), 24.8 (C-4"'). Anal. calcd. for $C_{23}H_{24}N_4$ (356.46): C, 77.50%; H, 6.79%; N, 15.72%. Found: C, 77.58%; H, 6.84%; N, 15.69%.

3.3.8.4. Cyclization of 2-(2-{[2-(sec-amino)benzyl](methyl)amino}benzylidene) malononitriles

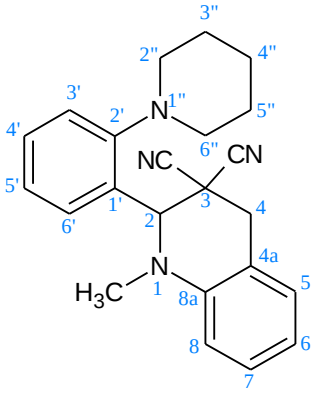
The vinyl precursors (0.84 mmol, for **51a**: **50a** – 0.27 g, for **51b**: **50b** – 0.30 g) in a 10 mL MW process vial were irradiated at the temperature and for the reaction time indicated (at 250 W maximum power level). The vial was subsequently cooled to ambient temperature, and 15 mL of DCM was added. The mixture was washed with water (3x15 mL), and the organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford the pure products.

2-[2'-(Dimethylamino)phenyl]-1-methyl-1,2,3,4-tetrahydroquinoline-3,3-dicarbonitrile (**51a**)



Heating: 135 °C, 10 min. White crystals (0.27 g, 99%). Mp.: 170–172 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.39–7.33 (2H, m, H-3', 4'), 7.30–7.25 (1H, m, H-7), 7.09–7.04 (3H, m, H-5, 5', 6'), 6.82–6.79 (1H, m, H-6), 6.78 (1H, dm, *J* = 8.0 Hz, H-8), 5.74 (1H, s, C*H*), 3.42 (1H, d, *J* = 16.0 Hz, H_x-4), 3.35 (1H, d, *J* = 16.0 Hz, H_y-4), 2.97 (3H, s, CH_3), 2.74 (6H, s, N(CH_3)$_2$). ^{13}C NMR (125 MHz, chloroform-*d*): 154.8 (C-2'), 144.6 (C-8a), 132.5 (C-1'), 131.3 (C-4'), 130.2 (C-7), 129.8 (C-5), 127.9 (C-6'), 126.0 (C-5'), 122.7 (C-3'), 118.3 (C-6), 116.2* (*C*N), 115.5* (*C*N), 114.5 (C-4a), 112.1 (C-8), 61.1 (C-2), 46.7 (N(*C*H$_3$)$_2$), 38.8 (*C*H$_3$), 35.5 (C-3), 34.8 (C-4). Anal. calcd. for $C_{20}H_{20}N_4$ (316.40): C, 75.92%; H, 6.37%; N, 17.71%. Found: C, 75.84%; H, 6.47%; N, 17.64%.

1-Methyl-2-[2-(piperidin-1-yl)phenyl]-1,2,3,4-tetrahydroquinoline-3,3-dicarbonitrile (**51b**)



Heating: 130 °C, 10 min. White crystals (0.30 g, 99%). Mp.: 167–169 °C. ^{1}H NMR (500 MHz, chloroform-*d*): 7.37–7.33 (1H, m, H-4'), 7.30–7.25 (2H, m, H-7, 3'), 7.08–7.01 (3H, m, H-5, 5', 6'), 6.82–6.78 (1H, m, H-8), 6.78 (1H, dm, *J* = 7.5 Hz, H-8), 5.63 (1H, s, C*H*), 3.40 (1H, d, *J* = 16.0 Hz, H_x-4), 3.32 (1H, d, *J* = 16.0 Hz, H_y-4), 2.95 (3H, s, CH_3), 3.00–2.70 (4H, m, H-2", 6"), 1.80–1.50 (6H, m, H-3", 4", 5"). ^{13}C NMR (125 MHz, chloroform-*d*): 154.6 (C-2'), 144.6 (C-8a), 132.5 (C-1'), 131.2 (C-4'), 130.2 (C-7), 129.8 (C-5), 127.8 (C-6'), 125.8 (C-5'), 123.0 (C-3'), 118.3 (C-6), 116.2* (*C*N), 115.2* (*C*N), 114.6 (C-4a), 112.1 (C-8), 61.3 (C-2), 55.0 (C-), 38.8 (C-2", 6"), 35.5 (*C*H$_3$), 34.8 (C-4), 27.3 (C-3", 5"), 24.8 (C-4"). Anal. calcd. for $C_{23}H_{24}N_4$ (356.46): C, 77.50%; H, 6.79%; N, 15.72%. Found: C, 77.49%; H, 6.89%; N, 15.90%.

4. Results

4.1. Synthesis of pyrido-fused ring system

The starting compounds (**35a-f**) were synthesized from 2-fluoroacetophenone and 2-fluorobenzophenone *via* microwave assisted nucleophilic substitution with dimethylamine, pyrrolidine or piperidine in water in the presence of K_2CO_3 at 130 ºC (Figure 45).

Firstly, the ring closed products (**37a**, **5h**, **5k**, **37d-f**) were prepared under one-pot reaction condition, furnishing the Knoevenagel reaction and the ring closure step sequentially, employed by our group previously [20]. Compounds **5h, k** were formed with relatively good yields and in a stereoselective manner, giving rise solely to the *cis* isomers (Table 4).

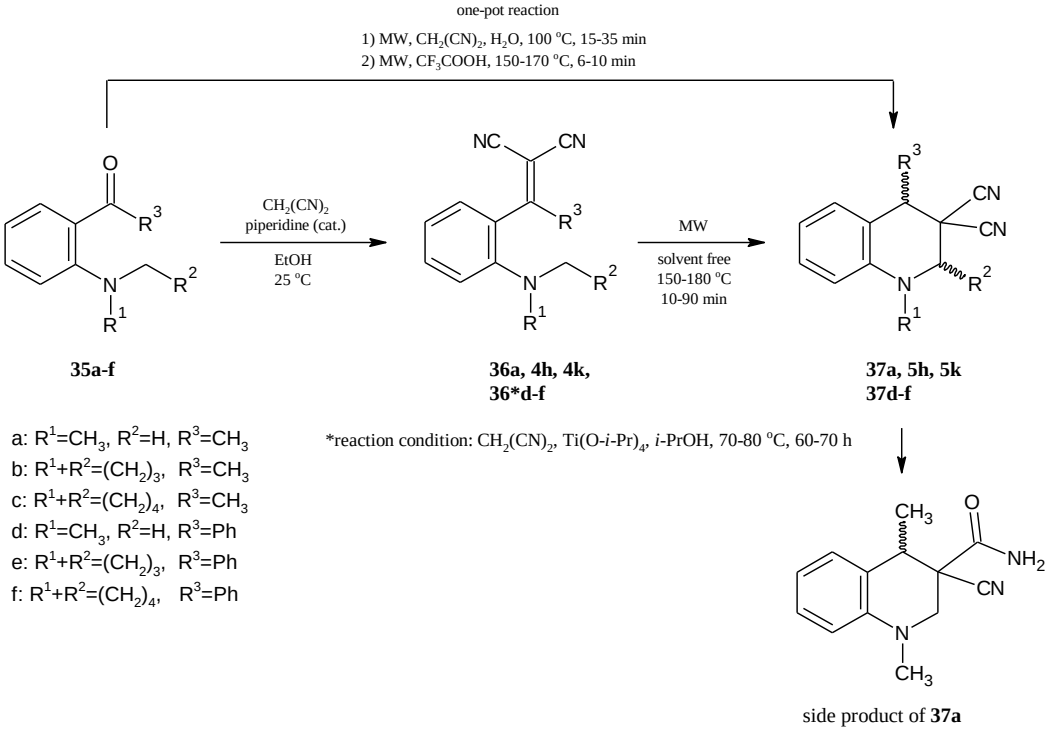


Figure 45: Microwave assisted diastereoselective cyclization reaction

Table 4. Yield and reaction time of one-pot condensations-cyclisations starting from compounds **35a-f**.

Compd.	$R^1 + R^2$	R^3	reaction time (min)[a]	yield (%)	isomer ratio of crude prod.[b]
37a	$R^1 = CH_3$, $R^2 = H$	CH_3	1) 35, 2) 10	10[c]	-
5h	$(CH_2)_3$	CH_3	1) 15, 2) 6	50	only *cis* isomer
5k	$(CH_2)_4$	CH_3	1) 12, 2) 5	60	only *cis* isomer
37d	$R^1 = CH_3$, $R^2 = H$	Ph	1) 60 min[d]	no prod.	-
37e	$(CH_2)_3$	Ph	1) 45 min[d]	no prod.	-
37f	$(CH_2)_4$	Ph	1) 50 min[d]	no prod	-

[a]1) reaction time for the Knoevenagel condensation, 2) reaction time for the cyclization
[b]Ratio of the diastereomers in the crude product was determined by ^{1}H NMR and/or HPLC.
[c]Acid amide side product was also formed in 10% yield.
[d]According to the TLC very few amount of the vinyl compound was formed, therefore the reaction was stopped.

Secondly, we planned to synthesize all of the vinyl compounds separately (**36a**, **4h**, **4k**, **36d-f**) for the solvent-free microwave assisted ring closuring reaction, expecting an improved yield. The Knoevenagel condensation of the compounds **35a-c** with malononitrile in ethanol at room temperature resulted in high yields of **36a, 4h** and **4k** (88%, 75% and 77% respectively). The condensation of the benzophenone derivatives (**35d-f**) did not take place under these conditions, presumably due to the hindered carbonyl group by the phenyl substituent. This observation prompted us to employ Lewis acid (Ti(O-*i*-Pr)$_4$) catalysed conditions, giving rise to **36d** and **36f** in 75% and 46% yields eventually [103]. In the case of compound **36e**, all these trials proved to be inefficient (best yield was only 6%), however, increasing the reaction temperature and the reaction time (110-120 °C, 87 h) rendered the ring closure reaction, significantly more effective (35% yield). The diastereomeric ratios of the crude products made by solvent-free microwave conditions, were determined based on ^{1}H NMR and/or HPLC data, collected in Table 5. In all the cases, the *cis* isomers were formed predominantly in the ring closure reactions. For compounds **5h** and **5k** the solvent-free conditions enabled the formation of the minor *trans* isomer, as well.

Table 5. Yield and reaction time of solvent free microwave cyclisations of compounds **36a, 4h, 4k** and **36d-f**.

Compd.	**$R^1 + R^2$**	**R^3**	**reaction time/temp. (min/ °C)**	**yield (%)**	**isomer ratio of crude prod. c/t (%)[a]**
37a	$R^1 = CH_3$, $R^2 = H$	CH_3	20/180	74	-
5h	$(CH_2)_3$	CH_3	10/180	65[b]	85:15
5k	$(CH_2)_4$	CH_3	10/180	70[b]	92:8
37d	$R^1 = CH_3$, $R^2 = H$	Ph	90/180	67	-
37e	$(CH_2)_3$	Ph	30/150	82[b]	82:18
37f	$(CH_2)_4$	Ph	10/190	95[b]	71:29

[a]Ratio of the diastereomers in the crude product was determined by ^{1}H NMR and/or HPLC.
[b]Total yield for the formed *cis* and *trans* isomers.

To confirm that no interconversion of the diastereomers takes place at the temperature of ring closure, the following experiments were performed. First, the temperature required for the ring closures of **36e** and **36f** was determined using differential scanning calorimetry (DSC) The thermograms obtained gave a good indication of the melting points (endothermic peaks, down) of the vinyl substances as well as the ring closure temperatures (exothermic peaks, up) (Figure 46). Previously, thermochemical study of ring closur reaction was thoroughly investigated by group of Mátyus in 2003 [104].

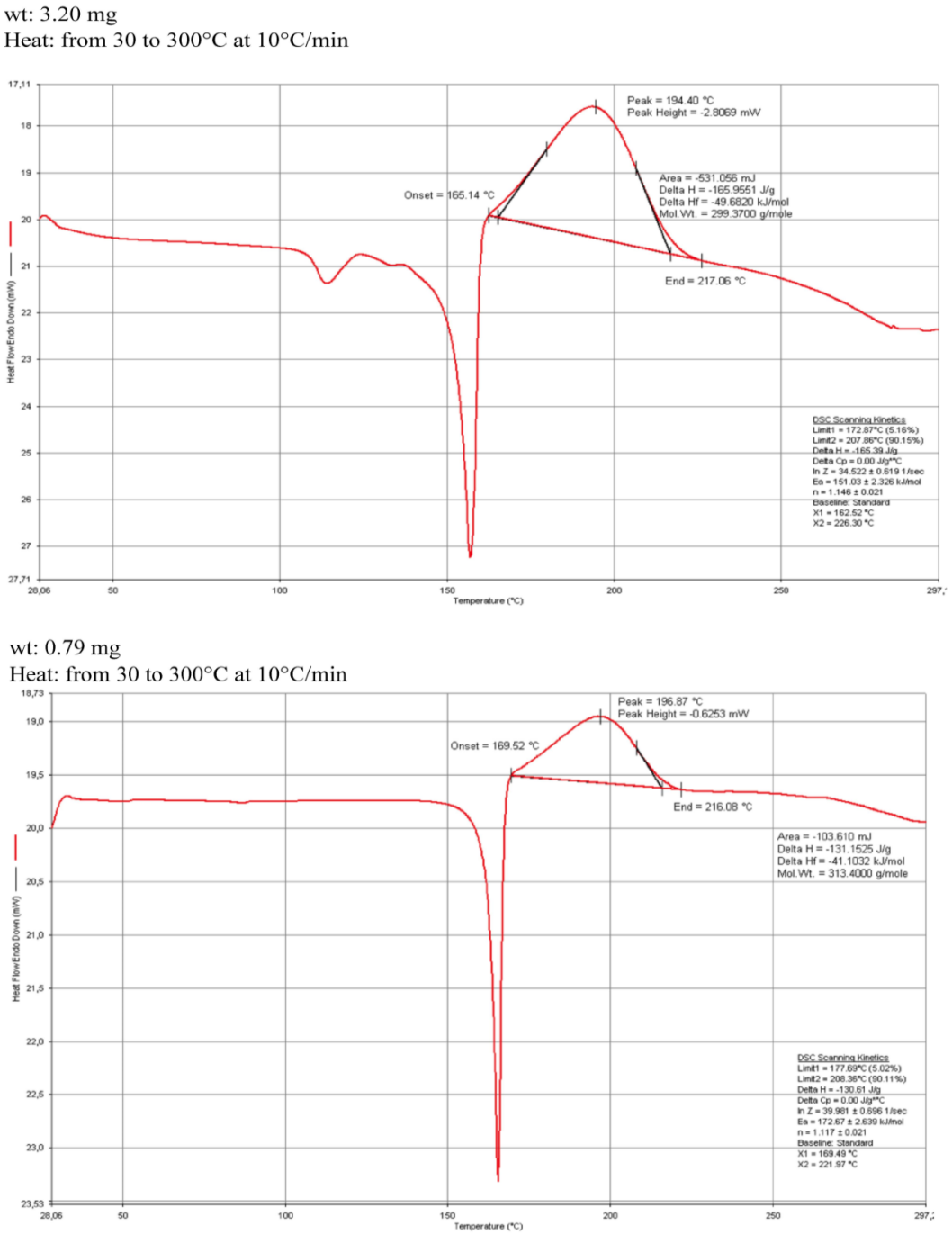
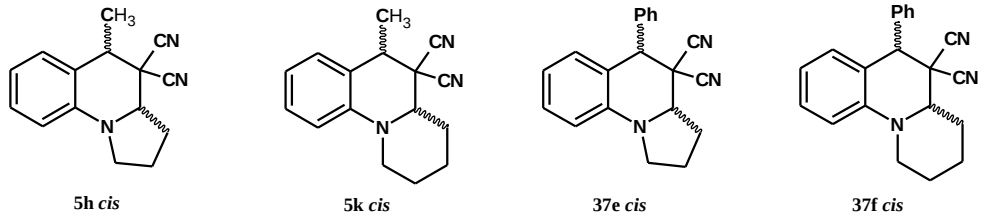


