

# **Solid-phase synthesis of aminopyrimidine and aminoquinazoline libraries**

*Theses of Ph.D. dissertation*

**Csaba Wéber**

Gedeon Richter Ltd  
Chemical and Biological Research and Development  
Budapest

University of Szeged  
Department of Organic Chemistry  
Szeged

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## **1. Introduction, objective and scope of the work**

In the 1990s besides the traditional way of synthesizing potentially biologically active compounds a new concept emerged in medicinal chemistry. The name of this new approach is combinatorial chemistry. The aim of using this new technique is to speed up the time consuming drug development process by reducing the time from target identification to finding a drug candidate. The essence of this new strategy is the concurrent synthesis of a large number of compounds instead of targeting one molecule at a time. Combinatorial chemistry can be a powerful tool in hit searching and in lead optimization as well. The efficiency of this new approach is due to the automation of the synthetic sequences. The solid-phase technique is more suitable for automation than solution-phase chemistry.

From the late 1990s the new combinatorial strategy gradually became a basic component of the original drug development process pursued in Gedeon Richter Ltd. These theses summarize one part of the work that has been done in order to integrate this new technology into the original drug development process of our firm.

Aminopyrimidines and aminoquinazolines have a wide range of biological activities. They can be found in many drugs such as Prazosin, Doxazosin, Alfuzosin, Trimetrexate, Tirilazad, Trimethoprim and Pyrimethamine. The derivatives of both types of compounds can be synthesized by aromatic nucleophilic substitution reactions of amines with chloropyrimidines and chloroquinazolines. Based on the literature this method seems to be the most suitable for the synthesis of aminopyrimidine and aminoquinazoline libraries as well.

The first objective of this project was to develop new synthetic pathways for the automated solid-phase synthesis of aminopyrimidine and aminoquinazoline libraries with a high structural diversity using a scaffold-based approach. The detailed study of the observations bearing chemical novelty was only our second aim.

## **2. Applied methods**

The determination of the effectiveness of the coupling to the solid support was based on measuring the nitrogen content of the resin. The conversion of the reactions conducted on solid-phase was determined based on measuring the nitrogen content of the resin and/or the HPLC-MS and  $^1\text{H}$  NMR analysis of the product(s) cleaved from the resin. The purities of the products were determined by HPLC-MS and/or  $^1\text{H}$  NMR spectroscopy.

For the structure determination of some products EI-MS, FAB-MS,  $^{13}\text{C}$  NMR,  $^1\text{H}$ - $^{13}\text{C}$  HSQC,  $^1\text{H}$ - $^{13}\text{C}$  HMBC, 1D NOE measurements and elemental analyses were used as well.

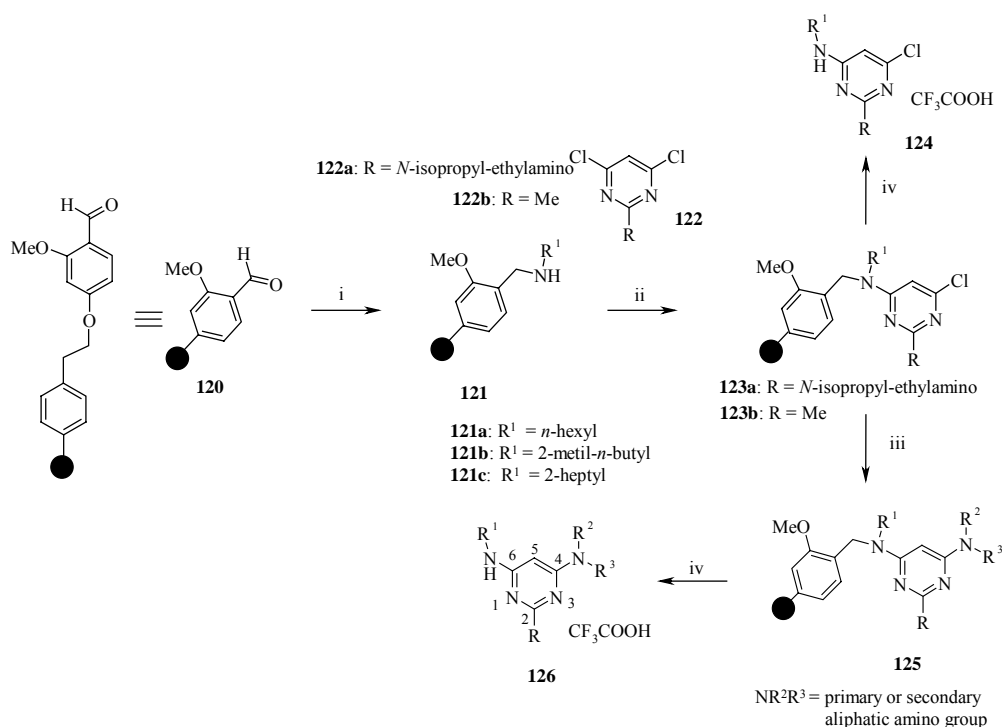
### 3. Summary of new scientific results\*

#### 3.1 A new procedure for the solid-phase synthesis of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines has been developed.

