Synthesis and a Configurational Correlation within cis- and trans-Oxazolotetrahydroisoquinolinones with an Angular Substituent

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5-Oxo-10α-R-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isoquinoline-10-carboxylic acids [R = phenyl (trans-4), benzyl (trans-8, cis-8)] were prepared by reaction of homophthalic anhydride (2) and a corresponding 2-oxazoline. The configurations of trans-8 and cis-8 were assigned unequivocally based on the 2D-H-NOESY NMR spectra of the corresponding methyl esters. Compounds trans-4, trans-8 and cis-8 were converted in two steps with retention of the configuration to the target aminocarbonyl derivatives which are interesting from a pharmaceutical point of view. An important experimental correlation between the chemical shift of 10-H and the configuration of all compounds prepared was derived.

Key words: Homophthalic Anhydride, 2-Oxazolines, 2D-H-NOESY, Oxazolotetrahydroisoquinolines, Diastereomers, Configurational Correlation

Introduction

Oxazolotetrahydroisoquinolinones of type 1 (Fig. 1) are precursors or targets in organic synthesis or are part of several important biologically active compounds. Chiral 1,2,3,4-tetrahydroisoquinolines are prepared in few steps by reduction and alkylation of the corresponding parent compound 1 [1, 2]. The naturally occurring antibiotics cervinomycin A1 and A2 were synthesized in four to seven steps, where the last of these was the reaction of an isocoumarin with an imine [3 – 5]. Kigamicins A, B, C, and D are novel anticancer agents containing one oxazolidine ring; they target the tolerance of cancer cells to nutrient starvation [6, 7]. TMC-66 is a new endothelin-converting enzyme inhibitor, produced from the Streptomyces species A5008 [8].

This paper continues the report of our attempts [9] to elucidate the chemical and especially the stereochemical outcome of the reaction of homophthalic anhydride with substituted oxazolines yielding oxazolotetrahydroisoquinolines with an angular substituent, and further transformations of the products. These studies deserve interest because the reaction proceeds with an unexpected elimination of the angular group in some cases [10]. Moreover, they are important for an easier total synthesis of kigamicins and TMC-66, because these compounds have an angular substituent.
Results and Discussion

The reaction of homophthalic anhydride (2) and two different oxazolines proceeded in the expected manner [11] with retention of the angular substituent, but with different diastereoselectivity. Thus, equimolar quantities of homophthalic anhydride (2) and 2-phenyl-2-oxazoline (3) gave in the presence of benzene at reflux only one product, identified [9] as acid 4 with an assumed trans-configuration (Scheme 1).

Under the same conditions, the reaction of homophthalic anhydride and 2-benzyl-2-oxazoline (7) gave both diastereomeric acids, trans-8 (48%) and cis-8 (16%) (Scheme 2). The three acids mentioned above were converted to different derivatives using transformations of their carboxyl group, namely preparation of the relevant esters, alcohols, acid chlorides and carboxamides. The latter are the target compounds from a pharmacological point of view.

Let us discuss the configuration of the compounds prepared since this was the crucial point. The stereochemistry of similar fused tetrahydroisoquinolines can be defined on the basis of the NMR values of the vicinal coupling constant between the protons at C-10 and C-10a [11 – 13]. However, the compounds prepared do not possess a proton at C-10a, which makes the determination of their configuration only possible through X-ray analysis or through 2D-NMR spectroscopy if both diastereomers are available. In our case, the diastereomeric acids trans-8 and cis-8 were converted to esters with diazomethane. The 2D-H-NOESY NMR spectrum of ester trans-9 showed that the methoxy protons and 11-H are not correlated, whereas there was a strong correlation between 10-H and the methylene protons 11-H. In the ester cis-9, the methylene group 11-H had a strong correlation with the methoxy group, but not with 10-H (Fig. 2).