Figure 46: DSC curves of compounds **36e** (upside) and **36f** (bottomside)

In a subsequent experiment, the pure *cis* isomers **5h, 5k** and **37e, 37f**, yielded in the ring closure reactions, were heated at the temperatures required for ring formation (Figure 47).



*reaction condition of the ring closur reaction

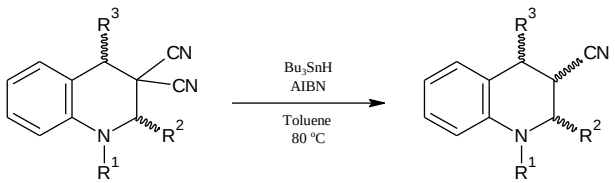
Figure 47: The heating test of the pure *cis* isomers

In order to determine the relative configuration of the *trans* isomer, the diastereomers were separated by column chromatography (**5h**) or semi-preparative HPLC (**5k, 37e, 37f**) and the structures of all the obtained isomers were elucidated using 1D and 2D NMR spectroscopy methods.

4.2. Synthesis of mononitrile derivatives

The decyanation reactions of compounds **37a, 5h *cis*, 5k *cis*** and **37d, 37e *cis*, 37f *cis*** were carried out by radical reduction driven by tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) in toluene (Figure 48) [105].

As the R^3 substituent is either methyl or phenyl, the anticipated number of diastereomers are four, yet only two diastereomers were formed during the reaction, as proved by NMR. Column chromatography allowed the separation of the diastereomers, which were employed for the subsequent steps in pure form.



37a, 5h, 5k
37d-f

38a-f

Figure 48: Chemoselective reductive elimination of the cyano group of the geminal dinitrile

In the case of compound **38**, the relative configuration of position 3a and 5 was identified as *cis* (this is the first configuration, which is indicated in the name of the compound) and that of 3a and 4 was identified as *cis* or *trans* (this is the second configuration, which is indicated in the name of the compound) (Figure 49). The formation of the mononitrile derivatives (**C-D** and **E-F** are enantiomers) from the two different enantiomers of *cis* dicarbonitrile compounds (**A** and **B**), following the elimination of two different configuration of the nitrile group are presented. The elimination of the nitrile group in *cis* position with the R^3 substituent results in the *cis-trans* isomer (**A** → **C** and **B** → **D**), while the elimination of the nitrile group in the *trans* position with the R^3 substituent results in the *cis-cis* isomer (**A** → **E** and **B** → **F**).

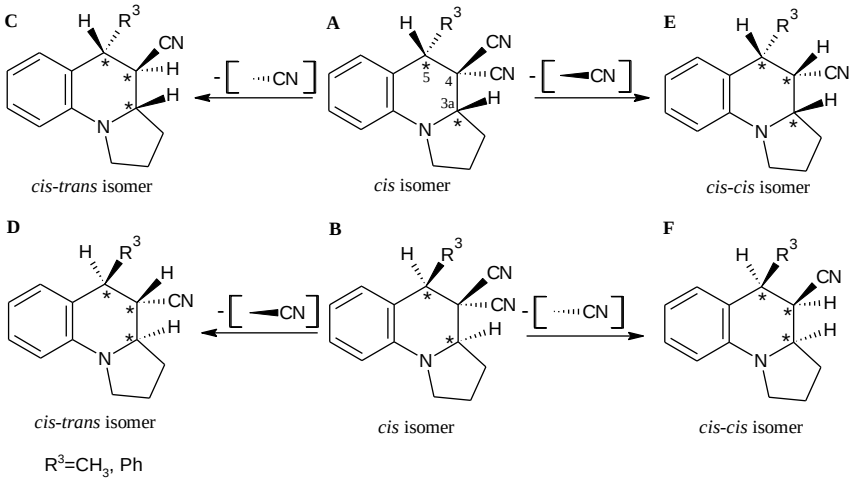


Figure 49: Reductive elimination of the nitrile group from the two different configurations

The yields, reaction times and the ratios of diastereomers of the crude product are listed in Table 6. In the case of the $R^1 = CH_3$ derivatives (**35a, 37d**), the removal of the nitrile group gave rise predominantly (**38a**) or exclusively (**38d**) to the *cis* isomer. Equivalent amounts of *cis-cis* and *cis-trans* isomers were formed in the case of compounds containing a pyrrolidine ring (**38b, 38e**) and predominantly the *cis-cis* isomer with a piperidine ring (**38c, 38f**).

Table 6. Yield and reaction time of the decyanations

Compd.	$R^1 + R^2$	R^3	reaction time	yield (%)	isomer ratio of crude prod. (%)
38a	$R^1 = CH_3$, R^2 = H	CH_3	1.5 h	80[a]	c/t 67:33
38b	$(CH_2)_3$	CH_3	24 h	53[a]	c-c/c-t 58:42
38c	$(CH_2)_4$	CH_3	24 h	72[a]	c-c/c-t 72:28
38d	$R^1 = CH_3$, R^2 = H	Ph	2 h	73	only *cis*
38e	$(CH_2)_3$	Ph	8 h	53[a]	c-c/c-t 50:50
38f	$(CH_2)_4$	Ph	3 h	71[b]	c-c/c-t 95:5

[a]Total yield for the formed *cis-cis* and *cis-trans* isomers.
[b]Yield for the formed *cis-cis* isomer.

4.3. Synthesis of aminomethyl derivatives

In the first step, the nitrile group was reduced with sodium borohydride in the presence of a catalytic amount of $NiCl_2$, followed by protection with di-*tert*-butyl dicarbonate (Boc_2O) in methanol (**39a-f**), furnishing the Boc protetcted product. In the second step, the carbamate product was treated with HCl/EtOAc at room temperature for 17-48 hours to afford the final product **40a-f** (Figure 50).

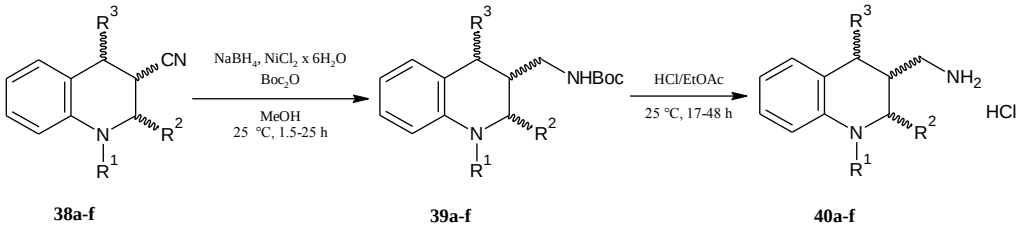


Figure 50: Preparation of aminomethyl derivatives

The SSAO activity of compounds **40a *cis*, 40b *cis-trans*, 40c *cis-trans*, 40d *cis*, 40e *cis-trans*** and **40f *cis-cis*** was tested on the microsomal fraction of rat aorta (Table 7, 8). 4-Phenylbutylamine (4-PBA) was used as the reference substrate [77, 106], while 2-bromoethylamine (2-BEA) was used as selective, irreversible inhibitor [107]. According to the hydrogen peroxide formation assay, compounds **40a *cis*** and **40e *cis-trans*** act as inhibitors of moderate potency as compared to 2-BEA, while compound **40b *cis*-tans**

behaves as a substrate (dose response curves see Appendix). *Deme et al., Arkivoc in press.*

Table 7. SSAO inhibition of compounds **40a, c, 40d-f** and 2-BEA

Compound	IC_{50} (µM)
2-BEA*	0.56 ± 0.12
40a *cis*	5.0 ± 0.4
40c *cis-trans*	14.7 ± 1.0
40d *cis*	17.8 ± 5.2
40e *cis-trans*	5.1 ± 0.5
40f *cis-cis*	31.0 ± 6.0

*2-BEA = 2-bromoethylamine

Table 8. SSAO activity of compounds **40b** and 4-PBA

Compound	K_m (µM)
4-PBA*	740 ± 55
40b *cis-trans*	0.94 ± 0.01

*4-PBA = 4-phenylbutylamine

4.4. Synthesis of spirocyclic ring systems

First, we tried to perform the Knoevenagel condensation reaction by the previously applied conditions, which are listed in Table 9 and 10 (Figure 51). The microwave assisted one-pot reaction of compound **35a** with ID in water resulted 27% ring closed product (**42a**) [20]. In order to improve the yield of the reaction, acid (Ti(O-*i*-Pr)$_4$) [103] as well as acide and base together (AcOH/NaOEt) [108] catalysts were used. According to the TLC the reaction mixture contained a lot of starting material as well as in the traditional condition (cat. piperidine, EtOH). On the basis of the former results this prompted us to employ another condition, thus the microwave reaction in *n*-BuOH in the presence of acetic acid after quite short reaction time proved the best (yield 49% (**42a**), 72% (**42b**) and 35% (**42c**) respectively)

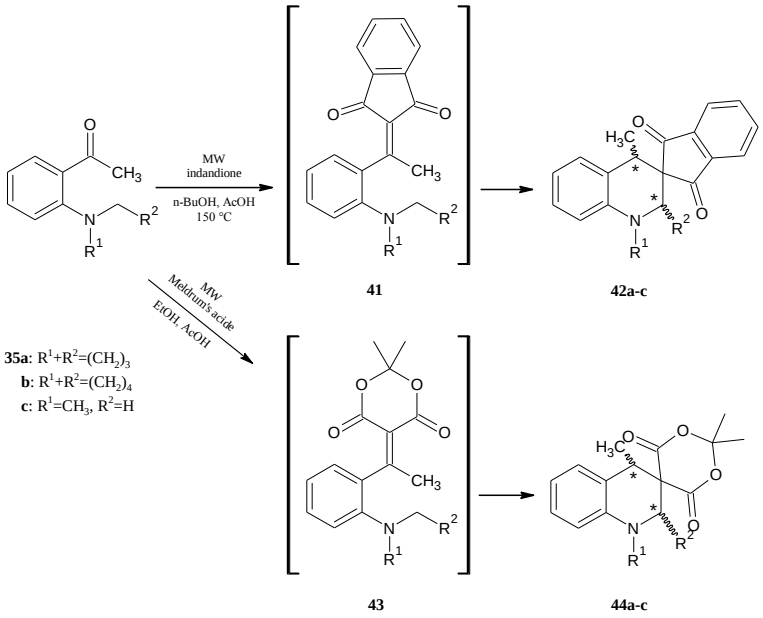


Figure 51: Synthesis of spirocyclic ring systems with indan-1,3-dione and Meldrum's acid from 2-(dialkylamino)acetophenone derivatives

Table 9: Reaction conditions to the synthesis of spirocyclic derivatives with indan-1,3-dione

R^1+R^2	Reaction condition	Crude product*	Yield (%)
$(CH_2)_3$	MW, H_2O, 100 °C, 25 min	n.d.	27
	MW, neat, 30 °C, 18 min	n.d.	lot of SM
	EtOH, piperidine, rt, 96 h	n.d.	6
	Ti(O-*i*-Pr)$_4$, *i*-PrOH, 80 °C, 3 d	n.d.	lot of SM
	piperidine, EtOH, rfx, 3 d	n.d.	lot of SM
	NaOEt, EtOH, rfx, 46 h	n.d.	27
	cat. AcOH, NaOEt, EtOH, rfx, 2 d	n.d.	lot of SM
	MW, ID (1.5 eq), cat. AcOH, *n*-BuOH, 150 °C, 20 min	75:25	49
$(CH_2)_4$	EtOH, piperidine, rt, 112 h	only cis	23
	MW, ID (1.5 eq), cat. AcOH, *n*-BuOH, 150 °C, 30 min	62:38	72
R^1=CH_3 R^2=H	cat. AcOH, NaOEt, EtOH, rfx, 2 d		lot of SM
	MW, ID (1.5 eq), cat. AcOH, *n*-BuOH, 150 °C, 25 min	-	35

*ratio of the diastereomers in the crude product were determined by 1H NMR and/or HPLC. SM: starting material; n.d.: not determined

The reaction with Meldrum's acid resulted in lower yields (31% (**44a**), 15% (**44b**), and 18% (**44c**) respectively) putatively the sensitivity of Meldrum's acid to the temperature and the sterically more hindered six membered ring in the product. In the case of the compound **44b** the traditional condition (cat. piperidine, EtOH, r.t., yield 59%) was proved be the best than the microwave condition in EtOH at 50 °C. Another alternative reaction, in the presence of $TiCl_4$/THF, resulted the ring closed product (**44a**, **44c**), as well [109]. Regarding the stereochemical outcome of these reactions - with ID as well as with Meldrum's acid, - the *cis* isomer was formed predominantly. In the case of compound **44a** and **44b** it was not possible to separate the two diastereomers, therefore the *trans* isomers were not characterized. In the course of the reaction of 2-(dimethylamino)acetophenone (**35c**) with ID or Meldrum's acid after the work-up, the vinyl compounds were isolated in low yield and characterized, as well. In other cases the ring closed product was formed directly.

