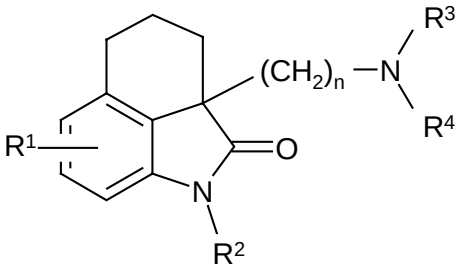
I. Introduction

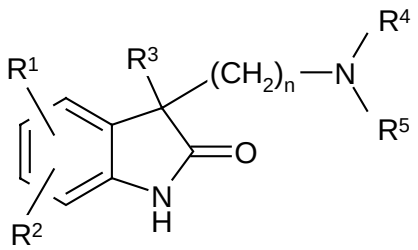
Serotonine (5-hydroxytryptamine, 5-HT) is one of the main neurotransmitters in the human body. Among the 14 known serotonine receptor subtypes, 5-HT_7 has been discovered as the last one. The physiological role of this receptor has not yet been fully clarified but it is supposed to have great significance in several diseases of the central nervous system.

In 1997, the researchers of Meiji Seika, a Japan pharmaceutical company, published a patent on the synthesis of selective 5-HT_7 antagonists containing a 2a,3,4,5-tetrahydro-1*H*-benzo[cd]indol-2-one skeleton. They also claimed the use of these compounds as medicines against depression and anxiety.



R^1 = H, halogen, alkyl, OH etc.
R^2 = H, alkyl, aralkyl
R^3, R^4 = various substituents
n = 2-6

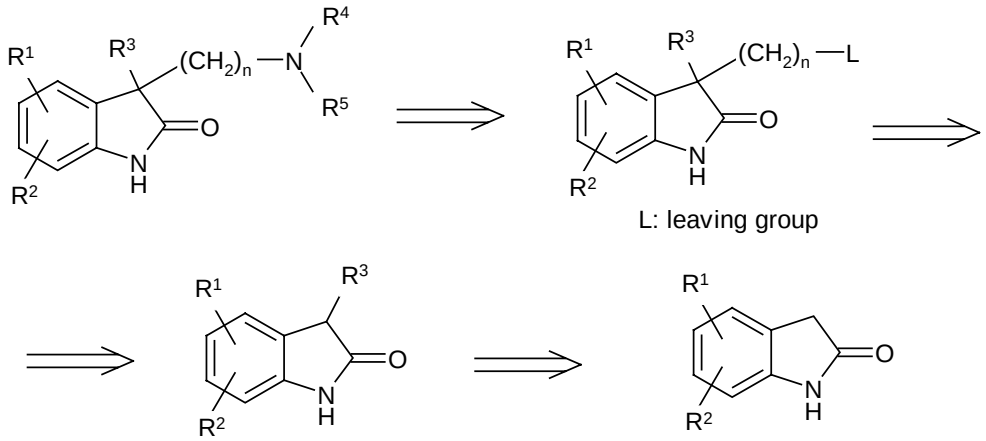
Meiji Seika



R^1, R^2 = H, F, Cl, Me etc.
R^3 = H, alkyl
R^4, R^5 = various substituents
n = 3-6

compounds to be synthesised

At the Chemical Research Division of Egis Pharmaceuticals Ltd., we have aimed at elaborating a practical synthesis of new, patentable compounds containing an oxindole skeleton, which can be derived from the Meiji Seika compounds by the „cleavage” of the saturated carbocycle.



