Investigation of bioactive carbonic acid derivatives and their application in the synthesis of imidacloprid, phenserine and desloratadine analogues.

Thesis of the PhD dissertation

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1. Introduction, aims

Among bioactive agents – pesticides, active pharmaceutical ingredients (API) – there are a significant number of carbonic acid derivatives, which are prepared from the appropriate acid derivatives. Their preparation directly from carbon-dioxide/carbamic acid is not a common method in organic synthesis.

At the Department of Organic Chemistry and Technology prof. Lajos Novák et al. successfully prepared imidacloprid (1, nitroguanidine derivative, pesticide) analogues recently and they also launched experiments to synthesize ACE inhibitors (Scheme 1.). In my PhD studies we aimed to synthesize a new analogue and an active metabolite of imidacloriprid (1) and we also planned to investigate the ring closure activity of the carbonic acid derivatives applied.

Our research group had launched experiments related to treat Alzheimer-disease. Having joined to this research the synthesis of the ACE inhibitor phenserine (phenylcarbamate, API), moreover its cycloalkano derivatives became the target molecules in my work.

At the Chemical Research Division of EGIS Pharmaceuticals supervised by Balázs Volk PhD. and Gyula Simig PhD. a new and efficient process was developed for preparing desloratadine (2, antihistamine, API) in which the API and carbon-dioxide form a stable crystalline ‘adduct’ with an unknown structure.

As a member of the project at the Research Division of EGIS Pharmaceuticals we decided to develop a scale-up process for the production of desloratadine-CO$_2$ “adduct” and to take effort to establish its exact structure.
2. Synthesis of imidacloprid analogues

For the benzene-fused derivative of imidaclopride (12) the benzimidazole part was prepared by using o-phenylenediamine (4) and an appropriate carbonic acid derivative (7). Using the derivatives 5 and 6 we could not synthesize the desired compound (8).

The product was prepared by alkylation of the benzimidazole derivative in both cases reaching the model (11) and target (12) compounds.

For the active metabolite of imidacloprid (13) an imidazol derivative, 16 was synthesized from the reaction of 14 and 6 compounds (Scheme 3.).
In contrast with previous observation in the production of alkylated benzimidazole compound we could not perform the alkylation of imidazol analogously. In order to overcome this difficulty we decided to alkylate 15 instead, prior to the ring closure step. Finally a regioisomer mixture (17, 18) was obtained. Isomers were isolated and forced to give imidazole derivative at acidic condition, separately. The desired compound (13) was formed in both cases (Scheme 3.).

Investigating the ring closure ability of the applied carbonic acid derivative they (5, 6, 7) were reacted with different types of diamines (19-22, 4) to give cyclic compounds at standard reaction conditions.

19: R = H
20: *R-R = cyclohexene
21: R = Ph
22: R = 4-chlorophenyl
4: *R-R = benzene

\[ \text{Scheme 4.} \]

The ring closure steps were resulted in the following yields (Table 1.):

<table>
<thead>
<tr>
<th>Net. yield[%]</th>
<th>Diamines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
</tr>
<tr>
<td>Carbonic acid</td>
<td></td>
</tr>
<tr>
<td>derivatives</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>7</td>
</tr>
</tbody>
</table>

Table 1.

According to the data presented in Table 1., it is obvious, that amins not bearing aromatic ring, undergo ring closure step easily with all of the carbonic acid derivatives. Presence of an aromatic substituent limit the reagent to 6, 7 derivatives, and in the case of benzene ring fusion only 7 can afford the desired product.
3. Preparation of the cycloalkanoidol analogue

The cycloalkanoidol framework was planned to synthesize by [3,3] sigmatropic aza-Claisen rearrangement followed by catalytic ring closure (Scheme 5.).