Table 10: Reaction conditions to the synthesis of spirocyclic derivatives with Meldrum's acid

R^1+R^2	Reaction condition	Crude product*	Yield (%)
$(CH_2)_3$	piperidine, EtOH, rt, 72 h	87:13	24
	NaOEt, EtOH, rfx, 43 h	n.d.	24
	NaOH, MeOH, rfx, 24 h	n.d.	no product
	$TiCl_4$/THF, THF, pyridine, rt, 24 h	80:20	26
	MW, Meldrum (4 eq), cat. AcOH, EtOH, 50 °C, 10 h	83:17	31
$(CH_2)_4$	piperidine, EtOH, rt, 70 h	64:36	59
	MW, Meldrum (4 eq), cat. AcOH, EtOH, 50 °C, 2.5 h	62:37	15
R^1=CH_3 R^2=H	cat. AcOH, NaOEt, EtOH, rfx, 24 h	-	lot of SM
	$TiCl_4$/THF, THF, pyridine, rt, 24	-	5
	MW, Meldrum (5.2 eq), cat. AcOH, EtOH, 45 °C, 9 h	-	18

*ratio of the diastereomers in the crude product were determined by 1H NMR and/or HPLC. SM: starting material; n.d.: not determined

In order to study the rate of the cyclization reaction in the presence of the two different electron withdrawing groups (ID *vs.* malononitrile), the following competition experiments were executed. The starting 2-(dimethylamino)acetophenone (**35a**) was reacted with one equivalent ID and one equivalent malononitrile, respectively in *n*-BuOH in the presence of a catalytic amount of acetic acid under microwave irradiation (Figure 52).

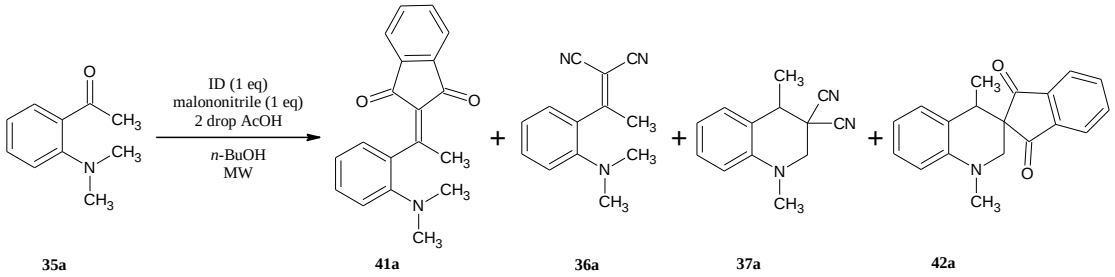


Figure 52: Competition experiment with malononitrile and ID

First, 170-180 °C was used for 15 minutes, then the temperature was reduced in order to see which product formed the fastest way (Table 11). The reactions were followed by NMR spectroscopic. The amount of the compound **42a** (30%) was two times more than the compound **37a** (13%) at high temperature, while 32% compound **36a** was presented in the reaction mixture. At lower temperature (100 °C) the amount of the product **36a** was almost four times more than the product **41a** and the ring closed product with ID (**42a**) was also observed in a few per cent. The ratios of the compound **41a** and **36a** were less at 50 °C than 100 °C. We performed the reaction without acetic acid as well and after 15 minutes one of the ring closed product appeared (**42a**) next to the formation of the two vinyl compounds (**41a** and **36a**).

Table 11: Results of the competition experiments in *n*-BuOH

Reaction condition	**Products (%)***			
	comp. **41a**	comp. **36a**	comp. **37a**	comp. **42a**
Temp (°C), Time (min)				
170-180, 15	1	32	13	30
100, 15	10	38	0	1
50, 15	16	29	0	0
100, 15**	18	42	0	5
100, 30**	11	42	traces	8

*ratio of the crude product was evaluated by ^{1}H NMR
**the reaction was carried out without AcOH

The competition experiment was executed in deuteromethanol (CD_3OD) and deuterochloroform ($CDCl_3$) at room temperature without acetic acid catalyst, as well (Table 12). This temperature was not enough for the formation of the ring closed product, but we saw clearly that the formation of compound **36a** was much more effective than the formation of compound **41a** after a long time.

Table 12: Results of the competition experiments in CD_3OD

Reaction condition	**Products (%)***			
	comp. **41a**	comp. **36a**	comp. **37a**	comp. **42a**
25 °C, Time (h)				
1	0	traces	0	0
8	0	17	0	0
5**	traces	traces	0	0
1 month**	traces	80	0	0

*ratio of the crude product was evaluated by ^{1}H NMR
**the reaction was carried out in $CDCl_3$

4.5. Synthesis of bridged biaryls with methylamino-N-methyl group

2-(chloromethyl)-*N,N*-dialkylanilines (**47a, b**) obtained *via* a known procedure from 2-fluorobenzaldehyde, were reacted with methylamine to provide the corresponding *N,N*-dialkyl-2-[(methylamino)methyl]anilines (**48a, b**). Arylation with 2-fluorobenzaldehyde afforded (2-*sec*-amino)benzylamines (**49a, b**), which upon reacting with malononitrile under mild conditions led to vinyl derivatives (**50a, b**). The cyclization of compound **50a,** and **50b**, based on our microwave assisted solvent-free protocol, exclusively took place *via* the first route, affording the six-membered ring product **51a** and **50b** in excellent yield. (Figure 53).

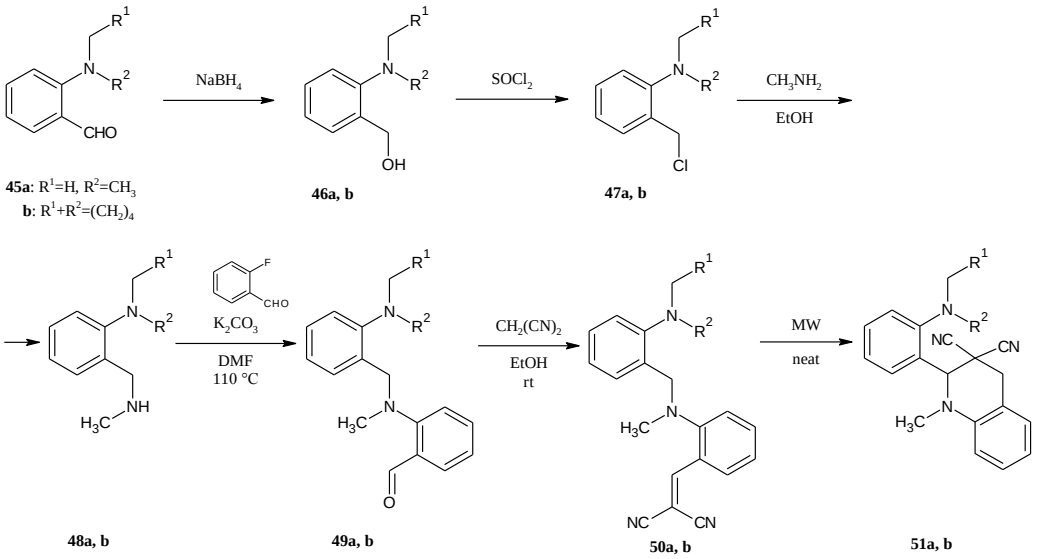


Figure 53: Synthesis of 2-2-{[2-(sec-amino)benzyl](methyl)amino}malononitriles

Differential scanning calorimetry (DSC) measurements complemented by parallel thermal gravimetry (between room temperature and 500 °C) were run for compounds **50b** to assess whether cyclization could be monitored with this method for novel scaffolds (Figure 54). The peak corresponding to the melting point (minimum) could be identified as an endothermic peak at 96.3 °C. The second exothermic peak (maximum) observed might indicate that cyclization did take place upon heating after the melting point corresponding to the temperature of ring closure.

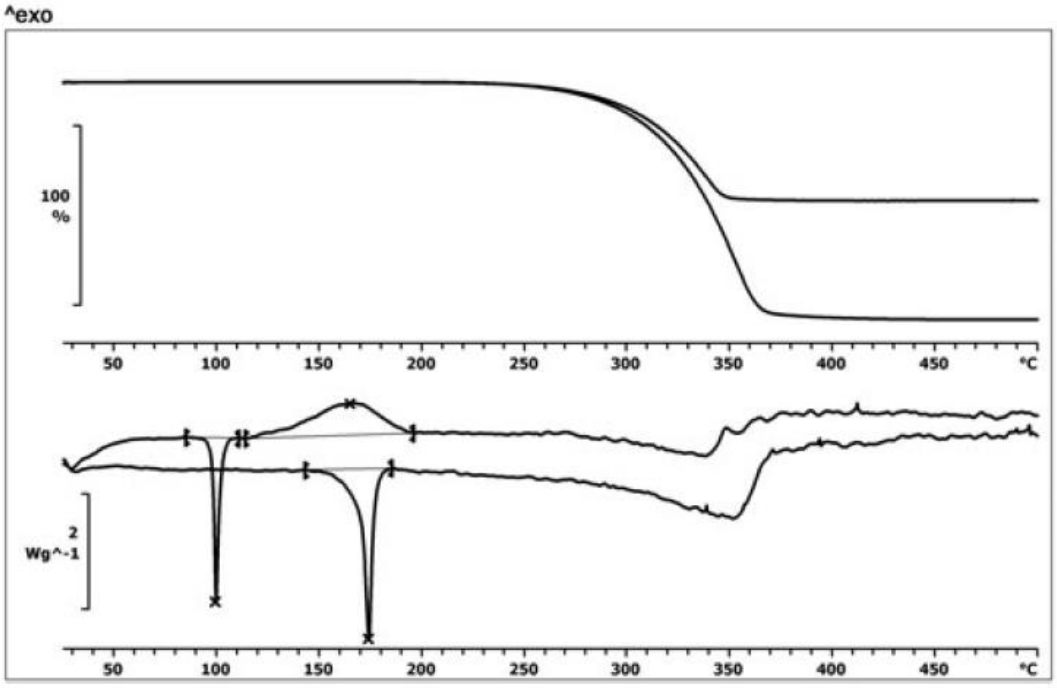
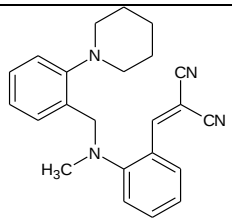
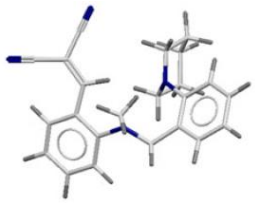
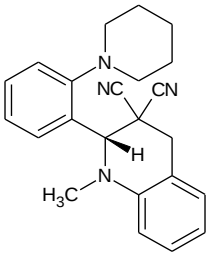
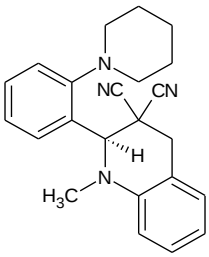
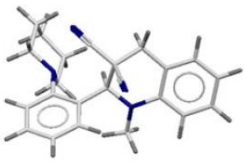
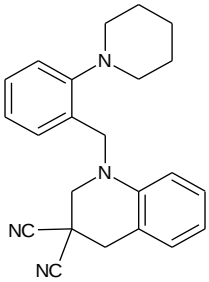
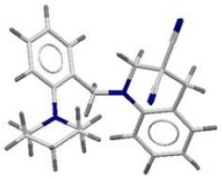
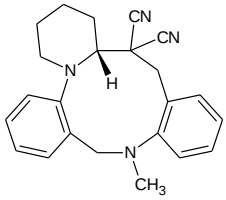
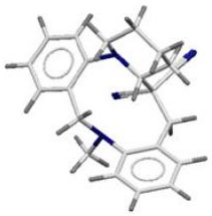
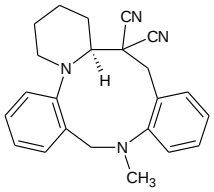
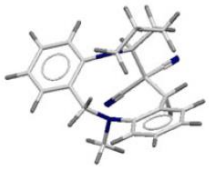


Figure 54: The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of compounds **50b** and **51b**

Integral of the area under the exothermic peak (related to cyclization) provide the enthalpy change (ΔH_r) of the reaction. These experimental enthalpy changes together with the calculated ones are listed in Table 13. The calculated heat of reaction values were determined as the differences of heat of formation of fused products and that of the starting vinyl compounds (full geometrical optimization was carried out for all compounds). In the case of compound **51b**, the two potential alternative products (with *N*-methyl: **52**, and with *ortho' tert*-amino moiety: **53**) were included, as well.

Table 13: Enthalpies of reaction determined by differential scanning calorimetry (DSC) (ΔH_r) and by calculation ($\Delta\Delta H_f = \Delta H_{f\ pr} - \Delta H_{f\ st}$). The tabulated data were taken from recent publication [97].

