Chapter 4

A benzo[f]quinoline enone prodrug and its corresponding catecholamine

Abstract

As described in Chapter 2, enone prodrugs of dopaminergic catecholamines represent a new type of prodrug in research on dopamine (DA) agonists. In this chapter, the extension of this prodrug concept to benzo[f]quinoline, trans-4-propyl-1,3,4,4a,5,6,8,9,10,10b-decahydrobenzo[f]quinolin-7(2H)-one \( \text{(4.1a)} \) was investigated, together with the corresponding catecholamine trans-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol \( \text{(1.27d)} \) which is known as a potent, centrally acting DA agonist. The microdialysis experiments of \((-)\) enantiomer of the enone \( \text{(4.1a)} \) and the racemic catecholamine \( \text{(1.27d)} \) demonstrated the dopaminergic activity after both \textit{sc} and \textit{po} administration.

This chapter is based on the work of Danyang Liu, Jan de Vries, Durk Dijkstra and Håkan Wikström in Groningen University; Dr. Claus T. Christoffersen, Division of Molecular and Cellular Pharmacology, Lundbeck A/S.
4.1 Introduction

Dopamine (DA) agonists have attracted considerable attention in the treatment of Parkinson’s disease (PD) due to their longer duration of action when compared to L-dopa. In addition, some of the DA agonists have been studied for their potential use as neuroprotective agents. DA agonist activities can be found in several classes of compounds including the 2-phenylethyl amines, apomorphine, aminotetralins, naphthoxazines, and ergoline derivatives. We have reported in Chapter 2 that the benzo[g]quinoline derived enone trans-1-propyl-2,3,4,4a,5,7,8,9,10,10a-decahydrobenzo[g]quinoline-6(1H)-one (GMC-6650, trans-1.2a), which did not show dopaminergic activity in vitro, induced DA agonistic effects in vivo and the active form is the corresponding catecholamine trans-N-(n-propyl)-6,7-di-OH-benzo[g]quinoline (TL-334, trans-1.26d). It is of interest to extend this prodrug concept to the benzo[f]quinoline (4.1a). Its corresponding catecholamine trans-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol (1.27d) is known as a potent, centrally acting DA agonist for decades.

![Chemical Structures](image)

**Figure 4.1** Structures of enones and their corresponding catecholamines: (S)-PD-148903 (2.1) and 5,6-di-OH-DOPAT (1.24); GMC-6650 (2.2a) and TL-334 (1.26d); benzo[f]-quinoline enone 4.1a and 1.27d.

In 1.27d, the DA moiety is incorporated in the rigid framework in a more coplanar arrangement, which is believed to be necessary for certain central and peripheral dopaminergic effects. The cis isomer (cis-1.27d) is a flexible molecule and it can exist in a conformation which is believed not to favor dopaminergic activity (Figure 4.2).
cis-1.27d and 1.27d were studied in some animal models years ago. It was found that trans isomers of this series of derivatives of dihydroxyoctahydrobenzo[f]quinoline (R=H, Me, Et, propyl, see 1.27a-d in Chapter 1) were effective dopaminergic agents whereas the cis isomers were inactive. All trans series were found more potent than apomorphine as emetic agents in dogs and N-propyl derivative showed to be the most potent one.12

These results support the hypothesis that central DA receptors prefer flat molecules. Assuming that both the cis and trans compounds are in their preferred conformations, both the isomers have their nitrogen atom approximately same distance from the plane of the aromatic ring (Dreiding model), thus, one explanation for the difference in potency between the cis and trans isomers could be steric interaction between the piperidine ring of the cis isomer and the DA receptors.14

Figure 4.2 The trans- and cis- conformation of 1.27d.

Concerning the enone compounds, (S)-PD-148903 (2.1) and GMC-6650 (2.2a), we have found that the corresponding catecholamines (1.24 and 1.26d) might be formed when administrated in vivo. Therefore, the investigation of 1.27d is also important for the in vivo study of 4.1a. In this chapter, both enone (4.1a) and the corresponding catecholamine (1.27d) were synthesized and pharmacologically evaluated by microdialysis.

4.2 Chemistry

4.2.1 Synthesis of trans-4-propyl-1,3,4,4a,5,6,8,9,10,10b-decahydrobenzo[f]quinolin-7(2H)-one (4.1a)

The synthesis of trans isomer 4.1a and cis isomer 4.1b is outlined in Scheme 4.1.
Scheme 4.1 The synthesis of cis- and trans isomers of 4.1. Reagents and conditions: a) NaOH/MeOH, 0°C; acrylonitrile, MeOH/H2O/2N HCl, 85°C to 100°C; b) Raney-Ni, MeOH, RT; c) PtO2, CH3OOH, 35 bar H2, 50°C; d) Jones' regent, acetone, RT; e) Br(Ph3P')(CH2)3CO2Et, t-BuOK, DMF, 0°C, 4h, RT 24 h; f) PPA, 100°C, 3h; g) 1-iodopropane, DMF, RT.

The sodium salt of 1,3-cyclohexanedione (4.2) was converted to the nitrile 4.3 via a Michael addition to acrylonitrile. The catalytic reduction of 4.3 with Raney-Ni would give the primary amine as intermediate. However, under the used reaction conditions, condensation with one of the keto groups occurred and after dehydration the octahydroquinolinone 4.4 had been formed. This enone underwent a second catalytic reduction to the amino alcohol 4.5 with PtO2 under 35 bar H2 at 50°C. A mixture of three diastereomers was obtained. It was unnecessary to separate these diastereomers because in the next step oxidation of the alcohol to the ketone 4.6 by Jones’ reagent would reduce the number of asymmetric centers in the molecule. The third ring (C) was constructed by the introduction of a C4 moiety to octahydroquinolinone 4.6 through a Wittig reaction. Although there was Ph3PO involved together with products, it was no problem to use this mixture for next step. By GC it was found that two products were
formed, probably a mixture of $E$ and $Z$ isomers (4.7). This mixture was used without further purification in the final ring closure with polyphosphoric acid (PPA) at 100°C.\textsuperscript{20} The separation of the trans (4.8a) and cis (4.8b) isomers of 4.8 was performed by column chromatography. These two isomers were obtained in a ratio 3:2. The final products 4.1a and 4.1b were obtained by alkylation from 4.8a and 4.8b, respectively. Racemic 4.1a was separated into their enantiomers (referred as (−)-4.1a and (+)-4.1a) by semi-preparative chiral HPLC with a Chiral AD column.