3.1.1 It has been shown that the 4-phenylethoxy-2-methoxybenzyl linker (**120**) can successfully be used for the solid-phase synthesis of 2-alkyl-4,6-diaminopyrimidines and 2,4,6-triaminopyrimidines (Scheme 1).

3.1.2 It has been proved that one of the chlorine atoms of 2-methyl- and 2-(*N*-isopropyl-ethylamino)-4,6-dichloropyrimidine derivatives (**122**) can selectively be replaced by secondary amines coupled to the solid support through an *o*-methoxybenzyl type linker.

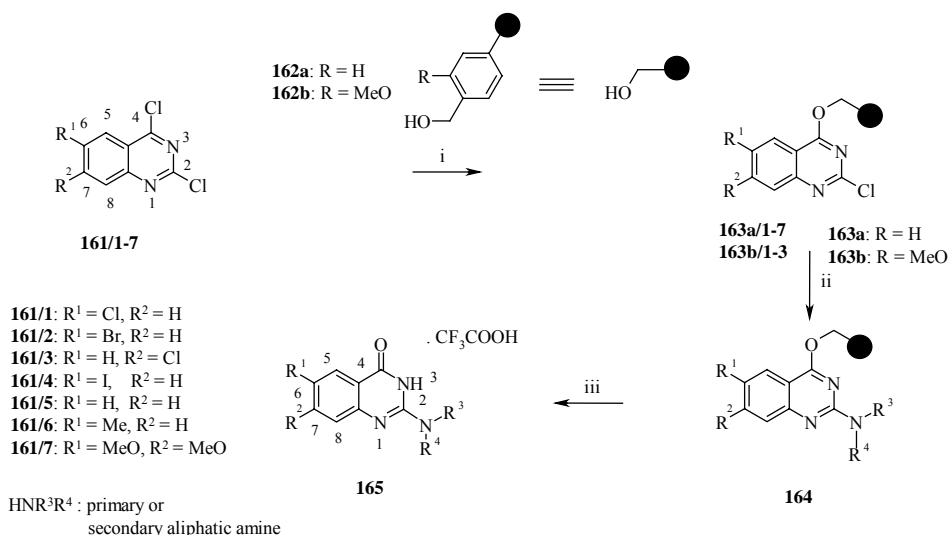
3.1.3 Optimal reaction conditions for the reaction of solid-phase coupled 6-amino-4-chloropyrimidine derivatives (**123a**, **123b**) and 4-6 membered cyclic secondary amines not branched at the  $\alpha$ -position has been determined (20-40 fold excess of amine, *N,N*-dimethylformamide (DMAC), 100 °C, 100 h).



Scheme 1. Solid-phase synthesis of aminopyrimidines: i, R<sup>1</sup>NH<sub>2</sub>, NaBH(OAc)<sub>3</sub>, DMF, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C; ii, DMF, *N*(*i*Pr)<sub>2</sub>Et, 25 °C; iii, HNR<sup>2</sup>R<sup>3</sup>, solvent or LiNR<sup>2</sup>R<sup>3</sup>, THF; iv, CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C.

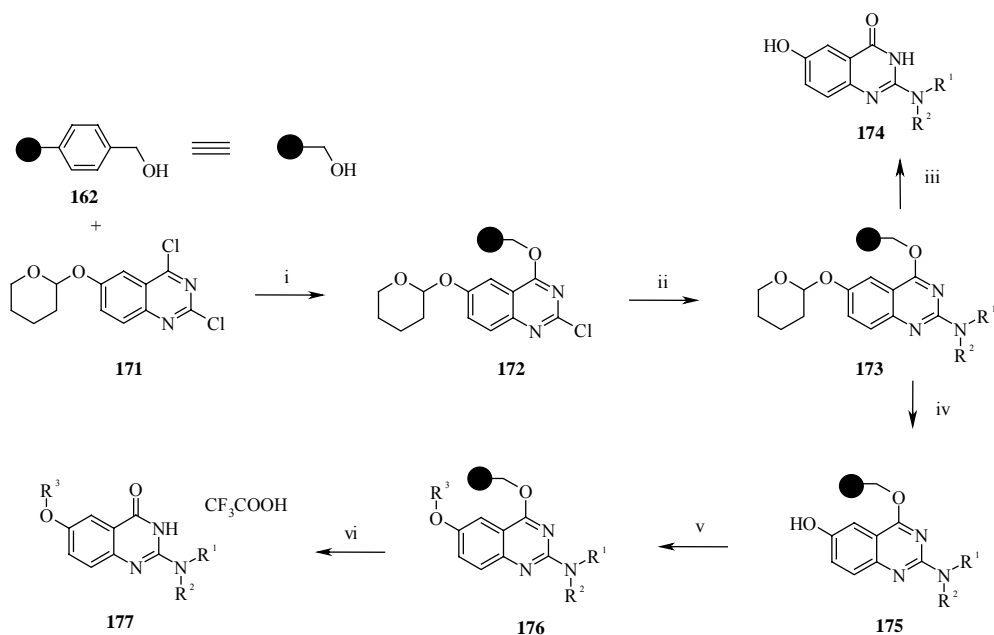
\* The numbering of the compounds is the same as used in the dissertation.

