Novel extensions of the *tert*-amino effect: synthesis of azecine- and oxazonine-fused ring systems

Doctoral thesis

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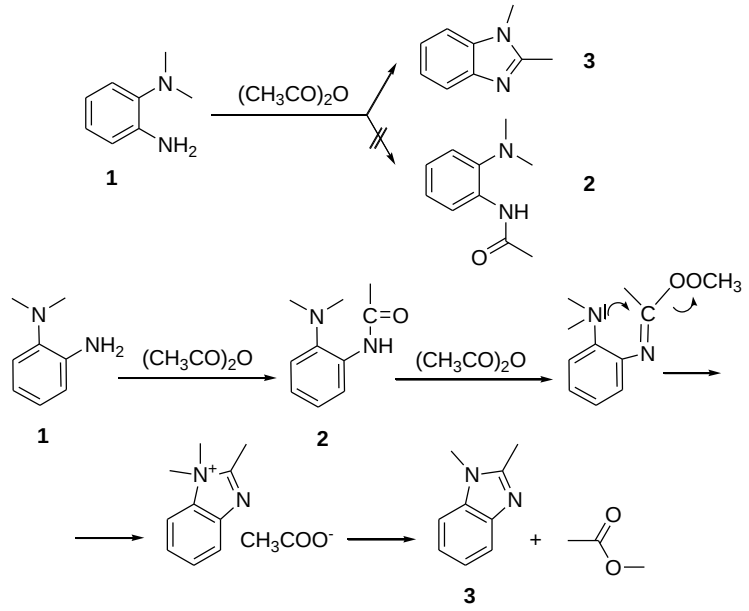
1 Introduction and literature review

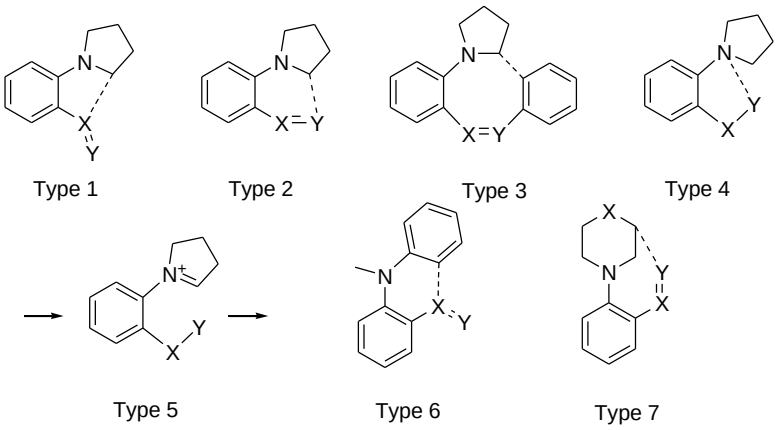
1.1 The tert-amino effect. Kinetic, thermodynamic and stereochemical aspects of type 2 reactions

The term *tert*-amino effect (or synonymously *t*-amino effect, T-reaction, α-cyclization of tertiary amines) was first used by Meth-Cohn and Suschitzky in 1972,[1] in a review aimed to collect and classify often unexpected cyclization reactions of *ortho*-substituted *tert*-anilines leading to the formation of fused heterocycles. According to their classification the surprising reaction sequence reported by Pinnow as early as 1895[2] could be considered as the first example of *tert*-amino effect (Scheme 1.). Namely, in an attempt to prepare the acetyl derivative (**2**) of *o*-aminodimethylaniline (**1**), instead of the desired product 1,2-dimethylbenzimidazole (**3**) was obtained.



Scheme 1. Unexpected cyclization under 'Pinnow conditions'.

Depending on the size of the ring formed and the mode of its formation, seven types of *tert*-amino effect cyclizations have been distinguished in the literature (as summarized in Scheme 2.).[1,3,4,5] The present work is related to novel extensions of type 2 cyclizations, therefore, the other types of *tert*-amino effect would not be discussed in detail herein.

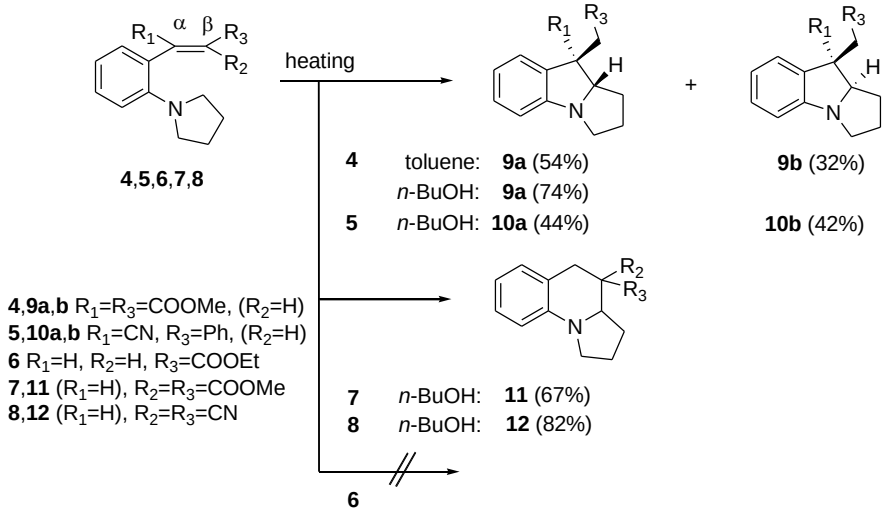


Scheme 2. Types of cyclizations *via tert*-amino effect.

Depending on the nature of the interacting moieties and the ring carrying them, cyclizations *via tert*-amino effect could be used for the synthesis of various heterocyclic core structures. The following examples might illustrate the synthetic scope and potential of the approach. The Reinhoudt group during their extensive work in the field, has described syntheses of 5*H*-pyrrolo- and 1*H*,6*H*-pyrido[1,2-*a*][3,1]benzoxazines,[6] pyrrolo[1,2-*a*]quinazolines and 5*H*-pyrrolo[1,2-*a*][3,1]benzothiazines,[7] pyrrolo- and pyrido[1,2-*a*]indoles[8,9,10] (with a *para*-quinone function),[11] pyrrolo[1,2-*a*]quinolines,[8] hexahydropyrazino[1,2-*a*]quinolines,[12] 3,1-benzoxazines and 3,1-benzothiazines,[13] (benzo)thieno[3,2-*e*]indolizines and (benzo)thieno[2,3-*c*]quinolizines[14] *via tert*-amino effect cyclizations.[15] Due to significant contributions of the Quintela group,[4] synthetic applicability of *tert*-amino effect cyclizations have been verified among heteroaromatic compounds, allowing straightforward preparation of [1,6]-[16] and [1,8]naphthyridines,[17,18,19] or pyrido[2,3-*d*]pyrimidines.[20] The above list is far from complete, however.

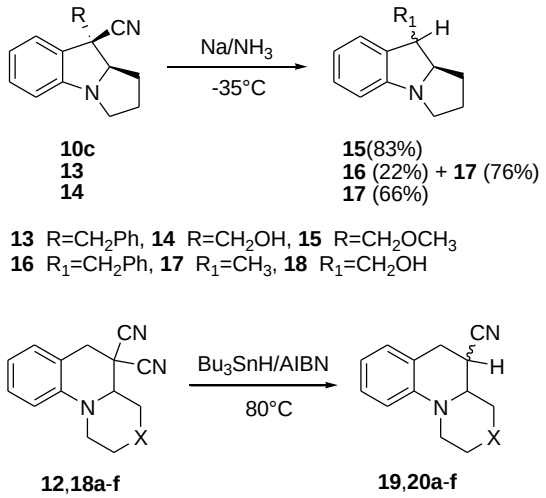
Although type 2 cyclizations have originally been described for compounds with X=Y substituents containing a heteroatom, Reinhoudt *et al*. demonstrated that *tert*-amino effect is operating also with C=C vinyl substituents.[8] Among a series of 2-vinyl-*N*,*N*-dialkylanilines, the effect of the substituents of the vinyl moiety on reactivity was studied, vinyl substituents optionally having one/two electron-withdrawing groups at the α/β position. Cyclization of compound **4**, possessing one electron-withdrawing group at the α and one at the β position of the vinyl moiety, led to **9a** and **9b** pyrrolo[1,2-*a*]indole isomers, the product ratio depending on the solvent used (Scheme

3.). Compound **5** with one electron-withdrawing group at the α position of the vinyl group, did not cyclize in toluene. However, heating in *n*-butanol (*n*-BuOH) afforded a mixture of **10a** and **10b** pyrrolo[1,2-*a*]indole isomers. Compound **6**, with one electron-withdrawing group at the β position of the vinyl group, gave no cyclization product, even after longer heating in *n*-BuOH or in acetonitrile in the presence of $ZnCl_2$. Cyclization of **7**, having two electron-withdrawing groups at the β-position of the vinyl substituent afforded the [1,2-*a*]quinoline **11**. Similar reaction was observed with **8**, the reaction time being considerably shorter applying *n*-BuOH, than in toluene.



Scheme 3. The effect of the substituents of the vinyl group on *tert*-amino effect cyclizations.

As shown by the above examples, 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 be a drawback regarding further transformations. Overcoming such limitations, several methods for removal or further functionalization of the electron-withdrawing groups have been described. Reinhoudt *et al*. aimed to develop a method for the removal of the cyano group at such a way, that would not result consequently in double bond formation.[10] Treatment of **10c** with sodium in liquid ammonia resulted in the formation of a 5:1 (*cis*:*trans*) mixture of the decyanated **15** isomers. Decyanation of **13** led to a mixture of products: **16** (22%, 1:3 *cis*:*trans*), besides formation of **17** isomers (*cis* (18%), *trans* (58%)). With decyanation of **14**, **16** isomers (66%, 1:3 *cis*:*trans*) were obtained, i.e. besides the cyano group also the methoxy group was reduced (Scheme 4.).



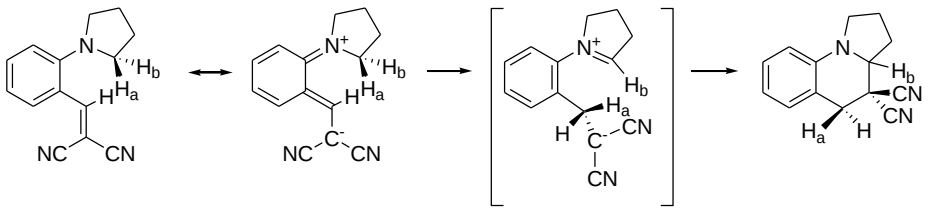
Scheme 4. Decyanation reactions.

Table 1. Products of reductive decyanation of geminal dinitriles.

Compound	X	Yield (%) (Product)	Diastereomeric ratio*
12	-	75 (**19**)	88:12
18a	CH_2	78 (**20a**)	25:75
18b	NCH_3	97 (**20b**)	44:56
18c	O	99 (**20c**)	44:56
18d	S	-	-
18e	S=O	-	-
18f	SO_2	99 (**20f**)	90:10

**diastereomers given in the order of elution*

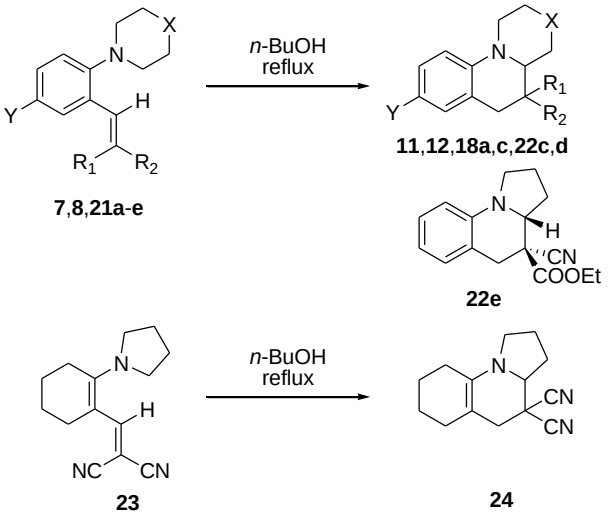
Gerlach described elimination of one cyano group of the geminal dinitrile moiety.[21] Reductive eliminations (**12**,**18a-f→19**,**20a-f**) were carried out in benzene or toluene, with 2,2'-azobisisobutyronitrile (AIBN) and tributyltinhydride (Bu_3SnH) (Scheme 4.). Mostly high yields were obtained, however the diastereomeric ratio was strongly dependent on the substrate choice (Table 1.).



Scheme 5. The proposed mechanism of *tert*-amino effect type 2 cyclisations.

The mechanism of type 2 cyclisations can be rationalized by the pathway shown in Scheme 5., comprising in the first, rate-limiting step hydrogen migration leading to a dipolar intermediate. Subsequently, a bond is formed between the two oppositely charged C1-C6 carbons, to afford a novel six-membered ring.

The mechanistic aspects were thoroughly explored by the Reinhoudt group.[22] Studying a series of 2-vinyl-*N*,*N*-dialkylanilines (**7**,**8**,**21a-e**), heating in refluxing *n*-BuOH afforded the cyclized products (**11**,**12**,**18a**,**c**,**22c-e**) in all cases (Scheme 6.). From **21e**, theoretically two diastereomers could be obtained, however formation of only one diastereomer (**22e**) upon cyclization was detected. This observation supports, that upon cyclization no rotation around the bond linking the vinyl α and the β carbon (bearing the electron-withdrawing groups) takes place between the hydrogen migration and the C-C bond formation. Kinetic experiments were carried out monitoring the reaction with ^{1}H-NMR spectroscopy (in dimethyl sulfoxide(DMSO)-d_6). The reaction rate of the cyclization of **8** was measured at seven different temperatures (66.1-92.8°C) and activation parameters were calculated (at 90°C: $\Delta H^{\#}$=22.2±0.4 kcal/mol, $\Delta S^{\#}$=-12.0±1.1 cal/mol·K, $\Delta G^{\#}$=26.6±0.8 kcal/mol). The $\Delta H^{\#}$ value found is very low compared to activation enthalpies of other sigmatropic [1,5]-H shifts, especially so considering partial decomposition of the conjugation in the aromatic ring. Cyclization of the non-aromatic compound **23** to **24** was significantly slower compared to its aromatic counterpart (2 days for **23** *vs* 2 hours for **8** in refluxing *n*-BuOH).

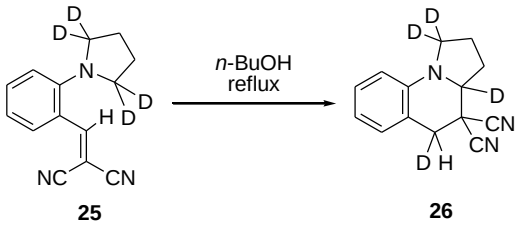


8 (2h) → **12** (82%)
21a (2h) → **18a** (78%)
21b (35h)→ **18c** (84%)
21c (20h) → **22c** (57%)
21d (4h) → **22d** (84%)
21e (6h) → **22e** (69%)
7 (22h) → **11** (67%)

	R_1	R_2	X	Y
8,**12**	CN	CN	-	H
21a,**18a**	CN	CN	CH_2	H
21b,**18c**	CN	CN	O	H
21c,**22c**	CN	CN	-	NO_2
21d,**22d**	CN	CN	-	Br
21e,**22e**	CN	COOEt	-	H
7,**11**	COOMe	COOMe	-	H

Scheme 6. *Tert*-amino effect type 2 cyclizations of 2-vinyl-*N*,*N*-dialkylanilines.

To verify hydrogen migration, deuterium kinetic isotope effect of the cyclization was measured, starting with the tetradeuterated compound **25** (Scheme 7.). A kinetic isotope effect (k_H/k_D) of 3.0±0.3 (91.2°C, DMSO-d_6) was found, indicating hydrogen migration to take place in the rate-determining step. No deuterium loss was observed (confirmed by ^{1}H-NMR and mass spectroscopy) during the formation of the product (**26**), indicating an intramolecular process.



25 **26**

Scheme 7. Study of kinetic isotope effect.

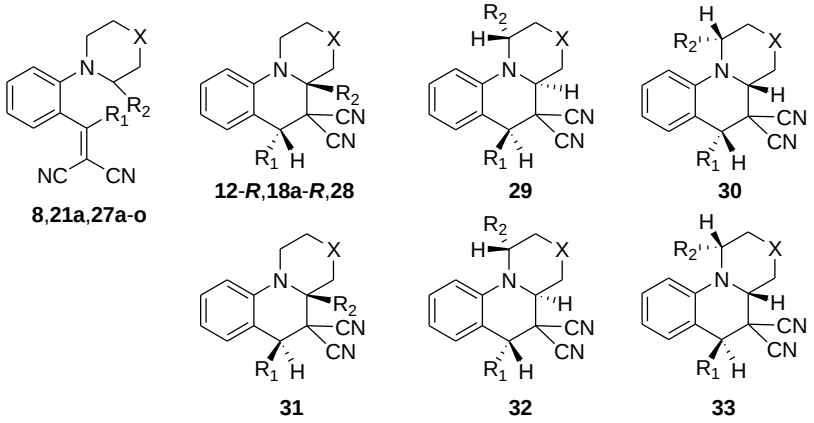
Studying solvent effect, replacing the polar DMSO with apolar toluene caused an approximately 150 fold decrease in the reaction rate (Table 2.). This is well in accordance with a highly polar transition state of the rate-determining step due to charge separation, therefore, solvation is much less favourable in apolar toluene.

Table 2. Rate constants of cyclizations of **7**,**8**,**21a-e**. Solvent and substituent effects.

compound	solvent	temperature (°C)	rate constant (10^{-4} sec^{-1})
8	toluene-d_8	93	0.067±0.005
8	DMSO-d_6	90.4	8.5±0.3
21a	DMSO-d_6	90.3	4.9±0.5
21b	DMSO-d_6	92	0.19±0.05
21c	DMSO-d_6	90.9	0.29±0.03
21d	DMSO-d_6	90.9	8.1±0.7
21e	DMSO-d_6	90.7	0.60±0.02
7	DMSO-d_6	89	0.078±0.010
25	DMSO-d_6	91.2	2.9±0.2

The effect of various substituents on the reaction rate was also studied. Replacement of cyano groups with less electron-withdrawing ester groups (**21e**,**7**) led to a decrease in the reaction rate. As in the transition state a partial negative charge is formed on the β carbon of the vinyl group, the presence of strongly electron-withdrawing groups is needed for charge delocalization and stabilization. A strongly electron-withdrawing nitro group on the aromatic ring decreases the reaction rate due to destabilization of the

positive charge on the amine nitrogen in the transition state. Studying the effect of different amine moieties, replacement of pyrrolidine with piperidine decreased the reaction rate, due to 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. Decrease of the reaction rate was even more pronounced in the case of a morpholine ring, due to the electron-withdrawing oxygen further destabilizing the transition state. In conclusion, the authors suggested, that the first step of the cyclization is an intramolecular [1,5] hydrogen transfer, although not sigmatropic rearrangement.



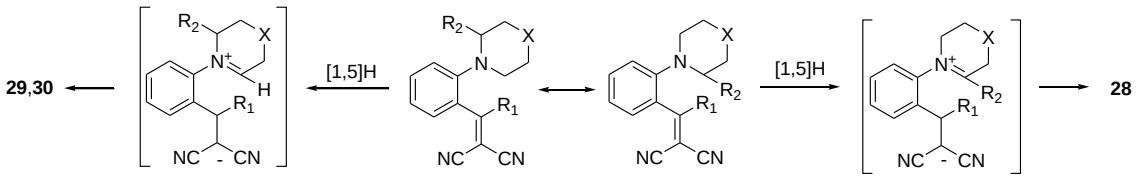
Scheme 8. Regioselectivity of type 2 cyclizations.

Table 3. Regioselectivity of type-2 cyclizations.

R_1	Compound	X	R_2	Reaction time (h)	Products
H	**8**	-	H	2	**12-*R*** (82%)
	27a	-	CH_3	2	**28a** (85%)
	27b	-	CH_2OCH_3	1.5	**28b** (46%), **29b** (19%), **30b** (17%)
	21a	CH_2	H	2	**18a-*R*** (78%)
	27c	CH_2	CH_3	1.5	**28c** (79%)
	27d	CH_2	CH_2CH_3	1.5	**28d** (80%)
	27e	CH_2	CH_2OCH_3	2.5	**28e** (71%), **29e**+**30e** (25%)
CH_3	**27f**	-	H	5	**28f** (79%)
	27g	-	CH_3	5	**28g** (79%),
	27h	-	CH_2OCH_3	5	**28h** (33%), **29h** (35%), **30h** (6%)
	27i	CH_2	H	2	**28i** (88%)
	27j	CH_2	CH_3	2	**28j** (88%)
	27k	CH_2	CH_2CH_3	2.5	**28k** (86%)
	27l	CH_2	CH_2OCH_3	3	**28l** (56%), **29l**+**30l** (35%, 7:2 ratio)
4-$C_6H_4CH_3$	**27m**	-	H	3 days	**28m**+**31m** (86%, 82:18 ratio)
	27n	-	CH_3	3 days	**28n**+**31n** (76%, 98:2 ratio), **29n**+**30n** (22%)
	27o	-	CH_2OCH_3	3 days	**28o**+**31o** (16%, 95:5 ratio), **29o**+**32o** (41%, 96:4 ratio), **30o**+**33o** (15%, 97:3 ratio)

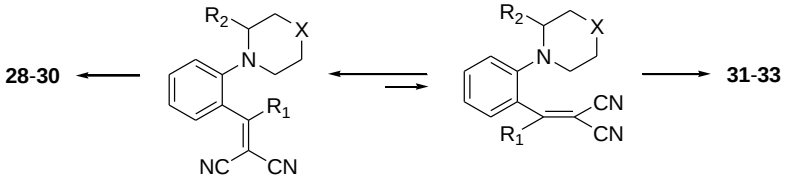
As an important aspect of synthetic utility, regio- and enantioselectivity of *tert*-amino effect cyclizations was addressed by the Reinhoudt group in the 1980's.[6,23] Cyclizations of a series of vinyl derivatives with different substituents at the α carbon of the vinyl moiety and the carbon adjacent to the amine nitrogen were studied, leading to the results summarized in Scheme 8. and Table 3.

Cyclization was found to occur regioselectively (e.g. **27a**,**c**,**d**→**28a**,**c**,**d**), yielding products in which the substituent at the bridgehead carbon is in *cis* position related to the benzyl hydrogen. The observed regioselectivity (preferential formation of **28** isomers) of the reaction 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 (Scheme 9.).



Scheme 9. Formation of regioisomers in type 2 cyclization 1.

If R_2=CH_2OCH_3, regioselectivity is lost due to steric hindrance and the electron-withdrawing effect of the oxygen, destabilizing the iminium bond.

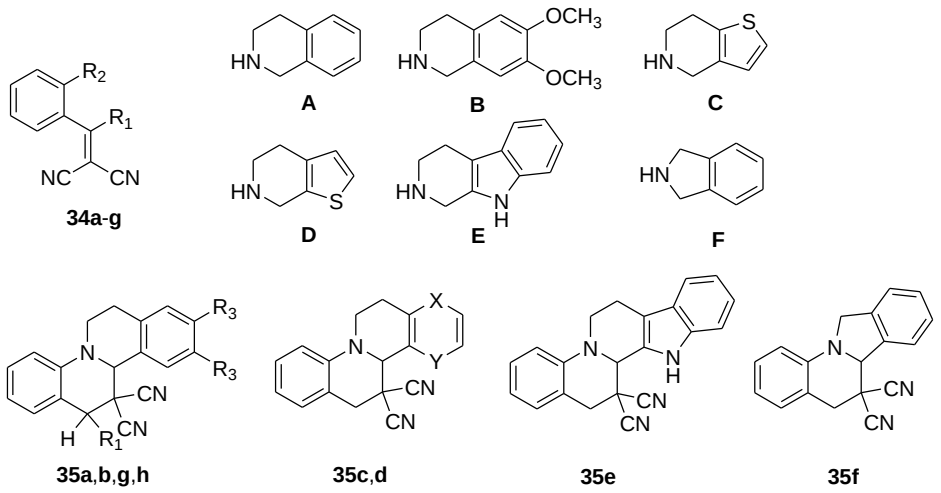


Scheme 10. Formation of regioisomers in type 2 cyclization 2.

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 **31**-**33** isomers in cyclization of **27o**, having a bulkier 4-methylphenyl R_1 group (Scheme 10.).

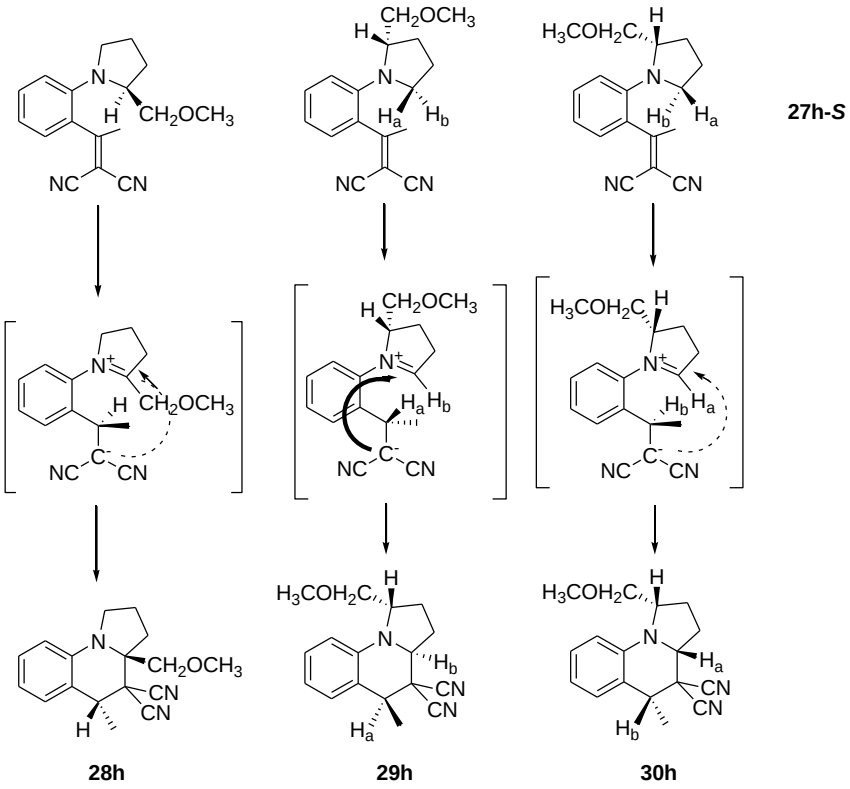
The cyclizations of **34a**-**g** (leading to **35a**-**g**) had similar regiochemical consequences[24] as discussed above, directed by better stabilization of the positive charge in the dipolar

intermediate (Scheme 11.). With **34a**,**b**,**f**,**g** starting compounds the ring closure occurred selectively at the benzyl carbon. Similarly, with heterocyclic analogues **34c**-**e**, ring closure proceeded at the NCH_2 adjacent to the thiophene or indole moiety.



34a R_1=H, R_2H=A; **34b** R_1=H, R_2H=B; **34c** R_1=H, R_2H=C; **34d** R_1=H, R_2H=D; **34e** R_1=H, R_2H=E; **34f** R_1=H, R_2H=F; **34g** R_1=CH_3, R_2H=A
35a R_1=H, R_3=H; **35b** R_1=H, R_3=OCH_3; **35c** X=S, Y=-; **35d** X=-, Y=S; **35g** R_1=CH_3, R_3=H

Scheme 11. Synthesis of tetra- and pentacyclic compounds *via tert*-amino effect.

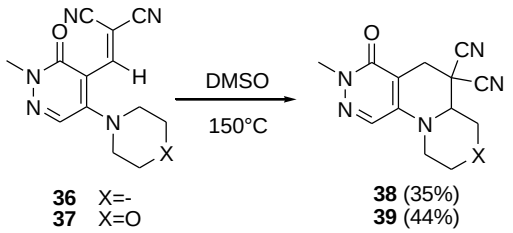


Scheme 12. Stereochemical outcome of type 2 cyclizations.

Cyclization of optically pure 2-vinyl-*N*,*N*-dialkylanilines verified, 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 **27h**-***S*** resulted in the formation of three products: **28h** (33%) obtained as one enantiomer and the two diastereomers **29h** (35%) and **30h** (6%) (Scheme 12.), i.e. retention of configuration of the original chiral centre was observed. 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 face from which the migrating hydrogen has left; the hydrogen shift proceeds suprafacially. Albeit the original chiral centre is lost temporarily, the chiral information is stored in a unique helical dipolar intermediate.[25,26]

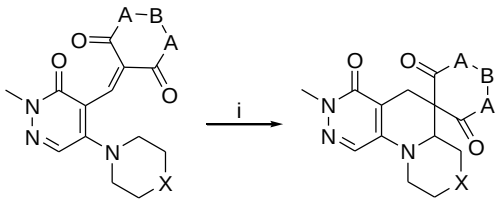
1.2 Synthesis of pyridazine-annelated ring systems via tert-amino effect

The first application of *tert*-amino effect cyclization for the synthesis of pyridazine-annelated ring systems was described by Mátyus *et al.*[27] Heating of **36**,**37** vinyl compounds in DMSO led to the expected [4,5]-annelated pyridazine derivatives **38**,**39** (Scheme 13.).



Scheme 13. Synthesis of [4,5]-annelated pyridazines *via tert*-amino effect.

Cyclizations have been extended to the synthesis of spirocyclic derivatives (**40**→**41**),[28] applying cyclic active methylene compounds *N*,*N*-dimethylbarbituric acid or Meldrum's acid (Scheme 14.). By incorporating the substituents of the vinyl moiety in a ring, cyclizations were observed to proceed at lower temperatures or within shorter reaction times.



i: xylene, $AlCl_3$, 150°C, 8h for **41a**,**b** or *N*,*N*-dimethylformamide (DMF), 110°C, 5h for **41c**
a: X=O, A=NCH_3, B=CO; **b**: X=-, A=NCH_3, B=CO; **c**: X=O, A=O, B=$C(CH_3)_2$

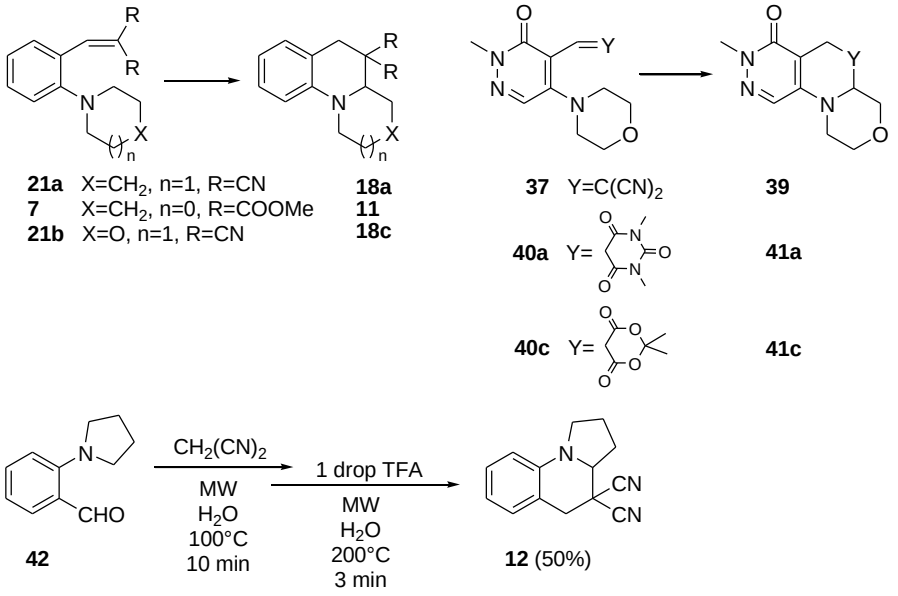
Scheme 14. Synthesis of spirocyclic pyridazinone derivatives.

Thermochemical aspects of the ring closure of 5-morpholino-4-vinylpyridazinones were studied by differential scanning calorimetry (DSC); DSC was found to be a valuable tool for monitoring thermal isomerizations.[29] With a series of 5-amino-4-vinylpyridazinones, the role of the substituents of the pyridazinone ring and the vinyl group on isomerization was studied.[30] To overcome problems related to longer reaction times or higher temperatures often needed for cyclization, microwave-assisted methods were elaborated applying pyridazine model compounds.[31,32] Solvent-free cyclizations tested might furnish environmentally more benign solutions for ring closure.[32]

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.[33,34,35] 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).[33,34,36]



Scheme 15. Microwave-assisted synthesis of pyrido-fused ring systems *via tert*-amino effect.

Table 4. Comparison of *tert*-amino effect cyclization conditions under conventional heating and microwave irradiation.

	Conventional heating			Microwave irradiation		
Product	Temp (°C)/ time (h)	Yield (%)	Solvent	Temp (°C)/ time (h)	Yield (%)	Solvent
18a	117/2 h	78	*n*-BuOH	200/3 min	80	*n*-BuOH
	150/5 min	99	neat	150/5 min	99	neat
11	117/22 h	67	*n*-BuOH	220/15 min	73	*n*-BuOH
	170/17 min	87	neat	170/17 min	86	neat
18c	117/35 h	84	*n*-BuOH	220/30 min	96	*n*-BuOH
	180/22 min	94	neat	180/22 min	94	neat
39	150/44 h	35	DMSO	210/42 min	29	DMSO
	200/20 min	78	neat	200/18 min	75	neat
41a	138/2 h	45	xylene	210/1 min	63	*n*-BuOH
	210/1 min	97	neat	210/1 min	96	neat
41c	100/5 h	79	DMF	200/30 min	73	DME*
	175/7 min	31	neat	175/7 min	55	neat

**DME: 1,2-dimethoxyethane*

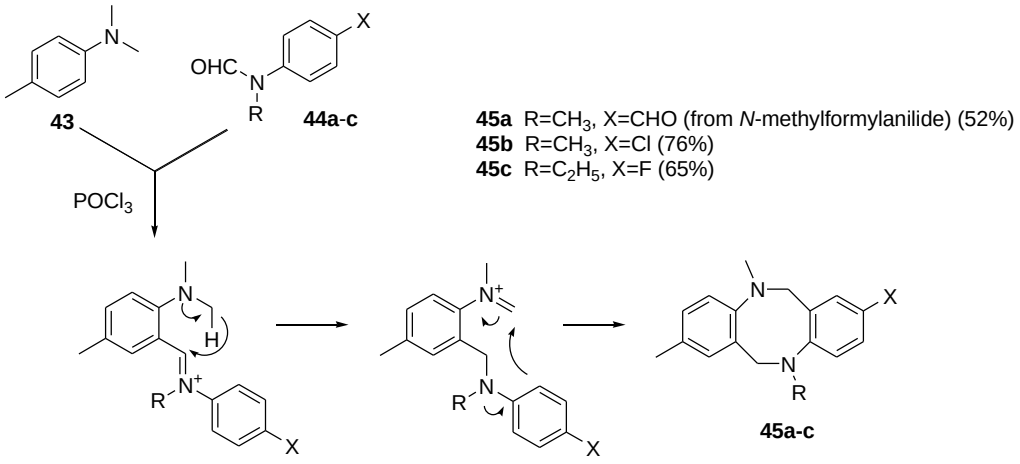
Tert-amino effect cyclizations often require prolonged heating in organic solvents with high boiling points (e.g. DMSO), making isolation of the products more challenging. Microwave-assisted synthesis of pyrido-fused heterocycles was studied by Kaval *et al*., comparing microwave irradiation protocols with conventional heating conditions.[31] 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 Scheme 15. and Table 4.). 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.[32] As an alternative for an environmentally friendly route, conversion of *ortho*-pyrrolidinobenzaldehyde (**42**) to the pyrido-fused product **12** using a one-pot procedure in water as solvent was described (Scheme 15.).