			Experimental			Theoretical
Comp.	**Structure**	**Optimized structure**	**T_m (°C)[a]**	**T_r (°C)[b]**	**ΔH_r (kJ mol^{-1})[c]**	**$\Delta\Delta H_f$ (kJ mol^{-1})[d]**
50b			**96.3**	**NA**	**NA**	**NA**
51b-*R*			**169.7**	**161.4**	**-47.07**	**-63.33**
51b-*S*			**169.7**	**161.4**	**-47.07**	**-63.24**
52			**NA**	**NA**	**NA**	**-61.70**

53-*R*			**NA**	**NA**	**NA**	**20.82**
53-*S*			**NA**	**NA**	**NA**	**28.17**

[a]T_m corresponds to the melting temperature (DSC endothermic peak).
[b]T_r corresponds to the temperature of cyclization (DSC exothermic peak).
[c]ΔH_r is the enthalpy of reaction.
[d]$\Delta\Delta H_f$ corresponds to the difference of calculated heats of formation as obtained by DFT method (B3P86).
NA: Not Available

5. Discussion

5.1. Pyrido-fused ring systems

Reinhoudt and co-workers synthesized the same derivatives starting from compound **4h**, **k** in refluxing *n*-BuOH for several hours, resulting exlusively in the *cis* isomer [5], as well. However, compound **37a** was isolated with only low yield and along with an acid amide side product by the nucleophilic addition of water (Figure 45), which can be a result of the longer reaction time than that applied in the case of compounds **5h, k**. Furthermore, the formation of vinyl compounds starting from compounds **35d-f** were rather ineffective as indicated by TLC.

In general, when R^3 is a methyl or phenyl group, the migrating hydrogen (H_a) can be traced throughout the course of the reaction. Reinhoudt *et al* linked the exclusive formation of the *cis* isomer to a specific geometry of the vinyl group, the [1,5] suprafacial migration of a hydrogen and the coordinated formation of a carbon-carbon bond. However, the formation and isolation of the small amount of *trans* isomer from these reactions, can be attributed to steric factors, which were not studied earlier in the literature.

The heating test of the pure *cis* isomers confirmed the formation of diastereomres take place solely during the reaction (Figure 47). The corresponding ^{1}H NMR assays and the TLC proved the exclusive presence of the *cis* isomers, excluding undoubtedly any theoretically possible epimerization process.

5.1.1. Recation mechanism

Summarizing our present and the earlier Reinhoudt's results, we were led to the assumption that the *cis*/*trans* diastereomeric ratio depends not only on the steric hindrance in the starting vinil compounds, but also the difference between the activation energy of the transition state leading to the *cis* and the *trans* isomer - based on the Curtin-Hammet principle. Theoreticaly, the two elementary steps mechanism, composed of an intramolecular hydride ion migration and a subsequent ring closure step. The two diastereomers can be derived from the two conformers of the starting vinyl molecules (SM1 and SM2). In the first step, compound **4** or **36** (starting materials; SM in Figure 55 and Figure 56) takes part in a 1,5-hydride shift *via* a well determined

but high transition states (**TS1** ***cis*** and **TS2** ***trans*** in STEP 1), resulting zwitterionic intermediates (**IM** ***cis***, **IM** ***trans***). In the subsequent final step (SEPT 2), these intermediates forms the six-membered ring between the two oppositely charged carbon atoms of **IM**s, involving a presumably low enthalpy barriers (**TS2** ***cis*** and **TS2** ***trans***, in STEP 2).

In this picture, the rate determining step is undoubtedly set by TS1 involving the hydride shift, due to its larger enthalpy barrier. Using analogies, the high reaction temperature (150 °C) allows one to estimate this enthalpy barrier as high as 120–130 kJ mol^{-1}. Supposing a fast second step, not providing time for free rotation in the zwitterionic intermediate state (IM), the product ratio should be also determined by the difference of the **TS1** ***cis*** and **TS1** ***trans***. Earlier, Reinhoudt's group did not published the cis/trans ratios (when $R^3 = CH_3$), however, according to our experimental HPLC investigations on the crude products, the cis/trans ratios were measured between 7:3 and 8:2. From these values, one can calculate a 3–5 kJ mol^{-1} enthalphy difference for the two TS1s by means of Arrhenius equation (1) at the reaction temperature (T), where $\Delta H^{\neq}_{\text{cis}}$ and $\Delta H^{\neq}_{\text{trans}}$ are the two activation enthalphy, R is the universal gas constant (supposing close or equal entropy changes is the two TS).

$$\frac{k_{cis}}{k_{trans}} = e^{\frac{\left(\Delta H^{\neq}_{TS1-trans} - \Delta H^{\neq}_{TS1-cis}\right)}{RT}} \qquad (1)$$

Finally, according to preliminary results of high level DFT calculations of Mucsi and Mátyus (unpublished), the overall enthalpy changes are beneficial toward the both products, meanwhile the entropy should decreases, due to the ring formation process.

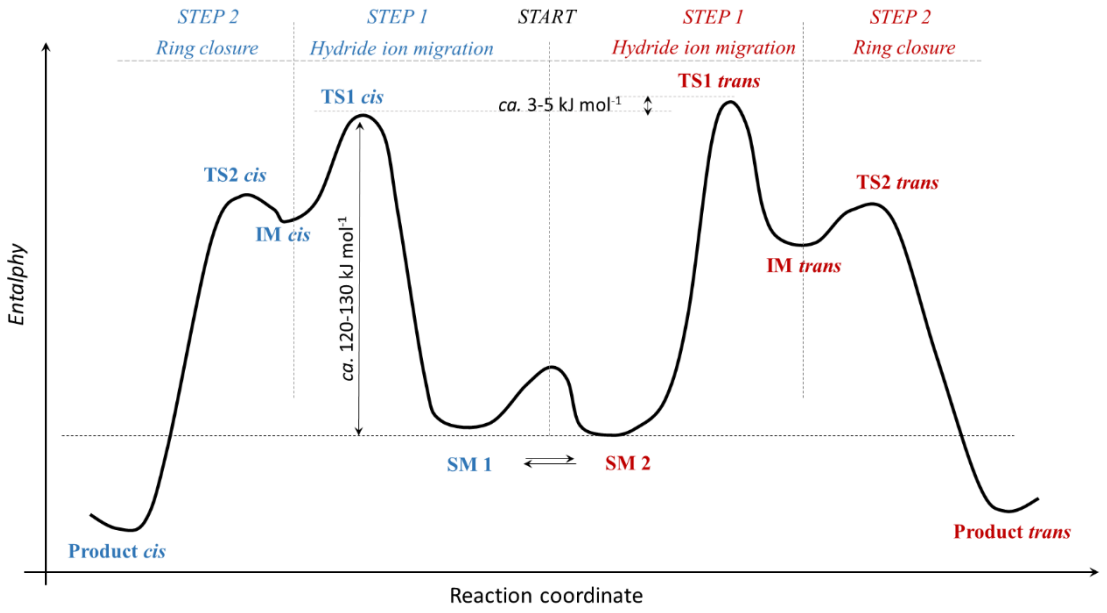


Figure 55. Schematic illustration of enthalpy profile of the reaction mechanism.

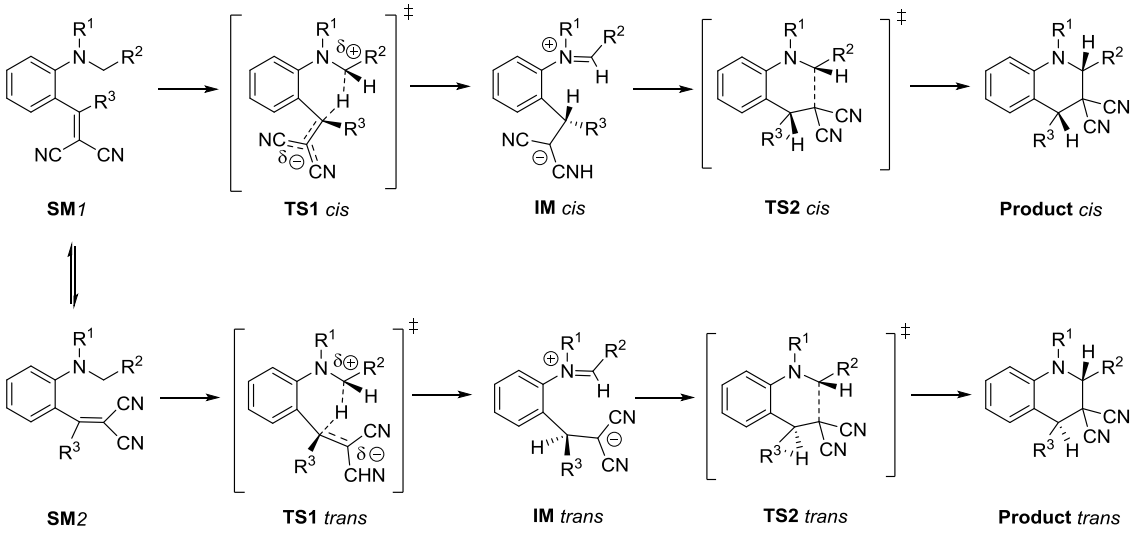


Figure 56: SM = strating material; IM = intermediate; TS = transition state

5.2. Mononitrile derivatives

The first example of decyanation of dialkylated malononitriles (geminal dinitriles) was published by Curran and Seong [110]. They proposed the mechanism to account for this reduction, with emphasis on the geminal substituent effect (Figure 57).

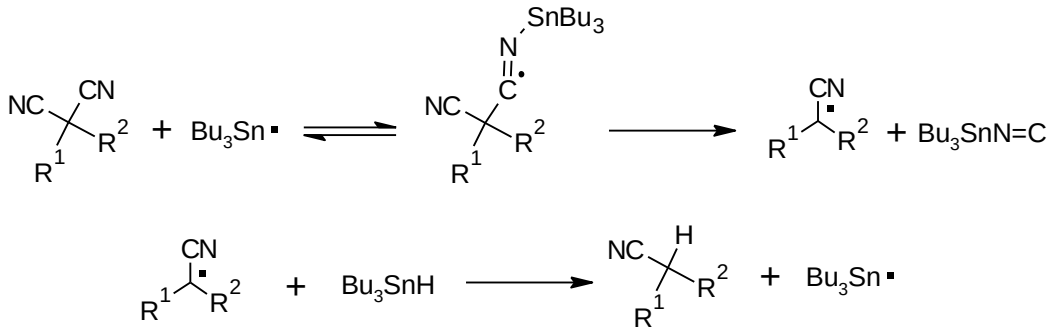


Figure 57: Proposed mechanism of reductive decyanation

Gerlach developed the synthesis of tricyclic cyano substituted tetrahydroquinolines from the geminal dinitriles by radical decyanation using Bu_3SnH [105]. The stereochemistry of the resulting nitrile has not yet been clarified, but both diastereomers formed. This procedure was employed previously in our research group to synthesize mononitrile naphthazepine derivatives [30]. Hattori *et al* used also this method to prepare the fused bicyclic *α*-amino acid [111], furthermore Kang *et al* proposed an alternative reaction employing samarium (II) iodide in THF/HMPA at 0 °C or room temperature [112, 113]. Beside the application of the procedure, we wished to clarify the stereochemical outcome of the reaction.

Our results suggest that the size of the R^3 substituent (methyl or phenyl) and the type of the secondary amino group (pyrrolidine or piperidine) might influence which nitrile group would be removed from the molecule (Figure 49). In the case of the most hindered compound **37f** with R^3 = Ph and a piperidine ring, the elimination of the nitrile group in the *trans* position is preferred (c-c/c-t 95:5). Therefore, we can conclude that, except for the 5-ring annelated tetrahydroquinoline derivatives (**5h, 37e**), the reductive elimination of a cyano group takes place in a chemo- and stereoselective manner.

5.3. Aminomethyl derivatives

The reduction of the mononitrile derivatives (**38a-f**) was performed as described by Caddik *et al* [114]. The aminomethyl products were synthesized by two steps reaction as depicted in Figure 50. Regarding the biological activity, previously remarkably SSAO activity of reduced naphthalene derivatives was described by Földi in her Ph.D. thesis [30].

Based on the K_m data, one can conclude that the affinity of compound **40b *cis-trans*** is higher than that of the substrate 4-PBA. The rest of the studied compounds showed only a weak enzyme inhibitory effect (Table 7 and 8).

5.4. Spirocyclic ring systems

In this section we are presenting our results related to the effect of cyclic electron withdrawing groups on the rate of the cyclization reactions. Since, the *β* carbon atom of the vinyl group is incorporated in the stronger electron withrawing moiety, we assumed that the cyclization would be faster than with malononitrile. 2-(dialkylamino)acetophenone derivatives (**35a-c**) were reacted with indan-1,3-dione (ID) and Meldrum's acid (Figure 51).

From the sum of the competition experiments, one can conclude that the formation of the vinyl compound substituted with malononitrile (**36a**) is faster than the formation of the vinyl compound substituted with ID (**41a**) (Figure 52). However, if the vinyl compound (**41a**) formed in the reaction mixture, the ring closure reaction could be faster in the case of ID, due to the stronger electron withdrawing effect of that group, compared to malononitrile (Table 11 and 12).

5.5. Bridged biaryls with methylamino-N-methyl group

As it was mentioned in the literature review (Chapter 1.2.) earlier, the extension of the *tert*-amino effect was studied extensively in our Institute, resulting medium and macrocyclic rings. The difference between the previous study and the present investigation is that the biaryl systems are connected nondirectly, namely the vinyl compound (**50b**) is bridged with a methylamino-*N*-methyl group between the phenyl rings bearing an amino and vinyl moiety in *ortho*- and *ortho'*-positions (Figure 58). These results have been published in 2012 [97].