- 3.1.4 It has been shown that the conversions of the reaction of **123a** with acyclic primary and secondary amines not branched at the  $\alpha$ -position (*n*-hexylamine, bis(*n*-butyl)amine) under the above mentioned (3.1.3.) conditions, either in DMAC or in *n*-butanol (*n*-BuOH) were lower than 20 % even in the case of using longer reaction time (140 h). In contrast, reactions performed using the Li salt of these amines afforded the expected triaminopyrimidines in high (> 80%) purity.
- 3.1.5 It was observed that 6-amino-4-chloro-2-methylpyrimidines (**123b**) are more reactive towards primary and secondary aliphatic amines than the 2-(*N*-isopropyl-ethylamino) derivatives (**123a**). As opposed to **123a** treatment of **123b** with alicyclic primary or secondary amines not branched at the  $\alpha$ -position (*n*-hexylamine, bis(*n*-butyl)amine) in *n*-BuOH gave the triaminopyrimidines in high yield and purity.
- 3.2 New procedure for the solid-phase synthesis of 6(7)-substituted 2-amino-4(3*H*)-quinazolones has been developed (Schemes 2-4).**
- 3.2.1 It has been proved that in 6(7)-substituted 2,4-dichloroquinazoline derivatives (**161/1-7**) the chlorine at the 4-position can be selectively replaced by the Li salt of solid-phase coupled *o*-methoxybenzyl alcohol and benzyl alcohol (Schemes 2 and 3).
- 3.2.2 It has been shown that treatment of solid-phase coupled 2-chloroquinazolines having electron withdrawing group(s) at the 6-position (**161/1-2**) with aliphatic primary or secondary amines not branched at the  $\alpha$  position gave pure product under the applied conditions (5-fold excess of amine, 20h, 90-100 °C, solvent: *N,N*-dimethylformamide (DMF), DMAC or *n*-BuOH).
- 3.2.3 It was observed that the reaction of 2-chloroquinazoline having electron donating groups (MeO) at the 6- and 7-position (**161/7**) with 5 and 6 membered secondary aliphatic amines not branched at the  $\alpha$ -position, under the above mentioned conditions (3.2.2) afforded pure products. In the case of acyclic primary and secondary amines not branched at the  $\alpha$ -position prolonged reaction time (140 h), more excess of amine (20-fold) and the use of *n*-BuOH or MeNO<sub>2</sub> as a solvent is needed to obtain pure products.
- 3.2.4 It was observed that the reaction of less active 2-chloroquinazoline derivatives (**163/5-7**) with acyclic primary and secondary amines in DMAC and DMF affords the formation of 2-(dimethylamino)quinazoline (**164, 165** NR<sup>3</sup>R<sup>4</sup> = NMe<sub>2</sub>) side product.

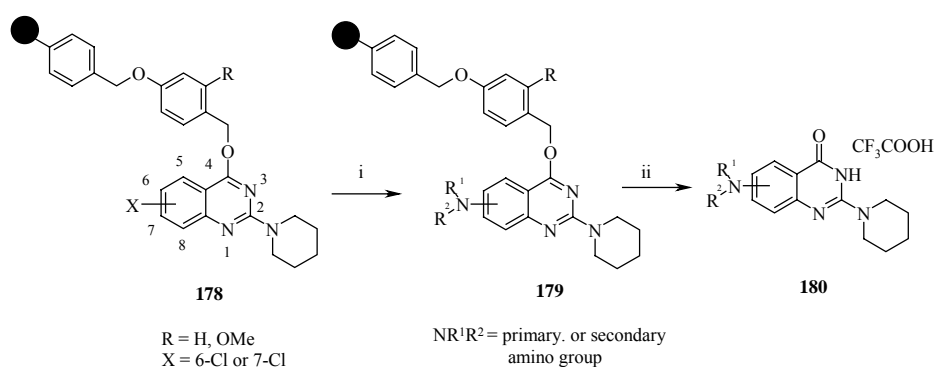


Scheme 2. Solid-phase synthesis of 6(7)-substituted 2-amino-4(3H)-quinazolones (**165**): i, *n*-BuLi, THF, -20 – 25 °C; ii, HNR<sup>3</sup>R<sup>4</sup>, DMF, 80-120 °C; iii, CF<sub>3</sub>COOH, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C.

- 3.2.5 It has been shown that 2,4-dichloro-6-(tetrahydropyran-2-yloxy)quinazoline (**171**) - similarly to **161/1-7** derivatives – can be coupled to a solid support via a benzyl alcohol type linkers(Scheme 3).
- 3.2.6 It was observed that the tetrahydropyranyl protecting group can be removed selectively from resin bound 2-amino-6-(2-tetrahydropyran-2-yloxy)quinazoline derivative (**173**) in the presence of the benzyl ether bond.
- 3.2.7 It has been shown that under the applied Mitsunobu conditions the reaction of resin bound 2-(piperidin-1-yl)-6-hydroxyquinazoline (**175**) with primary and secondary alcohols afforded pure products.
- 3.2.8 It was demonstrated that palladium catalyzed amination of resin bound 2-(piperidin-1-yl)-6(7)-chloroquinazoline derivatives (**178**) with aliphatic and aromatic acyclic secondary amines, using P(*t*Bu)<sub>3</sub> as a ligand, gives pure products (purity > 80 %).
- 3.2.9 It was demonstrated that palladium catalyzed amination of resin bound 2-(piperidin-1-yl)-6(7)-chloroquinazoline derivatives (**178**) with aliphatic primary amines, using 2-di-*t*-butylphosphino]biphenyl as a ligand, affords pure products (purity > 80 %).
- 3.2.10 It was observed that using a 2-methoxybenzyl alcohol type linker instead of 4-benzyloxybenzyl alcohol linker the formation of a side product obtained from 4-benzyloxybenzyl alcohol can be avoided.