Based on these data, the configurations of the diastereomeric acids 8, esters 9 and the derived compounds 10 – 12 were unequivocally established. Application of 2D-H-NOESY NMR spectroscopy to each individual diastereomeric pair is not convenient. Thus, we tried to find out a suitable correlation between chemical shift and configuration. The description of the 1H NMR spectra of the relevant isomers of all products obtained uses the arbitrary numbering shown in
the formulas of esters 9 and carboxamide trans-12a (Figs. 2 and 3).

A detailed analysis of the $^1$H NMR spectra of the diastereomeric compounds 9 – 12 with known configurations showed that only the chemical shifts of 10-H are significantly different in both isomers for configurational assignments. Thus, the signal for 10-H in all trans isomers was shifted downfield (∼ 4.4 – 4.5 ppm) in comparison to that in the cis isomers (∼ 4.00 ppm). This criterion $\delta_{\text{trans}}(10-\text{H}) > \delta_{\text{cis}}(10-\text{H})$ subsequently was applied to the remaining compounds 4 – 6a – j confirming their trans configuration.

Attention was paid to the question which diastereomer is thermodynamically favored. When acid cis-8 was treated with potassium carbonate in dry DMF, complete epimerization was established yielding acid trans-8, which was further converted to ester trans-9 by reaction with methyl iodide (Scheme 3A) [14, 15]. Treatment of a mixture of acids trans-8 and cis-8 with potassium carbonate and methyl iodide in dry DMF afforded only ester trans-9 (Scheme 3B). Ester cis-9 was dissolved in tetrahydrofuran and potassium carbonate was added, which resulted in a partial epimerization (the formation of a mixture of trans-9 and cis-9), and within 24 h ester trans-9 was the major product (Scheme 3C). It thus appeared that epimerization of acid cis-8 to trans-8 and subsequent methylation of the latter or complete epimerization of ester cis-9 took place, and that acid trans-8 and ester trans-9 are the thermodynamically more stable isomers, their formation being driven by the release of steric strain, which was induced by the presence of the angular benzyl group at C-10a.

Among the compounds prepared, the carboxamides trans-6a – j, trans-12a – d and cis-12a – d (Table 1) are of particular interest because they contain the fragment of an inverse amide of $\gamma$-aminobutyric acid (given in bold in Fig. 3), which is believed to play a key role in anxiety and epilepsy [16 – 18]. The presence of an angular phenyl or benzyl group at C-10a, the oxazole ring and the amine groups arising from the secondary cyclic amines are additional points that can evoke or modify the activity. Pharmacological screening of the majority of the prepared compounds has been initiated and the results will be published in a subsequent paper. These compounds and especially those featuring diastereomeric pairs are suitable for QSAR analyses and their experimental check.

Table 1. Nucleophilic (Nu) groups in compounds trans-6a – j, trans-12a – d and cis-12a – d, and their yields (in %).