4.2.2 Synthesis of trans-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol (1.27d)

The compound trans-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol (1.27d) was synthesized by the following strategy.

The intermediate 5,6-dimethoxy-2-tetralone (4.9) was prepared via two pathways. In the first synthetic route described in Scheme 4.2, β-tetralone 4.9 was obtained from 6-trimethoxynaphthalene (3.2) by Birch reduction and acid hydrolysis of the intermediate enol ether.\textsuperscript{21}

\begin{center}
\textbf{Scheme 4.2} The first synthetic route of β-tetralone 4.9. Reagents and conditions: a) NaOCH\textsubscript{3}, CuI, 2,4,6-trimethylpyridine; b) Na, C\textsubscript{2}H\textsubscript{5}OH, H\textsubscript{2}O, 36\% HCl.
\end{center}

Disadvantages of this pathway were that the preparation of trimethoxynaphthalene 3.2 from the di-bromo compound 3.1 gave variable yields (50\%-80\%).\textsuperscript{22} Therefore, an alternative was applied in an attempt to improve the overall yield (Scheme 4.3).\textsuperscript{23} It started from 2-hydroxy-3-methoxybenzaldehyde (4.10).\textsuperscript{24, 25, 26} After methylation,\textsuperscript{27} condensation and hydrogenation, the reduced di-methoxy cinnamic acid (4.13) was formed in an overall yield of 71\%. The propionic acid 4.13 was converted to the corresponding acid chloride 4.14 with thionyl chloride in high yield, followed by a reaction with diazomethane to the α-diazo ketone 4.15.\textsuperscript{28, 29} The next step in this route was the crucial conversion of α-diazo ketone 4.15 to 6-dimethoxy-2-tetralone (4.9), which was formed via a rhodium(II) acetate catalyzed cycloaddition.\textsuperscript{30, 31}
A benzo[f]quinoline enone prodrug and its corresponding catecholamine

Scheme 4.3 The second synthetic route of β-tetralone (4.9). Reagents and conditions: a) (CH₃)₂SO₄, KOH, 50°C; b) CH₂(COOH)₂, pyridine, piperidine, 80°C, reflux 4 h; c) 10% Pd/C, H₂, RT; d) SOCl₂, benzene, reflux 4 h; e) CH₂N₂, Et₂O, 5°C, RT overnight; f) [Rh(CH₃COO)₂]₂, CF₃COOH, DCM, 0.5 h.

During this reaction a cyclopropanated tricyclic intermediate has formed. 32 Under acidic conditions this intermediate rearranged to the desires tetralone. In the presence of p-TsOH, the aza-annulation of β-tetralone pyrrolidine enamine 4.16 with acrylamide gave the corresponding enamide 4.17. 12, 33 The benzylation of enamide 4.17 was performed with NaH in dimethoxyethane (DME) under reflux. After reduction of the lactam 4.18 with LiAlH₄, enamine 4.19 was formed, which was reduced with NaBH₃CN, 34 to obtain the stable benzylated octahydrobenzo[f]quinoline 4.20. The separation of cis- and trans-4.20 was performed by column chromatography. After de-benzylation under a 25 psi H₂ pressure with 10% Pd/C, the amine trans- and cis-4.21 were obtained. The propyl group was introduced to the amine 4.21 and formed trans- and cis-4.22. After hydrolysis with 48% HBr under reflux, the final diols trans- and cis-1.27d were obtained.
Scheme 4.4 The synthesis of trans- and cis-1.27d. Reagents and conditions: a) pyrrolidine, benzene, reflux, 3 h; b) acrylamide, 80°C, 1 h; c) NaH, C₆H₅CH₂Br, DME, reflux, 6 h; d) LiAlH₄, THF, reflux, 6 h; e) NaBH₃CN, MeOH, CH₃COOH, RT, overnight; f) 10% Pd/C, CH₃OH, 25 psi H₂, RT, overnight; g) CH₃CH₂CHO, DCM, NaBH₄, RT; h) 48% HBr, reflux.
4.3 Pharmacology

4.3.1 In vitro functional assay

A DA D₁ functional assay on stimulation of cAMP production in CHO cells stably expressing the human recombinant D₁ receptor was performed to investigate whether both enantiomers of 4.1a and both trans- and cis-1.27d isomers have any agonist at the D₁ receptor. To determine the activity at the DA D₂ receptor, a DA D₂ functional assay was performed on inhibition of cAMP production in CHO cells transfected with the human D₂ receptor.

4.3.2 In vivo pharmacology

The potential pharmacological effects of both enantiomers of 4.1a and both trans- and cis-1.27d isomers were studied by measuring their effects on extracellular DA levels in the corpus striatum, the brain area of interest in PD, using microdialysis in freely moving rats. The details were described in Chapter 2.

4.4 Results and discussion

4.4.1 In vitro functional assay

From Table 4.1 it can been seen that the forskolin-stimulated cAMP accumulation was inhibited by trans-1.27d in CHO cells transfected with the human D₂ receptor, with an EC₅₀ of 1.2 nM, causing a maximal inhibition. Meanwhile, a stimulation of forskolin-stimulated cAMP accumulation in CHO cells stably expressing the human recombinant D₁ receptor was found, with an EC₅₀ of 63 nM, causing an almost maximal stimulation.

The result of the functional assay showed that trans-1.27d is a full DA agonist on both D₁ and D₂ receptor subtypes, and it showed selectivity for the DA D₂ receptor over the D₁ receptor. Cis-1.27d showed weak D₁ activity (EC₅₀ 420 nM) and mild partial D₂ agonist activity (EC₅₀ of 44 nM). Both enantiomers of 4.1a were found no D₁ either D₂ receptor activity via cAMP accumulation assay.
Table 4.1 In vitro receptor functional assay (% intrinsic activity (EC\textsubscript{50} nM)) of both enantiomers of 4.1a, trans and cis 1.27d.

<table>
<thead>
<tr>
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<th>( \text{D}<em>1 \text{ EC}</em>{50} \text{ (nM)}^d )</th>
<th>IA (^c)</th>
<th>( \text{D}<em>2 \text{ EC}</em>{50} \text{ (nM)}^b )</th>
<th>IA</th>
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<tbody>
<tr>
<td>((-)-4.1a)</td>
<td>&gt;10000</td>
<td>-</td>
<td>&gt;10000</td>
<td>-</td>
</tr>
<tr>
<td>((+)-4.1a)</td>
<td>&gt;10000</td>
<td>-</td>
<td>&gt;10000</td>
<td>-</td>
</tr>
<tr>
<td>trans 1.27d</td>
<td>63</td>
<td>90%</td>
<td>1.2nM</td>
<td>100%</td>
</tr>
<tr>
<td>cis 1.27d</td>
<td>420</td>
<td>90%</td>
<td>44nM</td>
<td>58%</td>
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</table>

\(^a\): DA D\(_1\) functional assay on stimulation of cAMP production in CHO cells; \(^b\): DA D\(_2\) functional assay on inhibition of cAMP formation in CHO cells transfected with the human D\(_2\) receptor. \(^c\): IA: intrinsic activity; \(^d\): EC is the concentration (± S.D.) producing a half-maximal response.