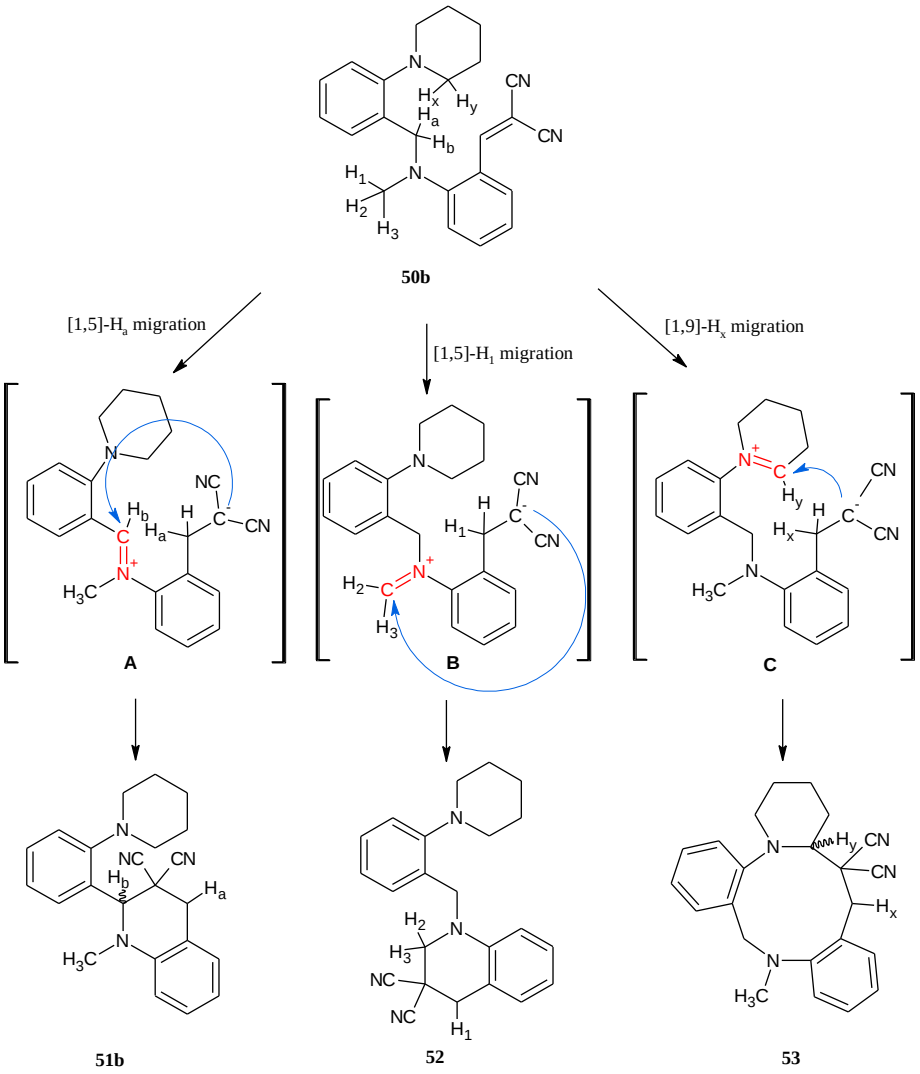


Figure 58: Three possible pathways to the formation of cyclized product

In this structure there are three possible pathways to the formation of cyclized product. (i) The hydrogen migration takes place from the methylene-carbon ([1,5] H_a migration); (ii) from the *N*-methyl-carbon ([1,5] H_1 migration); (iii) from the α carbon atom of the *sec*-amino group attached to the other phenyl ring ([1,9] H_x migration) leading to compounds **51b, 52** and **53** respectively (Figure 58).

From thermodynamic point of view, comparing all the computed reaction enthalpies ($\Delta\Delta H_f$) of the five possible isomers (**51b**-*R*, **51b**-*S*, **52**, **53**-*R* and **53**-*S*) from the starting state (**50b**) can confirm more the formation of the six member tetrahydroquinoline scaffold (exotherm values) versus the ten-membered ring products (**53**-*R* and **53**-*S*, endotherm values) (Table 13). However, at this stage, these results are

not suitable to draw conclusion, why the formation of **52** is not preferred, exhibiting analogue value.

From kinetic aspect, the rate determining step is the hydride migration, consequently, the reaction rate is controlled by the relative stability of the first dipolar intermediates. So, the exclusive formation of compound **51b** can be explained by assuming more effective stabilization of the trisubstituted iminium double bond between two phenyl ring in the dipolar intermediate (**A**) over a monophenyl derivative (**C**) or a disubstituted double bond (**B**).

The DSC experiment was monitored by TLC and ^{1}H NMR spectroscopy, which confirmed that only a simple thermal ring closure occurred in the case of compound **51b**. In the temperature range of the endothermic and exothermic peaks, no significant weight loss – that is, decomposition – was observed (Figure 54).

6. Conclusion

A facile and efficient microwave-assisted diastereoselective cyclization reaction was exploited for the preparation of condensed tetrahydroquinoline derivatives *via* the *tert*-amino effect. *Cis*-diastereoselectivity of the cyclizations was observed in all the cases, by the analysis of the crude products. The separation of the diastereomers by column chromatography or semi-preparative HPLC enabled the characterization of the relative configuration of both diastereomers by NOE interactions and the analysis of the vicinal coupling constans. We explain this result by assuming that the interchange of the conformation of the vinyl compound is a necessary, but not sufficient condition for the formation of the *cis* or *cis/trans* diastereomers, based on the Curtin-Hammet principle, confirmed by theoretical calculations, as well.

Regarding the spirocyclic derivatives (**42a-c** and **44a-c**), we can conclude that the cyclization reactions with indan-1,3-dion and Meldrum's acid are faster than with malononitrile, based on the experimental results - we were not able to isolated the vinyl compounds - and the competition experiments followed by ^{1}H NMR spectroscopy.

Extension of the *tert*-amino effect to biaryls, bridged with a methylamino-*N*-methyl group between the phenyl rings, was studied in the course of my PhD work, as well. The reactions proceeded along the one route of three possible pathways. Exclusively formation of compounds **51a** and **51b** can be explained by the thermochemical and kinetic point of view.

The further transformation of the compounds **37a, 5h, 5k** and **37d-f**, including the chemoselective reductive elimination of the cyano group, resulted two diastereomers, which were separated and fully characterized, except the **38f *cis*-*trans*** isomer. Reduction of the nitrile group afforded SSAO active aminomethyl derivatives (**40a-f**). One of them (**40b *cis*-*trans***) showed enzyme substrate activity, while two other compounds (**40a *cis*** and **40e *cis*-*trans***) inhibit this enzyme with a moderate potential, compared to that of the irreversible reference inhibitor 2-bromoethylamine, on the microsomal fraction of rat aorta.

7. Summary

Within the framework of the ongoing research project focusing on the *tert*-amino effect at the Department of Organic Chemistry, Semmelweis University, I have synthesized various tetrahydroquinoline compounds starting from simple starting materials, such as 2-dialkylamino acetophenone and 2-dialkylamino benzophenone derivatives by performing ring-closure reactions following the previous Knoevenagel condensation step. The obtained novel stereogenic centers and the substituents eligible for further transformation gave an opportunity to produce substances with potential biological activity.

First, I present the synthetic route starting from 2-dialkylamino acetophenone and 2-dialkylamino benzophenone derivatives, using one-pot microwave-assisted conditions along with the stereochemical outcomes.

Secondly, the ring-closed products were synthesized in a two steps procedure under microwave-assisted solvent-free condition from previously prepared 2-vinyl-*N*,*N*-dialkylaniline intermediates, as well. The isomeric ratios in the crude products were determined in all the cases, by using NMR spectroscopy.

The ring-closed dinitrile derivatives were suitable precursors of various aminomethyl derivatives known to act as substrates to SSAO. An additional stereogenic center was formed by a chemoselective denitrilation, then the reduction of nitrile moiety resulted the aminomethyl derivatives.

Furthermore, starting from 2-dialkylamino acetophenone and 2-dialkylamino benzophenone derivatives, I studied the effects of the respective substituents on the rate of the ring closure reaction. Employing 1,3-indanedione and Meldrum's acid, the stereochemical outcomes of which are described in the present dissertation, led to the formation of novel spirocyclic compounds.

Finally, I studied the perspectives of the extension of the *tert*-amino effect to biaryl systems bridged with methylamino-*N*-methyl group. Theoretically, these substances can be transformed into three different ring-closed products, however, only one route, allowing a tetrahydroquinoline product with a six-membered ring, involved exclusively and regioselectivity. The thermochemical features of the ring closure reactions, using computations (PM3, DFT) and experiments (DSC), were evaluated and then confirmed the experimental findings.

8. Összefoglaló

A Semmelweis Egyetem Szerves Vegytani Intézetében a *terc*-amino effektus területén folyó kutatás keretében 2-(dialkilamino)aceto- és benzofenon származékokból kiindulva különféle tetrahidrokinolinokat állítottam elő, Knoevenagel kondenzációt követő gyűrűzárási reakciók révén. A keletkezett két új sztereogén centrum és a további átalakításokra alkalmas szubsztituens kihívást és lehetőséget jelentettek biológiai hatás szempontjából is értékesnek ígérkező vegyületek előállítására.

Elsőként 2-(dialkilamino)aceto- és benzofenon származékokból kiindulva mikrohullámú körülmények között végrehajtott one-pot szintézis utat és annak sztereokémiai eredményeit mutatom be.

Továbbá, a gyűrűzárt vegyületeket a 2-vinil-*N*,*N*-dialkilanilinek izolálását követő olvadék reakcióval szintén mikrohullámú körülmények között is előállítottuk, vizsgálva a gyűrűzárás sebességét, hatékonyságát és a diasztereoszelektivitását. Minden esetben az izomer arányt a nyers termékből határoztuk meg NMR spektroszkópiával.

A gyűrűzárt dinitril származékok jó prekurzorai voltak az irodalomban már ismert SSAO szubsztrát hatással rendelkező aminometil származékok analógjainak. Kemoszelektív denitrilezést elvégezve egy újabb sztereogén centrumot kaptunk, majd a tiszta diasztereomerekből redukciós lépést követően állítottuk elő az aminometil származékokat.

A gyűrűzárás sebességét befolyásoló szubsztituenseknek hatását is tanulmányoztam szintén 2-(dialkilamino)acetofenon származékokból kiindulva. A reakcióhoz 1,3-Indándiont és Meldrum savat alkalmaztam, így új spirociklusos vegyületek sztereokémiai eredményeit is leírtuk.

A *terc*-amino effektus kiterjeszthetőségét is vizsgáltuk metilamino-*N*-metil csoporttal áthidalt biaril rendszereken, mely vegyületekből kiindulva a gyűrűzárás három lehetséges úton is végbemehet. A lehetséges gyűrűzárt termékek közül regioszelektív módon csak egy, hattagú gyűrűvel rendelkező tetrahidrokinolin származék keletkezett. A gyűrűzárás termokémiai hátterét számított (PM3, DFT) és kísérleti (DSC) eredményekkel is igazoltuk.

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10. Publication

10.1. Publications of the author related to the present work

Papers

1. Bottino P., Dunkel P., Schlich M., Galavotti L., **Deme R.**, Regdon G. Jr., Bényei A., Pintye-Hódi K., Ronsisvalle G., Mátyus P.: Study on the scope of *tert*-amino effect: New extensions of type 2 reactions to bridged biaryls.
   J. Phys. Org. Chem., **25**, 1033-1041 (**2012**) IF 1.578 (2012)

2. **Deme R.**, Schlich M., Mucsi Z., Karvaly G., Tóth G., Mátyus P.: Versatile synthesis of novel tetrahydroquinolines as potentially active semicarbazide-sensitive amine oxidase (SSAO) inhibitors *via tert*-amino effect.
   Arkivoc (V) 164-196 (**2016**) IF 1.177 (2015)

10.2. Publications of the author outside the scope of the present work

Papers

1. Énzsöly A., Dunkel P., Czompa A., **Deme R.**, Gyires K., Magyar K., Németh J., Mátyus P.: Szemikarbazid-szenzitív amin oxidáz gátlók mint új hatóanyagok gyulladásos szembetegségek kezelésére: Szelektív inhibitoroktól új típusú több-támadáspontú gyulladásgátló gyógyszerjelöltig.
   Magyar Tudomány, **6**, 48-52 (**2012**) IF-

2. Mátyus P., Huleatt P., Chai C.L.L., Sperlágh B., Khoo M.L., Magyar K., Papp-Behr Á., **Deme R.**, Túrós Gy., Gyires K.: New arylalkenylpropargylamine derivatives exhibiting neuroprotective action for the treatment of neurodegenerative diseases. Lajstromszám: PCT/HU2013/000122 esp@cenet link. Benyújtás éve: 2013. Közzététel éve: **2013.**

3. Huleatt P.B., Khoo M.L., Chua Y.Y., Tan T.W., Liew R.S., Balogh B., **Deme R.**, Gölöncsér F., Magyar K., Sheela D.P., Ho H.K., Sperlágh B., Mátyus P., Chai C.L.L.: Novel arylalkenylpropargylamines as neuroprotective, potent, and selective monoamine oxidase B inhibitors for the treatment of Parkinson's disease.
   J. Med. Chem. **58**(3), 1400-1419 (**2015**) IF 5.589 (2015)

4. Payrtis M., Sághy É., Mátyus P., Czompa A., Ludmerczki R., **Deme R.**, Sándor Z., Helyes Zs., Szőke É.: A novel 3-(4,5-diphenyl-1,3-oxazol-2-yl)propanal oxime compound is a potent transient receptor potential ankyrin 1 and vanilloid 1 (TRPA1 and V1) receptor antagonist.
   Neuroscience **324**, 151-162 (**2016**) IF 3.231 (2015)