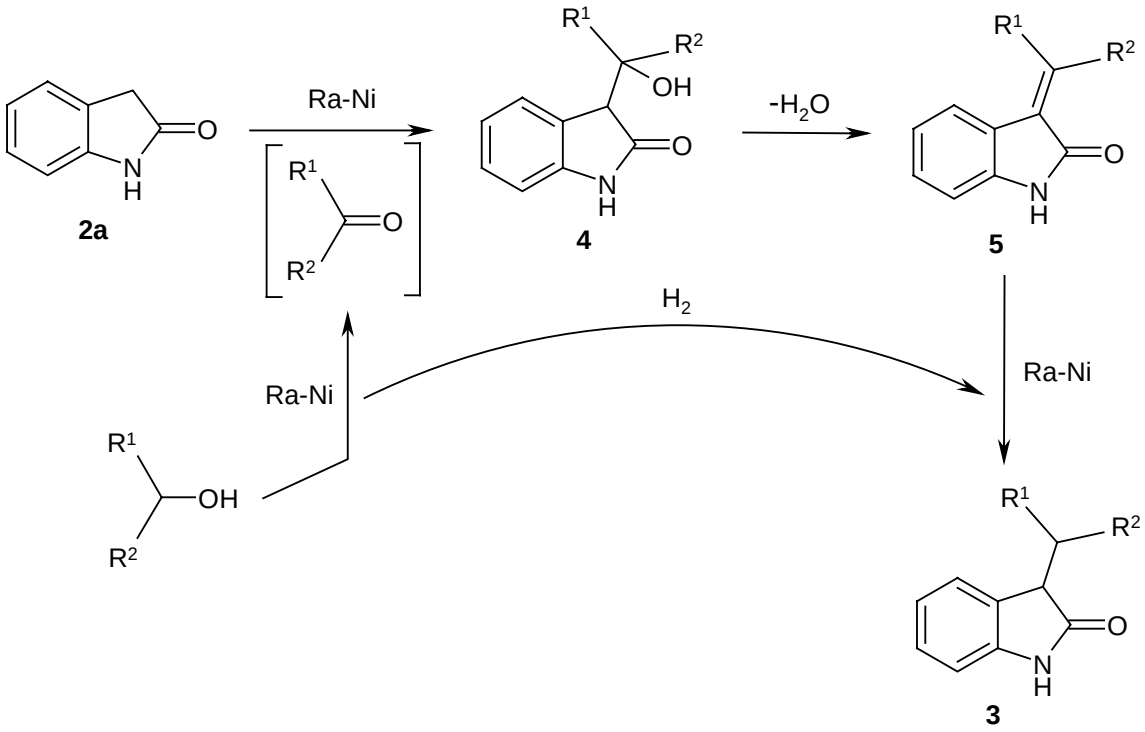
The retrosynthetic study shows that the planned synthetic route makes the preparation of 3-alkyloxindoles necessary. The subject of the dissertation is the elaboration of a new, practical synthesis of these compounds starting from oxindoles.

II. Methods

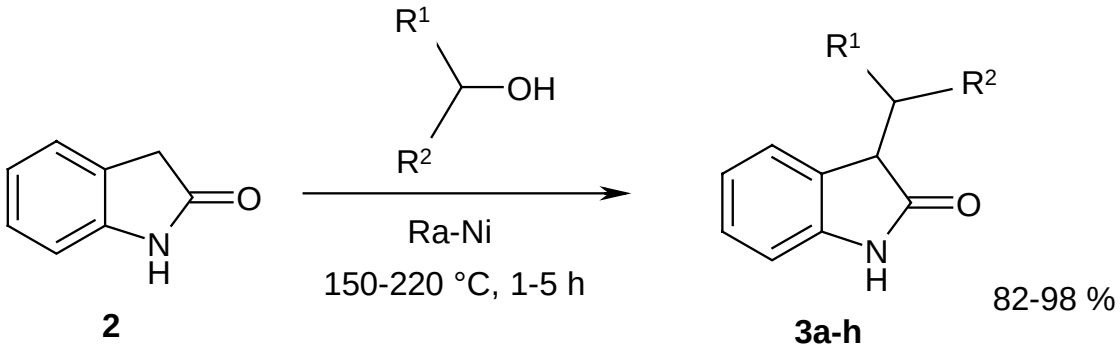
In the course of the work, the methodology of preparative organic chemistry has been applied. The reactions have been followed by thin layer chromatography. The structure determination of the synthesised compounds was carried out using IR, ^{1}H NMR, ^{13}C NMR, MS and GC-MS techniques.