<table>
<thead>
<tr>
<th>Comp.</th>
<th>Nu</th>
<th>Yield</th>
<th>Comp.</th>
<th>Nu</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-6a</td>
<td>pyrrolidin-1-yl</td>
<td>42</td>
<td>trans-12a</td>
<td>4-phenylpiperazin-1-yl</td>
<td>75</td>
</tr>
<tr>
<td>trans-6b</td>
<td>piperidin-1-yl</td>
<td>44</td>
<td>cis-12a</td>
<td>4-phenylpiperazin-1-yl</td>
<td>60</td>
</tr>
<tr>
<td>trans-6c</td>
<td>4-methylpiperazin-1-yl</td>
<td>81</td>
<td>trans-12b</td>
<td>4-(3-trifluoromethyl)piperazin-1-yl</td>
<td>60</td>
</tr>
<tr>
<td>trans-6d</td>
<td>4-phenylpiperazin-1-yl</td>
<td>75</td>
<td>cis-12b</td>
<td>4-(3-trifluoromethyl)piperazin-1-yl</td>
<td>45</td>
</tr>
<tr>
<td>trans-6e</td>
<td>4-(3-trifluoromethyl)phenyl-piperazin-1-yl</td>
<td>42</td>
<td>trans-12c</td>
<td>4-(2-methoxyphenyl)-piperazin-1-yl</td>
<td>56</td>
</tr>
<tr>
<td>trans-6f</td>
<td>4-(3-chlorophenyl)piperazin-1-yl</td>
<td>48</td>
<td>cis-12c</td>
<td>4-(2-methoxyphenyl)-piperazin-1-yl</td>
<td>50</td>
</tr>
<tr>
<td>trans-6g</td>
<td>1-(4-fluorophenyl)piperazin-4-yl</td>
<td>56</td>
<td>trans-12d</td>
<td>morpholin-4-yl</td>
<td>50</td>
</tr>
<tr>
<td>trans-6h</td>
<td>morpholin-4-yl</td>
<td>52</td>
<td>cis-12d</td>
<td>morpholin-4-yl</td>
<td>47</td>
</tr>
<tr>
<td>trans-6i</td>
<td>2,6-dimethylnorbornolin-4-yl</td>
<td>77</td>
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<td></td>
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<tr>
<td>trans-6j</td>
<td>thiomorpholin-4-yl</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Scheme 3.](image)

A detailed analysis of the $^1$H NMR spectra of the diastereomeric compounds 9 – 12 with known configurations showed that only the chemical shifts of 10-H are significantly different in both isomers for configurational assignments. Thus, the signal for 10-H in all trans isomers was shifted downfield (∼ 4.4 – 4.5 ppm) in comparison to that in the cis isomers (∼ 4.00 ppm). This criterion $\delta_{\text{trans}}(10-\text{H}) > \delta_{\text{cis}}(10-\text{H})$ subsequently was applied to the remaining compounds 4 – 6a – j confirming their trans configuration.

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### Conclusion

The reaction between homophthalic anhydride and 2-benzyl-2-oxazoline was not completely diastereoselective affording both diastereomers of the expected heterocyclic acids, trans-8 and cis-8. This gave the possibility to elucidate reliably their configuration us-
ing 2D-H-NOESY NMR spectroscopy of the corresponding methyl esters. On the basis of a careful examination of the $^1$H NMR data of the four compounds and all their derivatives, the following relationship was found to be general for the chemical shift of 10-H as a function of configuration: $\delta_{\text{trans}}(10-H) > \delta_{\text{cis}}(10-H)$.

It was applied to the remaining compounds prepared and can be used for configurational assignments of other oxazolotetrahydroisoquinolinones with an angular substituent at C-10a. Acid trans-8 and ester trans-9 are the thermodynamically most stable isomers. The carboxamides prepared are of practical interest because of the presence of four different pharmacophoric groups in their structures.

**Experimental Section**

Melting points were determined on a Kofler hot stage and are uncorrected. The $^1$H NMR spectra were obtained on a Bruker AM400 NMR spectrometer at 400.13 MHz in deuterochloroform as solvent, if not stated otherwise. The chemical shifts are given in ppm ($\delta$) relative to tetramethylsilane as internal standard. FAB mass spectra (low- and high-resolution) were obtained at the Mass Spectrometry Facility at the University of Notre Dame, Notre Dame, IN. Elemental analyses were obtained in the relevant laboratories at the Faculty of Chemistry, University of Sofia or at the Institute of Organic Chemistry, Bulgarian Academy of Sciences. The TLC analyses were obtained in the relevant laboratories at the Faculty of Chemistry, Bulgarian Academy of Sciences. The TLC plates. Merck silica gel 60 (0.040 – 0.063 mm) was used for chromatographic filtration and flash chromatography.

