

Budapest University of Technology and Economics

**SYNTHESIS OF BIOLOGICALLY ACTIVE NITROGEN-
HETEROCYCLES VIA PALLADIUM-CATALYZED REACTIONS**

Ph. D. thesis

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1. Introduction

Ph.D. thesis was prepared at the Department of Organic Chemistry and Technology. During my researches I worked with three, different type of compounds, which are supposedly pharmacologically active:

- compounds containing indole skeleton, presumed serotonerg receptor binding and easy barrier-transport.
- compounds containing quinoline skeleton, which are deemed to show selective serotonerg activity
- vindoline derivatives, which are - like *Vinca* alkaloids - supposed to inhibit cell division.

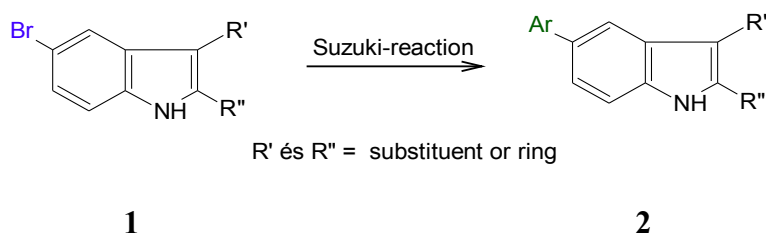
In all three cases palladium-catalyzed cross-coupling reactions were used to modify the skeletons. My task was to optimize the reaction conditions – catalyst, ligand, solvent, base – as well as to prepare the new derivatives.

Molecules having similar structures than endogen ones are expected to have similar receptor binding and effect, due to the structure-interaction correlation. This correlation is known well by researchers, and is used in elaborating new medicines.

Most substances having an effect on the serotonin system are the derivatives of tryptamine. For instance, *N,N*-diethyltryptamine has an antagonist effect on serotonin receptors, while bufotenine (dimethylserotonine) is used as a serotonerg agonist in medicinal therapy.

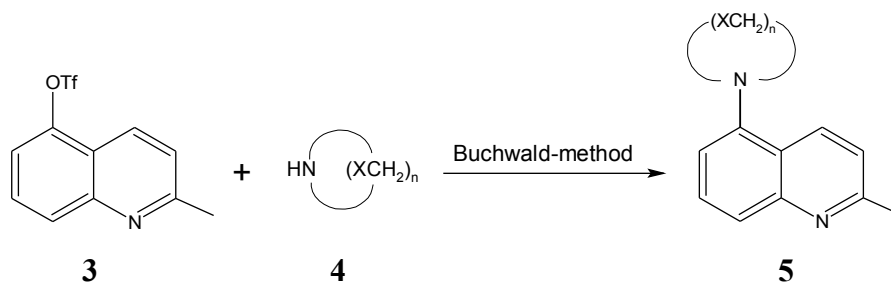
It's well known, that amino acids substituted with aromatic ring (e.g. tryptophan) have a large lipophilic surface, what allows of binding to receptors stronger and transporting through barriers easier (e.g. blood-brain barrier).

With this end in view, the aim of my work was preparing tryptamine derivatives 5-substituated with an aromatic ring. These derivatives were expected to have serotonin receptor binding together with good barrier-transport.



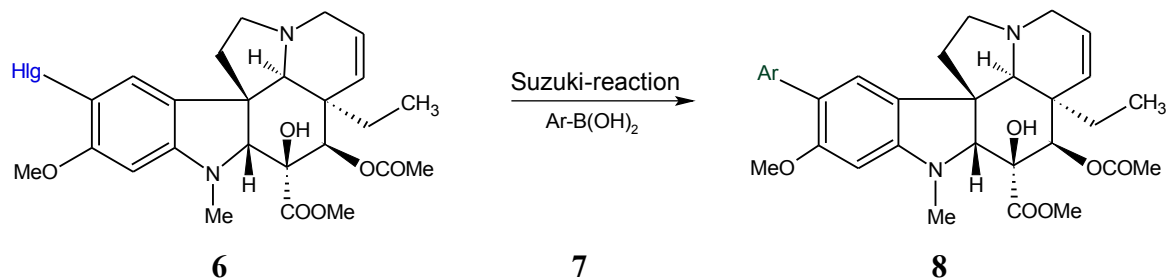
By designing the molecules, there can be substances prepared, which can bind selectively to more, different receptor types. These have the advantages of having diverse effects without pharmacokinetic interactions between the compounds.

5-Substituted quinaldine derivatives were expected to be selective serotonin reuptake-inhibitor and bind to one of the serotonin receptor subtypes selectively.