III. Theses

1. In 1958, Wenkert and his co-worker realized that the reaction of oxindole (**2a**) with alcohols, in the presence of ten fold mass of Raney nickel gave 3-alkyloxindoles (**3**) after long reaction times (72-84 h). The reaction steps of the alkylation sequence are shown in the following scheme:



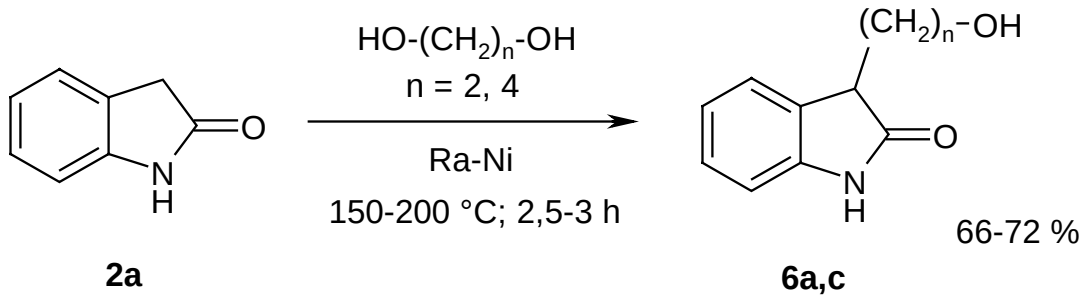
The original reaction of Wenkert gave low reproducibility and could not been scaled up. With a major improvement of this reaction, we have performed the alkylation under essentially new conditions, resulting in a practical synthetic route of the title compounds. The alkylation of oxindole (**2a**) has been carried out successfully in autoclaves, with various primary and secondary alcohols, in the presence of less than one mass equivalent of Raney nickel (0,1 g/mmol oxindole).



	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
R^1	H	Me	Ph	Me	Pr	*i*-Pr	Bn	-$(CH_2)_5$-
R^2	H	H	H	Me	H	H	H	