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

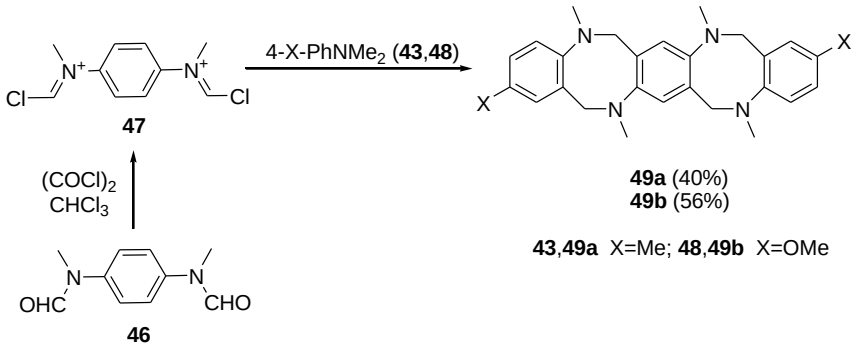
Tert-amino effect cyclizations have hardly been used for the synthesis of medium-sized or larger rings. As one such example, the Meth-Cohn group explored syntheses of dibenzazocines. Upon treatment of *p*-substituted *tert*-aniline **43** with *N*-formyl-*N*-substituted arylamides (**44**) in phosphorus oxychloride ($POCl_3$), dibenzo[1,5]diazocines (**45**) were formed.[37] The reaction pathway could be rationalized by Vilsmeier formylation *ortho* to the dimethylamino group, followed by 1,5 hydrogen shift. Subsequently C-C bond is formed between the iminium ion and the aromatic ring, affording unsymmetrical dibenzo[1,5]diazocine derivatives (Scheme 16.).

The methodology was later extended for the synthesis of linear fused analogues ('molecular bracelets').[38] Reacting 4-substituted *N,N'*-dimethylanilines (**43**,**48**) with Vilsmeier reagent (**47**) (formed from *N,N'*-dimethyl-*N,N'*-diformyl-*p*-phenylenediamine **46** upon treatment with oxalyl chloride) led to pentacyclic products **49** (Scheme 17.).

Applying 1- or 2-dimethylaminonaphthalene starting compounds, benzo[*b*]naphtho[1,2-*f*]- and benzo[*b*]naphtho[2,1-*f*][1,5]diazocines could be prepared using Vilsmeier reagents *via tert*-amino effect.[39] Following studies on molecular bracelets, treating *N,N,N',N'*-tetramethylbiphenyldiamine with Vilsmeier reagent formed from *N*-methylformylanilides with $POCl_3$ afforded bis-dibenzodiazocines.[40]



Scheme 16. Syntheses of dibenzo[1,5]diazocines *via tert*-amino effect.



Scheme 17. Synthesis of linear pentacyclic bis(benzodiazocino)benzenes *via tert*-amino effect.

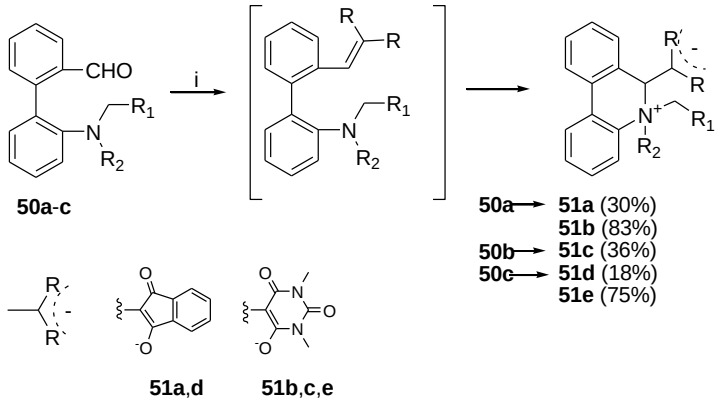
1.5 Novel extensions of the tert-amino effect to biaryl and fused systems

Recently, novel extensions of type 2 *tert*-amino effect cyclizations were elaborated in the Department of Organic Chemistry (Semmelweis University), positioning the interacting groups on two different aromatic rings.

Polonka-Bálint *et al*. studied extensions of the *tert*-amino effect to biaryl systems – 2-(2-vinylphenyl)-*tert*-anilines and pyridazinone analogues.[41,42] In the condensations expected to lead to the vinyl starting compounds, an interesting cyclization was observed in several cases. Treatment of **50a-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 (**51a-e**) (Scheme 18.). Such behaviour was not observed among the pyridazinone analogues.

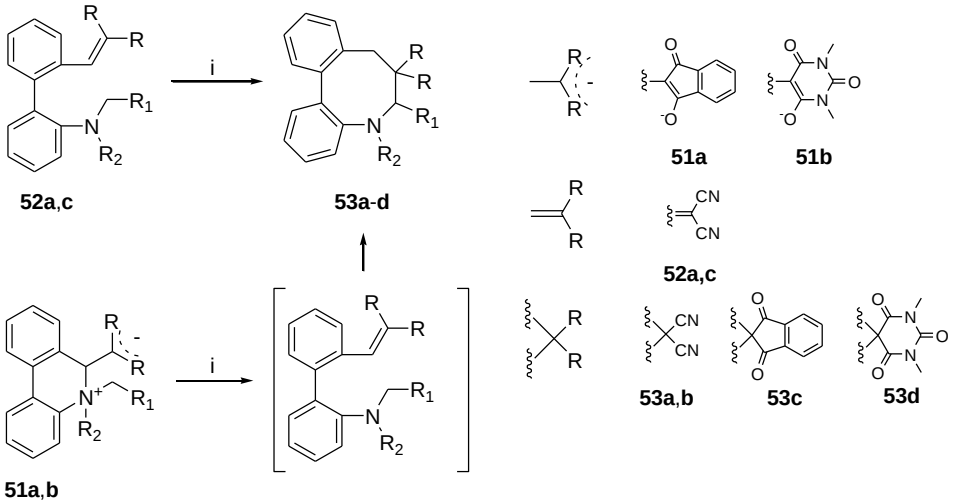
X-ray analysis of the **52a** vinyl compound (Scheme 19.) revealed, that the pyrrolidino and vinyl groups are located on the same side of the biaryl system, moreover, a

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 **50b** and **50c** aldehydes, with a 2.835 Å and 2.989 Å distance between the nitrogen and the carbonyl carbon.[43] Verifying the existence of an interaction, isomerization of **50b** and **50c** aldehydes under mild conditions (rt, $CHCl_3$, cat. CF_3COOH) led to zwitterionic phenantridinium derivatives (as will be discussed later).



50a,**51a**,**b** R_1+R_2=-$(CH_2)_3$-; **50b**,**51c** R_1+R_2=-$(CH_2)_4$-; **50c**,**51d**,**e** R_1=H, R_2=CH_3
i: 1*H*-indene-1,3(2*H*)-dione (**51a**,**d**) or *N*,*N*-dimethylbarbituric acid (**51b**,**c**,**e**), EtOH, rt, 24h

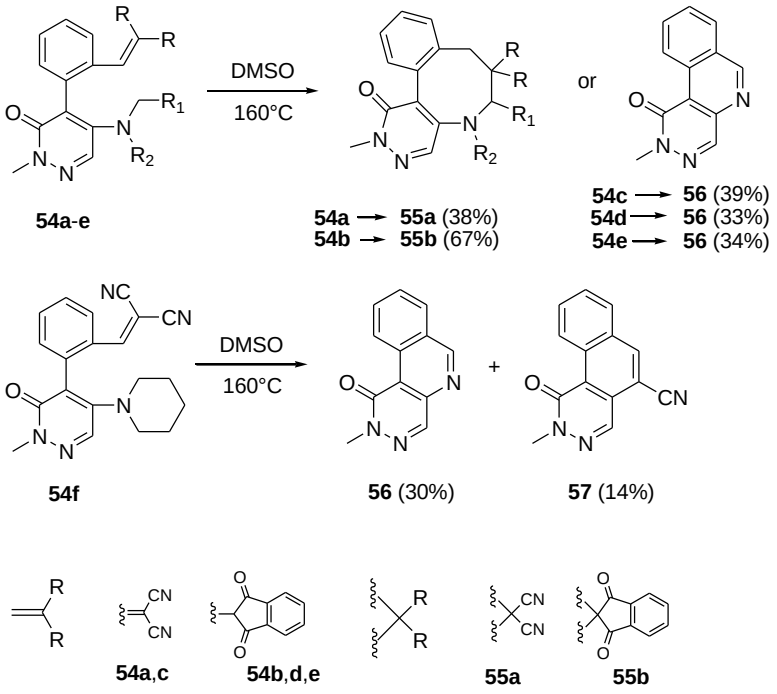
Scheme 18. Isomerization *via* carbon-nitrogen bond formation to phenantridines.



i: DMSO, 110/160°C
52a,**51a**,**b**,**53a**,**c**,**d** R_1+R_2=-$(CH_2)_3$-; **52c**,**53b** R_1=H, R_2=CH_3

Scheme 19. Synthesis of benzazocines *via tert*-amino effect.

Upon heating in DMSO, **52a**,**c** biphenylvinyl and **51a**,**b** phenantridinium compounds underwent isomerization to the corresponding dibenzazocines (**53a-d**) (Scheme 19.). With pyridazine analogues (**60a-f**), cyclization attempts led to unforeseen results, to pyridazinoisoquinoline (**56**) or benzophtalazinone derivatives (**57**) besides formation of the desired azocine derivatives (**55a**,**b**) in some cases – as summarized in Scheme 20.



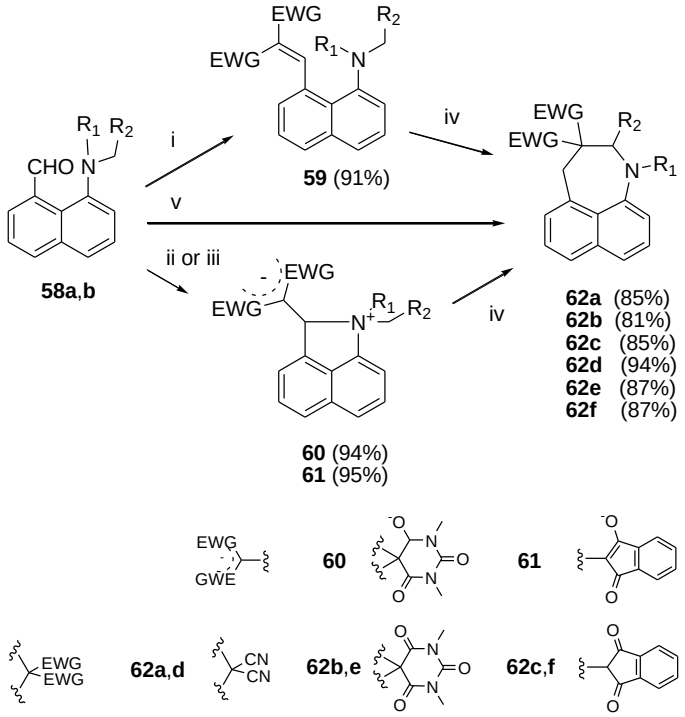
54a,**b**,**55a**,**b** R_1+R_2=-$(CH_2)_3$-; **54d** R_1+R_2=-$(CH_2)_4$-; **54c**,**54e** R_1=H, R_2=CH_3

Scheme 20. 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 **58a** 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 **60**,**61** (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 **59-61** vinyl/zwitterionic compounds in DMSO led to the formation of the expected 1,2-dihydronaphtho[1,8-*b*,*c*]azepines (Scheme 21.). For the **58b** pyrrolidino derivative the

cyclized products were obtained directly under the conditions of the Knoevenagel condensation.

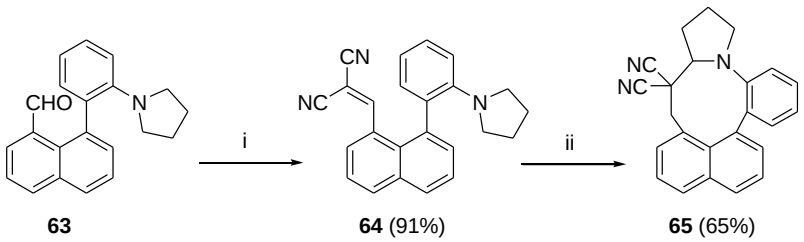
Turning to phenylnaphthyl derivatives, cyclization *via tert*-amino effect could be obtained only at higher temperatures in ionic liquid, leading to the appropriate pyrrolonaphtho[1,8-*e,f*]azonine (**64**→**65**) (Scheme 22.).



58a, **59**-**61**,**62a**-**c** R_1=CH_3, R_2=H; **58**, **62d**-**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

Scheme 21. Synthesis of naphthazepine derivatives *via tert*-amino effect.



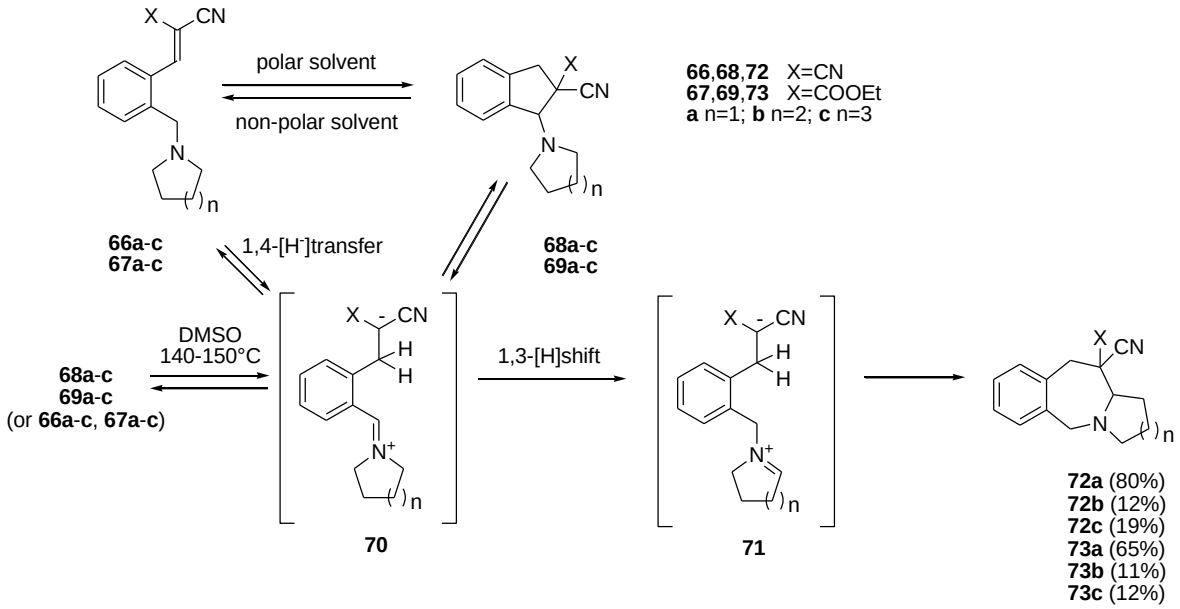
i: malononitrile, EtOH, piperidine, rt; ii: [bmim]BF_4, 190°C, 3h
[bmim]BF_4: 1-butyl-3-methylimidazolium tetrafluoroborate

Scheme 22. Synthesis of napthazonine ring system *via tert*-amino effect.

1.6 Recent applications of cyclizations via tert-amino effect

In the following section a brief overview of recent years' related literature is given, highlighting just some of the issues covered, including catalyst enhanced approaches or extensions for the synthesis of novel heterocyclic ring systems. To survey some of the most recent *tert*-amino effect related reports:

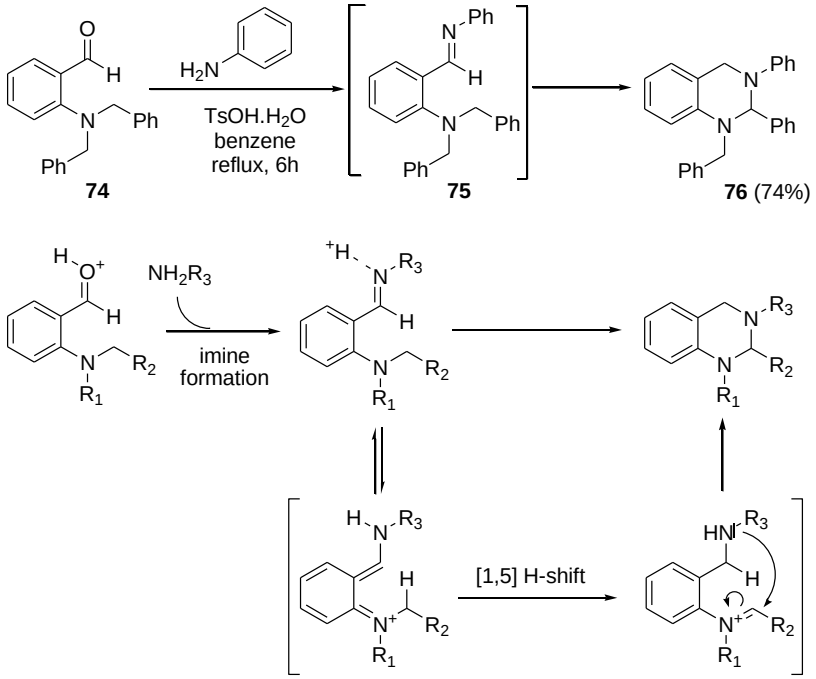
i) Gorulya *et al*. studied,[46] whether cyclization can proceed among derivatives having the aromatic ring and the tertiary amine moiety separated by a methylene group. Interestingly, they have found a reversible *tert*-amino effect cyclization suggested to occur *via* the **70** dipolar intermediate, formed by a 1,4-hydride transfer, leading to the formation of **68**,**69** from **66**,**67**. Studying the thermal behaviour of **68**,**69**(**66**,**67**), heating in DMSO at 140-150°C resulted in the formation of pyrrolobenzazepines (**72**,**73**) (Scheme 23.). Another sigmatropic process was considered as the mode of formation, the initial dipolar intermediate **70** undergoing a subsequent 1,3-hydrogen shift (**70**→**71**). For **73a-c** ester derivatives, the reaction proceeded diastereoselectively.



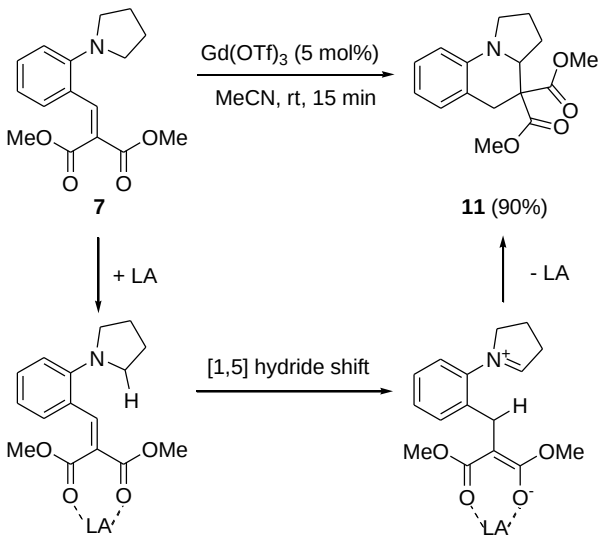
Scheme 23. *Tert*-amino effect among acrylonitrile derivatives.

ii) Mori *et al*. investigated cyclizations of imine derivatives and synthesis of quinazolines *via* Brønsted acid-catalyzed *tert*-amino effect reaction.[47] Treatment of *o*-formylaniline (**74**) with aniline in the presence of 10 mol% *p*-toluenesulfonic acid ($TsOH \cdot H_2O$) to obtain **75** imine resulted instead in the formation of the quinazoline

derivative **76**. Acid catalysis proved to be indispensable for the cyclization, suggested to proceed *via* the mechanism shown in Scheme 24. The authors studied the effect of different substituents of the aniline and the type of the amine moiety on reactivity as well.



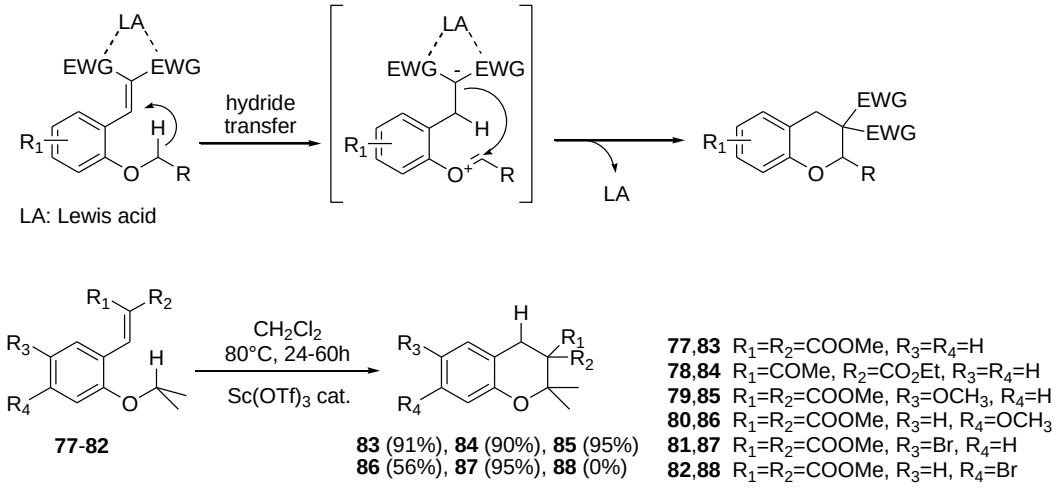
Scheme 24. Extension of the *tert*-amino effect for the synthesis of quinazolines.



Scheme 25. Lewis-acid (LA) catalysis of *tert*-amino effect cyclization.

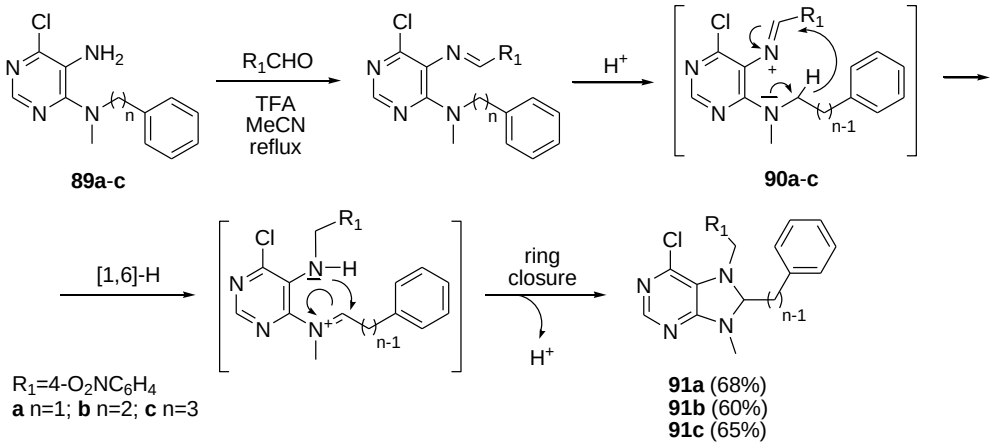
iii) Murarka *et al*. investigated application of Lewis acid catalysts for *tert*-amino effect cyclization[48] (Scheme 25.), aiming to broaden the applicability of the reaction, the scope of which is frequently limited by the often required harsh reaction conditions. Studying cyclization of alkylidene 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 **7** to **11**.

iv) McQuaid *et al*. reported hydride transfer initiated cyclization of *ortho*-vinylaryl alkyl ethers,[49] leading to substituted dihydrobenzopyrans, a reaction analogous to *tert*-amino effect (Scheme 26.). Aryl ether substrates are significantly less reactive compared to analogous *tert*-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 (**77**-**82**→**83**-**88**), 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.



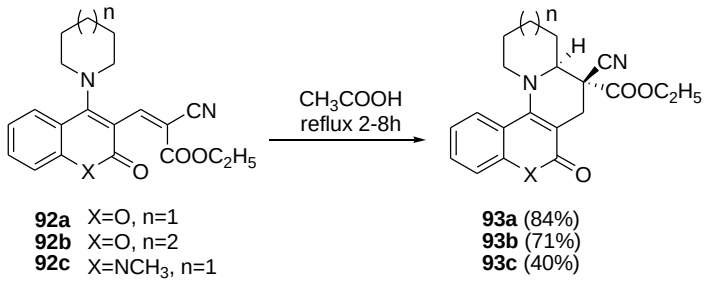
Scheme 26. Examples for hydride transfer initiated cyclizations of *ortho*-vinylaryl alkyl ethers.

v) Che *et al*. reported synthesis of 7,8,9-trisubstituted dihydropurine derivatives *via tert*-amino effect.[50] Treating **89a-c** substituted pyrimidines with an aromatic aldehyde in the presence of trifluoroacetic acid (TFA) led to the formation of the corresponding dihydropurine derivatives **91a-c**. The cyclization was suggested to proceed *via* an iminium intermediate (**90a-c**) undergoing a [1,6]-hydrogen shift, as shown in Scheme 27.



Scheme 27. Synthesis of 7,8,9-trisubstituted dihydropurine derivatives *via tert*-amino effect.

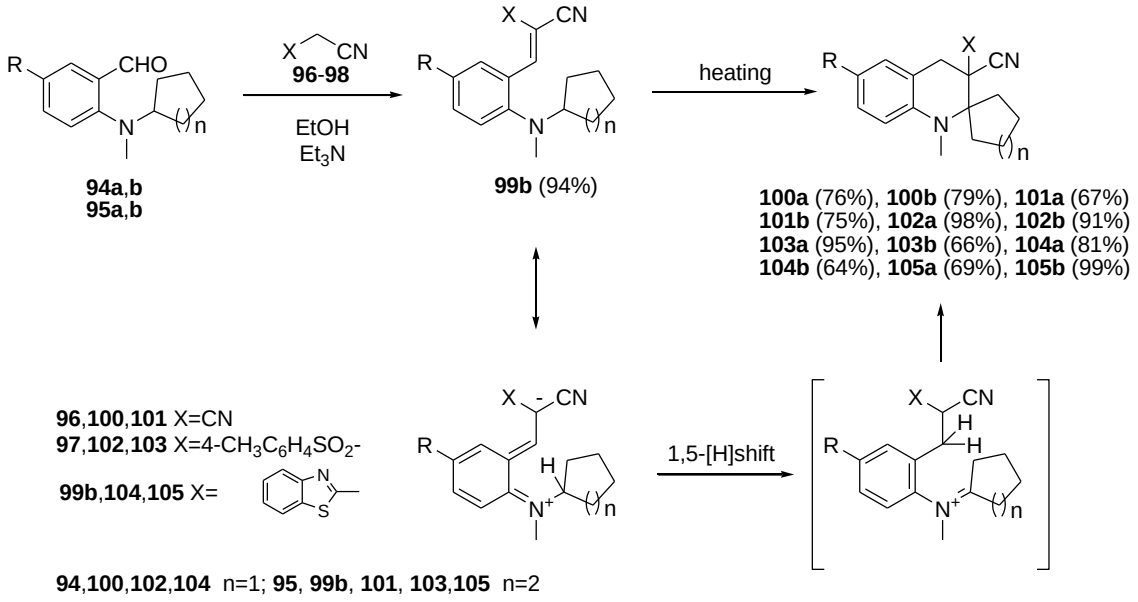
vi) Ivanov *et al*. applied *tert*-amino effect cyclizations to obtain 1,2-fused 5*H*-chromeno[4,3-*b*]pyridin-5-one and 6*H*-benzo[*h*][1,6]naphthyridin-5-one ring systems[51] from 3-vinyl-4-dialkylaminocoumarins/2-quinolones (e.g. **92a-c**). Cyclized products (**93a-c**) were obtained upon heating in glacial acetic acid (Scheme 28.).



Scheme 28. Extension of the *tert*-amino effect to coumarin and 2-quinolone systems.

vii) Syntheses of spirocyclic compounds *via tert*-amino effect have been earlier described by applying cyclic active methylene components, such as 1*H*-indene-1,3(2*H*)-dione, *N*,*N*-dimethylbarbituric acid or Meldrum's acid. Tverdokhlebov *et al*. studied

incorporation of a spiro centre by applying a suitable cycloalkylamino moiety instead.[52] Treatment of the appropriate aldehydes (**94a**,**b**,**95a**,**b**) with active methylene agents (**96-98**) led directly to spirocyclic 1,2,3,4-tetrahydroquinoline derivatives (**100**-**105**) under mild conditions (refluxing EtOH), except for **99b**, in this latter case the Knoevenagel adduct was isolated. Nevertheless, also **99b** could be converted to the corresponding quinoline **105b** in refluxing DMF (Scheme 29.).



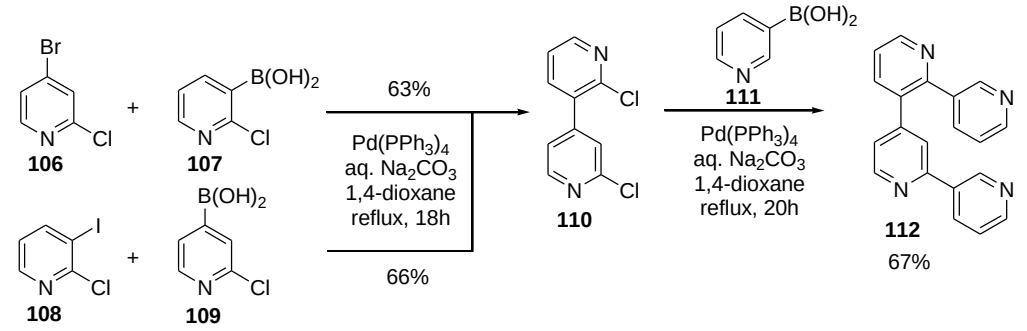
Scheme 29. Synthesis of 1,2,3,4-tetrahydroquinoline-2-spirocycloalkanes *via tert*-amino effect.

1.7 Regioselective Suzuki-couplings. Synthesis of unsymmetrically diaryl-substituted pyridazines

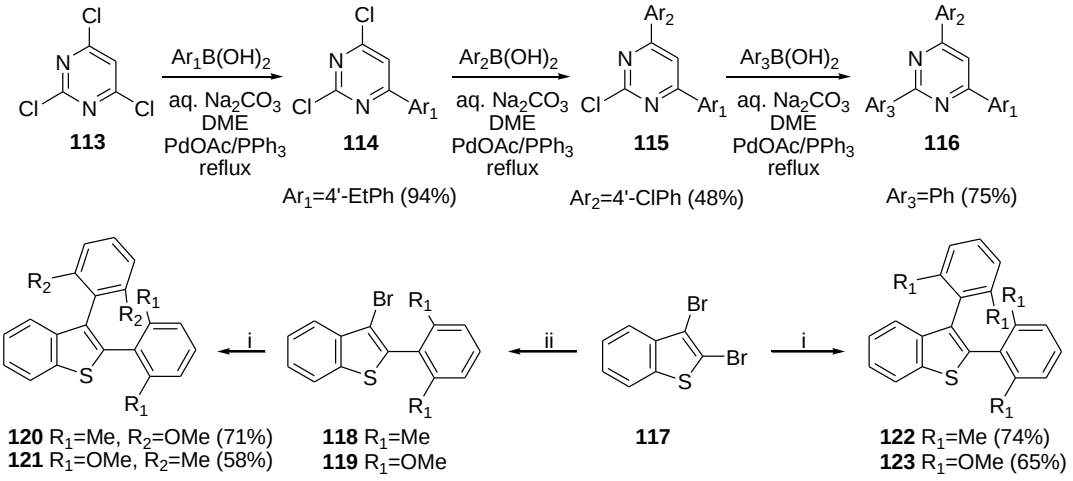
Suzuki reaction (i.e. palladium catalyzed cross-couplings of organoboron compounds and organic halides or triflates) became a powerful method for the formation of carbon-carbon bonds. The mechanism of Suzuki reaction (analogous to that of other cross-coupling reactions) involves: i) oxidative addition of an organic halide to the Pd(0) catalyst to form Pd(II) (the relative reactivity of halides decreasing in the order of I > OTf > Br >> Cl), ii) transmetallation between the alkylborate complex and Pd(II), iii) reductive elimination regenerating Pd(0) and leading to the formation of the carbon-carbon bond. Suzuki cross-coupling has several advantages, like the generally mild reaction conditions, commercial or synthetic availability of various boronic acids, relative safety of the boronic acids (compared to e.g. organostannanes) and the by-

products, moreover, the reaction is unaffected by the presence of water and tolerates various functional groups.[53,54]

Subsequent palladium-catalyzed Suzuki reactions could be conveniently used for the synthesis of unsymmetrically substituted terphenyls or heteroaryl derivatives. Selectivity could be achieved by substituting two different halogen atoms, exploiting their different reactivity – as exemplified by a two-step total synthesis of nemertelline (**112**) starting from 4-bromo-2-chloropyridine (**106**) or 2-chloro-3-iodopyridine (**108**).[55] The first couplings with chloropyridinyl boronic acids afforded selectively the 2,2'-dichloro-3,4'-bipyridine product (**110**) (Scheme 30.).



Scheme 30. Two-step total synthesis of nemertelline *via* subsequent Suzuki-couplings.



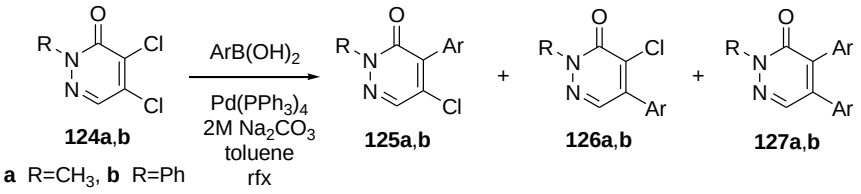
i) $ArB(OH)_2$ (for **122**,**123**: 2.5 eq) , $Pd(PPh_3)_4$, $Ba(OH)_2$, DME-H_2O, reflux
ii) $ArB(OH)_2$, $Pd(PPh_3)_4$, aq. Na_2CO_3, DME-EtOH, reflux

Scheme 31. Regioselective Suzuki-couplings on a heterocyclic core.