General procedure for the synthesis of compounds 6a – j

Acid trans-4 [9] (1 g, 3.3 mmol) was dissolved in dry THF (15 mL) and thionyl chloride (0.728 mL, 9.9 mmol) was added dropwise. The reaction mixture was refluxed for 15 min. Then the solvent was removed under reduced pressure, dry THF was added, followed by dropwise addition of the corresponding secondary amine NuH (9.9 mmol). After stirring for 30 min, ethyl acetate and water were added. The organic layer was separated, washed with water (10 × 100 mL) and dried with sodium sulfate. Ethyl acetate was removed under reduced pressure to give the crude product, which was subjected to flash chromatography to give the pure compound.

(±)-trans-10-[(Pyrrolidin-1-yl)carbonyl]-10a-phenyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isooquinolin-5-one, (trans-6a)

NuH: pyrrolidine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.49 g (42 %). M. p. 220 – 222 °C. – $^1$H NMR: $\delta$ = 3.48 – 3.51 (m, 4H, 12-H), 3.60 – 3.71 (m, 5H, 2-H, 11-H), 3.90 – 4.12 (m, 3H, 2-H, 3-H), 4.11 (s, 1H, 10-H), 4.14 (s, 1H, 10-H), 6.80 (m, 1H, 7-H), 7.21 – 7.34 (m, 4H, 8-H, 9-H, Ph), 8.10 (d, 1H, 6-H, J = 7.6 Hz). – HRMS (ESI-MS): $m/z = 363.2503$ (calcd. 363.1703 for C$_{23}$H$_{24}$N$_3$O$_3$, [M+H$^+$]).

(±)-trans-10-[(Piperidin-1-yl)carbonyl]-10a-phenyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isooquinolin-5-one, (trans-6b)


(±)-trans-10-[(4-Methylpiperazin-1-yl)carbonyl]-10a-phenyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isooquinolin-5-one, (trans-6c)

NuH: 1-methylpiperazine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 1.02 g (81 %). M. p. 204 – 206 °C. – $^1$H NMR: $\delta$ = 2.32 (s, 3H, N-C$\text{H}_3$), 3.60 – 3.78 (m, 6H, 2-H, 12-H), 4.10 – 4.16 (m, 4H, 11-H, 12-H), 4.34 – 4.33 (m, 2H, 3-H), 4.48 (s, 1H, 10-H), 6.83 (m, 1H, 7-H), 7.30 – 7.49 (m, 7H, 8-H, 9-H, Ph), 8.27 (d, 1H, 6-H, J = 6 Hz). – HRMS (ESI-MS): $m/z = 391.1903$ (calcd. 391.1896 for C$_{23}$H$_{23}$N$_3$O$_3$, [M+H$^+$]).

(±)-trans-10-[(4-Phenylpiperazin-1-yl)carbonyl]-10a-phenyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isooquinolin-5-one, (trans-6d)

NuH: 1-phenylpiperazine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 1.09 g (75 %). M. p. 258 – 260 °C. – $^1$H NMR: $\delta$ = 3.34 – 3.46 (m, 2H, 11-H), 3.51 – 3.59 (m, 3H, 2-H, 11-H), 3.71 – 3.80 (m, 1H, 2-H), 4.14 – 4.23 (m, 5H, 3-H, 12-H), 4.30 – 4.48 (m, 3H, 3-H), 4.56 (s, 1H, 10-H), 6.88 (m, 1H, 7-H), 7.19 – 7.50 (m, 12H, 8-H, 9-H, Ph, N-Ph), 8.17 (d, 1H, 6-H, J = 8.8 Hz). – HRMS (ESI-MS): $m/z = 454.2020$ (calcd. 454.2125 for C$_{26}$H$_{27}$N$_3$O$_3$, [M+H$^+$]).