4.4.2 In vivo microdialysis study

4.4.2.1 In vivo microdialysis of 4.1a

Both enantiomers of 4.1a were found to display no dopaminergic activity in vitro, however, biochemical experiments in vivo indicate that \((-\)-4.1a) was converted to a DA agonist.

Figure 4.3 showed that sc administration of racemic 4.1a. The 1 µmol/kg dose sc induced significantly decreased DA levels 45 min post-administration (p<0.05). A maximum decrease to 40% of basal values was found after 1.5 h. The decreased DA levels returned to basal levels after 3.5 h.

![Figure 4.3](image-url)

**Figure 4.3** Effect of (±)-4.1a (1 µmol/kg s.c, ■ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats (* p<0.05).
A benzofquinoline enone prodrug and its corresponding catecholamine

The results of microdialysis study of po and sc administration of (−)-4.1a are shown in Figure 4.4 and 4.5. Orally administration of 100 nmol/kg dose of (−)-4.1a did not affect the DA levels. After 1 h, 1000 nmol/kg po administration of (−)-4.1a induced DA decrease to 60% of basal levels. After 3 h, the DA release returned to basal levels.

Figure 4.4 Effect of (−)-4.1a (100, 1000 nmol/kg po, ◆ and ■ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats (* p<0.05).

Figure 4.5 showed that sc injection of (−)-4.1a in a dose of 100 nmol/kg did not modify DA release. After administration of dose 1000 nmol/kg by sc, a significant DA decrease to 40% of basal levels was observed after 75 min. The total decrease of DA release maintained for 4 h and after this period, the DA release slowly returned to basal levels. The sc administration of (+)-4.1a did not affect DA release. Apparently this enantiomer does not possess activity or is not converted to the catecholamine (1.27d).

Figure 4.5 Effect of (−)-4.1a (100, 1000 nmol/kg sc, ◆ and ■ resp.) and trans (+)-4.1 (1000 nmol/kg sc, ♦ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats (* p<0.05).
During the microdialysis experiments the rats did not display obviously stereotyped behaviour, like yawning, sniffing, penile grooming and locomotor activity.\textsuperscript{36, 37, 38}

4.4.2.2 In vivo microdialysis of 1.27d

Racemic 1.27d was administered to male Wistar rats \textit{sc} (10 nmol and 100 nmol/kg, Figure 4.6) or \textit{po} (100 nmol/kg, 1000 nmol/kg and 10 µmol/kg, Figure 4.7).

The results in Figure 4.6 showed a significant decrease in DA release after 100 nmol/kg \textit{sc} administration. After administration of 10 nmol/kg \textit{sc} no decrease of DA release was seen, but in contrast, an increase of DA release was observed. The maximum increase reached to 200% of basal DA levels. Comparing these two series (10 and 100 nmol/kg), it was found the shape of the lines in the figure was quite similar. During the experiment of 100 nmol/kg \textit{sc}, 1.27d also induced post-synaptic activity like sniffing, rearing and licking, which was consistent with the effects of a centrally acting DA agonist.

![Diagram](image)

**Figure 4.6** Effect of 1.27d (10 and 100 nmol/kg \textit{sc}, ◆ and ■ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats (* p<0.05).

Oral administration of 1.27d did not show the same potency as \textit{sc} administration (Figure 4.7).

The \textit{po} administration of 100 nmol/kg dose did not display any dopaminergic activity. A slight DA decrease to 80% of basal levels was shown 1 h post-administration of 1µmol/kg dose. The DA levels returned to basal levels after 3.5 h. The orally administration of 10 µmol/kg induced a significant decrease of DA release, which reached to 40% of basal levels and lasted for more than 4 h, and also showed a very strong stereotyped behaviour.
Figure 4.7 Effect of $1.27d$ (100 nmol/kg, 1 µmol/kg and 10 µmol/kg po, ◆, ■ and ▲ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats (* p<0.05).

sc Administration of cis-$1.27d$ is shown in Figure 4.8. As expected, the cis isomer of $1.27d$ did not show any effect on a striatal DA release.

Figure 4.8 Effect of cis-$1.27d$ (100 nmol/kg s.c. ■ resp.) on striatal DA release in freely moving rats. The results are the mean (± SEM) of data obtained from 4 rats.

From these results, it showed that $1.27d$ is a potent DA agonist. Due to the presence of catechol moiety in $1.27d$, sc administration was more efficient than po.
4.5 Conclusions

The lack of affinity of both enantiomers of 4.1a observed \textit{in vitro} and the dopaminergic effects of (−)-4.1a \textit{in vivo}, indicates a bioactivation mechanism similar to that of (−)-2.1 and its close analogues. In microdialysis experiments, (−)-4.1a is active at the dose of 1000 nmol/kg \textit{sc} as well as \textit{po}. Although the activities after both routes of administrations are weaker when compared with GMC-6650 (2.2a, see Chapter 2), the bioactivity of (−)-4.1a is more pronounced than the corresponding catecholamine 1.27d, which is potent at 100 nmol/kg \textit{sc}, but shows low activity until a 1000 nmol/kg when orally administration. It is interesting to note that the lower dose of 1.27d administered \textit{sc} (100 nmol/kg) induced an increase of DA release. A similar phenomenon was found for a low dose of (−)-4.1a (100 nmol/kg) after orally administration. This is difficult to explain. The reason for the increase of DA is unclear. The effect of 1.27d observed in this model after the administration of 1000 nmol/kg \textit{po} is stronger than that induced by apomorphine (1.23) which decreased DA release until 10 µmol/kg when administrated orally.

These properties suggest that (−)-4.1a is an interesting candidate for development into a drug to improve the symptoms of PD.

4.6 Experimental section

4.6.1 Chemistry

\textbf{General}. General conditions see Chapter 2 for details.

