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Dipartimento di Scienze del Farmaco

DOTTORATO DI RICERCA IN SCIENZE FARMACEUTICHE

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Dott.ssa Paola Bottino

Studies on extensions of tert-amino effect: Ring-fusion to bridged biaryls and steroids

DOCTORAL THESIS

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1. Introduction

The term "*Tert-amino effect*" was coined by Meth-Cohn and Suschitzky in 1972[1], to generalize cyclization reactions of certain tertiary anilines containing an unsaturated substituent in *ortho* position. According to Meth-Cohn, the ring closure can proceeds in two different ways, leading to the formation of fused heterocycles (**Figure 1**):

- One includes those cyclizations which result from an interaction between the unsaturated substituent in the *ortho* position and the nitrogen atom (**A**);
- The other includes those reactions that involves the unsaturated substituent in *ortho* and one of the α–methylene groups to the nitrogen atom (**B**).
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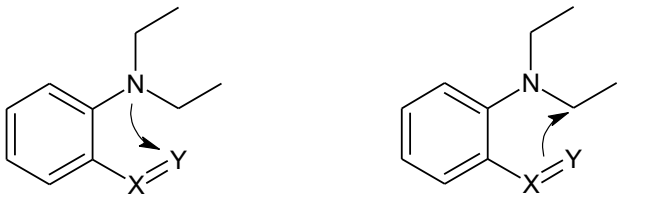


A

Interaction with the tertiary amine

B

Interaction with the α-methylene groups

Fig. 1: Types of interaction between dialkylamino groups and unsaturated substituent in *ortho* in the "*tert*-amino effect".

Afterwards, in recent works[2-4] new *tert*-amino effect types of cyclization have been described and at the moment we are able to distinguish seven types of *tert*-amino effect (**Figure 2**):

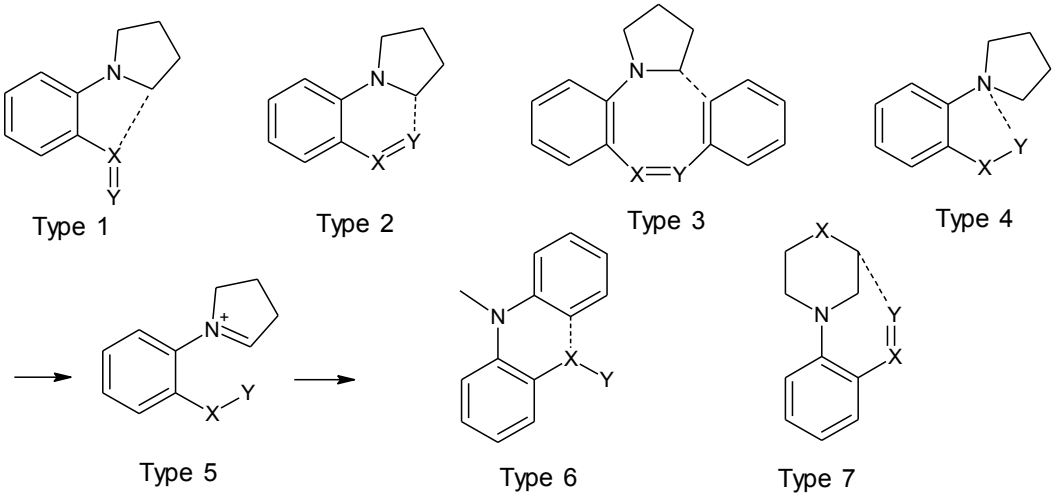


Fig. 2: Types of cyclization in "*tert-amino effect*".

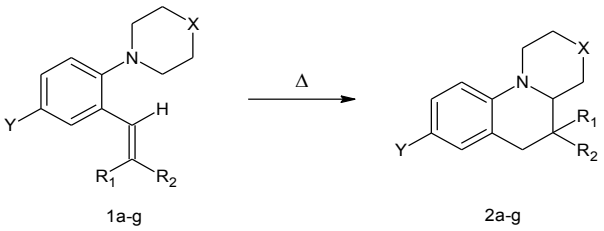
The common feature in these cyclizations is the unexpected reactivity of the dialkylamino group when a conjugated *ortho*-substituent (A=B) in the aromatic ring is present. The different features of those cyclizations include the size of the ring formed and the mode of its formation.

The present work is focused on the study of novel extensions of type 2 *tert*-amino effect and the other types of cyclization will not be treated.

1.1 Type 2 tert-amino effect

1.1.1 Mechanism of cyclization

Few reactions have been carried out using compounds in which A=B constitutes a vinyl group. Those reactions that occur upon heating depend on the substituent of the vinyl group[5,6]; it was observed that when a β-carbon atom of the vinyl group bears two electron-withdrawing groups, *e.g*. CN or COOR, the ring closure to a six-membered ring occurs leading to compound **2** (**Figure 3**):



	R_1	R_2	X	Y
a	CN	CN	-	H
b	CN	CN	CH_2	H
c	CN	CN	O	H
d	CN	CN	-	NO_2
e	CN	CN	-	Br
f	CN	COOEt	-	H
g	COOMe	COOMe	-	H

Fig. 3: Influence of different substituents of the vinyl groups in the cyclization reactions.

Groenen *et al*. [7], carried out studies in order to identify a possible mechanism of this reaction. Indeed, it can be assumed to occur in two consecutive steps. The first step involves a thermal suprafacial [1,5]-hydrogen shift of one α-methylene proton adjacent to the nitrogen of the amino group; this migrating hydrogen atom Ha remains at the same face of the molecule and a dipolar intermediate forms (**Figure 4**, compound **4**). Then, the former vinyl group rotates around its bond to the phenyl moiety leading to the formation of a new bond between the two opposite charged atoms and to the subsequent formation of the six-membered ring.

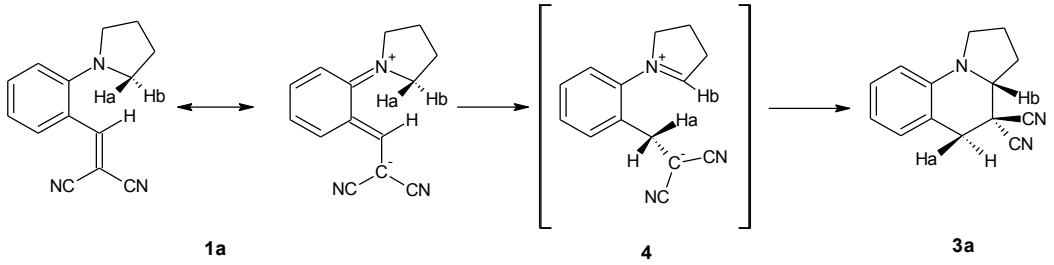


Fig. 4: Mechanism of six-membered ring formation.

Further experiments conducted by the same group of researcher, demonstrated the total hydrogen atom migration in the rate-determining step, by use of deuterated compounds (**Figure 5**):

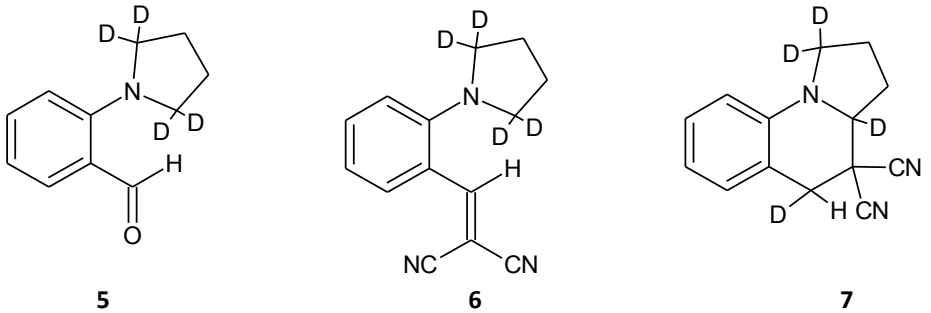


Fig. 5: Study of kinetic isotope effect.

Therefore, tetradeuterated compound **6** was synthesized by a Knoevenagel condensation of compound **5**. The ring closure reaction occurred at 91.2°C in DMSO-d_6 and a kinetic isotope effect of 3.0 +/- 0.3 was measured. Even though this kinetic isotope effect is the sum of a primary and secondary kinetic isotope

effect, its magnitude strongly indicated that migration of a hydrogen atom takes place in the rate-determining step of the reaction.

^{1}HNMR and mass spectra results of the ring closured compound **7**, showed that during the cyclization step no deuterium was lost in the substrate, confirming that the hydrogen (deuterium) migration is an intramolecular step.

Recent studies carried out in 2005 by the group of O'Leary[7a], showed an intramolecular reaction, not recognized as possible *tert*-amino effect, leading to a fused azepine formation. A possible mechanism of this conversion is reported on **Figure 6**.

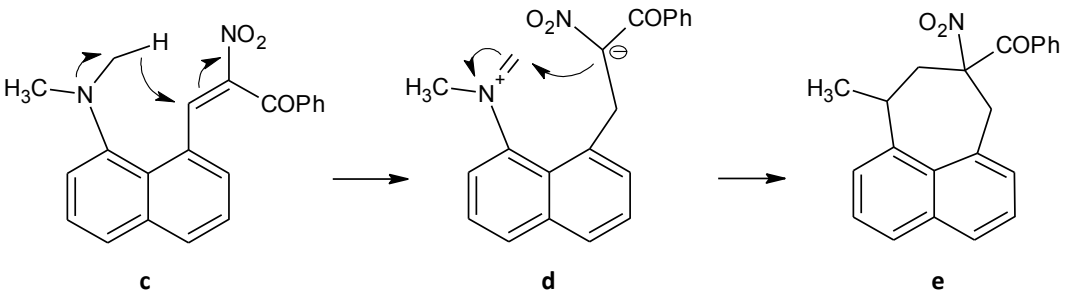


Fig. 6: Hydride donation mechanism

Starting from the di-substituted naphthalene compound **c**, a hydride donation from the *N*-methyl group to the electron-deficient alkene takes place, resulting in an iminium cation and a stabilized carbanion (compound **d**) and their subsequent reaction (compound **e**). The initial donation of hydride is supported by the close proximity of the groups and the electron-rich character of the dimethylamino group.

To confirm this hydride donation mechanism, intermediate's NMR spectra were measured. Samples of the reaction taken during the first hours of the rearrangement at 90°C, showed the presence of at least one intermediate species; even if complex spectra were obtained the singlet at 8.21 and 3.05 (broad) ppm provide evidence for the alkenyl hydrogen and dimethylamine groups of one isomer of the open chain form **c**.

1.1.2 Important parameters of cyclization reactions

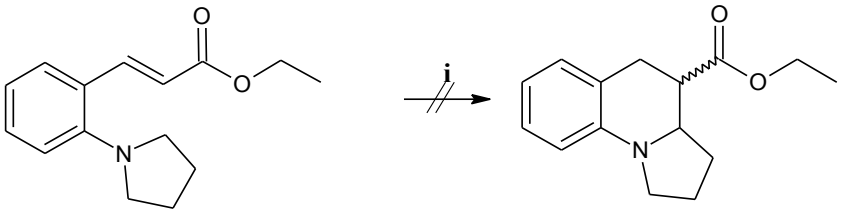
Different parameters are involved in the *tert*-amino cyclization reactions. Indeed, change of these parameters can modify the rate and the yield of the ring closure reaction. Therefore, those aspects were thoroughly explored by Reinhoudt group[7b].

- *Solvents*

The most common solvent used for those cyclization reactions is the DMSO, a polar solvent. When this is replaced by an apolar solvent (e.g. toluene), the reaction rate decrease by a factor of about 150. This quite drastic solvent effect firmly indicates that the transition state of the rate-determining step is highly polar in comparison with the ground state. In the apolar solvent a polar molecule will be less solvated and stabilized than in the polar solvent. Therefore, assuming that the mechanism of the reaction is the same in both solvents, the slower reaction in the apolar solvent must be due to a less favorable solvation of the transition state relative to the ground state than in the polar solvents. Moreover, this indicates that the charge separation takes place in the rate-determining step.

- *Substituents: the role of the β,β-vinyl electron-withdrawing group.*

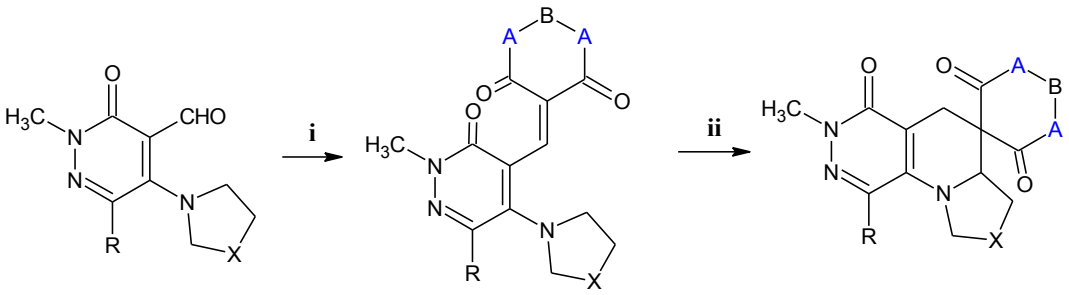
In the first example of tert-amino effect[1], the X=Y substituent in *ortho* position, contained at least one heteroatom, for example nitro, azo, azometin, karbonil, tiokarbonil groups. The first theory which said that the heteroatom is needed for the rearrangement, was destroyed by Reinhouldt and coworkers[5]. He recognized the *tert*-amino effect cause isomerization in *ortho*-vinyl-*N,N*-dialkylanilines bearing two strongly electron-withdrawing groups in β-position on the vinyl group[5]. They weren't able to obtain the cyclized product **9** starting from compound **8** which contained only one esther group (**Figure 7**):



8 **9**

Fig.7: derivatives containing only one electron-withdrawing group
(i) *n*-BuOH, Δ, 10 days or MeCN, ZnCl2, Δ, 3 days

Other examples proved that in type-2 *tert*-amino effect the presence of the double substituted vinyl group containing electron-withdrawing groups is necessary for the isomerization. Indeed, the electron-withdrawing groups are necessary for the delocalization of the negative charge on the β-positioned carbon atom of the vinyl group, during rearrangement. Some *tert*-amino effect reactions were carried out using ring form of electron-withdrawing groups which contained the terminal carbon atom of the vinyl group **11a-e**, in order to accelerate the isomerization reaction and to make possible the producing of spirociclyc compound **12a-e** (**Figure 8**, **table 2**) [4,8-11].



10 **11a-f** **12a-f**

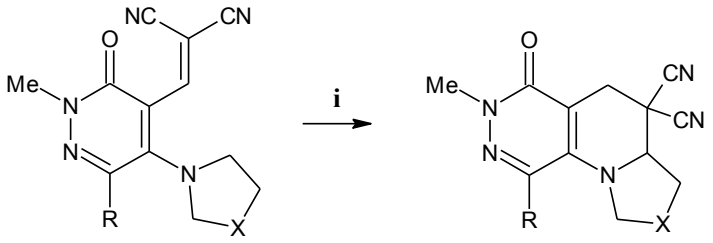
Fig.8: synthesis of spyrociclyc compounds
(i) 1,3-dimetilbarbituric acid or Meldrum-acid, toluene, AcOH, piperidin, 25°C, or 1,3-dimetilbarbituric acid, EtOH, 25°C; (ii) **12a-b**: xilol, AlCl3, 150°C or **12c**, **12e**:DMF, 110°C.

	R		t(h) Yield (%)		t(h) Yield (%)	k(DMSO-d_6, $10^{-4}sec^{-1}$)
11a	H	X=CH_2O A=NMe B=C=O	0.75 / 75%	**12a**	8 / 45%	80°C / 0.31 ± 0.05
11b	H	X= CH_2O A=O B=$C(CH_3)_2$	4.0/ 64%	**12b**	5 / 79%	-
11c	H	X= CH_2 A=NMe B=C=O	0.75 / 87%	**12c**	8 / 50%	93°C / 0.63 ± 0.01
11d	Ph	X= CH_2O A=NMe B=C=O*	-*	**12d**	1 / 88%	-
11e	Ph	X= CH_2 A=NMe B=C=O	1.0 / 86%	**12e**	3 / 40%	80°C / 40.86 ± 8.81
11f		X= CH_2CH_2 A=NMe B=C=O	-*	**12f**	1 / 82%	-

***11d, 11f** could not be isolated, **12d, 12f** were produced in a one-pot synthesis.

Table 2: reaction time and yields in case of **16a-f** and **17a-f** compounds.

Studies carried out by Matyus *et al*.[11], compared the acyclic (**Figure 9**, **Table 3**) and cyclic (**Figure 8**, **Table 2**) vinyl substituents' effect to the reaction rate of the ring closure. They noticed that, if the terminal carbon atom of the vinyl group is into pyrimidintrione moyiety, this derivative's ring closure is significantly faster than derivatives with acyclic vinyl groups; this reaction also can be carried out in milder reaction conditions – *e.g*. the aldehyde with morpholino group **10**, reaction with 1,3dimethyl barbituric acid, although the mild reaction condition, the spyrocyclic pyridazino[4',5':5,6]pyrido[2,1-*c*][1,4]oxazine (**12d**) ring system was obtained in a very small reaction time.



13a-e **14a-e**

Fig. 9: Cyclization of dicyano vinyl pyridazinone derivatives.
(i) **Table 3**

	R	X	Solvent / T (°C)		t(h) / Yield (%)	k (DMSO-d_6, $10^{-4}sec^{-1}$)
13a	H	CH_2	DMSO / 150	**14a**	44 / 44%	150 °C / 0.63 ± 0.07
13b	H	CH_2O	DMSO / 150	**14b**	39 / 35%	150 °C / 0.683 ± 0.02
13c	Ph	CH_2	DMF / 100	**14c**	9 / 67%	100 °C / 2.57 ± 0.457
13d	Ph	CH_2CH_2	DMF / 100	**14d**	3 / 47%	80 °C / 8.09 ± 0.08
13e	Ph	CH_2O	DMF / 100	**14e**	9 / 46%	100 °C / 2.30 ± 0.13

Table 3: Cyclization of dicyano vinyl pyridazinone derivatives.

Glukhavera *et al*., also examined the synthesis of the spyrocyclic derivatives of quinoline derivatives, using and comparing meldrum acid, barbituric acid and cyclohexane 1,3-dione as an active methylene group in knoevenagel condensation reaction[10]. This derivatives are react significantly faster in tertiary amino effect reactions, than the reagents with acyclic vinyl; the spyro-derivatives were achieved without isolation of the vinyl compounds.

- *Substituents: the role of the amino group.*

Kinetic examination[11] of the role of the amino group led to interesting informations. During the examination of acyclic vinyl substituted benzyl derivatives (**1a-g**, **Figure 3**) ring closure reaction, replacement of pyrrolidine ring (**1a**: k = 8,500 ± 0,3 $10^{-4}sec^{-1}$, 90,4°C, DMSO-*d6*) with piperidine (**1b**: k = 4,900 ± 0,05 $10^{-4}sec^{-1}$, 90,3°C, DMSO-*d6*) decrease the reaction rate (**Table 4**). This can be explained by the decreased overlap of the lone pair of the nitrogen with the

aromatic ring, therefore leading to a less effective delocalization of the positive charge on the amine nitrogen in the transition state. For morpholino ring analogue **1c,** the conjugation of the lone pair of the nitrogen atom decrease even more because of the electron-withdrawing effect of the oxygen atom in the ring; this lead to a less stable transition state and a decreasing of the reaction rate (**1c**: k=0,190 ± 0,05 10^{-4}sec-^{1}, 92^{o}C, DMSO-*d6*). Considering the acyclic dimethylamino group, the interaction of the lone pair of the nitrogen and the aromatic π-electron system decreased (k =1,76 ± 0,21 10^{-4}sec^{-1}, 120^{o}C, DMSO-*d6*)[12], because of the higher rotation around carbon-nitrogen bond.

Compound	Solvent	Temperature (°C)	Rate constant (10^{-4} sec^{-1})
1a	toluene d_8	93	0.067±0.005
1a	DMSO-d_6	90.4	8.5±0.3
1b	DMSO-d_6	90.3	4.9±0.5
1c	DMSO-d_6	92	0.19±0.05
1d	DMSO-d_6	90.9	0.29±0.03
1e	DMSO-d_6	90.9	8.1±0.7
1f	DMSO-d_6	90.7	0.60±0.02
1g	DMSO-d_6	89	0.078±0.010
6	DMSO-d_6	91.2	2.9±0.2

Table 4: Rate constants of different compounds during cyclization. Solvent and substituent effects.

Reaction rate constants of acyclic vinyl substituted benzyl derivatives:

k*pyrrolidine* > k*piperidine* > k*morpholino* >> k*dimethylamine*

In case of cyclic vinyl substituted benzyl derivatives, considering the pyrrolidine-substituted compound, the ring closure reaction was carried out using mild reaction condition (k = 4,900 ± 0,05 10^{-4}sec^{-1}, 90,3^{o}C, DMSO-*d6*). The effect of the morpholino and dimethylamine groups on the ring closure reaction rate was approximately equivalent. Activation paramenters of morpholino derivative and the dimethylamino derivative were equivalent too.

Reaction rate constants of cyclic vinyl substituted benzyl derivatives:

k*pyrrolidine* > k*morpholino* ≈ k*dimethylamine*

In case of pyridazine derivatives, the previous order changed:

$$k_{piperidine} > > k_{morpholino} \approx k_{pyrrolidine} > k_{dimethylamino}$$

It can be also observed the upside down order of the vinyl derivatives of the pyridazinone produced with dimethyl barbituric acid which contained hydrogen in position 6 (**Table 2**). The morpholino derivative cyclized slightly faster, and the reaction activation enthalphy ($\Delta H^{\#}$ = 23,0 ± 0,645 kcal/mol, $\Delta S^{\#}$ = -13,9 ± 1,545 kcal/mol) was also smaller than the pyrrolidine derivative's. This reverse tendency was also noticed in compounds bearing phenyl group in position 6 position. The **11d-f** derivatives, containing an amino group in the six-member ring, led to the cyclized products at room temperature. For **13b**,**d**,**e** malononitrile derivatives (**Table 3**) – similarly to the benzyl derivatives – the morpholino ring reacted slower than the piperidine derivative's. Comparing the effect of the pyrrolidine ring with the six-member rings, it was observed that the compound bearing pyrrolidine group cyclized with similar reaction rate than the compound bearing the morpholino moiety, in case of malononitrile derivatives.

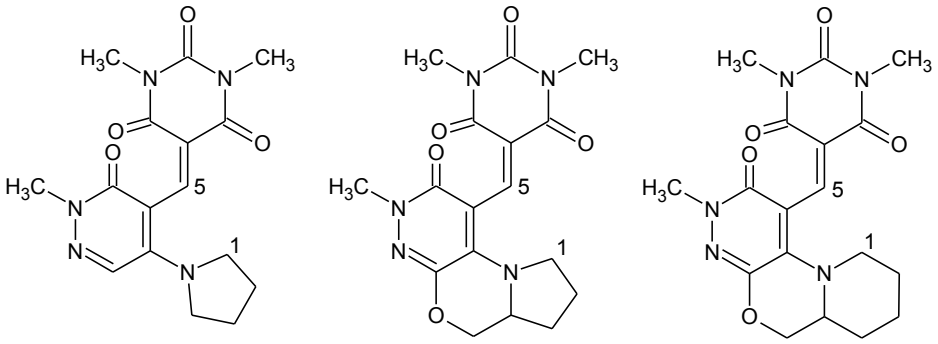
Reaction rate constants of cyclic vinyl substituted pyridazine derivatives (**Table 2**):

$$k_{piperidine} \approx k_{morpholino} > > k_{pyrrolidine} > k_{dimethylamine}$$

Considering cyclic vinyl substituted pyrrolidine derivatives, the ring closure reaction was slower. Although the dimethylamine substituted isomerization was slower than the pyrrolidine derivative at same temperature, the cyclization activation enthalphy of the two compounds were approximately equivalent; the reason of the difference was that the first one reaction's entrophy was more negative. Due to the Gibbs equilibrium, for the transition state the activation free enthalpy of the ring closure reaction of the dimethylamine derivative at 80°C was $\Delta G^{\#}$ = 26,1 kcal/mol, while for the pyrrolidine derivative it was $\Delta G^{\#}$ = 24,7 kcal/mol.

The effects of the different amino group to the reaction rate constants can be also explained by the influenced of every functional group in the 3D space.

For examination of the role of the conformational freedom of the amino groups to the rearrangement, Matyus *et al*., synthesized conformationally static analogues[13]. For these compounds no significant decrease of the reactivity was noticed, compared with the referenced compound (250^{o}C, solvent-free 30 minutes, 81%; 150^{o}C, DMSO, 6h, 54%).



11c **15a** **15b**

Figure 10: Structure of the conformationally static analogue.

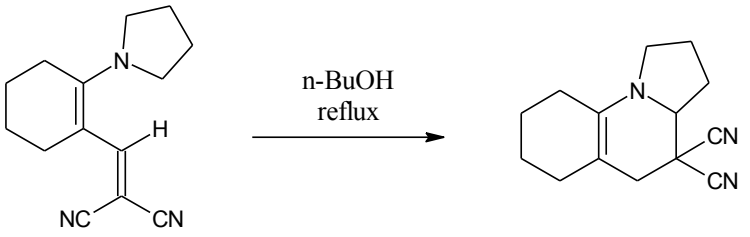
The conformational behave of the trioxopyrimidine side chain had no influence on the hydrogen moving, the acceptor carbon atom could link both moving hydrogen atoms in good position, independently if the NCH_2 group belongs to a five or a six member ring. In conclusion, the hydrogen moving is influenced by the C(1)H and C-5 distances, these lengths depend on the conformational moving of the NCH_2 functionalized saturated rings than on the position of the vinyl substituent.

- *Aromatic and non-aromatic systems*.

During kinetic studies, few results regarding the aromatic ring involved in the transition state, have been inquired[7]. It was observed that because of the strong electron withdrawing nitro group in position 5 (**1d**, **Table 4**), the reaction rate significantly decreased proving the importance of the interaction of the aromatic system and the positive charged nitrogen. On the contrary, if a bromine atom is present in position 5 - which has mainly electron-donator mesomeric effect next

to the electron withdrawing effect (**1e**) - the stability of the transition state increase , and because of this the reaction rate of the rearrangement increased too (k = 8,100 ± 0,700 $10^{-4}$$sec^{-1}$; **Figure 3**, **Table 4**).

In **Figure 11**, non-aromatic analogue compound (**16**) is shown; the rearrangement rate of this compound was much slower than compound **1a**, proving the influence of the aromatic system during isomerization (cyclization of compound **16** in refluxing with n-butanol took approximately 2 days, instead of 2 hours needed for compound **1a** under the same conditions). Comparing the rearrangement on the π-electron deficient analogues and on the π-electron rich analogues, it showed the same influence too.



16 **17**

Fig. 11: *Tert*-amino effect type 2 cyclizations of 2-vinyl-*N,N*-dialkylanilines.

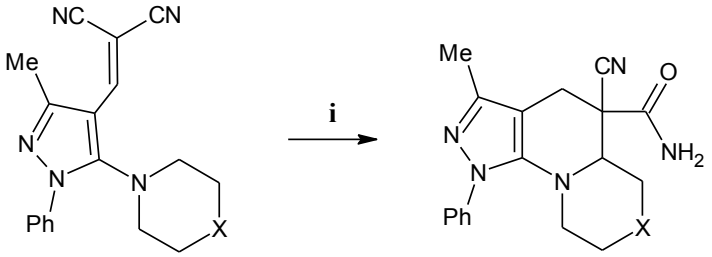
Replacing the benzyl ring with more electron-poor pyridazinone, significantly reduced the reactivity. Matyus and coworkers, first time used this method on diazines derivatives to produce tetrahydropyrido[4,5-*b*]pyridazine ring system (**Figure 9**)[4,8-11,13-18]. The authors condensated 5-pyrrolidine (X = -) and also 5-morpholino (X = O) pyridazin-4-carbaldehyde with malononitrile and reached appropriate **13a** and **13b** vinyl compounds, which were successfully cyclized in DMSO at 150°C (**Figure 9**, **Table 3**).

Later they also examined the rearrangement of 6-arylpyridazinon-derivatives **13c-e** and they experienced that the presence of the aryl group increase the rate of the rearrangement[11]. This effect probably could be due to the steric effect of the aryl group. Based on authors opinion, the big phenyl group decrease the conformation freedom of the tertiary amino group, and due to this it has favorable effect to the position of hydrogen involved in the moving;

this helps the reaction rearrangement acting as steric support for the tertiary amino group.

The rearrangement of the vinyl derivatives **18a-c**, produced from the reaction of the π-electron rich 5-*tert*-amino-1-phenil-3-methylpyrazolon-4-carbaldehydes and maloninitrile, was carried out in apolar toluene (**Figure 12**, **Table** 5), on the contrary of the rearrangement of the pyridazinone analogues where dipolar DMSO or DMF solvents were used.

In the pyrazolino-quinoline **19a-c** obtained by isomerizatin of compounds **18a-c**, in every case one of the nitrile group was reduced to amide. The authors could not find explanation for this[22].



18a-c **19a-c**

Figure 12: The reactions of the pyrazole derivatives containing dicyano vinyl groups. (i) toluene, $ZnCl_2$, Δ.

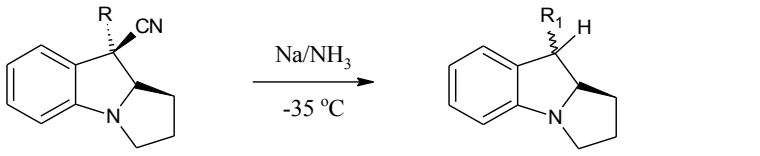
	X	t(h)/Yield (%)	k (DMSO-d_6)
18a	-	10 / 55%	-
18b	CH_2	5 / 63%	-
18c	O	12 / 60%	-

Table 5: The reactions of the pyrazole derivatives containing dicyano vinyl groups.

1.1.3 Removal of cyano group

As already showed, for the formation of six-membered rings the presence of two electron-withdrawing substituents at the β position of the vinyl moiety is required. From a synthetic point of view, this could represent a disadvantage for further transformations. Overcoming such limitations, several methods for

further functionalization or removal of the electron-withdrawing groups have been described. Reinhoudt *et al*. aimed to develop a method for the removal of the cyano group that would not result consequently in double bond formation[19]. Treatment of **20** with sodium in liquid ammonia resulted in the formation of a 5:1 (*cis*:*trans*) mixture of the decyanated **23** isomers. Decyanation of **21** led to a mixture of products: **24** (22%, 1:3 *cis*:*trans*), besides formation of **15** isomers (*cis* (18%), *trans* (58%)). With decyanation of **22**, **24** isomers (66%, 1:3 *cis*:*trans*) were obtained, i.e. besides the cyano group also the methoxy group was reduced (**Figure 13**).