In couplings of heterocycles, regioselectivity even for identical halogen atoms can occur due to i) different electrophilicity of the carbon atoms, Pd(0) reacting preferentially at

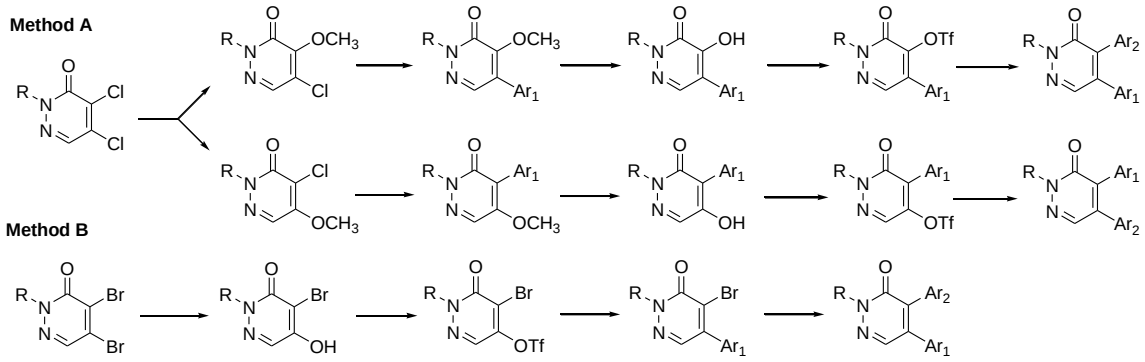
the most electron-deficient position; ii) coordination of Pd(0) to a heteroatom in the oxidative addition step, that might facilitate the reaction; iii) steric hindrance, that could substantially influence the oxidative addition and the transmetallation step, therefore, monosubstituted products might react slower.[56] Scheme 31. summarizes some examples of regioselective couplings on a heterocyclic core (pyrimidine: **113→114**, **114→115**; benzothiophene: **117→118**,**119**).[57,58]

Suzuki couplings of halopyridazin-3(2*H*)-ones have been extensively studied by the Maes-Lemiére group.[59] For such studies, mainly readily available chloropyridazinones were used, instead of the more favourable, but more expensive bromo or iodo derivatives, as also chloro substituent was found to show sufficient reactivity. Synthetic pathways applying Suzuki-coupling on pyridazine were later elaborated for the preparation of various pyridazino-fused ring systems with contributions of the groups of Mátyus and Riedl.[60] Although 4,5-dichloropyridazin-3(2*H*)-ones were found to afford the coupled products with high yields in Suzuki-reaction, selective arylations at the 4 or 5 position with one equivalent of boronic acid failed, as in such cases a mixture containing the (4/5)-monoaryl (**125**, **126**) and biaryl products (**127**) was obtained (Scheme. 32.)



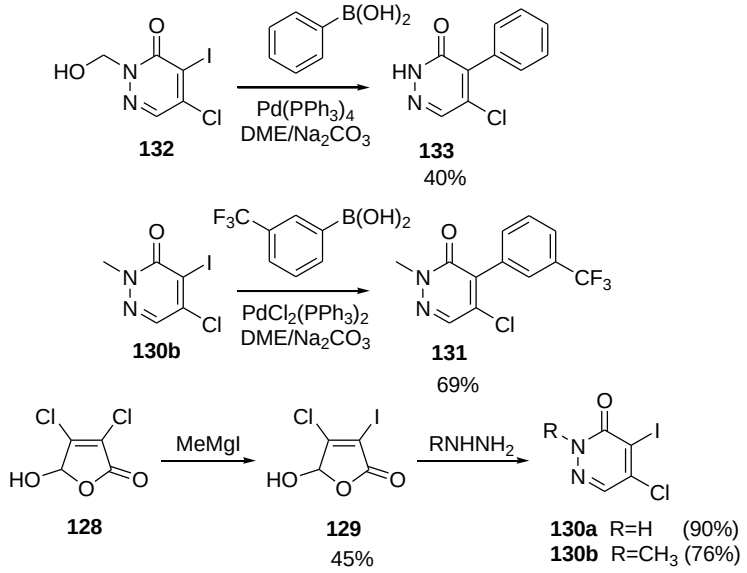
Scheme 32. Suzuki coupling of 4,5-dichloropyridazin-3(2*H*)ones.

To overcome selectivity problems, for the synthesis of unsymmetrically diarylated derivatives use of 'provisionally masked functionalities' (typically a methoxy group) (Method A) or exploitation of the different reactivity of bromo and triflate substituents (Method B) have been reported in the literature. The first approach comprises i) regioselective introduction of the methoxy group, ii) Suzuki coupling on the remaining chloro atom, iii) conversion of methoxy derivatives *via* hydroxyl compounds to triflates (i.e. a good leaving group for a second Suzuki reaction), iv) second Suzuki reaction. For comparison, the two approaches are summarized in Scheme 33.[59,61]



Scheme 33. Synthesis of unsymmetrically 4,5-diarylated 3(2*H*)-pyridazinones.

As the result of a screening, Gong and He achieved a direct, single step synthesis of 5-aryl-4-chloropyridazinones.[62] Coupling of 4,5-dichloro-2-methylpyridazin-3(2*H*)-one with phenylboronic acid (applied in 1:1 ratio) in DMF at rt with $Pd(PEt_3)_2Cl_2$ as catalyst afforded the 5-aryl product with a 170-fold selectivity. No further studies on the limitation and the scope of the approach were undertaken however.



Scheme 34. Regioselective Suzuki-couplings of 5-chloro-4-iodopyridazin-3(2*H*)-ones.

5(4)-Chloro-4(5)-iodopyridazin-3(2*H*)-ones - exploiting different reactivity of different halogens - have been rarely used for regioselective Suzuki couplings, despite the relatively easy accessibility of 5(4)-chloro-4(5)-iodopyridazin-3(2*H*)-ones *via* chloro displacement reactions of 4,5-dichloropyridazin-3(2*H*)-one[63] (as will be later discussed) or its mucochloric acid precursor (Scheme 34., **128→129**).[64] Such examples include

coupling reactions described by Stevenson *et al*.[65] and by Haider *et al*.[66] (**130b→131**, **132→133**),[92] applying the 5-chloro-4-iodo isomers, whereas couplings with 4-chloro-5-iodo isomers will be discussed herein.

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

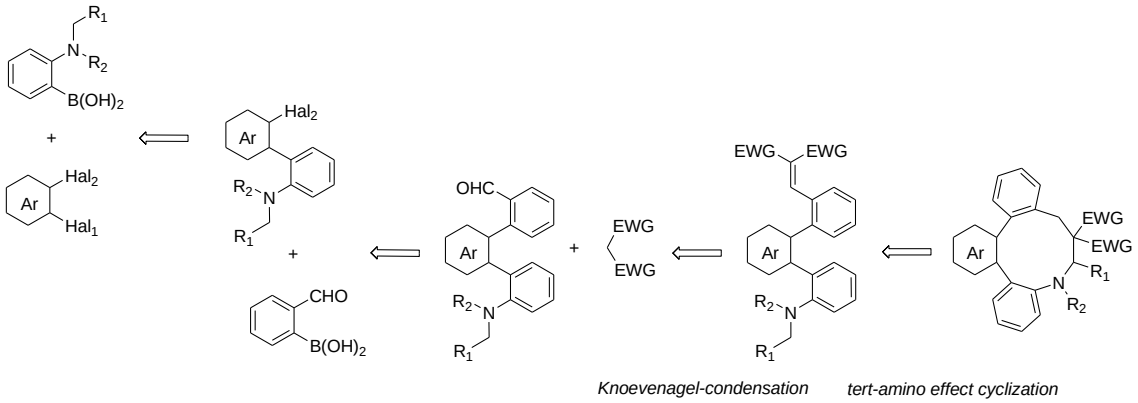
Vascular adhesion protein-1 (VAP-1) has recently become an emerging anti-inflammatory target,[67,68] as illustrated by the growing number of patent applications disclosing novel small molecule VAP-1 inhibitors.[69-73] Besides being an adhesion protein involved in inflammation, genetic encoding revealed sequence identity of VAP-1 and semicarbazide-sensitive amine oxidase (SSAO) [primary amine-oxidase, EC 1.4.3.21.],[74] 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.[75-79] 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.[80-84] 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.[69,70,72,73]

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 (as will be later discussed herein).

2 Aims of the work

Cyclizations *via tert*-amino effect have been successfully used for the synthesis of various heterocyclic compounds, as illustrated by the examples in the previous section. Recently, possible extensions of the *tert*-amino effect to compounds with the interacting *tert*-amino and vinyl groups in the *ortho* positions of connected aryl rings or in the *peri* positions of a fused ring system 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.

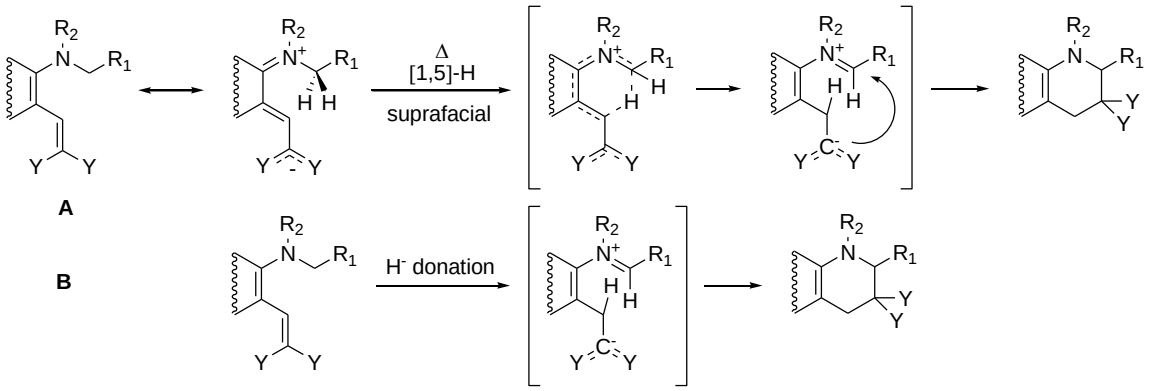
The aims of the present work were to explore further extensions of the *tert*-amino effect. We set out to study possible cyclizations of model compounds having the key vinyl and *tert*-amino moieties in *ortho-ortho"* positions of two aryl rings connected *via* a third benzene/pyridazine ring (Scheme 35.). Applying such novel type of cyclizations, synthesis of hitherto unpublished azecine-fused ring systems could be achieved, which themselves or through further modifications could be interesting compounds for our ongoing medicinal chemical projects.



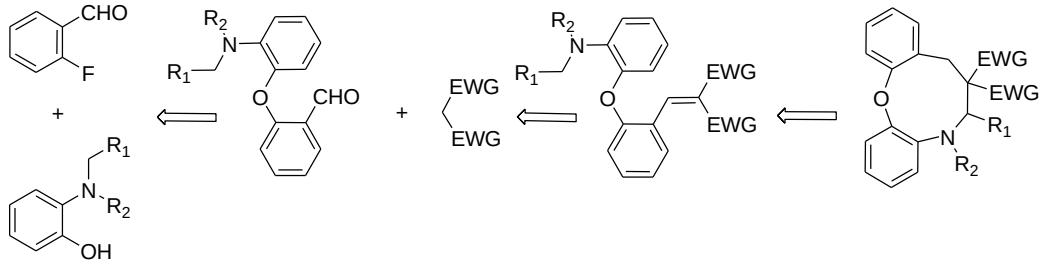
Scheme 35. Design and retrosynthetic route of the model compounds to be studied 1.

As the rate-limiting step of *tert*-amino effect type 2 cyclization, a [1,*n*] hydrogen migration has been suggested in the literature, which results in a dipolar intermediate. We also planned to study, whether *tert*-amino effect cyclization could operate in non-conjugated systems, where a previously suggested sigmatropic process (pathway A) cannot take place (Scheme 36.). Cyclization of such model compounds might demonstrate that the reaction could operate also *via* direct hydride donation (pathway

B), which may provide a broader significance for this type of cyclization reactions. For such studies, appropriately substituted biaryl-ether model compounds have been chosen (Scheme 37.).



Scheme 36. Cyclizations *via tert*-amino effect – mechanistic considerations.



Scheme 37. Design and retrosynthetic route of the model compounds to be studied 2.

Furthermore, as a part of our ongoing SSAO research program in the Department of Organic Chemistry (Semmelweis University), among oxime derivatives with potential VAP-1 inhibitory effect we also planned to utilize some aldehyde intermediates used for studying *tert*-amino effect.

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 capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature, if not indicated otherwise, in the solvent indicated, with a Varian Mercury Plus spectrometer at a frequency of 400 / 600 or 100 / 150 MHz or with a Bruker 400 MHz spectrometer, at a frequency of 400 or 100 MHz, and are reported in ppm. Spectra were recorded at 400 MHz (^{1}H) or 100 MHz (^{13}C), if not indicated otherwise. Chemical shifts are given on the δ-scale relative to tetramethylsilane or the residual solvent signal as an internal reference. 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-HMBC measurements were run.

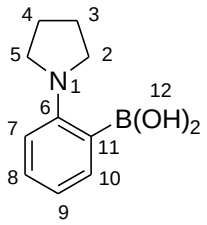
Mass spectra utilizing fast atom bombardment ionization were recorded on a VG-ZAB-2SEQ spectrometer. Elemental analyses were performed on a Carlo Erba 1012 apparatus. Microwave (MW) irradiation experiments were carried out in a monomode CEM-Discover MW reactor, using the standard configuration as delivered, including proprietary software. The experiments were executed either in 10 mL MW process vials or in open-vessel mode, with control of the temperature by infrared detection. After completion of the reaction, the vial/flask was cooled to 50 °C by air jet cooling. For flash column chromatography purification, Kieselgel 60 (Merck, 0.040-0.063 mm) was used; for TLC analysis, Silica gel 60 F_{254} (Merck) plates were applied. Solvent mixtures used for chromatography are always given in a vol/vol ratio. The structures of all compounds were consistent with their analytical and spectroscopic data. Compounds **136a**,[85] **138a**[86,87] and **135a**[63], **164a**[88], **164b**[89] and **164c**[89] were prepared according to the literature procedures cited. Compounds **136a**,[85] **138a**,[86,87] **135a**,[63] **140a**,[90,91] **140b**[92] and **151**[93,94] had melting points and spectral data identical with the published values. Spectroscopic data are provided for compounds described previously but not characterized spectroscopically.

Throughout the section an arbitrary numbering is used for the compounds.

3.1 Synthesis of boronic acids

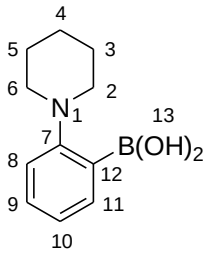
A four-neck, round-bottom flask was charged with 1-(2-bromophenyl)pyrrolidine[8] (4.97 g, 22.00 mmol; for **136b**) or 1-(2-bromophenyl)piperidine[8] (5.28 g, 22.00 mmol; for **136c**) and anhydrous THF (75 mL) under argon. *n*-BuLi (2.5 M solution in *n*-hexane, 9.90 mL, 24.75 mmol) was added to the solution dropwise (over 20 min) at -78 °C. The reaction mixture was stirred for 75 min at -78 °C, after which time $B(O^iPr)_3$ (10.15 mL, 44.00 mmol) was added dropwise (over 20 min) to the suspension, followed by a further 1 h of stirring at -78 °C. Subsequently, the reaction mixture was allowed to warm up to room temperature and stirred overnight. The following day, the reaction mixture was cooled to -70 °C and 1 M HCl solution (44 mL) was added slowly (over 15 min). The mixture was next allowed to warm up to 0 °C and stirred for 30 min. H_2O (100 mL) and EtOAc (100 mL) were added, the phases were separated and the organic layer was extracted with H_2O (3×100 mL). The pH of the combined aqueous layers was adjusted to 8 with 2 M NaOH. The aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product obtained was used without further purification.

2-(Pyrrolidin-1-yl)phenylboronic acid (136b)



Crude product: white crystals (3.03 g, ~85% pure according to ^{1}H NMR), R_f=0.40 (toluene:EtOH 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.10 (br s, 2H, H-12), 7.22-7.11 (m, 2H, H-8,10), 6.71-6.67 (m, 2H, H-7,9), 3.23-3.17 (m, 4H, H-2,5), 1.92-1.85 (m, 4H, H-3,4). ^{13}C NMR (CD_3OD): 148.3 (C-6), 135.2 (C-10), 125.6 (C-9), 123.6 (C-8), 117.7 (C-7), 56.0 (C-2,5), 25.7 (C-3,4) (C-B(OH)$_2$ was not observed).

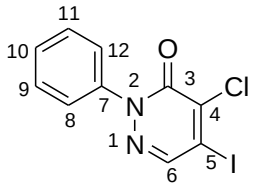
2-(Piperidine-1-yl)phenylboronic acid (136c)



Crude product: white crystals (3.83 g, ~70% pure according to ^{1}H NMR), R_f=0.37 (toluene:EtOH 2:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.34 (br s, 2H, H-13), 7.93 (dm, *J*=7.6 Hz, 1H, H-11), 7.45 (tm, *J*=7.6 Hz, 1H, H-9), 7.31 (dm, *J*=7.6 Hz, 1H, H-8), 7.24 (tm, *J*=7.6 Hz, 1H, H-10), 2.95-2.87 (m, 4H, H-2,6), 1.84-1.76 (m, 4H, H-3,5), 1.67-1.55 (br m, 2H, H-4). ^{13}C NMR ($CDCl_3$) δ (ppm): 160.4 (C-7), 136.5 (C-11), 132.4 (C-9),

126.2 (C-10), 121.7 (C-8), 56.1 (C-2,6), 27.3 (C-3,5), 24.3 (C-4) (C-$B(OH)_2$ was not observed).

3.2 Halogen displacement reactions of 4,5-dichloropyridazin-3(2H)-ones with sodium iodide



Compound **135b** was prepared by applying the procedure cited for **135a.**[63] To a solution of 4,5-dichloro-2-phenylpyridazin-3(2*H*)-one (3.62 g, 15.00 mmol) in DMF (30 mL), NaI (4.50 g, 30.00 mmol) was added, and the mixture was then heated at reflux for 1 h. Following this, further NaI (2.25 g, 15.00 mmol) was added to the mixture and it was heated at reflux again for 1 h. The latter procedure was repeated once more, and the mixture was heated at reflux for 25 h. Then the DMF was removed *in vacuo*. An aqueous solution (10%) of $Na_2S_2O_3$ was added to the residue until the colour of the iodine had disappeared. The solution was extracted with $CHCl_3$ (4×70 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness. Analytically pure **135b** could be obtained by recrystallization from MeOH. White crystals (3.24 g, 65%), mp 152-153 °C, R_f=0.21 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H, H-6), 7.59-7.54 (m, 2H, H-8,12), 7.50-7.45 (m, 2H, H-9,11), 7.44-7.39 (m, 1H, H-10). ^{13}C NMR ($CDCl_3$) δ (ppm): 155.6 (C-3), 144.3 (C-4), 142.8 (C-6), 141.5 (C-7), 129.6 (C-9/10/11), 129.5 (C-9/10/11), 125.8 (C-8,12), 105.2 (C-5). IR (KBr) υ_{max}: 3054, 1654, 1552, 1126, 896, 754, 688 cm^{-1}. HRMS: calcd for ($C_{10}H_6ClIN_2O+H^+$): 332.9292. Found: 332.9284.

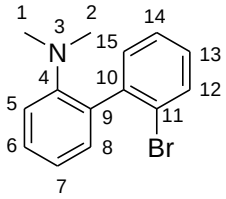
3.3 General procedure for Suzuki cross-coupling reactions. Synthesis of biaryl amines and triaryl aldehydes

To a solution of the appropriate halo compound (10.00 mmol, for **138a-c,150**: 1-bromo-2-iodobenzene (1.25 mL), for **139a**: **138a** (2.76 g), for **139b**: **138b** (3.02 g), for **139c**: **138c** (3.16 g), for **141a**,**c**,**d**: **135a** (2.70 g), for **141b**: **135b** (3.33 g), for **142a**: **141a** (2.64 g), for **142b**: **141b** (3.26 g), for **142c**: **141c** (2.90 g), for **142d**: **141d** (3.04 g)) in DME (50 mL), $Pd(PPh_3)_4$ (578 mg, 0.50 mmol) was added at room temperature under an argon flow. After stirring at room temperature for 10 min, the appropriate boronic acid (12.00 mmol, for **138a**,**141a**,**b**: **136a**[85] (1.98 g), for **138b**,**141c**: **136b** (2.29 g), for

138c,**141d**: **136c** (2.46 g), for **150**: 2-pivalamidophenylboronic acid[95,96] (2.65 g), for **139a-c**,**142a-d**: 2-formylphenylboronic acid (1.80 g)) and aq 2 M Na_2CO_3 solution (10 mL) were added, and the reaction mixture was heated at reflux at 110 °C (oil temperature) until the starting material had been consumed (24-48 h, monitored by TLC). The cooled reaction mixture was poured into H_2O (50 mL). After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel with the eluents indicated below.

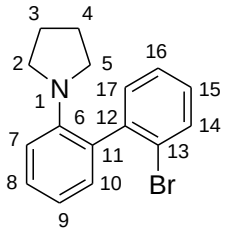
3.3.1 Biphenyl compounds and their pyridazine analogues

2'-Bromo-N,N-dimethylbiphenyl-2-amine (138a)[86,87]



The work-up and purification accorded to the literature procedure cited. White crystals (1.80 g, 65%), mp 55-57 °C (lit. mp 55-57°C)[87], R_f=0.64 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.66 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.37-7.29 (m, 3H, Ar-H), 7.19-7.11 (m, 2H, Ar-H), 7.06 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.00 (tm, *J*=7.6 Hz, 1H, Ar-H), 2.53 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ (ppm): 151.2 (Ar-qC), 143.2 (Ar-qC), 134.4 (Ar-qC), 133.6 (Ar-CH), 132.5 (Ar-CH), 132.5 (Ar-CH), 129.4 (Ar-CH), 128.8 (Ar-CH), 127.8 (Ar-CH), 124.6 (Ar-qC), 121.5 (Ar-CH), 118.6 (Ar-CH), 43.9 ($N(CH_3)_2$). IR (KBr) υ_{max}: 2964, 2834, 1452, 1262, 1022, 802, 744 cm^{-1}. Anal. calcd for $C_{14}H_{14}BrN$ (276.17): C 60.89; H 5.11; N 5.07. Found: C 60.85; H 5.00; N 5.06.

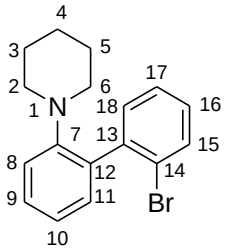
1-(2'-Bromobiphenyl-2-yl)pyrrolidine (138b)



Column chromatography: *n*-hexane: EtOAc 9:1. Colourless oil (1.63 g, 54%), R_f=0.67 (*n*-hexane:EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.64 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.37 (dm, *J*=7.6 Hz, 1H, Ar-H), 7.33-7.26 (m, 2H, Ar-H), 7.16 (ddd, *J*=7.2, 1.8, 0.8 Hz, 1H, Ar-H), 7.08 (dm, *J*=7.6 Hz, 1H, Ar-H), 6.86-6.79 (m, 2H, Ar-H), 2.99-2.85 (m, 4H, NCH_2), 1.80-1.72 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 148.1 (Ar-qC), 144.7 (Ar-qC), 133.1 (Ar-CH), 133.0 (Ar-CH), 132.9 (Ar-CH), 129.1 (Ar-CH), 128.7 (Ar-CH), 128.5 (Ar-qC), 127.4 (Ar-CH), 125.3 (Ar-qC), 117.4 (Ar-CH), 114.7 (Ar-

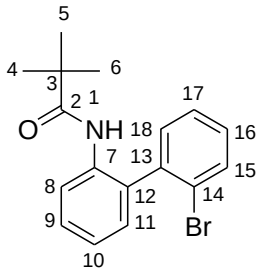
CH), 50.8 (NCH_2), 26.4 (CH_2). IR (KBr) υ_{max}: 2922, 1596, 1498, 1464, 1336, 1154, 1024, 746 cm^{-1}. HRMS: calcd for ($C_{16}H_{16}BrN+H^+$): 302.0544. Found: 302.0535.

1-(2'-Bromobiphenyl-2-yl)piperidine (138c)



Column chromatography: *n*-hexane. Colourless oil (1.93 g, 61%), R_f=0.8 (*n*-hexane:EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.64 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.38 (dm, *J*=7.6 Hz, 1H, Ar-H), 7.34-7.29 (m, 2H, Ar-H), 7.18-7.11 (m, 2H, Ar-H), 7.08-7.01 (m, 2H, Ar-H), 2.82-2.70 (m, 4H, NCH_2), 1.42-1.23 (m, 6H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.8 (Ar-qC), 142.7 (Ar-qC), 136.2 (Ar-qC), 133.4 (Ar-CH), 132.7 (Ar-CH), 131.9 (Ar-CH), 129.5 (Ar-CH), 128.7 (Ar-CH), 127.5 (Ar-CH), 124.7 (Ar-qC), 122.5 (Ar-CH), 119.8 (Ar-CH), 53.4 (NCH_2), 26.8 (CH_2), 24.9 (CH_2). IR (KBr) υ_{max}: 2932, 2794, 1462, 1228, 1026, 924, 748 cm^{-1}. Anal. calcd for $C_{17}H_{18}BrN$ (316.24): C 64.57; H 5.74; N 4.43. Found: C 64.88; H 5.83; N 4.54.

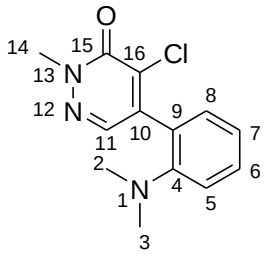
N-(2'-Bromobiphenyl-2-yl)-2,2-dimethylpropanamide (150)



Column chromatography: toluene:EtOAc 16:1. Colourless oil (2.69 g, 81%), R_f=0.47 (toluene: EtOAc 16:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.27 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.73 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.46-7.39 (m, 2H, Ar-H), 7.33-7.28 (m, 2H, Ar-H), 7.21-7.14 (m, 2H, Ar-H), 7.11 (br s, 1H, NH), 1.05 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 177.0 (CO), 139.5 (Ar-qC), 135.9 (Ar-qC), 133.7 (Ar-CH), 132.5 (Ar-CH), 132.4 (Ar-qC), 130.6 (Ar-CH), 130.0 (Ar-CH), 129.8 (Ar-CH), 128.7 (Ar-CH), 124.7 (Ar-CH), 124.7 (Ar-qC), 122.0 (Ar-CH), 40.3 ($C(CH_3)_3$), 28.0 (CH_3). IR (KBr) υ_{max}: 3438, 2960, 1688, 1518, 1442, 1304, 1160, 758 cm^{-1}. Anal. calcd for $C_{17}H_{18}BrNO$ (332.23): C 61.46; H 5.46; N 4.22. Found: C 61.26; H 5.42; N 4.33.

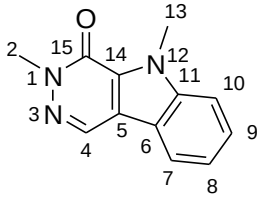
4-Chloro-5-[2-(dimethylamino)phenyl]-2-methylpyridazin-3(2H)-one (141a)

Column chromatography: *n*-hexane:EtOAc 2:1. Yellow crystals (1.98 g, 75%), mp 104-105 °C, R_f=0.36 (*n*-hexane:EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.74 (s, 1H, NCH), 7.40 (ddd, *J*=8.2, 7.5, 1.7 Hz, 1H, Ar-H), 7.27 (dm, *J*=7.5 Hz, 1H, Ar-H), 7.13 (dm,



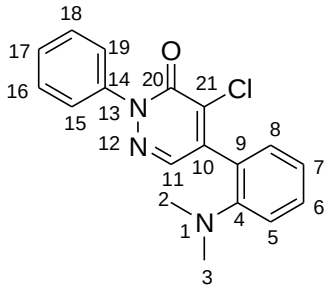
J=8.2 Hz, 1H, Ar-H), 7.08 (tm, *J*=7.5 Hz, 1H, Ar-H), 3.88 (s, 3H, NCH_3), 2.63 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.9 (CO), 152.3 (Ar-qC), 143.2 (Ar-qC), 138.7 (Ar-CH), 133.6 (Ar-qC), 131.7 (Ar-CH), 131.4 (Ar-CH), 126.5 (Ar-qC), 122.6 (Ar-CH), 119.3 (Ar-CH), 44.4 ($N(CH_3)_2$), 41.5 (NCH_3). IR (KBr) υ_{max}: 2922, 1652, 1266, 868, 740 cm^{-1}. Anal. calcd for $C_{13}H_{14}ClN_3O$ (263.72): C 59.21; H 5.35; N 15.93. Found: C 58.95; H 5.18; N 15.64.

3,5-Dimethyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one (140a)[90,91]



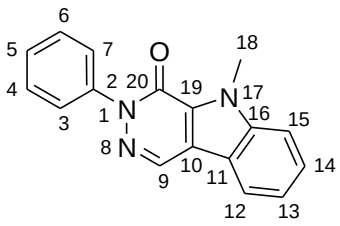
White crystals (recrystallized from MeOH, 299 mg, 14%), mp 214-215 °C (lit. mp 214-215°C)[91], R_f=0.23 (*n*-hexane:EtOAc 2:1). ^1H NMR ($CDCl_3$) δ (ppm): 8.42 (s, 1H, NCH), 7.97 (d, *J*=8.0 Hz, 1H, Ar-H), 7.58-7.52 (m, 1H, Ar-H), 7.48 (d, *J*=8.0 Hz, 1H, Ar-H), 7.39-7.35 (m, 1H, Ar-H), 4.32 (s, 3H, NCH_3), 3.91 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.7 (CO), 141.2 (Ar-qC), 132.9 (Ar-CH), 131.3 (Ar-qC), 127.9 (Ar-CH), 122.5 (Ar-CH), 121.7 (Ar-CH), 120.9 (Ar-qC), 118.2 (Ar-qC), 111.2 (Ar-CH), 39.9 (NCH_3), 32.2 (NCH_3). IR (KBr) υ_{max}: 3054, 2940, 1644, 1522, 1476, 1340, 952, 740 cm^{-1}. Anal. calcd for $C_{12}H_{11}N_3O$ (213.23): C 67.59; H 5.20; N 19.71. Found: C 67.23; H 5.03; N 19.56.

4-Chloro-5-[2-(dimethylamino)phenyl]-2-phenylpyridazin-3(2H)-one (141b)



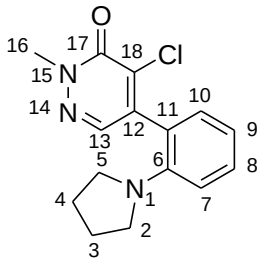
Column chromatography: *n*-hexane:EtOAc 3:1. Yellow crystals (2.28 g, 70%), mp 90-92 °C, R_f=0.33 (*n*-hexane:EtOAc 4:1). ^1H NMR ($CDCl_3$) δ (ppm): 7.88 (s, 1H, NCH), 7.72-7.67 (m, 2H, Ar-CH), 7.53-7.47 (m, 2H, Ar-CH), 7.46-7.36 (m, 3H, Ar-CH), 7.17 (dm, *J*=8.0 Hz, 1H, Ar-CH), 7.12 (tm, *J*=7.6 Hz, 1H, Ar-CH), 2.68 (s, 6H, $N(CH_3)_2$). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.2 (CO), 152.5 (Ar-qC), 143.0 (Ar-qC), 142.2 (Ar-qC), 139.5 (Ar-CH), 134.7 (Ar-qC), 131.8 (Ar-CH), 131.6 (Ar-CH), 129.5 (Ar-CH), 129.0 (Ar-CH), 126.4 (Ar-qC), 125.9 (Ar-CH), 122.7 (Ar-CH), 119.4 (Ar-CH), 44.6 ($N(CH_3)_2$). IR (KBr) υ_{max}: 2930, 2782, 1656, 1486, 1320, 1146, 756 cm^{-1}. Anal. calcd for $C_{18}H_{16}ClN_3O$ (325.79): C 66.36; H 4.95; N 12.90. Found: C 65.98; H 4.83; N 12.56.

5-Methyl-3-phenyl-3,5-dihydro-4H-pyridazino[4,5-b]indol-4-one (140b)[92]



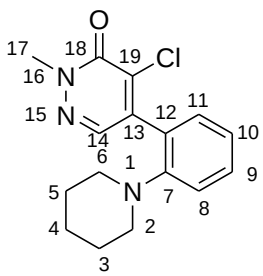
White crystals (recrystallized from MeOH, 551 mg, 20%), mp 171-172 °C (lit. mp 169°C)[92], R_f=0.17 (*n*-hexane:EtOAc 3:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.62 (s, 1H, NCH), 8.05 (dm, *J*=8.0 Hz, 1H, Ar-H), 7.67-7.48 (m, 6H, Ar-H), 7.45-7.39 (m, 2H, Ar-H), 4.38 (s, 3H, NCH_3). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.6 (CO), 142.6 (Ar-qC), 141.6 (Ar-qC), 133.9 (Ar-CH), 131.7 (Ar-qC), 129.6 (Ar-CH), 129.5 (Ar-CH), 128.6 (Ar-CH), 128.1 (Ar-CH), 126.9 (Ar-CH), 121.8 (Ar-CH), 121.0 (Ar-qC), 118.0 (Ar-qC), 111.4 (Ar-CH), 32.4 (NCH_3). IR (KBr) υ_{max}: 3054, 2928, 1658, 1530, 1300, 956, 738 cm^{-1}. Anal. calcd for $C_{17}H_{13}N_3O$ (275.30): C 74.17; H 4.76; N 15.26. Found: C 73.81; H 4.50; N 15.22.

4-Chloro-2-methyl-5-(2-pyrrolidin-1-ylphenyl)pyridazin-3(2H)-one (141c)



Column chromatography: *n*-hexane:EtOAc 4:1. Yellow crystals (2.20 g, 76%), mp 91-92 °C, R_f=0.24 (*n*-hexane:EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.75 (s, 1H, NCH), 7.31 (ddd, *J*=8.5, 7.2, 1.7 Hz, 1H, Ar-H), 7.14 (dd, *J*=7.7, 1.7 Hz, 1H, Ar-H), 6.91 (dd, *J*=8.5, 1.1 Hz, 1H, Ar-H), 6.86 (ddd, *J*=7.7, 7.2, 1.1 Hz, 1H, Ar-H), 3.87 (s, 3H, NCH_3), 3.04-2.98 (m, 4H, NCH_2), 1.89-1.81 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.6 (CO), 148.4 (Ar-qC), 144.6 (Ar-qC), 138.5 (Ar-CH), 132.9 (Ar-qC), 131.7 (Ar-CH), 131.0 (Ar-CH), 120.3 (Ar-qC), 118.4 (Ar-CH), 115.3 (Ar-CH), 51.7 (NCH_2), 41.6 (NCH_3), 26.4 (CH_2). IR (KBr) υ_{max}: 2920, 2854, 1656, 1446, 1358, 1022, 868, 746 cm^{-1}. Anal. calcd for $C_{15}H_{16}ClN_3O$ (289.76): C 62.18; H 5.57; N 14.50. Found: C 61.91; H 5.16; N 14.31.

