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A new synthesis of indole 5-carboxylic acids and 6-hydroxy-indole-5-carboxylic acids in the preparation of an o-hydroxylated metabolite of vilazodone

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Abstract—A major metabolite of the potential antidepressant *vilazodone* formed in rat, dog, monkey and human liver microsomes is the 5-cyano-6-hydroxy-1*H*-indole derivative. For the construction of the salicyl-like substituted indole we adapted a synthesis of *carmoxirole* using Japp–Klingemann type Fischer-indole synthesis protocols. Functional group interconversion of carboxylic acid via carboxamide into cyanide was performed with methanesulfonic acid chloride.

The heterocycle indole as anchored in tryptophan and its derivatives is an important structural element in peptides and peptido-mimetics as well as in indole alkaloids and is usually difficult to replace by other heterocycles without loosing the desired biological activity. Besides 3-alkylated indoles, important natural products as well as xenobiotics contain further differently substituted indoles. Numerous indole syntheses are described in the literature and numerous reviews summarise the methods.[1] Indole derivatives are frequently found to be active in various classes of pharmacologically important compounds. *Roxindole* **1a**,[2] *carmoxirole* **1b**[3] and *vilazodone* **2**[4] are only a few examples of indole containing drug candidates from our laboratory that received some clinical interest (Fig. 1). We learned that small modifications of substituents on the indole nucleus can dramatically change the properties of such compounds. Whereas *roxindole* **1a** is a potent centrally acting dopamine agonist with considerable serotonin reuptake inhibition and agonist activity at the serotonin (5-HT) receptor subtype 1A, *carmoxirole* **1b** is a peripherally acting selective dopamine agonist. In contrast, *vilazodone* **2** devoid of any dopaminergic activity is a potential antidepressant with an innovative dual mechanism of action: 5-HT re-uptake inhibition and agonism at the 5-HT_{1A} receptor.[5] *Vilazodone* **2** is metabolised in rat, dog, monkey and human liver microsomes[6] to an unusual 6-hydroxy-5-cyano-indole compound **3** and we did not find any report of an *ortho*-hydroxylation adjacent to a similar aromatic nitrile function.[7] As in our hands this metabolic conversion

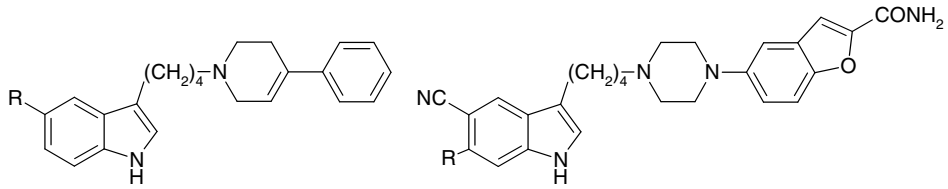

Figure 1. Pharmacologically interesting indole derivatives.