(±)-trans-10-[(4-(3-Trifluoromethylphenyl)piperazin-1-yl)carbonyl]-10a-phenyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isooquinolin-5-one, (trans-6e)

NuH: 1-(3-trifluoromethyl)phenylpiperazine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.70 g (42 %). M. p. 103 – 105 °C. – $^1$H NMR $\delta$ = 3.28 – 3.36 (m, 2H, 11-H), 3.70 – 3.77 (m, 4H, 2-H, 11-H), 4.02 – 4.10 (m, 1H, 3-H), 4.13 – 4.21 (m, 5H, 3-H, 12-H), 4.58 (s, 1H, 10-H), 6.86 (m, 1H, 7-H), 7.18 – 7.51 (m, 11H, 8-H, 9-H, Ph, N-Ph).

(±)-trans-10-[(4-(3-Chlorophenyl)-piperazin-1-yl)-carbonyl]-10a-phenyl-2,3,10a-tetrahydro-5H-[1,3]-oxazo-[3,2-b]-isoquinolin-5-one, (trans-6f).

NuH: 1-(3-chlorophenyl)piperazine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.75 g (48 %). M. p. 133 – 135 °C. – ¹H NMR: δ = 3.33 – 3.40 (m, 2H, 11-H), 3.50 – 3.57 (m, 3H, 12-H), 4.15 – 4.20 (m, 1H, 2-H), 4.56 (s, 1H, 10-H), 6.87 (m, 1H, 7-H), 7.22 – 7.42 (m, 11H, 8-H, 9-H, Ph), 8.16 (d, 1H, 6-H, J = 7.6 Hz). – HRMS ((+)-FAB): m/z = 488.1735 (calcld. 488.1695 for C₂₉H₂₇ClN₃O₃, [M+H]⁺).

(±)-trans-10-[(4-(4-Fluorophenyl)-piperazin-1-yl)-carbonyl]-10a-phenyl-2,3,10a-tetrahydro-5H-[1,3]-oxazo-[3,2-b]-isoquinolin-5-one, (trans-6g).

NuH: 1-(4-fluorophenyl)piperazine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.85 g (56 %). M. p. 219 – 221 °C. – ¹H NMR: δ = 3.10 – 3.28 (m, 2H, 11-H), 3.30 – 3.40 (m, 2H, 12-H), 3.47 – 3.53 (m, 1H, 2-H), 3.36 – 3.74 (m, 1H, 2-H), 3.98 – 4.06 (m, 5H, 3-H, 12-H), 4.11 – 4.16 (m, 1H, 3-H), 4.54 (s, 1H, 10-H), 6.80 (m, 1H, 7-H), 6.85 – 7.23 (m, 11H, 8-H, 9-H, Ph, Ph-CF₃), 8.14 (d, 1H, 6-H, J = 7.6 Hz). – HRMS ((+)-FAB): m/z = 472.2203 (calcld. 472.2031 for C₂₉H₂₇F₃N₃O₃, [M+H]⁺).

(±)-trans-10-[(Morpholin-1-yl)carbonyl]-10a-phenyl-2,3,10a-tetrahydro-5H-[1,3]-oxazo-[3,2-b]-isoquinolin-5-one, (trans-6h).

NuH: morpholine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.51 g (42 %). M. p. 228 – 230 °C. – ¹H NMR: δ = 3.47 – 3.52 (m, 2H, 2-H), 3.63 – 3.90 (m, 8H, 11-H, 12-H), 3.98 – 4.03 (m, 1H, 3-H, J = 10.3 Hz), 4.10 – 4.17 (m, 1H, 3-H), 4.50 (s, 1H, 10-H), 6.72 (m, 1H, 7-H), 7.23 – 7.46 (m, 7H, 8-H, 9-H, Ph), 8.11 (d, 1H, 6-H, J = 7.6 Hz). – HRMS ((+)-FAB): m/z = 379.1596 (calcld. 379.1652 for C₂₉H₂₇N₃O₃, [M+H]⁺).

(±)-trans-10-[(2,6-Dimethylmorpholin-1-yl)carbonyl]-10a-phenyl-2,3,10a-tetrahydro-5H-[1,3]-oxazo-[3,2-b]-isoquinolin-5-one, (trans-6i).