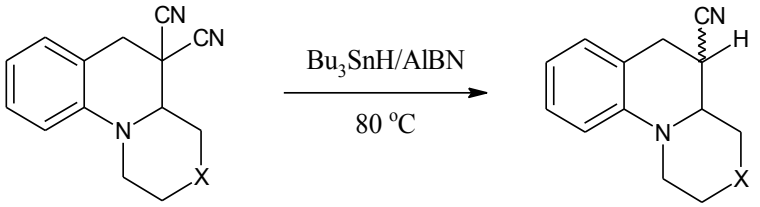
20
21
22

23(83%)
24(22%) + **25** (76%)
25(66%)

21 R=CH_2Ph, **12** R=CH_2OH, **23** R=CH_2OCH_3
24 R_1=CH_2Ph, **25** R_1=CH_3, **26** R_1=CH_2OH

Fig. 13: Decyanation reactions

Other eliminations of one cyano group of the geminal dinitrile moiety were described by Gerlach[20,21]. Reductive eliminations (**2a-c**,**26a-d**→**27a-c**,**28a-d**) were carried out in benzene or toluene, with 2,2' azobisisobutyronitrile (AIBN) and tributyltinhydride (Bu_3SnH). Mostly high yields were obtained, however the diastereomeric ratio was strongly dependent on the substrate choice (**Table 6**):



2a-c, 26a-d **27a-c, 28a-d**

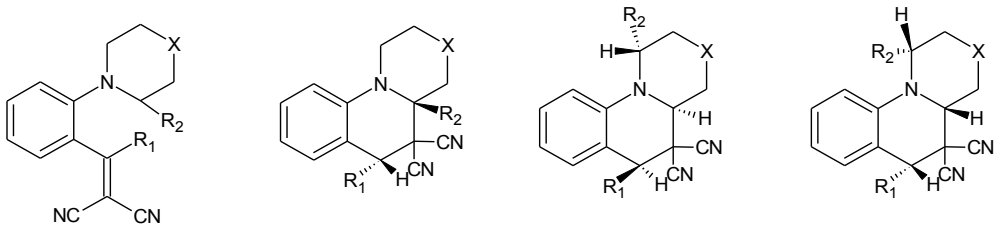
Compound	X	Yield (%)/(Product)	Diastereomeric ratio*
2a	-	75 (**28**) (17a)	88:12
2b	CH_2	78 (**29a**) (17b)	25:75
2c	O	99 (**29c**) (17c)	44:56
26a	NCH_3	97 (**29b**) (18a)	44:56
26b	S	-	-
26c	S=O	-	-
26d	SO_2	99 (**29f**) (18d)	90:10

**diastereomers given in the order of elution*

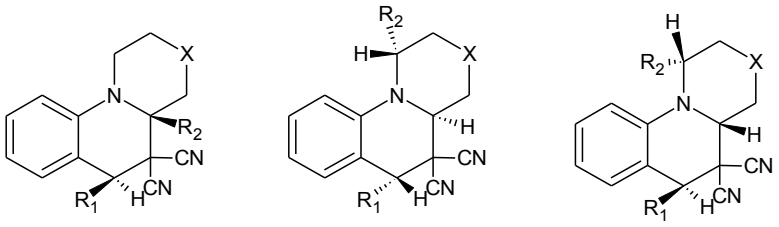
Table 6: Products of reductive decyanation of geminal dinitriles.

1.1.4 Regio- and enantioselectivity of tert-amino effect cyclization

Regio- and enantio-selectivity of *tert*-amino effect cyclizations represent an important aspect for the synthetic utility, and for this reason it was addressed by the Reinhoudt group in the 1980's[22,23]. Cyclizations of a series of vinyl derivatives with different substituents at the α carbon of the vinyl moiety and the carbon adjacent to the amine nitrogen were studied (results are summarized in **Figure 14** and **Table 7**). Cyclization was found to occur regioselectively (e.g. **29a**,**c**,**d**→**30a**,**c**,**d**), yielding products in which the substituent at the bridgehead carbon is in *cis* position related to the benzyl hydrogen.



1a,1b,29a-o **2a-*R*, 2b-*R*, 30a-o** **31** **32**



33 **34** **35**

Fig. 14: Regio-selectivity of type 2 cyclizations.

R_1	Compound	X	R_2	Reaction time (h)	Products
H	**1a**	-	H	2	**2a-*R*** (82%)
	29a	-	CH_3	2	**30a** (85%)
	29b	-	CH_2OCH_3	1.5	**30b** (46%), **31b** (19%), **32b** (17%)
	1b	CH_2	H	2	**2b-*R*** (78%)
	29c	CH_2	CH_3	1.5	**30c** (79%)
	29d	CH_2	CH_2CH_3	1.5	**30d** (80%)
	29e	CH_2	CH_2OCH_3	2.5	**30e** (71%), **31e**+**32e**(25%)
CH_3	**29f**	-	H	5	**30f** (79%)
	29g	-	CH_3	5	**30g** (79%)
	29h	-	CH_2OCH_3	5	**30h** (33%), **31h** (35%), **32h** (6%)
	29i	CH_2	H	2	**30i** (88%)
	29j	CH_2	CH_3	2	**30j** (88%)
	29k	CH_2	CH_2CH_3	2.5	**30k** (86%)
	29l	CH_2	CH_2OCH_3	3	**30l** (56%), **31l**+**32l** (35%, 7:2 ratio)
4-$C_6H_4CH_3$	**29m**	-	H	3 days	**30m**+**33m** (86%, 82:18 ratio)
	29n	-	CH_3	3days	**30n**+**33n** (76%, 98:2 ratio), **31n**+**32n** (22%)
	29o	-	CH_2OCH_3	3days	**30o**+**33o**(16%, 95:5 ratio), **31o**+**34o**(41%, 96:4 ratio), **32o**+**35o** (15%, 97:3 ratio)

Table7: Regioselectivity of type 2 cyclizations.

The observed regioselectivity of the reaction and the preferential formation of **30** isomers, was explained by a more efficient stabilization of a tetrasubstituted iminium double bond in the dipolar intermediate, therefore, C-C bond formation takes place selectively at the carbon substituted with R_2 (**Figure 15**):

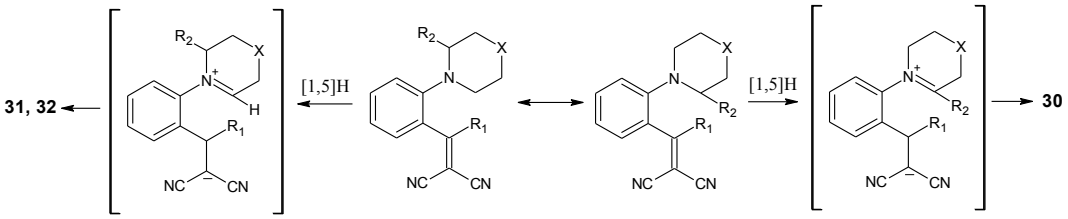


Fig. 15: Formation of regioisomers in type 2 cyclization 1.

If R_2=CH_2OCH_3, regioselectivity loss is observed; this result is due to steric hindrance and the electron withdrawing effect of the oxygen, destabilizing the iminium bond. R_1 substituent of the vinyl group directs relative configuration at the bridgehead carbon and the benzyl position, due to its effect on the conformation of the vinyl moiety in the starting compound, as illustrated by the

formation of **33**-**35** isomers in cyclization of **29o**, having a bulkier 4-methylphenyl R_1 group (**Figure 16**):

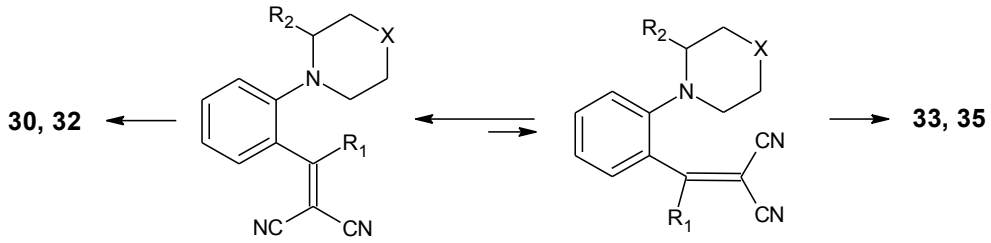
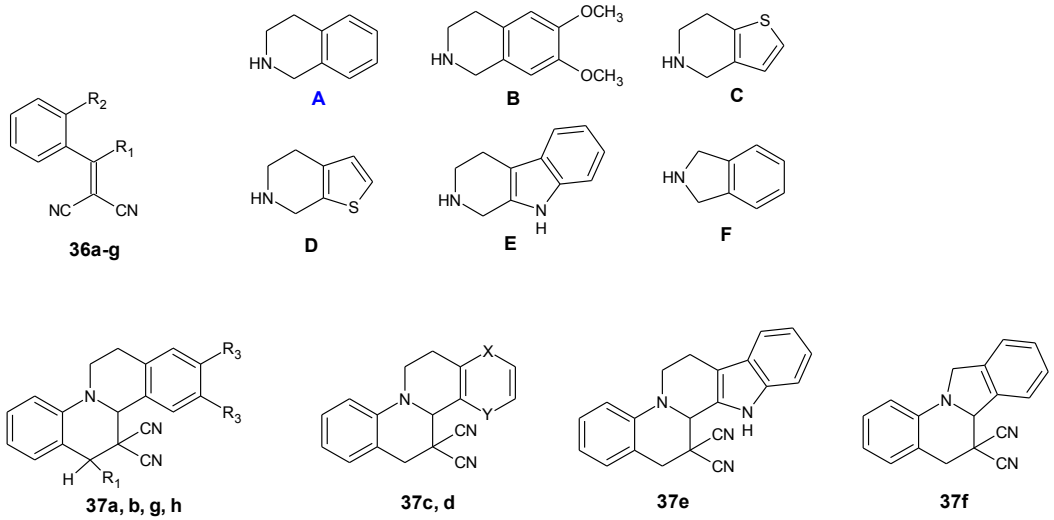


Fig. 16: Formation of regioisomers in type 2 cyclization 2.

The cyclizations of **36a**-**g,** leading to **37a**-**g**, had similar regiochemical effects [24], as previously discussed, due to a better stabilization of the positive charge in the dipolar intermediate (**Figure 17**). With **36a**,**b**,**f**,**g** starting compounds the ring closure occurred selectively at the benzyl carbon. Similarly, with heterocyclic analogues **36c**-**e**, ring closure proceeded at the NCH_2 adjacent to the thiophene or indole moiety.



36a R_1=H, R_2H=A; **36b** R_1=H, R_2H=B; **26c** R_1=H, R_2H=C; **36d** R_1=H, R_2H=D; **36e** R_1=H, R_2H=E; **36f** R_1=H, R_2H=F; **36g** R_1=CH_3, R_2H=A
37a R_1=H, R_3=H; **37b** R_1=H, R_3=OCH_3; **37c** X=S, Y=-; **37d** X=-, Y=S; **37g** R_1=CH_3, R_3=H

Fig. 17: Synthesis of tetra- and pentacyclic compounds *via tert*-amino effect.

Cyclization of optically pure 2-vinyl-*N,N*-dialkylanilines confirmed that with appropriate amino group and R_1,R_2 substituents, the reaction can run enantioselectively with self-reproduction of chirality, without need for an

auxiliary reagent[25]. Cyclization of chiral **29h-*S*** resulted in the formation of three products: i.e., **30h** (33%) obtained as one enantiomer and the two diastereomers **31h** (35%) and **32h** (6%) (**Figure 18**), showed retention of configuration of the original chiral centre. In the products of cyclization, the hydrogen atom undergoing 1,5-hydrogen shift is at the same face of the molecule as the substituent at the bridgehead carbon atom. Stereochemical consequences were rationalized by assuming, that in the dipolar intermediate, the carbanion adds to the iminium double bond from the same face from which the hydrogen migration has happened; the hydrogen shift proceeds suprafacially. Although the original chiral centre is lost temporarily, the chiral information is kept in a unique helical dipolar intermediate [25,26].

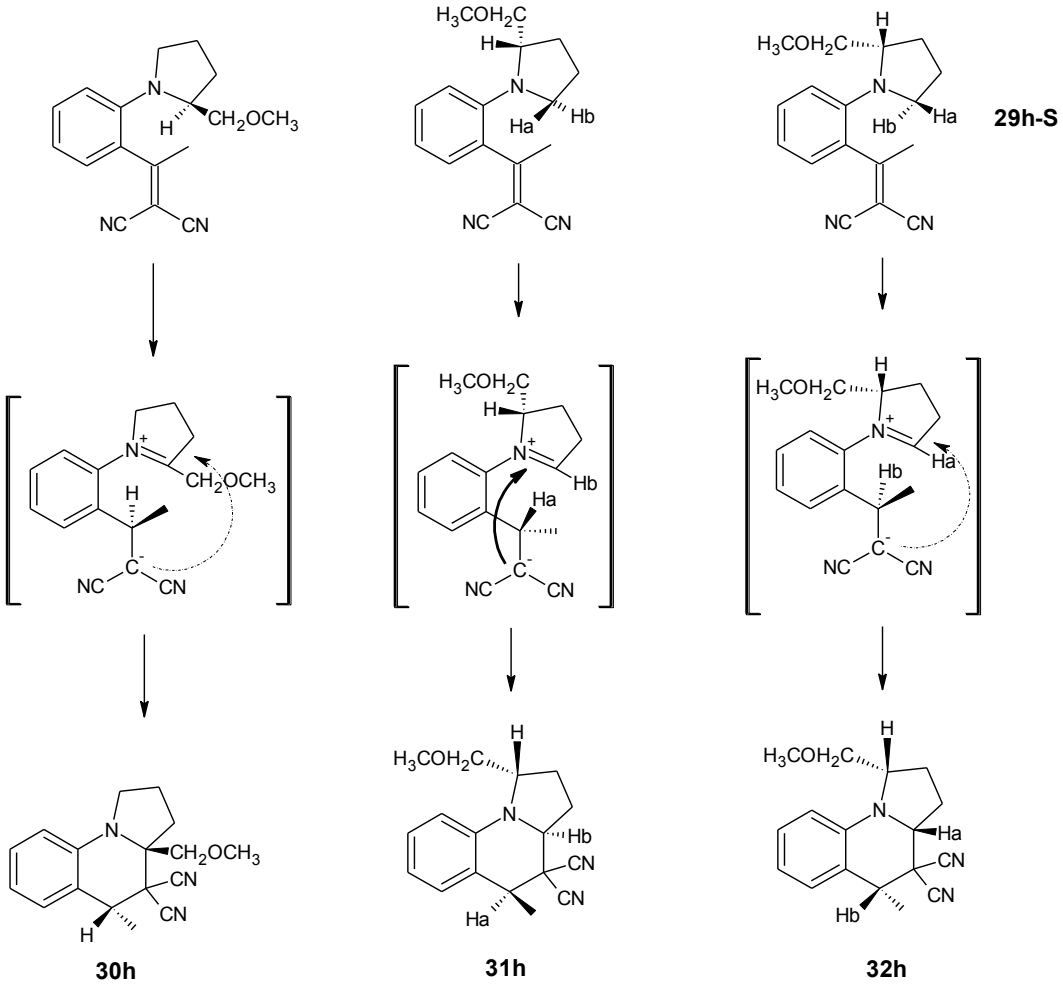
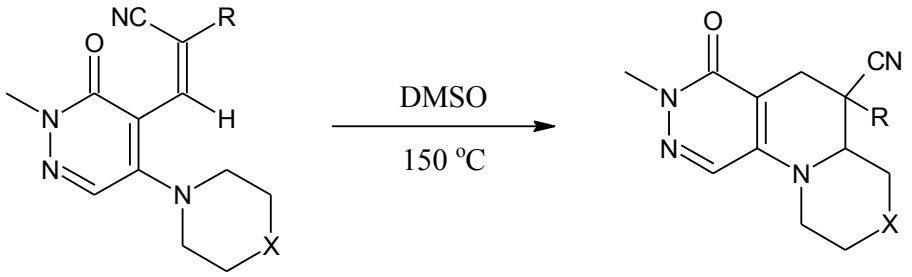


Fig. 18: Stereochemical outcome of type 2 cyclizations.

1.2 Tert-amino effect applications

The first application of *tert*-amino effect cyclization was described in 1994 by Mátyus *et al*.[27] for the synthesis of pyridazine-annelated ring systems. It has been showed that heating in DMSO of vinyl compounds **38**,**39** led to the formation of derivatives **40**, **41** (**Figure 19**):



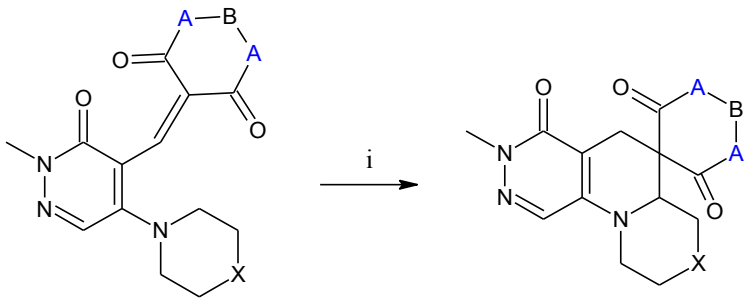
38 X= - , R= CN
39 X=O, R= CN

40 (35%)
41 (44%)

Fig. 19: Synthesis of [4,5]-annelated pyridazines via *tert*-amino effect.

In contrast, the ester analogue in which R= $CO_2C_2H_5$ was unreactive under similar conditions, and prolonged heating of the reaction mixture led to the formation of a complex mixture, from which none of the cyclized products was isolated. This result suggested that the reaction is significantly dependent on the induced effect of the substituents.

Extension of *tert*-amino effect were applied on preparation of complex ring systems including spyrocyclic derivatives[8] (compounds **43a-c**, **Figure 20**):



42a-c

43a (45%)
43b (50%)
43c (79%)

i: xylene, $AlCl_3$, 150°C, 8h, for **43a,b** or N,N-dimethylformamide (DMF), 110°C, 5h for **43c**
a: X=O, A=NCH_3, B=CO; **b:** X=-, A=NCH_3, B=CO; **c:** X=O, A=O, B=$C(CH_3)_2$

Fig. 20: Synthesis of spyrocyclic pyridazinone derivatives.

Upon heating compounds **42a-42c** underwent rearrangement to afford compounds **43a-43c**. Moreover, these experiments showed that kinetic parameters, such as temperatures and reaction times, can be modified; indeed, compound **43a** could be formed at lower temperature than that required for formation of a non-spirocyclic anologue. It was also observed that cyclization reaction of compound **42a**, was completed at 80°C in 270 min, while the corresponding malononitrile derivative[27] cyclized only at 150°C. Therefore, incorporation of the substituents of the vinyl moiety into a ring, resulted in cyclizations proceeding at lower temperatures or within shorter reaction times.

In 2005 D'yachenko *et al*.[28], have shown that the "*tert*-amino effect" could be applied to the formation of spiro-fused heterocycles. The formation of spyro compounds proceeds in most cases in good yields in a one-pot reaction. Spiro-fused quinolinepyrimidines **47** can be synthesized according to two procedures. One of them involves Knoevenagel condensation of 2-dialkylaminobenzaldehydes **44** with malonic ester, cyclization of the resulting benzylidenemalonic esters **45** to fused quinolines **46** and condensation of the latter with disubstituted urea to give the target products. Another procedure involves the reaction of 2-dialkylaminobenzaldehydes **44** with barbituric acids, where Knoevenagel condensation is accompanied by intramolecular cyclization of intermediate vinyl derivatives. Taking into account the results obtained in earlier studies, it can be assumed that this reaction proceeds in one step to give spyro-fused quinolines **47** (**Figure 21**).

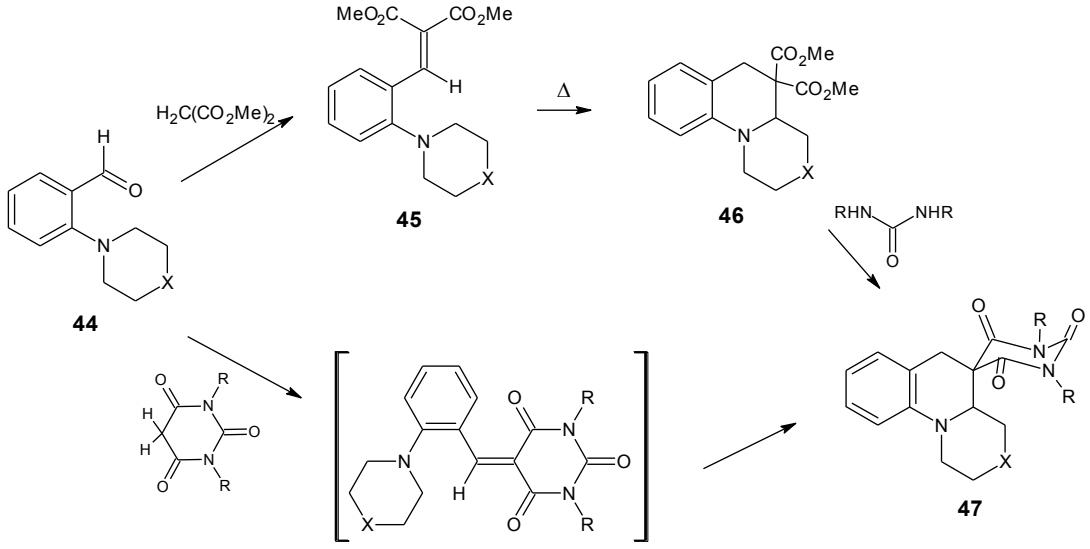
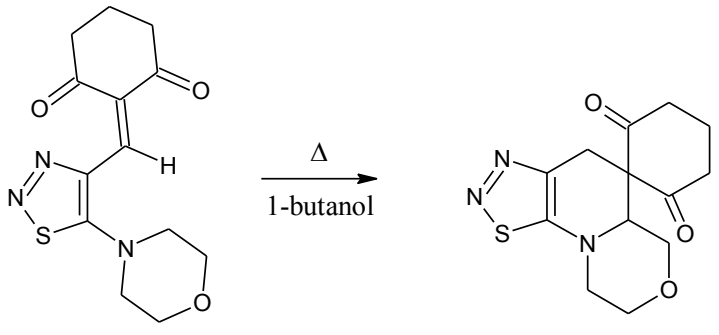


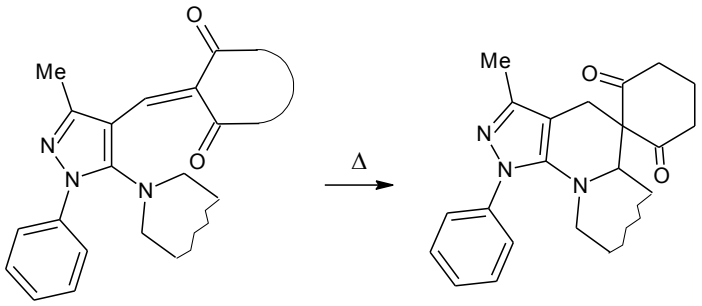
Fig.21.

The second method is preparatively more convenient because it involves one step. They demonstrated that the reactions of 2-dialkylaminobenzaldehydes **44** with dimethyl- and diphenylbarbituric acids afforded spyro compounds **47**. It should be noted that cyclization gave spyro-fused quinolines **47** in good yields on refluxing in toluene for 3 h. An increase in the reaction time led to a decrease in the yield and dezincification of the products. In this approach, the total yield of the target products **47** varied from 36 to 70 %

The *tert*-amino effect was used for the synthesis of a series of new spiro fused heterocycles as a class of compounds which offer biological interest. In contrast in the cyclization reactions of five membered ortho substituted heterocycles 4 vinyl-1,2,3-thiadiazoles **48** or 4-vinyl-1- phenylpyrazole **49** were isolated (**Figure 22**):



48



49

Fig.22

During studies of chromium *ortho*-aminophenylalkynyl complexes, Barluenga *et al*.[29], the formation of a carbene complex **41** was observed (**Figure 23**):

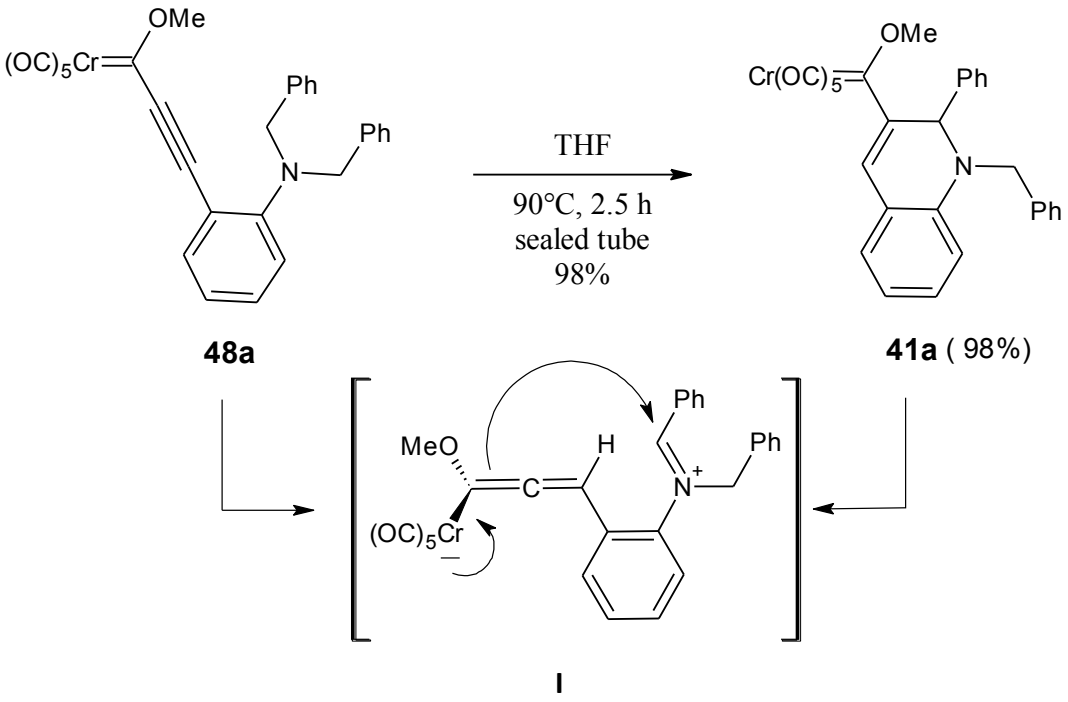
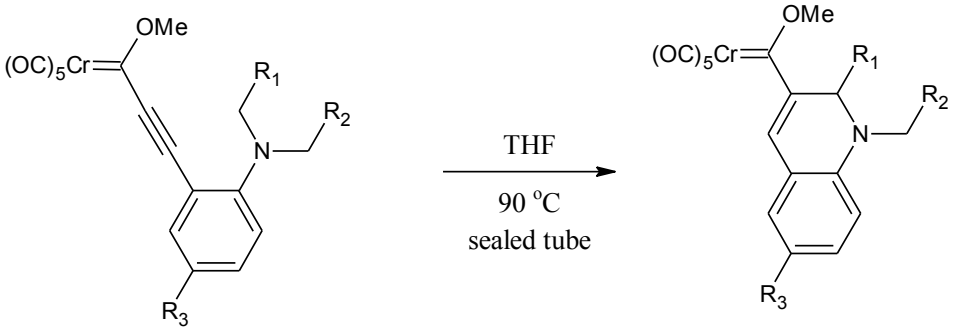


Fig. 23: Synthesis of 1,2-dihydroquinolinyl carbene complex **41**.

When a solution of 1a in THF was heated at 90°C in a sealed tube, new carbene complex **55a** was isolated in 98% yield after the workup. The formation of **51a** can be explained by an intramolecular two-step process which involves the migration of one hydride, from the benzylic carbon center to the highly

electrophilic β carbon of the triple bond of alkynyl carbene complex **50a**, to generate zwitterionic intermediate **I**. The subsequent cyclization step would then lead to new carbene complex **51a**. The presence of the strong electron withdrawing effect due to the chromium pentacarbonyl moiety is essential to provide a proper scenario for the [1,5]-hydride transfer/cyclization in which the internal *sp* carbon atom participates. This chemical behavior does not have any precedent in the chemistry of Fischer carbene complexes. Moreover, this reaction represents the first example of a hydride migration/cyclization cascade involving a triple bond.

Furthermore, they tried to determine the scope of this reaction by using different *ortho*-aminophenylalkynyl carbene complexes (compound **50**, **Figure 24**), in which the nitrogen atom and the phenyl ring substituents were modified.



50 **51**

Fig.24: Synthesis of 1,2-dihydroquinolinyl carbene complexes by a [1,5]-hydride transfer process.

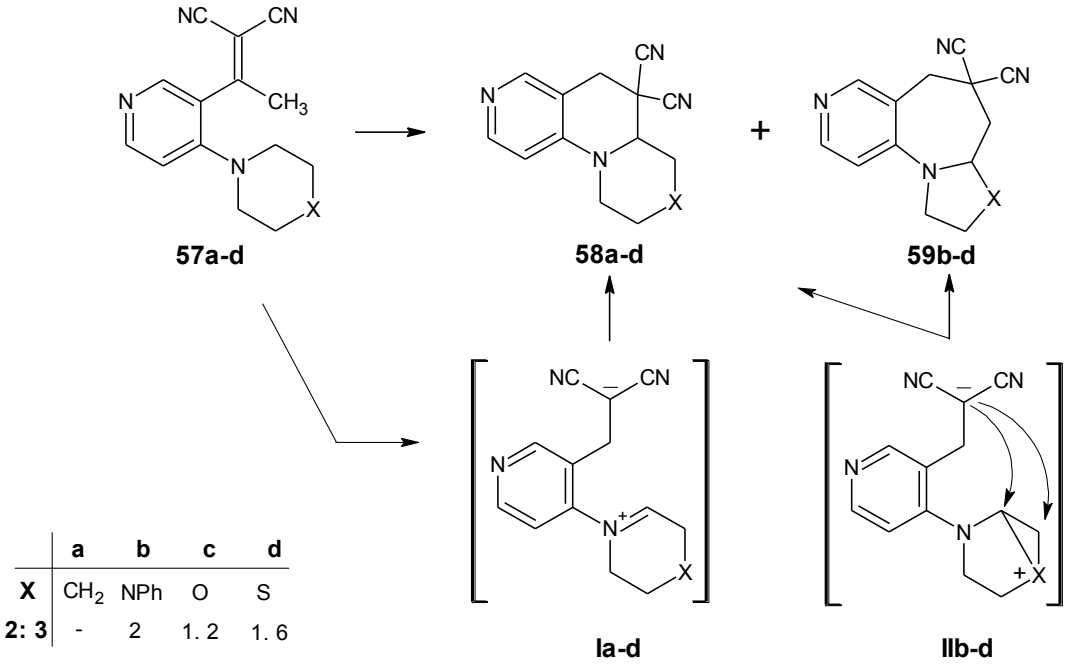
The results are summarized in **table 8** with respect to the influence of the substituents have shown that the substituents on the tertiary amine have a significant influence on the time and on the yield of the reaction.

Entry	44	R_1	R_2	R_3	45	t[h]	Yield[%]
50	**50a**	Ph	Ph	H	**51a**	2.5	98
51	**50b**	Ph	Ph	Me	**51b**	2	95
52	**50c**	Ph	Ph	Cl	**51c**	6	72
53	**50d**	4-Br-Ph	4-Br-Ph	H	**51d**	10	63
54	**50e**	4-Tol	4-Tol	H	**51e**	2	96
55	**50f**	Ph	H	H	**51f**	9	65
56	**50g**	Ph	*t*Bu	H	**51g**	1.5	85

Table 8: Influence of the substituents on the tertiary amine moiety.

These results can be explained by considering the hydride migration that gives rise to zwitterionic intermediate **I** as the rate-limiting step in the mechanism described above. Hence, according to what previously explained for the *tert*-amino effect, the reaction will be favored in the presence of substituents that can stabilize the positive charge that develops upon hydride migration.