**Scheme 3.** Solid-phase synthesis of 2-amino-6-alkoxy-4(3H)-quinazolones (**177**): i, 2.2 equiv. *n*-BuLi, 3 equiv. benzyl alcohol linker, THF, 25 °C; ii, 5 equiv.  $\text{HNR}^1\text{R}^2$  (secondary amine), DMF, 20 h, 100 °C; iii  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_2\text{Cl}_2$ , 25 °C; iv, 1 equiv.  $\text{BF}_3\cdot\text{Et}_2\text{O}$ , PhSH, THF, 25 °C, 1h; v, 10 equiv.  $\text{PPh}_3$ , 10 equiv. diisopropyl azodicarboxylate 10 equiv.  $\text{R}^3\text{OH}$  (primary or secondary alcohol), 16 h; vi,  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_2\text{Cl}_2$ , 25 °C.

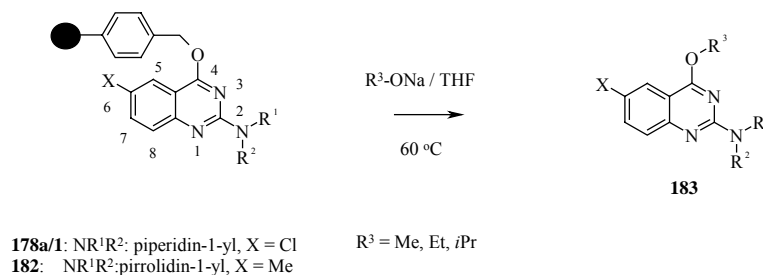


**Scheme 4.** Synthesis of 2,6(7)-Diamino-4(3H)-quinazolones (**180**) via Pd-catalyzed amination: i, 5 equiv.  $\text{HNR}^1\text{R}^2$ , 0.2 equiv. Pd-complex, 5 equiv.  $\text{NaOtBu}$ , *o*-xylene, 100 °C; ii,  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_2\text{Cl}_2$ .

3.2.11. It was demonstrated by the automated synthesis of two libraries containing a few hundred compound each that the developed methods are amenable for the automated solid-phase synthesis of 6(7)-substituted 2-amino-4(3H)-quinazolinone and 6-alkoxy-2-amino-4(3H)-quinazolinone derivatives (**165**, **177**).

### 3.3 A new procedure for the solid-phase synthesis of 2-amino-4-alkoxyquinazolines has been developed (Scheme 5).

- 3.3.1 It has been shown that 6(7)-substituted 2-aminoquinazoline derivatives coupled to solid support via benzyl alcohol linker (**178a/1**, **182**) can be cleaved from the resin with sodium salts of primary and secondary alcohols. The method gives 2-amino-4-alkoxyquinazoline derivatives (**183**) in a good yield and purity (Scheme 5).

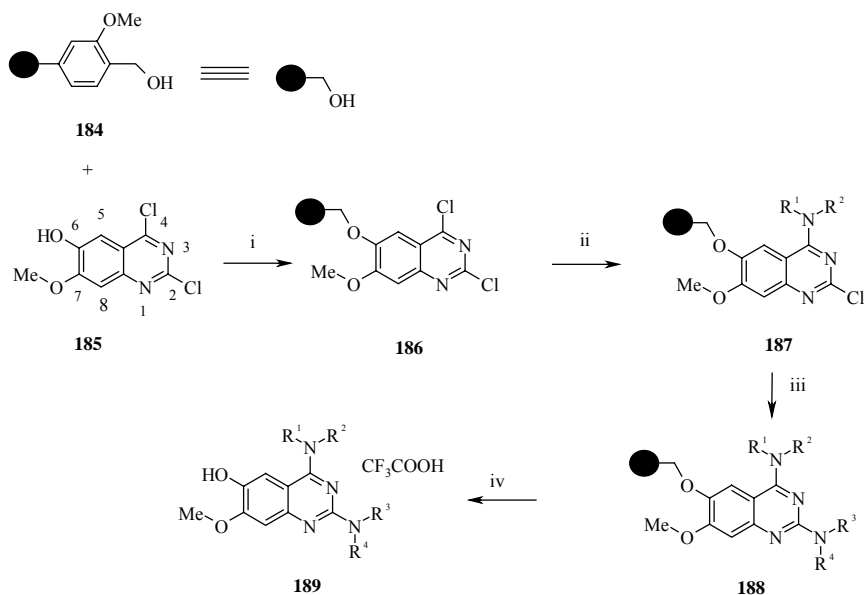


Scheme 5. Synthesis of 2-amino-4-alkoxyquinazolines by multifunctional cleavage.