Vincristine and vinblastine, isolated from *Catharanthus roseus*, are used in medication as antileukemic agents. Vindoline – extracted from the same plant – is the monomer of vincristine and vinblastine, but has only a weak effect.

In fact, vincristine and vinblastine are vindoline derivatives substituted with catharanthine in the position 15. In the hope of increasing the effectivity and reducing toxic side effects, vindoline was substituted with an aromatic group in position 15.

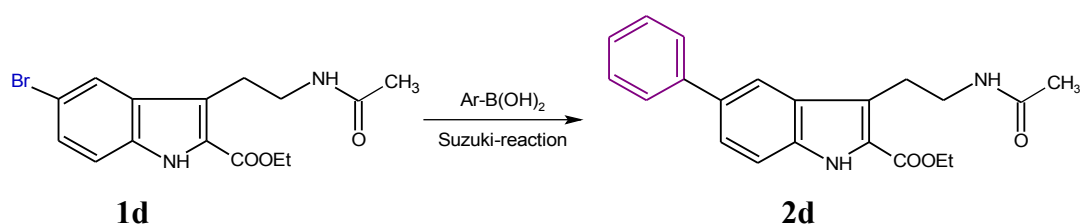


The aim of my work was to develop and optimize the coupling methods and to synthesize new derivatives via Buchwald- and Suzuki-reaction.

2. Results and discussion

2.1. Preparation of 5-aryltryptamine derivatives with Suzuki-reaction

5-Bromotryptamine 2-carbonicacid ethylester (**1a**) and its *N*-acylated derivatives (**1b**, **1c**) were substituted with different phenylboronic acids in Suzuki-reaction. Since the conversions in case of **1a** and **1b** proved to be low, the reaction parameters were optimized. For the optimization, **1d** was chosen as model compound. The reaction parameters (catalyst, ligand, base, solvent) were changed in 13 runs on the base of the literary data.



The highest conversion was reached in dimethylformamide solvent, in the presence of PdCl_2 catalyst, *bis*(diphenylphosphino)ferrocene (dppf) ligand, and K_3PO_4 base. For the preparation of the further derivatives (**2c**) this method was applied.

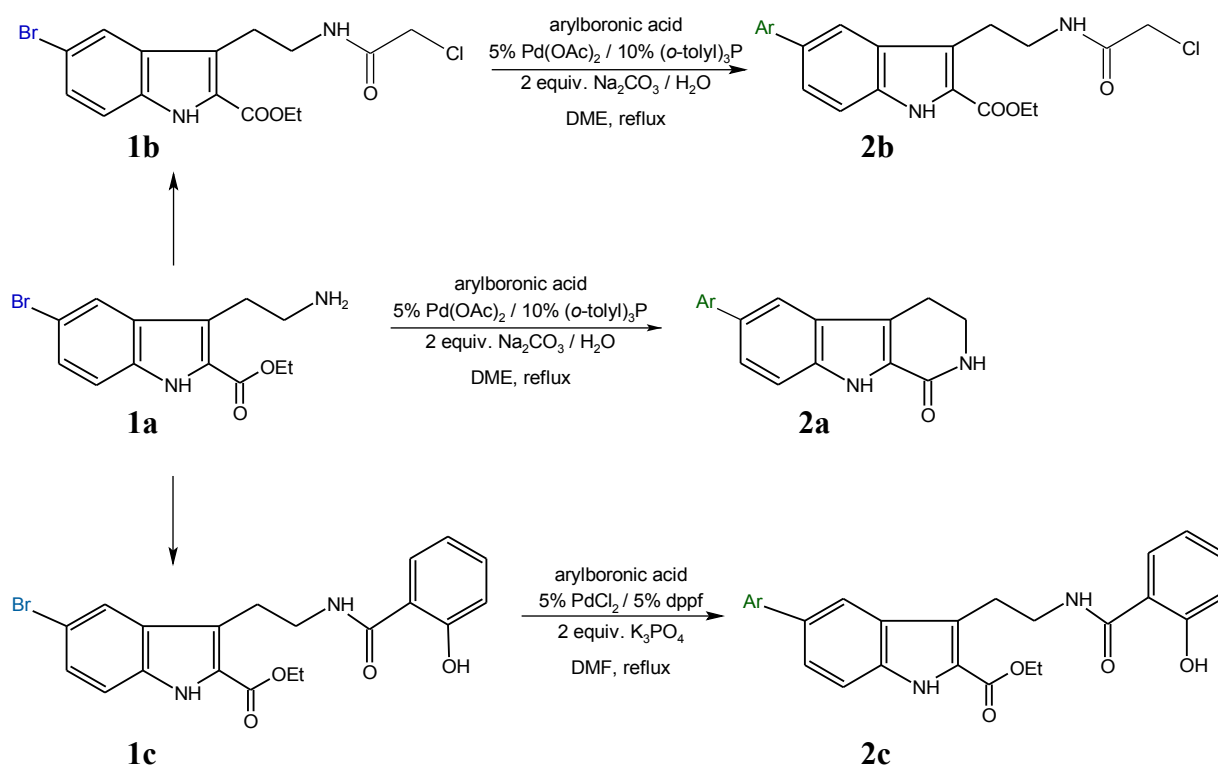
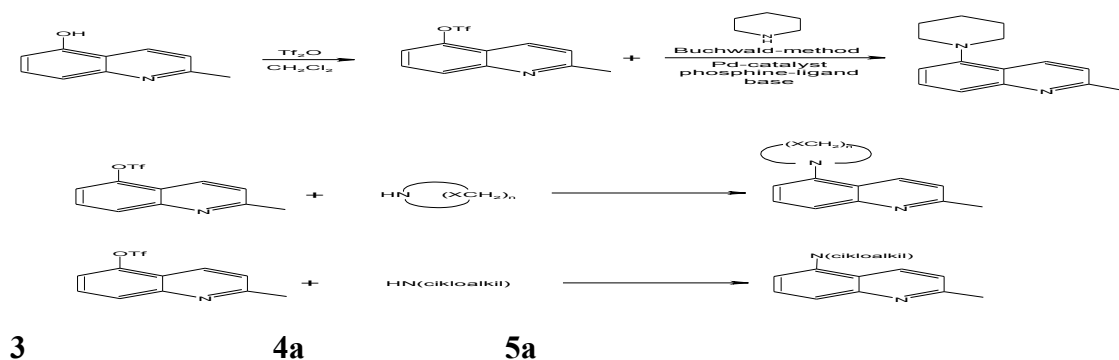