Formation of new heterocycles compound was also achieved by Quintela *et al*. in 1993, using as starting compounds 2-amino-3-vinylpyridines e 4-amino-3-vinylpyridines[30,31]. Regarding the latter compounds, it was studied the thermal isomerization of 3-vinylpyridines bearing different dialkylamino groups at position 4 of the pyridine ring; the results showed that all synthesized 4-amino-3-vinylpyridnes **57a-d** underwent the expected thermal isomerization to the corresponding fused 1,6-naphthyridine systems **58a-d**, but the piperazino, morpholino and thiomorpholino derivatives (**57b**, **57c** and **57d**) also lend themselves to the simultaneous formation of the fused azepines **59b**, **59c** and **59d**, respectively (**Figure 25**).



	a	b	c	d
X	CH_2	NPh	O	S
2: 3	-	2	1. 2	1. 6

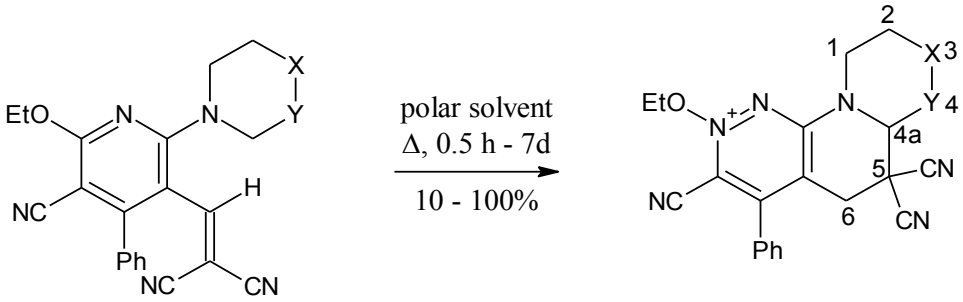
Fig. 25: Synthesis of the six and seven membered ring compounds.

This types of isomerization led to the synthesis of three ring systems. In case of compounds **59b-d**, the formation of a new seven membered ring constitutes a new *tert*-amino effect type of cyclization, due to an interaction between the *ortho*-substituent and the β -methylene group of the tertiary nitrogen.

The thermal isomerization of *ortho*-aminovinylpyridines **57a-d** can be assumed to occur in two or three consecutive steps (**Figure 25**). In all the cases, the first step in the cyclization of compounds **57a-d** involves a thermal [1,5]-hydrogen shift of one methylene proton adjacent to the nitrogen atom of the amino group, in order to yield the 1,5-dipolar intermediates **Ia-d**, with the "negative end" stabilized by the presence of two cyano groups; then intramolecular addition of the negatively charged carbon to the iminium double lead to the formation of the cyclized products **58a-d**. In cases **b**, **c** and **d**, the evolution towards mixtures of two cyclic isomers 2+3 can be explained by a simultaneous activation of the α- and β-methylene groups of the amino moiety of intermediates **I** by a neighboring-group mechanism. Thus, an anchimeric assistance of an unshared pair of electrons of the heteroatom **X** to the positive end of the 1,5-dipolar intermediate **Ib-d** can lead to the involvement of a second dipolar intermediate

IIb-d. In a third step, the opening of the ambident aziridine (**b**), oxirane (**c**) or thiirane ring (**d**) of intermediates **II** by an intramolecular addition of the carbanion to the α-position also gives rise to naphthyridines **58b-d**, whilst addition to the β-position leads to the competitive cyclization towards the fused azepines **59b-d**. The formation of the new carbon-carbon bond between the β-position of the vinyl group and the α- or β-position of the amino moiety, by a 6-*exo*-*tet* or 7-*exo*-*tet* cyclization of intermediates **IIb-d**, are both favored processes.

Quintela *et al*.[32], also reported the first example of the formation of a six-membered ring via thermal isomerization of 2-vinyl substituted dialkylaminopyridines. They provided an extremely simple three-step pathway to fused [1,8]naphthyridines, applying the reaction principle of *tert*-amino effect to a substituted pyridine as the key step. This annulation process provided a convenient approach to the synthesis of various other heterotri-and heterotetra-cyclic compounds containing the [1,8]naphthyridine group which had not previously been described in the literature. Compounds **61a-h** were successfully synthesized as shown in **Figure 26**:



60a-h **61a-h**

	a	**b**	**c**	**d**	**e**	**f**	**g**	**h**
X	-	CH_2	$(CH_2)_2$	$2(CH_2)_2$	NPh	O	S	-
Y	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	S

Fig.26

In 2006 Paramonov *et al.*[33], extended the *tert*-amino effect cyclization to novel spiro[[1,4]thiazino[4,3-a]quinoline-5,5'-pyrimidine]; when 2-thiomorpholino-5-trifluoromethylbenzaldehyde is reacted with barbituric acids under Knoevenagel condensation conditions, a novel heterocyclic system is formed:1,2,4,4a,5,6-hexahydrospiro[[1,4]thiazino[4,3-a]quinoline-5,5'-pyrimidine] -2',4',6'-triones (compound **64a,b**- **Figure 27**), two new C–C bonds are formed during the reaction

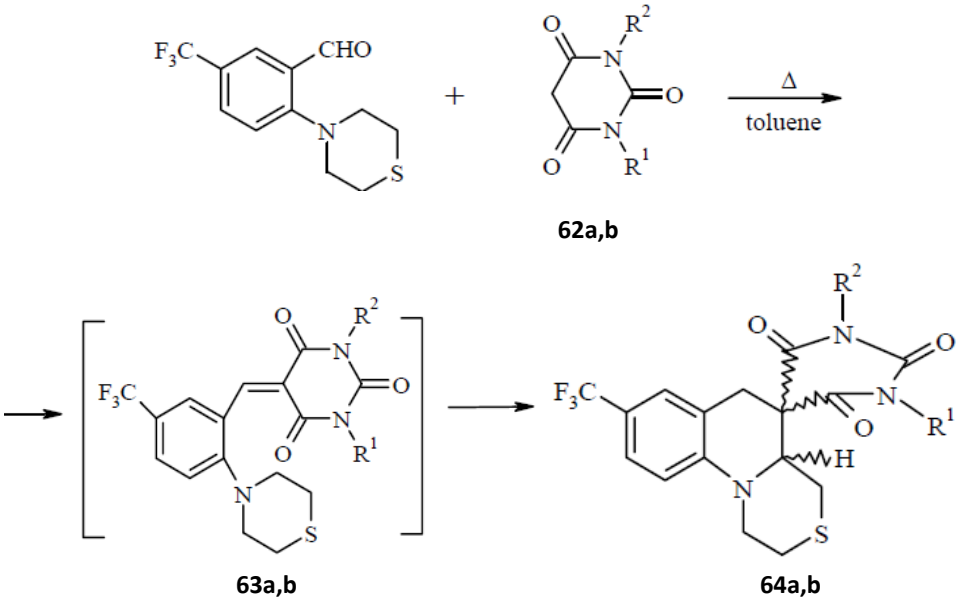


Fig. 27: 62–64 a) $R^1 = R^2 = Me$, **b**) $R^1 = H$, $R^2 = C_6H_4CF_3$-4

The reaction occurs through the *o*-vinyl derivatives **63** followed by their cyclization according to a *tert*-amino effect mechanism. When monosubstituted barbituric acids were used, two isomers could be formed. They have shown that with monosubstituted barbituric acid **62b**, a 1:1 mixture of spyro-linked condensed [1,2-a]quinolines **64b** is formed in 78% yield.

Other applications of *tert*-amino effect were studied by the group of Bhuyan using different molecule's structures[34-36]. In 1998, his research group was involved in the synthesis of novel uracil anologues *via* 1,5- and 1,6-intramolecular cycloaddition reaction[34]. this method of synthesis proved to be useful to demonstrate that 6-(tertiary amino)uracils are interesting precursors for the facile preparation of complex uracil analogues.

In 2006, Bhuyan *et al*.[35], reported the preparation of some novel classes of quinolizine-, indolizine-, and pyrido-1,4-oxazine-fused quinoline derivatives via a three-component reaction under solvent-free conditions by exploring the tertiary amino effect reaction strategy.

More recently, in their continued interest in uracils and the synthesis of diverse heterocyclic compounds of biological importance, Bhuyan reported the synthesis of some novel classes of spirosubstituted pyrido[2,3-d]pyrimidines using the *tert*-amino effect reaction strategy[36]. In these studies, 5-Formyl-6-tertiary-amino uracils (prepared from 6-chloro-5-formyl uracil derivative) reacted with barbituric acids in the presence of base catalyst to afford a novel class of spirosubstituted pyrido[2,3-d]pyrimidines *via* 1,6-electro-cyclisation in excellent yields. It was observed that the reactivity of 6-pyrrolidino uracils are comparatively high, and the yields of the products are also very good. On the other hand, 6-morpholino uracils are the least reactive, and the yields of the products are not good. Moreover, the reactivity of *N*,*N*-dimethylbarbituric acid is much better than that of *N*-methylbarbituric acid.

1.2.1 Novel extensions of tert-amino effect to medium-sized rings

New applications of *tert*-amino effect have been used for the synthesis of medium sized rings. Meth-Cohn et al., investigated the synthesis of some dibenzazocine; indeed, treatment of *p*-substituted *tert*-aniline **65** with *N*-formyl-*N*-substituted arylamides (**66**) in phosphorus oxychloride ($POCl_3$), led to the formation of dibenzo[1,5]diazocines (**67**)[37]. The reaction pathway consisted in i) a Vilsmeier formylation in *ortho* position to the dimethylamino group, ii) the following by 1,5 hydrogen shift and iii) the subsequent C-C bond formation between the iminium ion and the aromatic ring, affording dibenzo[1,5]diazocine derivatives (**Figure 28**).

This method was later extended to the synthesis of linear fused analogues[38]. Reaction of 4-substituted *N,N'*-dimethylanilines (**65**,**70**) with Vilsmeier reagent

(**69**) (formed from *N,N'*-dimethyl-*N,N'*-diformyl-*p*-phenylenediamine **68** upon treatment with oxalyl chloride) led to pentacyclic derivatives **71** (**Figure 29**).

Application of *tert*-amino effect using Vilsmeier reagents also led to benzo[*b*]naphtho[1,2- *f*]- and benzo[*b*]naphtho[2,1-*f*][1,5]diazocines[39]. In following studies, treatment of *N,N,N',N'*-tetramethylbiphenyldiamine with Vilsmeier reagent formed from *N*-methylformylanilides with $POCl_3$, afforded bis-dibenzodiazocines[40].

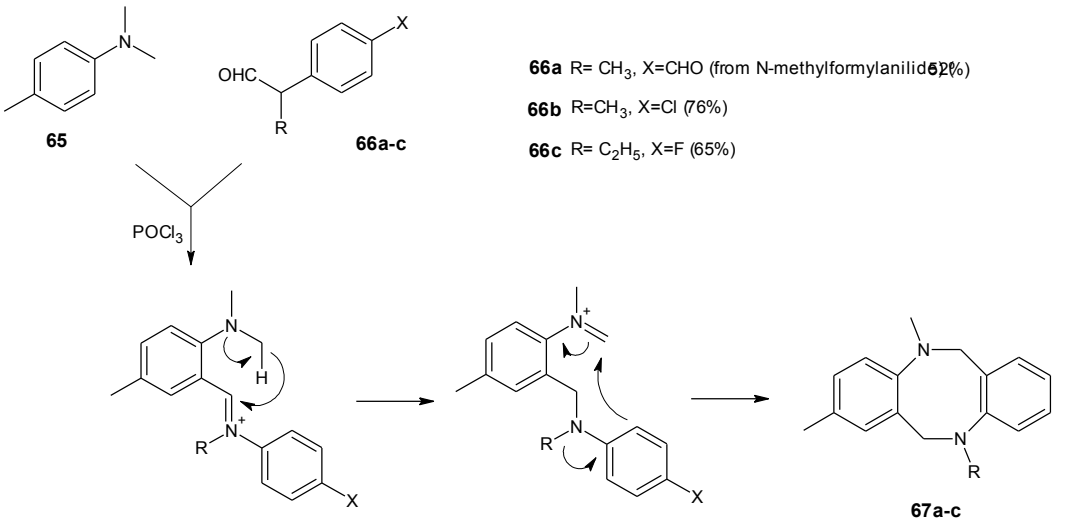


Fig.28: Synthesis of dibenzo[1,5]diazocines *via tert*-amino effect.

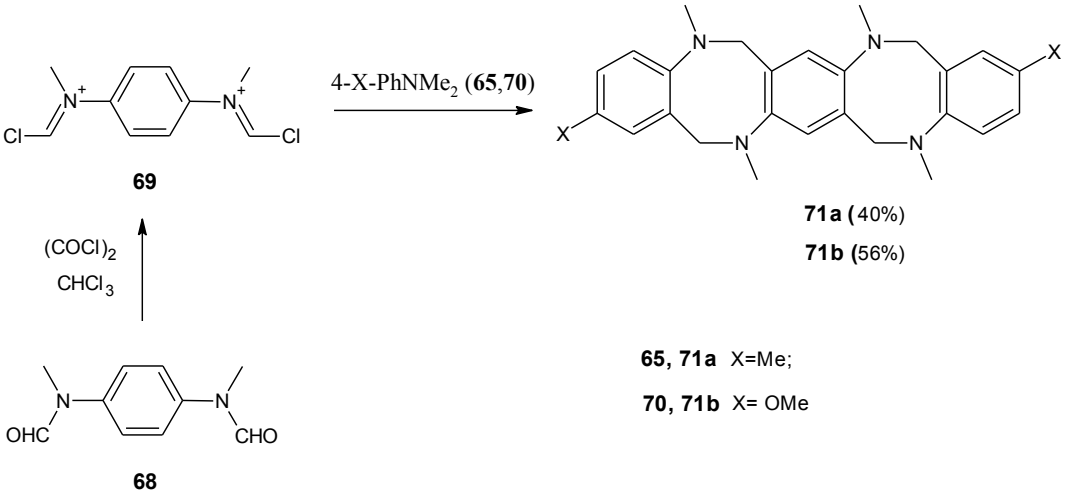
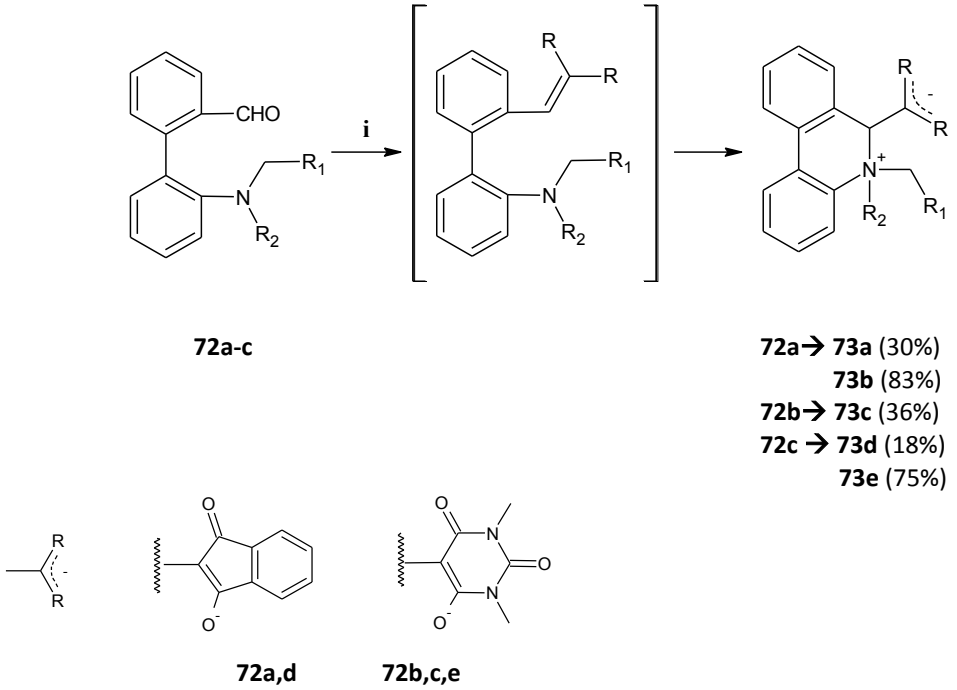


Fig. 29: Synthesis of linear pentacyclic bis(benzodiazocino)benzenes *via tert*-amino effect.

1.2.2 Novel extensions of the tert-amino effect to biaryl and fused systems

The *tert*-amino effect has been successfully applied to the synthesis of several heterocyclic scaffolds. Recently, novel extensions of type 2 *tert*-amino effect cyclizations were elaborated in the Department of Organic Chemistry (Semmelweis University), positioning the interacting groups – vinyl and tertiary amine mojeties - in *ortho*-*ortho*' on two different aromatic rings[41,42].

Polonka-Bálint *et al*., considered that appropriately *ortho*-*ortho*'-functionalized biphenyl or phenylpyridazine derivatives could be synthesized *via* the knoevenagel condensation of biaryl carbaldehydes. In the condensations expected to lead to the vinyl starting compounds, an interesting cyclization was observed in several cases. Treatment of **72a-c** aldehydes with cyclic active methylene agents 1*H*-indene-1,3(2*H*)-dione or *N*,*N*-dimethylbarbituric acid led to the formation of zwitterionic phenantridinium derivatives (**73a-e**) (**Figure 30**). Such behaviour was not observed among the pyridazinone analogues.



72a-c

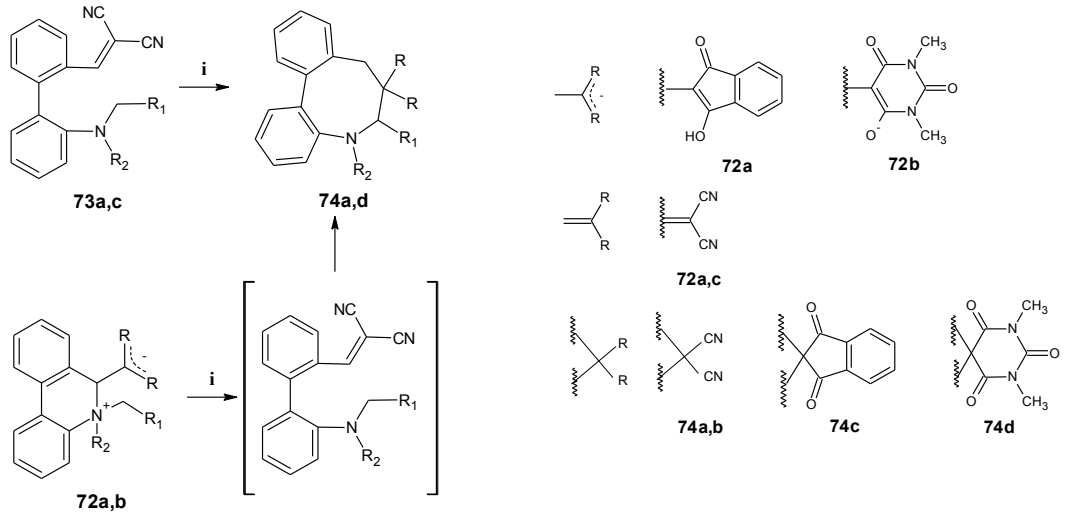
72a→ 73a (30%)
73b (83%)
72b→ 73c (36%)
72c → 73d (18%)
73e (75%)

72a,d **72b,c,e**

72a,**73a**,**b** R_1+R_2=-$(CH_2)_3$-; **72b**,**73c** R_1+R_2=-$(CH_2)_4$-; **72c**,**73d**,**e** R_1=H, R_2=CH_3
i: 1*H*-indene-1,3(2*H*)-dione (**73a**,**d**) or *N,N*-dimethylbarbituric acid (**73b**,**c**,**e**), EtOH, rt, 24h

Fig.30: Isomerization *via* carbon-nitrogen bond formation to phenantridines.

For such vinyl compound (e.g. **73a**, **Figure 31**) X-ray analysis revealed, that the pyrrolidino and vinyl groups are located on the same side of the biaryl system, moreover, a shortened distance was found between the nitrogen and the α-vinyl carbon (2.878 Å), indicating a nonbonding interaction. A similar effect was observed for **72b** and **72c** aldehydes, with a 2.835 Å and 2.989 Å distance between the nitrogen and the carbonyl carbon[43, 43a]. Verifying the existence of an interaction, isomerization of **72b** and **72c** aldehydes under mild conditions (rt, $CHCl_3$, cat. CF_3COOH) led to zwitterionic phenantridinium derivatives. Upon heating in DMSO, **73a,c** biphenylvinyl and **73a,b** phenantridinium compounds underwent isomerization to the corresponding dibenzazocines (**74a-d**, **Figure 31**).



i: DMSO, 110/160°C
73a,**72a**,**b**,**74a**,**c**,**d** R_1+R_2=-$(CH_2)_3$-; **73c**,**74b** R_1=H, R_2=CH_3

Fig.31: Synthesis of benzazocines *via tert*-amino effect.

With pyridazine analogues **75a-f**, cyclization attempts led to unforeseen results, to pyridazinoisoquinoline **77** or benzophtalazinone derivatives **78**, besides formation of the desired azocine derivatives **76a,b** in some cases (**Figure 32**).

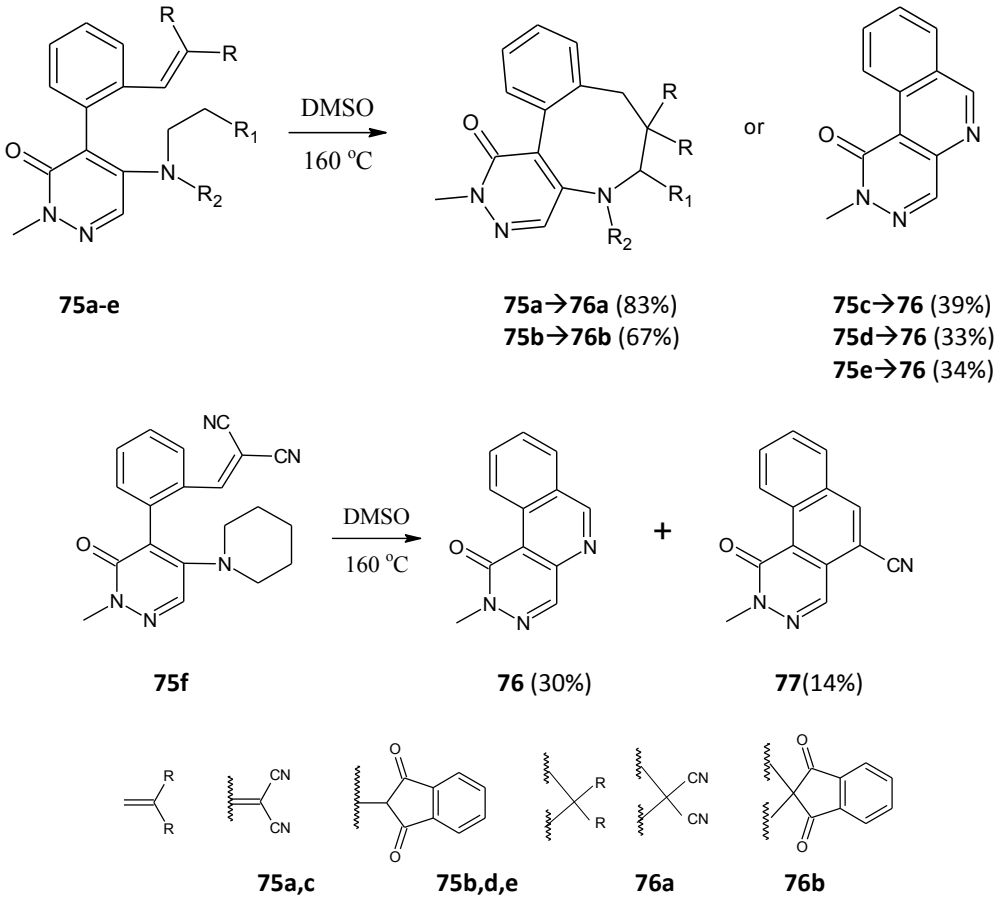
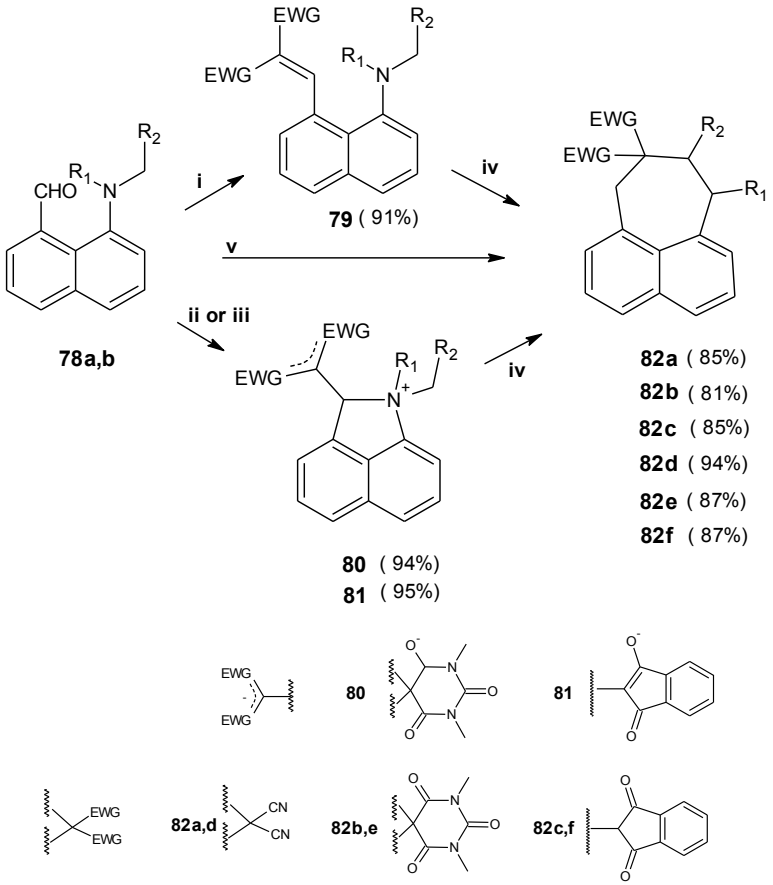


Fig. 32: Cyclizations of pyridazine biaryl derivatives.

As part of ongoing studies on novel possible extensions of the *tert*-amino effect, applications for the synthesis of naphthazepine and naphthazonine ring systems were described[44,45]. Starting vinyl compounds were prepared by Knoevenagel condensation. However, treating **78a** dimethylamino derivative with cyclic active methylene compounds (*N*,*N*-dimethylbarbituric acid or 1*H*-indene-1,3(2*H*)-dione) led to zwitterionic benzo[*d*,*e*]quinolinium derivatives **80,81** (similarly to the effect observed among biphenyl derivatives). Such isomerisation was not observed in the Knoevenagel condensation with the acyclic active methylene agent malononitrile. Heating **79-81** vinyl/zwitterionic compounds in DMSO led to the formation of the expected 1,2-dihydronaphtho[1,8-*b*,*c*]azepines (**Figure 33**). For the **78b** pyrrolidino derivative the cyclized products were obtained directly under the conditions of the Knoevenagel condensation.

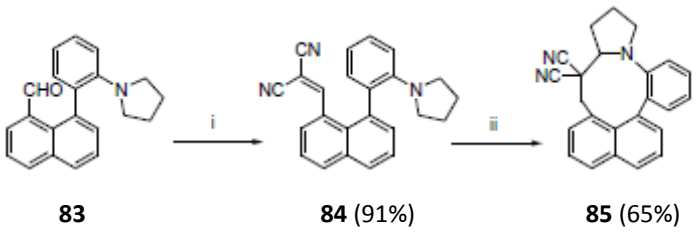
Turning to phenylnaphthyl derivatives, cyclization via *tert*-amino effect could be obtained only at higher temperatures in ionic liquid, leading to the appropriate pyrrolonaphtho[1,8-*e*,*f*]azonine (**84**→**85**) (**Figure 34**).



78a, **79**-**81**,**82a**-**c** R_1=CH_3, R_2=H; **78**, **82d**-**f** R_1+R_2=-$(CH_2)_3$-.

i: malononitrile, EtOH, piperidine, rt; ii) *N,N*-dimethylbarbituric acid, EtOH, piperidine, rt; iii) 1*H*-indene-1,3(2*H*)-dione, EtOH, piperidine, rt; iv) DMSO, heating; v) malononitrile/ *N,N*-dimethylbarbituric acid/1*H*-indene-1,3(2*H*)-dione, EtOH, piperidine, 80°C

Fig. 33: Synthesis of naphthazepine derivatives *via tert*-amino effect.



83 **84** (91%) **85** (65%)

i: malononitrile, EtOH, piperidine, rt; ii: $[bmim]BF_4$, 190°C, 3h
$[bmim]BF_4$: 1-butyl-3-methylimidazolium tetrafluoroborate

Fig. 34: Synthesis of naphthazonine derivatives *via tert*-amino effect.

Further works carried out by Matyus *et al*.[46], studied potential extensions of the *tert*-amino effect to bi- and triaryl systems and leading to the formation of novel oxazonine- and azecine-fused ring systems (**Figure 35**). In this model compounds, the interacting vinyl and *tert*-amino moieties were in *ortho*-*ortho'*/*ortho"* positions on two different aromatic rings, connected *via* a third benzene or pyridazinone ring or an oxygen bridge. The aldehyde intermediates used for the synthesis of vinyl starting compounds were prepared by the reaction of the appropriate *sec*-aminophenol and *o*-fluorobenzaldehyde or *via* two subsequent Suzuki-couplings from dihalo starting compounds with *ortho*-*sec*-aminoand 2-formylphenyl boronic acids. Cyclization of non-conjugated biaryl ethers demonstrated, that *tert*-amino effect could operate also *via* direct hydride transfer, therefore, this type of reaction might be of a broader significance.

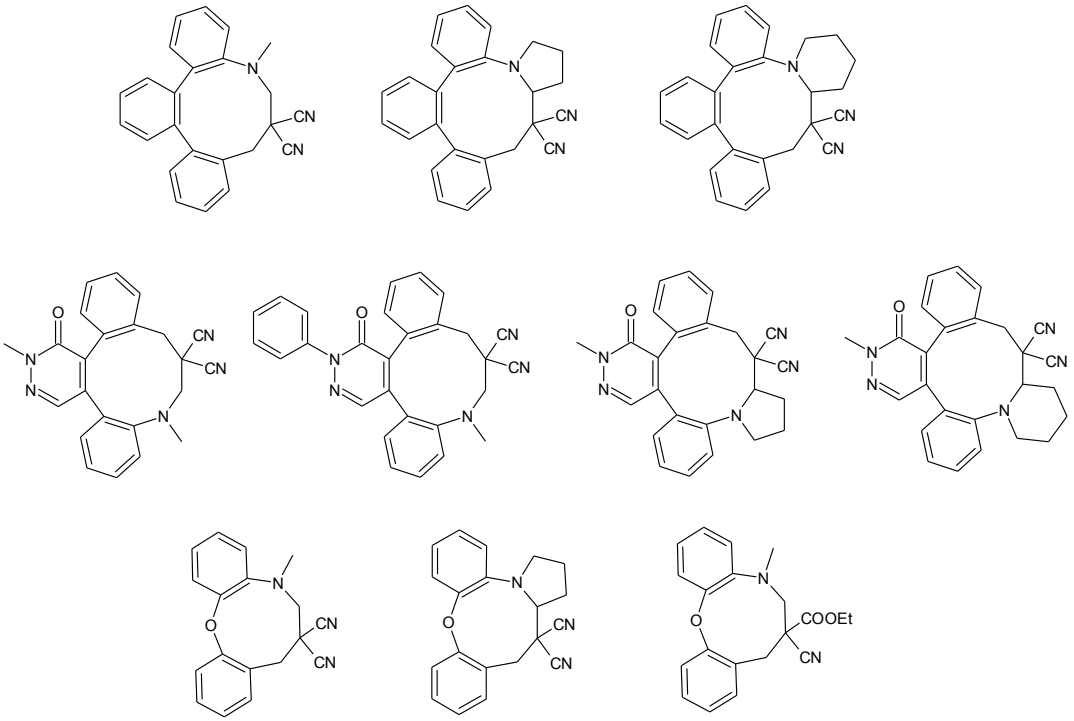


Fig.35: Azecine- and oxazonine-annelated products.