Keywords: Salicyl-substituted indoles; Japp–Klingemann; Fischer-indole synthesis.
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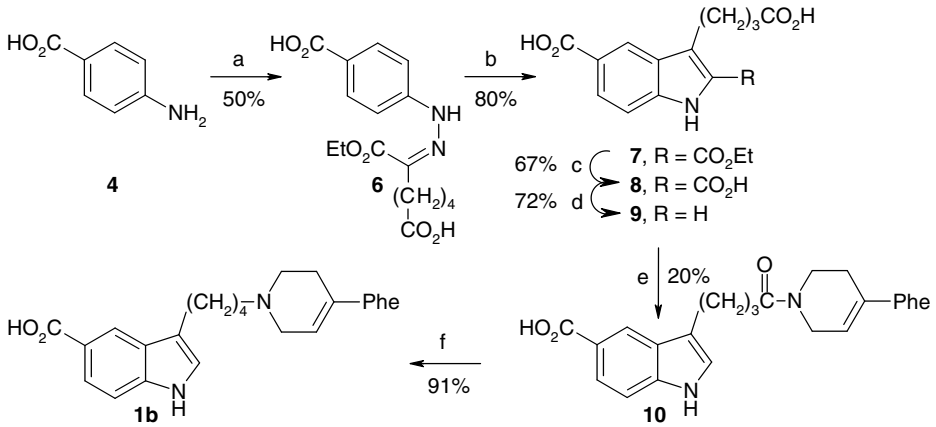
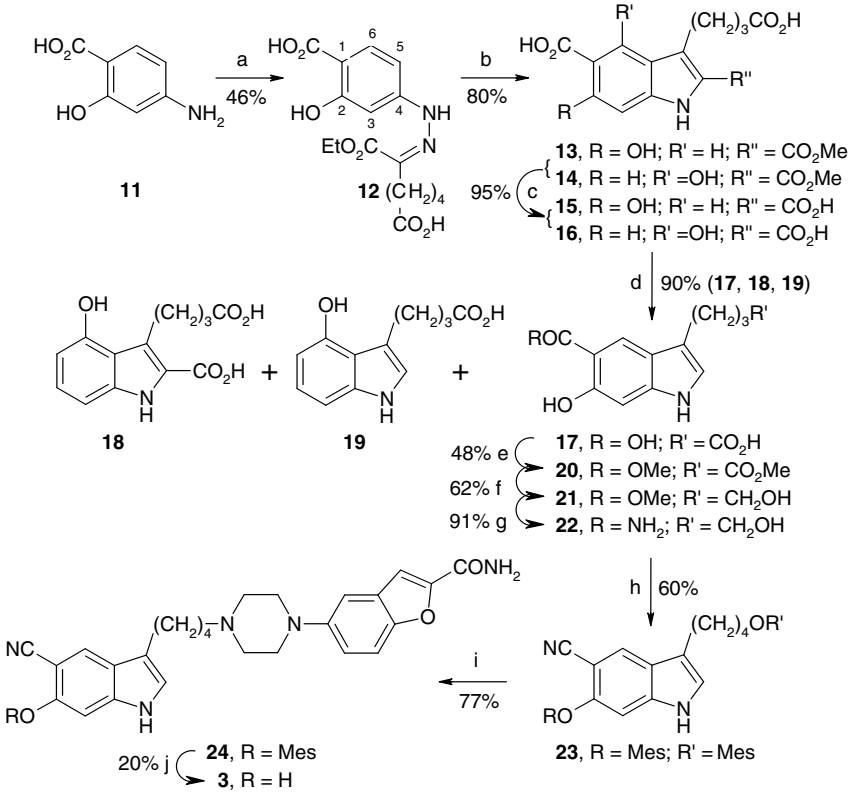


Scheme 1. Synthesis of *carmoxirole* **1b**. Reagents and conditions: (a) (i) **4**, HCl, $NaNO_2$, 0 °C; (ii) ethyl 2-oxo-cyclohexanone carboxylate **5**, H_2O, KOH; (b) CH_3CO_2H, H_2SO_4; 120 °C; (c) NaOH, H_2O, 80 °C; (d) KOH, H_2O; 280 °C; (e) CDI, 4-phenyl-1,2,3,6-tetrahydro-pyridin; (f) sodium-aluminium-bis-(2-methoxyethoxo)-hydride in toluene, THF.

could not be reproduced on a preparative scale by enzymatic or microbial systems, we had the task of producing this metabolite by chemical means. Therefore we were obliged to find a suitable synthetic pathway to this vicinal arrangement of a nitrile and a hydroxy function to be able to confirm the postulated structure of metabolite **3** of *vilazodone* **2** (Fig. 1). Furthermore we had to secure a sufficient supply of the compound as reference for the further clinical development of *vilazodone*.