### 3.4 A new method for the solid-phase synthesis of 2,4-diamino-6-hydroxy-7-methoxyquinazolines has been developed (Scheme 6).

- 3.4.1 It was demonstrated that 2,4-dichloro-6-hydroxy-7-methoxyquinazoline (**185**) can be coupled to solid support via an *o*-methoxybenzyl alcohol linker under Mitsunobu conditions.
- 3.4.2 It has been shown that the chlorine atoms of resin bound quinazoline (**186**) can be replaced selectively by aliphatic primary and secondary amines. The chlorine at the C-4 position can be substituted selectively at room temperature in THF by aliphatic primary amines having not more than one substituent at the  $\alpha$ -position and by aliphatic secondary amines not branched at the  $\alpha$ -position. The chlorine at the 2-position can be replaced in *n*-BuOH at 100 °C by aliphatic primary and secondary amines not branched at the  $\alpha$ -position .
- 3.4.3 It has been shown that the intended reaction of **187** with primary amines in DMF and DMAC resulted also in the formation of a significant amount of a side product (**189**, NR<sup>3</sup>R<sup>4</sup> = NMe<sub>2</sub>) avoidable by using *n*-BuOH as a solvent.
- 3.4.4 It has been demonstrated by the automated synthesis of a few hundred memberd 2,4-diamino-6-hydroxy-7-methoxyquinazoline library that the method is amenable for automation.

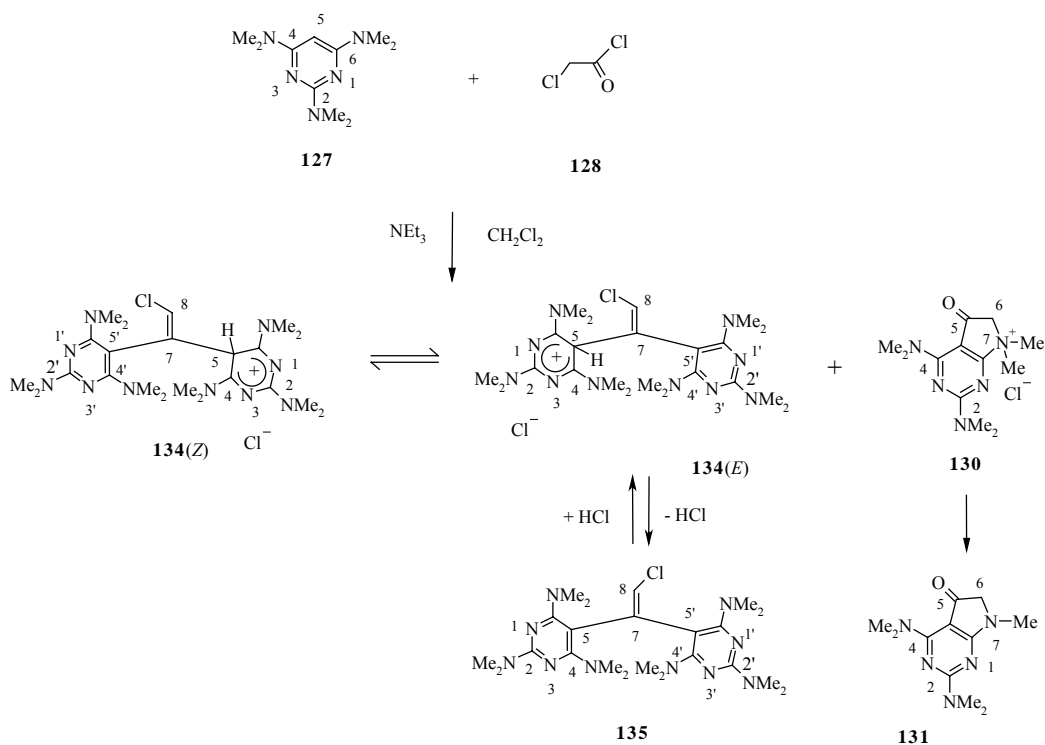




Scheme 6. Solid-phase synthesis of 2,4-diamino-6-hydroxy-7-methoxyquinazolines (**189**) i, diisopropyl azodicarboxylate,  $\text{PPh}_3$ , THF, 25 °C, 24 h; ii, 10 equiv.  $\text{HNR}^1\text{R}^2$ , THF, 25 °C; iii, 20 equiv.  $\text{HNR}^3\text{R}^4$ ,  $n\text{-BuOH}$  90 °C, 48 h; iv,  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_2\text{Cl}_2$ .