1.2.3 Catalysts in tert-amino effect

Harsh reaction conditions are typically required for the *tert*-amino effect transformations, therefore resulting in limited synthetic use. Aiming to broaden the applicability of the reaction, Murarka *et al*.[47] reported an efficient Lewis acid catalyzed approach that readily proceeds at room temperature and significantly enhances the applicability of this rearrangement. Studying cyclization of alkylidene malonates, Lewis acids were expected to enhance the reaction by chelation to the malonate moiety. Following a screening, as solvent acetonitrile and gadolinium triflate ($Gd(OTf)_3$) as catalyst proved to be the optimal conditions. Cyclization could be carried out with various malonate esters with different cyclic or acyclic amine subunits at room temperature under short times, as exemplified by the transformation of compound **86** to **87** (**Figure 36**):

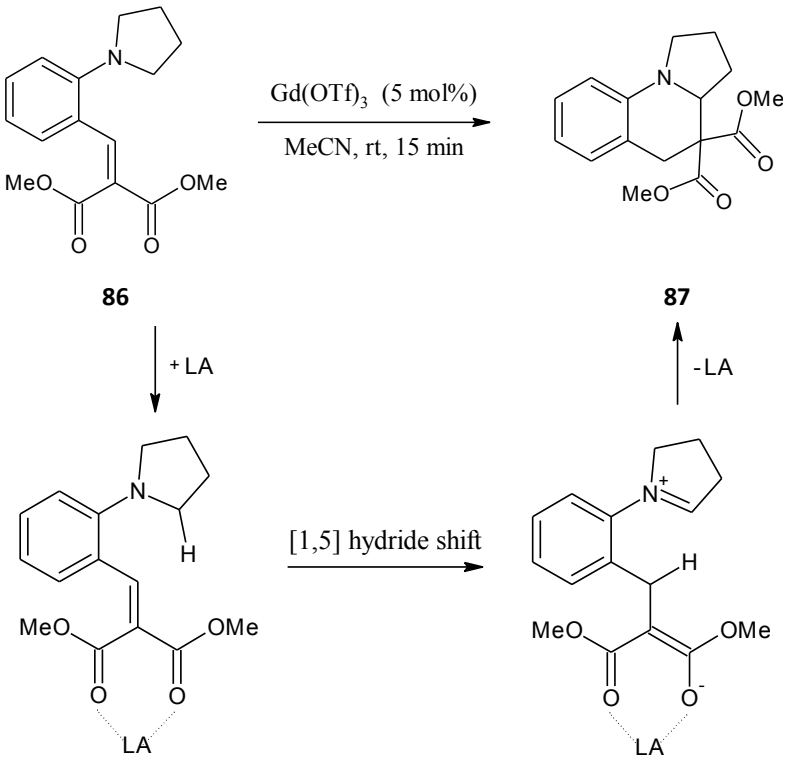


Fig.36: Lewis-acid (LA) catalysis of *tert*-amino effect cyclization.

McQuaid *et al*., reported hydride transfer initiated cyclization of *ortho*-vinylaryl alkyl ethers[44], leading to substituted dihydrobenzopyrans, a reaction

analogous to *tert*-amino effect (**Figure 37**). Aryl ether substrates are significantly less reactive compared to analogous tertiary amines, therefore the use of a Lewis-acid catalyst (scandium triflate - $Sc(OTf)_3$) was indispensable for cyclization. Studying the scope of the reaction, cyclization occurred both with cyclic and acyclic aliphatic ethers, while regarding the vinyl moiety, the best results were obtained with diester substrates. Substitution of the aryl ring strongly influenced the reactivity (**88**-**93**→**94-99**), depending on the ability of the substituents to stabilize the oxocarbenium ion transition state and their effect on the hydridophilicity of the alkene and hydride donor capacity of the ether moieties.

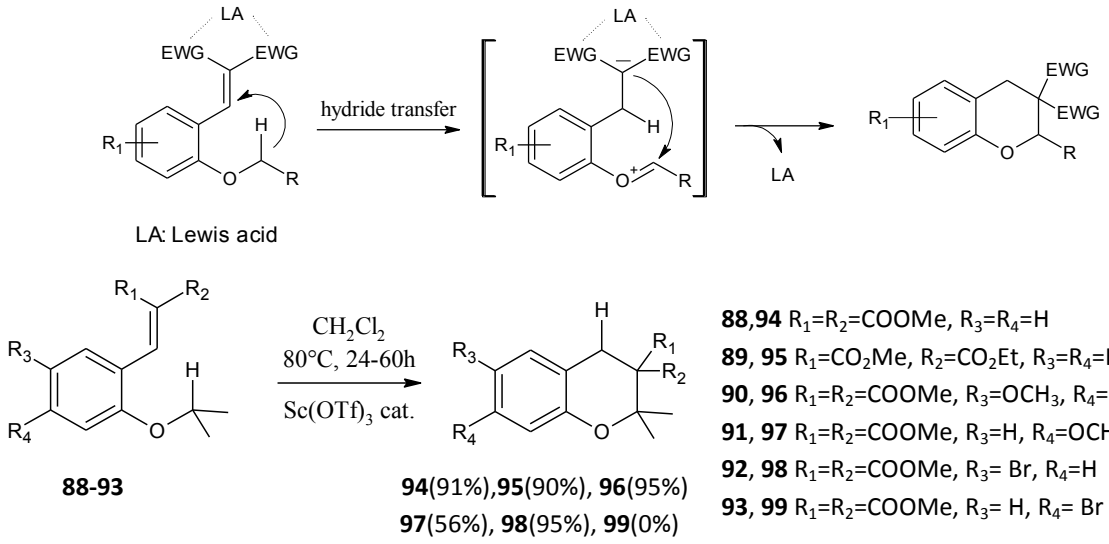


Fig. 37: Examples for hydride transfer initiated cyclizations of ortho-vinylaryl alkyl ethers.

Recently, Che *et al*.[49], developed a new method for the preparation of 7,8,9-trisubstituted dihydropurine derivatives *via* a cascade reaction, in which the key transformation was a [1,6]-hydrogen shift due to the *tert*-amino effect. Treating **100a-c** substituted pyrimidines with an aromatic aldehyde in the presence of trifluoroacetic acid (TFA) led to the formation of the corresponding dihydropurine derivatives **102a-c**. The cyclization was suggested to proceed *via* an iminium intermediate (**101a-c**) undergoing a [1,6]-hydrogen shift, as shown in **Figure 38**.

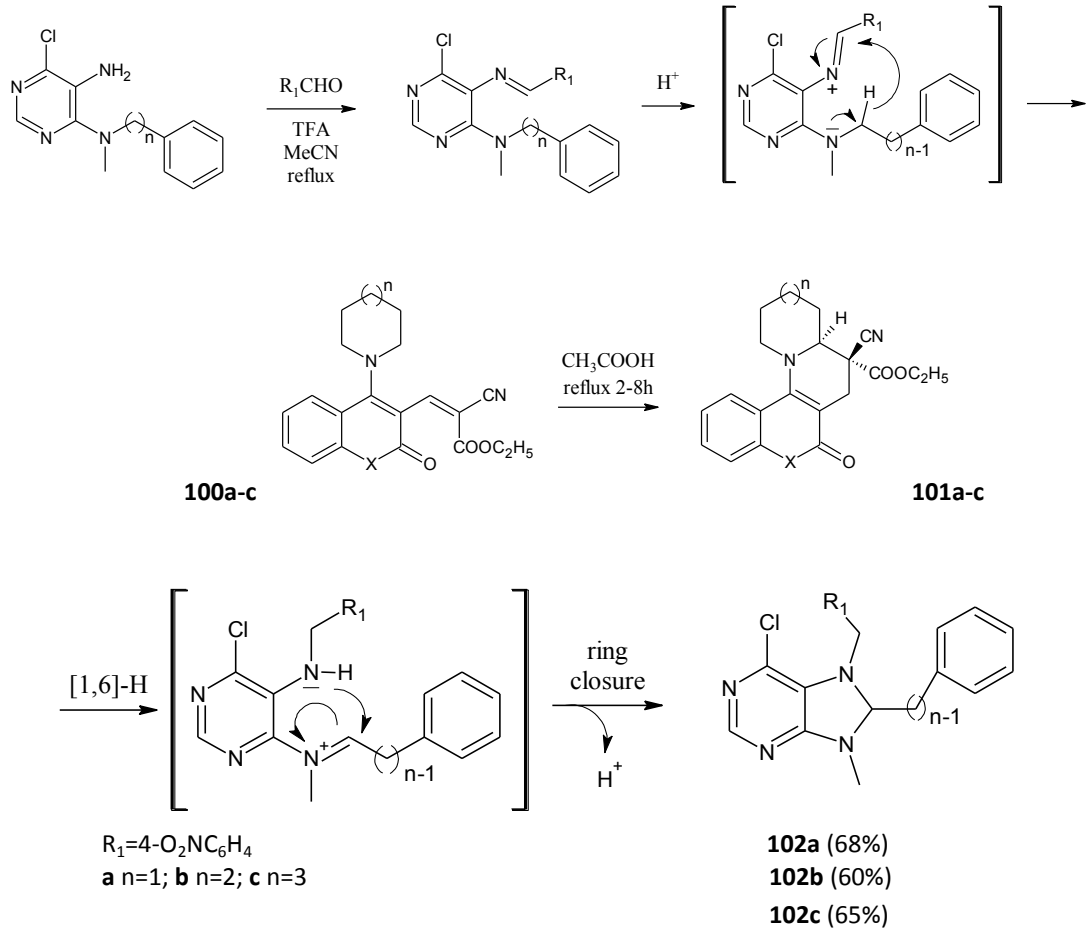


Fig.38: Synthesis of 7,8,9-trisubstituted dihydropurine derivatives *via tert*-amino effect.

Ivanov *et al*. [50], applied *tert*-amino effect cyclizations to obtain 1,2-fused 5*H*-chromeno[4,3-b]pyridin-5-one and 6*H*-benzo[*h*][1,6]naphthyridin-5-one ring systems from 3-vinyl-4-dialkylaminocoumarins/2-quinolones **103a-c**. Cyclized products **104a-c**, were obtained upon heating in glacial acetic acid (**Figure 39**).

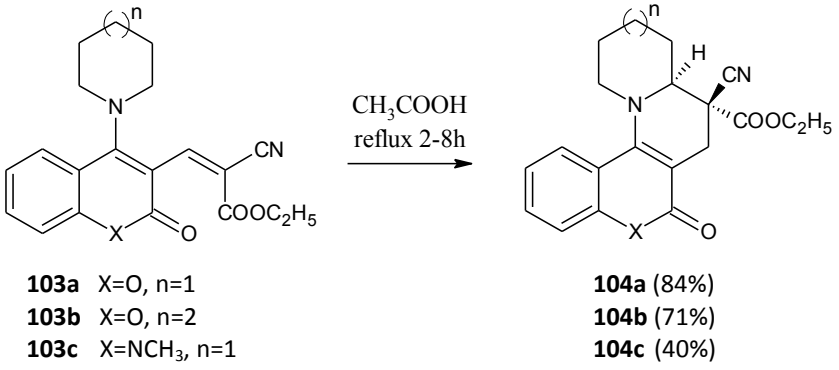


Fig.39: Extension of tert-amino effect to coumarin and 2-quinolone systems.

1.3 Microwave-assisted cyclizations via tert-amino effect

Microwave-assisted organic synthesis has recently gained increasing popularity, due to its numerous advantages, such as reduced reaction times, higher yields or efficient 'in core' heating[51-53]. Microwave irradiation is an electromagnetic irradiation corresponding to the 0.3-300 GHz frequency range (1 cm – 1 m wavelength). Compared to heat transfer via conductance with traditional heating methods, microwave irradiation results in an efficient internal heating by dipolar polarization and ionic conduction, by direct coupling of the irradiation energy and the reaction mixture. The effect of microwave irradiation on chemical reactions can be ascribed to: i) thermal/kinetic effects (rate accelerations due to high reaction temperatures attained under microwave conditions), ii) specific microwave effects (rate accelerations that cannot be achieved or duplicated by conventional heating, but are essentially thermal effects – e.g. overheating of polar liquids, presence of "hot spots", selective heating of solvents/catalysts/reagents, application of susceptors (an inert compound efficiently absorbing microwave radiation and transferring thermal energy) when the reagents and solvents do not absorb microwave radiation, elimination of wall effects caused by inverted temperature gradients) or the much debated iii) non-thermal (athermal) microwave effects (rate accelerations that cannot be rationalized by thermal/kinetic or specific microwave effects – effects resulting from the interaction of the electromagnetic field and the reaction mixture)[51,52,54].

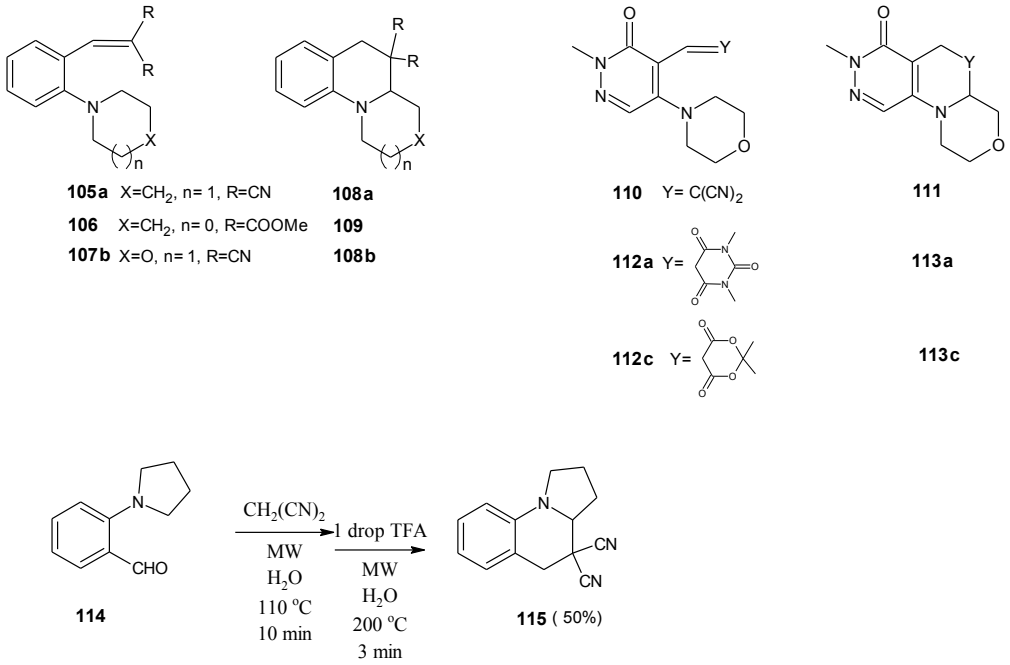


Fig. 40: Microwave-assisted synthesis of pyrido-fused ring systems *via tert*-amino effect.

	Conventional heating			Microwave irradiation		
Product	**Temp (°C)/ Time (h)**	**Yield (%)**	**Solvent**	**Temp (°C)/ Time (h)**	**Yield (%)**	**Solvent**
108a	117/2 h	78	*n*-BuOH	200/3 min	80	*n*-BuOH
	105/5 min	99	neat	150/5 min	99	neat
109	117/22 h	67	*n*-BuOH	220/15 min	73	*n*-BuOH
	170/17min	87	neat	170/17min	86	neat
108b	117/35 min	84	*n*-BuOH	220/30 min	96	*n*-BuOH
	180/22 min	94	neat	180/22 min	94	neat
111	150/44 h	35	DMSO	210/42 min	29	DMSO
	200/20 min	78	neat	200/18 min	75	neat
113a	138/ 2h	45	xylene	201/1 min	63	*n*-BuOH
	210/1 min	97	neat	201/1 min	96	neat
113c	100/5 h	79	DMF	200/30 min	73	DME*
	175/7 min	31	neat	175/7 min	55	neat

*****DME: 1,2-dimethoxyethane*

Table 9: Comparison of *tert*-amino effect cyclization conditions under conventional heating and microwave irradiation.

Tert-amino effect cyclizations often require prolonged heating in organic solvents with high boiling points (e.g. DMSO), making isolation of the products more challenging. Microwave-assisted synthesis of pyrido-fused heterocycles was studied by Kaval et al., comparing microwave irradiation protocols with conventional heating conditions[55]. The reaction rates of the cyclizations were

significantly enhanced upon microwave irradiation, reactions requiring hours or days under conventional heating running to completion within less than an hour in average (as summarized in **Figure 40**. and **Table 9**.). As a follow-up of the studies in the solution phase, environmentally more benign solvent-free procedures were elaborated, furnishing improved yields and cleaner reaction profiles[56]. As an alternative for an environmentally friendly route, conversion of *ortho*-pyrrolidinobenzaldehyde (**114**) to the pyrido-fused product **115** using a one-pot procedure in water as solvent, was described (**Figure 40**).

1.4 Semicarbazide-sensitive amine oxidase / vascular adhesion protein-1 – a brief overview.

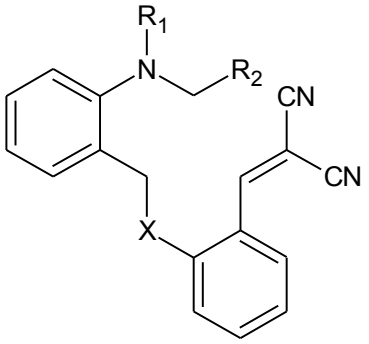
Vascular adhesion protein-1 (VAP-1) has recently become an emerging anti-inflammatory target[57,58], as illustrated by the growing number of patent applications disclosing novel small molecule VAP-1 inhibitors[59-63]. Besides being an adhesion protein involved in inflammation, genetic encoding revealed sequence identity of VAP- 1 and semicarbazide-sensitive amine oxidase (SSAO) [primary amine-oxidase, EC 1.4.3.21.][64], a copper-containing amine oxidase, possessing a unique topaquinone cofactor and catalyzing the oxidative deamination of primary aliphatic and arylalkylamines to the corresponding aldehydes. SSAO exists both as a membrane-bound protein and as a soluble form in the plasma, the latter may originate from the membrane-bound form by shedding. The major sources of SSAO include endothelial cells, smooth muscle cells and adipocytes. It has been well documented that VAP-1 is upregulated at sites of inflammation and plays an important role in leukocyte trafficking *via* its adhesive and enzymatic functions. VAP-1 inhibitors were indeed found to attenuate inflammation in several *in vivo* models[65-69]. Moreover, elevated VAP-1 levels were found in serum or tissue samples of patients with type 1 and 2 diabetes, congestive heart failure, Alzheimer's disease, multiple sclerosis, inflammatory skin diseases (psoriasis, atopic eczema) and inflammatory liver disease, therefore a possible role for VAP-1 in their pathogenesis has been also suggested[70-74]. Small-molecule inhibitors of VAP-1 identified so far include various hydrazine derivatives, arylalkylamines, propenyl- and propargylamines, oxazolidinones, haloalkylamines, 1,3,4-oxadiazines, 4,5,6,7-tetrahydroimidazo[4,5-*c*]pyridines, carbox(thi)amides, sulfonamides and thiazole derivatives[59,60,62,63]. During ongoing studies in the Department of Organic Chemistry (Semmelweis University), it has been recently found that novel arylalkyloxime derivatives can display significant VAP-1 inhibitory and anti-inflammatory effects.

2. Aims of work

As illustrated by the examples in the previous section, cyclizations *via tert*-amino effect have been successfully used for the synthesis of various heterocyclic compounds.

Recently, possible extensions of the *tert*-amino effect to compounds with the interacting *tert*-amino moiety and vinyl group in the *ortho* positions of connected aryl rings systems were studied at the Department of Organic Chemistry (Semmelweis University), elaborating therewith novel synthetic pathways to polyaryl fused hetero-ring systems with medium-sized rings.

Assuming this, in the present work we explored further extensions of the *tert*-amino effect. We set out to investigate the regiochemistry of possible cyclizations of non-directly connected biaryl systems. In this model, compounds bear the key vinyl and *tert*-amino moieties in *ortho*-*ortho'* positions of two aryl rings bridged with a saturated chain. As model compounds, molecules **122a-d** were chosen (**Figure 41**).



122a-d

122a: R_1=CH_3, R_2=H, X= NCH_3

122b: R_1=R_2=$(CH_3)_4$, X= NCH_3

122c: R_1=CH_3, R_2=H, X= O

122d: R_1=R_2=$(CH_3)_4$, X= O

Fig. 41: Model compounds of biaryl systems.

Therefore, the present experiments involved molecules in which the bridge contained the methylamino-*N*-methyl chain (**Figure 42**, **A**) or the CH_2-O chain (**Figure 42**, **B**). Applying such novel type of cyclizations, synthesis of hitherto unpublished fused ring systems could be achieved.

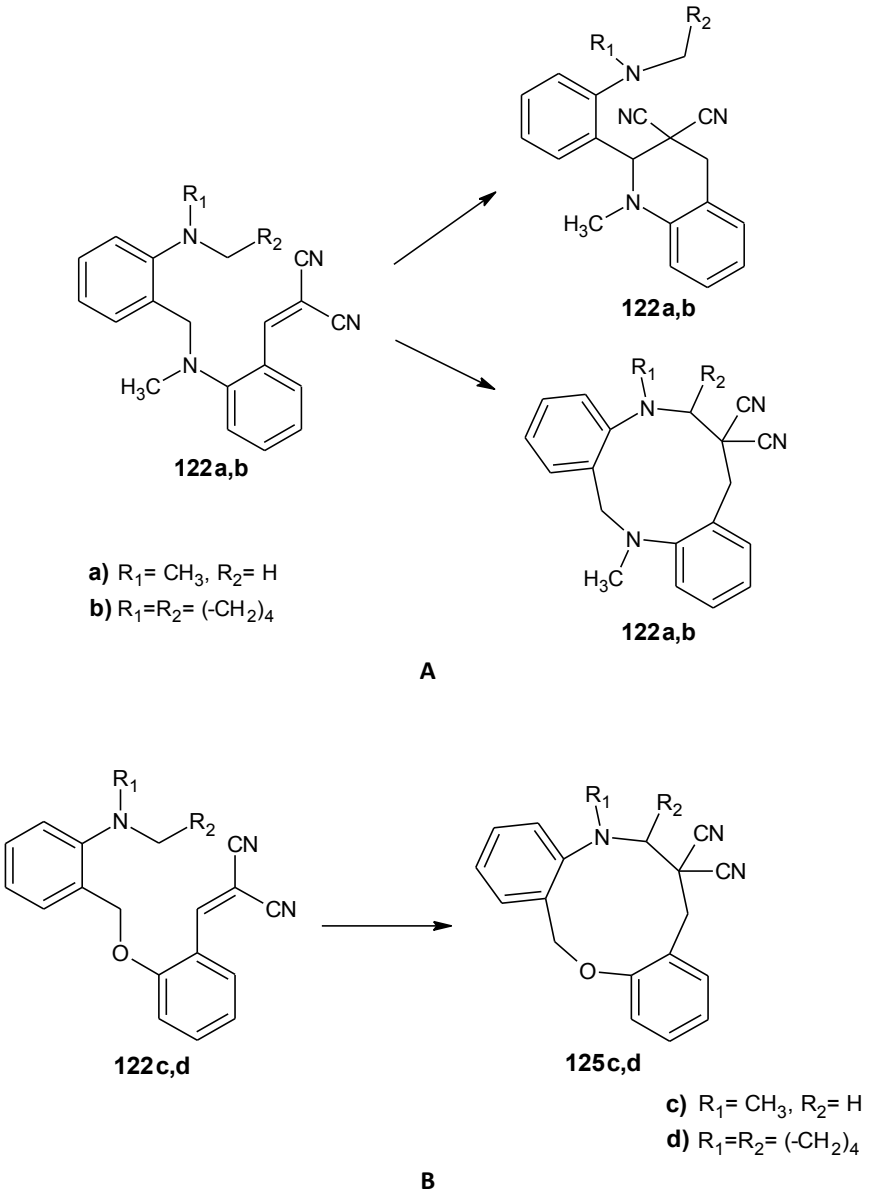
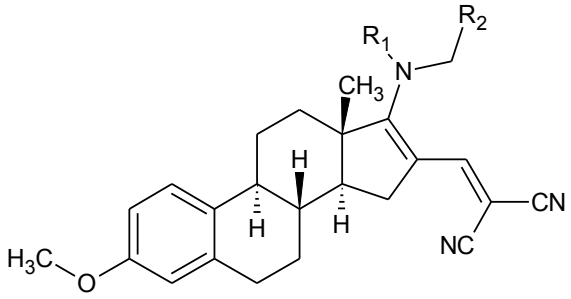


Fig.42: Design of the studied model compounds.

Considering the methylamino-*N*-methyl **122a,b** the presence of two tertiary amino groups in *ortho* position to a vinyl substituent in the same molecule, could lead to three different hydrogen migrations and types of cyclizations, respectively, although isomerization with the involvement of N-methyl group that bears as competitor a benzyl was not expected to take place at all. Possible formations of compounds **123a**,**b** and **124a**,**b** were rather considered.

As another model compound of type **122**, compounds **122c,d** were next prepared. A possible ring closure reaction could take place, leading to the formation of the corresponding ten-membered products **125c,d** (**Figure 40b**).
The Department of Organic Chemistry (Semmelweis University), is also involved in a *Semicarbazide Sensitive Amino-Oxidase* (SSAO) research program among compounds with potential VAP-1 substrate or inhibitory effects. Therefore we also planned to utilize the cyclized compounds **123a,b** for further studies for a possible SSAO activity**.**

As a fully unexplored field of *ter*t-amino effect, a steroid model compound **132** was proposed to be studied (**Figure 43**).



132a-c

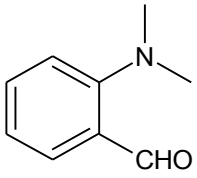
Fig.43: Design of the studied steroids model compounds. **a)** R_1= R_2=$(-CH_2)_3$, **b)** R_1= R_2= $(-CH_2)_4$, **c)**benzylamine

We prepared steroids molecules properly functionalized in D-ring, to study *tert*-amino effect in non-aromatic systems and also to open a new straightforward way to D-fused steroid-ring systems.

3. Materials and methods

All reagents and solvents were purchased from commercial sources and were utilized without further purification. Melting points were determined on a Büchi 540 (Büchi Labortechnik AG, Flawil, Switzerland) capillary melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature, in the solvent indicated, with a Varian Mercury Plus spectrometer (Agilent Technologies, Santa Clara, CA, USA) at a frequency of 400 or 100MHz or with a Bruker 500MHz (Bruker Biospin, Rheinstetten, Germany) spectrometer, at a frequency of 500 or 125MHz, and are reported in parts per million (ppm). Spectra were recorded at 500MHz (^{1}H) or 125 MHz (^{13}C), if not indicated otherwise. Chemical shifts are given on the d-scale relative to tetramethylsilane or the residual solvent signal as an internal reference. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, m=multiplet, dd= doublet doublet, dm= doublet multiplet, tm= triplet multiplet, and br = broad. For structure elucidation, one-dimensional ^{1}H, ^{13}C, DEPT, two-dimensional ^{1}H, ^{1}H-COSY, ^{1}H, ^{13}C-HSQC, ^{1}H, ^{13}C-HMBCmeasurements were run. Elemental analyses were performed on a Carlo Erba 1012 apparatus (Thermo Fisher Scientific, Milan, Italy), analyses indicated by the symbols of the elements affording satisfactory results.Microwave (MW) irradiation experiments were carried out in a monomode CEM-Discover MW reactor (CEM Corporation, Matthews, NC, USA) by using the standard configuration as delivered, including proprietary software. The experiments were executed in 10mL 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. For flash column chromatography purification, Kieselgel 60 (Merck 0.040–0.063mm) (Merck KGaA, Darmstadt, Germany) was used; for thin layer chromatography (TLC) analysis, silica gel 60F254 (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a v/v ratio. The structures of all compounds were consistent with their analytical and spectroscopic data.

2-(dimethylamino)-benzaldehyde



116a

To a solution of *o*-flurobenzaldehyde 97% (48.3 mmol, 5.1 mL) in dimethylformamide anhydrous (100 mL) was added dropwise dimethylamine 33% in EtOH (15 mL), then K_2CO_3 (47.8 mmol, 6.65 g) was added. The reaction was left to stir at 120°C, for 4 hours, under argon atmosphere.

The mixture was cooled down and filtrated under vacuum to give 6.83 g of crude compound. This was distilled under vacuum (0mbar, 55°C) to eliminate the DMF. The obtained product was purified by fractionary distillation to afford 5.044 g of a yellow oil.

Rf: 0.61 (hexane/ethyl acetate, 4/1).

Yield: 70%

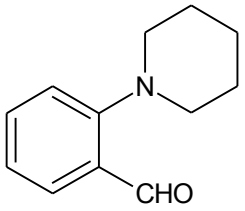
^{1}H NMR ($CDCl_3$):

δ(ppm): 10.23 (s, 1 H, C*H*O), 7.76 (d, 1 H, Ph-*H*), 7.45 (t, 1H, Ar), 7.05 (d, 1 H, Ar), 7.00 (d, 1 H, Ar), 2.92 (s, 6 H, NCH_3).

^{13}C NMR ($CDCl_3$):

δ(ppm): 45.50, 117.57, 120.58, 127.01, 130.92, 134.54, 155.73, 191.15.

2-piperidin-1-ylbenzaldehyde



116b

To a solution of *o*-flurobenzaldehyde 97% (32.23 mmol, 3.4 mL) in dimethylformamide anhydrous (50 mL) was added dropwise piperidine (48.34 mmol, 4.78 mL), then K_2CO_3 (32.23 mmol, 4.45 g) was added. The reaction was left to stir at 120°C, for 4 hours, under argon atmosphere.

The mixture was cooled down and filtrated under vacuum to give 6.23 g of crude compound. This was distilled under vacuum (0mbar, 55°C) to eliminate the DMF. The obtained product was purified by fractionary distillation to afford 3.97 g of a yellow oil.

Rf: 0.34 (hexane/ethyl acetate, 4/1).

Yield: 65%

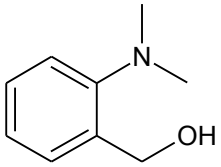
^{1}H NMR ($CDCl_3$):

δ(ppm): 10.3 (s, 1H, CHO), 7.8 (d, 1H, Ph-*H*), 7.5 (t, 1H, Ar), 7.1 (d, 1H, Ar), 7.05 (d, 1H, Ar),3.05 (t, 4H, NCH_2), 1.76 (m, 4H), 1.6 (m, 2H).

^{13}C NMR ($CDCl_3$):

δ(ppm): 24.03, 26.17, 55.59, 118.95, 121.93, 128.61, 129.16, 134.78, 156.97, 191.70.

[2-(dimethylamino)phenyl]methanol



117a

A solution of 2-(dimethylamino)-benzaldehyde (**116a**) (20.11 mmol, 3 g) in methanol anhydrous (40 mL) was cooled to 2 °C and sodium borohydride, $NaBH_4$, (30.16 mmol, 1.14 g) was slowly added in 10 min. Then, the reaction was left to reach room temperature and stirred for 20 min.

The flask was cooled down to 0-5°C and cold distilled water (5°C) was added to the mixture (40ml). Methanol was dried under vacuum and the aqueous phase was extracted 4 times with Ethyl acetate (4 x 25mL). The ethyl acetate phase was separated off, dried over $MgSO_4$, filtered and evaporated under vacuum to give 2.8523 g of a light yellow oil.

Rf: 0.22 (hexane/ethyl acetate, 4/1).