4-Chloro-2-methyl-5-(2-piperidin-1-ylphenyl)pyridazin-3(2H)-one (141d)



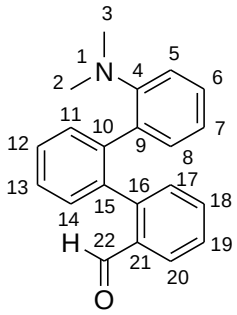
Column chromatography: CH_2Cl_2. Yellow crystals (1.97 g, 65%), mp 96-97 °C, R_f=0.38 (CH_2Cl_2:EtOAc 95:5). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.80 (s, 1H, NCH), 7.41 (ddd, *J*=8.4, 7.2, 1.6 Hz, 1H, Ar-H), 7.31 (dm, *J*=7.6 Hz, 1H, Ar-H), 7.15-7.09 (m, 2H, Ar-H), 3.88 (s, 3H, NCH_3), 2.81 (br m, 4H, NCH_2), 1.48 (br m, 6H, CH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.0 (CO), 152.6 (Ar-qC),

142.9 (Ar-qC), 139.2 (Ar-CH), 133.7 (Ar-qC), 131.6 (Ar-CH), 131.5 (Ar-CH), 127.8 (Ar-qC), 123.3 (Ar-CH), 120.3 (Ar-CH), 54.1 (NCH_2), 41.5 (NCH_3), 26.7 (CH_2), 24.6 (CH_2). IR (KBr) υ_{max}: 2918, 1654, 1448, 1228, 1022, 866, 750 cm^{-1}. Anal. calcd for $C_{16}H_{18}ClN_3O$ (303.79): C 63.26; H 5.97; N 13.83. Found: C 62.90; H 5.62; N 13.49.

3.3.2 Triphenyl compounds and their pyridazine analogues

At room temperature, in the ^1H and ^{13}C NMR spectra of some aldehydes (**139a-c**, **142a-d**) and vinyl (**152a-c**, **153a-d**) compounds, broad signals or two separate signal sets with different population ratios were observed, due to hindered rotation around the C-C bonds connecting the phenyl (and pyridazine) rings. For unambiguous structure elucidation, NMR spectra were also recorded at elevated temperatures (100/120 °C), if necessary.

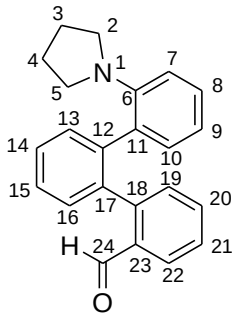
2''-Dimethylamino-1,1':2',1''-terphenyl-2-carbaldehyde (139a)



Column chromatography: toluene:*n*-hexane 1:1. Yellow crystals (2.11 g, 70%), mp 119-120 °C, R_f=0.35 (toluene:*n*-hexane 1:1). ^1H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 9.72 (s, 1H, H-22), 7.83 (dm, *J*=7.6 Hz, 1H, H-20), 7.57 (td, *J*=7.4, 1.4 Hz, 1H, H-12), 7.53-7.38 (m, 2H, H-11,13), 7.35-7.25 (m, 3H, H-8,14,19), 7.21-7.10 (m, 2H, H-6,18), 7.03 (tm, *J*=7.3 Hz, 1H, H-7), 6.70-6.63 (m, 2H, H-5,17), 1.97 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 191.5 (C-22), 150.3 (C-4), 145.6 (C-16), 140.6 (C-10), 136.9 (C-15), 134.6 (C-9), 133.8 (C-21), 131.6 (C-8), 131.5 (C-18), 131.2 (C-14), 130.6 (C-11), 130.4 (C-17), 128.6 (C-12), 128.5 (C-6), 126.8 (C-19), 126.5 (C-13), 125.0 (C-20), 122.2 (C-7), 118.0 (C-5), 42.6 (C-2,3). IR (KBr) υ_{max}: 2940, 2862, 1686, 1594, 1258, 1096, 940, 754 cm^{-1}. Anal. calcd for $C_{21}H_{19}NO$ (301.38): C 83.69; H 6.35; N 4.65. Found: C 83.33; H 6.21; N 4.54.

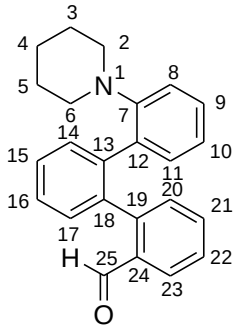
2''-Pyrrolidin-1-yl-1,1':2',1''-terphenyl-2-carbaldehyde (139b)

Column chromatography: toluene. Yellow crystals (1.74 g, 53%), mp 104-105 °C, R_f=0.40 (toluene). ^1H NMR (DMSO-d_6, 120 °C) δ (ppm): 9.65 (br s, 1H, H-24), 7.64 (br d, *J*=8.0 Hz, 1H, H-22), 7.56-7.48 (m, 2H, H-13,14), 7.47-7.35 (br m, 2H, H-15,20),



7.33-7.27 (m, 2H, H-16,21), 7.09 (br s, 1H, H-19), 7.05 (dm, *J*=7.2 Hz, 1H, H-10), 7.01 (tm, *J*=7.4 Hz, 1H, H-8), 6.73 (t, *J*=7.2 Hz, 1H, H-9), 6.50 (dm, *J*=8.0 Hz, 1H, H-7), 2.53-2.00 (br m, 4H, H-2,5), 1.54-1.51 (m, 4H, H-3,4). ^{13}C NMR (DMSO-d_6, 120 °C) δ (ppm): 189.6 (C-24), 147.0 (C-6), 144.0 (C-18), 141.5 (C-12), 136.6 (C-17), 132.6 (C-23), 131.5 (C-10), 131.2 (C-20), 130.4 (C-11), 130.4 (C-19), 129.7 (C-16), 129.6 (C-13), 127.6 (C-14), 127.2 (C-8), 126.3 (C-21), 126.0 (C-15), 125.0 (C-22), 117.8 (C-9), 114.2 (C-7), 49.3 (C-2,5), 23.7 (C-3,4). IR (KBr) υ_{max}: 2918, 2850, 1692, 1596, 1468, 1334, 754 cm^{-1}. Anal. calcd for $C_{23}H_{21}NO$ (327.42): C 84.37; H 6.46; N 4.28. Found: C 84.05; H 6.24; N 4.28.

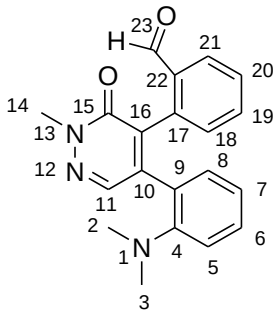
2''-Piperidin-1-yl-1,1':2',1''-terphenyl-2-carbaldehyde (139c)



Column chromatography: toluene. White crystals (2.53 g, 74%), mp 131-133 °C, R_f=0.30 (toluene). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.77 (br s, 1H, H-25), 7.66 (br d, *J*=7.6 Hz, 1H, H-23), 7.56-7.50 (m, 1H, H-15), 7.49-7.38 (br m, 3H, H-14,16,21), 7.35-7.29 (m, 2H, H-17,22), 7.21 (br m, 1H, H-20), 7.13 (tm, *J*=7.8 Hz, 1H, H-9), 7.09 (dm, *J*=7.8 Hz, 1H, H-11), 6.93 (t, *J*=7.6 Hz, 1H, H-10), 6.79 (dm, *J*=8.0 Hz, 1H, H-8), 2.52-2.38 (br m, 4H, H-2,6), 1.45-1.20 (m, 6H, H-3,4,5). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.6 (C-25), 150.9 (C-7), 144.3 (C-19), 140.3 (C-13), 135.9 (C-18), 134.2 (C-12), 132.6 (C-24), 131.6 (C-11), 131.4 (C-21), 131.0 (C-20), 130.3 (C-17), 127.9 (C-9), 127.6 (C-15), 126.4 (C-16), 126.4 (C-22), 125.3 (C-23), 121.4 (C-10), 118.1 (C-8), 51.8 (C-2,6), 24.5 (C-3,5), 22.9 (C-4). IR (KBr) υ_{max}: 2936, 2852, 1690, 1594, 1440, 1196, 756 cm^{-1}. HRMS calcd for ($C_{24}H_{23}NO+H^+$): 342.1858. Found: 342.1845.

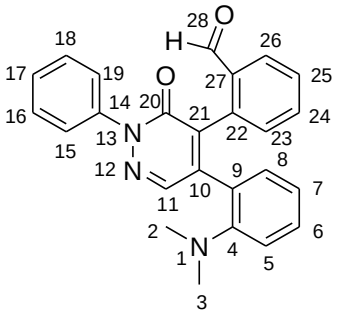
2-{5-[2-(Dimethylamino)phenyl]-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl} benzaldehyde (142a)

Column chromatography: toluene:EtOAc 4:1. Yellow crystals (2.43 g, 73%), mp 156-158 °C, R_f=0.26 (toluene:EtOAc 4:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.79 (s, 1H, H-23), 8.01 (s, 1H, H-11), 7.82 (dm, *J*=7.2 Hz, 1H, H-21), 7.41-7.33 (m, 2H, H-19,20), 7.20 (tm, *J*=7.2 Hz, 1H, H-6), 7.13 (br d, *J*=7.2 Hz, 1H, H-8), 6.94 (t, *J*=7.2 Hz,



1H, H-7), 6.89 (br d, *J*=7.2 Hz, 1H, H-18), 6.84 (dm, *J*=8.0 Hz, 1H, H-5), 3.77 (s, 3H, H-14), 2.34 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.4 (C-23), 159.0 (C-15), 150.5 (C-4), 141.3 (C-10), 137.6 (C-11), 135.9 (C-17), 134.6 (C-22), 134.5 (C-16), 131.9 (C-19), 130.1 (C-8), 129.4 (C-6), 129.3 (C-18), 127.6 (C-20), 126.9 (C-9), 126.6 (C-21), 121.1 (C-7), 118.0 (C-5), 42.6 (C-2,3), 39.3 (C-14). IR (KBr) υ_{max}: 2920, 2850, 1696, 1642, 1594, 1494, 1268, 736 cm^{-1}. Anal. calcd for $C_{20}H_{19}N_3O_2$ (333.38): C 72.05, H 5.74; N 12.60. Found: C 72.15; H 5.72; N 12.64.

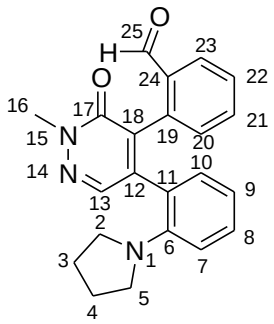
2-{5-[2-(Dimethylamino)phenyl]-2-phenyl-3-oxo-2,3-dihydropyridazin-4-yl} benzaldehyde (142b)



Column chromatography: toluene:EtOAc 3:1. Yellow crystals (2.69 g, 68%), mp 191-192 °C, R_f=0.51 (toluene:EtOAc 3:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.92 (s, 1H, H-28), 8.18 (s, 1H, H-11), 7.86 (dm, *J*=7.2 Hz, 1H, H-26), 7.72-7.68 (m, 2H, H-15,19), 7.55-7.49 (m, 2H, H-16,18), 7.45-7.37 (m, 3H, H-17,24,25), 7.24 (tm, *J*=7.8 Hz, 1H, H-6), 7.19 (br d, *J*=7.2 Hz, 1H, H-8), 7.00-6.93 (m, 2H, H-7,23), 6.89 (dm, *J*=8.0 Hz, 1H, H-5), 2.43 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.5 (C-28), 158.6 (C-20), 150.6 (C-4), 141.4 (C-14), 140.9 (C-10), 138.6 (C-11), 136.1 (C-21), 135.4 (C-22), 134.7 (C-27), 132.0 (C-24), 130.1 (C-8), 129.5 (C-6), 129.3 (C-23), 127.9 (C-16,18), 127.7 (C-25), 127.4 (C-26), 127.2 (C-17), 126.6 (C-9), 124.8 (C-15,19), 121.0 (C-7), 118.0 (C-5), 42.7 (C-2,3). IR (KBr) υ_{max}: 2918, 1702, 1646, 1492, 1302, 1140, 764 cm^{-1}. Anal. calcd for $C_{25}H_{21}N_3O_2$ (395.45): C 75.93; H 5.35; N 10.63. Found: C 75.73; H 5.11; N 10.56.

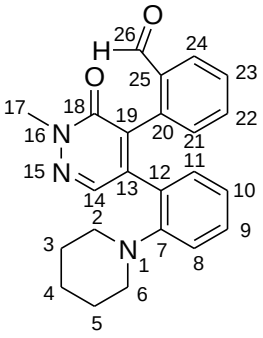
2-[2-Methyl-3-oxo-5-(2-pyrrolidin-1-ylphenyl)-2,3-dihydropyridazin-4-yl] benzaldehyde (142c)

Column chromatography: *n*-hexane:EtOAc 1:1. Yellow crystals (2.62 g, 73%), mp 185-187 °C, R_f=0.37 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.78 (s, 1H, H-25), 8.01 (s, 1H, H-13), 7.79-7.75 (m, 1H, H-23), 7.42-7.37 (m, 2H, H-21,22),



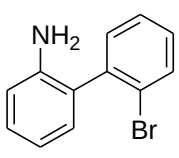
7.10 (tm, *J*=7.8 Hz, 1H, H-8), 7.03-6.95 (br m, 2H, H-10,20), 6.73 (br t, *J*=7.8 Hz, 1H, H-9), 6.66 (dm, *J*=8.0 Hz, 1H, H-7), 3.76 (s, 3H, H-16), 3.00-2.80 (br m, 4H, H-2,5), 1.85-1.70 (br m, 4H, H-3,4). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.3 (C-25), 158.8 (C-17), 147.1 (C-6), 142.5 (C-12), 137.6 (C-13), 135.3 (C-19), 134.2 (C-24), 134.1 (C-18), 132.0 (C-21), 130.3 (C-10), 129.6 (C-20), 128.9 (C-8), 127.6 (C-22), 127.0 (C-23), 122.7 (C-11), 118.0 (C-9), 114.9 (C-7), 50.0 (C-2,5), 39.2 (C-16), 24.1 (C-3,4). IR (KBr) υ_{max}: 2960, 1690, 1640, 1592, 1442, 1324, 760 cm^{-1}. Anal. calcd for $C_{22}H_{21}N_3O_2$ (359.42): C 73.52; H 5.89; N 11.69. Found: C 73.17; H 5.77; N 11.29.

2-[2-Methyl-3-oxo-5-(2-piperidine-1-ylphenyl)-2,3-dihydropyridazin-4-yl] benzaldehyde (142d)



Column chromatography: toluene:EtOAc 1:1. Yellow crystals (2.61 g, 70%), mp 171-172 °C, R_f=0.57 (toluene:EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 9.92 (s, 1H, H-26), 8.02 (s, 1H, H-14), 7.87-7.82 (m, 1H, H-24), 7.47-7.40 (m, 2H, H-22,23), 7.23 (tm, *J*=7.8 Hz, 1H, H-9), 7.05-7.00 (m, 2H, H-8,21), 6.97 (dm, *J*=7.2 Hz, 1H, H-11), 6.89 (t, *J*=7.2 Hz, 1H, H-10), 3.76 (s, 3H, H-17), 2.90-2.60 (br m, 4H, H-2,6), 1.60-1.40 (m, 6H, H-3,4,5). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 190.7 (C-26), 159.1 (C-18), 151.0 (C-7), 140.9 (C-13), 137.9 (C-14), 135.1 (C-20), 134.7 (C-25), 134.3 (C-19), 132.2 (C-22), 130.4 (C-11), 129.6 (C-21), 129.4 (C-9), 128.0 (C-12), 127.8 (C-23), 127.7 (C-24), 121.8 (C-10), 119.3 (C-8), 52.3 (C-2,6), 39.1 (C-17), 24.8 (C-3,5), 22.9 (C-4). IR (KBr) υ_{max}: 2942, 1692, 1640, 1592, 1442, 1226, 764 cm^{-1}. Anal. calcd for $C_{23}H_{23}N_3O_2$ (373.45): C 73.97; H 6.21; N 11.25. Found: C 73.59; H 5.82; N 11.15.

3.3.3 Synthesis of 2'-bromobiphenyl-2-amine (151)[93,94]



65% aq H_2SO_4 (30 mL) was added to **150** (1.99 g, 5.98 mmol) and the reaction mixture was heated at reflux for 15 h. After cooling to room temperature, the mixture was poured into H_2O (30 mL). The pH was adjusted to 8 with concentrated aq NH_3 and the aqueous phase was extracted with

CH_2Cl_2 (4×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. To the oil obtained, *n*-hexane was added to afford white crystals, which were filtered off and washed with *n*-hexane. White crystals (1.31 g, 88%), mp 48-50 °C (lit. mp 46-50 °C)[94], R_f=0.63 (toluene:EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.69 (dm, *J*=8.0, 1H, Ar-H), 7.38 (tm, *J*=7.6 Hz, 1H, Ar-H), 7.32 (dm, *J*=7.6 Hz, 1H, Ar-H), 7.27-7.20 (m, 2H, Ar-H), 7.03 (dm, *J*=7.6 Hz, 1H, Ar-H), 6.84 (tm, *J*=7.2 Hz, 1H, Ar-H), 6.79 (dm, *J*=8.0 Hz, 1H, Ar-H), 3.53 (br s, 2H, NH_2). ^{13}C NMR ($CDCl_3$) δ (ppm): 144.2 (Ar-qC), 140.6 (Ar-qC), 133.8 (Ar-CH), 132.4 (Ar-CH), 130.9 (Ar-CH), 129.9 (Ar-CH), 129.8 (Ar-CH), 128.5 (Ar-CH), 127.8 (Ar-qC), 125.0 (Ar-qC), 119.0 (Ar-CH), 116.2 (Ar-CH). IR (KBr) υ_{max}: 3374, 2920, 1616, 1466, 1254, 1026, 752 cm^{-1}. Anal. calcd for $C_{12}H_{10}BrN$ (248.12): C 58.09; H 4.06; N 5.65. Found: C 58.28; H 3.78; N 5.60.

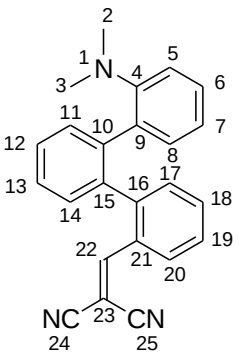
3.4 Aqueous N-heterocyclizations of 2'-bromobiphenyl-2-amine

A 10 mL MW process vial was charged with **151** (248 mg, 1.00 mmol), dihaloalkane (1.10 mmol) (for **138b**: 1,4-dibromobutane (0.13 mL), for **138c**: 1,5-dibromopentane (0.15 mL)), K_2CO_3 (162 mg, 1.10 mmol) and water (2 mL). The mixture was irradiated in a closed vessel with pressure control at 120 °C for 60 min (hold time) at 70 W maximum power. After completion of the reaction, the mixture was extracted with EtOAc (4×5 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by column chromatography (*n*-hexane:EtOAc 9:1). **138b**: 266 mg, 88%, **138c**: 269 mg, 85%.

3.5 General procedure for the synthesis of triaryl vinyl compounds via Knoevenagel condensation

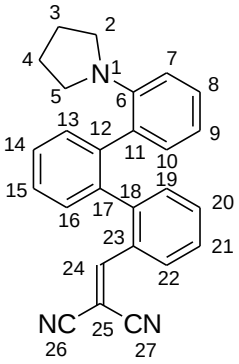
To a solution of the aldehyde (**139a-c** and **142a-d**) (2.00 mmol) in EtOH (10 mL), malononitrile (132 mg, 2.00 mmol) and a few drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC, reaction time: 1-2 h). The mixture was then evaporated to dryness, and EtOH (2 mL) was added to the crude product. The precipitated crystals were filtered off and washed with EtOH to afford the analytically pure product.

{[2''-(Dimethylamino)-1,1':2',1''-terphenyl-2-yl]methylidene}malononitrile (152a)



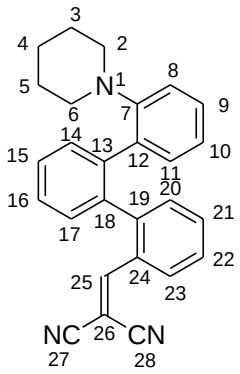
Orange crystals (643 mg, 92%), mp 157-158 °C, R_f=0.57 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.74 (tm, *J*=7.2 Hz, 1H, H-18), 7.69-7.64 (m, 1H, H-20), 7.60 (td, *J*=7.6, 1.2 Hz, 1H, H-12), 7.56-7.47 (m, 3H, H-11,13,17), 7.45-7.28 (m, 3H, H-14,19,22), 7.25-7.19 (m, 2H, H-6,8), 7.03 (tm, *J*=7.6 Hz, 1H, H-7), 6.57 (dd, *J*=7.7, 1.3 Hz, 1H, H-5), 1.95 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 160.4 (C-22), 149.4 (C-4), 144.4 (C-16), 141.5 (C-10), 136.6 (C-15), 133.0 (C-18), 132.9 (C-8), 131.4 (C-17), 131.0 (C-9), 130.9 (C-14), 130.0 (C-11), 129.6 (C-12), 129.3 (C-6), 127.5 (C-13), 127.2 (C-19), 127.1 (C-21), 126.0 (C-20), 122.0 (C-7), 117.2 (C-5), 114.4 (C-24/25), 112.6 (C-24/25), 79.8 (C-23), 41.1 (C-2,3). IR (KBr) υ_{max}: 2772, 2224, 1582, 1494, 1430, 1336, 948, 758 cm^{-1}. Anal. calcd for $C_{24}H_{19}N_3$ (349.43): C 82.49; H 5.48; N 12.03. Found: C 82.48; H 5.30; N 11.91.

{[2''-(Pyrrolidin-1-yl)-1,1':2',1''-terphenyl-2-yl]methylidene}malononitrile (152b)



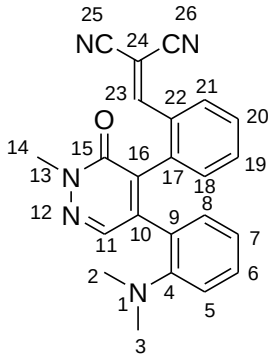
Red crystals (676 mg, 90%), mp 152-153 °C, R_f=0.52 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.73-7.66 (m, 2H, H-20,22), 7.60-7.46 (m, 4H, H-13,14,15,19), 7.44 (tm, *J*=7.8 Hz, 1H, H-21), 7.33 (dm, *J*=7.6 Hz, 1H, H-16), 7.20-7.14 (m, 2H, H-10,24), 7.11 (tm, *J*=7.6 Hz, 1H, H-8), 6.86 (tm, *J*=7.6 Hz, 1H, H-9), 6.40 (dm, *J*=8.0 Hz, 1H, H-7), 2.65-2.55 (m, 2H, H-2,5), 2.10-2.00 (m, 2H, H-2,5), 1.70-1.60 (m, 2H, H-3,4), 1.50-1.35 (m, 2H, H-3,4). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 159.4 (C-24), 146.9 (C-6), 143.6 (C-18), 142.5 (C-12), 137.1 (C-17), 133.1 (C-20), 133.0 (C-10), 131.5 (C-19), 130.4 (C-16), 129.8 (C-13), 129.3 (C-14), 128.9 (C-8), 127.7 (C-23), 127.6 (C-21), 127.5 (C-15), 126.9 (C-11), 125.7 (C-22), 119.1 (C-9), 114.6 (C-26/27), 113.8 (C-7), 112.8 (C-26/27), 79.6 (C-25), 49.5 (C-2,5), 24.8 (C-3,4). IR (KBr) υ_{max}: 2920, 2226, 1640, 1440, 1342, 1160, 954, 752 cm^{-1}. Anal. calcd for $C_{26}H_{21}N_3$ (375.47): C 83.17; H 5.64; N 11.19. Found: C 82.80; H 5.47; N 11.02.

{[2''-(Piperidin-1-yl)-1,1':2',1''-terphenyl-2-yl]methylidene}malononitrile (152c)



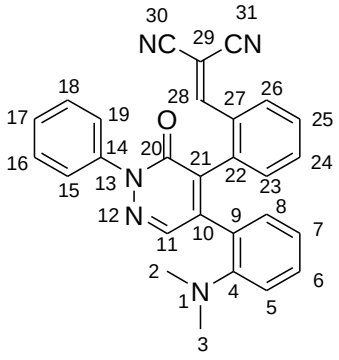
Orange crystals (709 mg, 91%), mp 156-158 °C, R_f=0.54 (toluene). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 7.73-7.66 (m, 2H, H-21,23), 7.65-7.57 (m, 2H, H-15,20), 7.54-7.36 (m, 5H, H-14,16,17,22,25), 7.28-7.17 (m, 2H, H-9,11), 7.06 (tm, *J*=7.6 Hz, 1H, H-10), 6.71 (dm, *J*=8.0 Hz, 1H, H-8), 2.55-2.45 (br m, 2H, H-2,6), 2.05-1.95 (br m, 2H, H-2,6), 1.37-1.11 (br m, 6H, H-3,4,5). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 160.7 (C-25), 150.7 (C-7), 144.2 (C-19), 141.2 (C-13), 136.9 (C-18), 133.3 (C-20), 133.2 (C-12), 133.1 (C-11), 132.9 (C-21), 131.0 (C-17), 130.5 (C-14), 129.5 (C-9), 129.4 (C-15), 128.0 (C-24), 127.5 (C-16), 127.4 (C-22), 126.2 (C-23), 122.8 (C-10), 118.2 (C-8), 114.4 (C-27/28), 112.7 (C-27/28), 80.5 (C-26), 51.6 (C-2,6), 24.8 (C-3,5), 23.6 (C-4). IR (KBr) υ_{max}: 2930, 2222, 1656, 1580, 1438, 1272, 1026, 752 cm^{-1}. HRMS: calcd for ($C_{27}H_{23}N_3$+H^+): 390.1970. Found: 390.1958.

(2-{5-[2-(Dimethylamino)phenyl]-2-methyl-3-oxo-2,3-dihydropyridazin-4-yl}benzylidene)malononitrile (153a)



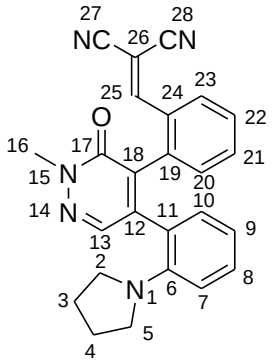
Orange crystals (671 mg, 88%), mp 161-162 °C, R_f=0.33 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.02 (s, 1H, H-11), 7.97-7.90 (m, 2H, H-21,23), 7.53-7.40 (m, 2H, H-19,20), 7.28-7.15 (m, 3H, H-6,8,18), 6.98 (tm, *J*=7.8 Hz, 1H, H-7), 6.81 (dm, *J*=8.0 Hz, 1H, H-5), 3.79 (s, 3H, H-14), 2.32 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 159.7 (C-23), 158.5 (C-15), 150.1 (C-4), 142.4 (C-10), 137.5 (C-11), 136.3 (C-17), 132.6 (C-16), 131.6 (C-19), 130.5 (C-18), 130.4 (C-8), 129.8 (C-6), 129.4 (C-22), 127.8 (C-20), 126.2 (C-21), 125.8 (C-9), 121.0 (C-7), 117.7 (C-5), 113.4 (C-25/26), 112.1 (C-25/26), 81.6 (C-24), 42.3 (C-2,3), 39.5 (C-14). IR (KBr) υ_{max}: 2920, 2232, 1750, 1634, 1380, 1170, 732 cm^{-1}. Anal. calcd for $C_{23}H_{19}N_5O$ (381.43): C 72.42; H 5.02; N 18.36. Found: C 72.03, H 4.78, N 18.23.

(2-{5-[2-(Dimethylamino)phenyl]- 3-oxo-2-phenyl-2,3-dihydropyridazin-4-yl} benzylidene)malononitrile (153b)



Orange crystals (754 mg, 85%), mp 145-147 °C, R_f=0.70 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.22 (s, 1H, H-11), 8.09 (s, 1H, H-28), 7.95 (dm, *J*=7.6 Hz, 1H, H-26), 7.76-7.70 (m, 2H, H-15,19), 7.57-7.40 (m, 5H, H-16,17,18,24,25), 7.35-7.20 (m, 3H, H-6,8,23), 7.00 (t, *J*=7.2 Hz, 1H, H-7), 6.85 (dm, *J*=7.6 Hz, 1H, H-5), 2.40 (s, 6H, H-2,3). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 159.8 (C-28), 158.2 (C-20), 150.2 (C-4), 142.2 (C-10), 141.4 (C-14), 138.5 (C-11), 136.1 (C-22), 133.9 (C-21), 131.6 (C-24), 130.5 (C-23), 130.4 (C-8), 129.9 (C-6), 129.4 (C-27), 127.8 (C-16,18), 127.8 (C-25), 127.2 (C-17), 126.2 (C-26), 125.4 (C-9), 124.8 (C-15,19), 121.0 (C-7), 117.7 (C-5), 113.4 (C-30/31), 112.1 (C-30/31), 81.8 (C-29), 42.3 (C-2,3). IR (KBr) υ_{max}: 2918, 2228, 1646, 1496, 1142, 756 cm^{-1}. Anal. calcd for $C_{28}H_{21}N_5O$ (443.50): C 75.83; H 4.77; N 15.79. Found: C 75.59; H 4.56; N 15.74.

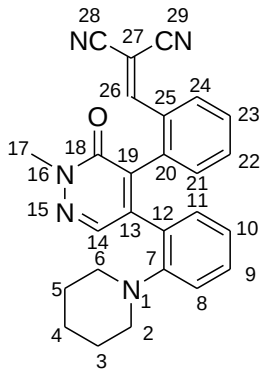
(2-{2-Methyl-3-oxo-5-[2-(pyrrolidin-1-yl)phenyl]-2,3-dihydropyridazin-4-yl} benzylidene)malononitrile (153c)



Orange crystals (733 mg, 90%), mp 112-115 °C (dec), R_f=0.60 (toluene:EtOAc 1:1). ^{1}H NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 8.12 (s, 1H, H-13), 7.87 (s, 1H, H-25), 7.73 (dm, *J*=8.0 Hz, 1H, H-23), 7.64 (tm, *J*=7.6 Hz, 1H, H-21), 7.57 (dm, *J*=7.6 Hz, 1H, H-20), 7.45 (tm, *J*=7.6 Hz, 1H, H-22), 7.19-7.11 (m, 2H, H-8,10), 6.84 (tm, *J*=7.6 Hz, 1H, H-9), 6.49 (dm, *J*=8.4 Hz, 1H, H-7), 3.75 (s, 3H, H-16), 2.95-2.88 (m, 2H, H-2,5), 2.24-2.18 (m, 2H, H-2,5), 1.85-1.75 (br m, 2H, H-3,4), 1.58-1.50 (m, 2H, H-3,4). ^{13}C NMR (DMSO-d_6) δ (ppm) (major rotamer at 25 °C): 159.6 (C-25), 158.9 (C-17), 146.9 (C-6), 144.1 (C-12), 137.9 (C-13), 136.1 (C-19), 132.2 (C-21), 131.4 (C-20), 131.3 (C-18), 131.2 (C-10), 130.2 (C-8), 128.7 (C-24), 128.6 (C-22), 126.3 (C-23), 120.1 (C-11), 118.5 (C-9), 114.3 (C-27/28), 114.0 (C-7), 112.8 (C-27/28), 80.9 (C-26), 50.2 (C-2,5), 40.3 (C-16), 25.1 (C-3,4). IR (KBr) υ_{max}: 2952, 2226, 1636, 1442, 1352,

1014, 752 cm^{-1}. Anal. calcd for $C_{25}H_{21}N_5O$ (407.47): C 73.69; H 5.19; N 17.19. Found: C 73.35; H 4.88; N 16.91.

(2-{2-Methyl-3-oxo-5-[2-(piperidin-1-yl)phenyl]-2,3-dihydropyridazin-4-yl} benzylidene)malononitrile (153d)



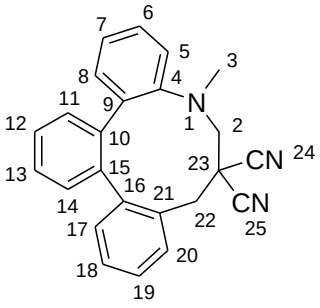
Yellow crystals (750 mg, 89%), mp 186-187 °C, R_f=0.76 (toluene:EtOAc 1:1). ^{1}H NMR (DMSO-d_6, 100 °C) δ (ppm): 8.08 (s, 1H, H-26), 8.04 (s, 1H, H-14), 7.95 (dm, *J*=7.6 Hz, 1H, H-24), 7.52-7.42 (m, 2H, H-22,23), 7.30-7.24 (m, 2H, H-9,21), 7.03-6.91 (m, 3H, H-8,10,11), 3.78 (s, 3H, H-17), 2.74-2.65 (br m, 4H, H-2,6), 1.66-1.43 (m, 6H, H-3,4,5). ^{13}C NMR (DMSO-d_6, 100 °C) δ (ppm): 160.1 (C-26), 158.6 (C-18), 150.8 (C-7), 142.2 (C-13), 137.8 (C-14), 135.8 (C-20), 132.8 (C-19), 131.7 (C-22), 130.9 (C-21), 130.5 (C-11), 129.9 (C-25), 129.8 (C-9), 127.9 (C-23), 127.3 (C-12), 126.5 (C-24), 121.8 (C-10), 119.1 (C-8), 113.2 (C-28/29), 112.0 (C-28/29), 82.3 (C-27), 52.2 (C-2,6), 39.3 (C-17), 24.7 (C-3,5), 22.9 (C-4). IR (KBr) υ_{max}: 2934, 2230, 1640, 1586, 1442, 1228, 1016, 762 cm^{-1}. Anal. calcd for $C_{26}H_{23}N_5O$ (421.49): C 74.09; H 5.50; N 16.62. Found: C 73.73; H 5.19; N 16.29.

3.6 MW-assisted isomerization of vinyl compounds in DMSO

A solution of the vinyl precursor (**152a-c** and **153a-d**) (0.25 mmol) in 1 mL dry DMSO was irradiated in an open vessel or in a 10 mL MW process vial at the temperature and for the reaction time shown in Table 5. The reaction mixture was subsequently cooled to ambient temperature and poured into CH_2Cl_2 (15 mL). The organic layer was washed with H_2O (3×15 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography on silica gel with the eluents indicated below.

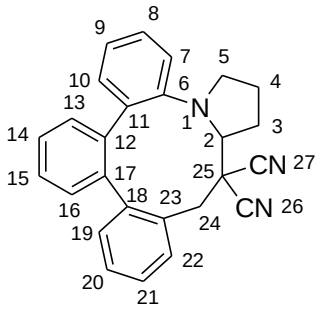
5-Methyl-5,8-dihydrotribenzo[b,d,f]azecine-7,7(6H)-dicarbonitrile (155a)

Column chromatography: *n*-hexane:EtOAc 97:3. White crystals, mp 149-152 °C, R_f=0.36 (*n*-hexane:EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.65 (dm, *J*=8.0 Hz, 1H, H-20), 7.51-7.46 (m, 1H, H-12), 7.42-7.38 (m, 2H, H-11,13), 7.35-7.31 (m, 1H, H-8),



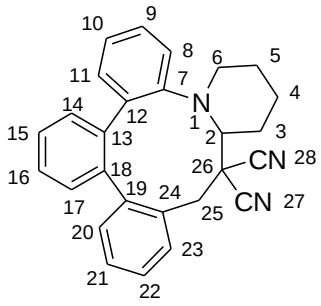
7.19-7.09 (m, 4H, H-6,7,14,19), 6.96 (tm, *J*=7.6 Hz, 1H, H-18), 6.73-6.67 (m, 2H, H-5,17), 3.55 (d, *J*=13.1 Hz, 1H, H-2), 3.52 (d, *J*=13.8 Hz, 1H, H-22), 3.40 (d, *J*=13.8 Hz, 1H, H-22), 2.85 (d, *J*=13.1 Hz, 1H, H-2), 2.41 (s, 3H, H-3). ^{13}C NMR ($CDCl_3$) δ (ppm): 153.0 (C-4), 144.1 (C-16), 141.6 (C-15), 140.4 (C-10), 139.2 (C-9), 132.5 (C-17), 131.1 (C-21), 131.0 (C-8), 130.2 (C-14), 130.0 (C-11), 129.6 (C-6), 129.1 (C-20), 128.6 (C-12), 128.0 (C-19), 127.6 (C-18), 127.5 (C-13), 126.1 (C-7), 123.0 (C-5), 117.6 (C-24/25), 116.7 (C-24/25), 59.0 (C-2), 44.2 (C-3), 38.5 (C-23), 35.9 (C-22). IR (KBr) υ_{max}: 2952, 2858, 2244, 1444, 1258, 1072, 954, 756 cm^{-1}. Anal. calcd for $C_{24}H_{19}N_3$ (349.43): C 82.49; H 5.48; N 12.03. Found: C 82.65; H 5.69; N 11.96.