2. Scaling-up of the alkylation reaction with ethanol and isobutyl alcohol has also been performed successfully.

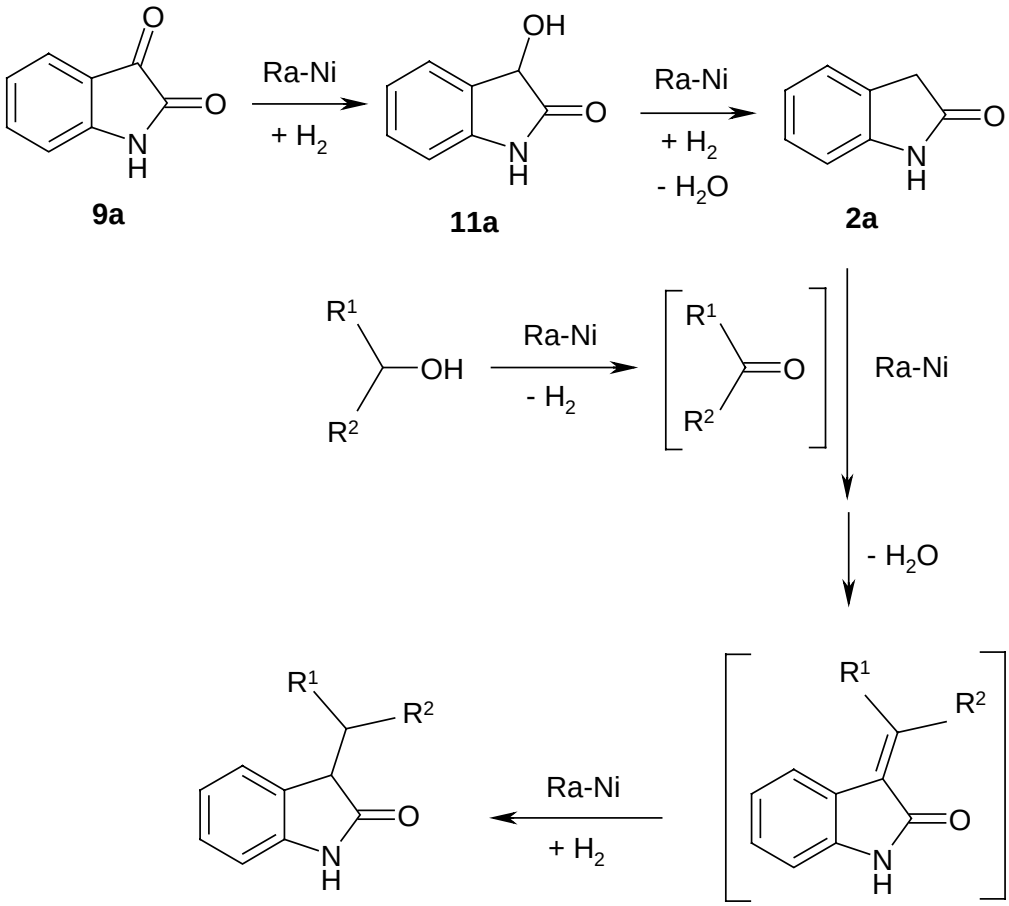
3. The synthetic usefulness of the method is demonstrated most of all by its extension to the synthesis of 3-(ω-hydroxyalkyl)oxindoles (**6**), using diols instead of alcohols, under the conditions applied before. The hydroxyalkylation of oxindole (**2a**) with ethylene glycol led to the formation of 3-(2-hydroxyethyl)oxindole (**6a**) in 66 % yield. Alternative methods in the literature for the preparation of **6a** involve complicated multistep procedures. The reaction could be performed with butane-1,4-diol, as well, resulting in the previously unknown 3-(4-hydroxybutyl)oxindole (**6c**) in good yield (72 %). The terminal hydroxy group of these 3-(ω-hydroxyalkyl)oxindoles can be further functionalized, so they are valuable building blocks in medicinal and synthetic organic chemistry.



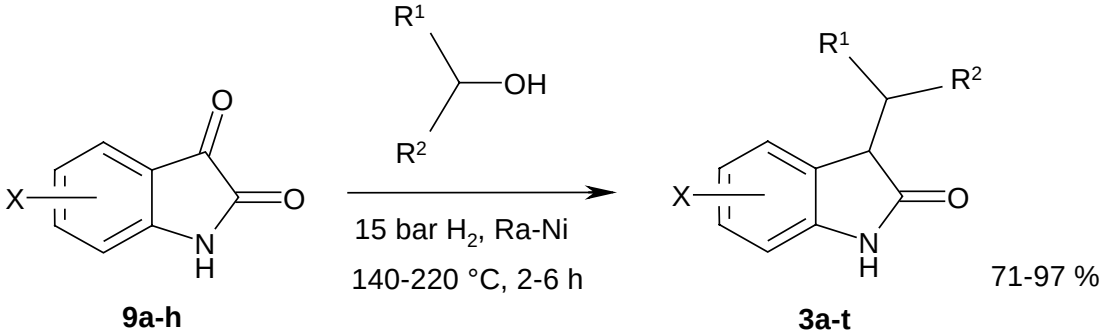
2a **6a,c**

Scaling up of the hydroxyalkylation reaction of oxindole with butane-1,4-diol up to 50 g starting material was also successful. It was observed that a diol excess of 4.5 equivalents is satisfactory, and tetrahydrofurane can be used as an inert solvent in the reaction.