Yield: 94%

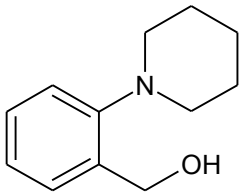
^{1}H NMR ($CDCl_3$):

δ(ppm): 2.71 (s, 6H, NC*H*$_3$), 4.81 (s, 2H, C*H*$_2$O), 7.05-7.27 (m, 4*H*, Ar)

^{13}C NMR ($CDCl_3$):

δ(ppm): 44.56, 64.82, 120.03, 124.38, 128.13, 128.36, 135.19, 151.92.

2-(piperidine-1-yl phenyl)methanol



117b

A solution of 2-piperidin-1-ylbenzaldehyde (**116b**) (2.64 mmol, 0.5 g) in methanol anhydrous (8 mL) was cooled to 2 °C and sodium borohydride, $NaBH_4$, (3.96 mmol, 150 mg) was slowly added in 10 min. Then, the reaction was left to reach room temperature and stirred for 20 min.

The flask was cooled down to 0-5°C and cold distilled water (5°C) was added to the mixture. Methanol was dried under vacuum and the aqueous phase was extracted 4 times with Ethyl acetate (4 x 10mL). The ethyl acetate phase was separated off, dried over $MgSO_4$, filtered and evaporated under vacuum to give 0.43 g of a light yellow oil.

Rf: 0.42 (hexane/ethyl acetate, 4/1).

Yield: 84%

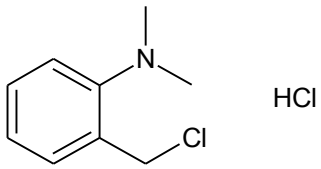
^{1}H NMR ($CDCl_3$)[400MHz]:

δ(ppm): 1.59 (m, 2H), 1.75 (m, 4H,), 2.91 (t, 4H, NCH_2), 4.81 (s, 1H, C*H*$_2$O), 6.03 (s, 1H, O*H*), 7.00-7.27 (m, 4H, Ar).

^{13}C NMR ($CDCl_3$)[150MHz]:

δ(ppm): 24.62, 27.39, 54.53, 65.88, 121.53, 125.31, 128.78, 128.97, 136.18, 152.57.

2-(chloromethyl)-N,N-dimethylaniline hydrochloride



118a

A solution of [2-(dimethylamino)phenyl]methanol (**117a**) (6.61 mmol, 1 g) in 10 mL of dichloromethane (DCM) anhydrous, was cooled to 2 °C and a solution of thionyl chloride ($SOCl_2$) (33.07 mmol, 2.4 mL) in 2mL of DCM anhydrous was added dropwise for 15 min. The reaction was stirred for 30 min. in low temperature and then for 1 hour in room temperature.

Dichloromethane and thionyl chloride were evaporated under vacuum. Diethyl ether was added and a yellow precipitate formed. This was filtered under vacuum, washed by diethyl ether and dried to afford 1.23 g of white hygroscopic solid.

mp: 142-144°C

Yield: 90%

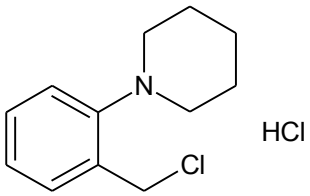
^{1}H NMR ($CDCl_3$):

δ(ppm): 3.36 (s, 6H, NCH_3), 5.39, (s, 2H, CH_2Cl), 7.52-7.61 (m, 4H, Ar).

^{13}C NMR ($CDCl_3$):

δ(ppm): 41.90, 47.41, 120.52, 130.75, 130.90, 131.77, 133.64, 140.61.

1-[2-(chloromethyl)phenyl]piperidine hydrochloride



118b

A solution of 2-(piperidine-1-yl phenyl)methanol (**117b**) (8.7 mmol, 1.67 g) in 10 mL of dichloromethane (DCM) anhydrous, was cooled to 2 °C and a solution of thionyl chloride ($SOCl_2$) (43.06 mmol, 3.16 mL) in 5mL of DCM anhydrous was added dropwise for 20 min. The reaction was stirred for 30 min. in low temperature and then for 1 hour in room temperature.

Dichloromethane and thionyl chloride were evaporated under vacuum. Diethyl ether was added and a yellow precipitate formed. This was filtered under vacuum, washed by diethyl ether and dried to afford 1.88 g of white solid.

mp: 156-158°C

Yield: 88%

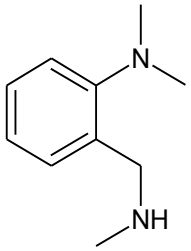
^{1}H NMR ($CDCl_3$):

δ(ppm): 1.5-3.8 (m, 10H), 5.41 (s, 2H, CH_2Cl), 7.50 (m, 3H, Ar), 7.64 (m, 1H, Ar).

^{13}C NMR ($CDCl_3$):

δ(ppm): 21.81, 22.86, 42.16, 57.45, 120.11, 130.44, 132.74, 134.60, 139.77.

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



119a

To 40wt% aq. methylamine (67 mL, 776.00 mmol) at -10 °C, a solution of the 2-(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride **118a** (19.42 mmol, 4.00 g in EtOH (70 mL) was added dropwise. The mixture was stirred at -10 °C for 2 h.

The solvent was removed in vacuum, 30 mL H_2O was added, and the mixture was extracted with EtOAc (3 x 30 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 (5 x 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness.

The crude product was purified by fractionary distillation under reduced pressure (102 °C, 5 mmHg) to give a colorless oil (1.28 g).

Yield: 40%

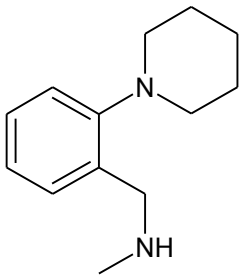
^{1}H NMR ($CDCl_3$):

δ (ppm): 2.44 (s, 3H, CH_3), 2.70 (s, 6H, $N(CH_3)_2$), 3.83 (s, 2H, CH_2), 7.02–7.06 (m, 1H, Ar–H), 7.11 (dd, 1H, J = 1.0, 8.0Hz, Ar–H), 7.20–7.25 (m, 1H, Ar–H), 7.31 (dd, 1H, J = 1.5, 7.5Hz, Ar–H).

^{13}C NMR ($CDCl_3$):

δ (ppm): 36.8, 45.7, 52.9, 119.9, 124.0, 128.3, 130.3, 134.9, 153.3

N-methyl-1-(2-piperidin-1-ylphenyl)methanamine



119b

To 40wt% aq. methylamine (67 mL, 776.00 mmol) at -10 °C, a solution of the 1-[2-(chloromethyl)phenyl]piperidine hydrochloride **118b** (19.42 mmol, 4.78 g in EtOH (70 mL) was added dropwise. The mixture was stirred at -10 °C for 2 h.

The solvent was removed in vacuum, 30 mL H_2O was added, and the mixture was extracted with EtOAc (3 x 30 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 (5 x 30 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness.

The crude product was purified by fractionary distillation under reduced pressure (102 °C, 5 mmHg) to give a colorless oil (2.42 g).

Yield: 60%

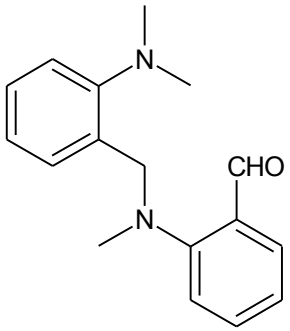
^{1}H NMR (DMSO-*d*$_6$):

δ (ppm): 1.45–1.55 (m, 2H, CH_2), 1.60–1.68 (m, 4H, CH_2), 2.30 (s, 3H, CH_3), 2.75 2.85 (m, 4H, CH_2), 3.66 (s, 2H, CH_2), 6.97–7.10 (m, 1H, Ar–H), 7.04 (dm, 1H, J = 1.0, 7.0 Hz, Ar–H), 7.15–7.19 (m, 1H, Ar–H), 7.36 (dm, 1H, J = 7.0 Hz, Ar–H).

^{13}C NMR (DMSO-*d*$_6$):

δ (ppm): 23.9, 26.2, 36.1, 50.6, 53.5, 119.2, 122.8, 127.2, 129.1, 134.5, 152.3.

2-{[2-(dimethylamino)benzyl](methyl)amino}benzaldehyde



120a

A suspension of the amine compound *N*,*N*-dimethyl-2-[(methylamino)methyl] aniline (**119a**) (4.29 mmol, 705 mg), 2-fluorobenzaldehyde (4.29 mmol, 0.45 mL), and K_2CO_3 (6.54 mmol, 904 mg) in 12 mL dimethylformamide 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 vacuum, and the crude product obtained was purified by flash column chromatography on silica gel (n-hexane/EtOAc 9:1) to afford 1.07 g of yellow oil.

Rf: 0.16 (hexane/EtOAc 9:1)

Yield: 93%

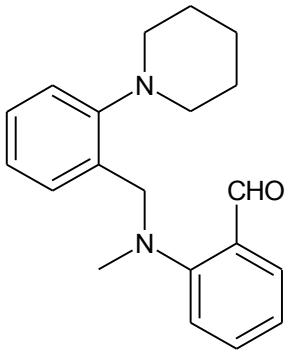
^{1}H NMR ($CDCl_3$):

δ (ppm): 2.63 (s, 6H, $N(CH_3)_2$), 2.86 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.98–7.02 (m, 1H, Ar–H), 7.02–7.06 (m, 1H, Ar–H), 7.11 (dm, 1H, J = 8.0 Hz, Ar–H), 7.12 (dm, 1H, J = 8.0 Hz, Ar–H), 7.21–7.26 (m, 1H, Ar–H), 7.41–7.46 (m, 2H, Ar–H), 7.80 (dm, 1H, J = 7.5 Hz, Ar–H), 10.33 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$):

δ (ppm): 43.4, 45.6, 58.1, 119.6, 120.0, 121.5, 124.0, 128.1, 128.5, 129.2, 130.7, 132.4, 135.2, 153.5, 156.6, 192.0.

2-[methyl(2-piperidin-1-ylbenzyl)amino]benzaldehyde



120b

A suspension of the amine compound *N*-methyl-1-(2-piperidin-1-ylphenyl)methanamine (**119b**) (4.29 mmol, 876 mg), 2-fluorobenzaldehyde (4.29 mmol, 0.45 mL), and K_2CO_3 (6.54 mmol, 904 mg) in 12 mL dimethylformamide 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 vacuum, and the crude product obtained was purified by flash column chromatography on silica gel (n-hexane/EtOAc 4:1) to afford 1.26 g of yellow oil.

Rf: 0.65 (hexane/EtOAc 4:1)

Yield: 95%

^{1}H NMR ($CDCl_3$):

δ (ppm): 1.50–1.60 (m, 2H, CH_2), 1.60–1.70 (m, 4H, CH_2), 2.75–2.85 (m, 4H, CH_2), 2.88 (s, 3H, CH_3), 4.44 (s, 2H, CH_2), 6.97–7.02 (m, 1H, Ar–H), 7.01–7.06 (m, 1H, Ar–H), 7.10 (dm, 1H, J = 8.0Hz, Ar–H), 7.11 (dm, 1H, Ar–H), 7.20–7.25 (m, 1H, Ar–H), 7.39 (dm, 1H, J = 7.5Hz, Ar–H), 7.40–7.45 (m, 1H, Ar–H), 7.79 (dm, 1H, Ar–H), 10.30 (s, 1H, CHO).

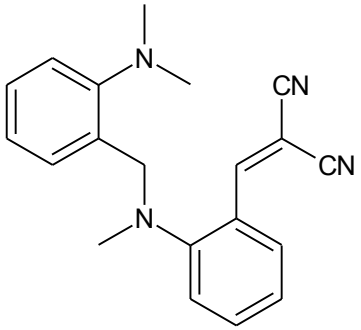
^{13}C NMR ($CDCl_3$):

δ (ppm): 24.9, 27.2, 43.7, 55.0, 57.4, 119.6, 120.7, 121.2, 124.1, 128.0, 128.6, 129.2, 130.8, 132.9, 135.2, 153.7, 156.5, 192.0.

Elemental analysis:

Anal. Calcd for ($C_{20}H_{24}N_2O$): C, 77.89; H, 7.84; N, 9.08. Found: C, 78.06; H, 7.99; N, 9.08

2-(2-{[2-(Dimethylamino)benzyl](methyl)amino} benzylidene) malononitrile



122a

A mixture of the 2-{[2-(dimethylamino)benzyl](methyl)amino}benzaldehyde (**120a**) (4.86mmol, 1.30 g) and malononitrile (4.86mmol, 321mg) in 24mL EtOH was stirred for 3 h at room temperature.

The solvent was removed in vacuum, and the crude product obtained was purified by flash column chromatography on silica gel (eluent: n-hexane/EtOAc 4:1), to afford 1.32 g of an orange oil.

Rf: 0.36 (hexane/EtOAc 4:1)

Yield: 86%

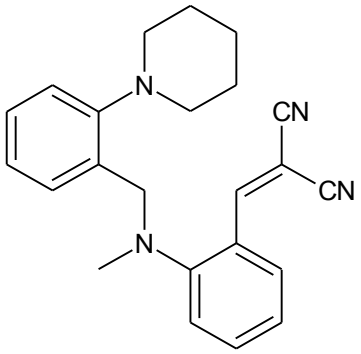
^{1}H NMR ($CDCl_3$):

δ (ppm): 2.61 (s, 6H, CH_3), 2.82 (s, 3H, CH_3), 4.29 (s, 2H, CH_2), 7.03–7.11 (m, 2H, Ar–H), 7.14 (dm, 2H, J = 8.5 Hz, Ar–H), 7.24–7.29 (m, 2H, Ar–H), 7.45–7.49 (m, 1H, Ar–H), 8.01 (dm, 1H, J = 8.0 Hz, Ar–H), 8.12 (s, 1H, CH).

^{13}C NMR ($CDCl_3$):

δ (ppm): 43.5, 45.7, 58.4, 80.7, 113.7, 115.0, 120.6, 120.6, 122.9, 124.2, 125.0, 129.1, 129.6, 129.9, 132.0, 135.3, 153.5, 155.8, 159.0.

2-(2-{[2-(Piperidin-1-yl)benzyl](methyl)amino}benzylidene)malononitrile



122b

A mixture of the 2-[methyl(2-piperidin-1-ylbenzyl)amino]benzaldehyde (**120b**) (4.86mmol, 1.50 g) and malononitrile (4.86mmol, 321mg) in 24mL EtOH was stirred for 3 h at room temperature.

The precipitated crystals were filtered off and washed with EtOH, to afford 1.56 g of orange crystals.

m.p.: 95-96 °C

Yield: 90%

^{1}H NMR ($CDCl_3$):

δ (ppm): 1.50–1.60 (m, 2H, CH_2), 1.65–1.70 (m, 4H, CH_2), 2.65–2.75 (m, 4H, CH_2), 2.85 (s, 3H, CH_3), 4.26 (s, 2H, CH_2), 7.03–7.14 (m, 3H, Ar–H), 7.19 (dm, 1H, J = 8.5 Hz, Ar–H), 7.22–7.28 (m, 2H, Ar–H), 7.45–7.50 (m, 1H, Ar–H), 8.00 (dm, 1H, J = 8.0 Hz, Ar–H), 8.03 (s, 1H, CH).

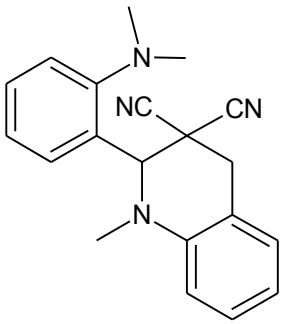
^{13}C NMR ($CDCl_3$):

δ (ppm): 24.8, 27.3, 44.2, 55.0, 57.5, 80.6, 113.7, 115.0, 120.7, 121.0, 122.9, 123.0, 124.4, 125.0, 129.1, 129.4, 129.9, 132.6, 135.3, 153.6, 155.7, 158.9

Elemental analysis:

Anal. Calcd for ($C_{23}H_{24}N_4O$): C, 72.50; H, 6.79; N, 15.72. Found: C, 77.58; H, 6.83; N, 15.68.

2-(2-(Dimethylamino)phenyl)-1-methyl-1,2-dihydroquinoline-3,3 (4H)-dicarbonitrile



123a

The vinyl precursors 2-(2-{[2-(Dimethylamino)benzyl](methyl)amino} benzylidene) malononitrile (**122a**) (0.84 mmol, 266 mg) in a 10mL MW process vial was irradiated at 135 °C for 10 min. (at 250W maximum power level). The vial was subsequently cooled to ambient temperature, and 15 mL CH_2Cl_2 was added. The mixture was washed with H_2O (3 x 15 mL), and the organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford 266 mg of white crystals.

m.p.: 170-172 °C

Yield: 100%

^{1}H NMR ($CDCl_3$):

δ (ppm): 2.74 (s, 6H, CH_3), 2.97 (s, 3H, CH_3), 3.35 (d, 1H, J = 16.0 Hz, CH_2), 3.42 (d, 1H, J = 16.0 Hz, CH_2), 5.74 (s, 1H, CH), 6.78 (dm, 1H, J = 8.0 Hz, Ar–H), 6.79–6.82 (m, 1H, Ar–H), 7.04–7.09 (m, 3H, Ar–H), 7.25–7.30 (m, 1H, Ar–H), 7.33–7.39 (m, 2H, Ar–H).

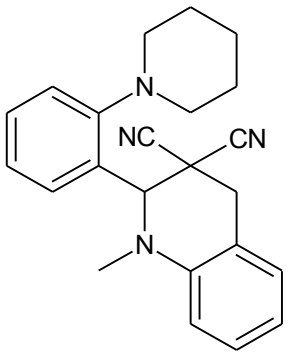
^{13}C NMR ($CDCl_3$):

δ (ppm): 34.8, 35.5, 38.8, 46.7, 61.1, 112.1, 114.5, 115.5, 116.2, 118.3, 122.7, 126.0, 127.9, 129.8, 130.2, 131.3, 132.5, 144.6, 154.8.

Elemental analysis:

Anal. Calcd for ($C_{20}H_{20}N_4$): C, 75.92; H, 6.37; N, 17.71. Found: C, 75.58; H, 6.45; N, 17.54.

1-Methyl-2-(2-(piperidin-1-yl)phenyl)-1,2-dihydroquinoline-3,3(4H)-dicarbonitrile



123b

The vinyl precursors 2-(2-{[2-(Piperidin-1-yl)benzyl](methyl)amino}benzylidene) malononitrile (**122b**) (0.84 mmol, 299 mg) in a 10mL MW process vial was irradiated at 130 °C for 10 min. (at 250W maximum power level). The vial was subsequently cooled to ambient temperature, and 15 mL CH_2Cl_2 was added. The mixture was washed with H_2O (3 x 15 mL), and the organic layer was dried ($MgSO_4$), filtered, and evaporated to dryness to afford 299 mg of white crystals.

m.p.: 167-169 °C

Yield: 100%

^{1}H NMR ($CDCl_3$):

δ (ppm): 1.50–1.80 (m, 6H, CH_2), 2.70–3.00 (m, 4H, CH_2), 2.95 (s, 3H, CH_3), 3.32 (d, 1H, J= 16.0Hz, CH_2), 3.40 (d, 1H, J=16.0Hz, CH_2), 5.63 (s, 1H, CH), 6.78 (dm, 1H, J=7.5Hz, Ar–H), 6.78–6.82 (m, 1H, Ar–H), 7.01–7.08 (m, 3H, Ar–H), 7.25–7.30 (m, 2H, Ar–H), 7.33–7.37 (m, 1H, Ar–H).

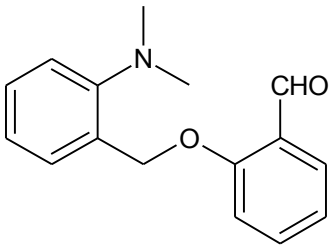
^{13}C NMR ($CDCl_3$):

δ (ppm): 24.8, 27.3, 34.8, 35.5, 38.8, 55.0, 61.3, 112.1, 114.6, 115.2, 116.2, 118.3, 123.0, 125.8, 127.8, 129.8, 130.2, 131.2, 132.5, 144.6, 154.6

Elemental analysis:

Anal. Calcd for ($C_{23}H_{24}N_4$): C, 77.50; H, 6.79; N, 15.72. Found: C, 77.49; H, 6.88, N, 15.89.

2-{[2-(dimethylamino)benzyl]oxy}benzaldehyde



121a

To a solution of salicylaldehyde (43.66 mmol, 4.65 mL) in dimethylformamide anhydrous (150 mL), was added K_2CO_3 (87.33 mmol, 12.07 g) under argon atmosphere; the yellow suspension was left to stir for 1 hour in room temperature and then 2(chloromethyl)-*N*,*N*-dimethylaniline hydrochloride (**118a**) (43.66 mmol, 9 g) was added. The suspension was left to stir for 6 hours in room temperature.

The mixture was filtered and dried under vacuum. The resulting product was added with water (50ml) and extracted 8 times with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and evaporated in vacuum to give 8.38 g of crude compound (red liquid).

The crude product was purified by column chromatography (toluene/ethyl acetate 50:1) to afford 4.0415 g of yellow oil

Rf: 0.37 (toluene/ethyl acetate 50:1)

Yield: 35%

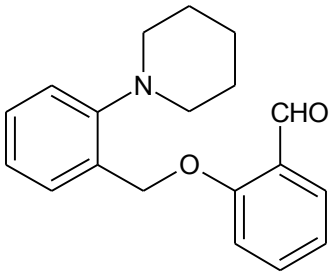
^{1}H NMR ($CDCl_3$):

δ (ppm): 2.74 (s, 6H, NC*H*$_3$), 5.29 (s, C*H*$_2$O), 6.99-7.85 (m, 8H, Ar), 10.57 (s, 1H, C*H*O).

^{13}C NMR ($CDCl_3$):

δ (ppm): 45.24, 66.37, 113.13, 119.14, 120.68, 123.38, 125.06, 128.28, 128.91, 129.14, 130.25, 135.88, 152.45, 161.24, 189.86.

2-[(2-piperidin-1-ylbenzyl)oxy]benzaldehyde



121b

To a solution of salicylaldehyde (1.22 mmol, 0.13 mL) in dimethylformamide anhydrous (7 mL), was added K_2CO_3 (2.44 mmol, 12.07 0.34g) under argon atmosphere; the yellow suspension was left to stir for 1 hour in room temperature and then 1-[2-(chloromethyl)phenyl]piperidine hydrochloride (**118b**) (1.22 mmol, 0.3 g) was added. The suspension was left to stir for 6 hours in room temperature.

The mixture was filtered and dried under vacuum. The resulting product was added with water (50ml) and extracted 8 times with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and evaporated in vacuum to give 284 mg of crude compound (red liquid).

The crude product was purified by column chromatography (Hexane/Ethyl acetate 40:1) to afford 115.6 mg of a colorless oil.

Rf: 0.22 (Hexane/Ethyl acetate 40:1)

Yield: 32%

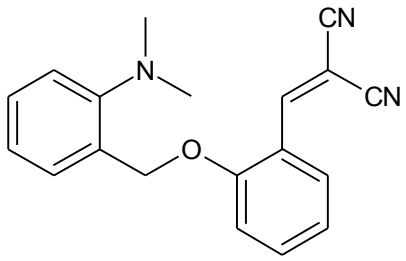
^{1}H NMR ($CDCl_3$):

δ (ppm): 1.59 (m, 2H), 1.73 (m, 4H), 2.88 (m, 4H, NC*H*$_2$), 5.29 (s, 2H, C*H*$_2$O), 6.99-7.85 (m, 8H, Ar), 10.57 (s, 1H, C*H*O).

^{13}C NMR ($CDCl_3$):

δ (ppm): 24.19, 26.63, 54.55, 66.09, 113.14, 119.79, 120.60, 123.57, 125.03, 128.25, 128.92, 128.98, 130.82, 135.85, 152.62, 161.32, 189.87.

(2-{[2-(dimethylamino)benzyl]oxy}benzylidene)malononitrile



122c

To a solution of 2-{[2-(dimethylamino)benzyl]oxy}benzaldehyde (**121a**) (3.92 mmol, 1 g) in EtOH (8 mL) was added malononitrile (3.92 mmol, 285 mg) and piperidine (catalytic amount). The reaction was left to stir for 2 hours in room temperature under argon atmosphere.

A yellow precipitate formed. This was filtered to give 919 mg of bright yellow crystals.

m.p.: 97.7-99.1 °C

Rf: 0.44 (hexane/ethyl acetate, 4:1)

Yield: 77%

^{1}H NMR ($CDCl_3$):

δ (ppm): 2.73 (s, 6H, NCH_3), 5.28 (s, 2H, CH_2O), 7.03-7.54 (m, 7H, Ar), 8.2 (d, 1H, Ar), 8.36 (s, 1H, C*H*=C).

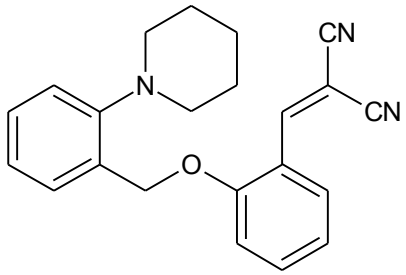
^{13}C NMR ($CDCl_3$):

δ (ppm): 45.31, 66.85, 81.20, 113.06, 113.15, 114.39, 119.34, 120.38, 121.20, 123.56, 128.73, 129.31, 129.50, 136.47, 152.59, 154.51, 158.35.

Elemental analysis:

Anal. calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.07; H, 5.69; N, 13.69.

{2-[(2-piperidin-1-ylbenzyl)oxy]benzylidene}malononitrile



122d

To a solution of 2-[(2-piperidin-1-ylbenzyl)oxy]benzaldehyde (**121b**) (4.06 mmol, 1.2 g) in EtOH (10 mL) was added malononitrile (4.2 mmol, 282 mg) and piperidine (catalytic amount). The reaction was left to stir for 2 hours in room temperature under argon atmosphere.

A yellow precipitate formed. This was filtered to give 1.12 g of bright yellow crystals.

m.p.: 114,1-116,3 °C

Rf: 0.19 (hexane/ethyl acetate, 20:1)

Yield: 80%

^{1}H NMR ($CDCl_3$):

δ(ppm): 1.59 (m, 2H), 1.72 (m, 4H), 2.87 (m, 4H, NC*H*$_2$), 5.27 (s, 2H, C*H*$_2$O), 7.02-7.53 (m, 7H, Ar), 8.20 (d, 1H, Ar), 8.35 (s, 1H, C*H*=C).

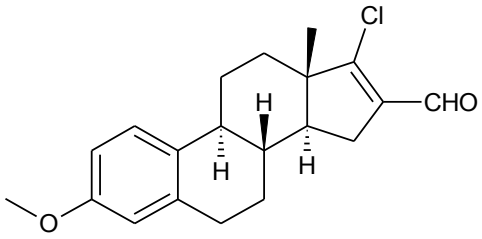
^{13}C NMR ($CDCl_3$):

δ(ppm): 24.14, 26.63, 54.68, 66.53, 81.18, 113.08, 113.17, 114.41, 120.02, 120.36, 121.12, 123.81, 128.74, 129.14, 129.33, 130.14, 136.44, 152.77, 154.55, 158.44.

Elemental analysis:

Anal. calcd for $C_{22}H_{21}N_3O$ (343.42): C, 76.94; H, 6.16; N, 12.24. Found: C, 76.94; H, 6.24; N, 11.95.

17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16-carbaldehyde



127

A solution of 3-methoxyestra-1(10),2,4-trien-17-one (**126**) (6.00 g, 21.09 mmol) in dry $CHCl_3$ (100 mL) was added dropwise to a cold and stirred solution of $POCl_3$ (30 mL) and DMF (30 mL). The mixture was allowed to attain room temperature and then refluxed under argon for 5 h.

The solution was poured into ice and extracted 3 times with DCM; the organic phase was dried over $MgSO_4$, filtered and evaporated in vacuum and purified by column chromatography on silica gel (dichloromethane), to afford 4.54 g of white solid.

mp: 125.2-127.8 °C

Rf: 0.27 (toluene)

Yield: (62%)

^{1}H NMR ($CDCl_3$):

δ (ppm): 1.00 (s, 3H), 1.44 (m, 1H), 1.63 (m, 2H), 1.64 (m, 1H), 1.74(m, 1H), 1.95 (m, 1H), 2.00(m, 1H), 2.15(dd, 1H), 2.31(m, 1H), 2.44(m, 1H), 2.65(dd, 1H), 2.83(m, 1H), 3.00(m, 1H), 3.78 (s, 3H), 6.65(d, 1H), 6.72(dd, 1H), 7.18(d, 1H), 10.01(s, 1H).

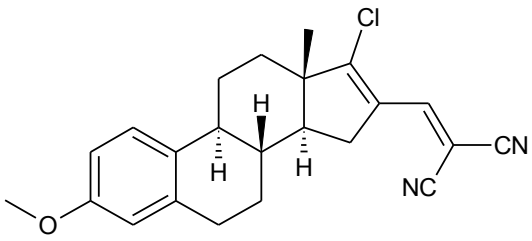
^{13}C NMR ($CDCl_3$):

15.9, 26.6, 27.7, 28.9, 30.2, 33.7, 37.9, 44.7, 51.7, 53.7, 55.9, 112.3, 114.5, 126.6, 132.5, 137.1, 138.4, 158.3, 163.2, 188.8.

Elemental anlalysis:

Anal. Calcd for $C_{20}H_{23}ClO_2$: C, 72.61; H, 7.01. Found: C, 72.39; H, 6.96.

{[17-chloro-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile



131

A suspension of 17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16-carbaldehyde (**127**) (3.00 g, 9.06 mmol) and maloninitrile (0.6 g, 9.06 mmol) in tert-butanol (60 mL) containing catalytic amount of piperidine, was stirred in room temperature under argon for 2 h.

The suspension was filtered under vacuum, washed with diethyl ether, dried and recrystalized from acetonitrile, to afford 2.95 g of yellow needles.

mp: 232-234 °C (dec.)

Rf: 0.71 (chloroform)

Yield: (86%)

^{1}H NMR ($CDCl_3$):

δ (ppm): 0.99 (s, 3H), 1.48 (m, 1H), 1.62(m, 2H), 1.67(m, 1H), 1.82(m, 1H), 2.00(m, 1H), 2.02(m, 1H), 2.33(m, 1H), 2.46(m, 1H), 2.55(dd, 1H), 2.84-2.99(m, 2H), 3.06(dd, 1H), 3.78(s, 3H), 6.65(d, 1H), 6.72(dd, 1H), 7.17(d, 1H), 7.74(s, 1H).

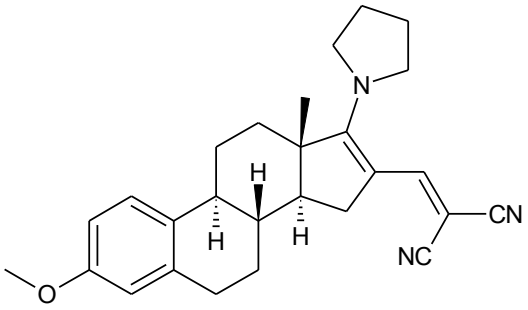
^{13}C NMR ($CDCl_3$):

δ (ppm):16.2, 26.6, 27.8, 30.1, 31.2, 33.9, 37.9, 44.7, 51.1, 54.0, 55.9, 82.8, 112.4, 113.3, 114.5, 114.8, 126.6, 132.2, 132.9, 138.3, 152.2, 158.4, 165.5.

Elemental anlalysis:

Anal. Calcd for $C_{23}H_{23}N_2OCl$: C, 72.91; H, 6.12; N, 7.39. Found: C, 72.88; H, 6.09; N, 7.20.