6,7,8,8a-Tetrahydrotribenzo[e,g,i]pyrrolo[1,2-a]azecine-9,9(10H)-dicarbonitrile (155b)



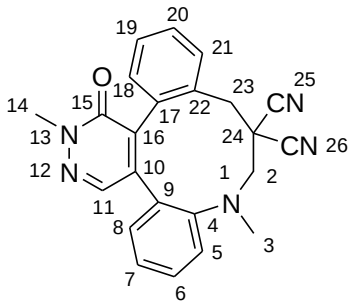
Column chromatography: *n*-hexane:EtOAc 7:1. White crystals, mp 137-140 °C, R_f=0.43 (*n*-hexane:EtOAc 7:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.65 (dm, *J*=8.0 Hz, 1H, H-22), 7.50-7.45 (m, 1H, H-14/15), 7.42-7.36 (m, 2H, H-13/16,14/15), 7.29-7.25 (m, 1H, H-13/16), 7.16-7.05 (m, 4H, H-8,9,13,21), 6.93 (tm, *J*=7.6 Hz, 1H, H-20), 6.66 (dd, *J*=7.6, 1.4 Hz, 1H, H-19), 6.49 (dm, *J*=7.6 Hz, 1H, H-7), 3.55 (d, *J*=14.0 Hz, 1H, H-24), 3.47 (dd, *J*=8.4, 2.0 Hz, 1H, H-2), 3.35 (d, *J*=14.0 Hz, 1H, H-24), 3.08-2.99 (m, 1H, H-5), 2.69-2.61 (m, 1H, H-5), 2.52-2.41 (m, 1H, H-3), 2.32-2.23 (m, 1H, H-3), 2.11-1.94 (m, 2H, H-4). ^{13}C NMR ($CDCl_3$) δ (ppm): 152.7 (C-6), 144.1 (C-18), 141.5 (C-12), 141.5 (C-17), 140.2 (C-11), 132.1 (C-19), 131.8 (C-23), 131.1 (C-10), 129.8 (C-13/16), 129.4 (C-13/16), 129.3 (C-8), 128.7 (C-22), 128.5 (C-14/15), 127.9 (C-21), 127.4 (C-14/15), 127.4 (C-20), 125.9 (C-9), 122.7 (C-7), 117.6 (C-26/27), 117.3 (C-26/27), 70.1 (C-2), 56.2 (C-5), 45.0 (C-25), 37.1 (C-24), 31.3 (C-3), 24.2 (C-4). IR (KBr) υ_{max}: 2954, 2242, 1690, 1640, 1440, 1264, 1092, 756 cm^{-1}. HRMS: calcd for ($C_{26}H_{21}N_3$+H^+): 376.1814. Found: 376.1804.

7,8,9,9a-Tetrahydro-6H-tribenzo[e,g,i]pyrido[1,2-a]azecine-10,10(11H)-dicarbonitrile (155c)



Column chromatography: toluene. White crystals, mp 141-143 °C, R_f=0.61 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.72 (dm, *J*=8.0 Hz, 1H, H-23), 7.51-7.36 (m, 3H, H-15,16,17), 7.28-7.23 (m, 1H, H-11), 7.16-7.03 (m, 4H, H-9,10,14,22), 6.91 (tm, *J*=7.6 Hz, 1H, H-21), 6.81-6.76 (m, 1H, H-20), 6.62 (dd, *J*=8.0, 1.3 Hz, 1H, H-8), 3.46 (d, *J*=13.6 Hz, 1H, H-24), 3.37 (d, *J*=13.6 Hz, 1H, H-25), 3.21 (dm, *J*=5.5 Hz, 1H, H-2), 2.86-2.77 (m, 1H, H-6), 2.64-2.57 (m, 1H, H-6), 2.38-2.15 (m, 3H, H-3,5), 1.84-1.75 (m, 1H, H-5), 1.47-1.34 (m, 1H, H-4), 1.24-1.16 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$): 151.4 (C-7), 143.9 (C-19), 141.4 (C-18), 141.2 (C-13), 138.8 (C-12), 132.1 (C-20), 131.7 (C-24), 131.4 (C-11), 130.0 (C-14), 129.6 (C-17), 128.7 (C-9), 128.7 (C-23), 128.5 (C-16), 127.8 (C-22), 127.5 (C-15), 127.2 (C-21), 124.8 (C-10), 123.2 (C-8), 118.7 (C-27/28), 118.1 (C-27/28), 59.4 (C-2), 48.7 (C-6), 43.4 (C-26), 37.8 (C-25), 25.3 (C-3), 19.8 (C-4), 19.8 (C-5). IR (KBr) υ_{max}: 2928, 2244, 1634, 1442, 1228, 1054, 754 cm^{-1}. Anal. calcd for $C_{27}H_{23}N_3$ (389.49): C 83.26; H 5.95; N 10.79. Found: C 82.95; H 5.68; N 10.58.

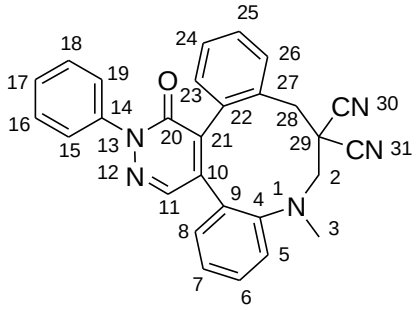
5,14-Dimethyl-13-oxo-5,8,13,14-tetrahydrodibenzo[b,f]pyridazino[4,5-d]azecine-7,7(6H)-dicarbonitrile (156a)



Column chromatography: *n*-hexane:EtOAc 4:1. White crystals, mp 289-294 °C (dec), R_f=0.39 (*n*-hexane: EtOAc 1:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.86 (s, 1H, H-11), 7.66 (dm, *J*=8.0 Hz, 1H, H-21), 7.31-7.20 (m, 4H, H-6,7,8,20), 7.05 (tm, *J*=7.6 Hz, 1H, H-19), 6.85 (dm, *J*=7.6 Hz, 1H, H-5), 6.63 (dd, *J*=7.6, 1.4 Hz, 1H, H-18), 3.93 (s, 3H, H-14), 3.58 (d, *J*=13.6 Hz, 2H, H-2,23), 3.24 (d, *J*=13.6 Hz, 1H, H-23), 2.79 (d, *J*=13.6 Hz, 1H, H-2), 2.62 (s, 3H, H-3). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 160.4 (C-15), 152.8 (C-4), 142.1 (C-10), 140.6 (C-16), 137.4 (C-11), 135.9 (C-17), 133.1 (C-9), 132.6 (C-22), 131.5 (C-6), 131.0 (C-18), 129.6 (C-20), 129.3 (C-8), 129.3 (C-21), 128.9 (C-19), 126.8 (C-7), 124.4 (C-5), 117.3 (C-25/26), 116.2 (C-25/26), 59.2 (C-2), 45.4 (C-3), 41.4 (C-14), 38.1 (C-24), 36.9 (C-23). IR (KBr) υ_{max}: 2920, 2242, 1644, 1448, 1260,

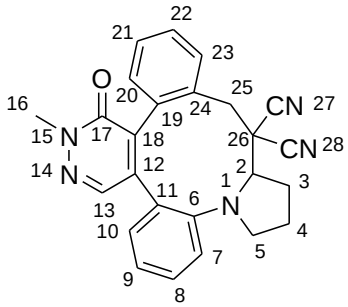
1014, 764 cm^{-1}. Anal. calcd for $C_{23}H_{19}N_5O$ (381.43): C 72.42; H 5.02; N 18.36. Found: C 72.22; H 4.84; N 18.22.

5-Methyl-13-oxo-14-phenyl-5,8,13,14-tetrahydrodibenzo[b,f]pyridazino[4,5-d]azecine-7,7(6H)-dicarbonitrile (156b)



Column chromatography: *n*-hexane:EtOAc 4:1. White crystals, mp 195-198 °C, R_f=0.70 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 8.03 (s, 1H, H-11), 7.82-7.75 (m, 2H, H-15,19), 7.67 (dm, *J*=7.8 Hz, 1H, H-26), 7.52-7.48 (m, 2H, H-16,18), 7.43-7.39 (m, 2H, H-17,25), 7.32-7.22 (m, 3H, H-6,7,8), 7.08 (tm, *J*=7.8 Hz, 1H, H-24), 6.89 (dm, *J*=7.8 Hz, 1H, H-5), 6.72 (dm, *J*=7.8 Hz, 1H, H-23), 3.61 (d, *J*=13.8 Hz, 1H, H-2), 3.58 (d, *J*=13.8 Hz, 1H, H-28), 3.31 (d, *J*=13.8 Hz, 1H, H-28), 2.80 (d, *J*=13.8 Hz, 1H, H-2), 2.69 (s, 3H, H-3). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 159.9 (C-20), 152.9 (C-4), 142.2 (C-10), 142.2 (C-21), 141.9 (C-14), 138.5 (C-11), 135.9 (C-22), 133.0 (C-9), 132.9 (C-27), 131.7 (C-6), 131.0 (C-23), 129.7 (C-25), 129.4 (C-16,18), 129.3 (C-8), 129.3 (C-26), 129.0 (C-17), 129.0 (C-24), 126.9 (C-7), 125.9 (C-15,19), 124.5 (C-5), 117.2 (C-30/31), 116.2 (C-30/31), 59.3 (C-2), 45.6 (C-3), 38.1 (C-29), 37.0 (C-28). IR (KBr) υ_{max}: 2922, 2242, 1652, 1490, 1294, 1126, 758 cm^{-1}. Anal. calcd for $C_{28}H_{21}N_5O$ (443.50): C 75.83; H 4.77; N 15.79. Found: C 75.62; H 4.54; N 15.41.

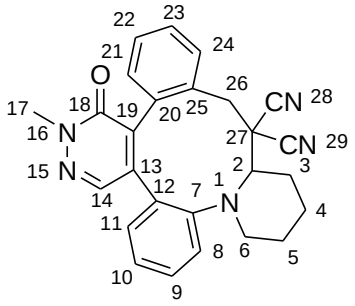
3-Methyl-4-oxo-3,9,10a,11,12,13-hexahydrodibenzo[e,i]pyridazino[4,5-g]pyrrolo [1,2-a]azecine-10,10(4H)-dicarbonitrile (156c)



Column chromatography: *n*-hexane:EtOAc 1:1. White crystals, mp 184-188 °C, R_f=0.35 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm): 7.87 (s, 1H, H-13), 7.68 (dm, *J*=7.8 Hz, 1H, H-23), 7.26-7.18 (m, 4H, 8,9,10,22), 7.02 (tm, *J*=7.2 Hz, 1H, H-21), 6.64-6.58 (m, 2H, H-7,20), 3.94 (s, 3H, H-16), 3.56 (d, *J*=14.4 Hz, 1H, H-25), 3.42-3.35 (m, 2H, H-2,5), 3.27 (d, *J*=14.4 Hz, 1H, H-25), 2.75-2.68 (m, 1H, H-5), 2.55-2.48 (m, 1H, H-3), 2.38-2.30 (m, 1H, H-3), 2.22-2.15 (m, 1H, H-4), 2.12-2.04

(m, 1H, H-4). ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm): 160.6 (C-17), 152.5 (C-6), 143.5 (C-12), 140.5 (C-18), 137.3 (C-13), 136.0 (C-19), 134.2 (C-11), 132.8 (C-24), 131.3 (C-8), 130.6 (C-20), 129.4 (C-10/22/23), 129.3 (C-10/22/23), 129.1 (C-10/22/23), 128.8 (C-21), 126.7 (C-9), 124.4 (C-7), 117.1 (C-27/28), 117.0 (C-27/28), 70.7 (C-2), 56.9 (C-5), 44.8 (C-26), 41.7 (C-16), 37.9 (C-25), 31.2 (C-3), 24.3 (C-4). IR (KBr) υ_{max}: 2918, 2246, 1644, 1444, 1266, 1016, 758 cm^{-1}. HRMS: calcd for ($C_{25}H_{21}N_5O$ +H^+): 408.1824. Found: 408.1811.

3-Methyl-4-oxo-3,9,11,12,13,14-hexahydro-4H-dibenzo[e,i]pyridazino[4,5-g]pyrido [1,2-a]azecine-10,10(10aH)-dicarbonitrile (156d)



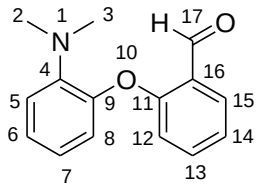
Column chromatography: toluene:EtOAc 2:1. Yellow crystals, mp 140-144 °C, R_f=0.38 (toluene:EtOAc 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.16 (s, 1H, H-14), 7.59 (dm, *J*=8.0 Hz, 1H, H-24), 7.33 (dd, *J*=7.2, 1.8 Hz, 1H, H-11), 7.22 (tm, *J*=8.0 Hz, 1H, H-23), 7.19-7.10 (m, 2H, H-9,10), 7.06 (dm, *J*=8.0 Hz, 1H, H-8), 7.00 (tm, *J*=8.0 Hz, 1H, H-22), 6.62 (dm, *J*=7.6 Hz, 1H, H-21), 3.79 (s, 3H, H-17), 3.72 (d, *J*=14.0 Hz, 1H, H-26), 3.14 (dm, *J*=7.0 Hz, 1H, H-2), 3.04 (tm, *J*=14.5 Hz, 1H, H-6), 3.01 (d, *J*=14.0 Hz, 1H, H-26), 2.56 (dm, *J*=14.5 Hz, 1H, H-6), 2.41-2.31 (m, 1H, H-3), 2.28-2.15 (m, 1H, H-4), 2.00-1.94 (m, 1H, H-3), 1.80-1.73 (m, 1H, H-4), 1.35-1.22 (m, 2H, H-5). ^{13}C NMR (DMSO-d_6) δ (ppm): 159.1 (C-18), 150.0 (C-7), 142.2 (C-13), 138.3 (C-19), 137.2 (C-14), 135.8 (C-20), 132.5 (C-25), 131.7 (C-12), 130.1 (C-21), 129.6 (C-9), 129.5 (C-11), 129.3 (C-22), 128.0 (C-23), 127.6 (C-24), 124.3 (C-10), 123.6 (C-8), 117.9 (C-28/29), 117.1 (C-28/29), 58.5 (C-2), 48.8 (C-6), 42.2 (C-27), 40.3 (C-17), 36.2 (C-26), 23.9 (C-3), 18.8 (C-5), 18.7 (C-4). IR (KBr) υ_{max}: 2932, 2240, 1648, 1444, 1228, 1014, 764 cm^{-1}. Anal. calcd for $C_{26}H_{23}N_5O$ (421.49): C 74.09; H 5.50; N 16.62. Found: C 73.77; H 5.38; N 16.36.

3.7 General procedure for the synthesis biaryl ethers

To a solution of the appropriate phenol (15.00 mmol, for **166a**: 2-(dimethylamino)phenol (2.06 g), for **166b**: 2-(pyrrolidin-1-yl)phenol (2.45 g), for **166c**: 2-(piperidin-1-yl)phenol (2.65 g)) in DMA (15 mL), 2-fluorobenzaldehyde (1.58 mL,

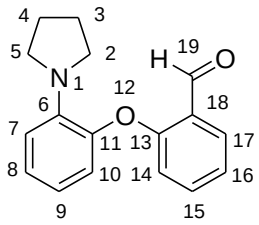
15.00 mmol) and K_2CO_3 (4.15 g, 30.00 mmol) were added. The mixture was heated at 160°C (oil temperature) under argon atmosphere for 1.5 h. To the cooled reaction mixture EtOAc (20 mL) was added. The organic phase was washed with H_2O (1×20 mL) and aq saturated Na_2CO_3 solution (1×20 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel (eluent for **166a**: toluene→toluene:EtOAc 10:1 gradient, for **166b**,**c**: toluene).

2-[2-(Dimethylamino)phenoxy]benzaldehyde (166a)



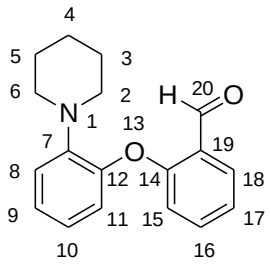
Yellow crystals (1.92 g, 53%), mp 100-101 °C, R_f=0.40 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.65 (s, 1H, H-17), 7.91 (dm, *J*=7.6 Hz, 1H, H-15), 7.44-7.39 (m, 1H, H-13), 7.21-6.89 (m, 5H, H-5,6,7,8,14), 6.68 (dm, *J*=8.0 Hz, 1H, H-12), 2.79 (s, 3H, H-2,3). ^{13}C NMR ($CDCl_3$) δ (ppm): 190.1 (C-17), 161.1 (C-11), 147.7 (C-9), 146.0 (C-4), 136.4 (C-13), 128.9 (C-15), 126.5 (C-16), 126.4 (C-5/6/7/8), 123.0 (C-14), 122.5 (C-5/6/7/8), 122.5 (C-5/6/7/8), 119.6 (C-5/6/7/8), 117.3 (C-12), 43.6 (C-2,3). IR (KBr) ν_{max}: 3060, 1680, 1596, 1496, 1472, 1226, 754 cm^{-1}. Anal. calcd for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.81. Found: C, 75.07; H, 6.18; N, 5.65.

2-[2-(Pyrrolidin-1-yl)phenoxy]benzaldehyde (166b)



Yellow crystals (1.98 g, 51%), mp 82-83 °C, R_f=0.30 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.64 (d, *J*=0.7, 1H, H-19), 7.90 (dm, *J*=8.0 Hz, 1H, H-17), 7.45-7.40 (m, 1H, H-15), 7.15-7.04 (m, 2H, H-9,16), 6.94 (dm, *J*=8.0 Hz, 1H, H-7), 6.82 (dm, *J*=8.0 Hz, 1H, H-10), 6.74 (tm, *J*=7.6 Hz, 1H, H-8), 6.69 (dm, *J*=8.0 Hz, 1H, H-14), 3.36-3.31 (m, 4H, H-2,5), 1.86-1.82 (m, 4H, H-3,4). ^{13}C NMR ($CDCl_3$) δ (ppm): 190.3 (C-19), 162.0 (C-13), 142.9 (C-11), 142.7 (C-6), 136.5 (C-15), 128.9 (C-17), 126.8 (C-9), 126.0 (C-18), 123.5 (C-7), 122.4 (C-16), 118.5 (C-8), 116.7 (C-14), 116.3 (C-10), 50.7 (C-2,5), 26.0 (C-3,4). IR (KBr) ν_{max}: 3068, 1690, 1598, 1498, 1478, 1452, 1230, 752 cm^{-1}. Anal. calcd for $C_{17}H_{17}NO_2$+1/4 C_7H_8 (267.32+23.04): C, 77.55; H, 6.54; N, 4.83. Found: C, 77.19; H, 6.51; N, 5.02.

2-[2-(Piperidin-1-yl)phenoxy]benzaldehyde (166c)

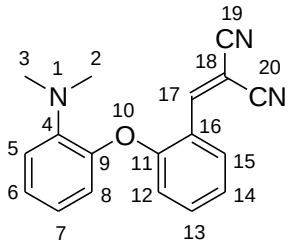


Yellow oil (2.38 g, 56%), R_f=0.30 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 10.69 (s, 1H, H-20), 7.90 (dm, *J*=7.6 Hz, 1H, H-19), 7.38 (dm, *J*=7.6 Hz, 1H, H-16), 7.23-6.97 (m, 5H, H-8,9,10,11,17), 6.63 (dm, *J*=7.6 Hz, 1H, H-15), 3.01-2.89 (m, 4H, H-2,6), 1.45-1.31 (m, 6H, H-3,4,5). ^{13}C NMR ($CDCl_3$) δ (ppm): 190.2 (C-20), 161.4 (C-14), 148.0 (C-7/12), 146.4 (C-7/12), 136.0 (C-16), 128.6 (C-18), 126.7 (C-8/9/10/11), 125.8 (C-19), 123.3 (C-8/9/10/11), 123.1 (C-8/9/10/11), 122.5 (C-17), 120.9 (C-8/9/10/11), 116.6 (C-15), 52.7 (C-2,6), 26.8 (C-3,5), 24.8 (C-4). IR (KBr) ν_{max}: 3446, 3066, 1690, 1600, 1492, 1452, 1244, 754 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO_2$ (281.35): C, 76.84; H, 6.81; N, 4.98. Found: C, 75.57; H, 6.91; N, 5.80.

3.8 Syntheses of biaryl vinyl compounds via Knoevenagel condensation

To a solution of the aldehyde (**166a-c**) (2.00 mmol) in EtOH (2.50 mL), malononitrile (for **167a-c**: 132 mg, 2.00 mmol) or ethyl cyanoacetate (for **167d-f**: 0.21 mL, 2.00 mmol), and a few drops of piperidine were added. The mixture was stirred at room temperature until the starting material had been consumed (monitored by TLC, reaction time: 2–3 h). Work-up: i) the reaction mixture was evaporated to dryness and the crude product obtained was purified by flash column chromatography on silica gel with toluene eluent (**167a**) or ii) the precipitated crystals were filtered off and washed with 5×1 ml EtOH to afford the analytically pure product (**167b-f**).

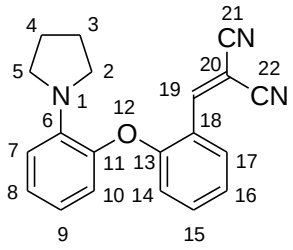
{2-[2-(Dimethylamino)phenoxy]benzylidene}propanedinitrile (167a)



Orange crystals (411 mg, 71%), mp 76-78 °C, R_f=0.35 (*n*-hexane:EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.50 (s, 1H, H-17), 8.28 (dm, *J*=8.0 Hz, 1H, H-15), 7.46-7.40 (m, 1H, H-13), 7.22-7.11 (m, 2H, H-6,14), 7.04 (dm, *J*=8.0 Hz, 1H, H-5), 6.98-6.93 (m, 1H, H-7), 6.91 (dm, *J*=8.0 Hz, 1H, H-8), 6.66 (dm, *J*=8.0 Hz, 1H, H-12), 2.75 (s, 6H, H-2,3). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.4 (C-11), 154.8 (C-17), 147.0 (C-9), 146.0 (C-4), 136.8 (C-13), 129.2 (C-15), 127.0 (C-6), 123.3 (C-14), 122.8 (C-8), 122.7 (C-7), 121.5 (C-16), 119.8 (C-5), 116.9 (C-12), 114.9 (C-19/20), 113.6 (C-19/20), 82.8 (C-18), 43.6 (C-2,3). IR (KBr) ν_{max}: 2782, 2224, 1590,

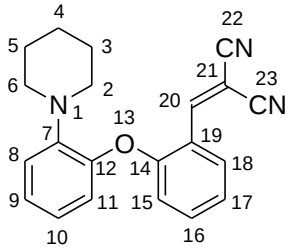
1496, 1476, 1240, 748 cm^{-1}. Anal. calcd for $C_{18}H_{19}NO_2$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 74.82; H, 4.59; N, 13.86.

{2-[2-(Pyrrolidin-1-yl)phenoxy]benzylidene}propanedinitrile (167b)



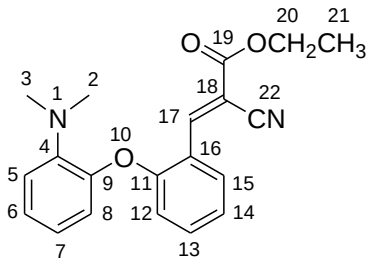
Orange crystals (410 mg, 65%), mp 92-93 °C, R_f=0.60 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.46 (s, 1H, H-19), 8.29 (dm, *J*=8.0 Hz, 1H, H-17), 7.48-7.41 (m, 1H, H-15), 7.18-7.09 (m, 2H, H-9,16), 6.86 (dm, *J*=8.0 Hz, 1H, H-7), 6.83 (dm, *J*=8.0 Hz, 1H, H-10), 6.78-6.71 (m, 1H, H-8), 6.70 (dm, *J*=8.0 Hz, 1H, H-14), 3.32-3.23 (m, 4H, H-2,5), 1.92-1.83 (m, 4H, H-3,4). ^{13}C NMR ($CDCl_3$) δ (ppm): 159.2 (C-13), 154.8 (C-19), 142.8 (C-11), 142.3 (C-6), 137.0 (C-15), 129.2 (C-17), 127.3 (C-9), 123.4 (C-7), 123.0 (C-16), 121.2 (C-18), 118.8 (C-8), 116.6 (C-10), 116.6 (C-14), 114.9 (C-21/22), 113.6 (C-21/22), 82.7 (C-20), 50.7 (C-2,5), 26.0 (C-3,4). IR (KBr) ν_{max}: 3424, 3042, 2228, 1590, 1498, 1478, 1452, 1236, 766 cm^{-1}. Anal. calcd for $C_{20}H_{17}N_3O$ (315.37): C, 76.17; H, 5.43; N, 13.32. Found: C, 76.60; H, 5.80; N, 12.52.

{2-[2-(Piperidin-1-yl)phenoxy]benzylidene}propanedinitrile (167c)



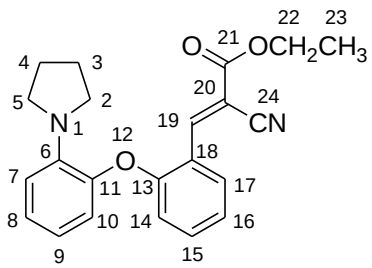
Yellow crystals (231 mg, 35%), mp 128-130 °C, R_f=0.50 (*n*-hexane:EtOAc 10:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.53 (s, 1H, H-20), 8.26 (dm, *J*=8.0 Hz, 1H, H-18), 7.43-7.38 (m, 1H, H-16), 7.23-7.18 (m, 1H, H-8/9/10/11), 7.14-7.09 (m, 1H, H-17), 7.08-7.04 (m, 1H, H-8/9/10/11), 7.03-7.00 (m, 2H, H-8/9/10/11), 6.63 (dm, *J*=8.4 Hz, 1H, H-15), 2.92-2.87 (m, 4H, H-2,6), 1.45-1.32 (m, 6H, H-3,4,5). ^{13}C NMR ($CDCl_3$) δ (ppm): 158.7 (C-14), 154.8 (C-20), 147.6 (C-7/12), 146.2 (C-7/12), 136.5 (C-16), 128.9 (C-18), 127.2 (C-8/9/10/11), 123.7 (C-8/9/10/11), 123.0 (C-8/9/10/11), 121.2 (C-8/9/10/11), 121.0 (C-19), 116.5 (C-15), 114.9 (C-22/23), 113.7 (C-22/23), 82.4 (C-21), 52.7 (C-2,6), 26.8 (C-3,5), 24.7 (C-4). IR (KBr) ν_{max}: 3040, 2224, 1586, 1478, 1448, 1226, 752 cm^{-1}. Anal. calcd for $C_{21}H_{19}N_3O$ (329.40): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.33; H, 5.47; N, 12.22.

Ethyl 2-cyano-3-{2-[2-(dimethylamino)phenoxy]phenyl}prop-2-enoate (167d)



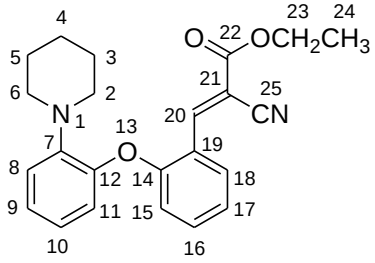
Pale yellow crystals (488 mg, 73%), mp 104-106 °C, R_f=0.45 (*n*-hexane:EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.92 (s, 1H, H-17), 8.38 (dm, *J*=8.0 Hz, 1H, H-15), 7.40-7.35 (m, 1H, H-13), 7.19-7.10 (m, 2H, H-5/6/7/8,14), 7.04-7.01 (m, 1H, H-5/6/7/8/9), 6.96-6.89 (m, 2H, H-5/6/7/8/9), 6.65 (dm, *J*=8.4 Hz, 1H, H-12), 4.37 (q, *J*=7.2 Hz, 2H, H-20), 2.76 (s, 6H, H-2,3), 1.39 (t, *J*=7.2 Hz, 3H, H-21). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.3 (C-19), 158.6 (C-11), 150.1 (C-17), 147.5 (C-9), 146.0 (C-4), 135.3 (C-13), 129.8 (C-15), 126.5 (C-5/6/7/8), 123.2 (C-14), 122.7 (C-5/6/7/8), 122.5 (C-5/6/7/8), 122.2 C-16), 119.6 (C-5/6/7/8), 116.7 (C-12), 116.5 (C-22), 103.7 (C-18), 63.2 (C-20), 43.6 (C-2,3), 14.8 (C-21). IR (KBr) ν_{max}: 3058, 2782, 2218, 1734, 1602, 1498, 1452, 758 cm^{-1}. Anal. calcd for $C_{20}H_{20}N_2O_3$ (336.38): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.31; H, 5.62; N, 8.28.

Ethyl 2-cyano-3-{2-[2-(pyrrolidin-1-yl)phenoxy]phenyl}prop-2-enoate (167e)



Yellow crystals (620 mg, 86%), mp 111-112 °C, R_f=0.36 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.89 (s, 1H, H-19), 8.39 (dm, *J*=8.0 Hz, 1H, H-17), 7.42-7.35 (m, 1H, H-15), 7.15-7.07 (m, 2H, H-9,16), 6.87 (dm, *J*=8.0 Hz, 1H, H-7), 6.80 (dm, *J*=8.0 Hz, 1H, H-10), 6.75-6.71 (m, 1H, H-8), 6.67 (dm, *J*=8.0 Hz, 1H, H-14), 4.38 (q, *J*=7.2 Hz, 2H, H-22), 3.32-3.25 (m, 4H, H-2,5), 1.87-1.81 (m, 4H, H-3,4), 1.40 (t, *J*=7.2 Hz, 3H, H-23). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.4 (C-21), 159.5 (C-13), 150.1 (C-19), 142.8 (C-11), 142.7 (C-6), 135.5 (C-15), 129.8 (C-17), 126.9 (C-9), 123.5 (C-7), 122.7 (C-16), 121.8 (C-18), 118.5 (C-8), 116.6 (C-24), 116.4 (C-14), 116.3 (C-10), 103.6 (C-20), 63.2 (C-22), 50.7 (C-2,5), 26.1 (C-3,4), 14.9 (C-23). IR (KBr) ν_{max}: 3446, 3044, 2216, 1734, 1602, 1502, 1480, 1452, 746 cm^{-1}. Anal. calcd for $C_{22}H_{22}N_2O_3$ (362.42): C, 72.91; H, 6.12; N, 7.73. Found: C, 73.17; H, 6.25; N, 7.41.

Ethyl 2-cyano-3-{2-[2-(piperidin-1-yl)phenoxy]phenyl}prop-2-enoate (167f)

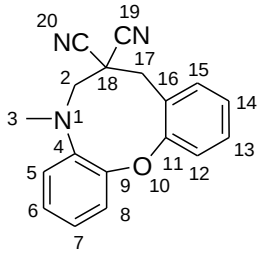


Pale yellow crystals (600 mg, 80%), mp 60-62 °C, R_f=0.33 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 8.96 (s, 1H, H-20), 8.37 (dm, *J*=8.0 Hz, 1H, H-18), 7.36-7.31 (m, 1H, H-16), 7.21-7.15 (m, 1H, H-8/9/10/11), 7.12-6.98 (m, 4H, H-8/9/10/11,17), 6.61 (dm, *J*=8.4 Hz, 1H, H-15), 4.38 (q, *J*=7.2 Hz, 2H, H-23), 2.94-2.89 (m, 4H, H-2,6), 1.42-1.31 (6H, H-3,4,5), 1.39 (t, *J*=7.2 Hz, 3H, H-24). ^{13}C NMR ($CDCl_3$) δ (ppm): 163.4 (C-22), 158.9 (C-14), 150.1 (C-20), 147.8 (C-7/12), 146.3 (C-7/12), 135.0 (C-16), 129.5 (C-18), 126.8 (C-8/9/10/11), 123.4 (C-8/9/10/11), 123.2 (C-8/9/10/11), 122.7 (C-17), 121.5 (C-19), 120.9 (C-8/9/10/11), 116.6 (C-25), 116.1 (C-15), 103.2 (C-21), 63.2 (C-23), 52.7 (C-2,6), 26.8 (C-3,5), 24.8 (C-4), 14.9 (C-24). IR (KBr) ν_{max}: 3432, 3062, 2222, 1726, 1600, 1488, 1450, 758 cm^{-1}. Anal. calcd for $C_{23}H_{24}N_2O_3$ (376.45): C, 73.38; H, 6.43; N, 7.44. Found: C, 72.90; H, 6.68; N, 7.36.

3.9 MW-assisted isomerization of biaryl vinyl compounds in DMSO

A solution of the vinyl precursor (**167a**,**b**,**d**) (2.00 mmol) in 1 mL dry DMSO was irradiated in a 10 mL MW process vial at the temperature and for the reaction time as indicated below. The reaction mixture was subsequently cooled to ambient temperature and poured into CH_2Cl_2 (15 mL). The organic layer was washed with H_2O (3×15 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography on silica gel with *n*-hexane:EtOAc 4:1 eluent.

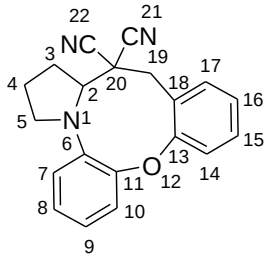
5-methyl-5,6-dihydrodibenzo[b,h][1,4]oxazonine-7,7(8H)-dicarbonitrile (168a)



Heating: 150°C, 15 min. Column chromatography: toluene. White crystals, mp 178-180 °C, R_f=0.34 (*n*-hexane:EtOAc 9:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.39-7.33 (m, 2H, H-8,15), 7.24-7.13 (m, 2H, H-6,13), 7.12-7.08 (m, 1H, H-7), 7.05-7.01 (m, 1H, H-5), 6.83-6.78 (m, 1H, H-12), 3.77 (br s, 2H, H-2), 3.69 (br s, 2H, H-17), 2.79 (s, 3H, H-3). ^{13}C NMR ($CDCl_3$) δ (ppm): 157.2 (C-11), 150.3 (C-9), 145.5 (C-4), 131.8 (C-15), 130.6 (C-13), 126.3 (C-6), 124.5 (C-8), 124.5 (C-14), 124.5 (C-16), 123.8 (C-7), 119.9 (C-5), 118.3 (C-12), 115.6 (C-19), 115.6 (C-20), 64.8 (C-2), 40.8 (C-

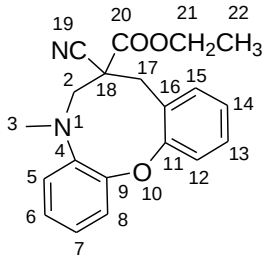
3), 39.3 (C-17), 36.4 (C-18). IR (KBr) ν_{max}: 3420, 3002, 2248, 1600, 1490, 1450, 756 cm^{-1}. Anal. calcd for $C_{18}H_{15}N_3O$ (289.33): C, 74.72; H, 5.23; N, 14.52. Found: C, 75.17; H, 4.66; N, 13.85.