4. Oxindole is usually prepared by the reduction of isatin. We have found that the reduction of isatin (**9a**) to oxindole (**2a**) in the presence of Raney nickel, in hydrogen atmosphere, and the 3-alkylation of oxindole can be carried out in one pot. The reaction steps of the complicated reaction sequence are illustrated in the following scheme:



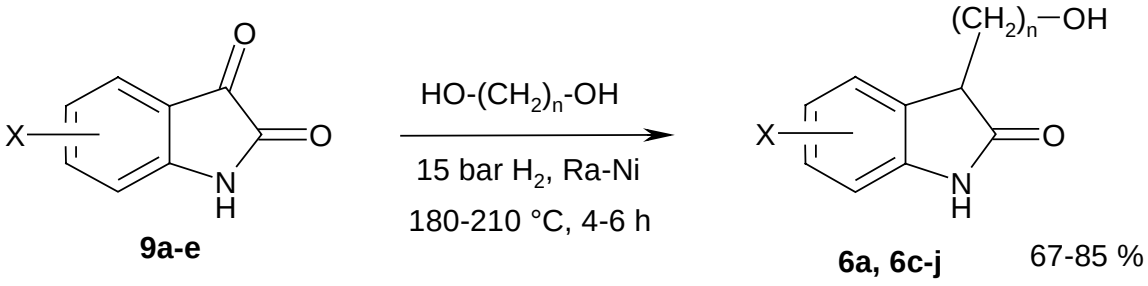
5. The reaction has been extended to several alcohols, resulting in the first one-step procedure for the synthesis of 3-alkyloxindoles starting from isatins. It has been concluded that the alkylation can also be performed with isatins substituted on the aromatic ring, provided the substituent is compatible with the elevated temperature and the hydrogen atmosphere. We have performed the scaling-up of the reaction with substituted isatins, even with 70 g starting material. In the scaled-up reactions, the relative amount of Raney nickel could be further reduced, down to 0.17 mass equivalent.



	3a	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3k**
R^1	H	Me	Ph	Me	Pr	*i*-Pr	Bn	-$(CH_2)_5$-	3-MeO-Ph
R^2	H	H	H	Me	H	H	H		H
X	H	H	H	H	H	H	H	H	H

	3l	**3m**	**3n**	**3o**	**3p**	**3q**	**3r**	**3s**	**3t**
R^1	2-Me-Ph	Me	Me	Me	Me	Me	Me	Me	CH_2OMe
R^2	H	H	H	H	H	H	H	H	H
X	H	5-F	6-F	5-Me	7-Me	7-Et	7-*i*-Pr	7-MeO	H

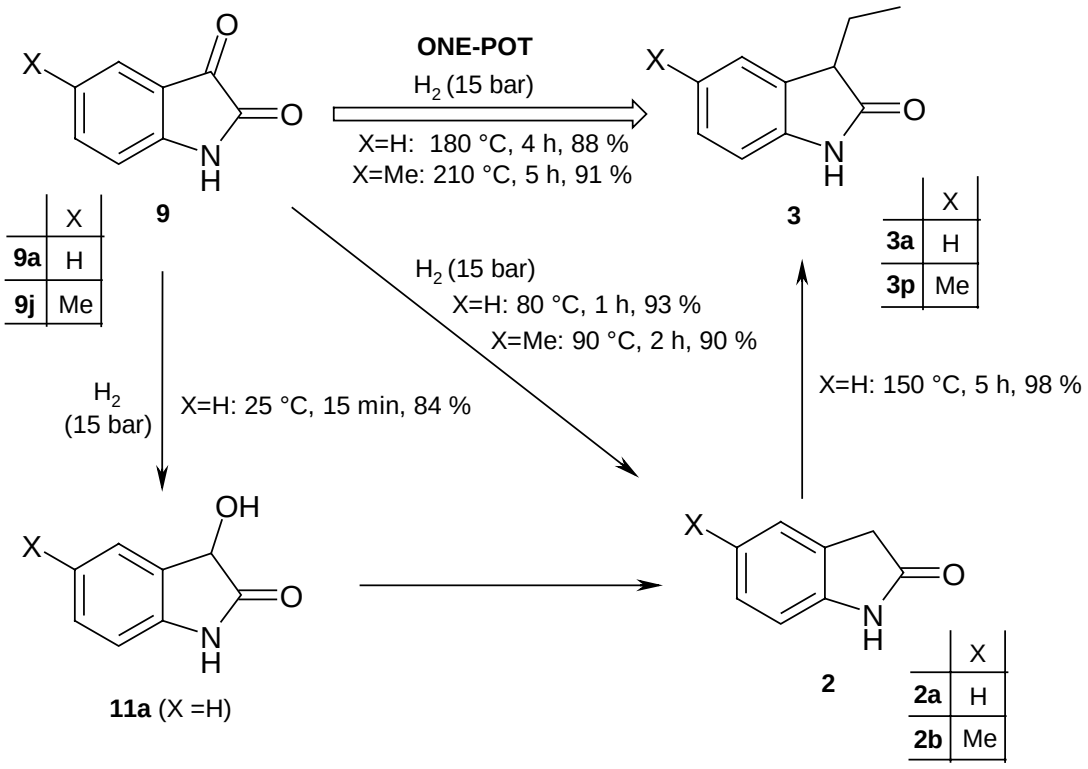
6. Similarly to the reactions starting from oxindole (**2a**), those starting from isatin (**9a**) could be extended to diols, as well. The reductive alkylation of isatins (**9**) with ethylene glycol, butane-1,4-diol and pentane-1,5-diol at temperatures around 200 °C gave the 3-(ω-hydroxyalkyl)oxindoles (**6**) in good yields, even in scaled-up reactions.