{[3-methoxy-17-pyrrolidin-1-ylestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile



132a

A solution of pyrrolidine (3.8 mmol, 0.32 mL) in EtOH (5 mL) was added dropwise to a suspension of {[17-chloro-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile (**131**) (1.9 mmol, 723 mg) in EtOH (15 mL). The mixture was left to stir in room temperature for 2 h.

The suspension was filtered under vacuum, washed with diethyl ether and dried to afford 762 mg of an orange solid.

mp: 239-241 °C (dec.).

Rf: 0.34 (hexane: ethyl acetate 2:3)

Yield: (96%).

^{1}H NMR ($CDCl_3$):

δ (ppm):1.08(s, 3H), 1.43(m, 1H), 1.58(m, 2H), 1.70(m, 1H), 1.88(m, 1H), 1.93(m, 2H), 2.05(m, 1H), 2.12(m, 2H), 2.28(m, 1H), 2.31(m, 1H), 2.48(m, 1H), 2.55(dd, 1H), 2.81-2.96(m, 2H), 3.04(dd, 1H), 3.75(m, 4H), 3.78(s, 3H), 6.65(d, 1H), 6.71(dd, 1H), 7.14(d, 1H), 7.45(s, 1H).

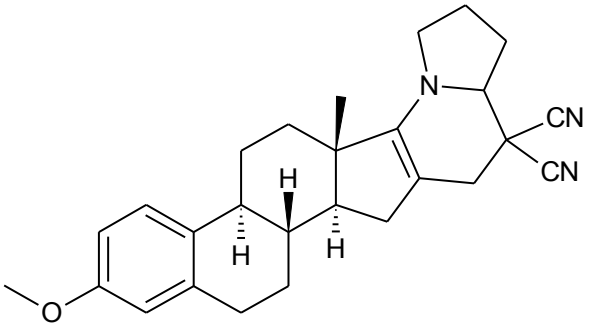
^{13}C NMR ($CDCl_3$):

δ (ppm): 15.7, 26.1, 26.1, 27.4, 27.6, 30.2, 31.6, 36.6, 38.1, 43.7, 51.2, 52.9, 54.3, 54.3, 55.9, 58.6, 110.1, 112.5, 114.4, 119.1, 120.9, 126.5, 132.1, 138.6, 151.6, 158.4, 174.7.

Elemental analysis:

Anal. Calcd for $C_{27}H_{31}N_3O$: C, 78.42; H, 7.56; N, 10.16. Found: C, 78.6; H, 7.55; N, 10.09.

(4bS,6aS,13aS,13bR)-2-methoxy-6a-methyl-4b,5,6,6a,8,9,10,10a,12,13,13a,13b,14,15-tetradecahydro-11H-naphtho[2',1':4,5]indeno[1,2-e]indolizine-11,11-dicarbonitrile



133a

{[3-methoxy-17-pyrrolidin-1-ylestra-1(10),2,4,16-tetraen-16-yl]methylene} malononitrile (**132a**) 300mg was stirred in preheated oil bath at 250°C for 30 minutes. The reaction was monitored by TLC in every 10 minutes.

The crude product was purified by column chromatography on silica gel (dichloromethane) to afford 160 mg of the diastereomers mixture as light yellow solid.

mp: 169-171°C

Rf: 0.707, 0.634 (dichloromethane)

Yield: 54%

^{1}H NMR ($CDCl_3$):

δ (ppm): 0.92(s, 3H), 1.01(s, 3H), 1.44(m, 1H), 1.58(m, 1H), 1.61(m, 1H), 1.72(m, 1H), 1.74(m, 1H), 1.78(m, 1H), 1.79(m, 1H), 1.91(m, 1H), 1.96(m, 1H), 2.03(m, 1H), 2.05 (m, 2H), 2.08(m, 2H), 2.13(m, 2H), 2.23(m, 1H), 2.30(m, 1H), 2.37(m, 1H), 2.51(m, 1H), 2.73(m, 1H), 2.78(m, 2H), 2.87(m, 1H), 2.81-3.01(m, 2H), 3.28(m, 1H), 3.41(m, 1H), 3.54(m, 1H), 3.56(m, 1H), 3.64(m, 1H), 3.67(m, 1H), 3.78(s, 3H), 6.64(m, 1H), 6.71(m, 1H), 7.18(m, 1H).

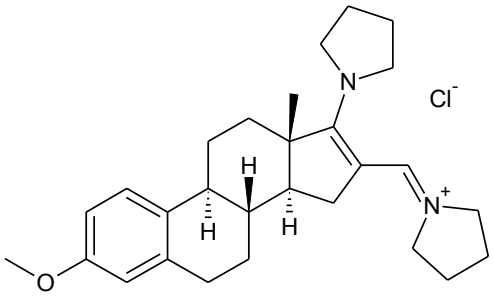
^{13}C NMR ($CDCl_3$):

δ (ppm): 16.8, 17.1, 24.9, 25.0, 27.0, 27.2, 27.9, 28.0, 29.4, 29.6, 30.3, 32.8, 33.2, 34.7, 35.5, 36.6, 36.6, 36.9, 37.5, 44.5, 44.8, 46.4, 47.9, 48.4, 49.9, 54.1, 55.5, 55.9, 65.2, 66.0, 99.3, 103.1, 112.1, 114.5, 115.2, 115.5, 116.8, 116.9, 126.6, 133.2, 138.6, 151.7, 152.2, 158.2.

Elemental analysis:

Anal. Calcd for $C_{27}H_{31}N_3O$: C, 78.42; H, 7.56; N, 10.16. Found: C, 78.52; H, 7.71; N, 10.18.

3-methoxy-16-(pyrrolidinium-1-ylidenemethyl)-17-pyrrolidin-1-ylestra-1(10),2,4,16-tetraene chloride



129a

To a solution of 17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16carbaldehyde (**127**) (0.91 mmol, 0.3 g) in acetonitrile anhydrous (5 mL), was added dropwise a solution of freshly distilled pyrrolidine (4.5 mmol, 0.38 mL), in acetonitrile anhydrous (3 mL). The reaction was left to stir for 5 hours in room temperature under argon atmosphere.

The solution was evaporated by in vacuum till dryness. 30mL of H_2O were added and extracted 3times with dichloromethane (3 x 20mL). The organic phase was dried over $MgSO_4$, filtered and evaporated in vacuum to give 495mg of a red/yellow oil. This was crystallized by ether to give 367 mg of a yellow solid.

mp: 71.1-73.7 °C

Yield: 70%

Rf: 0.16 (ethyl acetate/methanol, 1:1)

Mass spectrum: (M*) 419.3054 Diff. 0.74 ppm

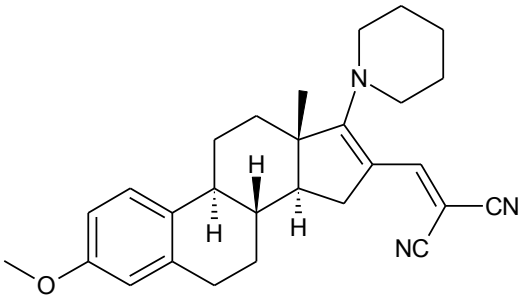
^{1}H NMR (CDCl3):

δ (ppm): 1.11(s, 3H), 1.45(m, 1H), 1.56(m, 2H), 1.69(m, 1H), 1.80-2.05(m, 8H), 1.91(m, 1H), 1.93(m, 1H), 2.29(m, 1H), 2.34(m, 1H), 2.43(m, 1H), 2.50(m, 1H), 2.88(m, 1H), 2.83-2.93(m, 2H), 3.78(s, 3H), 3.85(m, 4H), 4.25(m, 4H), 6.64(m, 1H), 6.72(m, 1H), 7.15(m, 1H), 8.62(s, 1H, N*H*).

^{13}C NMR (CDCl3):

δ (ppm): 15.4, 24.8, 26.0, 26.6, 27.3, 27.4, 30.1, 31.6, 36.3, 38.0, 43.4, 50.7, 50.9, 52.8, 53.01, 55.9, 56.9, 58.4, 102.3, 112.4, 114.5, 126.7, 131.9, 138.1, 155.4, 158.4, 180.4.

{[3-methoxy-17-piperidin-1-ylestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile



132b

A solution of piperidine (9.88 mmol, 0.98 mL) in EtOH (5 mL) was added dropwise to a suspension of {[17-chloro-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile (**131**) (2.47 mmol, 936 mg) in EtOH (20 mL). The mixture was left to stir in room temperature for 2 h.

The suspension was filtered under vacuum, washed with diethyl ether and dried to afford 897.7 mg of an orange solid.

mp: 214-216°C (dec.).

Rf: 0.71 (Hexane/Ethyl acetate 2:3)

Yield: (85%)

^{1}H NMR ($CDCl_3$):

δ (ppm): 1.04 (s, 3H), 1.42 (m, 1H), 1.58(m, 1H), 1.60 (m, 1H), 1.70(m, 2H), 1.76(m, 1H), 1.76(m, 2H), 1.77(m, 2H), 1.82 (m, 1H), 2.03(m, 1H), 2.18(m, 1H), 2.29(m, 1H), 2.40(dd, 1H), 2.42(m, 1H), 2.83(m, 1H), 3.01(dd, 1H), 3.54(m, 2H), 3.65(m, 2H), 3.78(s, 3H), 3.95(m, 1H), 6.65(d, 1H), 6.71(dd, 1H), 7.14(d, 1H), 7.21(s, 1H).

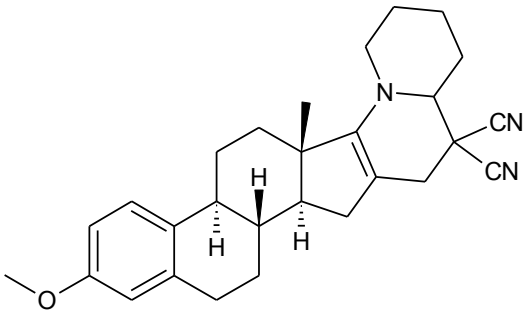
^{13}C NMR ($CDCl_3$):

δ (ppm): 16.4, 24.2, 27.2, 27.2, 27.4, 29.3, 30.2, 35.7, 38.0, 43.9, 48.9, 53.6, 53.6, 55.9, 59.7, 109.6, 112.5, 114.4, 118.4, 120.2, 126.5, 132.2, 138.6, 151.2, 158.4, 181.7.

Elemental analysis:

Anal. Calcd for $C_{28}H_{33}N_3O$: C, 78.65; H, 7.78; N, 9.83. Found: C, 78.3; H, 7.78; N, 9.67.

(4bS,6aS,14aS,14bR)-2-methoxy-6a-methyl-4b,5,6,6a,9,10,11,11a,13,14,14a,14b,15,16-tetradecahydronaphtho[2',1':4,5]indeno[2,1-c]quinolizine-12,12(8H)-dicarbonitrile



133b

{[3-methoxy-17-piperidin-1-ylestra-1(10),2,4,16-tetraen-16-yl]methylene} malononitrile (**132b**) 300mg was stirred in preheated oil bath at 230°C for 30 minutes. The reaction was monitored by TLC in every 10 minutes.

The crude product was purified by column chromatography on silica gel (dichloromethane) to afford 160 mg of the diastereomers mixture as light yellow solid.

mp: 180-182°C

Rf: 0.72, 0.73 (dichloromethane)

Yield: 54%

^{1}H NMR ($CDCl_3$):

δ (ppm): 0.99(s, 3H), 1.01(s, 3H), 1.41(m, 1H), 1.42(m, 1H), 1.49(m, 1H), 1.52-1.73(m, 2H), 1.55(m, 1H), 1.58(m, 1H), 1.59(m, 1H), 1.65(m, 1H), 1.70(m, 1H), 1.72(m, 1H), 1.80(m, 1H), 1.80(m, 1H), 1.86(m, 1H), 1.88(dd, 1H), 1.89(m, 1H), 1.95(m, 1H), 1.98(m, 1H), 1.98(dd, 1H), 2.05(dd, 1H), 2.10(m, 1H), 2.10(m, 1H) 2.17(dd, 1H), 2.18(m, 1H), 2.24(m, 1H), 2.27(m, 1H), 2.34(m, 1H), 2.35(m, 1H), 2.54(m, 1H), 2.57(m, 1H), 2.68(d, 1H), 2.78(d, 1H), 2.84(d, 1H), 2.91(d, 1H), 2.81-2.95(m, 2H), 2.98(dd, 1H), 3.08(dd, 1H), 3.78(s, 3H), 3.78(m, 1H), 3.81(m, 1H), 6.64(d, 1H), 6.71(dd, 1H), 7.16(d, 1H),

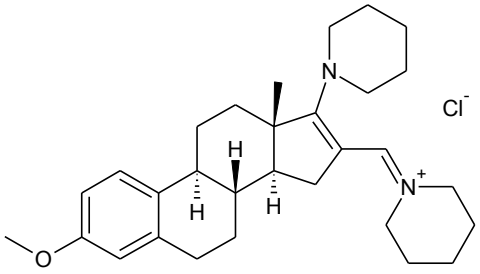
^{13}C NMR ($CDCl_3$):

δ (ppm): 16.8, 17.3, 23.9, 24.6, 25.6, 25.8, 27.1, 27.7, 27.8, 27.9, 28.2, 29.4, 30.3, 33.6, 35.6, 36.2, 36.3, 37.4, 37.5, 37.9, 38.6, 44.3, 44.4, 47.1, 48.8, 49.5, 50.1, 53.4, 55.9, 56.1, 61.7, 62.5, 102.6, 103.9, 112.1, 112.2, 114.4, 114.5, 115.0, 115.2, 116.1, 116.2, 126.6, 133.0, 133.2, 138.6, 153.8, 154.6, 158.2.

Elemental analysis:

Anal. Calcd for $C_{28}H_{33}N_3O$: C, 78.65; H, 7.78; N, 9.83. Found: C, 78.49; H, 7.84; N, 9.66.

3-methoxy-16-(piperidinium-1-ylidenemethyl)-17-piperidin-1-ylestra-1(10),2,4,16-tetraene chloride



129b

To a solution of 17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16carbaldehyde (**127**) (0.91 mmol, 0.3 g) in acetonitrile anhydrous (5 mL), was added dropwise a solution of freshly distilled pyrrolidine (4.5 mmol, 0.47 mL), in acetonitrile anhydrous (3 mL). The reaction was left to stir for 5 hours in room temperature under argon atmosphere.

The solution was evaporated by in vacuum till dryness. 30mL of H_2O were added and extracted 3 times with dichloromethane (3 x 20mL). The organic phase was dried over $MgSO_4$, filtered and evaporated in vacuum to give 495mg of a red/yellow oil. This was crystallized by ether to give 398 mg of an orange solid.

NMR spectroscopic data showed both 3-methoxy-16-(piperidinium-1-ylidenemethyl)-17-piperidin-1-ylestra-1(10),2,4,16-tetraene chloride (**129b**) and 3-methoxy-17-piperidin-1-ylestra-1(10),2,4,16-tetraene-16-carbaldehyde (**128b**), in a 7:3 ratio.

mp: 62-80 °C

Rf: 0.31, 0.79 (ethyl acetate/methanol, 1:1)

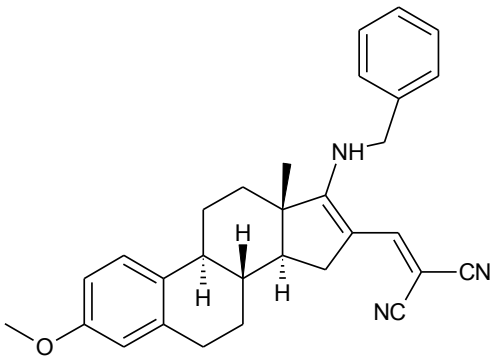
^{1}H NMR (DMSO):

δ (ppm): 1.03(s, 3H), 1.50-1.75(m, 12H), 1.56(m, 1H), 1.75(m, 1H), 1.82(m, 1H), 2.30(m, 1H), 2.25(m, 1H), 2.26(m, 1H), 2.77(m, 1H), 2.75-2.89(m, 2H), 3.41(m, 4H), 3.57(m,4H), 3.69(s, 3H), 6.63(d, 1H), 6.70(dd, 1H), 7.16(d, 1H), 7.55(s, 1H).

^{13}C NMR (DMSO):

δ (ppm): 15.6, 22.5, 23.2, 26.5, 26.6, 26.6, 26.7, 28.8, 29.4, 34.3, 37.3, 43.0, 47.8, 52.2, 52.2, 55.4, 99.2, 112.1, 113.9, 126.5, 131.9, 137.7, 157.7, 189.6, 153.7.

{[17-(benzylamino)-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile



132c

A solution of benzylamine (5.84 mmol, 0.64 mL) in EtOH (5 mL) was added dropwise to a suspension of {[17-chloro-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}malononitrile (**131**) (2.92 mmol, 1.11 g) in EtOH (10 mL). The mixture was left to stir in room temperature for 2 h.

The suspension was filtered under vacuum to afford 910 mg of a yellow shiny powder

mp: 224-226.5 °C(dec.)

Yield: 70%

Rf: 0.13 (ethyl acetate)

^{1}HNMR ($CDCl_3$):

δ(ppm): 1.06(s, 3H), 1.53(m, 1H), 1.60(m, 1H), 1.62(m, 1H), 1.91(m, 1H), 1.92(m, 1H), 2.10(m, 1H), 2.23(m, 1H), 2.27(m, 1H), 2.31(dd, 1H), 2.45(m, 1H), 2.57(dd, 1H), 2.85-2.93(m, 2H), 3.76(s, 3H), 5.16(s, 1H), 5.66(s, 1H), 6.63(d, 1H), 6.68(dd, 1H), 7.07(d, 1H), 7.09(m, 2H), 7.26(m, 1H), 7.35(m, 2H), 7.37(s, 1H).

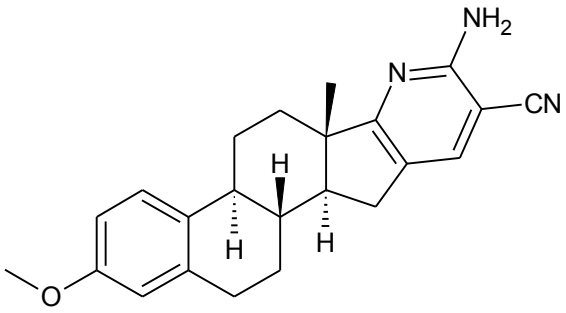
^{13}CNMR ($CDCl_3$):

δ(ppm): 16.0, 26.4, 27.0, 29.2, 29.4, 35.6, 37.0, 43.1, 49.2, 49.4, 54.6, 55.2, 100.0, 111.6, 113.9, 114.2, 114.2, 117.4, 125.9, 135.9, 125.5, 125.9, 128.8, 127.1, 137.5, 141.8, 157.6, 165.1.

Elemental analysis:

Anal. Calcd for $C_{30}H_{31}N_3O$: C, 80.14; H, 6.95; N, 9.35. Found: C, 79.64; H, 6.99; N, 9.15.

(4bS,6aS,11aS,11bR)-8-amino-2-methoxy-6a-methyl-5,6,6a,11,11a,11b,12,13-octahydro-4bH-naphtho[2',1':4,5]indeno[1,2-b]pyridine-9-carbonitrile



138

{[17-(benzylamino)-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene} malononitrile (**132c**) 630.69mg, was stirred in the preheated oil bath at 235 °C for 30 minutes The reaction was monitored by thin layer chromatography (TLC) in every 10 minutes.

The crude product was purified by column chromatography (hexane/ethyl acetate 4:1) to afford 123 mg of a yellow powder.

mp: 273-275 °C

Rf: 0.14 (hexane/ethyl acetate 4:1)

Yield: 14%

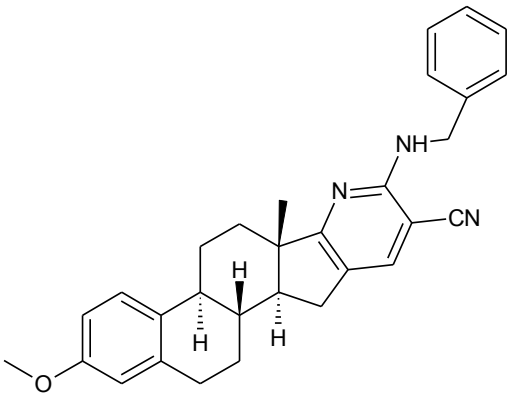
^{1}H NMR ($CDCl_3$):

δ(ppm): 0.96(s, 3H), 1.50(m, 1H), 1.70(m, 2H), 1.72(m, 1H), 1.80(m, 1H), 1.99(m, 1H), 2.24(m, 1H), 2.35(m, 1H), 2.47(m, 1H), 2.47(dd, 1H), 2.73(dd, 1H), 2.83-3.02(m, 2H), 3.79(s, 3H), 5.10(s, 2H, NH_2) 6.66(d, 1H), 6.73(dd, 1H), 7.23(d, 1H), 7.48(s, 1H).

^{13}C NMR ($CDCl_3$):

δ(ppm): 17.9, 26.9, 28.1, 29.7, 30.3, 33.9, 38.2, 44.9, 47.2, 55.3, 55.9, 88.0, 112.2, 114.6, 118.4, 126.4, 126.8, 132.9, 137.3, 138.4, 158.2, 160.0, 178.6.

(4bS,6aS,11aS,11bR)-8-(benzylamino)-2-methoxy-6a-methyl-5,6,6a,11,11a,11b,12,13-octahydro-4bH-naphtho[2',1':4,5]indeno[1,2-b]pyridine-9-carbonitrile



137

{[17-(benzylamino)-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene} malononitrile (**132c**) 630.69mg, was stirred in the preheated oil bath at 235 °C for 30 minutes The reaction was monitored by thin layer chromatography (TLC) in every 10 minutes.

The crude product was purified by column chromatography (hexane/ethyl acetate 4:1) to afford 44 mg of a yellow oil.

mp: 209.2-211.2 °C

Rf: 0.6 (hexane/ethyl acetate, 4:1)

Yield: 7%

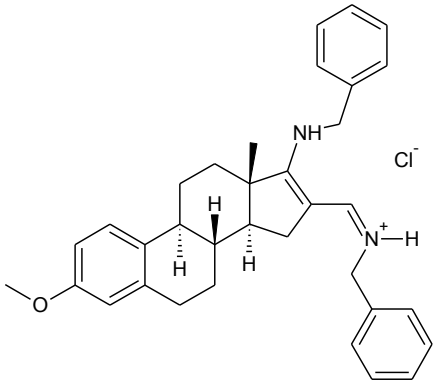
^{1}H NMR ($CDCl_3$):

δ(ppm): 0.95(s, 3H), 1.50(m, 1H), 1.69(m, 2H), 1.72(m, 1H), 1.79(m, 1H), 1.98(m, 1H), 2.28(m, 1H), 2.35(m, 1H), 2.45(dd, 1H), 2.46(m, 1H), 2.70(dd, 1H), 2.84-3.02(m, 2H), 3.79(s, 3H), 4.74(d, 2H, CH_2-Ph), 5.42(t, 1H, N*H*), 6.66(d, 1H), 6.74(dd, 1H), 7.24(d, 1H), 7.27(m, 1H), 7.34(m, 2H), 7.40(m, 2H), 7.45(s, 1H).

^{13}C NMR ($CDCl_3$):

δ(ppm): 17.8, 26.9, 28.1, 29.7, 30.3, 33.9, 38.3, 45.1, 46.0, 47.3, 55.4, 55.9, 87.8, 112.2, 114.5, 118.9, 126.4, 126.8, 128.0, 128.8, 129.2, 133.1, 137.4, 138.5, 139.9, 158.2, 159.3, 178.1.

N-{(1Z)-[17-(benzylamino)-3-methoxyestra-1(10),2,4,16-tetraen-16-yl]methylene}(phenyl)methanaminium chloride



129c

To a solution of 17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16carbaldehyde (**127**) (1.5 mmol, 0.5 mg) in EtOH 3 (mL) and molecular sieves (3A, 0.4-0.8mm), was added dropwise benzylamine (1.5 mmol, 0.16 mL) and the reaction was left to stir overnight.

The brown suspension was filtered under vacuum and washed with diethyl ether to 380.8 mg of a yellow powder

Yield: 47%

mp: 160-169 °C

Rf: 0.80 (ethyl acetate/methanol, 1:1)

Mass Spectrum: [491(M+H)]

^{1}H NMR (DMSO):

δ(ppm): 1.03(s, 3H), 1.39(m, 1H), 1.49(m, 1H), 1.54(m, 1H), 1.62(m, 1H), 1.63(m, 1H), 1.81(m, 1H), 2.04(dd, 1H), 2.25(m, 1H), 2.38(m, 1H), 2.44(m, 1H), 2.51(dd, 1H), 2.72-2.92(m, 2H), 3.69(s, 3H), 4.45(d, 2H, CH_2N), 4.82(d, 2H, CH_2N), 6.62(d, 1H), 6.70(dd, 1H), 7.19(d, 1H), 7.25-7.55(m, 10H, Ar), 7.87(d, 1H, C*H*=N), 9.33(m, 1H, NH^+), 9.81(m, 1H, N*H*).

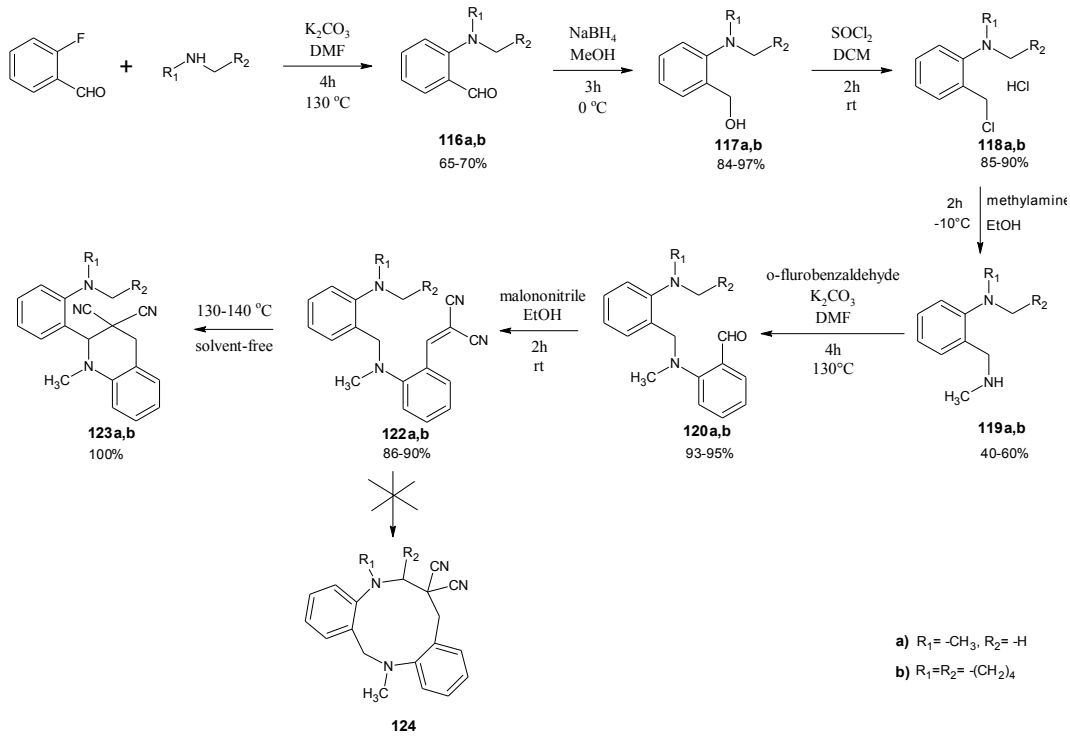
^{13}C NMR (DMSO):

δ(ppm): 16.9, 25.6, 26.6, 28.5, 29.0, 32.4, 36.8, 42.9, 48.4, 49.4, 50.4, 52.3, 54.9, 99.0, 111.5, 113.5, 126.0, 126.8, 127.6, 127.7, 127.7, 128.6, 128.9, 131.5, 135.3, 137.3, 137.3, 155.9, 157.2, 180.9.

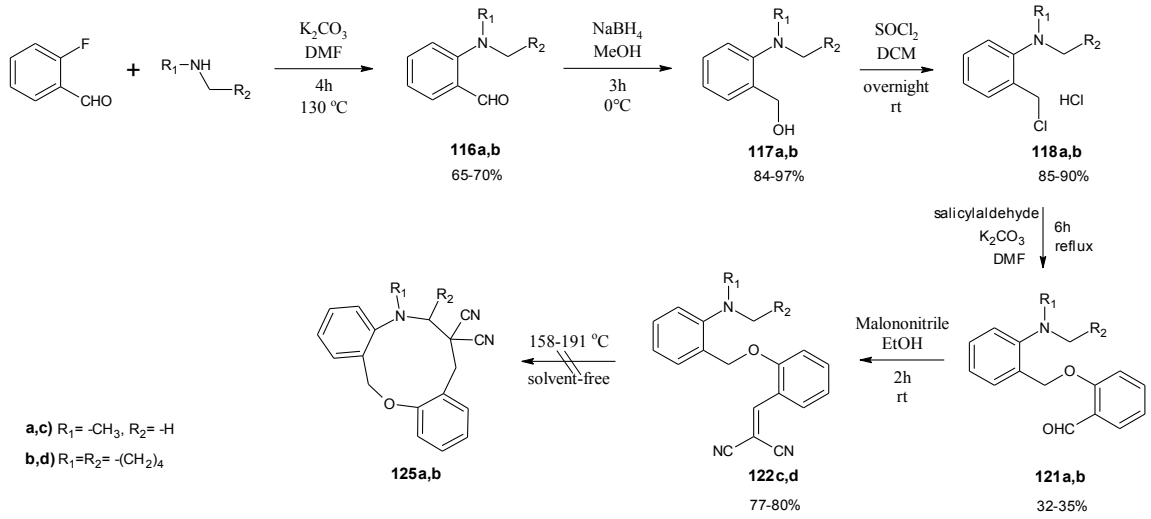
4. Results and discussion

4.1 Extension of the tert-amino effect to biaryl compounds, synthesis of fused ring systems

Our aim was to study on the one hand, whether *tert*-amino effect can operate among biaryl derivatives with the *ortho*-positioned *tert*-amino and vinyl groups on aryl rings linked with a saturated chain (**Figure 38**). The general scheme of synthesis is shown in **Figure 45**:



A



B

Fig. 45: Scheme of **122** model compound synthesis.

4.1.1 Synthesis of chloro-derivatives

Two series of *ortho*-vinyl *tert*-aniline compounds were synthesized for studying *tert*-amino effect cyclizations, expected to lead to fused heterocycles products. Compounds **118** were prepared *via* three consecutive reaction steps, as shown in **Figure 46**.

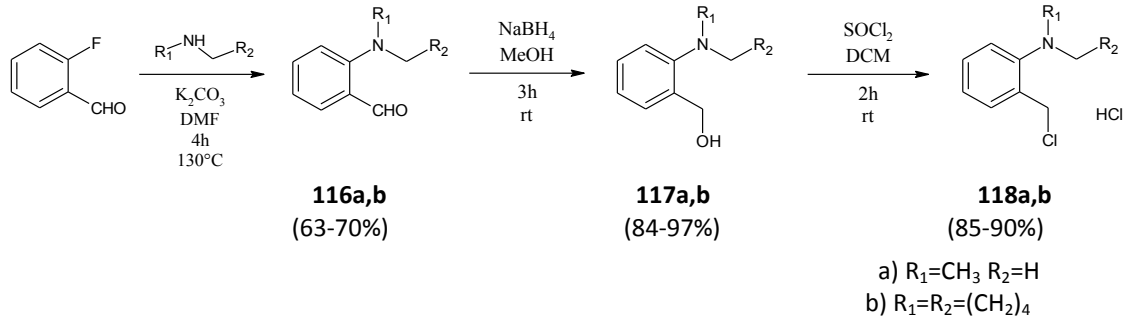


Fig. 46: Synthesis of **118a,b** chloro-derivatives.