5,6,7,7a-tetrahydrodibenzo[e,h]pyrrolo[1,2-a]oxazonine-8,8(9H)-dicarbonitrile (168b)



Heating: 100°C, 15 min. White crystals, mp 172-174 °C, R_f=0.58 (toluene). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.43-7.37 (m, 1H, H-15), 7.29 (dm, *J*=8.0 Hz, 1H, H-14), 7.18-7.14 (m, 2H, H-16,17), 7.11-7.06 (m, 1H, H-8), 6.92 (dm, *J*=8.0 Hz, 1H, H-7), 6.89 (dm, *J*=8.0 Hz, 1H, H-10), 6.83-6.78 (m, 1H, H-9), 5.35 (br s, 1H, H-2), 3.95-3.87 (m, 1H, H-5), 3.74 (d, *J*=14.8 Hz, 1H, H-19), 3.48-3.41 (m, 1H, H-5), 3.03 (d, *J*=14.8 Hz, 1H, H-19), 2.65-2.56 (m, 1H, H-3), 2.36-2.24 (m, 2H, H-3,4), 2.09-1.97 (m, 1H, H-4). ^{13}C NMR ($CDCl_3$) δ (ppm): 156.3 (C-13), 146.1 (C-11), 140.4 (C-6), 135.0 (C-17), 131.4 (C-15), 126.6 (C-8), 125.5 (C-16), 124.1 (C-18), 122.9 (C-10), 122.9 (C-14), 121.3 (C-9), 118.8 (C-7), 116.3 (C-21/22), 114.6 (C-21/22), 62.9 (C-2), 51.9 (C-5), 45.6 (C-20), 38.5 (C-19), 32.7 (C-3), 23.2 (C-4). IR (KBr) ν_{max}: 3448, 3058, 2972, 2246, 1598, 1494, 1452, 760 cm^{-1}. Anal. calcd for $C_{18}H_{15}N_3O$ (289.33): C, 76.17; H, 5.43; N, 13.32. Found: C, 75.36; H, 5.00; N, 12.53.

Ethyl 7-cyano-5-methyl-5,6,7,8-tetrahydrodibenzo[b,h][1,4]oxazonine-7-carboxylate (168d)



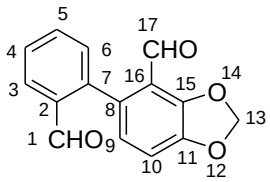
White crystals, mp 110-112 °C, R_f=0.43 (*n*-hexane:EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 7.37-7.31 (m, 2H, H-8,15), 7.17-7.09 (m, 2H, H-6,13), 7.08-7.02 (m, 2H, H-7,14), 7.00 (dm, *J*=8.0 Hz, 1H, H-5), 6.75 (dm, *J*=8.0 Hz, 1H, H-12), 4.33 (q, *J*=7.2 Hz, 2H, H-21), 4.01 (d, *J*=13.2 Hz, 1H, H-17), 3.91 (d, *J*=14.8 Hz, 1H, H-2), 3.37 (dd, *J*=14.8, 1.8 Hz, 1H, H-2), 3.03 (dd, *J*=13.2, 1.8 Hz, 1H, H-17), 2.73 (s, 3H, H-3), 1.37 (t, *J*=7.2 Hz, 3H, H-22). ^{13}C NMR ($CDCl_3$) δ (ppm): 168.8 (C-20), 157.3 (C-11), 150.7 (C-9), 146.4 (C-4), 131.7 (C-15), 129.7 (C-13), 126.7 (C-16), 125.9 (C-6), 124.4 (C-8), 124.2 (C-14), 123.0 (C-7), 119.7 (C-5), 118.8 (C-19), 118.1 (C-12), 64.0 (C-2), 63.8 (C-21), 48.7 (C-18), 40.5 (C-3), 38.2 (C-17), 14.7 (C-22). Anal. calcd for $C_{18}H_{15}N_3O$ (289.33): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.59; H, 5.29; N, 8.23.

3.10 Syntheses of carbaldehyde oximes

3.10.1 General procedure for Suzuki cross-coupling reactions of 5-bromo-1,3-benzodioxole-4-carbaldehyde

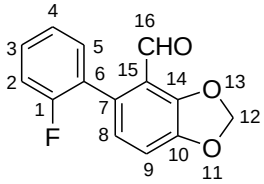
To a solution of 5-bromo-1,3-benzodioxole-4-carbaldehyde (0.458 g, 2.00 mmol) in DME (15 mL), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) was added at room temperature under an argon flow. After stirring at room temperature for 10 min, the appropriate boronic acid (3.00 mmol, for **179a**: 2-formylphenylboronic acid (450 mg), for **179b**: 2-fluorophenylboronic acid (420 mg), for **179c**: 2-chlorophenylboronic acid (469 mg), for **179d**: 2-bromophenylboronic acid (602 mg)) and aq 2 M Na_2CO_3 solution (2.5 mL) were added, and the reaction mixture was heated at reflux at 110 °C (oil temperature) until the starting material had been consumed (24 h, monitored by TLC). The cooled reaction mixture was poured into H_2O (30 mL). After separation of the phases, the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product obtained was purified by flash column chromatography on silica gel with the eluents indicated below.

5-(2-Formylphenyl)-1,3-benzodioxole-4-carbaldehyde (179a)



Column chromatography: *n*-hexane:EtOAc 9:1. Pink crystals (400 mg, 79%), mp 76-78 °C, R_f=0.67 (toluene:MeOH 3:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.90 (s, 1H, CHO), 9.80 (s, 1H, CHO), 8.05-8.00 (m, 1H, Ar-H), 7.67-7.61 (m, 1H, Ar-H), 7.59-7.54 (m, 1H, Ar-H), 7.34-7.31 (m, 1H, Ar-H), 7.05 (d, *J*=7.8 Hz, 1H, Ar-H), 6.76 (d, *J*=7.8 Hz, 1H, Ar-H), 6.24 (AB, *J*=1.1 Hz, 2H, CH_2). Anal. calcd for $C_{15}H_{10}O_4$ (254.24): C, 70.86; H, 3.96. Found: C, 70.87; H, 3.92.

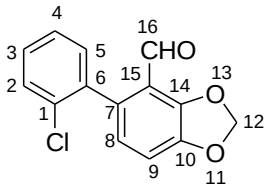
5-(2-Fluorophenyl)-1,3-benzodioxole-4-carbaldehyde (179b)



Column chromatography: *n*-hexane:EtOAc 4:1. Yellow crystals (453 mg, 93%), mp 84-86 °C, R_f=0.30 (*n*-hexane:EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.82 (d, *J*=2.9 Hz, 1H, CHO), 7.43-7.36 (m, 1H, Ar-H), 7.33-7.20 (m, 2H, Ar-H), 7.17-7.11 (m, 1H, Ar-

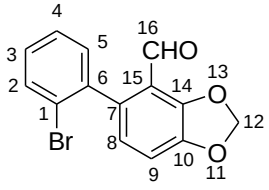
H), 7.05 (d, *J*=8.0 Hz, 1H, Ar-H), 6.83 (d, *J*=8.0 Hz, 1H, Ar-H), 6.20 (s, 2H, CH_2). Anal. calcd for $C_{14}H_9FO_3$ (244.22): C, 68.85; H, 3.71. Found: C, 68.91; H, 3.53.

5-(2-Chlorophenyl)-1,3-benzodioxole-4-carbaldehyde (179c)



Column chromatography: *n*-hexane:EtOAc 4:1. Yellow crystals (420 mg, 81%), mp 84-86 °C, R_f=0.39 (*n*-hexane:EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.69 (s, 1H, CHO), 7.49-7.44 (m, 1H, Ar-H), 7.40-7.28 (m, 3H, Ar-H), 7.04 (d, *J*=8.0 Hz, 1H, Ar-H), 6.76 (d, *J*=8.0 Hz, 1H, Ar-H), 6.20 (AB, *J*=1.2 Hz, 2H, CH_2). Anal. calcd for $C_{14}H_9ClO_3$ (260.67): C, 64.51; H, 3.48. Found: C, 64.37; H, 3.30.

5-(2-Bromophenyl)-1,3-benzodioxole-4-carbaldehyde (179d)

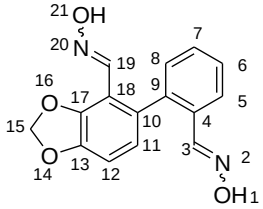


Column chromatography: *n*-hexane:EtOAc 9:1. Yellow crystals (900 mg, 59%), mp 89-91 °C, R_f=0.70 (toluene:MeOH 3:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 9.68 (s, 1H, CHO), 7.69-7.63 (m, 1H. Ar-H), 7.41-7.36 (m, 1H, Ar-H), 7.33-7.25 (m, 2H, Ar-H), 7.04 (d, *J*=8.0 Hz, 1H, Ar-H), 6.73 (d, *J*=8.0 Hz, 1H, Ar-H), 6.21 (AB, *J*=1.4 Hz, 2H, CH_2). Anal. calcd for $C_{14}H_9BrO_3$+1/4 C_6H_{14} (305.12+21.55): C, 56.99; H, 3.83. Found: C, 56.53; H, 2.85.

3.10.2 General method for the conversion of aldehydes to oximes

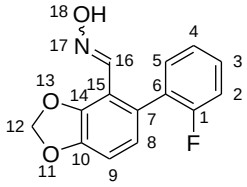
To an ice-cooled and stirred suspension of the appropriate aldehyde (for **180a**: **179a** (0.350 g, 1.38 mmol), for **180b**: **179b** (0.350 g, 1.43 mmol), for **180c**: **179c** (0.350 g, 1.34 mmol), for **180d**: **179d** (0.350 g, 1.15 mmol), for **181a**: **139a** (0.452 g, 1.50 mmol), for **181b**: **142a** (0.500 g, 1.50 mmol), for **181c**: **142c** (0.450 g, 1.25 mmol)) in EtOH (15 mL) a solution of NaOAc.$3H_2O$ (1.3 eq) and NH_2OH.HCl (1.3 eq) in H_2O (5 mL) were added dropwise within 5 minutes. The resulting suspension was stirred at room temperature until the starting material was consumed (2-4 h, monitored by TLC). The reaction mixture was evaporated to dryness, to the residue H_2O (10 mL) was added. The aqueous phase was extracted with 4×10 mL EtOAc, the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness. The crude product was purified by recrystallization (two times) from a mixture of EtOH:H_2O (4:1).

5-{2-[(hydroxyimino)methyl]phenyl}-1,3-benzodioxole-4-carbaldehyde oxime (180a)



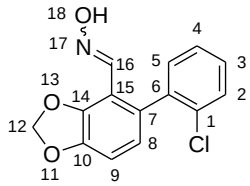
Pink crystals (114 mg, 29%), mp 227-229 °C, R_f=0.15 (*n*-hexane:EtOAc 3:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.39 (s, 1H, OH), 11.30 (s, 1H, OH), 7.88-7.83 (m, 1H, Ar-H), 7.64 (s, 1H, OH-NH=C-*H*), 7.46 (s, 1H, OH-N=C-*H*), 7.45-7.40 (m, 2H, Ar-H), 7.23-7.17 (m, 1H, Ar-H), 6.99 (d, *J*=8.0 Hz, 1H, Ar-H), 6.67 (d, *J*=8.0 Hz, 1H, Ar-H), 6.17+6.15 (AB, *J*=1.0 Hz, 2H, CH_2). Anal. calcd for $C_{15}H_{12}N_2O_4$ (284.27): C, 63.38; H, 4.25; N, 9.85. Found: C, 63.30; H, 4.14; N, 9.73.

5-(2-Fluorophenyl)-1,3-benzodioxole-4-carbaldehyde oxime (180b)



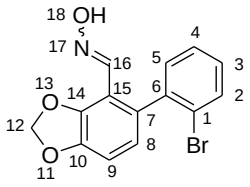
White crystals (180 mg, 49%), mp 197-198 °C, R_f=0.44 (*n*-hecane:EtOAc 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.38 (s, 1H, OH), 7.66 (d, *J*=2.2 Hz, 1H, OH-N=C-*H*), 7.49-7.42 (m, 1H, Ar-H), 7.34-7.24 (m, 3H, Ar-H), 7.00 (d, *J*=8.0 Hz, 1H, Ar-H), 6.78 (d, *J*=8.0 Hz, 1H, Ar-H), 6.15 (s, 2H, CH_2). Anal. calcd for $C_{14}H_{10}FNO_3$ (259.23): C, 64.87; H, 3.89; N 5.40. Found: C, 64.82; H, 3.65; N, 5.34.

5-(2-Chlorophenyl)-1,3-benzodioxole-4-carbaldehyde oxime (180c)



White crystals (0.079 g, 21%), mp 182-183 °C, R_f=0.30 (*n*-hexane:EtOAc 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.37 (s, 1H, OH), 7.57-7.53 (m, 1H, Ar-H), 7.51 (s, 1H, OH-N=C-*H*), 7.46-7.39 (m, 2H, Ar-H), 7.33- 7.29 (m, 1H, Ar-H), 7.00 (d, *J*=7.8 Hz, 1H, Ar-H), 6.69 (d, *J*=7.8 Hz, 1H, Ar-H), 6.15 (AB, *J*=1.0 Hz, 2H, CH_2). Anal. calcd for $C_{14}H_{10}ClNO_3$ (275.69): C, 60.99; H, 3.66; N, 5.08. Found: C, 61.41; H, 3.42; N, 5.03.

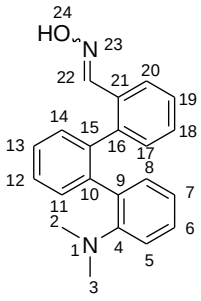
5-(2-Bromophenyl)-1,3-benzodioxole-4-carbaldehyde oxime (180d)



Yellow crystals (0.139 g, 38%), mp 168-169 °C, R_f=0.40 (*n*-hexane:EtOAc 2:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.37 (s, 1H, OH), 7.74-7.70 (m, 1H, Ar-H), 7.49 (s, 1H, OH-N=C-*H*), 7.48-7.43 (m, 1H, Ar-H), 7.37-7.33 (m, 1H, Ar-H), 7.33-7.28 (m, 1H, Ar-H), 6.99 (d, *J*=8.0 Hz, 1H, Ar-H), 6.66 (d, *J*=8.0 Hz, 1H, Ar-H), 6.15 (AB, *J*=7.4,

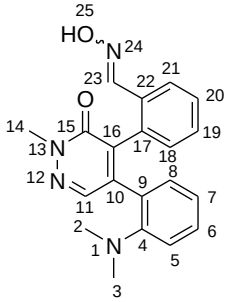
1.0 Hz, 2H, CH_2). Anal. calcd for $C_{14}H_{10}BrNO_3$ (320.14): C, 52.52; H, 3.15; N, 4.38. Found: C, 52.66; H, 2.97; N 4.35.

2''-[(hydroxyimino)methyl]-N,N-dimethyl-1,1':2',1''-terphenyl-2-amine (181a)



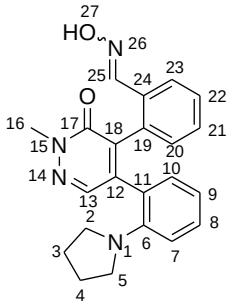
White crystals (371 mg, 78%), mp 85-86 °C, R_f=0.44 (*n*-hexane:EtOAc 9:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.06+10.96 (s, 1H, OH), 7.88-7.77 (br m, 2H), 7.55-7.38 (br m, 3H, Ar-H), 7.33-6.75 (br m, 6H, Ar-H), 6.72-6.63 (br m, 1H, Ar-H), 6.55-6.45 (br m, 1H, Ar-H), 2.01 (br s, 6H, NCH_3). Anal. calcd for $C_{21}H_{20}N_2O.C_2H_5OH$ (316.40+46.07): C, 76.21; H, 7.23; N, 7.73. Found: C, 75.83; H, 7.10; N, 7.73.

5-[2-(dimethylamino)phenyl]-4-{2-[(hydroxyimino)methyl]phenyl}-2-methylpyridazin-3(2H)-one (181b)



Yellow crystals (356 mg, 68%), mp 170-171 °C, R_f=0.32 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.16 (s, 1H, OH), 8.04 (s, 1H, NCH), 7.86-7.66 (br m, 2H, Ar-H), 7.28-6.47 (br m, 7H, Ar-H), 3.75 (s, 3H, NCH_3), 2.24 (br s, 6H, $N(CH_3)_2$). Anal. calcd for $C_{20}H_{20}N_4O_2$ (348.40): C, 68.95; H, 5.79; N, 16.08. Found: C, 68.82; H, 5.61; N, 16.03.

4-{2-[(hydroxyimino)methyl]phenyl}-2-methyl-5-[2-(pyrrolidin-1-yl)phenyl] pyridazin-3(2H)-one (181c)

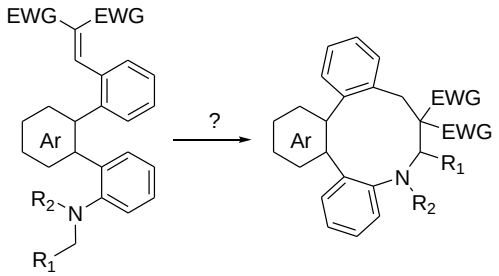


Yellow crystals (226 mg, 48%), mp 190-191 °C, R_f=0.37 (*n*-hexane:EtOAc 1:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 11.16 (s, 1H, OH), 8.14-7.90 (br m, 1H, NCH), 7.81-7.55 (br m, 2H, Ar-H), 7.32-6.91 (br m, 4H, Ar-H), 6.86-6.48 (br m, 3H, Ar-H), 3.73 (br s, 3H, NCH_3), 3.10-2.85 (br m, 4H, NCH_2), 1.90-1.60 (br m, 4H, CH_2). Anal. calcd for $C_{22}H_{22}N_4O_2$+1/2 C_2H_6O (374.44+23.04): C, 69.50; H, 6.29; N, 14.10. Found: C, 69.49; H, 5.85; N, 14.61.

4 Results and discussion

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

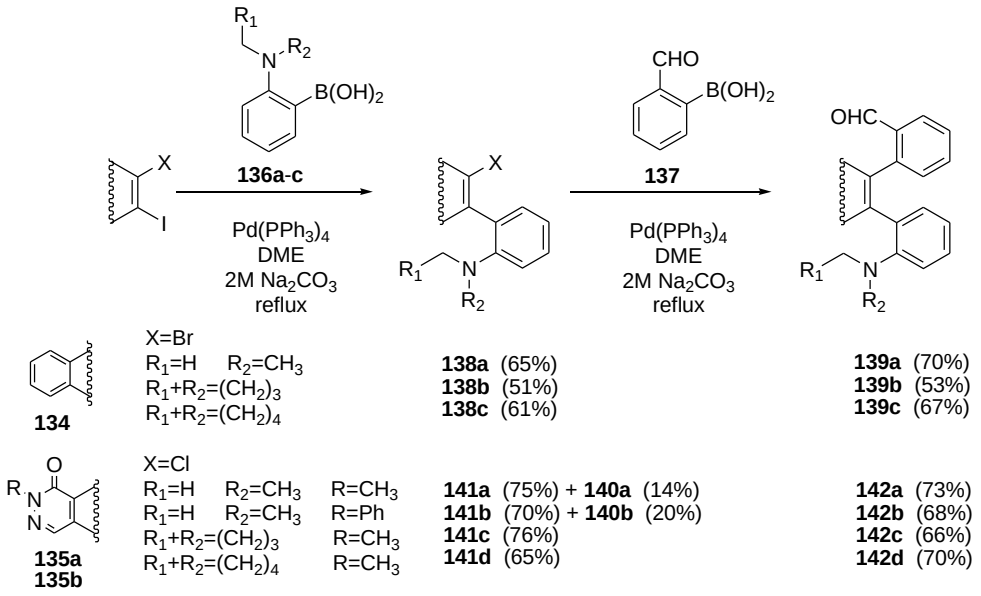
Our aim was to study on the one hand, whether *tert*-amino effect can operate among triaryl derivatives with the *ortho*-positioned *tert*-amino and vinyl groups on aryl rings linked *via* a third aryl ring (Scheme 38.). As model compounds, 2-[(2-vinylphenyl)phenyl]-*tert*-anilines and their pyridazinone analogues were chosen.



Scheme 38. Model compounds planned for studies of novel extensions of the *tert*-amino effect 1.

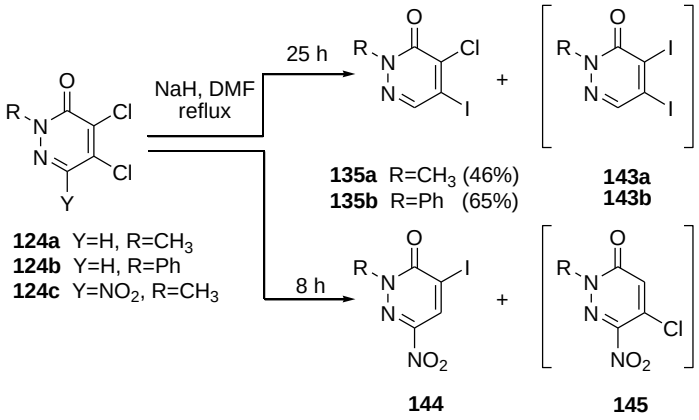
4.1.1 Synthesis of aldehyde intermediates.

Two series of *ortho*-vinyl *tert*-aniline compounds were synthesized for studying *tert*-amino effect cyclizations, expected to lead to azecine-fused products. A series of benzene (**139a-c**) and pyridazinone (**142a-d**) derivatives was prepared (Scheme 39.), *via* two consecutive Suzuki reactions; carrying out couplings first with boronic acids having an *ortho-sec*-amino substituent (**136a-c**) (affording **138a-c** and **141a-d**), followed by coupling with the commercially available 2-formylphenylboronic acid (**137**) (leading to **139a-c** and **142a-d**, respectively). As unsymmetrically substituted derivatives were aimed, dihalo substrates were chosen, in which different reactivity of the halogens in Suzuki coupling could be exploited for the selective formation of the products. Therefore, the synthesis of the benzene series started from the commercially available 2-bromoiodobenzene (**134**), while for the pyridazinone series, 4-chloro-5-iodo-2-methyl- (**135a**)[63] and 4-chloro-5-iodo-2-phenylpyridazin-3(2*H*)-one (**135b**) were selected as starting materials to carry out regioselective Suzuki couplings.



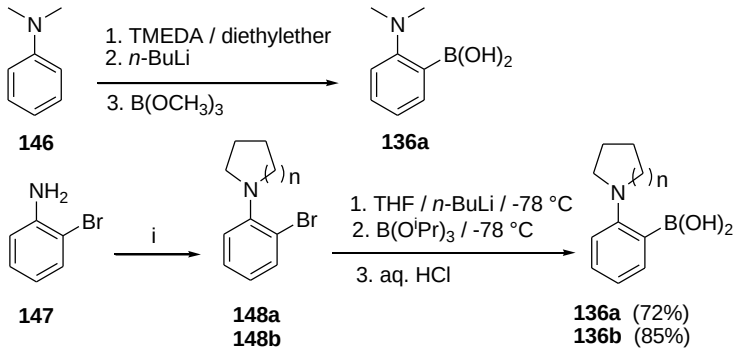
Scheme 39. Synthesis of **139a-c**,**142a-d** triaryl aldehydes.

4-chloro-5-iodopyridazin-3(2*H*)-ones **135a**,**b** applied by us were prepared according to the method elaborated at the Department of Organic Chemistry (Semmelweis University), starting from **124a**,**b** 4,5-dichloropyridazin-3(2*H*)-ones (Scheme 40.). Halogen displacement reaction of the **124a** 2-methyl derivative with sodium iodide in DMF at 150°C resulted in the formation of the 4-chloro-5-iodo derivative **135a** as the main product, besides the formation of the diiodo derivative **143a** (detected by NMR in the crude product in a 17/3 ratio). Analytically pure **135a** could be obtained by recrystallization. Similar results were obtained with the 2-phenyl derivative, with formation of the 4-chloro-5-iodo isomer (**135b**) as the main product. Interestingly, reaction of the 6-nitro derivative **124c** with sodium iodide in DMF at 150°C afforded the 4-iodo product (**144**), besides the 5-chloro derivative (**145**) as minor component (detected by NMR in 3/1 ratio). Albeit the formation of the various iodo-derivatives is strongly substituent and reaction condition-dependent, regioselectivity could be predicted by mechanistic considerations. Reactions of 4-chloro-, 5-chloro- and 4,5-dichloropyridazin-3(2*H*)-ones with 57% hydrogen iodide have been thoroughly studied as well at the Department of Organic Chemistry (Semmelweis University), which has been recently supplemented by further studies on 6-(2,4-dichloro)phenyl derivatives.[63,97]



Scheme 40. Halogen displacements of 4,5-dichloropyridazin-3(2*H*)-ones with sodium iodide.

The boronic acids used for the first series of Suzuki couplings were prepared from *N*,*N*-dimethylaniline (**146**) or the appropriate *ortho*-haloarylamines (**148a**,**b**). The latter could be obtained from 2-bromoaniline (**147**) by the method described by Verboom *et al.*[8] 2-Dimethylaminophenylboronic acid (**136a**) was prepared by a literature procedure,[85] while pyrrolidino and piperidino boronic acids **136b** and **136c** were obtained in good yields from the corresponding *ortho*-haloarylamines by a method analogous to that used for the synthesis of 2-(4-methylpiperazin-1-yl)-[98] and 4-pyrrolidinophenylboronic[99] acids – namely by *ortho*-lithiation and subsequent reaction with triisopropyl borate in tetrahydrofurane (THF) (Scheme 41.).



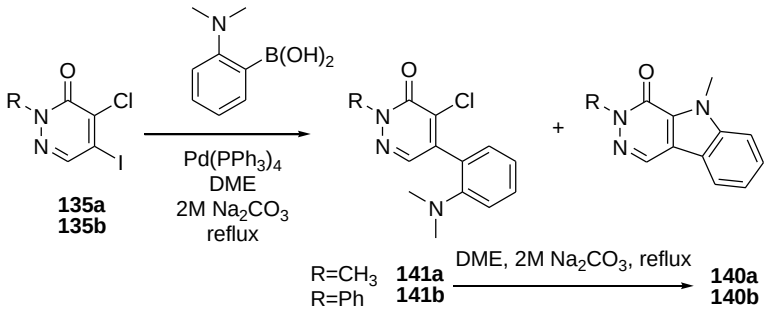
a n=1, **b** n=2
i) $Br(CH_2)_4Br$ (for **131a**) or $Br(CH_2)_5Br$ (for **131b**), $(i\text{-}Pr)_2EtN$, toluene, 110°C, 20h

Scheme 41. Synthesis of *ortho-sec*-aminophenylboronic acids.

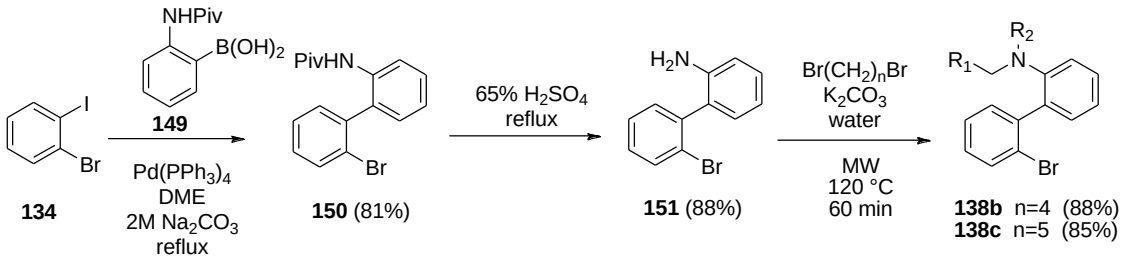
Suzuki couplings with **136a-c** boronic acids could be carried out smoothly in a DME/2M aq. Na_2CO_3 biphasic system, with $Pd(PPh_3)_4$ catalyst, affording **138a-c** and

141a-d biaryl products. Subsequent couplings with 2-formylphenylboronic acid led to **139a-c** and **142a-d** aldehyde products in good yields (Scheme 39.).

In the Suzuki coupling of **135a**,**b** with 2-dimethylaminophenylboronic acid, formation of an indole by-product (**140a**,**b**) was observed, presumably *via* intramolecular substitution of the coupled product (Scheme 42.). Subjecting the **141a**,**b** products to Suzuki coupling conditions (48 h reflux in DME/2 M aq Na_2CO_3), **140a**,**b** indole derivatives were formed in different ratio depending on the 2-substituent. In the case of a 2-CH_3 group, a starting material:product ratio of 3.5:1 was obtained (as compared with a 5:1 ratio following Suzuki reaction). The presence of a 2-phenyl group resulted in a starting material:product ratio of 1.56:1 (*vs* 3.5:1 observed following Suzuki reaction).



Scheme 42. Formation of indole by-products.



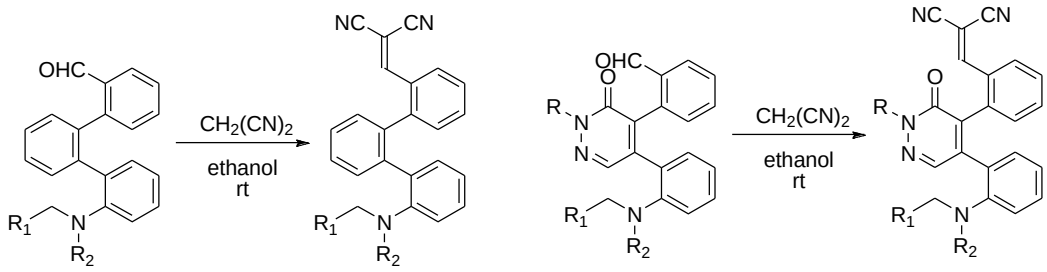
Scheme 43. Synthesis of biaryl amines *via* microwave-assisted *N*-heterocyclization.

As an alternative route for the synthesis of **138b**,**c** biaryl amines – applying a common amine intermediate – Suzuki coupling was first carried out with 2-pivaloylaminophenylboronic acid (**149**), followed by deprotection in aq H_2SO_4 (**150→151**) (Scheme 43.). (2-pivaloylaminophenylboronic acid was prepared by the literature method,[95,96] starting from pivaloylanilide. Pivaloylanilide can be obtained

from aniline with pivaloyl chloride in dichloromethane/aq Na_2CO_3 mixture. Subsequent *ortho*-lithiation, reaction with trimethyl-borate followed by hydrolysis (with cc. HCl) affords **149**). The obtained primary amine (**151**) could be converted in high yields to the desired *N*-heterocyclic (pyrrolidino or piperidino) derivatives *via* the microwave-assisted *N*-heterocyclization described by Ju and Varma,[100] with dihaloalkanes in alkaline aqueous medium.

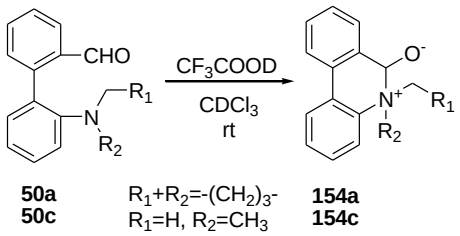
4.1.2 Synthesis of vinyl compounds and studies on *tert*-amino effect cyclization

Vinyl compounds **152a-c** and **153a-d** were obtained in good yields from **139a-c** and **142a-d** aldehydes (prepared *via* Suzuki reactions of **138a-c** and **140a-d** amines with 2-formylphenylboronic acid) *via* Knoevenagel condensation under mild conditions (in ethanol at room temperature in the presence of piperidine, with malononitrile as the active methylene agent) (Scheme 44.).



Scheme 44. Syntheses of **152a-c**,**153a-d** vinyl derivatives *via* Knoevenagel condensation.

The structures of several aldehyde and vinyl intermediates (**142a, 152a**, **153a**) were confirmed by X-ray diffraction (as summarized in Fig. 1.). In the biphenyl series, in compounds **50a** and **50c**, the nitrogen and the carbonyl carbon were found to be very close to each other (**50a**: 2.989 Å, **50c**: 2.835 Å). Moreover, under mild conditions (in NMR tube at room temperature, in $CDCl_3/CF_3COOD$) a zwitterionic cyclized product was obtained, confirming an interaction between the amine and carbonyl moieties indicated by the short distance observed by X-ray crystallography (Scheme 45.).



Scheme 45. Cyclization of **50a** and **50c** aldehydes.

Among triphenyl derivatives no such cyclization was observed. According to X-ray crystallography, in compound **142a**, the dimethylamino group adopts a pyramidal geometry, with the lone pair directing towards the aldehyde moiety, the nitrogen and carbonyl carbon distance is significantly longer however (3.308 Å), than that observed among biphenyls.