![Scheme 5.]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>X-group</th>
<th>R-group</th>
<th>n</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>H</td>
<td>H</td>
<td>1</td>
<td>37c, 37t</td>
</tr>
<tr>
<td>28</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>38c, 38t</td>
</tr>
<tr>
<td>29</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>39c, 39t</td>
</tr>
<tr>
<td>30</td>
<td>MeO</td>
<td>H</td>
<td>1</td>
<td>40c, 40t</td>
</tr>
<tr>
<td>31</td>
<td>MeO</td>
<td>Me</td>
<td>1</td>
<td>41c, 41t</td>
</tr>
</tbody>
</table>

Scheme 5.

Taken an effort to perform the arrangements to the compound 32-36, the resulted reaction mixtures were separated, which resulted in three isolated products in most cases. Surprisingly two of them were the desired tricyclic target molecules (37c-41c, 37t-41t), and a rearranged, non-ring-closured compound (42-46, Scheme 6., Table 2.).

![Scheme 6.]

The related yields (Table 2.) show that in case of ring closure the cis configuration is preferred and substrates having five-membered ring are not likely to give the trans isomer.
Beside the model tricyclic compound (37c-39c, 37t-39t) the substrates bearing methoxy-group (30, 31) – which is necessary for the remaining synthetic steps – reveal different results. Presumably due to the steric hindrance of N-methyl group 31 did not provide the related tricyclic product (41c). Alternatively latter compound was prepared from 40c by methylation process.

Taking attempts to introduce the carbamoyl-function before the ring closure step we tried to alkylate 47 with the corresponding cyclic halogenides (51-53, Scheme 7.). However, instead of alkylated products (54-56) these reactions gave a rearranged compound (57) in each case, independently from the halogenides. Blind experiments – in which no alkylating agents were added to the car bamates - resulted in the same observation. This carbamate-carbamide transformation was extended to other substrates (48, 49) as well.
Concerning to our results rising from carbamate-carbamide transformation (Table 3.) this rearrangement is likely to occur in the case of aromatic substrates (47, 48).

Aliphatic carbamates show less transformation activity (59), or the anticipated carbonate is not present in the reaction mixture (60).

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R-group</th>
<th>Net. yield [%]</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>Ph-</td>
<td>74</td>
<td>57</td>
</tr>
<tr>
<td>48</td>
<td>α-naphthyl-ethyl-</td>
<td>60</td>
<td>58</td>
</tr>
<tr>
<td>49</td>
<td></td>
<td>17</td>
<td>59</td>
</tr>
<tr>
<td>50</td>
<td>cyclohexyl-</td>
<td>-</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 3.

Due to this unexpected transformation of our substrates we decided to prepare the target molecule based on known procedure of relevant publications. Thus 41c was demethylated and the resulted hydroxy-compound (62) was reacted with phenyl-isocyanate (63) to obtain the desired final compound 64.

![Scheme 8.](image-url)
4. Scaling-up the process of desloratadine and its CO$_2$ adduct

Our efforts to develop scalable experiments were based on previous patents$^{a,b}$ of EGIS Pharmaceuticals Plc. Having continued this work and had seen concurrent patents we found that the process for preparing desloratadine (3) could be improved further, by optimization (Scheme 9.). One of the relevant patents$^c$ narrows our scope regarding to the reaction media (ethanol) and the applied reaction temperature (boiling point).

Using steel autoclaves instead of glass vessels can provide solution by carrying out the hydrolytic step of loratadine (65) under pressure exceeding the boiling point of ethanol at atmospheric condition. As a result of the improved process the target molecule can be produced in high yield and reasonable purity (Table 8.).

In addition the amount of base applied for the hydrolysis can be reduced by 2/3 and at pilot scale the process can provide similar results than that of laboratory experiments.