Table 1.

	Arylboric acid (7) Ar=	2a	2b	2c
		Yield (%)		
a	phenyl-	33	55	35
b	4-methylphenyl-	19	20	28
c	4-phenoxyphenyl-	30	27	32
d	3,5-bis(trifluoromethyl)phenyl-	42	62	44
e	3,5-difluorophenyl-	29	37	52

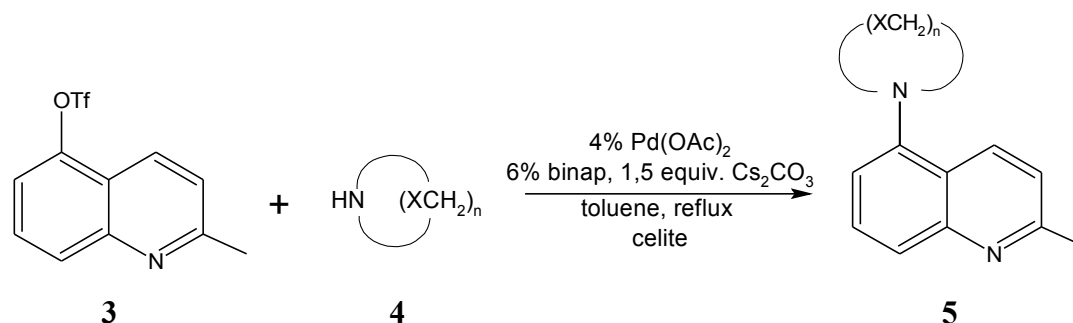
2.2. Preparation of *N*-substituted aminoquinaldines with Buchwald reaction

The syntheses of *N*-(cycloalkylamino)quinaldines were planned from 5-hydroxyquinaldine, via quinaldine-5-triflate, with palladium-catalyzed cross-coupling. For the first, the preparation of 5-piperidinyl-quinaldine (**5a**) with Buchwald-coupling was optimized.



The best result from the 16 attempts was chosen and then quinaldine-5-triflate (**3**) was reacted with cyclic amines (Table 2.).

The most sufficient conditions proved to be: refluxing the starting materials in toluene under argon atmosphere for 5 hours, in the presence of 4% $\text{Pd}(\text{OAc})_2$ catalyst, 6% binap (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), 1.5 equiv. Cs_2CO_3 as base, led to a conversion 99%. For the preparation of the further derivatives (**5**) this method was then applied.