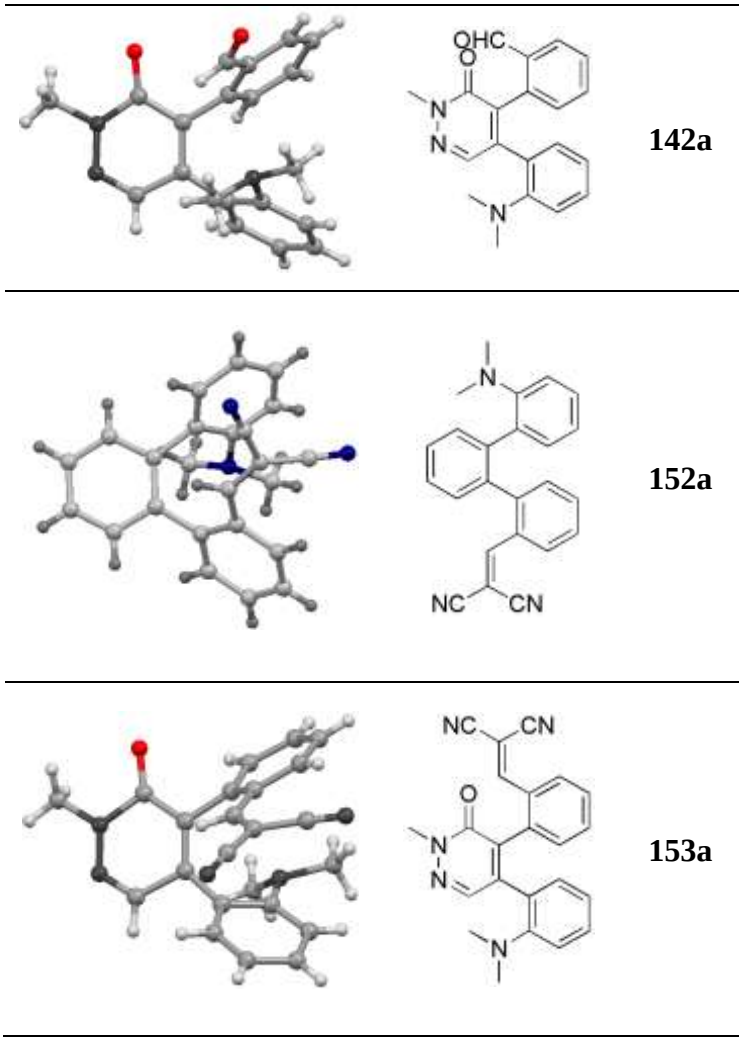
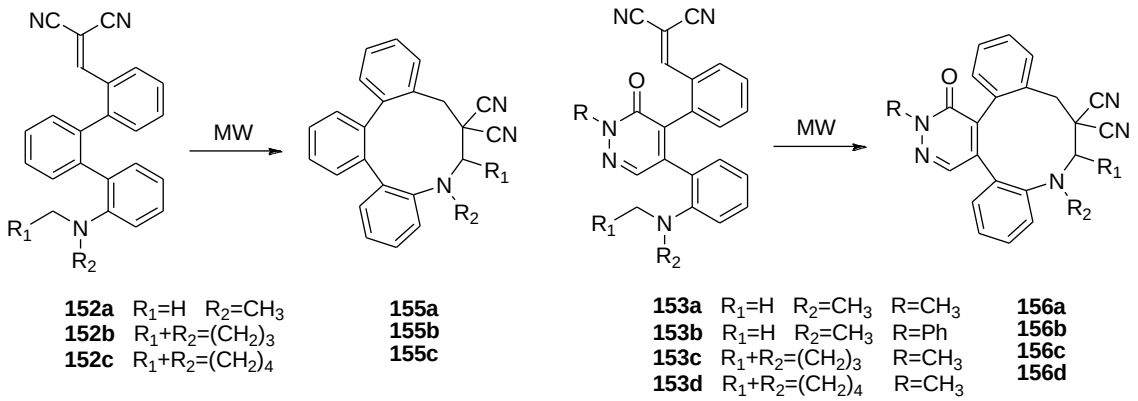


Figure 1. X-ray structures of **142a**,**152a** and **153a**.

Tert-amino effect cyclizations often require higher temperatures or longer reaction times. Therefore, experiments on the thermal isomerisation of vinyl compounds **152a-c** and **153a-d** were carried out in a microwave instrument, what seemed feasible with regard to the rate enhancements and yields frequently observed in the literature. Moreover, Kaval *et al*. described microwave-assisted *tert*-amino effect cyclizations,[31,32] observing beneficial effects in several cases. Trying first heating under solvent-free conditions, irradiation of **152a** (at 160 °C, for 45 min) resulted in the formation of 66% of azecine product **155a**, while 21% of the starting material was recovered. Applying longer reaction times or higher temperatures led only to an increased rate of decomposition, and hence a lower isolated yield of the azecine product. As for **152b** and **153a** solvent-free reactions led to high rates of decomposition, with no sufficient product observable in the reaction mixture, the further experiments were carried out in the solution phase in DMSO, a solvent frequently used for *tert*-amino effect cyclizations.

Heating **152a-c** and **153a-d** in DMSO solution led to the expected azecine-fused products (i.e. products, in which new C-C bond is formed between the carbon adjacent to the amine nitrogen and the β vinyl carbon) **155a-c** and **156a-d** in all cases, the pyridazine analogues behaving similarly to their benzene counterparts in this respect (Scheme 46.).[101]



152a R_1=H R_2=CH_3
152b R_1+R_2=$(CH_2)_3$
152c R_1+R_2=$(CH_2)_4$

155a
155b
155c

153a R_1=H R_2=CH_3 R=CH_3
153b R_1=H R_2=CH_3 R=Ph
153c R_1+R_2=$(CH_2)_3$ R=CH_3
153d R_1+R_2=$(CH_2)_4$ R=CH_3

156a
156b
156c
156d

Scheme 46. Formation of fused azecine ring systems *via tert*-amino effect cyclization.

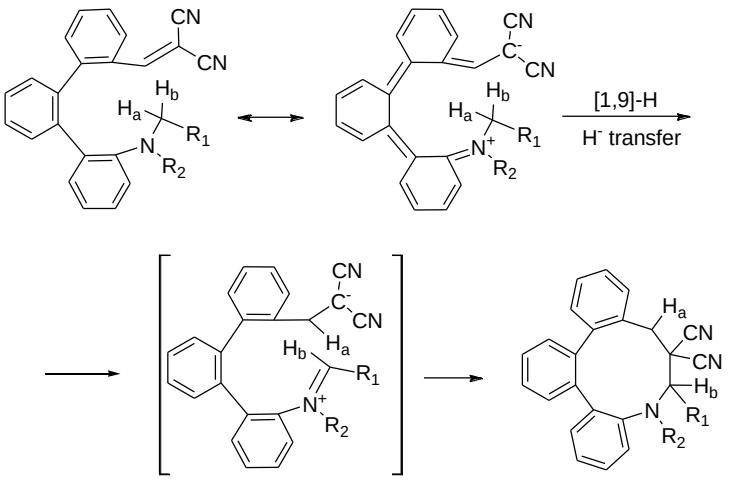
A limitation to the synthetic applicability of the approach is however, that the reaction of derivatives with cyclic amine groups resulted in the formation of the azecine products only with poor or moderate yields. For the *N,N*-dimethylamino derivatives (**152a** and

153a,**b**) no such problem was met, the desired fused products (**155a** and **156a**,**b**) were obtained in good yields. Upon heating pyrrolidino and piperidino derivatives (**152b**,**c** and **153c**,**d**) however, parallelly to the formation of the product (as monitored by HPLC) a high rate of decomposition occurred (leading to a drop in the isolated yield), therefore optimal conditions were difficult to be found, even at relatively low reaction temperatures (Table 5).

Table 5. Synthesis of azecine-fused systems.

Compound	Temp (°C) / time (min)[a]	Product (yield)[c] (+starting material recovered)
152a	200/150	**155a** (85%)
	100/30	**155b** (19%), **152b** (50%)
152b	100/90	**155b** (11%), **152b** (6%)
	150/2	**155b** (11%), **152b** (2%)
	150/5	**155c** (32%), **152c** (20%)
152c	150/10	**155c** (13%), **152c** (2%)
	175/2	**155c** (34%), **152c** (3%)
153a	200/150	**156a** (83%)
153b	200/150	**156b** (80%)
	100/180	**156c** (20%), **153c** (11%)
153c	125/10	**156c** (16%), **153c** (24%)
	150/1	**156c** (14%), **153c** (21%)
	150/5	**156d** (24%), **153d** (30%)
153d	175/5	**156d** (44%), **153d** (2%)
	175/10	**156d** (18%), **153d** (7%)
	200/1[b]	**156d** (51%), **153d** (6%)

[a]Hold time for MW-assisted experiments; reactions were carried out in open vessels (if not indicated otherwise) on a 0.25 mmol scale, at a maximum power level of 200 W
[b]Reaction was carried out in a 10 mL sealed MW process vial
[c]Isolated yields



Scheme 47. *Tert*-amino effect cyclization leading to fused azecine ring systems.

The cyclization can be rationalized by a two-step mechanism, the first, rate-limiting step involving either a [1,9]-hydrogen migration or, more likely, direct hydride donation between the interacting groups, resulting in a dipolar intermediate, the next step comprising bond formation between the oppositely charged carbons (Scheme 47.).

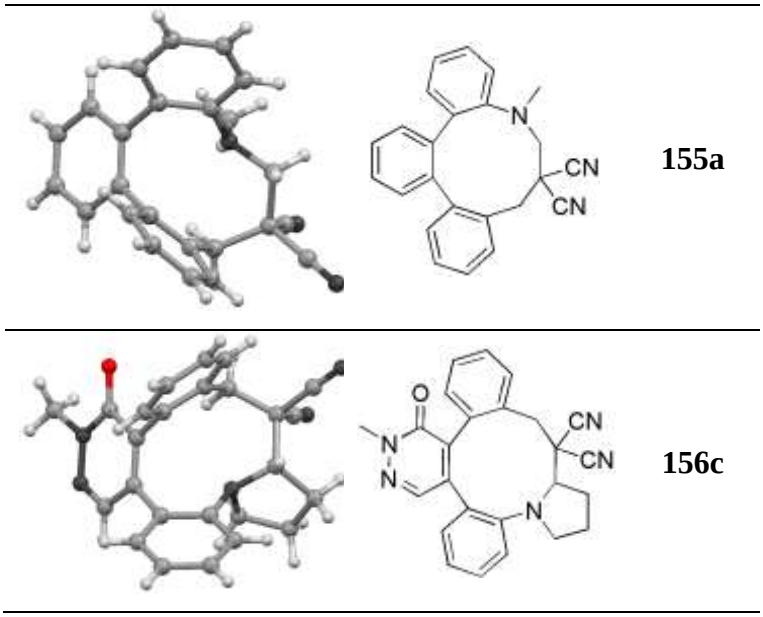


Figure 2. X-ray structures of **155a** and **156c**.

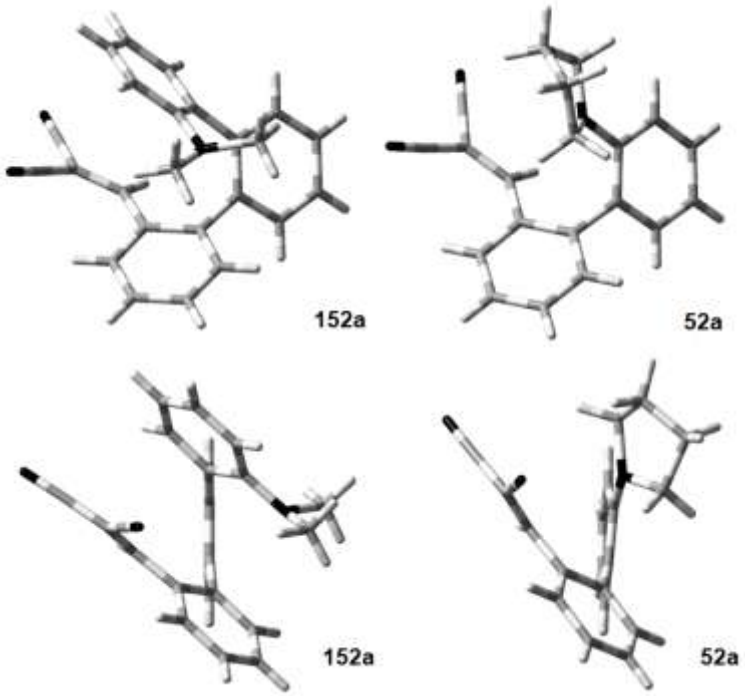
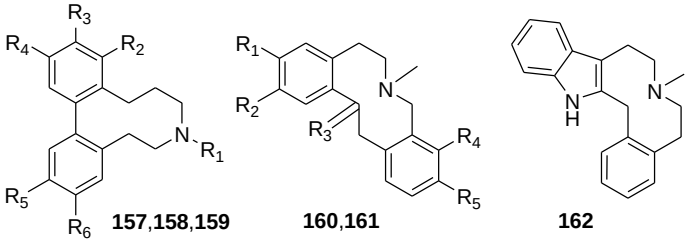


Figure 3. Geometric arrangement of the interacting functionalities.

The structures of two azecine-fused products (**155a** and **156c**) were confirmed by X-ray crystallography (as summarized in Fig. 2.). In the biphenyl series described by Polonka-Bálint *et al.*,[42] investigation of the geometric arrangement of the *ortho, ortho'* functionalities in the vinyl precursors by X-ray analysis revealed a weak interaction. Namely, in the biaryl analogue of compound **152a**, the *tert*-amino and vinyl groups were located on the same face of the biaryl system (compound **52a**), their distance from each other being considerably short (2.878 Å for the *tert*-amino nitrogen – α-vinyl carbon). Studying the analogue **152a** triphenylvinyl derivative by X-ray crystallography, two conformers were found in the asymmetric unit, while the corresponding distances between the *tert*-amino nitrogen and the α-vinyl carbon (located on opposite faces of the triaryl system) were found to be significantly longer (4.25 and 3.98 Å for the two conformers found, respectively) (Fig. 3.). (In comparison, the corresponding N-C_α distance was found to be 4.15 Å for the pyridazinone analogue **153a**). Interestingly, two conformers were also found in the asymmetric unit of azecine **156c**.

The cyclization could be well monitored by NMR spectroscopy, the NMR signals of the methylene hydrogens adjacent to the nitrogen and the carbon bearing the electron-withdrawing groups in the azecine-fused products are characteristic of the ring closure (as illustrated by the spectra of **152a** vinyl compound and its azecine counterpart (**155a**) – Appendix/Fig. 1A.). As an example, characteristic NMR data of **152a** and **52a** vinyl compounds in comparison with their cyclic azecine (**155a**) and azocine (**53a**) counterparts are the following (in ppm, $CDCl_3$/DMSO-d_6 for **152a**): i) -**CH**=$C(CN)_2$ (vinyl compounds) – ^{1}H: 7.31 (**152a**) / 7.58 (**52a**), ^{13}C: 160.4 (**152a**) / 162.4 (**52a**), ii) -**CH_2**-$C(CN)_2$-CHR_1- (cyclic products) – ^{1}H: 3.40 and 3.52 (**155a**) / 3.38 and 3.64 (**53a**); ^{13}C: 35.9 (**155a**) / 40.1 (**53a**). Additionally, the appearance of these signals in the NMR spectra is accompanied by the disappearance of the signal broadening or signal duplication phenomena observed for the tricyclic vinyl (and aldehyde) compounds, due to hindered rotation (signal broadening is illustrated by the spectra of **142a** recorded at ambient temperature in comparison with the spectra recorded at 100°C (Appendix/Fig. 2A.), whereas disappearance of signal broadening due to the formation of the cyclized product is illustrated by the spectra of **152c** vinyl compound and its cyclized counterpart **155c** (Appendix/Fig. 3A.)).

The azecine-fused compounds prepared *via tert*-amino effect cyclization represent the first members of hitherto unpublished ring systems, however a literature survey revealed, that although only a few related compounds have been reported, some benzazecine derivatives might represent interesting biological activities. As an example for such compounds, dysazecine (**157**) was the first alkaloid with a dibenzo[*d,f*]azecine skeleton isolated from plants, moreover, it was suggested to be a biosynthetic intermediate to homoerythrina alkaloids.[102] Compound **158**, with a dibenzo[*d,f*]azecine skeleton might be a biogenetic precursor of *Schelhammera* and *Cephalotaxus* alkaloids.[103-105]



157: R_1=CH_3, R_2=H, R_3+R_4=-OCH_2O-, R_5=OCH_3, R_6=OCH_3
158: R_1=H, R_2=H, R_3=OH, R_4=OCH_3, R_5=OCH_3, R_6=OH
159: R_1=CH_3, R_2=OCH_3, R_3+R_4=-OCH_2O-, R_5=H, R_6=H
160: R_1+R_2=-OCH_2O-, R_3=O, R_4+R_5=-OCH_2O-, R_6=-
161: R_1=OH, R_2=H, R_3=-, R_4=OCH_3, R_5=OCH_3, R_6=-

Scheme 48. Some representatives of fused azecine ring systems.

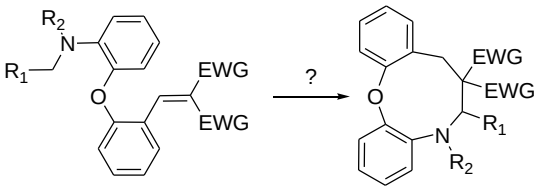
The esters of cephalotaxine, a representative of the latter group were found to exhibit antitumor activity.[106] To represent compounds assayed for a specific purpose, the dyshomoerythrine derivative **159** was meant to act as an insecticide,[107] the benzazecine alkaloid protopine (**160**) served as a potential antimalarial lead compound[108] while compound **161** was prepared as an analgetic.[109] Further pharmacological properties of the protopine alkaloids (e.g. neuroprotective[110] or anti-inflammatory[111] effects) have been thoroughly studied. LE300 (**162**) and its derivatives are novel types of nanomolar dopamine receptor antagonists[112,113] (Scheme 48.).

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

As a continuation of the studies on azecine-fused systems, we set out to explore whether *tert*-amino effect can operate also among non-conjugated derivatives. Such an extension

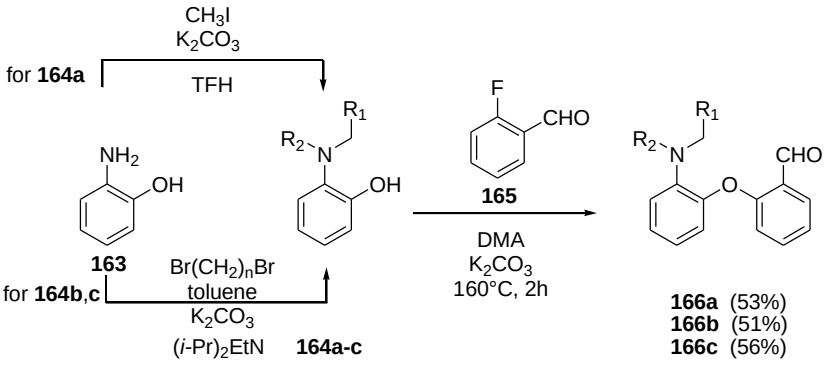
might be interesting from a mechanistic point of view. As there is no option for (the previously suggested) sigmatropic process, cyclization of non-conjugated derivatives could demonstrate, that ring closure *via tert*-amino effect could operate also with direct hydride donation from an *N*-alkyl group to an electron-deficient alkene, facilitated by the close proximity of the groups and the electron-rich character of the *N*-alkyl group. Such a mechanism was suggested by Wallis *et al*. for the cyclization of appropriately substituted naphthalene derivatives, however without any reference to *tert*-amino effect.[114]

As model compounds, 2-(2-vinyl)phenoxy-*tert*-anilines were chosen, having the interacting groups positioned on two aromatic rings connected by an oxygen bridge (Scheme 49.).



Scheme 49. Model compounds planned for studies of novel extensions of the *tert*-amino effect 2.

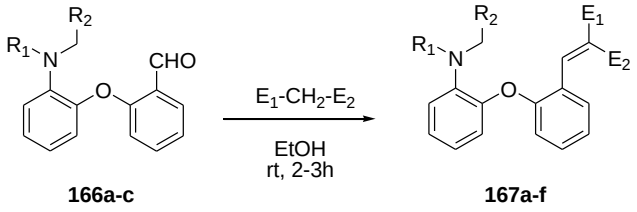
166a-c aldehydes were prepared from commercially available 2-fluorobenzaldehyde (**165**) and the corresponding 2-aminophenols (**164**). The latter were synthesized by literature methods, starting from 2-aminophenol (**163**) (**164a**: with methyl iodide in THF, with K_2CO_3 base; **164b**,**c**: with 1,4-dibromobutane or 1,5-dibromopentane in toluene, with *N*-ethyldiisopropylamine base)[88,89] (Scheme 50.).



a: R_2=CH_3, R_1=H; **b**: R_1+R_2=$(CH_2)_3$; **c**: R_1+R_2=$(CH_2)_4$

Scheme 50. Synthesis of **166a-c** aldehydes.

The vinyl precursors for the cyclization studies were prepared by the Knoevenagel condensation of **166a-c**, using malononitrile or ethyl cyanoacetate as active methylene agents, affording **167a-f** products typically with good yields under mild conditions (Scheme 51.). Regarding **167d-f** derivatives, formed by the treatment of **166a-c** aldehydes with ethyl cyanoacetate, judged by the NMR spectra (δ_H of vinyl protons (in $CDCl_3$): **167d**: 8.92 ppm, **167e**: 8.89 ppm, **167f**: 8.96 ppm) exclusively the *E* isomers were formed (the less bulkier nitrile group being in *cis* position to the benzene ring), in accordance with former examples reported in the literature.[22,27,115,116]

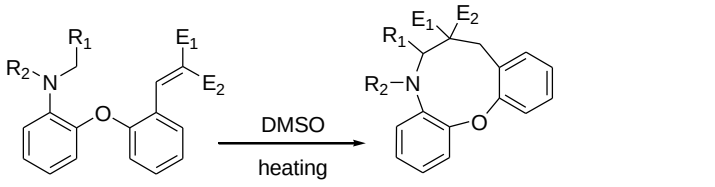


166a-c **167a-f**

a,d: R_1=CH_3, R_2=H; **b,e**: R_1+R_2=$(CH_2)_3$; **c,f**: R_1+R_2=$(CH_2)_4$
167a-c: E_1=E_2=CN; **167a** (71%); **167b**: (65%); **167c**: (35%)
167d-f: E_1=COOEt, E_2=CN; **167d**: (73%); **167e**: (86%); **167f**: (80%)

Scheme 51. Synthesis of **167a-f** vinyl precursors.

Cyclizations were attempted in DMSO solution in microwave reactor. First, short irradiations (15/30 min) were screened in the 50-200°C temperature range. In the dinitrile series, in preliminary experiments the expected oxazonine products were formed from **167a** and **167b**, albeit only in modest yields (besides recovering unreacted starting compound for **167a** (Scheme 52.)).



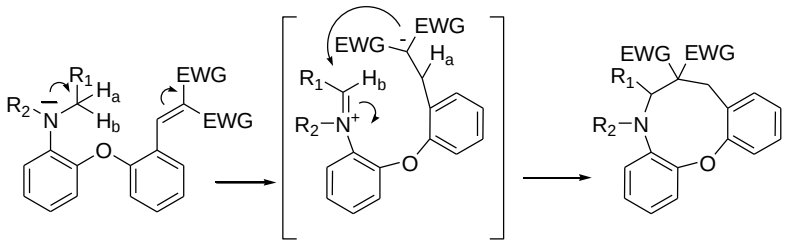
167a-f **167a** (150°C, 15 min) → **168a** (27%) + **167a** (43%)
167b (100°C, 15 min) → **168b** (21%)
167d (175°C, 15 min) → **168d** (28%) + **167d** (37%)

Scheme 52. Synthesis of fused oxazonines *via tert*-amino effect.

For **167c** no conversion was observed at lower temperatures (50-100°C), while higher temperatures (125-200°C) led only to decomposition of the vinyl precursor. Similar

result was obtained for **167e**,**f** from the ester series, having cyclic amine moieties. **167d** however could be cyclized, apparently due to its better thermal stability, as higher temperature (175°C) was required for the reaction to take place. The reaction was not run till full conversion also in this latter case, due to the decomposition observed after prolonged heatings.

The cyclization can be rationalized by the mechanism depicted in Scheme 53., by hydride donation between the interacting amine and vinyl moieties.



Scheme 53. *Tert*-amino effect cyclization of biaryl ethers.

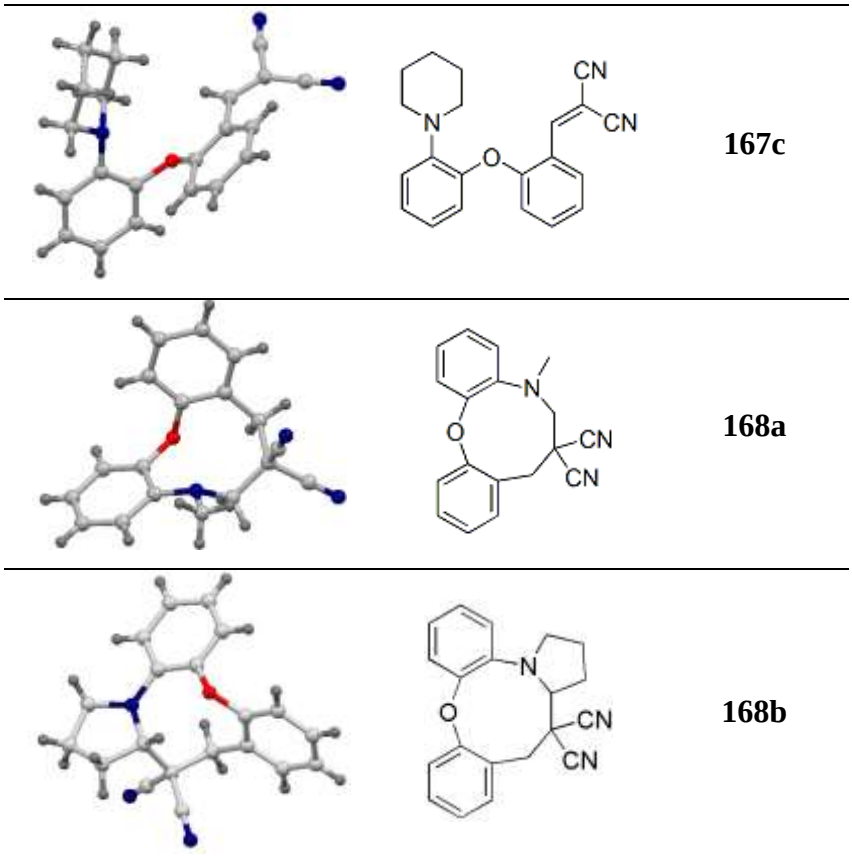


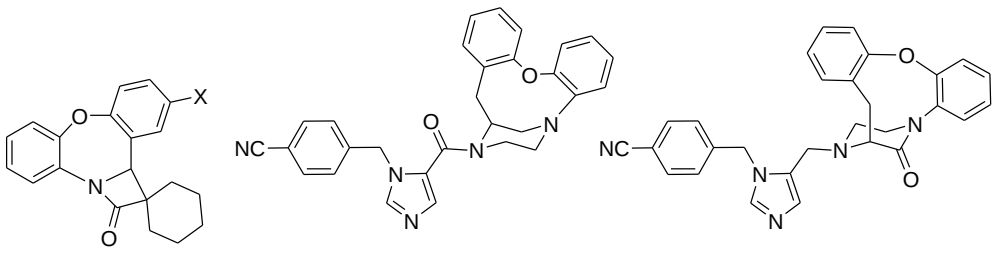
Figure 4. X-ray structures of **167c** and **168a**,**b**.

The ring closure could be well monitored by NMR spectroscopy also among biaryl-ethers, by the appearance of the characteristic NMR signals of the methylene hydrogens adjacent to the nitrogen and the carbon bearing the electron-withdrawing groups in the products (as illustrated by the spectra of the **167b** vinyl compound and its oxazonine counterpart **168b** (Appendix/Fig. 4A.)).

Structures of **167c** and **168a**,**b** were confirmed by X-ray crystallography (Fig. 4.) as well. Studying the position of the interacting groups that might be relevant for cyclization, the distance between the tertiary amine nitrogen and the α vinyl carbon was found to be 4.37 Å in compound **167c**. Regarding the oxazonine-fused products, theoretically, inversion of the pyrrolidino nitrogen might result in detectable isomers. Interestingly however, in **168b**, the pyrrolidino nitrogen was found to be planar, located in the plane of the aromatic ring.

With the cyclization of **167b** and **167d**, a new stereogenic centre is formed. In HPLC experiments with chiral column, two peaks could be detected, in an almost 1:1 ratio, presumably due to the formation of the two enantiomers (Appendix/Fig. 6A.). Similar results were obtained in the triphenyl series as well (Appendix/Fig. 5A.), studying **155b** pyrrolidino and **155c** piperidino derivatives.

According to the above preliminary results, although the reaction conditions are still to be optimized, with proper choice of the amine and the vinyl moiety however, *tert*-amino effect can operate also among biaryl-ethers (i.e. non-conjugated systems), leading to the formation of the corresponding fused oxazonine ring systems.



169 **170** **171**

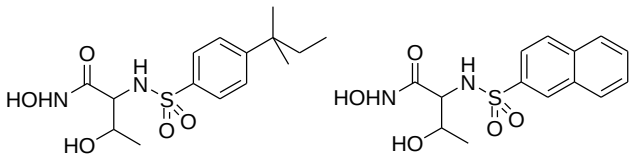
Scheme 54. Oxazonine derivatives of potential pharmacological interest.

Nine-membered biaryl-fused heterocycles represent a relatively less studied group in the literature. Of the related oxazonine derivatives revealed by literature survey, bridged compounds **169** (a spiro-fused polycyclic β-lactam derivative)[117] and **170-171** (prepared

as farnesyl-protein transferase inhibitors)[118] could be mentioned as interesting representatives of pharmacological interest (Scheme 54.).

4.3 Synthesis of SSAO inhibitor oximes

Arylalkyloxime derivatives have recently been found in the Department of Organic Chemistry (Semmelweis University) to display significant VAP-1 inhibitory and anti-inflammatory effects.[119] Mlíčková *et al.* described inhibitory effect of pyridine carbaldoximes and alkyl pyridyl ketoximes on copper-containing amine oxidases of plant (pea seedling (*Pisum sativum*) amine oxidase - PSAO) and bacterial (*Arthrobacter globiformis* amine oxidase - AGAO) origine.[120] Hydroxylamine itself was reported to have an inhibition value of 10^{-6} M, whereas micromolar K_i values were observed for the pyridine carbaldoximes and alkyl pyridyl ketoximes studied (acting as non-competitive inhibitors), presumably due to complexing of the active site copper. Such an effect was suggested in the case of hydroxamic acid VAP-1 inhibitors with an amino acid moiety,[121] exemplified by the structures (**172**,**173**) shown in Scheme 55. Hiraoka *et al.* studied inhibitory effect of oxime compounds on bovine serum amine oxidase (BSAO) and human serum SSAO. The most effective inhibitor among the derivatives studied was 2-butanone oxime (acting as a non-competitive inhibitor), with IC_{50} values of 6.7 μM (BSAO) and 6.5 μM (human SSAO).[122]



172 IC_{50}=4 nM

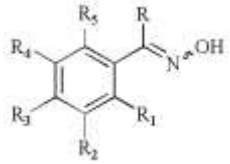
173 IC_{50}=54 nM

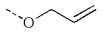
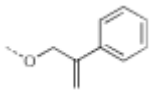
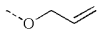
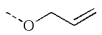
Scheme 55. Copper chelating hydroxamic acid VAP-1 inhibitors.

As the starting point of oxime-related studies at the Department of Organic Chemistry (Semmelweis University), the VAP-1 inhibitory effect of benzaldehyde oxime (**174a**) was found to be in the micromolar range. [The SSAO inhibitor properties of the oximes were assayed on human recombinant VAP-1 (expressed in Chinese Hamster Ovary cells, as described by Smith *et al.*[74]), by the colorimetric method of Holt,[123] in collaboration with the Finnish pharmaceutical company Biotie]. A study on the effects

of various substituents of the phenyl ring on VAP-1 inhibition showed that activity in general remained intact in the case of *ortho* substitutions (Table 6.). Turning to bulkier aryl substituents however, the inhibitory activity was completely lost. Substitution of the oxime carbon proved to be detrimental to the activity as well.

Table 6. VAP-1 inhibitory activity of phenyl oximes.



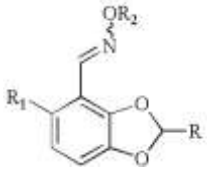
Compd	R	R_1	R_2	R_3	R_4	R_5	VAP-1 inhibition IC_{50}, μM
174a	H	H	H	H	H	H	131
174b	H	OH	H	H	H	H	113
174c	H	F	H	H	H	H	21
174d	H		H	H	H	H	123
174e	H		H	H	H	H	209
174f	H	H	H	H	OCH_3	CH_3	130
174g	H	OH	OCH_3	H	H	Br	35
174h	H	OH	OCH_3	H	Br	H	63
174i	CH_3		H	H	Br	H	35%[a]
174j	CH_3		H	Br	H	H	35%[a]

[a] % inhibition measured at 800 μM concentration

In the next two series of compounds, the phenyl core was changed either to benzodioxole (Table 7.) or uracile (Table 8.). *Ortho*-hydroxy (**175a**) and bromo (**175b**) derivatives showed good activity also in the benzodioxole group, *ortho*-ethoxy (**175c**) or allyloxy (**175d**) substituents being less favourable (Table 7.). Substitutions of the oxime OH group afforded inactive compounds (**175e**,**f**). Interestingly, also attachment of a methyl substituent to the dioxole ring led to an inactive derivative (**175g**).

Among oximes with an uracile skeleton, starting from the active 6-chloro derivative (**176a**), a series of 6-*O*-alkyl, *S*-alkyl and *S*-aryl derivatives were prepared and studied. $C_{1\text{-}3}$ alkylthio compounds were less active than the alkoxy analogues. Bulkier phenyl containing substituents either at the oxime oxygen (**176g**,**l**) or adjacent to the oxime group (**176e**) were not favourable, however, *O*-methyl oxime derivatives (**176f**,**k**) showed good activity, unlike the effect observed in the benzodioxole series.

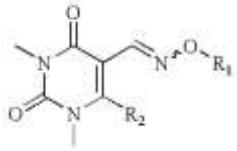
Table 7. VAP-1 inhibitory activity of benzodioxole oximes.

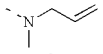
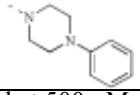


Compd	R	R_1	R_2	VAP-1 inhibition IC_{50}, μM
175a	H	OH	H	4.3
175b	H	Br	H	14.9
175c	H	OCH_2CH_3	H	40
175d	H		H	95
175e	H	Br	CH_3	27%[a]
175f	H	Br		9%[a]
175g	CH_3	Br	H	35%[a]

[a] % inhibition measured at 500 μM concentration

Table 8. VAP-1 inhibitory activity of uracile oximes.



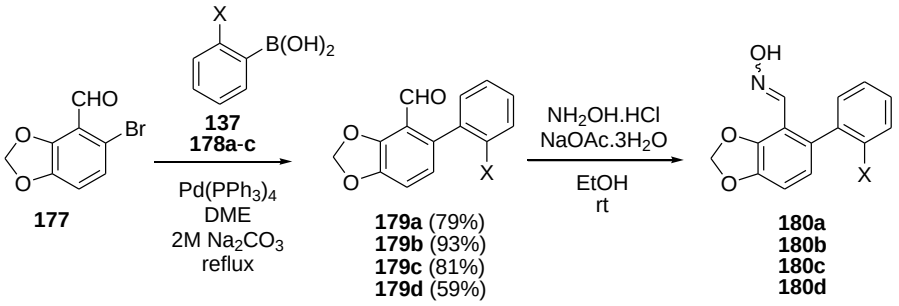
Compd	R_1	R_2	VAP-1 inhibition IC_{50}, μM
176a	H	Cl	2.8
176b	H	SCH_3	48
176c	H	SCH_2CH_3	111
176d	H	$SCH_2CH_2CH_3$	58
176e	H		106
176f	CH_3	SCH_2CH_3	113
176g		SCH_2CH_3	40%[a]
176h	H	OCH_3	30
176i	H	OCH_2CH_3	53
176j	H	$OCH_2CH_2CH_3$	18
176k	CH_3	OCH_2CH_3	29
176l		OCH_2CH_3	22%[a]
176m	H		41
176n	H		339

[a] % inhibition measured at 500 μM concentration

Studying the *in vivo* anti-inflammatory and analgesic effects of the representatives of the most active *in vitro* inhibitors (**175b**,**176b**,**176i**) in carrageenan-induced rat paw

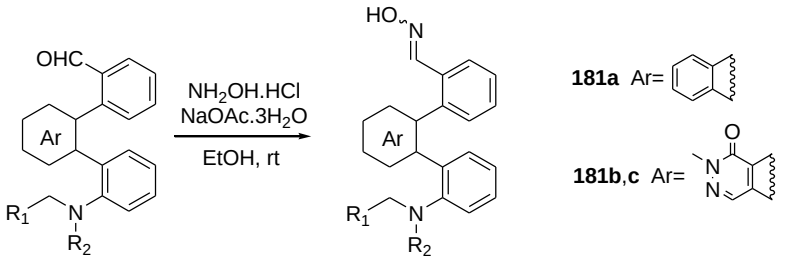
oedema and acetic acid induced writhing in mice, compounds **175b**, **176b** and **176i** showed remarkable activities.[119]

As part of the ongoing studies on novel oxime VAP-1 inhibitors, further benzodioxole derivatives were prepared. For the synthesis of **180a-d** oxime derivatives, the precursor biphenyl aldehydes (**179a-d**) were prepared with Suzuki coupling starting from 5-bromo-1,3-benzodioxole-4-carbaldehyde (**177**), with 2-formyl- (**137**) or 2-halo(fluoro/chloro/bromo)phenylboronic acids (**178a-c**). The couplings afforded the biaryl products (**179a-d**) with good yields. The synthesis of the oxime products was carried out with hydroxylamine hydrochloride in ethanol, in the presence of sodium acetate at room temperature (Scheme 56.). Bulkier *ortho*-aryl substitution led to a drop in activity, of **180a-d** only the bis-oxime derivative **180a** retained some VAP-1 inhibitor activity (IC_{50}=180 μM).