\textbf{Materials}. All the reagents and solvents were commercially available and were used without further purification with the exception of DMF, which was distilled from P2O5 and dried over 4Å molecular sieves; THF, which was distilled from sodium/bezophenone and dried on sodium wire; HBr 48% water solution, which was distilled and used freshly.

4.6.1.1 Chemistry of 4.1a and 4.1b

\textit{3-(2,6-Dioxocyclohexyl) propanenitrile (4.3).}^{15} \text{NaOH (7.86 g, 196.5 mmol)} was added to methanol (60 mL) and the suspension was heated at reflux for 0.5 h. After filtration of this hot solution, the resulting filtrate was cooled to 0°C, followed by the addition of 1, 3-cyclohexanedione (4.2) (21 g, 187.5 mmol). The formed red solution was stirred for a further 0.5 h at 0°C and was evaporated \textit{in vacuo}. Hot acetone (100 mL) was added to the
residue and the suspension was cooled down to precipitate sufficiently. After filtration, a light yellow solid was obtained (25 g, 98% yield). Mp.: 49-52°C.

The sodium salt (25 g, 185.2 mmol) was dissolved in a mixture of methanol (25 mL), distilled H2O (1 mL) and 2N HCl (1 mL) while stirring. Acrylonitrile (70 mL) was added slowly. The reaction was stirred at 85°C for 1 h and refluxed for 30 min. After the reaction was cooled to RT, acetone (100 mL) was added, and the solid was precipitated and filtrated, followed by the washing with acetone twice, dried in vacuo. Mp.: 206-208°C (lit. 204-206°C15). The dried crystals were dissolved in H2O (50 mL) at 0°C and the solution was adjusted to pH=2 with conc. HCl. This mixture was extracted with CH2Cl2 (3 x 50 mL), washed with brine (3 x 15 mL), dried over MgSO4. After filtration and evaporation, a white solid 4.3 was obtained (14 g, 46% yield). Mp.: 113-115°C (lit. 116-118°C15). 1H-NMR (CDCl3) δ 1.92-2.05 (m, 2H), 2.42-2.57 (m, 6H), 2.59-2.70 (m, 2H) ppm; 13C-NMR (CDCl3) δ 203.5, 111.2, 57.4, 35.8, 19.1, 16.6, 14.5 ppm; MS (EI) m/z 165 (M+).

2,3,4,6,7,8-Hexahydro-5(1H)-quinolinone (4.4).15 4.3 (13 g, 78.8 mmol) was dissolved in methanol (200 mL) and Raney-Ni (12 g) was added in portions. The hydrogenation took place under 2 bar H2 at RT overnight. The suspension was filtered over Celite® and the filtrate was evaporated in vacuo to give a yellow oil which was crystallized from acetone (50 mL) to yield 7 g of white crystals 4.4 (60% yield). Mp.: 127-128°C (lit. 125-126°C15). 1H-NMR (CDCl3) δ 5.30 (br, 1H); 3.28 (m, 2H); 2.29 (m, 6H); 1.90 (m, 2H); 1.78 (m, 2H) ppm; 13C-NMR (CDCl3) δ 192.7, 157.7, 130.3, 40.0, 34.9, 27.8, 20.2, 19.6, 17.5 ppm; MS (EI) m/z 151(M+).

Decahydro-5-quinolinol (4.5).16 4.4 (1.9 g, 12.6 mmol) dissolved in acetic acid (6 mL), was hydrogenated for 3 days at 50°C with H2 (35 bar) and PtO2 (180 mg) as catalyst. The mixture was filtered over Celite® and the filtrate was evaporated to obtain a white solid. Aqueous 4N NaOH solution was added to the solid until pH >10 and the slurry was extracted with CH2Cl2 (5 x 20 mL), washed with brine (3 x 10 mL), dried over MgSO4. The solvent was filtered and evaporated in vacuo to afford a light yellow oil 4.5 (1.45 g, 75% yield), which was a three components isomeric mixture indicated by GC analysis. This mixture was used in the next step without further purification.
Octahydro-5(1H)-quinolinone (4.6). Jones’ reagent (3.6 mL) was added rapidly to a stirred solution of 4.5 (850 mg, 5.48 mmol) in warm acetone (150 mL). The resulting mixture was stirred at RT for 1 h. Iso-propyl alcohol (2 mL) was added dropwise to the suspension until the excess Jones’ reagent was reduced. Aqueous 1N NaOH solution was added (pH > 9), and the suspension was evaporated in vacuo to remove acetone. Additional water (5 mL) was added to the remaining residue, which was extracted with CHCl₃ (6 x 40 mL), washed with brine, dried over MgSO₄. A solid 4.6 was obtained (600 mg, 72% yield) which was used in the next step without further purification. ¹H-NMR (CDCl₃) δ 2.99 (m, 1H), 2.27-2.57 (m, 5H), 1.57-2.26 (m, 7H), 1.17-1.45 (m, 2H) ppm; ¹³C-NMR (CDCl₃) δ 209.2, 60.6, 53.4, 44.9, 39.6, 31.1, 24.1, 22.1, 21.7 ppm; MS (EI) m/z 153 (M⁺).

Ethyl 4-octahydro-5(1H)-quinolinylidenebutanoate (4.7). To a cooled (0°C) suspension of t-BuOK (660 mg, 5.9 mmol) in dry DMF (4 mL) under N₂ was added dropwise a solution of (3-ethoxycarbonylpropyl)-triphenyl phosphonium bromide (3.75 g, 8.2 mmol) in dry DMF (20 mL). When the addition was completed, the mixture was stirred at 0°C for 30 min. A solution of 4.6 (570 mg, 3.7 mmol) in dry DMF (4 mL) was added dropwise at 0°C. After the reaction was stirred at 0°C for 4 h, it was allowed to rise to RT and the stirring was continued overnight. While cooling, water (60 mL) was added to the reaction, and the obtained slurry was extracted with n-hexane (6 x 50 mL). The combined organic layers were washed with brine (3 x 15 mL) and dried over MgSO₄. The solvent was filtered and evaporated in vacuo to give a solid 4.7 (800 mg) which contained according to GC analysis 30% Ph₃PO. The mixture was used directly for the next step.