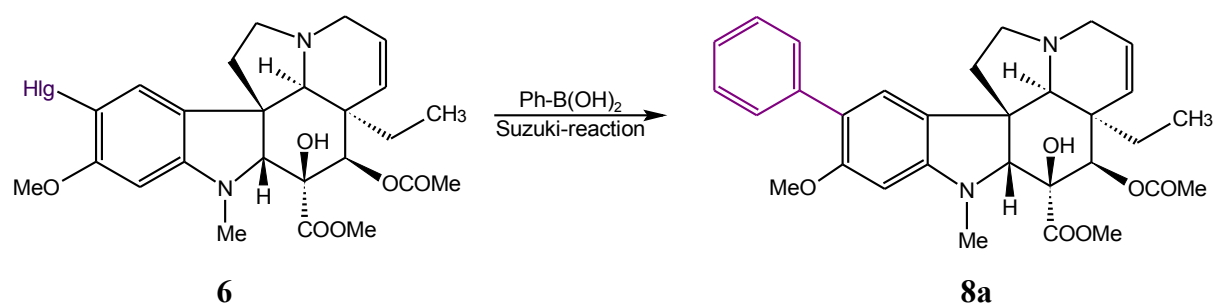
The above conditions proved to be applicable in case of aromatic amines – for example 2-aminopyridine – as well.

Table 2.

	4	5 GC yield(%)
a	piperidine	99
b	piperazine	53
c	morfoline	99
d	2,6-dimethylmorfoline	63
e	pyrrolidine	99
f	8-methoxybenzazepine	18

2.3. Preparation of vindoline derivatives via Suzuki-coupling

The substitution of vindoline in the position 15 was carried out from 15-halogene derivatives (**6**). The Suzuki-couplings of 15-bromo and 15-iodovindolines with phenylboronic acid were optimized in 17 runs. With 15-bromovindoline, only low conversion rates were obtained. Therefore, 15-iodovindoline was used in the further attempts. Only this change of the substituent (Br to I) caused a surprising increase (from 24% to 92%).



For the preparation of the further phenylvindolines the most sufficient reaction conditions were chosen: Pd(OAc)₂ catalyst, (*o*-tolyl)₃P ligand, and K₃PO₄ as base in dimethoxyethane solvent. These reaction parameters proved to be efficient in case of 1-naphthylboronic acid, the reduced aromatic 5-chloro-2-tiophenylboronic acid, and vinylboronic acid dibuthylester as well.

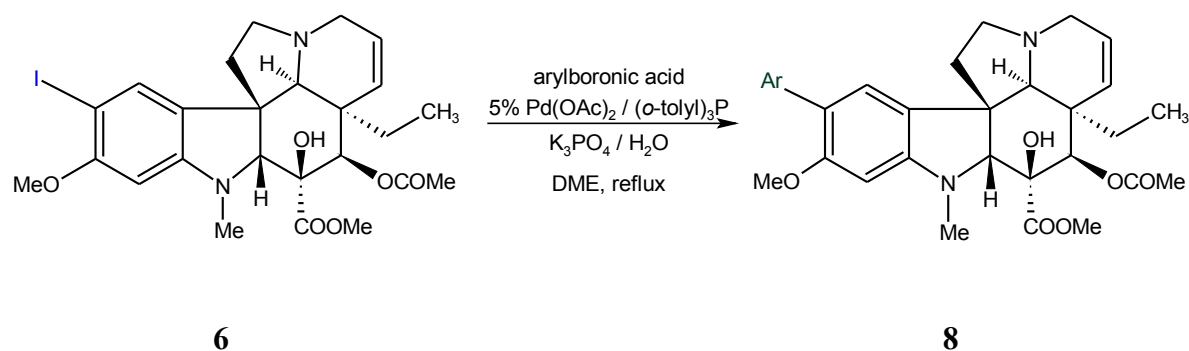


Table 3.

	Arylboronic acid (7) Ar=	Yield (%) 8
a	phenyl-	40
b	4-methylphenyl	32
c	4-methoxyphenyl-	not isolated
d	4-phenoxyphenyl-	26
e	3-nitrophenyl-	69
f	3,5-difluorophenyl-	54
g	3,5-bis(trifluoromethyl)phenyl-	63
h	1-naphtyl-	35
i	5-chloro-2-tiophenyl-	not isolated

During my work, the next experiences were acquired about palladium-catalyzed cross-coupling reactions:

Although the structure of the catalyst-ligand complexes were isolated and determined in more cases, the structure-effectiveness correlations are not properly explained. So it's worthwhile – and in most cases, necessary – to optimize the reaction parameters as far as possible.

The expected results can be obtained not only by applying a new source of catalyst or phosphine ligand, but finding out:

- an appropriate solvent or solvent mixture
- the quality and the quantity of the base
- the proper rate of the catalyst and the ligand.

These experiences were published in 3 papers in international journals (1-3.).