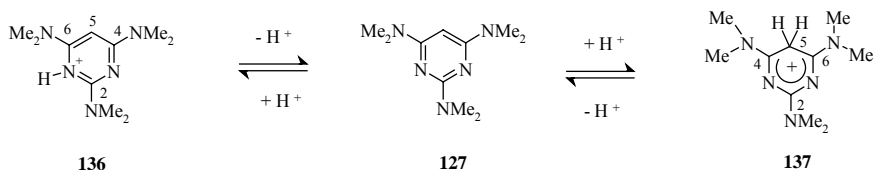
**3.5 The classical concept of the protonation of aminopyrimidines has been modified by our results. It has been proved that 2,4,6-triaminopyrimidines can be protonated at the C(5)-position forming  $\sigma$ -complexes. The first stable cationic  $\sigma$ -complexes of pyrimidines have been prepared.**

- 3.5.1 It has been proved that treatment of 2,4,6-tris(dimethylamino)pyrimidine with chloroacetyl chloride in dichloromethane in the presence of triethylamine resulted in the formation of 2,4,6-tris(dimethylamino)-5-[1-(2,4,6-tris(dimethylamino)pyrimidin-5-yl)-2-chlorovinyl]pyrimidinium chloride (**134**) and [7,7-dimethyl-2,4-bis(dimethylamino)-5-oxo-6,7-dihydro-5H-pirrol[2,3-d]pyrimidin-7-ium] chloride (**130**) (Scheme 7).
- 3.5.2 It has been proved by NMR inversion transfer measurements that **134**(E) and **134**(Z) interconvert in  $\text{DMSO}-d_6$  solution.
- 3.5.3 It has been proved that the deprotonation of **134** by strong bases ( $\text{NaH}$ ,  $\text{NaOEt}$ ) gives 2,4,6-tris(dimethylamino)-5-[1-(2,4,6-tris(dimethylamino)pyrimidin-5-yl)-2-chlorovinyl]pyrimidine (**135**) which protonates at the C(5)-position reforming **134**.
- 3.5.4 It was observed that in dichloromethane at room temperature quaternary ammonium salt **130** spontaneously transforms into tertiary amine **131** by demethylation.



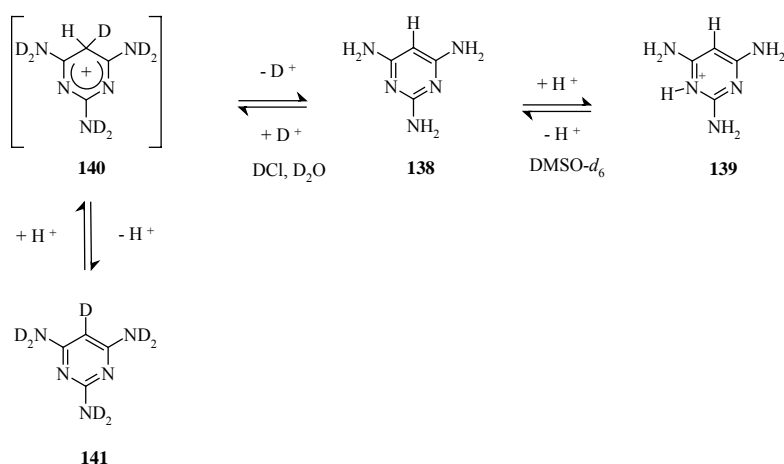
Scheme 7. The reaction of 2,4,6-tris(dimethylamino)pyrimidine (**127**) with chloroacetyl chloride in the presence of  $\text{NEt}_3$  leads to a stable cationic  $\sigma$ -complex (**134**).

- 3.5.5 It has been proved by NMR spectroscopy that the C(5) and N(1) protonated forms of [2,4,6-tris(dimethylamino)pyrimidinium] chloride in aqueous solution ( $\text{H}_2\text{O}:\text{D}_2\text{O} = 9:1$ ) interconvert. Inversion transfer measurements proved that the interconversion is under the applied conditions, slow on the chemical shift time scale and moderately fast on the relaxation time scale (Scheme 8.).
- 3.5.6 The  $\text{pK}_a$  values of C(5) and N(1) protonation of **127** have been determined by NMR titration.  $\text{pK}_{a(\text{C5})} = 6,87$ .  $\text{pK}_{a(\text{N1})} = 6.89$  ( $25^\circ\text{C}$ ).



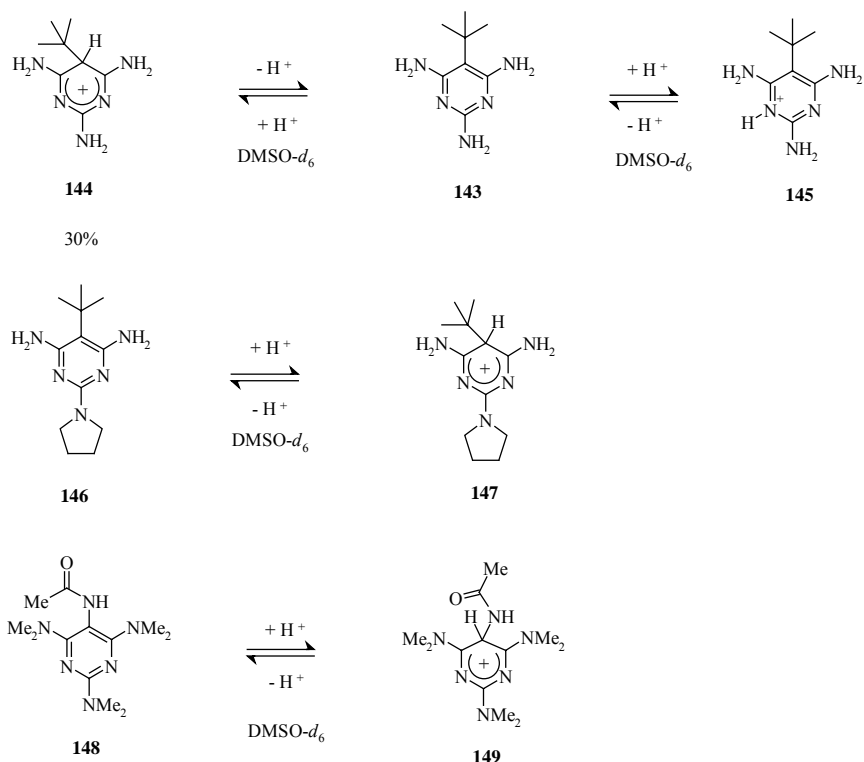
Scheme 8. Protonation of 2,4,6-tris(dimethylamino)pyrimidine.