9a-e **6a, 6c-j** 67-85 %

	6a	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**	**6j**
X	H	H	5-F	6-F	5-	7-Me	H	5-F	6-F
n	2	4	4	4	4	4	5	5	5

7. The synthesis of 3-alkyloxindoles (**3**) from isatins (**9**) has been studied in detail. The reduction of isatin (**9a**) to 3-hydroxyoxindole (**11a**) in the presence of Raney nickel, in ethanol, under 15 bar hydrogen can be accomplished in 15 minutes at room temperature. At an elevated temperature (80 °C, 1 h) the reduction of isatin can be stopped at the stage of oxindole (**2a**). Under more vigorous conditions (150 °C, 5 h) ethanol becomes a reagent and oxindole (**2a**) will be alkylated to give 3-ethyloxindole (**3b**), as described above. This latter step does not need hydrogen atmosphere. It can be seen that there is a significant difference between the temperatures, so the individual steps can be carried out selectively.

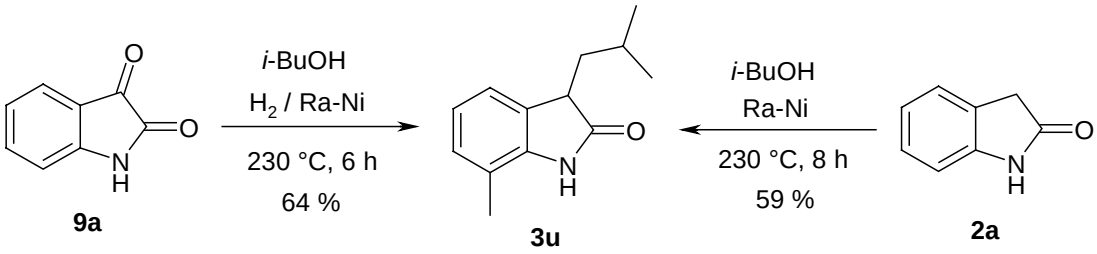


	X
9a	H
9j	Me

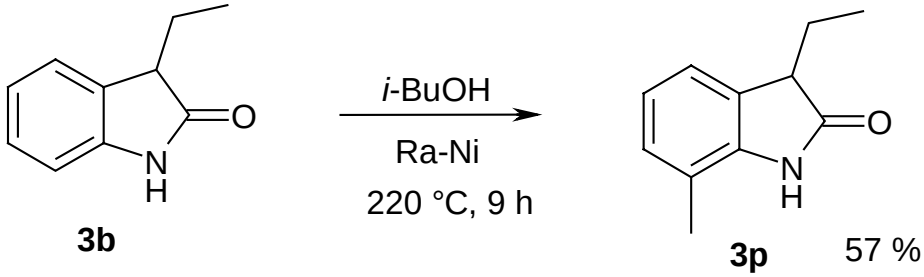
	X
3a	H
3p	Me

	X
2a	H
2b	Me

8. It has been observed that the reaction of isatin (**9a**) with isobutyl alcohol in the presence of Raney nickel, under more vigorous conditions (230 °C, 6 h) than those needed for the 3-alkylation, an unexpected 7-methylation also occured. The same reaction has been found between oxindole (**2a**) and isobutyl alcohol or propanol under similar conditions.



It has been shown that the unexpected regioselective 7-methylation reaction can be carried out starting from 3-ethyl- (**3b**) and 3,3-diethyloxindole (**12a**), as well.



9. The mechanism of the 7-methylation reaction has been studied with 3-ethyl- (**3b**) and 3,3-diethyloxindole (**12a**) as starting materials. It has been reasoned that various alcohols (e. g. propanol, butanol, isobutyl alcohol), diglyme or paraformaldehyde can also be the source of the 7-methyl group. We suppose that even in the reaction with alcohols, the *in situ* formed formaldehyde reacts as the primary reagent. Experiments have been carried out regarding the role of the NH group of the oxindole skeleton, the intermediates of the reaction pathway and the regioselectivity. On the basis of the experimental data, a possible Fries-type mechanism has been suggested.