1,3,4,4a,5,6,8,9,10,10b-Decahydrobenzo[f]quinolin-7(2H)-one (4.8a, b). The solid 4.7 (800 mg) was dissolved in CH₂Cl₂ (2 mL) and this solution was added to PPA (6 g) at 100°C while stirring. After stirring at 100°C for 4 h, the reaction mixture was allowed to cool to 80°C, then crushed ice 30 g was slowly introduced. The solution was cooled to RT and extracted with ether to remove the containing Ph₃PO. The water layer was neutralized with ammonia aqua solution (25%) until pH=8. The solution was extracted with CH₂Cl₂ (5 x 50 mL). The combined dichloromethane layers were washed with brine (3 x 10 mL) and dried over MgSO₄. The solvent was filtered and evaporated in vacuo, and the obtained residue was purified by column chromatography.
A benzo[\ff]quinoline enone prodrug and its corresponding catecholamine (Al\textsubscript{2}O\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{2}/methanol, gradient). The first fraction was obtained as a light yellow oil (136 mg, 18% yield over two steps) which was identified as the trans isomer 4.8a. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ 3.39-3.45 (dt, 1H, \textit{J} = 1.9 Hz, \textit{J} = 11.7 Hz), 2.46-2.90 (m, 3H), 2.18-2.42 (m, 6H), 1.80-2.08 (m, 6H), 1.12-1.32 (m, 2H) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) δ 197.9, 155.5, 130.2, 57.6, 45.4, 44.8, 35.9, 27.5, 26.2, 25.0, 25.4, 21.0, 20.8 ppm; MS (EI) m/z 205 (M\textsuperscript{+}). HRMS 205.14758 (obsd). calcd for C\textsubscript{13}H\textsubscript{19}NO 205.14666. The second fraction was identified as cis isomer 4.8b (90 mg, 12% yield over two steps). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ 3.04 (dt, 1H, \textit{J} = 3.2 Hz, \textit{J} = 9.0 Hz), 2.69-2.97 (m, 2H), 2.09-2.56 (m, 8H), 1.85-2.04 (m, 3H), 1.68-1.81 (m, 2H), 1.42-1.61 (m, 3H) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) δ 197.7, 156.7, 130.2, 50.5, 41.2, 39.5, 36.3, 27.6, 24.7, 23.5, 23.1, 21.1, 19.3 ppm; MS (EI) m/z 205 (M\textsuperscript{+}).

\textit{trans}-4-Propyl-1,3,4,4a,5,6,8,9,10,10b-decahydrobenzo[\ff]quinolin-7(2H)-one (\textit{trans}-4.1a). To a stirred solution of 4.8a (50 mg, 0.24 mmol) in DMF (1 mL) was added K\textsubscript{2}CO\textsubscript{3} (67.3 mg, 0.49 mmol), followed by the addition of 1-iodopropane (83 mg, 0.49 mmol). After the reaction was stirred overnight, water (3 mL) was added, and the solution was extracted with ether (4 x 30 mL). The combined organic layers were washed with brine (3 x 10 mL) and dried over MgSO\textsubscript{4}. After filtration and evaporation, the residue was purified by column chromatography (NH\textsubscript{3} treated silica, CH\textsubscript{2}Cl\textsubscript{2}/methanol = 30:1); a light yellow oil 4.1a was obtained (35 mg, 60% yield). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ 2.97 (d, 1H, \textit{J} = 11.7 Hz), 2.52-2.71 (m, 1H), 1.92-2.48 (m, 14H), 1.61-1.86 (m, 2H), 1.35-1.48 (dt, 2H, \textit{J} = 7.3 Hz, \textit{J} = 7.7 Hz), 0.88-1.31 (m, 2H), 0.79-0.84 (t, 3H, \textit{J} = 7.3 Hz) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) δ 197.8, 155.6, 130.0, 62.1, 53.2, 51.6, 44.0, 35.8, 26.5, 26.4, 24.0, 23.5, 21.2, 20.9, 16.4, 10.5 ppm; MS (EI) m/z 247 (M\textsuperscript{+}). HRMS 247.19460 (obsd). calcd for C\textsubscript{16}H\textsubscript{25}NO 247.19360.

\textit{cis}-4-Propyl-1,3,4,4a,5,6,8,9,10,10b-decahydrobenzo[\ff]quinolin-7(2H)-one (\textit{cis}-4.1b). To a stirred solution of 4.8b (40 mg, 0.19 mmol) in DMF (1 mL) was added K\textsubscript{2}CO\textsubscript{3} (55 mg, 0.40 mmol), followed by the addition of 1-iodopropane (44 mg, 0.26 mmol). After the reaction was stirred overnight, water (3 mL) was added. The solution was extracted with ether (4 x 25 mL). The combined organic layers were washed with brine (3 x 10 mL) and dried over MgSO\textsubscript{4}. After filtration and evaporation, the residue was purified by column chromatography (NH\textsubscript{3} treated silica, CH\textsubscript{2}Cl\textsubscript{2}/methanol = 30:1); a light yellow oil 4.1b was obtained (35 mg, 60% yield). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ 2.87 (d, 1H, \textit{J} = 11.7 Hz), 2.52-2.71 (m, 1H), 1.92-2.48 (m, 14H), 1.61-1.86 (m, 2H), 1.35-1.48 (dt, 2H, \textit{J} = 7.3 Hz, \textit{J} = 7.7 Hz), 0.88-1.31 (m, 2H), 0.79-0.84 (t, 3H, \textit{J} = 7.3 Hz) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) δ 197.8, 155.6, 130.0, 62.1, 53.2, 51.6, 44.0, 35.8, 26.5, 26.4, 24.0, 23.5, 21.2, 20.9, 16.4, 10.5 ppm; MS (EI) m/z 247 (M\textsuperscript{+}). HRMS 247.19460 (obsd). calcd for C\textsubscript{16}H\textsubscript{25}NO 247.19360.
CH$_2$Cl$_2$-methanol = 30:1) and a light yellow oil 4.1b was obtained (32 mg, 65% yield). $^1$H-NMR (CDCl$_3$) $\delta$ 2.91 (dt, 1H, $J = 3.2$ Hz, $J = 9.0$ Hz), 2.25-2.60 (m, 8H), 1.78-2.16 (m, 5H), 1.64 (m, 4H), 1.24-1.52 (m, 4H), 0.88 (t, 3H, $J = 7.3$ Hz) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 197.8, 158.4, 129.6, 55.2, 54.9, 45.1, 40.8, 36.5, 28.2, 24.4, 23.7, 21.3, 20.8, 19.1, 12.8, 10.5 ppm; MS (EI) m/z 247 (M$^+$).