- 3.5.7 It was observed that in  $\text{D}_2\text{O}$  solution of 2,4,6-triaminopyrimidine (**138**) the proton at the C(5)-position is exchanged by deuterium. Although the presence of the C(5)-protonated form is not detectable directly by NMR spectroscopy, the proton-deuterium exchange at the C(5)-position proves the C(5)-protonation (Scheme 9).



*Scheme 9. Protonation of 2,4,6-triaminopyrimidine (138).*

- 3.5.8 It was observed that in DMSO-*d*<sub>6</sub> solution of 2,4,6-triaminopyrimidine- and 2-methyl-4,6-triaminopyrimidine trifluoroacetates (**126**, Scheme 1) the C(5) protonated form is not detectable directly by NMR spectroscopy, but in DMSO-*d*<sub>6</sub> solution containing 5% D<sub>2</sub>O the H-C(5) proton is exchanged for deuterium within 24-48 hours.
- 3.5.9 It has been proved by NMR spectroscopy that in DMSO-*d*<sub>6</sub> solution of 2,4,6-triamino-5-(*t*-butyl)pyrimidinium tetrafluoroborate the amount of C(5)-protonated form is 30 mol% (Scheme 10).
- 3.5.10 It has been shown by NMR spectroscopy that in the case of the salts of some C(5)-substituted 2,4,6-triaminopyrimidines (**147**, **149**) in DMSO-*d*<sub>6</sub> solution only the C(5)-protonated form is detectable.
- 3.5.11 Based on the statements of paragraphs 3.5.3, 3.5.5 and 3.5.7-10 it is assumed that in the basic form of the investigated 5-substituted 2,4,6-triaminopyrimidines (**135**, **143**, **145**, **148**) steric repulsion takes place between the substituents at the 4-5 and 5-6 positions. As a result of the C(5)-protonation, the aromatic character of the ring is destroyed and an sp<sup>2</sup>→sp<sup>3</sup> hybridization change takes place at C(5). In consequence of this process the steric repulsion is decreased and the positive charge can be delocalised to the extranuclear N atoms. It is supposed that the formation of stable cationic pyrimidine σ-complexes is the result of these two, steric and electronic effects.



Scheme 10. Protonation of 5-substituted aminopyrimidines.

#### 4. The significance and possible use of the results

- 4.1 The developed new methods for the synthesis of aminopyrimidines and aminoquinazolines provide new possibilities for the automated synthesis of the libraries of these compounds and can contribute to the development of new solid-phase procedures in this area.
- 4.2 The usefulness of the new solid-phase methods was demonstrated by the parallel automated synthesis (Tecan CombiTec automated synthesizer) of three libraries (6(7)-substituted 2-aminoquinazolines, 6-alkoxy-2-amino-4(3*H*)-quinazolones and 2,4-diamino-6-hydroxyquinazolines) containing 1200 compounds overall. The prepared compounds became part of Gedeon Richter Ltd.'s compound library.
- 4.3 The work done and the experiences gained furthered the process of integrating combinatorial chemistry into the original drug discovery system of Gedeon Richter Ltd.
- 4.4 The observed C(5)-protonation feature might be of interest in structure-activity studies of pharmaceutically active triaminopyrimidines and can help to predict or explain some chemical reactions of these compounds as well.