10. Using the ^{13}C NMR chemical shifts of 105 oxindole derivatives synthesised at our laboratory, along with the chemical shifts of 254 derivatives found in the literature, a model has been set up for the determination of the substituents' effects on the ring carbon NMR signals. By means of these calculated substituent effects, the ^{13}C NMR shifts of oxindole derivatives can be accurately predicted.

IV. Publications, presentations and patents in connection with the PhD dissertation

Papers:

Raney nickel-induced 3-alkylation of oxindole with alcohols and diols
Balázs Volk, Tibor Mezei, Gyula Simig, *Synthesis*, **2002**, 595-597.

New one-pot synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles from isatins
Balázs Volk, Gyula Simig, *European Journal of Organic Chemistry*, **2003**, 3991-3996.

New routes to oxindole derivatives
Márta Porcs-Makkay, Balázs Volk, Rita Kapiller-Dezsőfi, Tibor Mezei, Gyula Simig, *Monatshefte für Chemie (Chemical Monthly)*, **2004**, *135*, 697-711.

Interpretation of substituent-induced ^{13}C NMR chemical shifts of oxindoles
Rita Kapiller-Dezsőfi, Balázs Volk, *New Journal of Chemistry*, **2004**, accepted for publication.

Patents:

Piperazine derivatives of alkyloxindoles
Balázs Volk, József Barkóczy, István Gacsályi, Katalin Pallagi, Gyula Simig, Tibor Mezei, Gábor Gigler, György Lévay, Krisztina Móricz, Csilla Leveleki, Nóra Sziray, Rita Kapiller-Dezsőfi, Gábor Szénási, András Egyed, László Hársing
HU 04/00953 (May 11, 2004)

Piperazine derivatives of alkyloxindoles
Balázs Volk, József Barkóczy, István Gacsályi, Katalin Pallagi, Gyula Simig, Tibor Mezei, Gábor Gigler, György Lévay, Krisztina Móricz, Csilla Leveleki, Nóra Sziray, Rita Kapiller-Dezsőfi, Gábor Szénási, András Egyed, László Hársing
HU 04/00954 (May 11, 2004)