**Preparative chiral HPLC separation of 4.1a.** A 20 mg/mL solution of racemic trans-4.1a in 2-propanol was injected into a HPLC system using a Waters 510 HPLC pump fitted with a 100 µL loop and a Chiralpack AD preparative column (250 x 10 mm), 40 µL per injection. Mobile phase was a mixture produced by an ISCO model 2360 gradient programmer and consisted of 99.5% hexane [containing 0.1% triethylamine (w/w)] and 0.5% 2-propanol. Flow rate of the mobile phase was 3.7 mL min$^{-1}$. The two enantiomers were detected by a Waters 486 millipore tuneable absorbance detector ($\lambda = 254$ nm, AUFS = 2.0) and were recorded on paper using a Kipp & Zonen flatbed recorder (chart speed 5 mm min$^{-1}$). After evaporation of the mobile phase, the optical rotation of the two fractions was determined using a Perkin Elmer 241 polarimeter. First fraction: $[\alpha]_d^{20} = +124.7^\circ$ (c=0.019, methanol), its HCl salt mp 186-188°C; Second fraction: $[\alpha]_d^{20} = -125^\circ$ (c=0.020, methanol), its HCl salt mp 162-164°C. The purity of both enantiomers were analyzed by the same HPLC system but fitted with a Chiralpack AD analytical column (250 x 4.6 mm) and a 20 µL loop (e.e > 99% for both enantiomers).

### 4.6.1.2 Chemistry of 1.27d

**(E)-3-(2,3-Dimethoxyphenyl)-2-propenic acid (4.12).** 4.10 (38 g, 0.25 mol) was melted by warming on a water-bath, 50°C. A solution of KOH (20.5 g, 0.37 mol) in H$_2$O (30 mL) was added dropwise within 15 min to this vigorously stirred melt. After addition, dimethyl sulphate (30.0 mL, 0.32 mol) was added dropwise. When the color of the reaction mixture changed to green, the rate of the addition of the alkali was slightly increased. When the addition was completed, the brown reaction mixture was poured into a beaker and was kept as such overnight. The resulting crystals were collected by suction filtration and grounded in an ice-cold water. After drying, recrystallization from n-hexane yielded 4.11 (37 g, 89% yield) as colorless needles, mp 51-53°C (lit. 51-52°C, Et$_2$O/petroleum$^{39}$). To this aldehyde 4.11 (21.6 g, 0.13 mol), malonic acid (27 g, 0.26 mol), piperidine (1.9 mL) and pyridine (60 mL) were added, and the mixture was heated at 80°C for 2 h and refluxed for a further 2 h at 115°C. The mixture
was cooled and poured with stirring into cold aqueous 1N HCl. The white precipitate was collected by suction filtration and washed by enough water. The solid \textbf{4.12} was dried in a vacuum desiccator (25 g, 92% yield). An analytical sample was re-crystallized from 2-butanol to provide white crystals, Mp.: 179-182°C (lit. 179-180°C, 2-butanol\textsuperscript{40}); IR (cm\textsuperscript{-1}, KBr) 1683 (C=O), 1631 (C=C); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \) 8.10 (d, 1H, \( J = 16.2 \) Hz), 6.94-7.25 (m, 3H), 6.50 (d, 1H, \( J = 16.2 \) Hz), 3.88 (s, 3H), 3.87 (s, 3H) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \( \delta \) 170.5, 151.6, 147.1, 140.1, 126.7, 122.7, 117.9, 117.0, 112.8, 59.9, 54.4 ppm.

\textbf{3-(2,3-Dimethoxyphenyl) propanic acid (4.13).} The propenic acid \textbf{4.12} (15.9 g, 76.4 mmol) was dissolved in EtOH (200 mL) and hydrogenated overnight over 10% Pd/C (1.5 g) under 3.5 bar H\textsubscript{2} at RT. The mixture was filtered and the solvent was evaporated to yield \textbf{4.13} as a light yellow solid (14 g, 87% yield), re-crystallized from benzene to get white crystals, Mp.: 68-69°C (lit. 69-70°C, benzene/petroleum ether\textsuperscript{41}); IR (cm\textsuperscript{-1}, KBr) 1771 (C=O); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \) 6.77-6.98 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 2.96 (m, 2H), 2.67 (m, 2H) ppm; \textsuperscript{13}C-NMR (CDCl\textsubscript{3}) \( \delta \) 177.7, 151.2, 145.6, 132.5, 122.4, 120.2, 109.3, 59.1, 54.2, 33.2, 23.8 ppm.

\textbf{3,4-Dihydro-5,6-dimethoxy-2(1H)-naphthalenone (4.9).} Thionyl chloride (4 mL) was added under N\textsubscript{2} to a stirred solution of \textbf{4.13} (2 g, 9.5 mmol) in benzene. After refluxing for 4 h, the reaction mixture was cooled, and the volatiles were evaporated to afford \textbf{4.14} as a light yellow oil (2.1 g, 97% yield). IR (cm\textsuperscript{-1}, neat), 2834 (OCH\textsubscript{3}), 1799 (C=O). This acetyl chloride \textbf{4.14} in anhydrous ether (25 mL) was added dropwise over 15 min period to a stirred solution of freshly prepared CH\textsubscript{2}N\textsubscript{2} (approx. 2.6 g) in dry Et\textsubscript{2}O (80 mL) at 5°C, and the reaction was allowed to stand overnight under N\textsubscript{2} at RT. Removal of the solvent under reduced pressure yielded \textbf{4.15} (2.1 g, 98% yield), IR (cm\textsuperscript{-1}, neat) 2834 (OCH\textsubscript{3}), 2102 (CHN\textsubscript{2}), 1643 (C=O). This diazoketone \textbf{4.15} (2.1 g, 9.0 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) and this solution was added to a rapidly stirred solution of [Rh(CH\textsubscript{3}COO)\textsubscript{2}]\textsubscript{2} (20 mg) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) under N\textsubscript{2}. After refluxing for 15 min, a drop of CF\textsubscript{3}COOH was added and the refluxing was continued for further 15 min. After cooling, the reaction mixture was washed with sat. NaHCO\textsubscript{3} and brine, dried over MgSO\textsubscript{4}. After filtration and evaporation, a brown oil was obtained which was purified by column chromatography on silica to afford \textbf{4.9} as white needles (1.4 g, 75% yield). Mp.: 63-65°C (lit. 61-63°C, from n-hexane\textsuperscript{21}); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \( \delta \) 6.75 (dd, 2H, \( J = 8.4 \) Hz, \( J = 4.8 \) Hz), 3.80 (s, 3H), 3.76 (s, 3H), 3.45 (s, 2H), 3.06 (t, 2H, \( J = 6.6 \) Hz), 2.44 (t, 2H, \( J = 6.6 \) Hz);
$^{13}$C-NMR (CDCl$_3$ $\delta$ 209.5, 149.9, 144.5, 129.1, 124.9, 121.9, 109.3, 59.3, 54.4, 42.9, 36.3, 19.8 ppm; MS (EI) m/z 206 (M$^+$).