## 5. Publications connected to the dissertation

1. Csaba Wéber, Attila Bielík, Györgyi I. Szendrei, István Greiner  
*Novel solid-phase synthesis of 2,6-disubstituted 4(3H)-quinazolinones for combinatorial library generation*  
*Tetrahedron Lett.* **2002**, 43, 2971-2974.  
Impact factor: 2,357
2. Ádám Demeter, Csaba Wéber, János Brlik  
*Protonation of the Pyrimidine Ring at the C(5) Position: Formation of a Stable Cationic sigma-Complex*  
*J. Am. Chem. Soc.* **2003**, 125, 2535-2540.  
Impact factor: 6,201
3. Csaba Wéber, Ádám Demeter, Györgyi I. Szendrei, István Greiner  
*Solid-phase synthesis of 2,6- and 2,7-diamino-4(3H)-quinazolinones via palladium catalyzed amination*  
*Tetrahedron Lett.* **2003**, 43, 7533-7536.  
Impact factor: 2,357
4. Csaba Wéber, Györgyi I. Szendrei, István Greiner  
*Solid-phase synthesis of a 2-amino-4(3H)-quinazolinone library*  
*PharmaChem*, **2003**, 2. (July/August) 25-27.  
Impact factor: -
5. Demeter Ádám, Wéber Csaba, Brlik János, Veszprémi Tamás, Németh Balázs  
*Rutin acilezéstől stabilis pirimidin  $\sigma$ -komplexekig: A pirimidin gyűrű szén protonálódása*  
*Acta Pharmaceutica Hungarica* **2004**, 74, 29-38.  
Impact factor: -
6. Csaba Wéber, Attila Bielík, Györgyi I. Szendrei, György M. Keserű, István Greiner  
*Solid-phase synthesis of an N-(phenylalkyl)cinnamide library via Horner-Wadsworth-Emmons reaction*  
*Bioorg. Med. Chem. Lett.* **2004**, 14, 1279-1281.  
Impact factor: 2,051
7. Ádám Demeter, Csaba Wéber  
*Carbon-Protonation of the Pyrimidine Ring: The Story of a Small Molecule NMR Problem*  
*Concepts in Magnetic Resonance* **2004**, (közlésre elfogadva)  
Impact factor: 2,262

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**The sum of impact factors (2002): 15,228**

## 6. Scientific lectures and posters connected to the dissertation

1. Wéber Csaba, Demeter Ádám, I. Szendrei Györgyi, Tuba Zoltán, Mahó Sándor  
*Triaminopirimidinek reakciói alfa-halo-savhalogenidekkel (lecture)*  
(Reaction of triaminopyrimidines with alpha-haloacyl halides)  
MTA Heterociklusos Munkabizottság ülése, Balatonszemes, May 25-26, 2000
2. CsabaWéber , György M. Keserű, Györgyi I. Szendrei , Attila Bielik, István Greiner  
*Combinatorial Solid-Phase Synthesis of a Quinazoline Library Having Potentially Selective Alpha<sub>1A</sub>-Adrenoreceptor Activity (poster)*  
Combinatorial Chemistry 2000 (London, England, July 11-14, 2000)  
Programme & Abstract Book page 26, P-CCH18.
3. Csaba Wéber, Attila Bielik, György M. Keserű, Györgyi I. Szendrei, István Greiner  
*Combinatorial Solid-Phase Synthesis of a 4(3H)-Quinazoline Library (poster)*  
EUROCOMBI-1, 1<sup>st</sup> Symposium of the European Society for Combinatorial Sciences, (Budapest, July 1-5, 2001)  
Abstract Book, page 57, P-38.
4. Csaba Wéber , Györgyi I. Szendrei , István Greiner  
*Solid-Phase Synthesis of 2,7-Diamino-4(3H)-quinazolinones via Palladium-Catalyzed Amination (poster)*  
Balticum Organicum Syntheticum (BOS 2002), (Vilnius, Latvia, June 23-27, 2002)  
Abstract Book, page 135, P-84.
5. Demeter Ádám, Wéber Csaba, Brlik János  
*A pirimidingyűrű protonálódása: egy stabilis szigma-komplex képződése (lecture)*  
(Protonation of the pyrimidine ring: the formation of a stable  $\sigma$ -complex)  
Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium (Visegrád, September 30-October 1, 2002)
6. Wéber Csaba, Demeter Ádám, I. Szendrei Györgyi  
*Váratlan reakciók aminopirimidinek körében (lecture)*  
(Unexpected reactions of aminopyrimidines)  
MTA Heterociklusos Munkabizottság ülése (Balatonszemes, May 29-30, 2003)
7. Wéber Csaba, Demeter Ádám, I. Szendrei Györgyi  
*Váratlan reakciók aminopirimidinek körében (poster)*  
(Unexpected reactions of aminopyrimidines)  
MKE Vegyészkonferencia (Hajdúszoboszló, June 26-28, 2003)  
Program és Előadásösszefoglalók, (Programme and Abstract Book) page 167, P-119.
8. Ádám Demeter, Csaba Wéber, Tamás Veszprémi, Balázs Németh  
*Carbon-protonation of 2,4,6-triaminopyrimidines: an NMR and quantum chemical study (poster)*  
45<sup>th</sup> Rocky Mountain Conference on Analytical Chemistry, (Denver, CO, USA, July 27-August 1, 2003)  
Abstract Book, page 115, P-242.
9. Demeter Ádám, Wéber Csaba, Veszprémi Tamás, Németh Balázs

*Aminopirimidinek protonálódásának újabb aspektusai (lecture)*

*(New aspects of the protonation of aminopyrimidines)*

Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium (Eger, September 22-23, 2003)

10. Wéber Csaba, Demeter Ádám, Veszprémi Tamás, Németh Balázs

*A pirimidingyűrű C-5 protonálódása: stabil kationos szigma-komplexek és új reakciók aminopirimidinek körében (lecture)*

*(C(5)-Protonation of the pyrimidine ring: stable cationic  $\sigma$ -complexes and some new reactions of aminopyrimidines)*

IX. Nemzetközi Vegyészkonferencia, (Cluj-Napoca, Romania, November 14-16, 2003)