3. Publications

Publications on the subject of the thesis:

1. M. Fekete, M.Törincki, L. Novák: Palladium-catalyzed amination of quinaldine-5-triflate; *Central European Journal of Chemistry*, 2007, accepted for publication.
2. M. Fekete, P. Kolonits, Ngo Thi Hien, L. Novák: Synthesis of Novel Tryptamine and β -Carboline Derivatives via Palladium-Catalyzed Reaction of Bromotryptamine with Organic Boronic Acids *Central European Journal of Chemistry* 792, 3, 4, (2005)
3. M. Fekete, P. Kolonits, L. Novák: Preparation of New Vindoline Derivatives by Palladium-Catalyzed Cross-Coupling Reaction *Heterocycles*, 65, 1, 165-171 (2005)
4. Fekete M., Kolonits P., Novák L., Új indolvázias vegyületek előállítása Suzuki-reakcióval; XI. International Conference of Chemistry, Kolozsvár, *Conference Book*, 274-278, (2005).
5. Fekete M., Kolonits P., Novák L.: Új vindolinszármazékok előállítása Suzuki-reakcióval; X. International Conference of Chemistry, Kolozsvár, *Conference Book*, 211-215, (2004)

Other publications:

8. Keglevich Gy., Chuluunbaatar T., Dajka B., Namkhainyambuu BA., Fekete M., Kollar L., Toke L. : The dual reactivity of 1-(2,4,6-trialkylphenyl)phospholes having a flattened P-pyramid *Phosphorus Sulfur and Silicon and the Related Elements* 177 (8-9) 1991 - 1992 (2002)
9. Keglevich Gy., Fekete M., Chuluunbaatar T., Dobo A., Bocskei Zs., Toke L. : Convenient method for the reduction of the double-bond of cyclic vinylphosphine oxides using borane. *Magyar Kémiai folyóirat* 107 (12) 533 - 537 (2001)
10. Keglevich Gy., Fekete M., Chuluunbaatar T., Dobo A., Harmat V., Toke L. : One-pot transformation of cyclic phosphine oxides to phosphine- boranes by dimethyl sulfide-borane. *Magyar Kémiai folyóirat* 107 (12) 538 - 543 (2001)
11. Keglevich Gy., Fekete M., Chuluunbaatar T., Dobo A., Harmat V., Toke L. : One-pot transformation of cyclic phosphine oxides to phosphine-boranes by dimethyl sulfide-borane *Journal of the Chemical Society-Perkin Transactions 1* 160 (24) 4451 - 4455 (2000)
12. Keglevich Gy., Fekete M., Chuluunbaatar T., Dobo A., Bocskei Zs., Toke L. : Convenient method for the reduction of the double-bond of cyclic vinylphosphine oxides using borane *Synthetic Communications* 30 (23) 4221 - 4231 (2000)

Presentations, posters:

1. Fekete M., Kolonits P., Novák L., Új indolvázias vegyületek előállítása Suzuki-reakcióval; XII. International Conference of Chemistry, Csíkszereda, 2006._
2. M. Fekete, P. Kolonits, L. Novák: Preparation of new indole derivatives by palladium catalyzed cross-coupling reaction; I. European Chemistry Congress, Budapest, 2006, poster.
3. Fekete M., Kolonits P., Novák L., Új indolvázias vegyületek előállítása Suzuki-reakcióval; XI. International Conference of Chemistry, Kolozsvár, 2005.
4. Fekete M., Kolonits P., Novák L.: Új indolvázias vegyületek előállítása Suzuki-reakcióval; Magyar Kémikusok Egyesülete Vegyészkonferencia, Hajdúszoboszló, 2005.
5. Hazai L., Fekete M., Új vindolinszármazékok szintézise; II. Medichem, 1. Konferencia, 2005.
6. Fekete M., Kolonits P., Novák L., Új vindolinszármazékok előállítása Suzuki-reakcióval; X. International Conference of Chemistry, Kolozsvár, 2004.
7. Fekete M., Novák L.: Új indolvázias vegyületek előállítása Suzuki-reakcióval; MTA Terpenoidkémiai és Elemorganikus Munkabizottság 2004.
8. Fekete M., Szerves Kémia Tanszék: Új indolvázias vegyületek előállítása Suzuki-reakcióval. BME Vegyészmérnöki Kar, I. Doktoráns Konferencia, 2003.
9. Novák L., Hazai L., Szabó L., Fekete M., Gorka Á., Szántai Cs.: Új vindolin-származékok előállítása és vizsgálata. BME Szerves Kémia Tanszék: II. Medichem Konferencia 2002.