The synthesis started from the commercially available *ortho*-fluorobenzaldehyde; the first step consisted in a substitution reaction, using two secondary amines, dimethylamine and piperidine respectively, to achieve compounds **116a**,**b** in good yields[75]. Analytically pure products were obtained by fractionary distillation under reduced pressure.

The second step involved a reduction reaction of compounds **116a**,**b** by use of sodium borohydride ($NaBH_4$) in methanol at room temperature[75], which led to the formation of compounds **117a**,**b**, purified by column chromatography.

The last step of this reaction line is the substitution reaction of hydroxyl groups of compound **117a**,**b** by thionyl chloride in dichloromethane, which resulted in the formation of the chloro-derivatives hydrochloride **118a**,**b**[75].

^{1}HNMR spectra of compounds **117a**,**b** and **118a**,**b** showed the same signals; thus, identification of these products was obtained by ^{13}C NMR measurements; the characteristic peak at 40ppm of the carbon bearing the chloro atom instead of the peak at 60 ppm of the carbon linked to the hydroxyl group, confirmed the structures of these products (**Figure 47**).

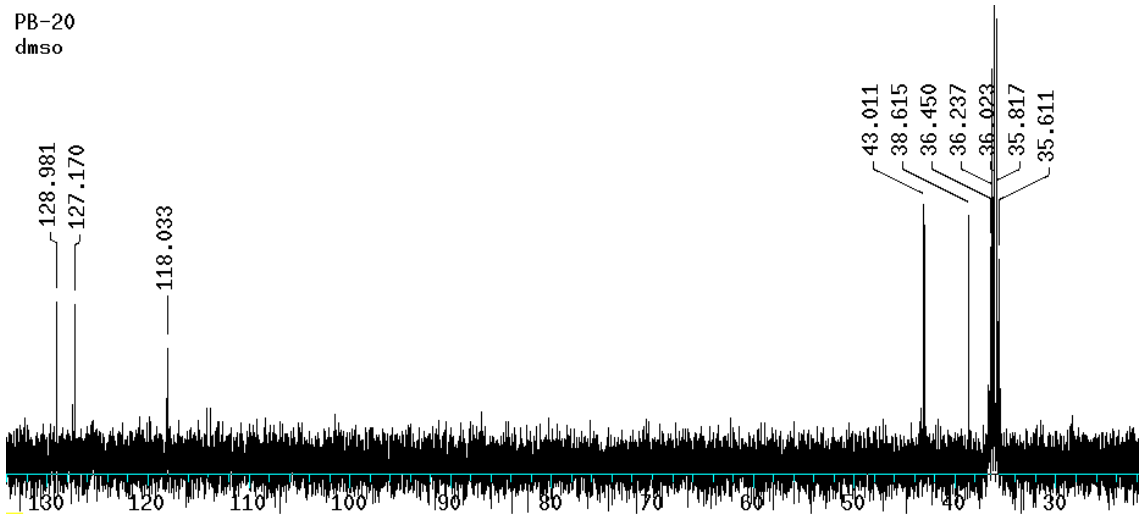


Fig. 47: ^{13}C NMR spectrum of chloro-derivatives intermediate.

4.1.2 Synthesis of aldehyde intermediates

Starting from the chloro-derivatives **118a**,**b**, two different ways of synthesis were followed, as shown in **Figure 48**:

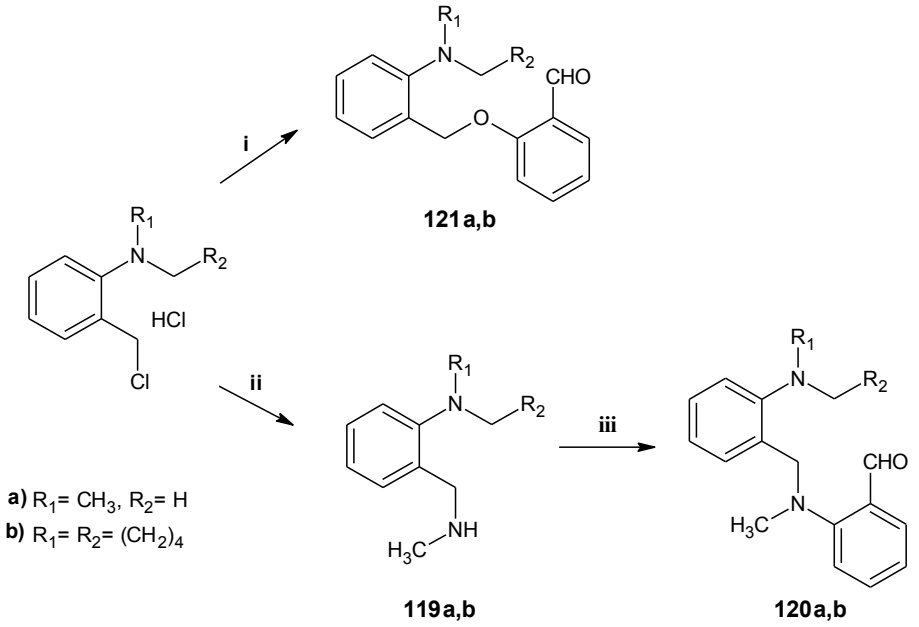


Figure 48: Synthesis of aldehyde intermidiates.
i: salicylaldehyde, DMF, K_2CO_3, 6h, reflux; **ii**: methylamine, EtOH, 2h, room temperature;
iii: *o*-fluorobenzaldehyde, K_2CO_3, DMF.

In the first case (**i**) the synthesis of the bridged biaryl compounds with a CH_2-O chain was considered; products **116a**,**b** were obtained through a substitution step using salicylaldehyde as reagent in basic conditions[76]. This reaction consisted in to two consecutive steps: the salicylaldehyde salt formation and the subsequent substitution on the carbon bearing the chloro atom, to achieve compound **116a**,**b**. Purification was carried out by flash master chromatography in case of compound **116a**, while compound **116b** was used crude for the next step.

In case of compounds **120a**,**b** synthesis, the chloro derivatives 118a,b are reacted with 40wt% aqueous methylamine in ethanol (**ii**) to afford compounds **119a**,**b**; subsequently they undergo substitution reaction with *o*-fluorobenzaldehyde in basic condition. Finally, both piperidine and dimethylamine derivatives, were

purified by fractionary distillation under reduced pressure to afford the aimed methylamino-*N*-methyl bridged aldehydes compounds (**120a**,**b**).

4.1.3 Synthesis of vinyl compounds

Synthesis of vinyl compounds **122a**,**b** and **122c**,**d** were carried out *via* Knoevenagel condensation[77] reaction under mild conditions (**Figure 49**): malononitrile was used as the active methylene agent in ethanol at room temperature in the presence of piperidine as catalyst.

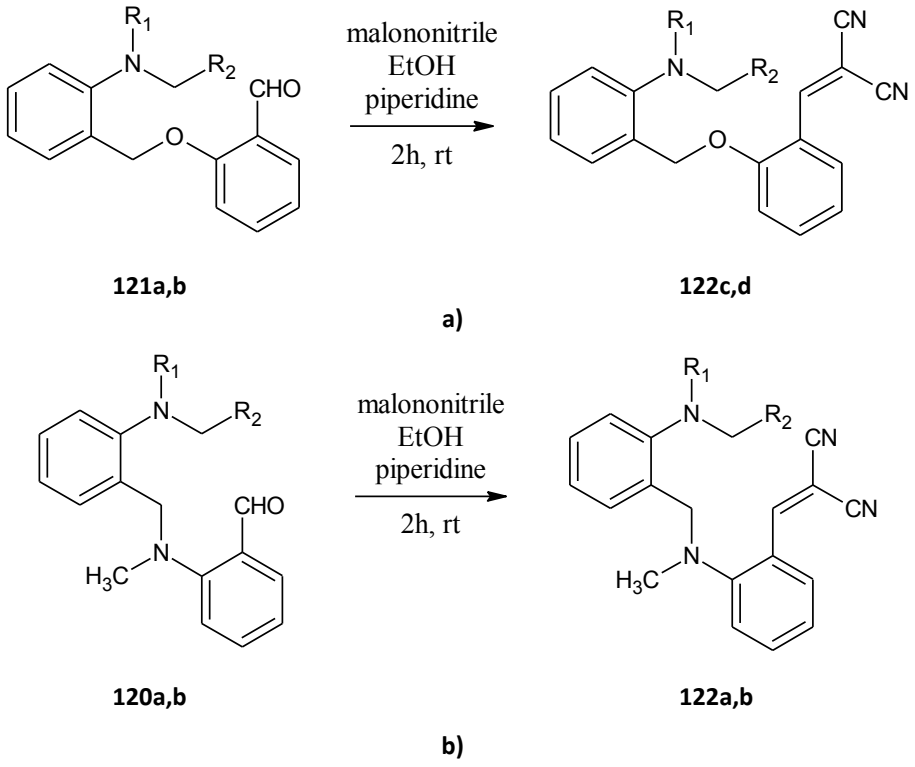
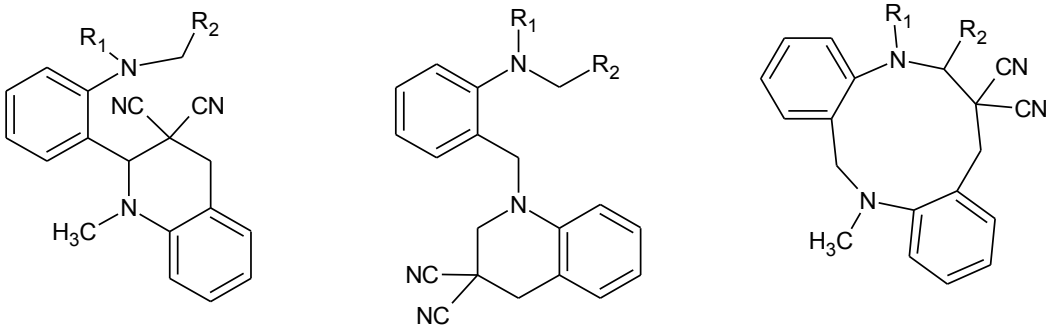


Figure 49: Syntheses of **117a**,**b**, **117c**,**d** vinyl derivatives *via* Knoevenagel condensation.

The structures of the vinyl compounds were confirmed by ^{1}H and ^{13}C NMR measurements and by elementary analysis; the ^{1}H NMR spectra showed the specific peak between 7.00-7.60 ppm, of the hydrogen belonged to the α-carbon in the vinyl moiety.

4.1.4 Studies on *tert*-amino effect cyclization

The vinyl compounds **1227a**,**b** may a priori cyclize in three different pathways, either with involvement of methylene-carbon, N-methyl-carbon, or the α-carbon of the *sec*-amino group attached to the other phenyl ring (leading to compounds **123a**,**b**, **124a**,**b**, or **126a**,**b**, respectively, as shown in **Figure 50**. Not fully unexpected, cyclization, following our solvent-free protocol, exclusively took place *via* the first route, affording the products with six-membered **123a**,**b** ring in excellent yield.



123a,**b** **126a**,**b** **124a**,**b**

Fig.50: Possible cyclization pathways of compounds **122a**,**b**.

Tert-amino effect cyclizations often require higher temperatures or longer reaction times. Therefore, experiments on the thermal isomerisation of vinyl compounds **122a**,**b** were carried out in a microwave instrument, what seemed feasible with regard to the rate enhancements and yields frequently observed in the literature. Heating under solvent-free conditions, irradiation of **122a** (at 130°C, for 10 min.) resulted in the formation of 100% of fused product **123a** (**Figure 51a**), as well as for the cyclized product **123b** starting from compound **122b** (**Figure 51b**).

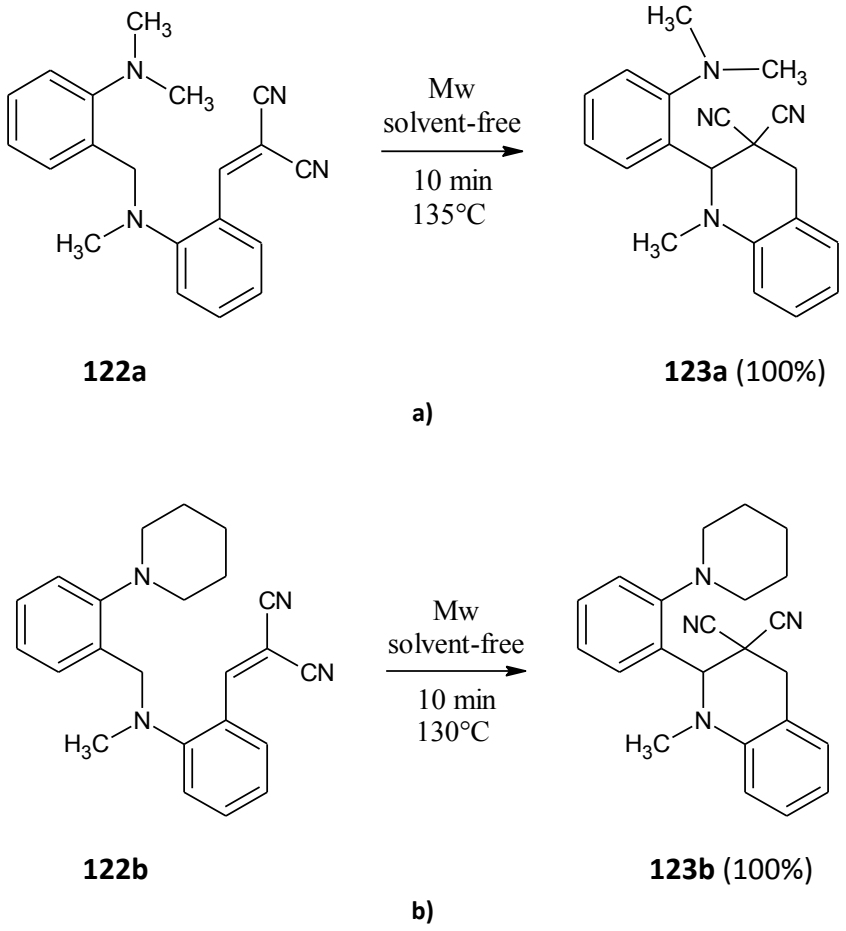


Fig. 51: Formation of fused ring systems *via tert*-amino effect cyclizations.

The cyclization was well monitored by NMR spectroscopy; the NMR signals of the methylene hydrogen adjacent to the nitrogen and the carbon bearing the electron-withdrawing groups in the six-membered products are characteristic of the ring closure. As an example, characteristic NMR data of **122a** and **122b** vinyl compounds in comparison with their cyclic derivatives **123a** and **123b** counterparts are the following (in ppm, $CDCl_3$/DMSO-d_6 for **122a**): i) -CH=C(CN)$_2$ (vinyl compounds) – ^{1}H: 7.31 (**122a**) / 7.58 (**122b**), ^{13}C: 160.4 (**122a**) / 162.4 (**122b**), ii) -CH_2-$C(CN)_2$-CHR_1- (cyclic products) – ^{1}H: 3.40 and 3.52 (**123a**) / 3.38 and 3.64 (**123b**); ^{13}C: 35.9 (**123a**) / 40.1 (**123b**). Additionally, the appearance of these signals in the NMR spectra is accompanied by the disappearance of the signal related to the hydrogen belonging to the α-carbon of the vinyl moiety.

Thermochemical studies of compounds **122a**,**b** were carried out. Previous differential scanning calorimetry (DSC) study of *tert*-amino effect[78] showed the

applicability of this method for detection of the ring closure. Calculations (PM3, DFT) and experimental data (DSC) suggested that the cyclization is an exothermic process that also could be well detected on the DSC curves. Differential scanning calorimetry measurements complemented by parallel thermal gravimetry (between room temperature and 500 °C) were run for vinyl compounds **122a**,**b** (**Figure 52**) to assess whether cyclization could be monitored with this method for novel scaffolds.

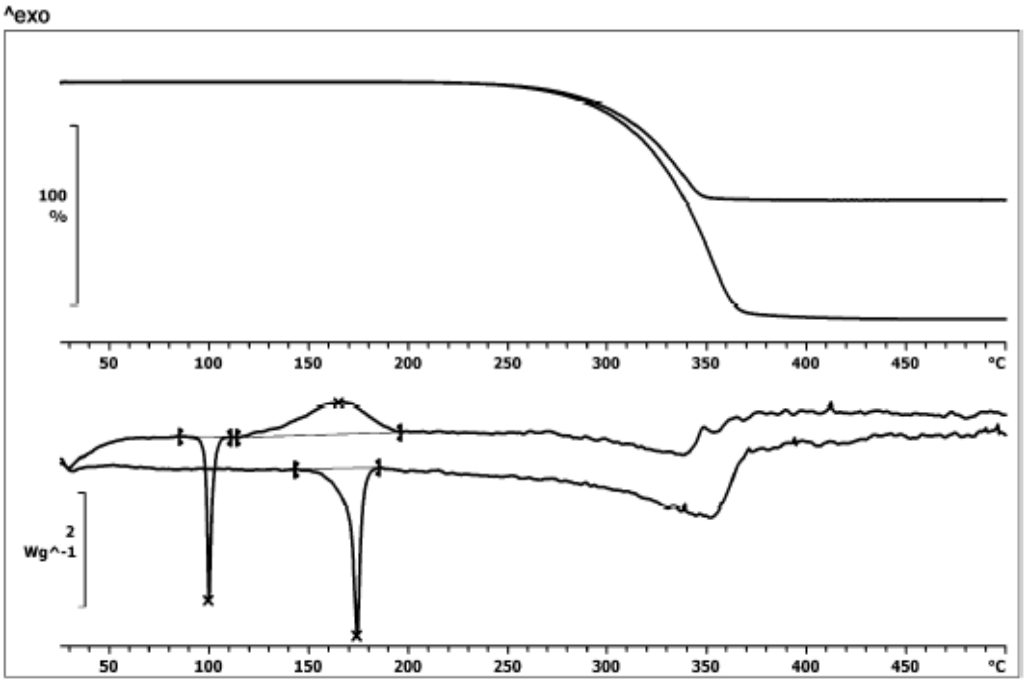


Fig. 52: The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of compounds **122a 123a**.

In the temperature range of the endothermic and exothermic peaks, no significant weight loss – corresponding to decomposition – was observed. The peak related to the melting points could be identified as endothermic peak at 96.3 °C. The second peak observed, the exothermic one, might indicate that cyclization did take place upon heating; therefore, it corresponds to the temperature of ring closure.

TLC monitoring and ^{1}H NMR (**Figure 53**) spectrum recorded from the sample following the DSC experiment confirmed that thermal ring closure occurred in the case of **122a**,**b**.

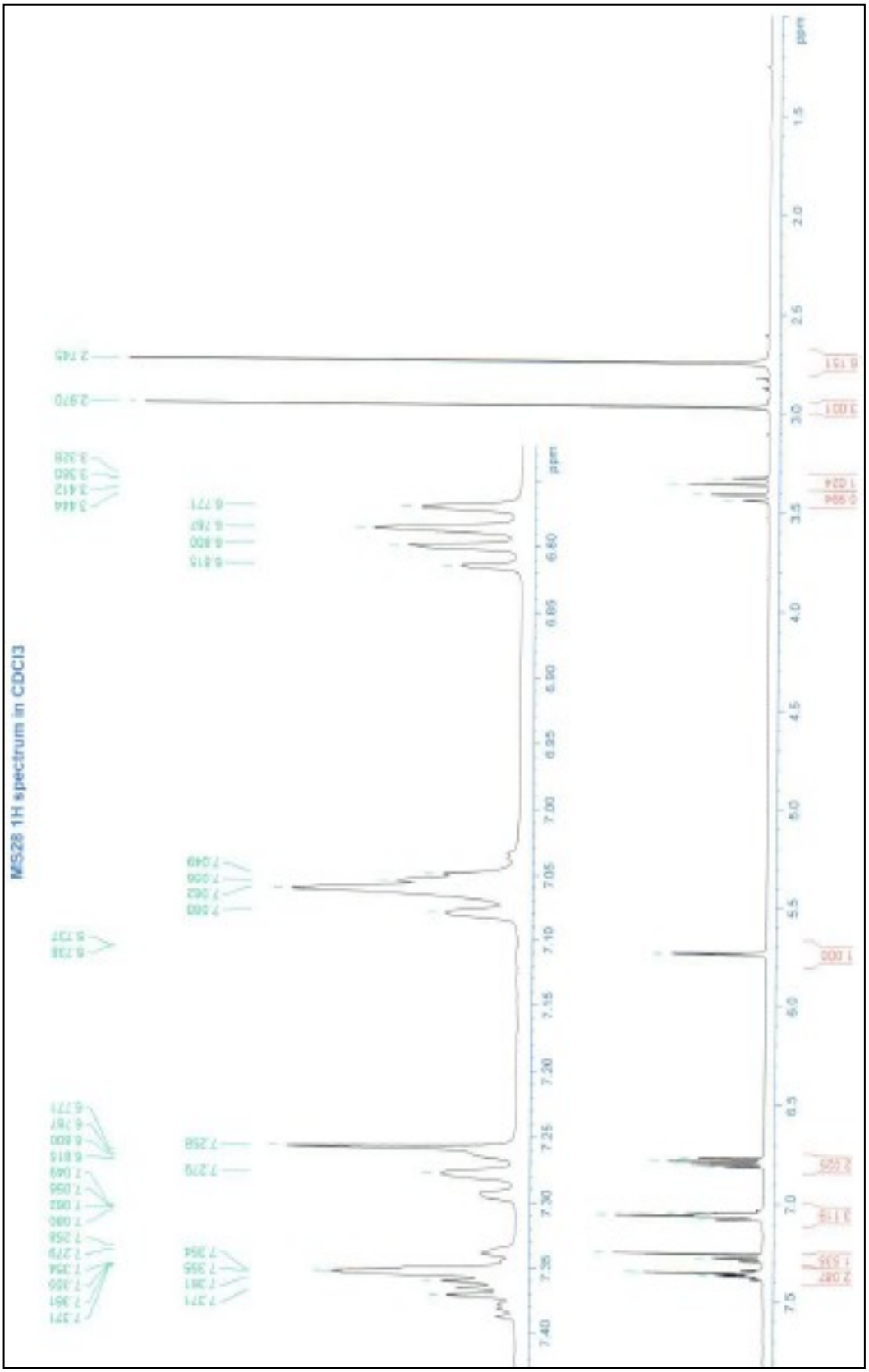


Fig. 53: ^{1}H NMR spectrum of cyclized compound **123a**

To avoid a possible rearrangement of the already formed six-membered ring at higher temperature, a DSC measurement of this compound was studied. In **Figure 52**, the down curve shows an endothermic peak, corresponding to the melting point of the cyclized compound **123a**, but no other important peak was observed, until the total decomposition of the compound over 300°C.

Table 1. Enthalpies of reaction determined by differential scanning calorimetry (DSC) (ΔH_r) and by calculation ($\Delta\Delta H_f = \Delta H_{f\,pr} - \Delta H_{f\,st}$)

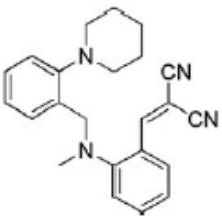
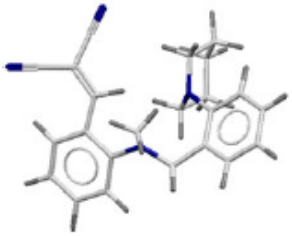
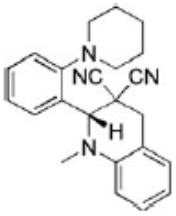
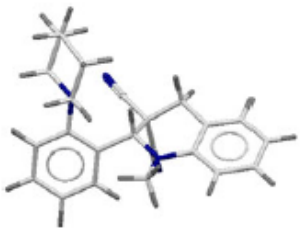
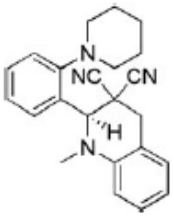
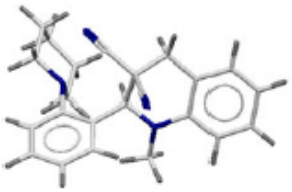
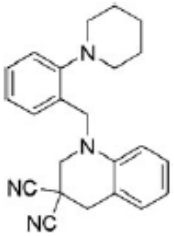
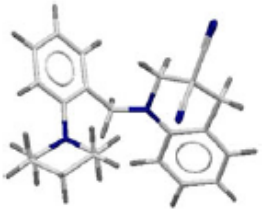
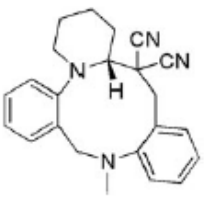
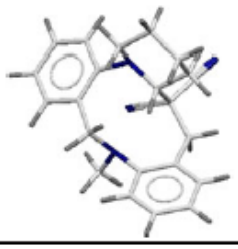
Compound	Structure	Optimized structure	T_m (°C)[a]	T_r (°C)[b]	ΔH_r (kcal/mol)[c]	$\Delta\Delta H_f$ (kcal/mol)[d]
7b			96.3	NA	NA	NA
8b-*R*			169.7	161.4	−11.26	−15.15
8b-*S*			169.7	161.4	−11.26	−15.13
13			NA	NA	NA	−14.76
14-*R*			NA	NA	NA	4.98

Table 1. *(Continued)*

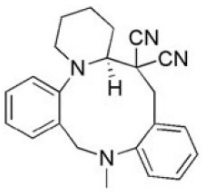
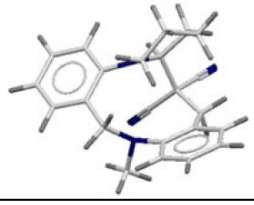
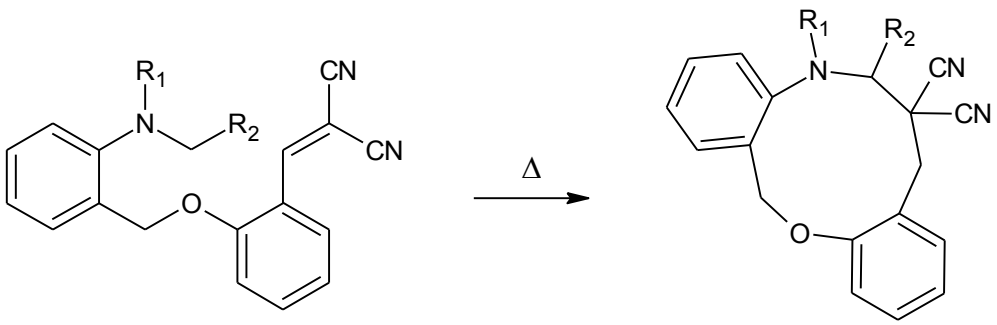
Compound	Structure	Optimized structure	T_m (°C)[a]	T_r (°C)[b]	ΔH_r (kcal/mol)[c]	$\Delta\Delta H_f$ (kcal/mol)[d]
14-*S*			NA	NA	NA	6.74

Table 10: Enthalpies of reaction determined by differential scanning calorimetry (DSC) (ΔHr) and by calculation ($\Delta\Delta H_f = \Delta H_{f\ pr} - \Delta H_{f\ st}$)

Integrals of the areas under the exothermic peaks (related to cyclization) provide the enthalpy changes of the reactions. These experimental enthalpy changes together with the calculated ones are listed in **Table 10**. 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). Also, the two potential alternative products of **122a**,**b** (with N-methyl: **126a**,**b**, and with *ortho*' *tert*-amino moiety: **124a**,**b**) were included as well.

This fused compounds prepared *via tert*-amino effect cyclizations represent the first members of unpublished ring systems.

Concerning the vinyl compounds **122c,d** in which the aromatic rings are bridged with a CH_2-O chain only the ten membered ring formation was expected to take place, in both dimethylamine and piperidine derivatives (**Figure 54**, **125c,d**).



122c,d **125c,d**

Fig.54: Possible cyclization pathway of compounds **122c,d**.

DSC measurement of vinyl compounds **122c,d** showed the endothermic peaks, corresponding to the their melting point and a possible ring closure reaction, which might have taken place in temperature range of 182-191 °C for the dimethylamine compound and between 207-216 °C for the piperidine derivative (**Figure 55**).

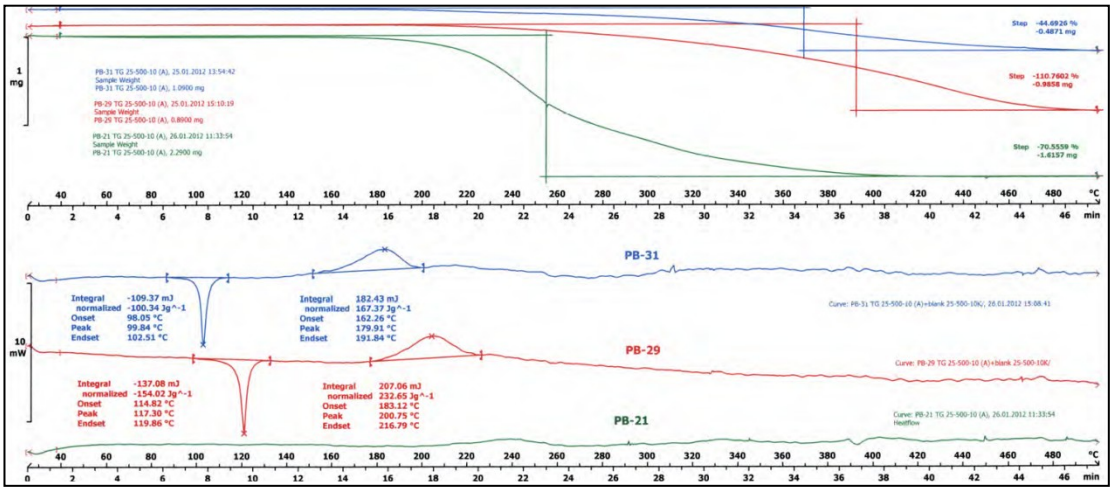


Fig. 55: The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of compounds **122c,d**.

Many preparative experiments using microwave conditions or preheated oil bath, have been carried out to obtain the aimed products **125c**,**d**; different reaction conditions have been use, as summarized in **Table 11**.

Conversely of what the DSC measurements have shown, unfortunately in all of these experiments only decomposition was observed and the corresponding cyclized products **125c,d** could not be isolated, for both dimethylamine and piperidine derivatives.

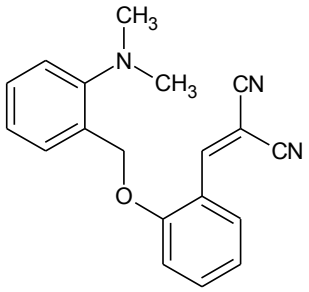
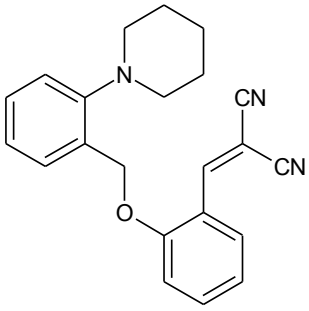
	Solvent	Temperature	Time	Catalyst
	DMSO	50°C	1 hour	/
	DMSO	50°C	5 hour	/
	DMSO	75°C	30 min	/
	DMSO	75°C	1 hour	/
	DMSO	100°C	15 min	/
	DMSO	100°C	30 min	/
	DMSO	125°C	30 min	/
	DMSO	150°C	1 hour	/
	/	75°C	30min	/
	/	75°C	1h	/
	/	100°C	30min	/
	/	120°C	30min	/
	/	150°C	30 min	/
	/	200°C	2 min	/
	/	120°C	2 h	Al_2O_3
	Acetonitrile	60°C	2 h	$Gd(Tf)_3$

Table 11: Reaction conditions.