**7,8-Dimethoxy-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one (4.17).** 4.9 (4 g, 19.4 mmol), pyrrolidine (2.1 g, 29.6 mmol) and a catalytic amount of $p$-TsOH were heated to reflux in benzene (80 mL) under N$_2$ in a Dean-Stark apparatus for 3 h. After the volatiles were evaporated, acrylamide (4.2 g, 59.2 mmol) was added and the mixture was stirred at 80°C for 1 h and at 130°C for 30 min in order to polymerize excess acryl amide. The reaction was cooled down to RT and H$_2$O (40 mL) was added. A dark solid was precipitated, which was collected by suction filtration. The obtained solid was dissolved in CH$_2$Cl$_2$ and active charcoal was added. After refluxing for 20 min, the dark solution was filtered over Celite®. Evaporation of the solvent in vacuo afforded 4.17 as a light-green solid (3 g, 60% yield). Analytic sample was crystallized from methanol, mp: 230°C-233°C (lit. 233-236°C$^{12}$); $^1$H-NMR (CDCl$_3$) $\delta$ 8.37 (1H), 6.78 (dd, 2H, $J = 8.4$ Hz, $J = 17.4$ Hz), 3.85 (s, 3H), 3.79 (s, 3H), 2.94 (m, 2H), 2.65 (m, 4H), 2.35 (m, 2H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 170.1, 149.5, 144.5, 129.4, 126.7, 125.4, 115.5, 108.2, 106.8, 58.9, 54.3, 29.1, 23.6, 19.5, 19.3 ppm; MS (EI) m/z 259 (M$^+$).

**4-Benzyl-7,8-dimethoxy-1,4,5,6-tetrahydrobenzo[f]quinolin-3(2H)-one (4.18).** The mixture of 4.17 (1.5 g, 5.8 mmol) and NaH 60% (300 mg, 7.5 mmol) in 50 mL of anhydrous dimethoxyethane (DME) was heated under reflux for 3 h. After cooling to RT, 1-(bromomethyl)benzene (1.2 g, 7.0 mmol) was introduced to the cooled reaction and the reaction mixture was heated under reflux for further 6 h. The reaction was stirred at RT overnight. Excess NaH was destroyed by addition of 3 mL of H$_2$O and solvent was evaporated in vacuo. The residue was partitioned between CH$_2$Cl$_2$ and H$_2$O and the combined organic layers were dried over Na$_2$SO$_4$. After filtration and evaporation, the obtained residue was purified by column chromatography (Al$_2$O$_3$, n-hexane/ethyl acetate, gradient) to give 4.18 (1.5 g, 74% yield) as yellow oil. $^1$H-NMR (CDCl$_3$) $\delta$ 7.15-7.34 (m, 5H), 6.81 (dd, 2H, $J = 8.5$ Hz, $J = 24.2$ Hz), 4.98 (s, 2H), 3.84 (s, 3H), 3.76 (s, 3H), 2.65-2.87 (m, 6H), 2.36 (m, 2H) ppm; $^{13}$C-NMR (CDCl$_3$) $\delta$ 168.7, 149.6, 144.2, 136.4, 133.0, 127.2, 125.0, 124.8, 115.7, 112.2, 108.3, 59.0, 54.3, 42.8, 30.3, 21.7, 19.9, 19.8 ppm; MS (EI) m/z 349 (M$^+$).
4-Benzyl-7,8-dimethoxy-1,2,3,4,5,6-hexahydrobenzo[f]quinoline (4.19). To a suspension of LiAlH₄ (485 mg, 12.8 mmol) in THF (25 mL) was added dropwise a solution of 4.18 (1.78 g, 5.1 mmol) in THF (50 mL) solution dropwise. Under N₂ atmosphere the resulting suspension was refluxed for 3 h. After cooling, excess LiAlH₄ was destroyed by dropwise addition of H₂O (0.5 mL), 10% NaOH (0.5 mL) and H₂O (2.0 mL). The solution was stirred with Na₂SO₄ for 15 min. After filtration and washing the cake with ethanol, the combines filtrates were evaporated in vacuo. The obtained residue was partitioned between ethyl acetate and H₂O. The combined organic layers were washed with brine, dried over Na₂SO₄. After filtration and evaporation, 4.19 was obtained as a yellow oil (1.5 g, 88% yield) and was used in the next step without any purification.

4-Benzyl-7,8-dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (4.20). NaBH₃CN (640 mg, 10.2 mmol) was added in portions to the crude 4.19 (1.5 g, 4.5 mmol) dissolved in MeOH (40 mL), acetic acid was added to the solution until pH=4. This mixture was stirred overnight at RT. Excess hydride was quenched by adding concentrated HCl. This mixture was stirred at RT for 30 min. After evaporation, the solution was alkalized with 4N NaOH to pH=9 and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄. The solvent was filtered and evaporated in vacuo to yield 4.20 as a yellow oil with a cis/trans ratio 50/50 according to GC analysis. Separation with column chromatography (NH₃ treated silica, CH₂Cl₂/MeOH, gradient) obtained cis-4.20 (550 mg, 32% yield over two steps), trans-4.20 (500 mg, 29.2% yield over two steps). The amines were converted to their HCl salts and then re-crystallized from MeOH/ether to obtain cis-4.20 HCl salt, 500 mg, Mp.: 236-239°C (lit. 241-244°C); ¹H-NMR (CDCl₃) δ 7.86 (m, 2H), 7.35 (m, 3H), 6.74 (m, 2H), 3.80-4.45 (m, 2H), 3.76 (s, 3H), 3.71 (s, 3H), 1.20-3.76 (m, 12H) ppm; ¹³C-NMR (CDCl₃) δ 149.3, 144.5, 129.7, 128.3, 127.9, 127.7, 127.0, 125.9, 122.7, 109.7, 58.3, 56.0, 55.3, 54.2, 46.3, 35.3, 27.0, 20.9, 20.7, 13.4 ppm; MS (EI) m/z 337 (M⁺). Trans-4.20 HCl salt, 450 mg, Mp.: 262-265°C (lit. 262-264°C); ¹H-NMR (CDCl₃) δ 7.48 (m, 5H), 6.81 (dd, 2H, J = 8.8 Hz, J = 28.1 Hz), 3.83 (m, 2H), 106.14 (s, 3H), 3.78 (s, 3H), 1.20-3.76 (m, 12H) ppm;
trans-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (trans-4.21) HCl salt. The trans-4.20 HCl salt (200 mg, 0.54 mmol) was dissolved in MeOH (35 mL) and hydrogenated over 10% Pd/C (80 mg) at 25 psi at RT overnight. After filtration of the catalyst and evaporation of the solvent, a white solid trans-4.21 (130 mg, 85% yield) was obtained. Analytic sample was re-crystallized from MeOH/ether, Mp.: 270°C-272°C (lit. 268-270°C[11]). 1H-NMR (CDCl3) δ 6.78 (dd, 2H, J = 8.8 Hz, J = 9.3 Hz), 3.86 (s, 3H), 3.77 (s, 3H), 0.87-3.72 (m, 13H) ppm; 13C-NMR (CDCl3) δ 149.4, 144.8, 129.3, 126.9, 122.5, 109.5, 58.4, 54.2, 50.7, 37.0, 34.3, 27.1, 20.9, 20.6, 17.7 ppm; MS (EI) m/z 247 (M+).