Our synthetic approach was the adaptation of a synthesis of *carmoxirole* **1b**[3b] employing the Japp–Klingemann type Fischer-indole synthesis as described previously for the synthesis of *roxindole* **1a**.[2f] The indole-5-carboxylic acid derivatives could be prepared as indicated in Scheme 1. At first commercially available 4-amino benzoic acid **4** without further protection of the carboxylic acid was diazotised and reacted under alkaline conditions with ethyl-2-oxo-cyclohexanone carboxylate **5** according to Japp–Klingemann to form the ring open hydrazone **6**.[8] This hydrazone could be transferred into the 1*H*-indole-2,5-dicarboxylic acid-2-ethyl ester **7** by treatment with sulfuric acid in glacial acetic acid. The remaining ester group was saponified under basic conditions to the tri-carboxylic acid **8**. When heating an aqueous solution of equivalent amounts of potassium hydroxide and **8** for 6 h to 280 °C in an autoclave selective decarboxylation occurred in position 2 of the indole **9** leaving the other carboxylic acid residues intact. Compound **9** was converted into the monoamide **10** with carbonyl diimidazole (CDI) and 4-phenyl-1,2,3,6-tetrahydro-pyridine (with traces of the isomer 4-[5-(4-phenyl-3,6-dihydro-2*H*-pyridine-1-carbonyl)-1*H*-indol-3-yl]butanoic acid as by-product). After chromatographic purification **10** was reduced with sodium-aluminium-bis-(2-methoxy-ethoxo)-dihydride in 3% overall yield to the selective dopaminergic autoreceptor agonist *carmoxirole* **1b**.

This procedure was modified subsequently to construct the desired 5-cyano-6-hydroxy indole metabolite **3** of *vilazodone* **2** starting with readily available 4-amino-salicylic acid (**11**) again without using any protection of the carboxylic acid and adjacent hydroxy function. To obtain the 5-cyanoindole substitution of *vilazodone* we planned to transfer the carboxylic acid in two steps into the cyano-group (Scheme 2).[9] The indole was prepared according to the Japp–Klingemann procedure as described above. During the indole ring formation besides the desired 6-hydroxy indole **13** the 4-hydroxy isomer **14** was formed by cyclisation to position 3 of the aryl hydrazone **12**. On a 2 kg scale a 6:1 mixture of the isomers **13** and **14** could be detected by ^1H NMR. The 6-hydroxy derivative **13** shows in DMSO-d_6 two distinct singlets at 8.26 and 6.80 ppm whereas the 4-hydroxy isomer **14** gives rise to two doublets at 7.58 and 6.91 ppm and a vicinal coupling constant of 8.8 Hz. As it was not possible to purify the mixture on this stage of synthesis, the two subsequent steps (c, d) were performed with the mixture of 4- and 6-hydroxy indole (**13/14**). After the usual ester hydrolysis to the tri-acids **15/16**, surprisingly the decarboxylation proceeded differently for the two isomers. The 6-hydroxy indole isomer **15** reacted as previously observed with compound **8**: the CO_2 cleavage was faster in position 2 than in position 5. In contrast, for the 4-hydroxy derivative **16**: the decarboxylation proceeded faster in position 5 than in position 2.[10] After purification by acid/base separation and chromatography the intermediate **17** was isolated. Traces of the 4-hydroxy-2-carboxylic acid **18** and the 4-hydroxy indole **19** could also be collected. Subsequently the desired di-acid **17** was transferred into the corresponding di-methyl ester **20** and the aliphatic ester group was reduced selectively to the alcohol **21** by reduction with lithium aluminium hydride, leaving the aromatic ester function intact. We decided to form the cyano-group at this stage to avoid selectivity problems after coupling of the indole moiety to the basic 5-piperazin-1-yl-benzofuran-2-carboxamide building block having another competing carboxylic group. The methyl ester **21** was stirred in aqueous ammonia over night forming the amide **22** in quantitative yield. Several reagents were tested to eliminate water from the amide to generate the nitrile **23**. Methanesulfonic acid chloride gave the best results.[11] To accomplish complete water cleavage we had to use an excess of 10 equiv of methanesulfonic acid chloride. This excess led in turn to simultaneous activation of the alkyl