4.2 Extension of the tert-amino effect steroid scaffolds

The starting compound used in this project was 17-chloro-3-methoxyestra-1(10),2,4,16-tetraene-16-carbaldehyde **127** which has been previously prepared by chloroformylation of 3-methoxyestra-1(10),2,4-trien-17-one **126** under Vilsmeier-Haack conditions [79]. The whole synthetic pathway is shown in **Figure 56**:

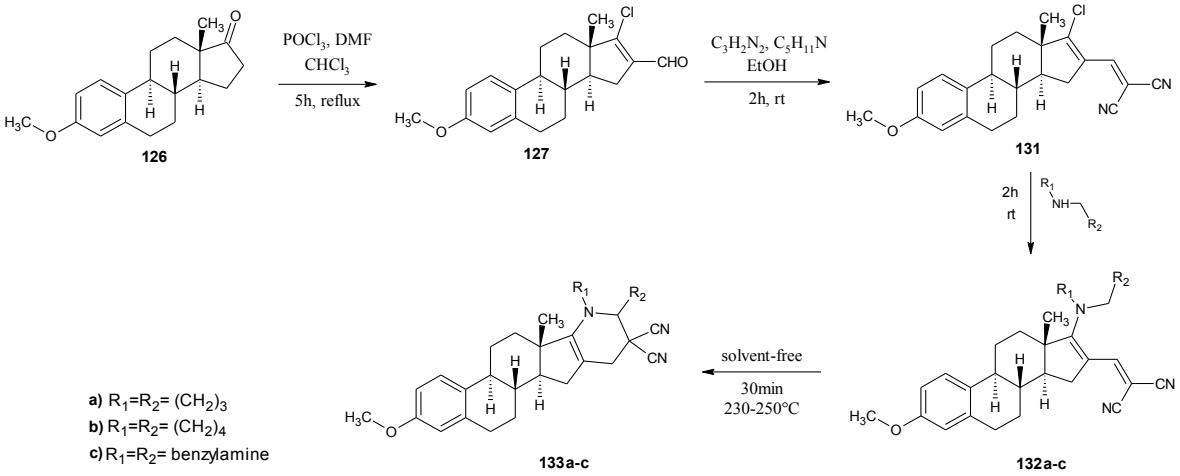


Fig. 56: synthetic route of the steroids model compounds to be studied.

In order to obtain compounds **132a-c** a previous pathway, consisted into two consecutive reactions, substitution step and subsequent Knoevenagel condensation, as showed in **Figure 57**:

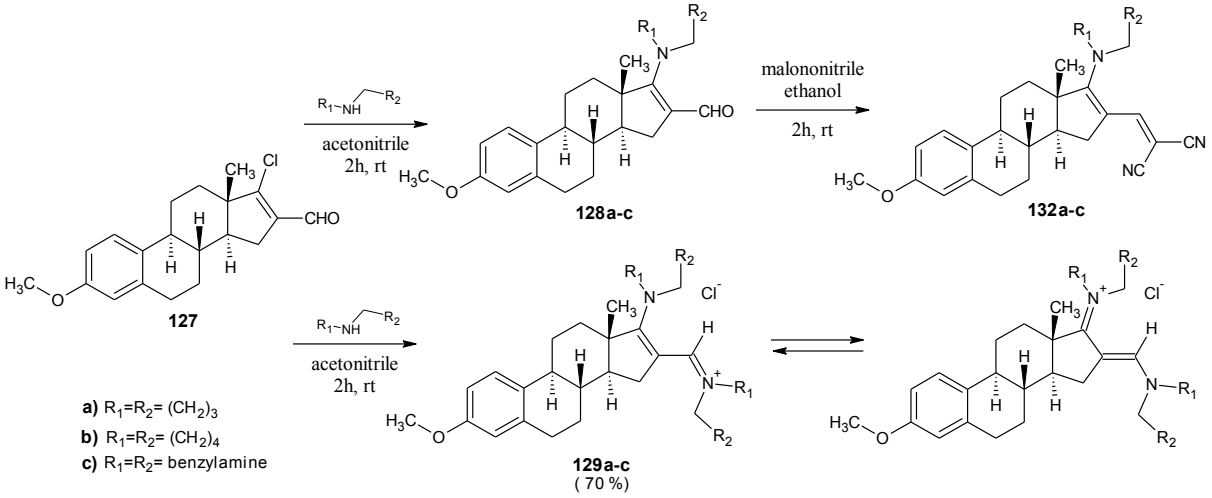


Fig. 57: Previous way of synthesis for compounds **132a-c**.

On the contrary, the first substitution step by the three different amines, in acetonitrile for 2 hours at room temperature[80-82], provided us a different result from the aimed products **128a-c**: the amines reacted with both chloro and aldehyde moieties to give, *bis*-pyrrolidine, *bis*-piperidine and *bis*-benzylamine products (in high yield) stable in mesomeric forms (compounds **129a-c**, **Figure 56**).

Therefore starting from compound **127**, we provided an alternative way, which consists in a former Knoevenagel condensation reaction with malononitrile[77], to give the corresponding compound **131**, followed by a latter substitution step[80-82], which leads to compounds **132a-c** (**Figure 58**).

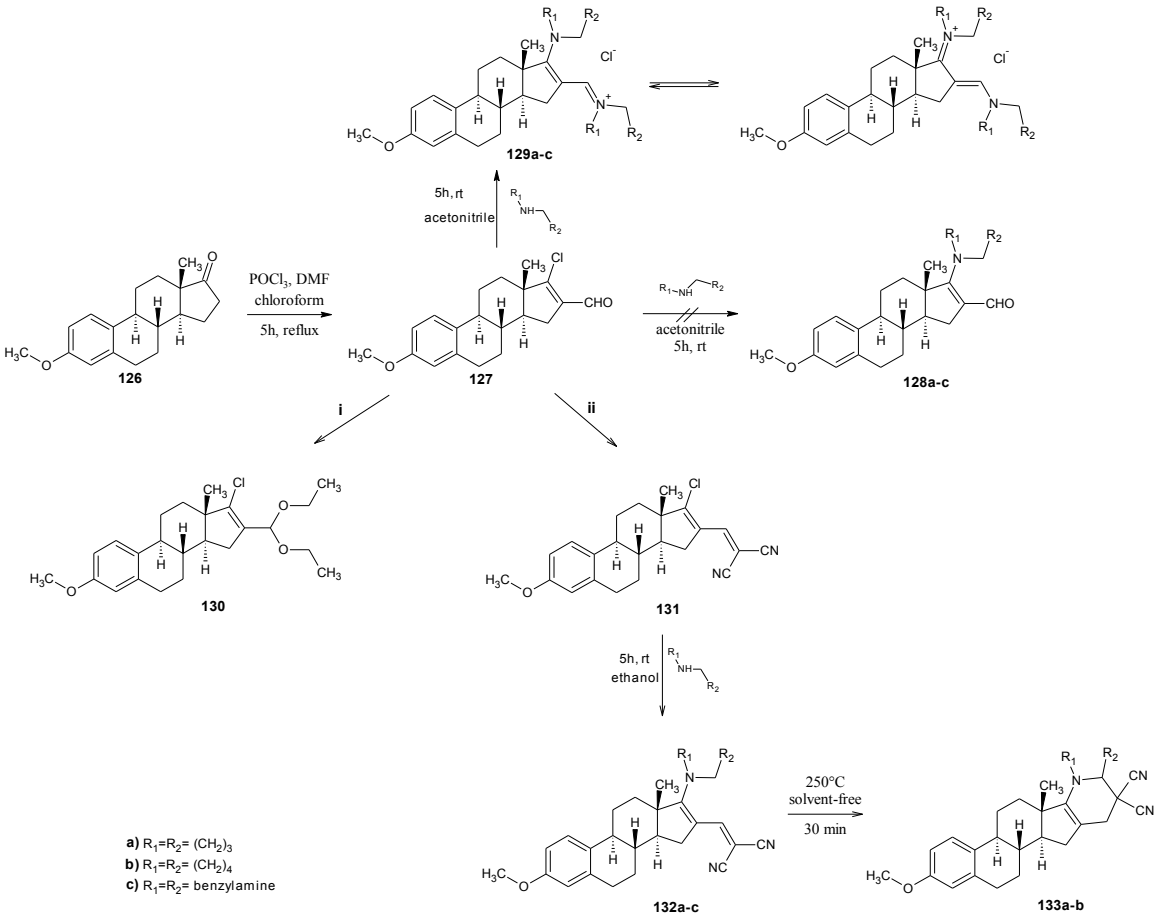


Fig.58: Synthetic route of the steroids model compounds to be studied.
i: malononitrile, piperidine (catalytic amount), ethanol, 2h, rt;
ii: malononitrile, piperidine (catalytic amount), *t*-butanol, 2h, rt.

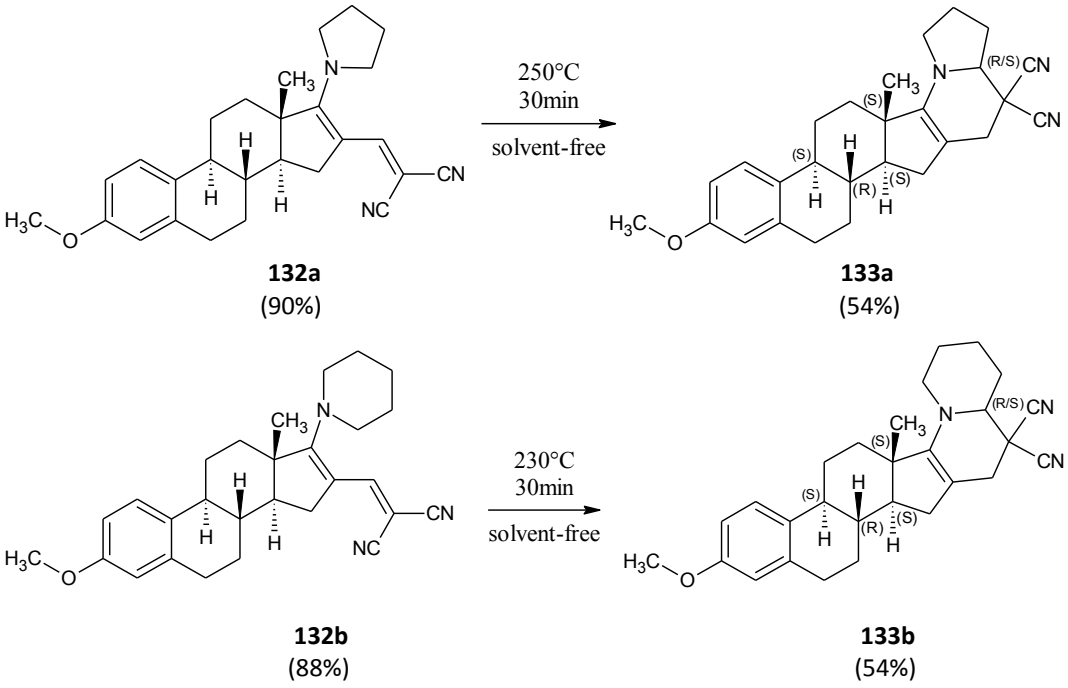
Moreover, it was noticed that synthesis of vinyl compounds derivatives using malononitrile, piperidine (catalyst) and ethanol, led to the formation of the side acetal product **130** in 50% yield (**Figure 58**, **i**). The structure of compound **130** was confirmed by NMR spectra and Mass spectra. To understand if solvent's properties were important during this knoevenagel condensation step, the reaction was repeated in the same reaction conditions, but by replacement of

ethanol with *t*-butanol (**Figure 58**, **ii**). The obtained results showed us the formation of the vinyl compound **131** in high yields (80-85%) confirming the influence of the solvent in this condensation reaction.

The last step in order to obtained the functionalized D-ring steroids, consisted in a substitution reaction of the chloro atom on the vinyl compound **131** with the secondary amine - pyrrolidine and piperidine respectively - and with benzylamine. The reaction was carried out in ethanol, for 2 hours at room temperature to achieve compounds **132a-c** in high yields (85-90%).

4.2.1 Studies on steroids cyclization by *tert*-amino effect.

Concerning vinyl compounds **132a-b** (respectively, the pyrrolidine and the piperidine substituted) their cyclization reaction occurred in preheated oil bath, at 230°C – 250°C, in solvent-free condition, for 30 minutes (**Figure 59**).



132a (90%) **133a** (54%)

132b (88%) **133b** (54%)

Fig.59: Formation of D-fused steroid ring systems *via tert*-amino effect cyclizations.

Both cyclized compounds **133a** and **133b**, were isolated as a mixture of two diastereomers in a 1:1 ratio, because of the presence of four chiral centers (C11(S), C(12)S, C(13)R, (C14)S) in the starting compound **126** and the formation

of a new chiral centre in this reaction step. Unfotunately their separation is still under ongoing studies.

Thermochemical studies of compounds **132a**,**b** were also carried out. Differential Scanning Calorimetry (DSC) measurements complemented by parallel thermal gravimetry (between room temperature and 500 °C) were run for these vinyl compounds (**Figure 60**) to assess whether cyclization could be monitored with this method for novel scaffolds.

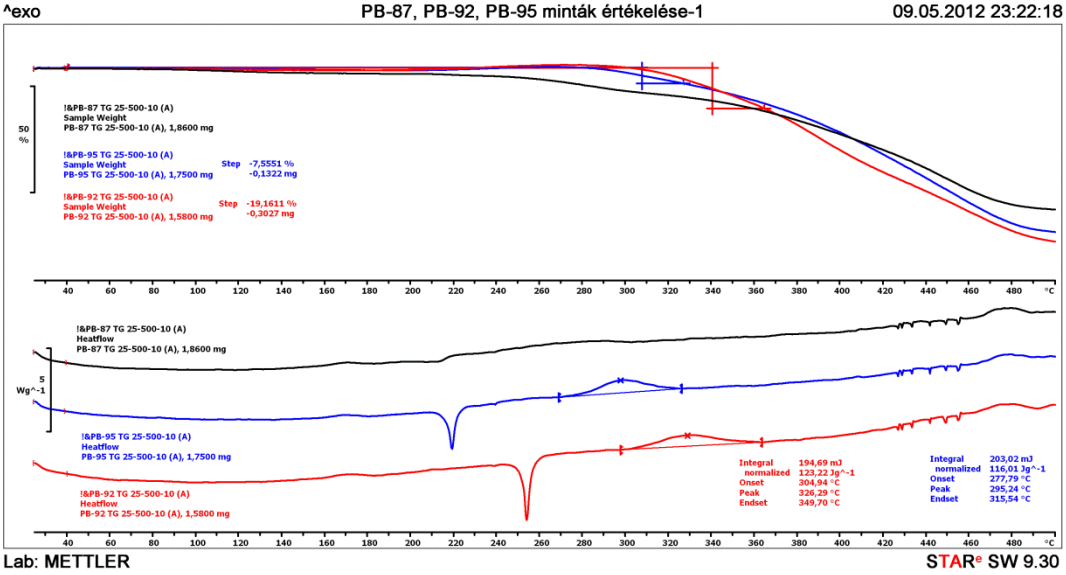


Fig.60: The thermogravimetry (upper) and differential scanning calorimetry (lower) curves of vinyl compounds **132a,b**.

DSC curves showed for both vinyl derivatives, the endothermic peaks, which corresponded to the compounds' melting points, and the exothermic peaks, corresponding to the thermal isomerization reaction. In this case, for both **132a** (red curve, **Figure 60**) and **132b** (blue curve, **Figure 60**) compounds, the thermal gravimetric studies showed a significant weight loss in the temperature range of the exothermic peaks, which correspond to decomposition.

This thermal gravimetric results partially explained the low yield of these reactions (54%), but to find a better reason, we planned to investigate the reversibility of these reactions. Not surprisingly, the cyclized products **133a** and **133b** underwent ring-opening reactions in preheated oil bath at 200°C; this was

confirmed by TLC in hexane/ethyl acetate 2/3, which showed Rf values of the vinyl compounds **132a** and **132b**.

4.2.2 X-ray diffraction studies.

Application of *tert*-amino effect on steroid scaffolds have been carried out to study the *tert*-amino effect in non – aromatic systems and thus, to understand the influence of the aromatic ring on the *tert*-amino effect cyclizations.

It was observed[7] that during the transition state of the thermal isomerization, the conjugation in the aromatic ring is partially destroyed, suggesting his not important role for the cyclization reaction. Indeed, it is a better opinion, that the planarity of the molecule is an important requirement for the cyclization.

X-ray diffraction studies of steroid vinyl compound **132a** were carried out also to study the planarity of this molecule, in order to understand the possible mechanism of the cyclization reaction. The results showed that the pyrrolidine ring, the D-ring and the vinyl moiety of compound **132a** belong to the same plane, thereby explaining why the thermal isomerization of the non-aromatic steroid system occurred.

The structure of the vinyl steroid intermediate **132a** was confirmed by X-ray diffraction studies (**Figure 61**).

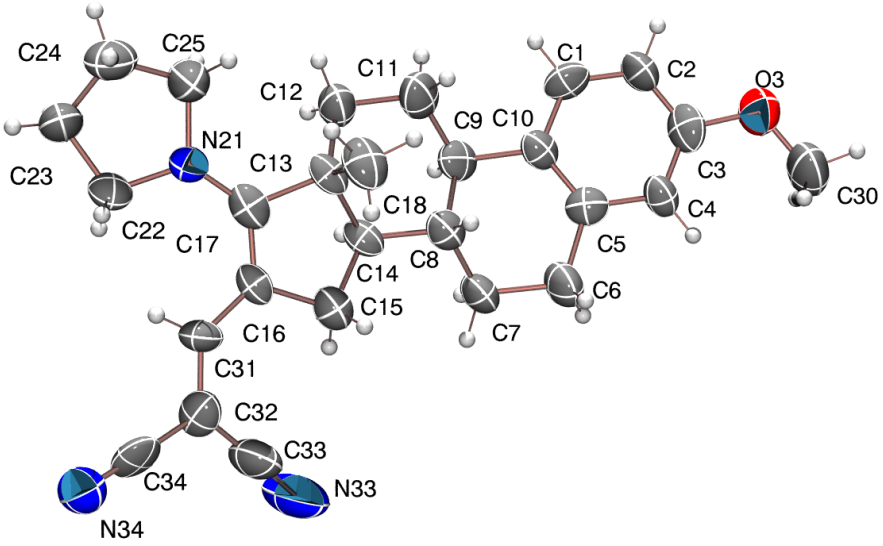


Fig. 61: X-ray structure of compound **132a**.

Selected bond length (Å) and bond angle (°) data are reported on **table 12**:

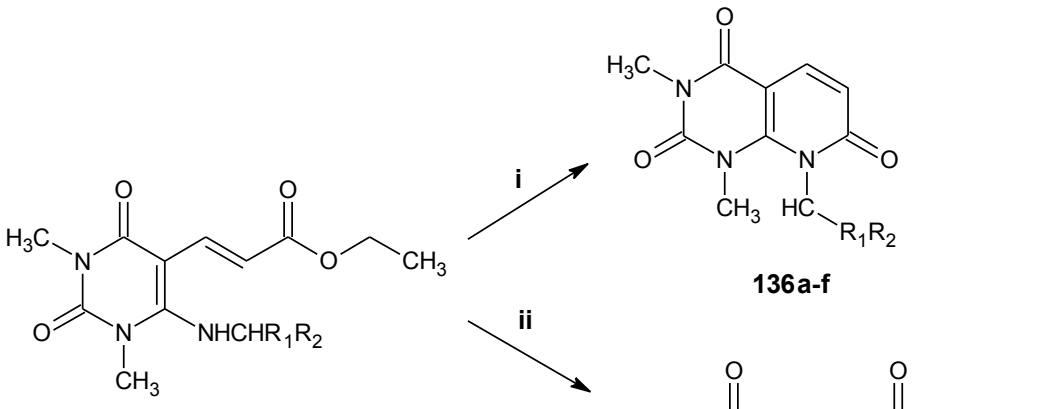
Name	PB79
C23 – C24	1.486(11)
C31 – C16	1.352(10)
C16 – C17	1.380(11)
C17 – C13	1.527(10)
C31 – C32	1.375(11)
C33 – N33	1.130(11)
C34 – N34	1.144(9)
C3 – O3	1.367(9)
N33 - H15A	2.703
N33 – H15B	3.478
C33 – C32 – C31	127.2(9)
C16 – C17 – N21	127.4(8)
C16 – C17 – C13	108.0(9)

Table 12: Selected bond length (Å) and bond angle (°) data of compound **132a**.

Search of the Cambridge Structural Database[83] (CSD, Version 5.31, February 2012) using the ConQuest program[84] had shown that C3 substituted ring system bearing C16=C17 double bond has been prepared only very limited number of cases. For the results of the query see the csd.pdf file. The only case when there is no other ring at C16-C17 is an indazol substituent [85] at C16.

4.2.3 Studies on steroid benzyl amine derivatives.

Experiments on steroid bearing the benzyl amine group (**132c**) have been carried out according to the results obtained by Matyus *et al*. in 1985[86]. Indeed, starting from 6-chloro-5-(2-ethoxycarbonylethenyl)-1,3-dimethyluracil they synthesized the novel 6-substituted benzylamino derivatives **135c-f**, which gave both 2,4,7-trioxopyrido[2,3-d]pyrimidines **136c**,**e** and 6-substituted benzylidenamino **137c**,**f** products were obtained (**Figure 62**):



a) R_1=$CH_3(CH_2)_2$; R_2=H

b) R_1= $CH_3(CH_2)_3$; R_2=H

c) R_1= C_6H_5; R_2=H

d) R_1= 4-MeO-C_6H_4; R_2=H

e) R_1= 4-Cl-C_6H_4; R_2=H

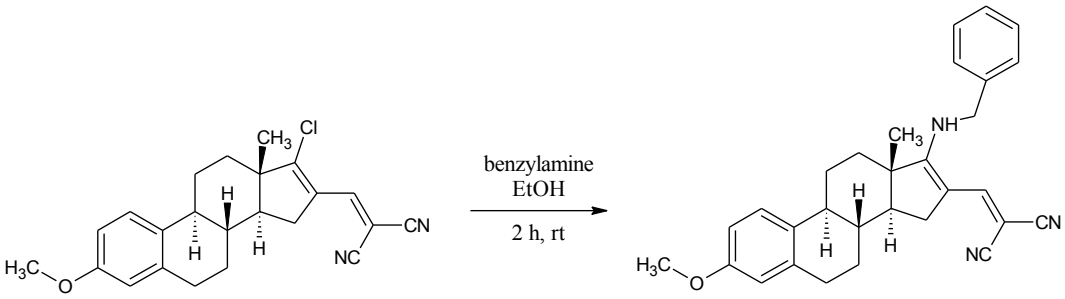
f) R_1= C_6H_5; R_2= Me

Fig. 62: 6-substituted benzylamino derivatives reactions.
i: DBN, Et_3N, DMF; **ii:** abs.xylene, 135 °C.

Refluxing of **135c-f** in a mixture of triethylamine and dimethylformamide in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) yielded exclusively the new 8-substituted benzylpyrido [2,3-d] pyrimidines **136c,e**. The cyclization could also be achieved by heating the amines in acetic acid for several hours. However, boiling of **135c-f** in absolute xylene or nitrobenzene at 130 or 140 °C led to the formation of 5-(2-ethoxycarbonylethyl)-uracil derivatives **137c-f**. Similarly, **137c** was also formed when **135c** was melted at 185 °C for a short period of time. All

of these results point out the decisive role of reaction conditions with respect to yield different type of products. Thus, either increasing the nucleophilicity of the 6-amino nitrogen or the electrophilicity of the carbonyl carbon in the side chain by base or acid catalysis favoured the intramolecular aminolysis, i.e. the cyclization. On the other hand, [1,5] rearrangements were preferred under neutral conditions by thermal activation.

According to these results, we planned to study the possible thermal reactions of a vinyl compound in which the tertiary amine group is replaced by benzylamine. Therefore, compound **132c** was synthesized starting from compound **127**, as shown in **Figure 63**:



127 **132c** (70%)

Fig. 63: Synthesis of the vinyl compound **132c**.

The expected possible products which could be obtained from the thermal reaction of the vinyl compound **132c** are summarized in **Figure 64**:

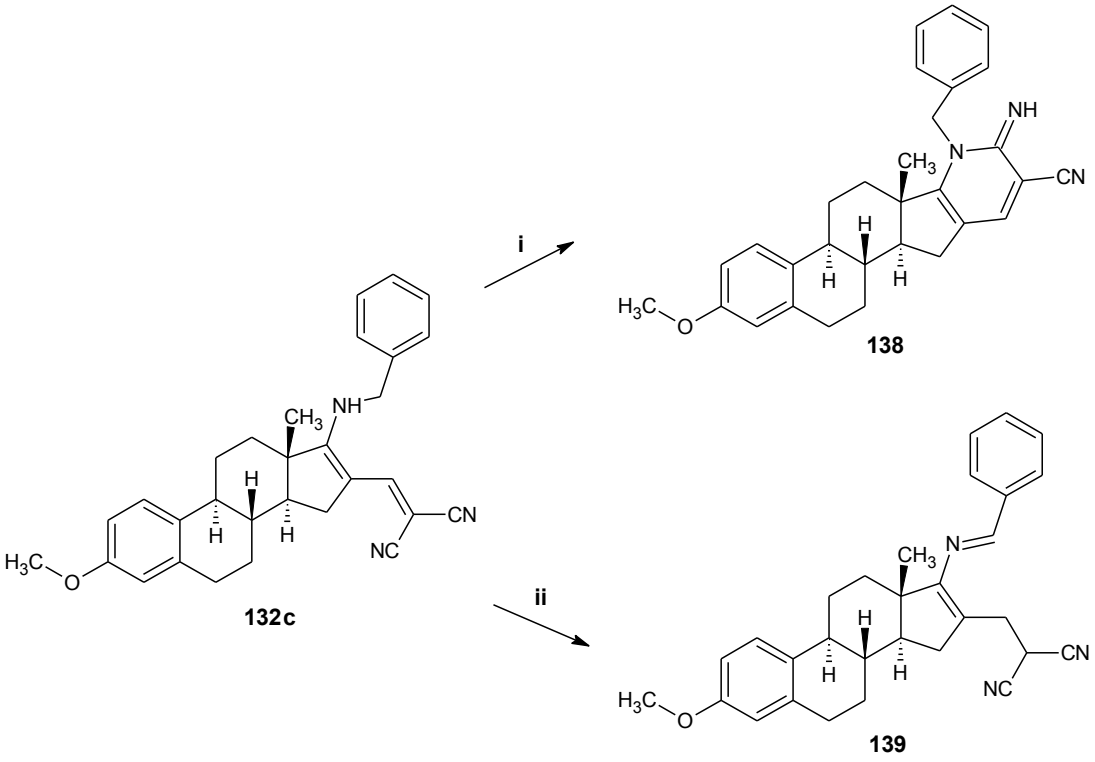


Fig. 64: Possible products of vinyl compound **132c**.

These compounds might be obtained through two different pathways:

1) reaction between the nitrogen lone pair and the electron-deficient carbon atom of the cyano group (**i**), which leads to the formation of the cyclized product **138**:

2) [1,5]-hydrogen shift of the secondary amine group to the β position of vinyl double bond (**ii**), which leads to the formation of compound **139**.

Our experiment were carried in preheated oil bath at 250 °C for 30 minutes, in solvent-free condition, leading to the following compounds (**Figure 65**):

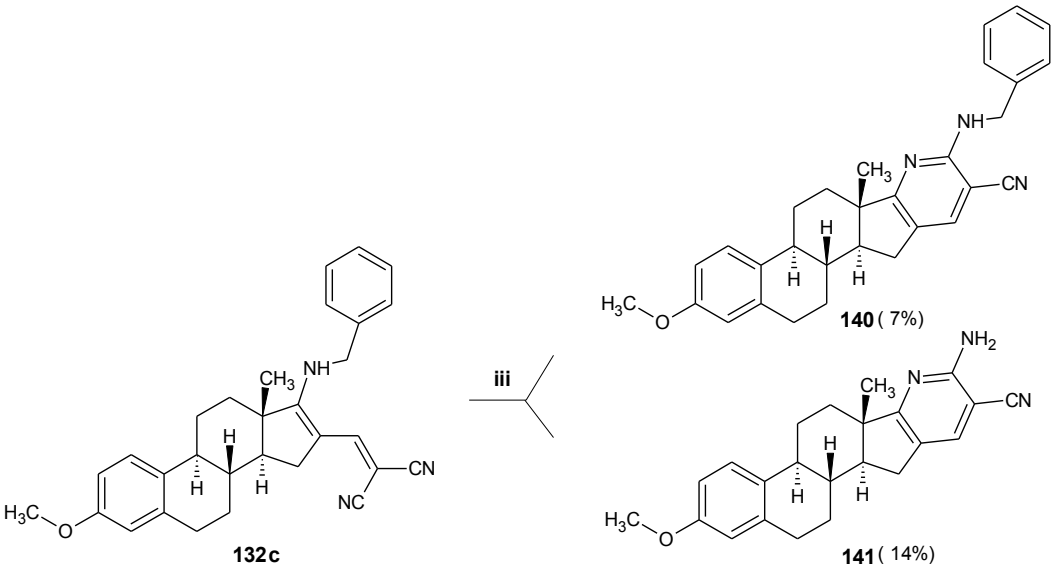


Fig.65: Synthetic route of steroid model compound **132c**.
iii: 250 °C, solvent-free, 30min.

These results showed us that only the first mechanism explained in **Figure 64** (**i**) occurred. Rearrangement of compound **138** and subsequent lost of the phenyl group linked to the tertiary amine, led to the formation of compound **141**.

For the other isolated product **140** of this reaction we were not able to find a possible mechanism to explain his formation.

The low yields of this reaction and the possibility to have different mechanisms operating in it, pushed us to carry out more experiments on this field, then this reaction is still under ongoing studies.

5. Conclusion

Based on the results discussed above, it can be concluded, that:

1) *tert*-amino effect type 2 cyclizations in biaryl derivatives bridged with a methylamino-*N*-methyl chain, exclusively occurs only between the methylene-carbon and the β-carbon of the vinyl moiety **123a**,**b** in 100% yield. This observations can be explaind by a preferably formation of six-membered ring.

2) *tert*-amino effect type 2 cyclizations in biaryl derivatives bridged with a methyl-oxygen chain, doesn't occur in all of our preparative works.

3) Ring closure of properly functionalized steroid ring systems on the D-ring, occurs although the tertiary amino and the vinyl groups are connected through a non – aromatic system, opening a new straightforward pathway for synthesis of novel steroids.

Further studies on these model compounds will be carry out – in both biaryl systems and steroids derivatives - in order to investigate the influence of different substituents on the *tert*-amino effect isomerization.

6. References

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7. Appendix

X-ray diffraction studies

A good looking single crystal of the compound was fixed on the top of a glass fiber using epoxy glue. Data were collected at 293(1) K, Enraf Nonius MACH3 diffractometer, Mo Kα radiation λ = 0.71073 Å, ω motion. Raw data was evaluated using the XCAD4 software[1a], the structure was solved using direct methods by the SIR- 92 software[2a] and refined on F2 using SHELX-97[3a] program. Refinement was performed anisotropically for non hydrogen atoms. Hydrogen atoms were placed into geometric position. Terminal methyl groups were refined using the riding model. Figures were prepared with the WINGX-97 suite.[4a] The PLATON program[5a] was used for crystallographic calculations.

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