137,**179a** X=CHO; **178a**, **179b**, **180b** X=F; **178b**, **179c**, **180c** X=Cl;
178c, **179d**, **180d** X=Br; **180a** X=-CH=N-OH

Scheme 56. Synthesis of **180a-d** oximes.



139a,**142a**,**142c**

181a R_1=H, R_2=CH_3 (78%)
181b R_1=H, R_2=CH_3 (68%)
181c R_1+R_2=$(CH_2)_3$ (48%)

Scheme 57. Synthesis of **181a-c** oxime derivatives.

Exploiting some of the aldehyde intermediates used throughout *tert*-amino effect related experiments, **181a-c** triaryl oximes were prepared. *Ortho*-aryl substitution led to a loss of activity already in the analogue biaryl oximes however.

In conclusion, arylalkyloximes could act as effective inhibitors of human VAP-1. The most potent compounds exhibit a micromolar *in vitro* enzyme inhibition and show considerable anti-inflammatory effect *in vivo*. Screening of various derivatives in the course of our studies demonstrated, that despite the relative simplicity of the structures, the activity significantly depends on the core structure and its substitution pattern.

Recently interesting novel activities of VAP-1 inhibitors have been reported, such as inhibition of neoangiogenesis.[124,125,126] Based on these novel findings, cancer metastasis or age-related macular degeneration – as reference examples of diseases benefiting from inhibition of angiogenesis might be among the future therapeutic fields to be targeted by VAP-1 inhibitors.

5 Conclusions

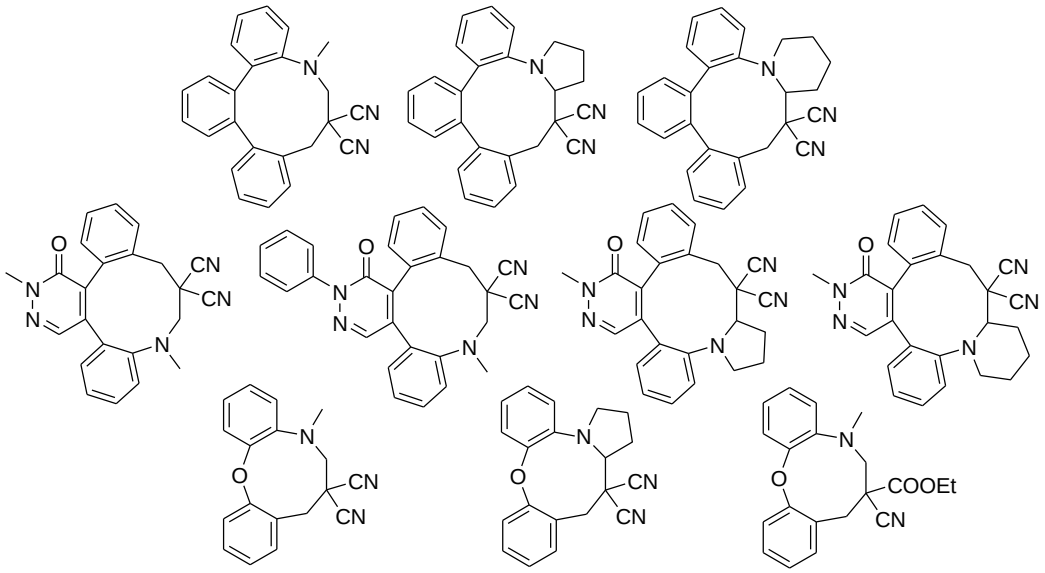
Based on the results discussed above, it can be concluded, that:

i) *tert*-amino effect type 2 cyclizations can operate among triaryl derivatives, having the interacting groups positioned on two different aromatic rings linked *via* a third aryl ring, or among non-conjugated biaryl derivatives, having an oxygen linker between the aromatic rings

ii) the result of the reaction highly depends on the amine and vinyl substituents, however, with proper choice of the substrate fused ring systems with medium-sized nitrogen heterocycles can be obtained

iii) ring closure of biaryl-ethers demonstrate, that *tert*-amino effect cyclizations might occur also *via* a direct hydride donation, therefore might be of broader significance

iv) novel extensions of the *tert*-amino effect might offer straightforward synthetic pathways to fused azecine and oxazonine ring systems (Scheme 58.).



Scheme 58. Azecine- and oxazonine-annelated products.

Applying aldehyde intermediates used for *tert*-amino effect related studies and further benzaldehydes, oxime derivatives were prepared and assayed *in vitro* on human recombinant VAP-1.

6 Summary

The term '*tert*-amino effect' was first used by Meth-Cohn and Suschitzky in 1972, to describe unusual cyclizations of *ortho*-substituted *tert*-anilines, due to an increased reactivity. In a special subtype of *tert*-amino effect type 2 reactions a new C-C bond is formed between the α carbon of the *tert*-aniline group and the β atom of an *ortho*-vinyl substituent, resulting in the formation of a tetrahydropyridine ring. Type 2 cyclizations have been widely used for the synthesis of various fused ring systems, but only rarely for the synthesis of medium-sized rings or macrocycles.

In the course of my PhD work, I took part in *tert*-amino effect related studies. We studied potential extensions of the *tert*-amino effect to bi- and triaryl systems and *via* type 2 cyclizations novel oxazonine- and azecine-fused ring systems were synthesized. In the applied 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 2-fluorobenzaldehyde or *via* two subsequent Suzuki-couplings from dihalo starting compounds with *ortho*-*sec*-amino- and 2-formylphenyl boronic acids. The structures of several intermediates were determined by X-ray diffraction. Cyclization of non-conjugated biaryl ethers demonstrate, that *tert*-amino effect could operate also via direct hydride transfer, therefore, this type of reaction might be of a broader significance.

As a part of the ongoing vascular-adhesion protein-1 (VAP-1) research program in the Department of Organic Chemistry, starting from some of the intermediates used for *tert*-amino effect related studies and further biaryl aldehydes, potentially VAP-1 inhibitor derivatives were prepared.

7 Magyar nyelvű összefoglaló (Summary in Hungarian)

A *terc*-amino effektus elnevezést Meth-Cohn és Suschitzky használta először 1972-ben, *orto*-szubsztituált *terc*-anilinek termikus izomerizációval lejátszódó gyűrűzáródási reakciójára. A *terc*-amino effektus 2. típusa szerinti reakciók egy külön csoportja esetén a tercier anilin csoport α szénatomja és egy *orto* vinilszubsztituens β atomja között létesül kötés, tetrahidropiridin gyűrű képződését eredményezve. A *terc*-amino effektus 2. típusával végbemenő gyűrűzárásokat széles körben alkalmazták kondenzált gyűrűrendszerek előállítására, alig található azonban példa a *terc*-amino effektus felhasználására nagyobb tagszámú gyűrűk szintézisében.

Doktori munkám során a *terc*-amino effektus vizsgálatával kapcsolatos kutatómunkába kapcsolódtam be. Vizsgáltuk a *terc*-amino effektus kiterjeszthetőségét di- és triaril modellvegyületekre, a *terc*-amino effektus 2. típusa szerinti gyűrűzárás révén új oxazonin- és azecin-anellált gyűrűrendszereket állítottunk elő. A felhasznált modellvegyületekben az egymással kölcsönhatásba lépő vinil- és *terc*-amino csoport *orto-orto'/orto"* helyzetű volt két - egy harmadik benzol vagy piridazinon gyűrűn vagy oxigénhídon keresztül kapcsolódó - aromás gyűrűn. A vinilvegyületeket a megfelelő aldehidekből képeztük, amelyeket *terc*-aminofenol és 2-fluorbenzaldehid reakciójával vagy két, egymást követő Suzuki kapcsolással állítottunk elő dihalo kiindulási vegyületekből *orto* helyzetben *szek*-amino csoportot tartalmazó illetve 2-formilfenilboronsavval. Több intermedier szerkezetét röntgendiffrakciós mérésekkel is igazoltuk. A nem-konjugált diaril-éterek gyűrűzárása alátámasztja, hogy a *terc*-amino effektus direkt hidridanion átadás révén is megvalósulhat, ezáltal általánosabb jelentőségű lehet ez a típusú reakció.

Doktori munkám részben kapcsolódik a Szerves Vegytani Intézetben folyó vaszkuláris adhéziós protein-1-en (VAP-1) ható szerek kutatásához. A *terc*-amino effektus vizsgálatához használt intermedierekből, illetve további diaril aldehidekből potenciálisan VAP-1 gátló származékokat állítottunk elő.

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9 Appendix

9.1. 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 F^2 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.

Main experimental conditions of crystal structure determination are summarized in Table 1A,2A.

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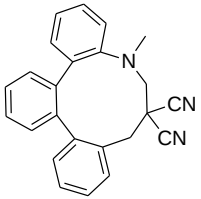
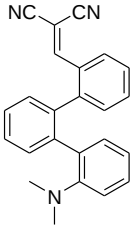
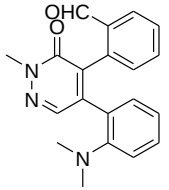
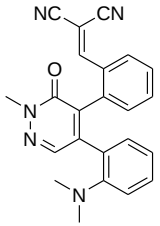
				
Compound number	**155a**	**152a**	**142a**	**153a**
Moiety formula	$C_{24}H_{19}N_3$	$C_{24}H_{19}N_3$	$C_{20}H_{19}N_3O_2$	$C_{23}H_{19}N_5O$
Formula weight	349.42	349.42	333.38	381.43
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	C 2/c (No. 15)	P21/n (No. 14)	P-1 (No. 2)	C 2/c (No. 15)
Lattice parameters				
a (Å)	16.8195(10)	15.014(7)	9,337(2)	17.1244(1)
b (Å)	7.1776(10)	15.101(10)	10,094(2)	10.2027(10)
c (Å)	32.427(3)	17.890(6)	11,079(2)	23.3586(10)
α (°)	90	90	66,12(1)	90
β (°)	98.13(2)	107.77(1)	70,75(1)	96.14(1)
γ (°)	90	90	71,92(1)	90
V (Å^3)	3875.4(7)	3840(3)	882,4(3)	4057.7(5)
Z	8	8	2	8
Dimensions of crystal (mm)	0.3 / 0.25 / 0.2	0.35 / 0.25 / 0.2	0.2 / 0.15 / 0.1	0.3 / 0.26 / 0.2
Crystal color and habit	Colorless prism	Orange red block	Colourless prism	Yellow prism
D_{calc} (g cm^{-3})	1.198	1.209	1.255	1.249
μ(Mo-Kα) / mm^{-1}	0.07	0.07	0.08	0.08
Θ_{max} (°)	25.5	25.5	25.3	25.3
Decay (%)	2	2	3	1
No. observed reflections [I>2.00σ(I)]	1993	6007	1269	1325
No. independent reflections	3719	7390	3538	4106
No. variables	245	491	229	265
Residuals: $R_1(F)$ / $wR_2(F^2)$	0.060 / 0.159	0.080 / 0.208	0.062 / 0.147	0.069 / 0.204
Goodness of fit	0.95	1.25	0.97	0.94
Max./Min. peak in final difference map / e Å^{-3}	0.15 / -0.17	0.23 / -0.27	0.19 / -0.16	0.28 / -0.31

Table 1A.

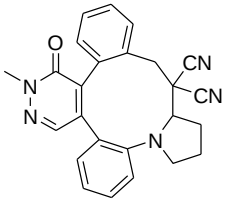
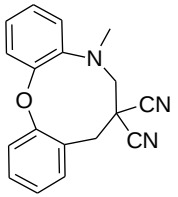
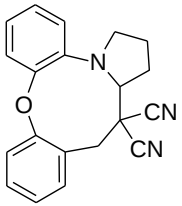
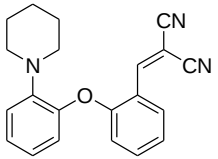
				
Compound number	**156c**	**168a**	**168b**	**167c**
Moiety formula	$C_{25}H_{21}N_5O$	$C_{18}H_{15}N_3O$	$C_{20}H_{17}N_3O$	$C_{21}H_{19}N_3O$
Formula weight	407.47	289.33	315.37	329.40
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	P21/c (No. 14)	P212121 (No. 19)	I2/a (No. 15)	C 2/c (No. 15)
Lattice parameters				
a (Å)	14.3323(10)	8.745(1)	18.753(5)	27.317(5)
b (Å)	21.9155(10)	9.836(1)	9.183(5)	8.519(5)
c (Å)	15.2114(10)	17.535(1)	41.064(5)	19.641(5)
α (°)	90	90	90	90
β (°)	116.86(1)	90	98.37(5)	127.83(5)
γ (°)	90	90	90	90
V (Å^3)	4262.5(5)	1508.3(2)	6996(4)	3610(2)
Z	8	4	8	4
Dimensions of crystal (mm)	0.35 / 0.3 / 0.26	0.66 / 0.3 / 0.25	0.35 / 0.23 / 0.14	0.35 / 0.25 / 0.2
Crystal color and habit	Colourless prism	Colourless prism	Colourless prism	Colourless prism
D_{calc} (g cm^{-3})	1.27	1.276	1.232	1.212
μ(Mo-Kα) / mm^{-1}	0.08	0.08	0.08	0.08
Θ_{max} (°)	25.1	26.0	25.5	25.5
Decay (%)	0	6	3	1.06
No. observed reflections [I>2.00σ(I)]	4448	1401	3092	1955
No. independent reflections	7861	1710	6416	3725
No. variables	561	200	459	226
Residuals: $R_1(F)$ / $wR_2(F^2)$	0.063 / 0.168	0.056 / 0.140	0.143 / 0.404	0.073 / 0.191
Goodness of fit	1.01	1.10	1.04	1.06
Max./Min. peak in final difference map / e Å^{-3}	0.19 / -0.20	0.20 / -0.21	0.95 / -0.39	0.27 / -0.35

Table 2A.

9.2. Exemplary NMR spectra of aldehyde, vinyl intermediates and cyclized products

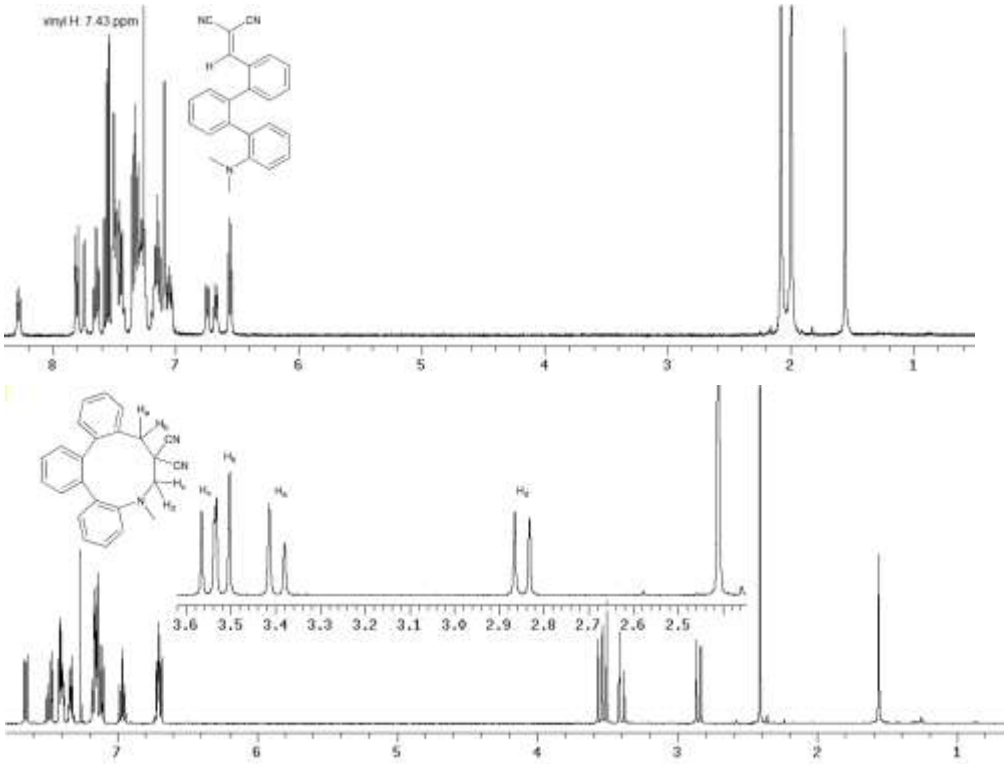


Figure 1A. Monitoring of ring closure by ^{1}H-NMR.

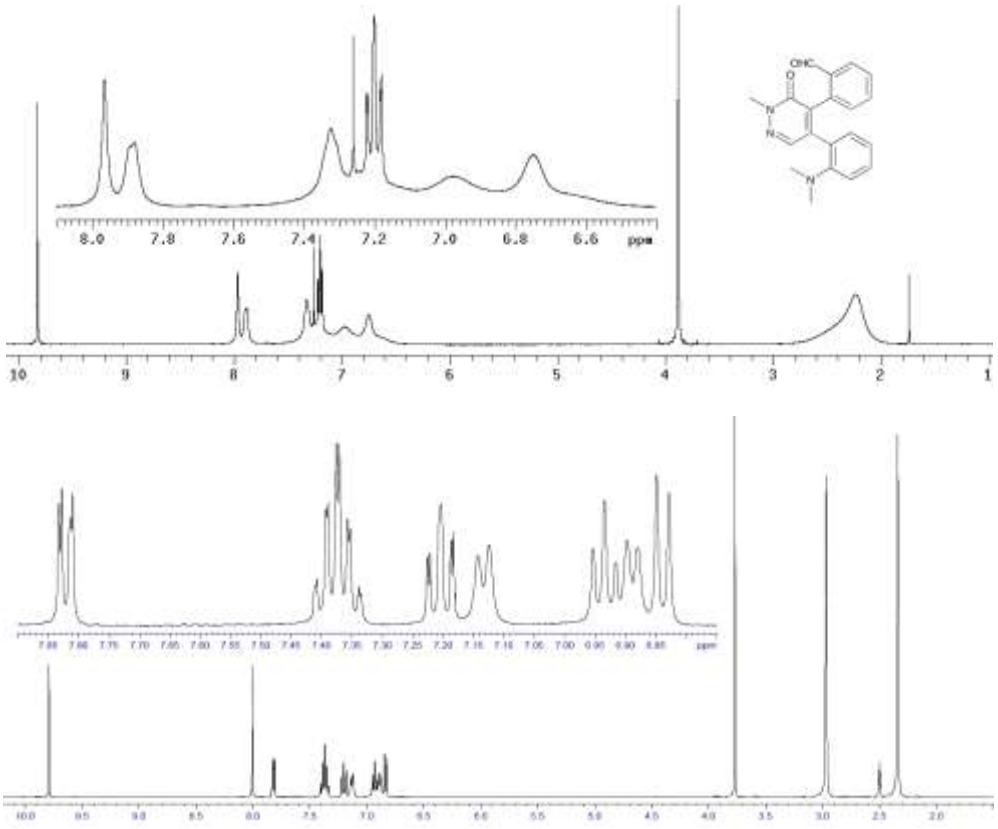


Figure 2A. Signal broadening observed at ambient temperature

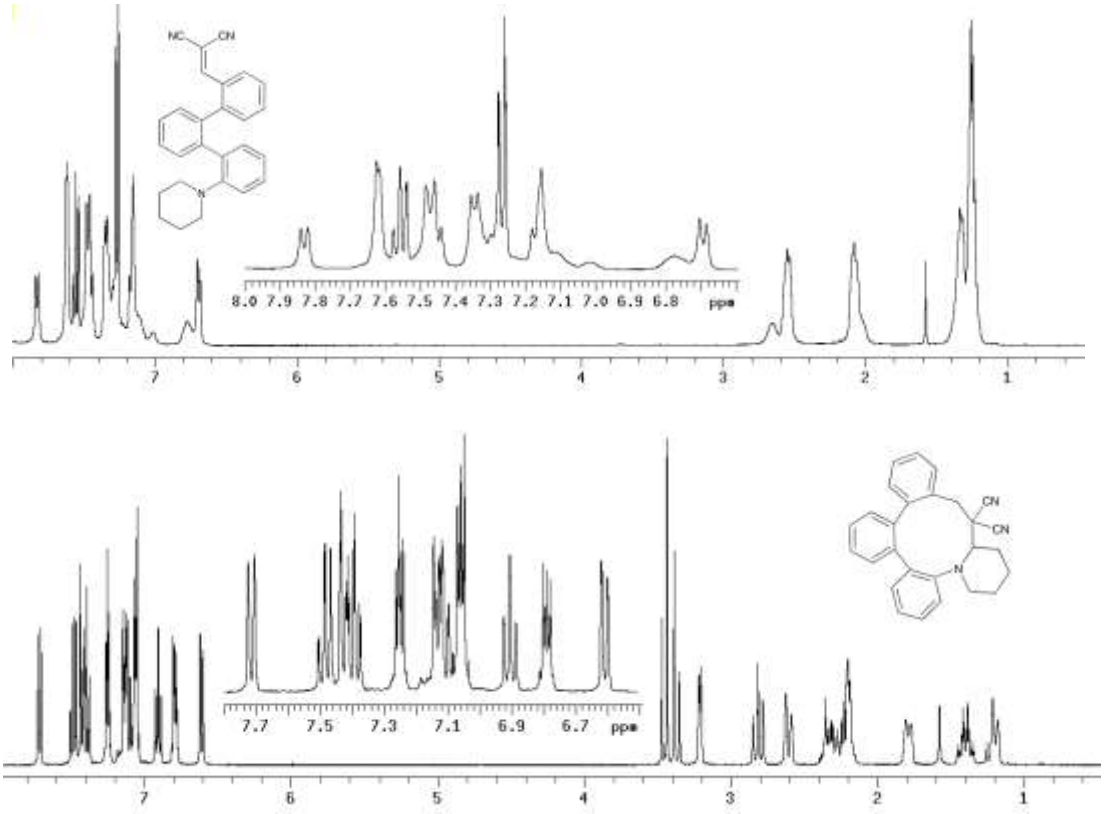


Figure 3A. Disappearance of signal broadening due to ring closure.

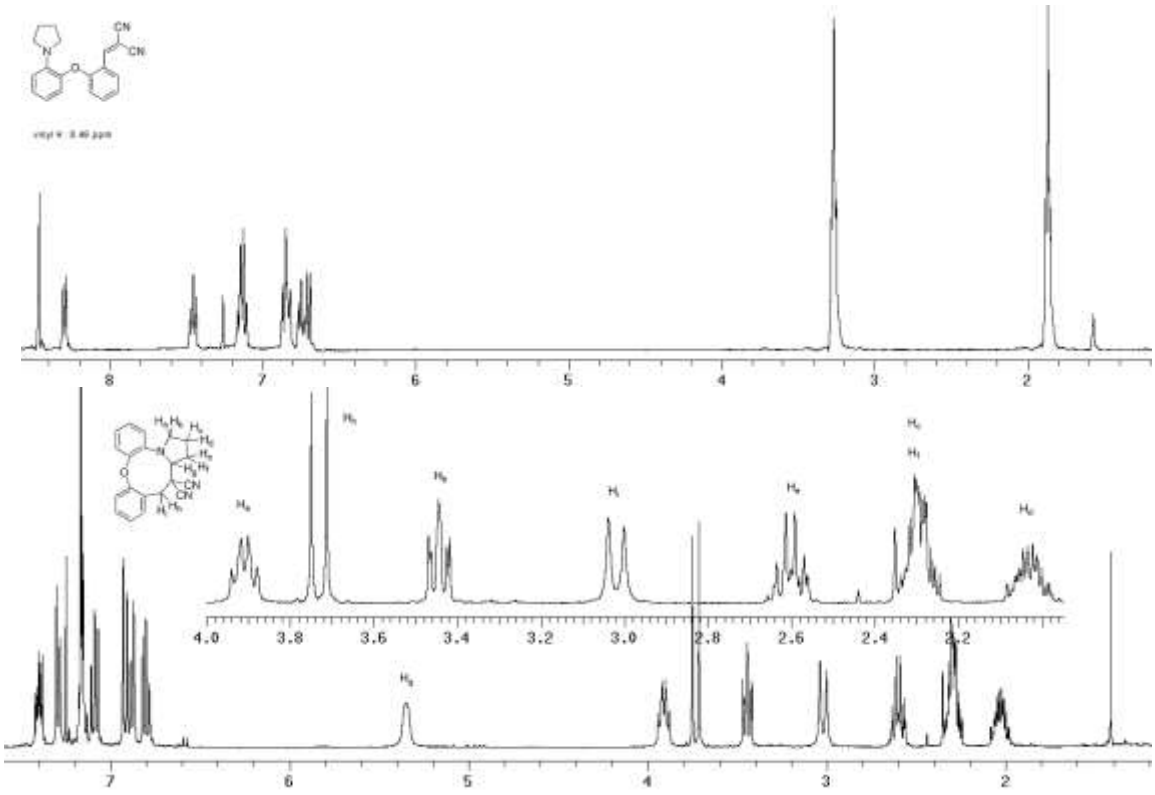
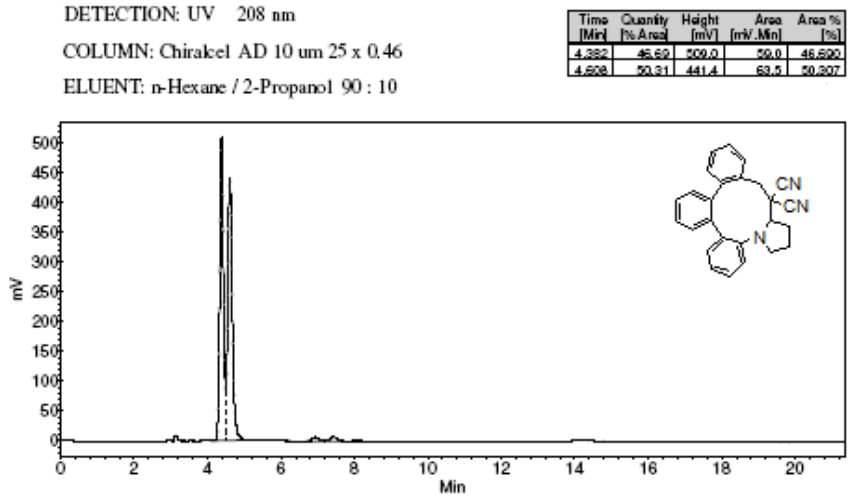


Figure 4A. Monitoring of ring closure by ^{1}H NMR.

9.3. HPLC spectra of the cyclized products



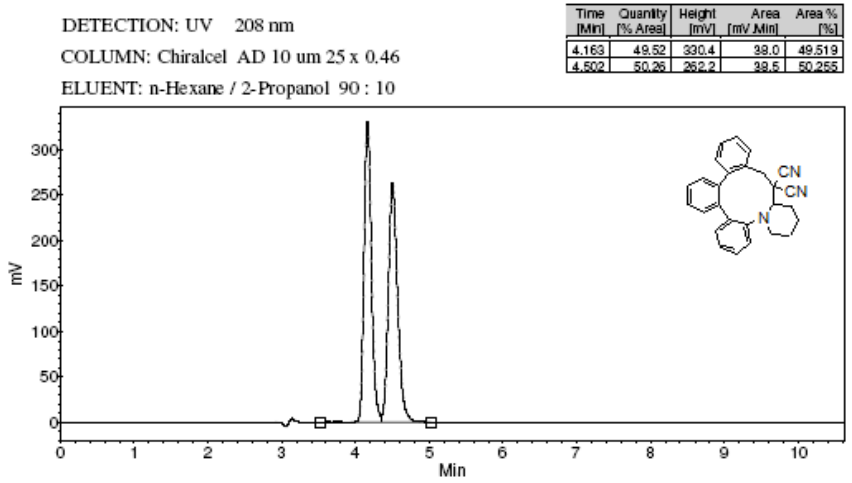
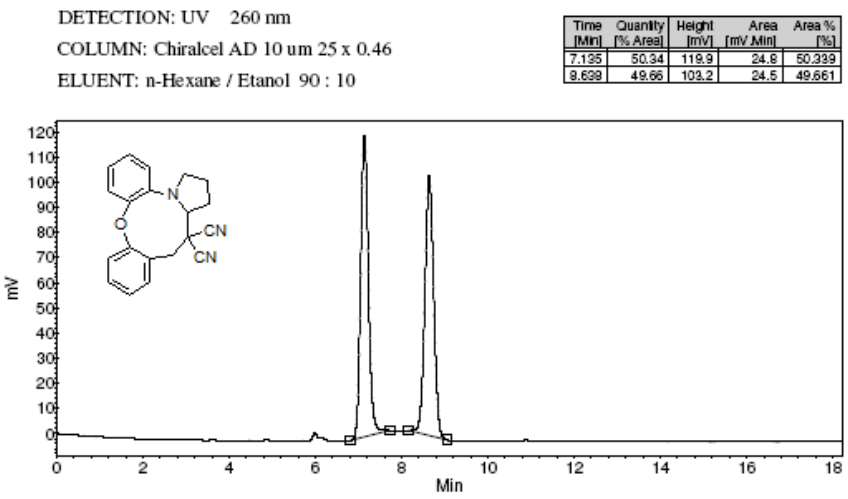


Figure 5A.



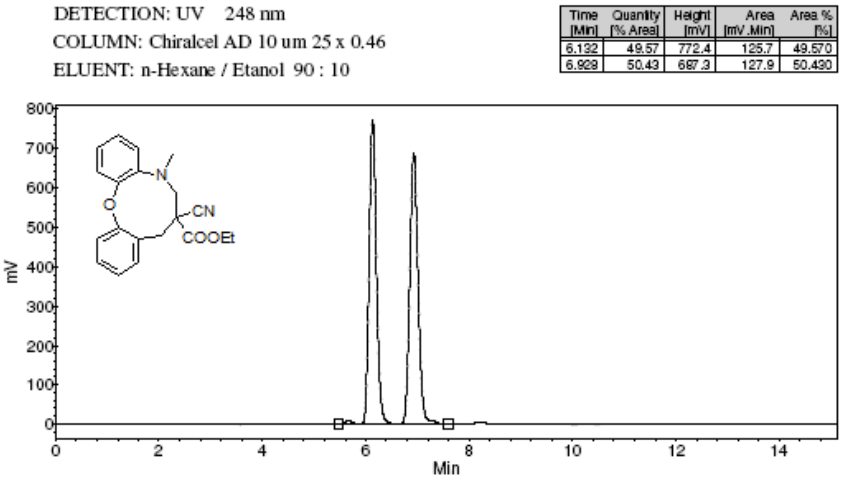


Figure 6A.

10 Publications

10.1 Publications of the author related to the present work

Papers

1. **Dunkel P**, Túrós G, Bényei A, Ludányi K, Mátyus P: Synthesis of novel fused azecine ring systems through application of the *tert*-amino effect. *Tetrahedron* 2010;66:2331-2339. **(IF 3.219 (2009))**
2. **Dunkel P**, Gelain A, Barlocco D, Haider N, Gyires K, Sperlágh B, Magyar K, Maccioni E, Fadda A, Mátyus P: Semicarbazide-sensitive amine oxidase/vascular adhesion protein 1: Recent developments concerning substrates and inhibitors of a promising therapeutic target. *Curr Med Chem* 2008;15:1827-1839. **(IF 4.823)**

Presentations

1. Mátyus P, **Dunkel P**, Tóth-Sarudy É, Túrós G, Pihlavisto M, Magyar K, Soltész Z, Carpene C: Semicarbazide-sensitive amine oxidase (SSAO): A potential target for the treatment of diabetes and its complications. 237th American Chemical Society National Meeting & Exposition, Salt Lake City, 2009.
2. **Dunkel P**, Mátyus P: New semicarbazide sensitive amine-oxidase (SSAO) inhibitors. 6th Meeting of the European Network of Doctoral Studies in Pharmaceutical Science, Palermo, 2009.
3. Polonka-Bálint Á, **Dunkel P**: Új típusú azocin és azecin gyűrűrendszerek előállítása új úton: a *terc*-amino effektus kiterjesztése. Clauder Ottó Emlékverseny, Budapest, 2007.

Posters

1. **Dunkel P**, Túrós G, Bényei A, Ludányi K, Mátyus P: Synthesis of novel tribenzo-fused azecine and a pyridazino analog ring systems via *tert*-amino effect. Advances in Synthetic Chemistry, Edinbourgh, 2009.
2. Deme R, **Dunkel P**, Bálint Á, Mátyus P: Azocin és azecin gyűrűrendszerek előállítása a *terc*-amino effektus alkalmazásával. Congressus Pharmaceuticus Hungaricus XIV., Budapest, 2009.

3. Földi ÁA, **Dunkel P**, Ludányi K, Mátyus P: *terc*-Amino effektus kiterjesztése: makrociklusos és *orto*- és *peri*-kondenzált gyűrűrendszerek szintézise. Centenáriumi Vegyészkonferencia 2007, Sopron, 2007.
4. **Dunkel P**, Földi ÁA, Ludányi K, Mátyus P: Synthesis of macrocyclic and *ortho*- and *peri*-fused ring systems: extension of the *tert*-amino effect. European School of Medicinal Chemistry, Urbino, 2007.

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

Papers

1. Énzsöly A, **Dunkel P**, Récsán Z, Győrffy H, Tóth J, Marics G, Bori Z, Tóth M, Zelkó R, Di Paolo ML, Mátyus P, Németh J. Preliminary studies of the effects of vascular adhesion protein-1 inhibitors on experimental corneal neovascularization. *J Neural Transm* 2011; DOI 10.1007/s00702-011-0595-8. (**IF 2.259 (2009**))
2. Mercader J, Iffiú-Soltész Z, Brenachot X, Földi Á, **Dunkel P**, Balogh B, Attané C, Valet P, Mátyus P, Carpéné C: SSAO substrates exhibiting insulin-like effects in adipocytes as a promising treatment option for metabolic disorders. *Fut Med Chem* 2010;2:1735-1749. **(IF: -)**
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