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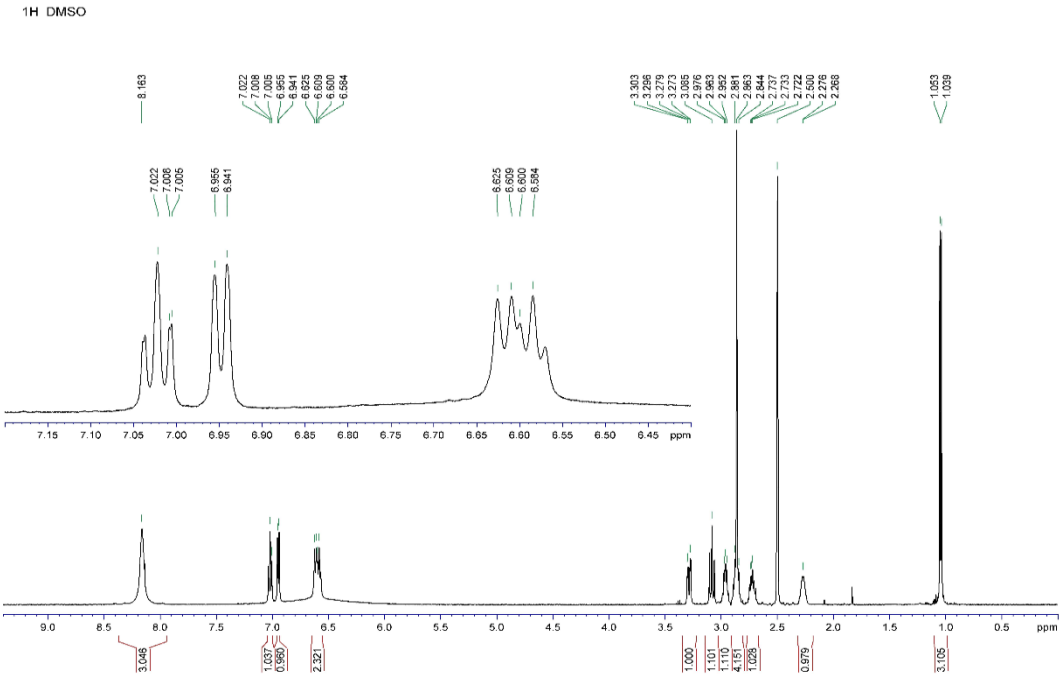
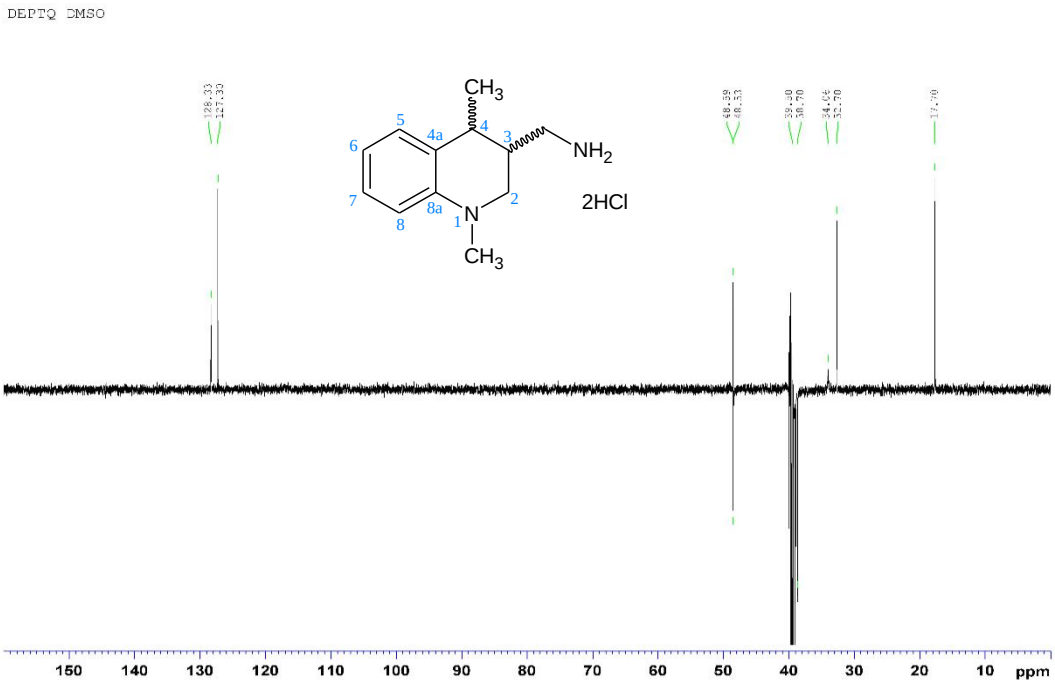
12. Appendix

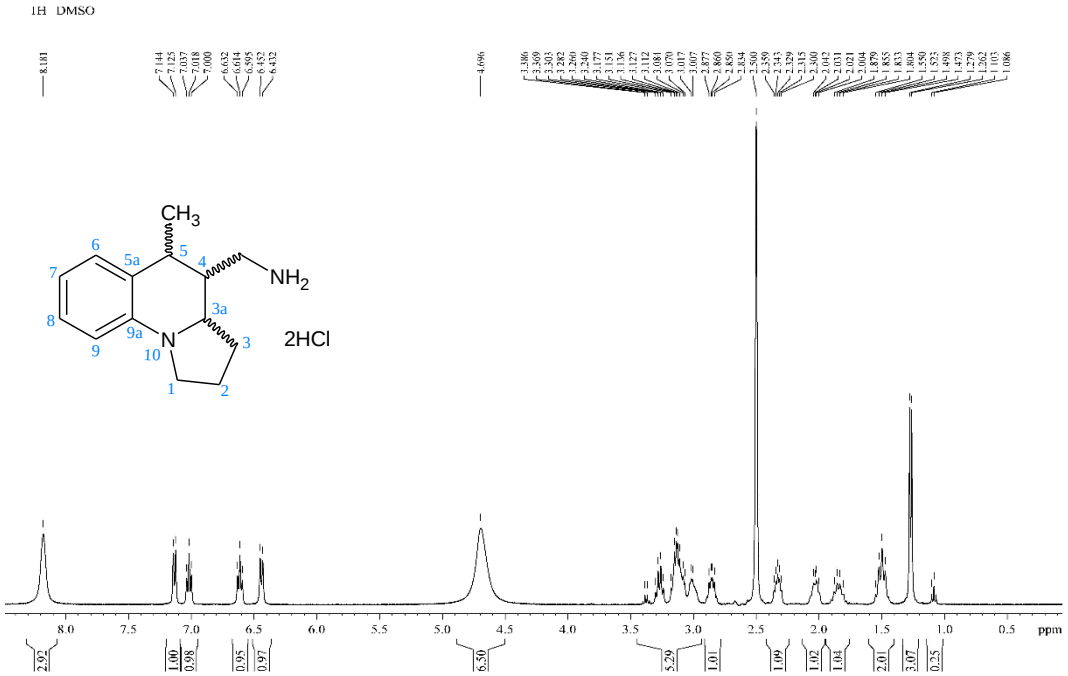
12.1. ^{1}H and ^{13}C NMR/DEPTQ spectra of selected compounds



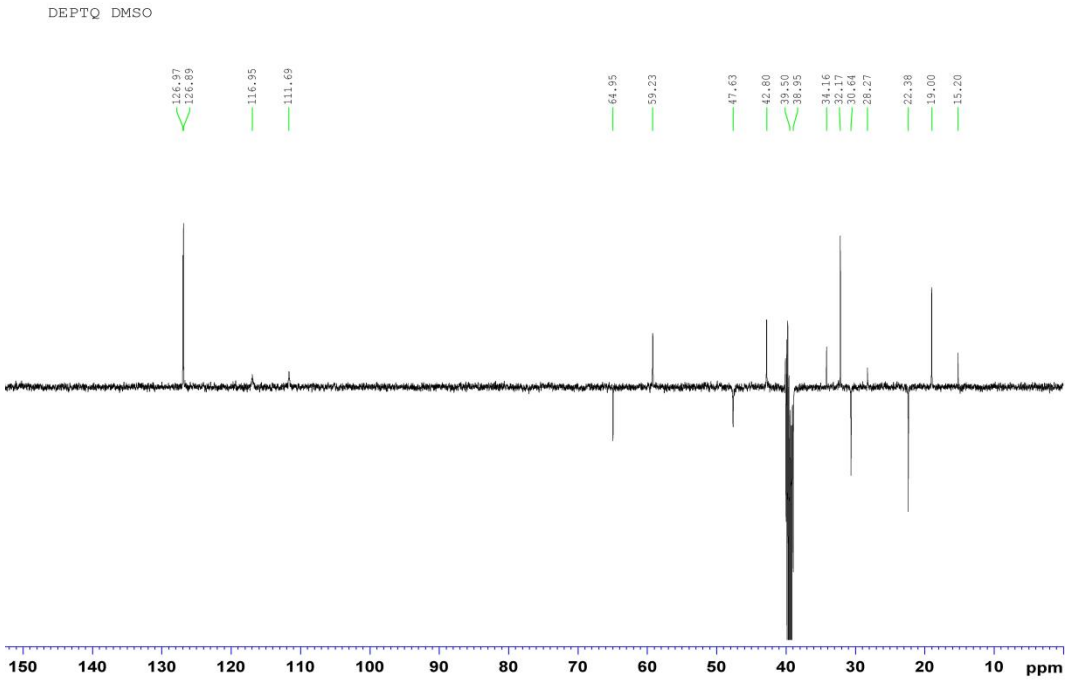
^{1}H NMR spectrum of (*cis*-(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinolin-3-yl)methanamine dihydrochloride (**40a *cis***); 500 MHz.



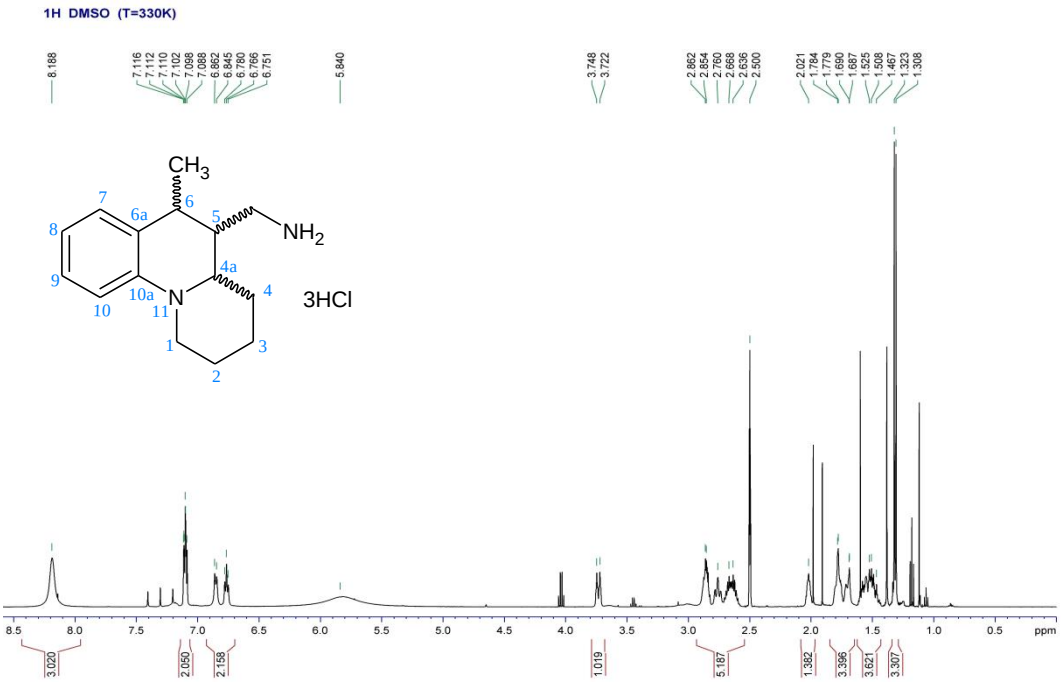
DEPTQ spectrum of (*cis*-(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinolin-3-yl)methanamine dihydrochloride (**40a *cis***); 125 MHz.



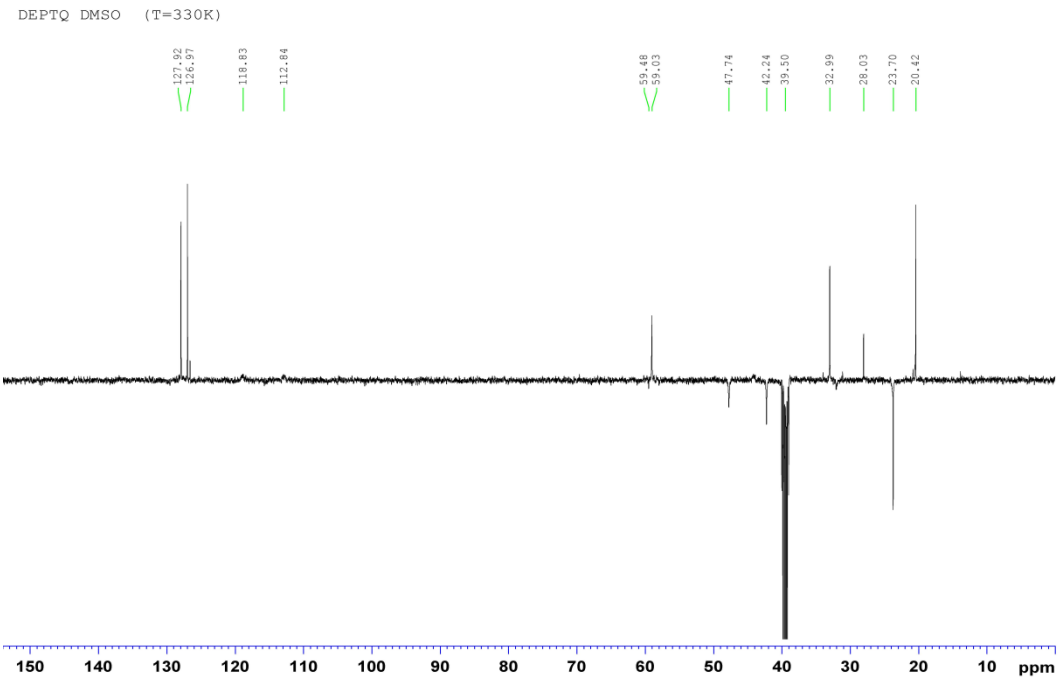
^{1}H NMR spectrum of [*cis-trans*-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (**40b *cis-trans***); 400 MHz.