Scheme 2. Synthesis of metabolite **3**. Reagents and conditions: (a) (i) **11**, HCl, $NaNO_2$, 0 °C; (ii) ethyl 2-oxo-cyclohexanone carboxylate **5**, H_2O, KOH; (b) CH_3CO_2H, H_2SO_4; 120 °C; (c) NaOH, H_2O, 80 °C; (d) KOH, H_2O; 280 °C; (e) MeOH, cat. H_2SO_4; (f) $LiAlH_4$, THF; (g) MeOH, NH_3–H_2O (25%); (h) DCM/THF, $MeSO_2Cl$, TEA, 0 °C to rt; (i) 5-piperazin-1-yl-benzofuran-2-carboxamide, NMP, 120 °C; (j) KOH, MeOH.

alcohol and protection of the aromatic 6-hydroxy-function on the indole as di-mesylate **23**. Alkylation of 5-piperazin-1-yl-benzofuran-2-carboxamide with this di-mesylate **23** led to precursor **24**. In the final step selective cleavage of the remaining 6-indolyl mesylate by potassium hydroxide in methanol and usual work-up gave the free base of **3** in 0.8% overall yield.[12]

With the application of the Japp–Klingemann indole synthesis, starting off with unprotected 4-amino salicylic acid, we were able to prepare for the first time substantial amounts of the unusual hydroxylated metabolite of *vilazodone*. This hydroxylation led to a significant decrease in the important dual activity profile of *vilazodone*. Furthermore, it could be shown, that the decarboxylation of indole-2-carboxylic acids depends on the substitution pattern of the indole nucleus. Besides the selective decarboxylation several alkaline steps could be performed successfully to distinguish the different aliphatic and aromatic hydroxy and acid functions. Efforts are ongoing in our group to prepare further indole derivatives with an aromatic substitution pattern as found in salicylic acid.

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7. For 6-methoxy-1*H*-indolyl-5-carboxamides see, for example: Mavunkel, B. J.; Chakravarty, S.; Perumattam, J. J.; Luedtke, G. R.; Liang, X.; Lim, D.; Xu, Y.-j.; Laney, M.; Liu, D. Y.; Schreiner, G. F.; Lewicki, J. A.; Dugar, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3087.

8. It is possible to separate the hydrazone isomers by fractioned crystallisation from acetonitrile.
9. Two reasons have to be mentioned why the functional group interconversion was set about at the end: (1) the experience with the above described synthesis of *carmoxirole* indicated that the 5-carboxylic acid is well suited for the whole syntheses and (2) we expected cyano hydrolysis during the Fischer-indole synthesis because of the harsh acidic conditions; for less harsh conditions see: Gorohovsky, S.; Meir, S.; Shkoulev, V.; Byk, G.; Gellerman, G. *Synlett* **2003**, *10*, 1411–1414.
10. We tried the decarboxylation of the mixture under microwave irradiation conditions, too, hoping that the ratio for the 4-hydroxy compound could be inverted but these conditions had no effect on the reaction's outcome.
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12. **3** ^{1}H NMR (DMSO-d_6) δ 10.96 (br s, 1H); 10.62 (br s, 1H); 10.33 (br s, 1H); 8.09 (br s, 1H); 7.81 (s, 1H); 7.65 (br s, 1H); 7.54 (d, 1H; $J = 8.9$ Hz); 7.46 (s, 1H); 7.27 (d, 1H; $J = 1.8$ Hz); 7.22 (dd, 1H; $J = 8.9$ Hz; $J = 2.3$ Hz); 7.12 (d, 1H; $J = 1.8$ Hz); 6.95 (s, 1H); 3.75 (br d, 2H; $J = 8.2$ Hz); 3.68 (br d, 2H; $J = 5.8$ Hz); 3.41 (s, 4H); 2.69 (br t, 2H; $J = 7.3$ Hz); 1.79 (m, 2H); 1.66 (m, 2H); mp: 307 °C, decomp.