Pyridine derivatives of dialkyloxindoles
Balázs Volk, József Barkóczy, István Gacsályi, Katalin Pallagi, Gyula Simig, Tibor Mezei, Gábor Gigler, György Lévay, Krisztina Móricz, Csilla Leveleki, Nóra Sziray, Rita Kapiller-Dezsőfi, Gábor Szénási, András Egyed, László Hársing
HU 04/00955 (May 11, 2004)

Pyridine derivatives of alkyloxindoles
Balázs Volk, József Barkóczy, István Gacsályi, Katalin Pallagi, Gyula Simig, Tibor Mezei, Gábor Gigler, György Lévay, Krisztina Móricz, Csilla Leveleki, Nóra Sziray, Rita Kapiller-Dezsőfi, Gábor Szénási, András Egyed, László Hársing
HU 04/00956 (May 11, 2004)

Piperazine derivatives of dialkyloxindoles
Balázs Volk, József Barkóczy, István Gacsályi, Katalin Pallagi, Gyula Simig, Tibor Mezei, Gábor Gigler, György Lévay, Krisztina Móricz, Csilla Leveleki, Nóra Sziray, Rita Kapiller-Dezsőfi, Endréné Flórián, Gábor Szénási, András Egyed, László Hársing
HU 04/00957 (May 11, 2004)

Oral presentations:

Raney nickel-induced 3-alkylation of oxindoles with alcohols
Balázs Volk
Presentation session of the Society of Hungarian Chemists (MKE), Egis Group, Budapest (Hungary), May 29, 2002.

New routes to oxindole derivatives
Márta Porcs-Makkay, Balázs Volk, Tibor Mezei, Gyula Simig
10th Blue Danube Symposium on Heterocyclic Chemistry, Vienna (Austria), Sept 3-6, 2003.

Unexpected 7-methylation of oxindoles
Balázs Volk, Rita Kapiller-Dezsőfi, Gyula Simig
Presentation session of the Heterocyclic Chemistry Committee of the Hungarian Academy of Sciences (MTA), Balatonszemes (Hungary), May 20-21, 2004.

Poster presentations:

Raney nickel-induced 3-alkylation of oxindole with alcohols and diols
Balázs Volk, Tibor Mezei, Gyula Simig
XVIIth International Symposium on Medicinal Chemistry, Barcelona (Spain), Sept 1-5, 2002.

Prediction of ^{13}C NMR spectra of oxindoles using substituent effects
Rita Kapiller-Dezsőfi, Balázs Volk
Conference for Chemists, Hajdúszoboszló (Hungary), June 26-28, 2003.

One-pot synthesis of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles from isatins
Balázs Volk, Gyula Simig
Conference for Chemists, Hajdúszoboszló (Hungary), June 26-28, 2003.

One-pot reductive alkylation of isatins to 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles
Balázs Volk, Gyula Simig
XVIIIth International Symposium on Medicinal Chemistry, Copenhagen (Denmark)-Malmö (Sweden), Aug 15-19, 2004.

Preparation of 3-alkyl- and 3-(ω-hydroxyalkyl)oxindoles from isatins
Balázs Volk, Tibor Mezei, Gyula Simig
XXIst European Colloquium on Heterocyclic Chemistry, Sopron (Hungary), Sept 12-15, 2004.

V. Publications, presentations and patents not in connection with the PhD dissertation

Cytochrome P450 catalyzed nitric oxide synthesis: a theoretical study
György M. Keserű, Balázs Volk, György T. Balogh, *Journal of Biomolecular Structure & Dynamics*, **2000**, *17*, 759-767.

Cytochrome P450 catalyzed nitric oxide synthesis

Balázs Volk, György T. Balogh, György M. Keserű

Hungarian-German-Italian-Polish Joint Meeting on Medicinal Chemistry, Budapest, Sept 2-6, 2001 (poster presentation).

New desloratadine pseudopolymorph

Tibor Mezei, Gyula Simig, Gyula Lukács, Márta Porcs-Makkay, Balázs Volk, Enikő Molnár, Valéria Hoffmann-Fekete, Zsuzsanna Szent-Királlyi

HU 04/01373 (July 4, 2004).