cis-7,8-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (cis-4.21) HCl salt. This compound was prepared from cis-4.20 (200 mg, 0.54 mmol) using the same procedure described in trans-4.21. The product was obtained as a white solid (123 mg, 81% yield). An analytic sample was re-crystallized from MeOH/ether, Mp.: 243°C-246°C (lit, 243-245°C); 1H-NMR (CDCl3) δ 6.82 (dd, 2H, J = 8.5 Hz, J = 21.5 Hz), 3.87 (br, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 1.64-3.77 (m, 12H) ppm; 13C-NMR (CDCl3) δ 149.0, 144.8, 129.3, 126.9, 122.5, 109.5, 58.3, 54.3, 51.0, 39.8, 35.9, 27.9, 22.4, 21.6, 20.5 ppm; MS (EI) m/z 247 (M+).

trans-7,8-Dimethoxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (trans-4.22). To a stirred solution of trans-4.21 (50 mg, 0.20 mmol) in CH2Cl2 (5 mL) under N2, Et3N (40 mg, 0.40 mmol) was added, followed by the addition of dried MgSO4 while stirring. Propionaldehyde (35 mg, 0.60 mmol) was dropped dropwise. The solution was stirred at RT overnight. NaBH₄ (15 mg, 0.44 mmol) was added in portions. After stirring for 2 h, the solution was evaporated in vacuo. The residue was partitioned between H2O (10 mL) and CH2Cl2 (4 x 20 mL). The combined organic layers were washed with brine, dried over MgSO4. The solvent was filtered and evaporated in vacuo to afford a yellow oil, which was purified by column chromatography on NH₃ treated silica (CH2Cl2/MeOH, gradient), trans-4.22 was obtained as a light yellow oil (30 mg, 52% yield). 1H-NMR (CDCl3) δ 6.71 (d, 1H, J = 8.4 Hz), 6.92 (d, 1H, J = 8.4 Hz), 3.78 (s,
A benzo[f]quinoline enone prodrug and its corresponding catecholamine

3H), 3.74 (s, 3H), 0.87-3.00 (m, 16H), 0.84 (t, 3H, J = 7.3 Hz) ppm; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 148.9, 144.4, 131.4, 129.0, 119.3, 108.5, 61.8, 58.4, 54.2, 53.7, 51.6, 40.3, 28.2, 24.8, 23.9, 21.7, 16.4, 10.6 ppm; MS (EI) m/z 289 (M\(^+\)).

cis-7,8-Dimethoxy-4-propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (cis-4.22). This compound was prepared from cis-4.21 (50 mg, 0.20 mmol) using the same procedure described in trans-4.22. Purification of the residue afforded cis-4.22 (28 mg, 50% yield). \(^1\)H-NMR (CDCl\(_3\)) \(\delta\) 6.73 (dd, 2H, J = 8.4 Hz, J = 22.3 Hz), 3.77 (s, 3H), 3.74 (s, 3H), 0.91-3.01 (m, 16H), 0.87 (t, 3H, J = 7.3 Hz) ppm; \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 148.8, 144.7, 133.5, 128.6, 122.4, 108.9, 58.3, 55.6, 55.1, 54.3, 45.3, 37.9, 28.9, 23.7, 21.7, 19.0, 13.0, 10.5 ppm; MS (EI) m/z 289 (M\(^+\)).

trans-4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol (1.27d). The phenols were obtained by heating the appropriate methoxy trans-4.22 in 48% HBr for 2 h at 135\(^\circ\)C under N\(_2\). The HBr was evaporated, and the residue was recrystallized from MeOH / ether to obtain trans-1.27d.

cis-4-Propyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline-7,8-diol (cis-1.27d). The phenols were obtained by heating the appropriate methoxy cis-4.22 in 48% HBr for 2 h at 135\(^\circ\)C under N\(_2\). The HBr was evaporated, and the residue was re-crystallized from MeOH / ether to obtain cis-1.27d.

4.6.2 Pharmacology

Animals. Animals used for the biochemical and behaviour activity experiments were male rats of a Wistar derived strain (Harlan, the Netherlands) weighing 300-350 g. The rats were placed in a room at controlled environmental conditions (21\(^\circ\)C, humidity 60-65%; lights on at 8 a.m. and off at 8 p.m.). Animals were not used during the first week after arrival in the laboratory. Animal procedures were conducted in accordance with
guidelines published in the NIH guide for the care and use of laboratory animals and all protocols were approved by the Groningen University Animal Care Committee.

**Drugs.** All enone compounds (both enantiomers of 4.1a and racemic 4.1a) were tested as their hydrochloride salts and catecholamines (both trans and cis isomers of 1.27d) were tested as hydrobromide salts unless noted otherwise. The drugs were dissolved in physiological (0.9%) saline immediately prior to use. All in vivo experiments were performed at the Animal Laboratory Unit of the University of Groningen, The Netherlands.

**Surgery and brain microdialysis.** On-line brain microdialysis in freely moving animals has previously been described. The details were described in Chapter 2.

**4.6.3 Receptor functional assay**

The intrinsic activity of compounds both enantiomers of 4.1a and cis- and trans-1.27d at the DA D1 and D2 receptor were determined according to methods previously described with some modification. The details were described in Chapter 3.

**4.7 References**


A benzo[f]quinoline enone prodrug and its corresponding catecholamine


A benzo[f]quinoline enone prodrug and its corresponding catecholamine