The importance of desloratadine–CO$_2$ adduct, as a substrate of the desloratadine itself is marginal (in preparative manner), however excellent purity can be reached (Table 8.) using this technique.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Solvent</th>
<th>NaOH [mol equivalent]</th>
<th>Net. yield [%]</th>
<th>Purity (HPLC) [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>MeOH$^a$</td>
<td>10,5</td>
<td>94</td>
<td>99,8</td>
</tr>
<tr>
<td>65</td>
<td>EtOH$^c$</td>
<td>10,5</td>
<td>88,7</td>
<td>99,5</td>
</tr>
<tr>
<td>65</td>
<td>2-Methoxyethanol$^a$</td>
<td>6-7</td>
<td>91,5</td>
<td>99,1</td>
</tr>
<tr>
<td>65</td>
<td>EtOH</td>
<td>3,75</td>
<td>94, $96^a$</td>
<td>99</td>
</tr>
<tr>
<td>66</td>
<td>EtOH$^b$</td>
<td>-</td>
<td>63,0</td>
<td>99,8</td>
</tr>
<tr>
<td>66</td>
<td>EtOH</td>
<td>-</td>
<td>87$^e$</td>
<td>99,97</td>
</tr>
</tbody>
</table>

$^a$WO 2006003479; $^b$WO 2008050162; $^c$WO 2004029039; $^d$Pilot Scale, running from 1.5 kg loratadine; $^e$Improved process

Table 8.
5. The structure of desloratadine-CO$_2$ adduct

Previously our research group observed and described$^5$ an adduct (66) deriving from the reaction desloratadine and CO$_2$. To determine the exact structure of the crystalline product, we searched for relevant publications providing spectral information about similar amin-CO$_2$ adduct in solid and solution-state. These data give rise to the theory if the questioned structure is more likely to be a covalent compound (67) than molecular adduct. The unusually high stability and poor solubility data support this interpretation.

![Scheme 10.](image)

The solid state $^{13}$C-NMR spectrum of desloratadine-CO$_2$, and -$^{13}$CO$_2$ compounds are in agreement with the ammonium-carbamate structure.

However solvent-state measurements do not correspond with that of solid state observations. Evaluating the $^1$H-NMR-spectrum of 67 (CDCl$_3$) only a slight downfield shift can indicate the presence of CO$_2$ in the signals of piperidine ring. Heteronuclear correlated 2D NMR measurements did not reveal any bond formed between desloratadine and CO$_2$.

In our opinion this contradiction can be solved by presuming dynamic equilibrium in the solution between the amine (3), the CO$_2$, the water content of sample/solvent, the products (67, 68) and the hydrogen-carbonate anion. At the standard condition of NMR measurements we could only observe the sum of the signals, which can be misleading about the location of CO$_2$. Influencing this equilibrium (solvent or temperature effect) the components, even the free carbamic acid, (68) can be detectable giving the chance to identify the ammonium-carbamate structure indirectly in solution-state.
6. Theses

The benzene-fused imidacloprid analogue and one of its active metabolite have been prepared successfully. Investigating the ring-closure ability of the applied carbonic acid derivatives with different types of diamines at standard reaction condition, we declared that dimethyl nitrodithioimidocarbonate is the most effective agent.

Based on aza-Claisen type rearrangement we have synthesized one of the phenserine cyclopentanoindol derivatives. At the condition of aza-Claisen type rearrangement we have observed a spontaneous ring closure reaction leading to the desired tricyclic framework. This observation has been extended to cyclohexa- and cycloheptaindol derivatives.

Attempts to introduce carbamoyl-function into the molecule before the ring closure reaction have failed, however a carbamate-carbamide rearrangement has been described. This observation has been extended to other carbamates.

A scalable and patent-free process has been designed for preparing desloratadine and its ammonium-carbamate derivative. The target molecule can be synthesized in high yield and reasonable purity by this method.

We have determined the structure of desloratadine-CO$_2$ compound as an ammonium-carbamate derivative and we have stated that this salt participate in a system in equilibrium occurring in solvent phase. This observation has been supported by special NMR technique.
7. Publications:

   *Heterocycles* **2001**, *55*, 1, 45-58. IF: 0.970; FID: 8


3. Király I., Hornyánszky G., Kupai K., Novák L.: Synthesis of cycloalkanoindoles, the carba analogs of physostigmine
   *Heterocycles* **2008**, *75*, 1, 43-56. IF: 0.980; FID: 2

4. Mezei T., Volk B., Király I., Simig Gy.: A new Addition compound of desloratadine with carbon dioxide