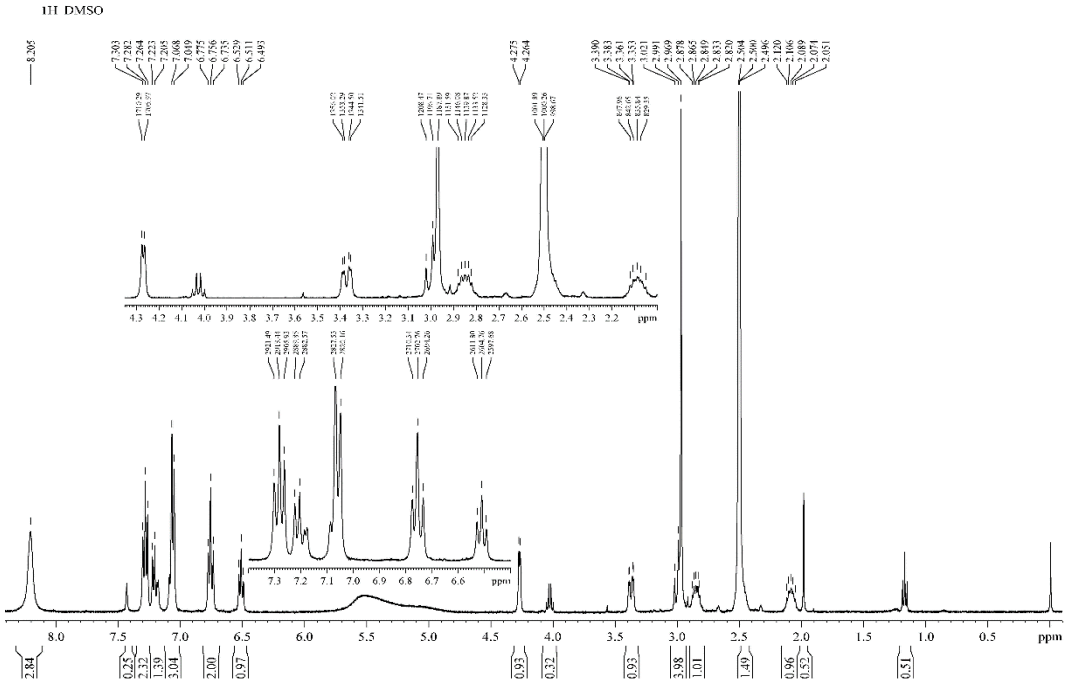
DEPTQ spectrum of [*cis-trans*-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (**40b *cis-trans***); 125 MHz.



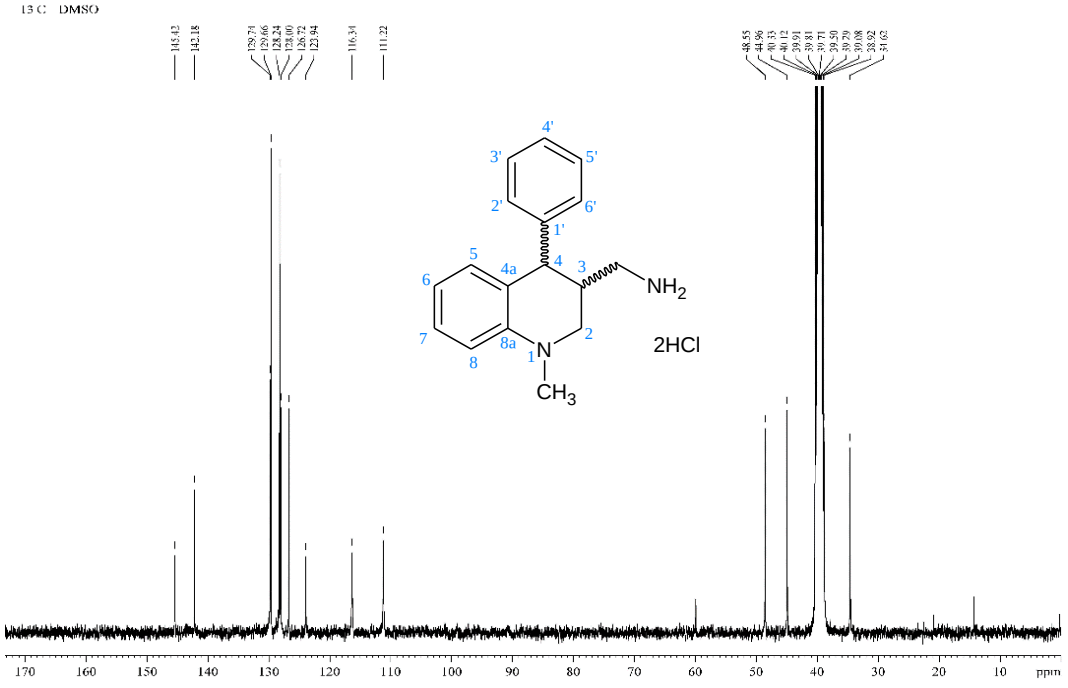
^{1}H NMR of [*cis*-*trans*-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine dihydrochloride **(40c *cis*-*trans*);** 500 MHz.



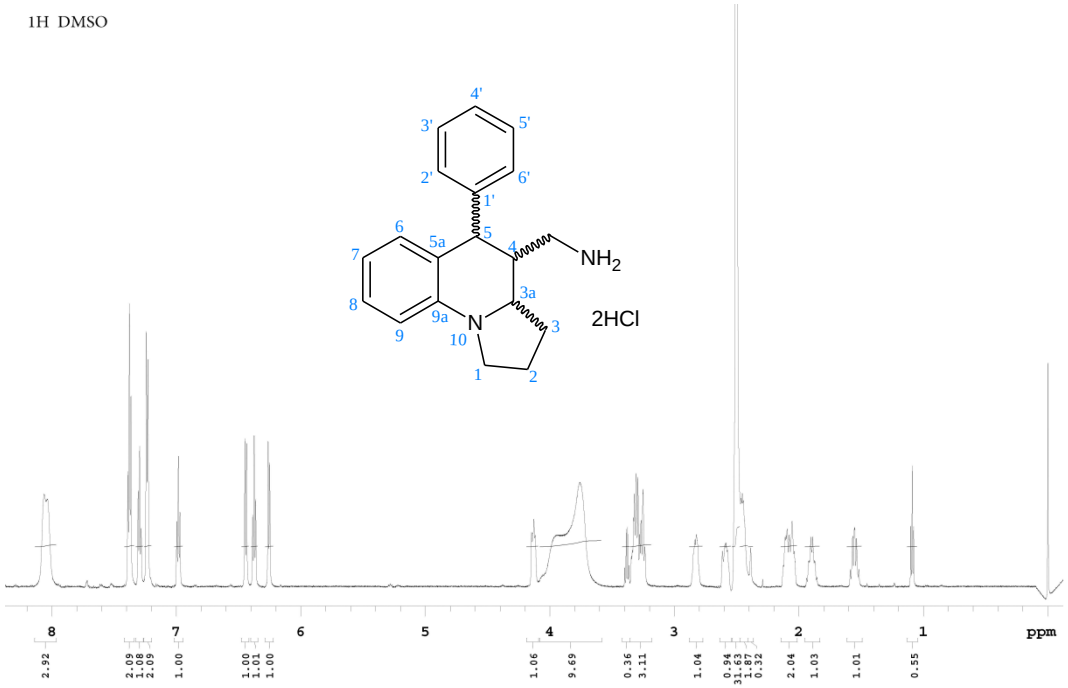
DEPTQ spectrum of [*cis*-*trans*-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine dihydrochloride **(40c *cis*-*trans*);** 125 MHz.



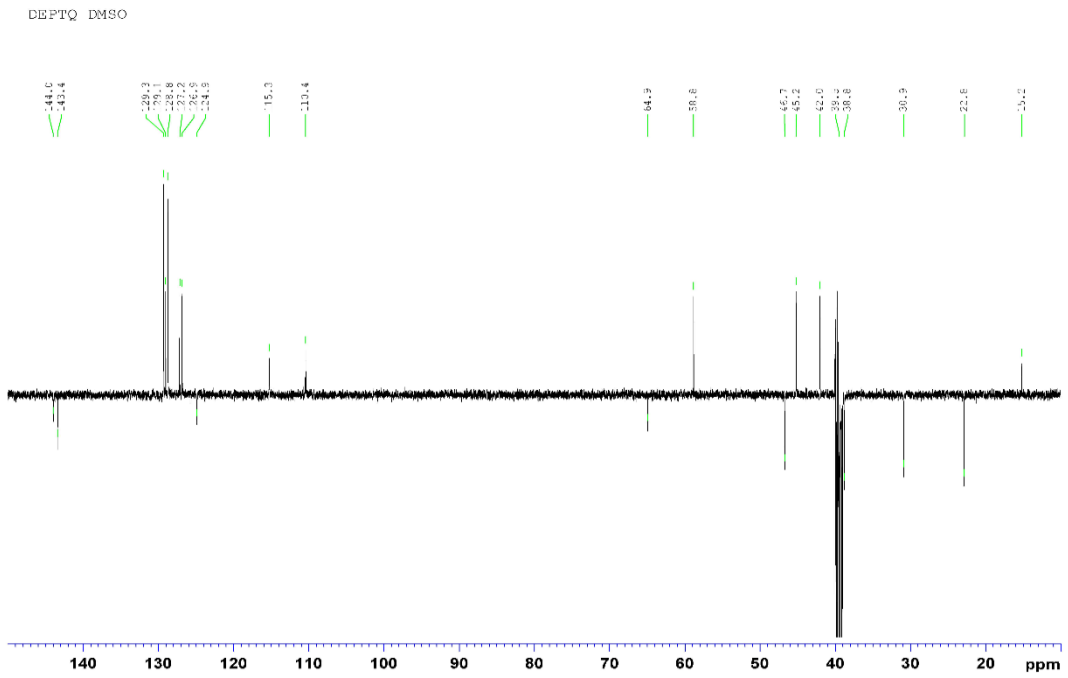
^{1}H NMR spectrum of [*cis*-(±)-1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]methanamine dihydrochloride (**40d *cis***); 400 MHz.



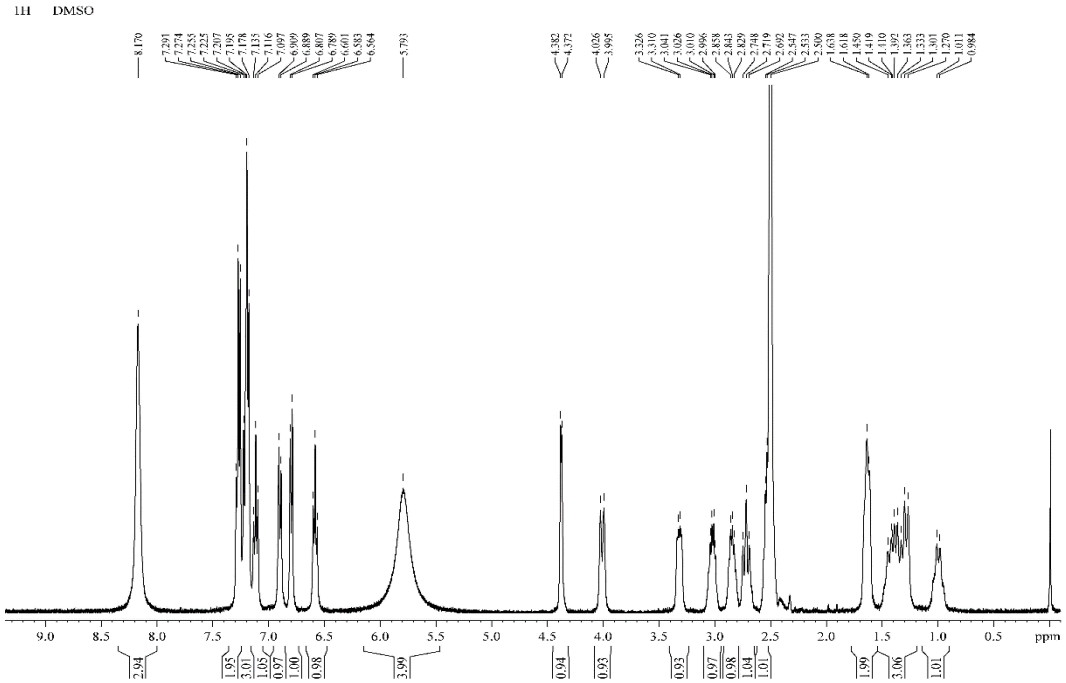
^{13}C NMR spectrum of [*cis*-(±)-1-Methyl-4-phenyl-1,2,3,4-tetrahydroquinolin-3-yl]methanamine dihydrochloride (**40d *cis***); 100 MHz.



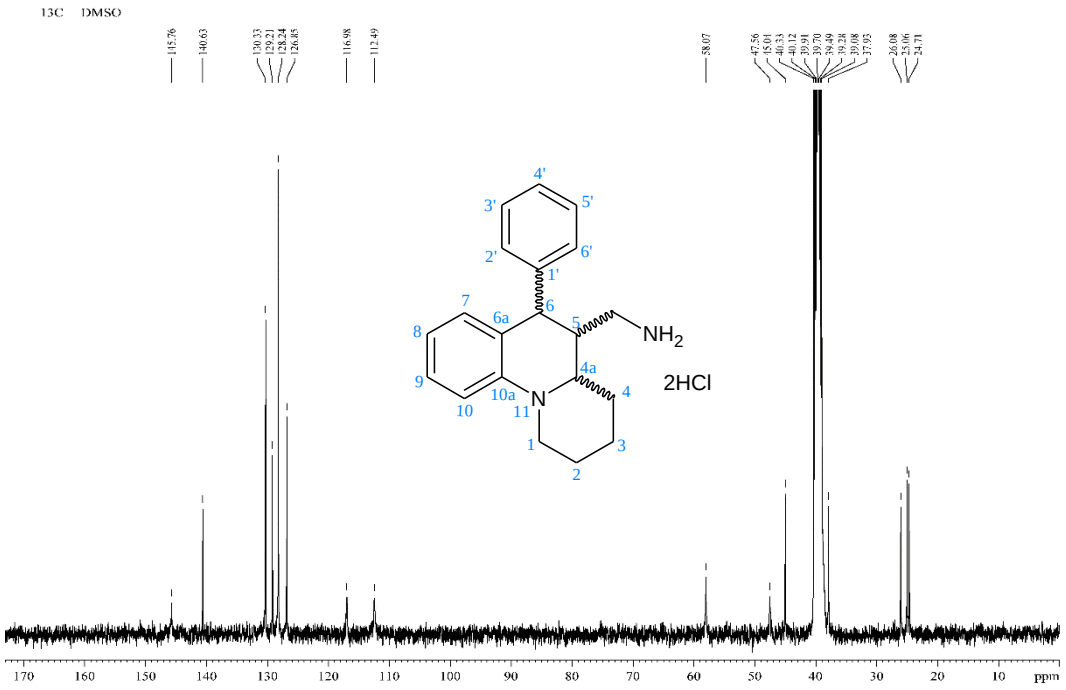
^{1}H NMR spectrum of [*cis-trans*-(±)-5-Phenyl-1,2,3,3a,4,5-pyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (**40e *cis-trans***); 600 MHz**.**



DEPTQ spectrum of [*cis-trans*-(±)-5-Phenyl-1,2,3,3a,4,5-pyrrolo[1,2-*a*]quinolin-4-yl]methanamine dihydrochloride (**40e *cis-trans***); 125 MHz.

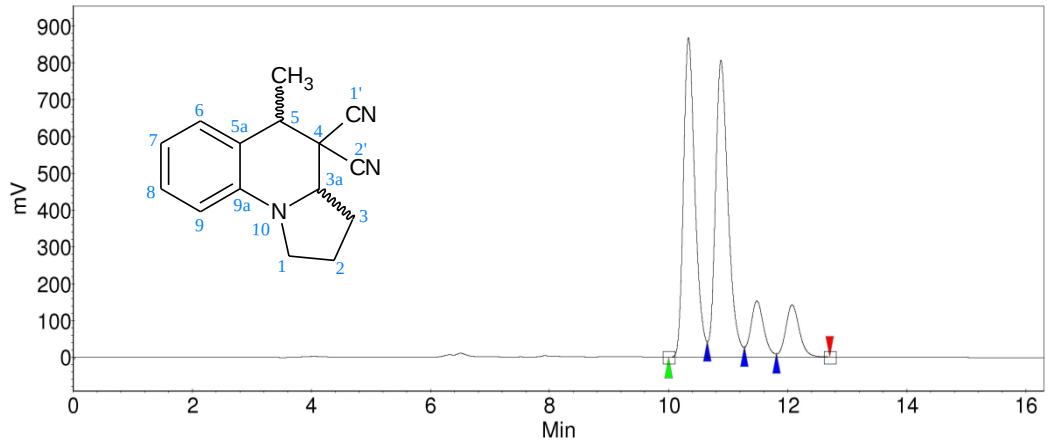


^{1}H NMR spectrum of [*cis*-*cis*-(±)-6-Phenyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine dihydrochloride (**40f *cis*-*cis***); 400 MHz.



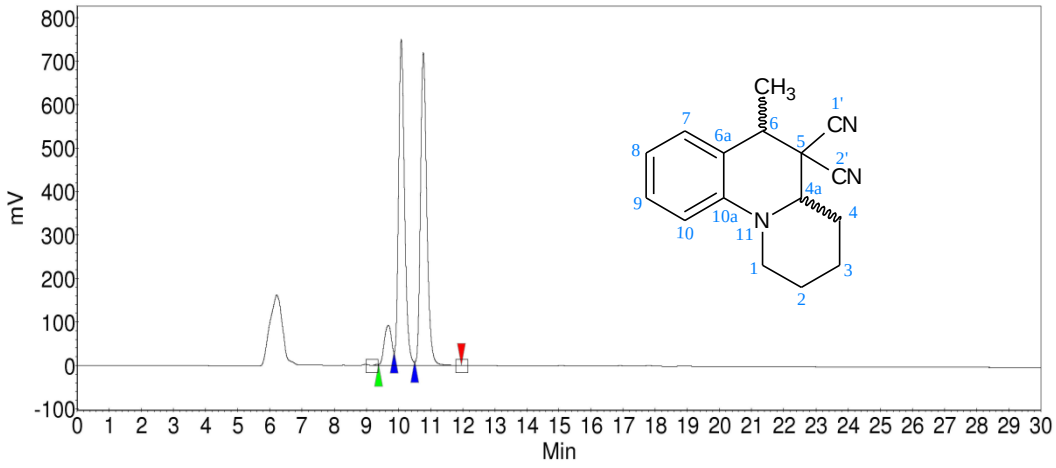
^{13}C NMR spectrum of [*cis*-*cis*-(±)-6-Phenyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinolin-5-yl]methanamine dihydrochloride (**40f *cis*-*cis***); 100 MHz.

12.2. HPLC chromatograms of selected compounds



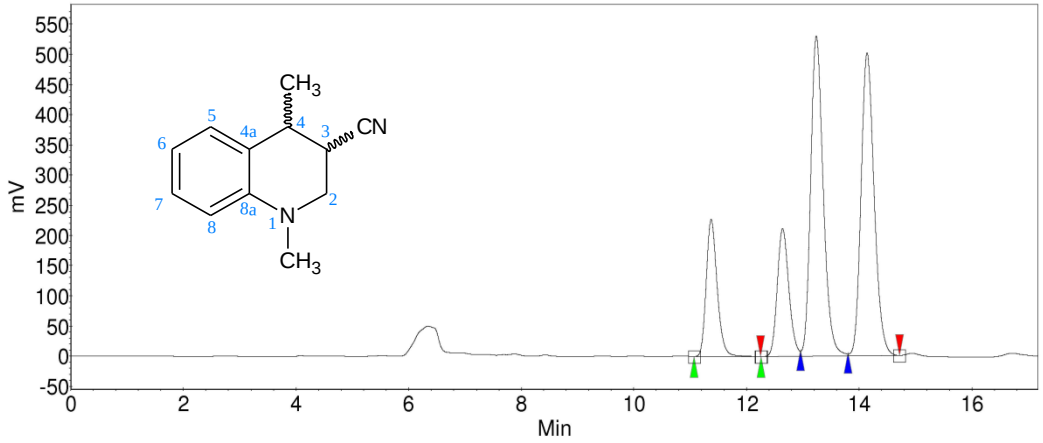
Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	10.337	41.38	867.9	193.5	41.378
2	UNKNOWN	10.882	42.35	806.9	198.1	42.352
3	UNKNOWN	11.485	8.24	152.7	38.5	8.238
4	UNKNOWN	12.075	8.03	141.9	37.6	8.032
Total			100.00	1969.4	467.7	100.000

HPLC chromatogram of *cis/trans*-(±)-5-Methyl-1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile **(5h cis/trans)** before the separation of the diastereomers; OJ-H, mobile phase ratio 10:90.



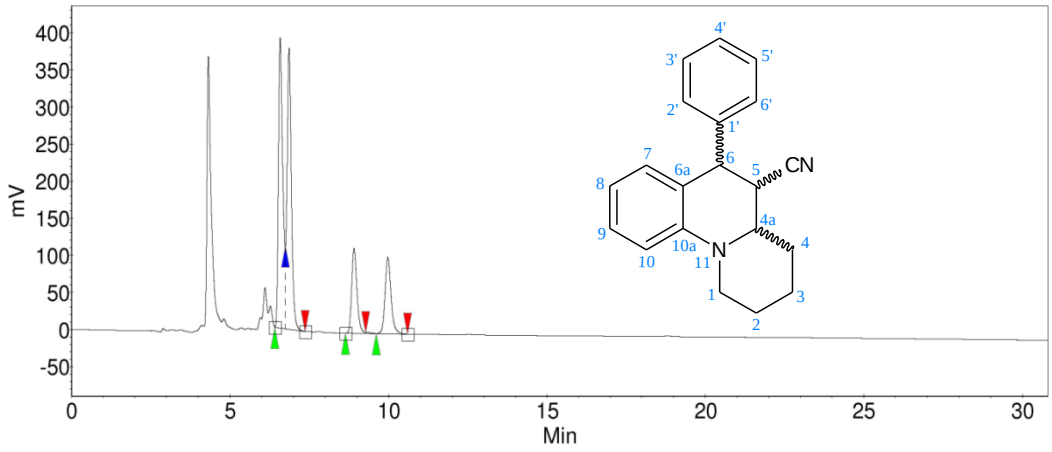
Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	9.683	7.05	92.6	24.8	7.054
2	UNKNOWN	10.087	46.29	750.3	162.7	46.291
3	UNKNOWN	10.772	46.65	720.0	163.9	46.655
Total			100.00	1562.8	351.4	100.000

HPLC chromatogram of *cis/trans*-(±)-6-Methyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5,5-dicarbonitrile **(5k cis/trans)** before the separation of the diastereomers; AD-H, mobile phase ratio 75:25.



Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	11.373	13.58	227.1	50.8	13.584
2	UNKNOWN	12.643	13.51	211.7	50.6	13.512
3	UNKNOWN	13.240	36.69	530.4	137.3	36.694
4	UNKNOWN	14.142	36.21	502.1	135.5	36.210
Total			100.00	1471.3	374.2	100.000

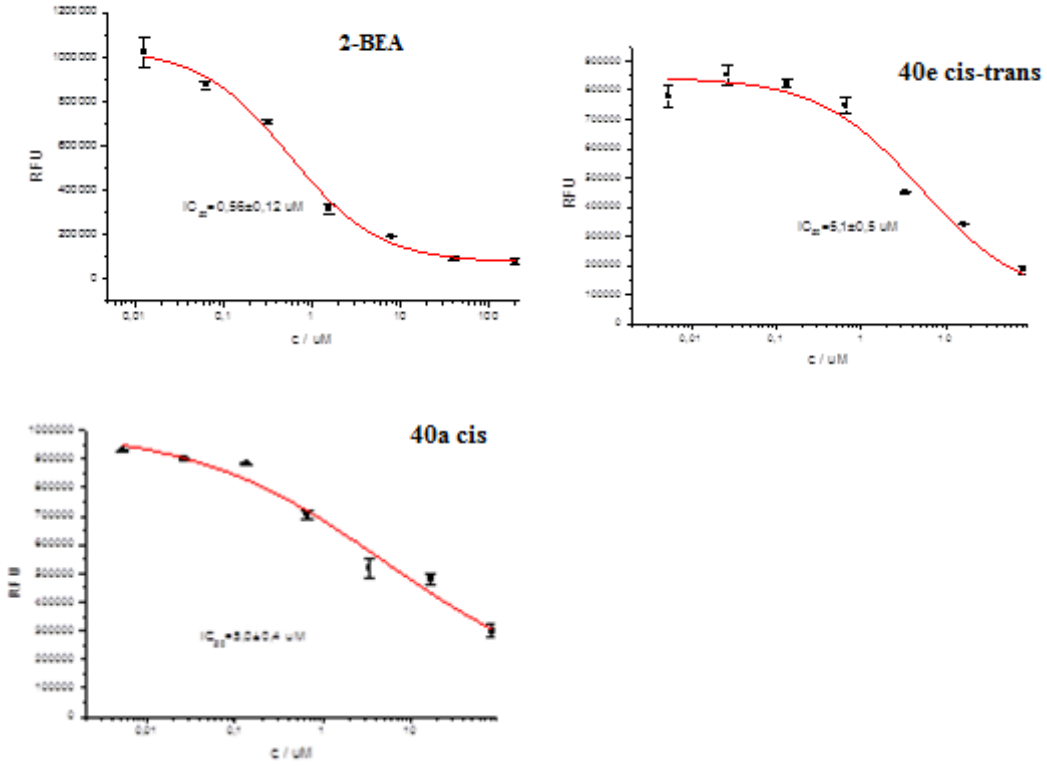
HPLC chromatogram of *cis/trans*-(±)-1,4-Dimethyl-1,2,3,4-tetrahydroquinoline-3-carbonitrile **(38a *cis/trans*)** before the separation of the diastereomers; OJ-H, mobile phase ratio 50:50.



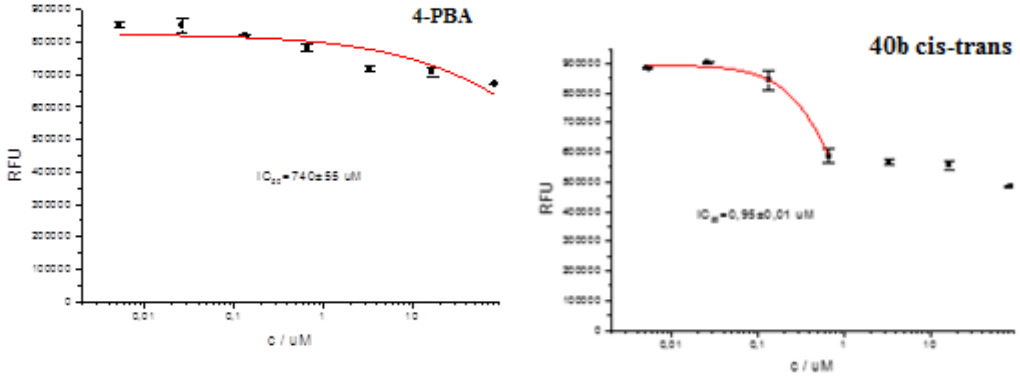
Index	Name	Time [Min]	Quantity [% Area]	Height [mV]	Area [mV.Min]	Area % [%]
1	UNKNOWN	6.580	36.97	391.1	61.7	36.974
2	UNKNOWN	6.862	36.40	379.2	60.8	36.401
3	UNKNOWN	8.910	13.07	114.8	21.8	13.070
4	UNKNOWN	9.975	13.56	103.5	22.6	13.555
Total			100.00	988.6	166.9	100.000

HPLC chromatogram of *cis-cis/cis-trans*-(±)-6-Phenyl-1*H*-2,3,4,4a,5,6-hexahydropyrido[1,2-*a*]quinoline-5-carbonitrile **(38f *cis-cis/cis-trans*)** before the separation of the diastereomers; AD-H, mobile phase ratio 50:50.

12.3. Dose response curves of selected compounds



Dose response curves of 2-BEA, compound **40a *cis*** and **40e *cis-trans***



Dose response curves of 4-PBA and compound **40b *cis-trans***