NuH: 2,6-dimethylmorpholine. Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.68 g (52 %). M. p. 207 – 209 °C. – ¹H NMR: δ = 1.05 – 1.44 (m, 6H, CH₂), 3.42 – 3.56 (m, 5H, 2-H, 11-H, 12-H), 3.65 – 3.73 (m, 3H, 2-H, 11-H), 3.89 – 4.23 (m, 2H, 3-H), 4.50 (s, 1H, 10-H), 7.16 – 7.36 (m, 7H, 8-H, 9-H, Ph), 7.61 (m, 1H, 7-H), 8.10 (d, 1H, 6-H, J = 7.2 Hz). – HRMS ((+)-FAB): m/z = 407.2003 (calcld. 407.1965 for C₂₉H₂₅N₂O₄, [M+H]⁺).

Methyl ester of (±)-cis-5-oxo-10a-benzyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isoquinoline-10-carboxylic acid, (cis-9)

Recrystallized from ethyl acetate/petroleum ether. Yield: 0.38 g (73%). M. p. 200 – 202 °C. – 1H NMR: δ = 2.33 – 2.38 (m, 1H, 2-H), 2.83 (d, 1H, 11-H, J = 10 Hz), 3.16 (d, 1H, 11-H, J = 10 Hz), 3.80 – 3.87 (m, 3H, 2-H, 3-H), 4.03 (m, 3H, OCH3), 4.40 (s, 1H, 10-H), 6.49 (m, 1H, 7-H), 6.80 – 7.50 (m, 7H, 8-H, 9-H, Ph), 8.15 (d, 1H, 6-H, J = 8 Hz). – Anal. for C20H19NO4: calcd. C 71.20, H 5.68, N 4.15; found C 71.18, H 5.70, N 4.18.

Methyl ester of (±)-cis-5-oxo-10a-benzyl-2,3,10,10a-tetrahydro-5H-[1,3]-oxazolo-[3,2-b]-isoquinoline-10-carboxylic acid, (trans-9)

Recrystallized from ethyl acetate/petroleum ether. Yield: 0.45 g (86%). M. p. 154 – 156 °C. – 1H NMR: δ = 2.33 – 2.38 (m, 1H, 2-H), 2.83 (d, 1H, 11-H, J = 10 Hz), 3.16 (d, 1H, 11-H, J = 10 Hz), 3.80 – 3.87 (m, 3H, 2-H, 3-H), 4.03 (m, 3H, OCH3), 4.40 (s, 1H, 10-H), 6.49 (m, 1H, 7-H), 6.80 – 7.50 (m, 7H, 8-H, 9-H, Ph), 8.15 (d, 1H, 6-H, J = 8 Hz). – Anal. for C20H19NO4: calcd. C 71.20, H 5.68, N 4.15; found C 71.18, H 5.70, N 4.18.

Conversion of cis-8 to trans-8 and trans-9

The acid cis-8 (150 mg, 0.45 mmol) was dissolved in dry DMF (1 mL) and dry potassium carbonate (94 mg, 0.67 mmol) was added. The mixture was stirred at r.t. overnight and the progress of the reaction was monitored by TLC. The reaction mixture was divided in two halves. One half was evaporated under reduced pressure to remove the solvent, and the resulting gummy product was subjected to flash chromatography to give 65 mg of trans-9. The other half of the reaction mixture was treated with methyl iodide (28 µL, 0.45 mmol) for 5 h at r.t. The solvent was evaporated and the resulting crude product was subjected to flash chromatography to yield 60 mg of trans-9.

Conversion of a mixture of cis-8 and trans-8 to trans-9

A mixture of equimolar amounts of acids cis-8 and trans-8 (total of 100 mg) was dissolved in dry DMF (1 mL), dry potassium carbonate (63 mg, 0.45 mmol) was added followed by methyl iodide (56 µL, 0.9 mmol). The mixture was stirred at r.t. overnight and the progress of the reaction was monitored by TLC. The solvent was evaporated and the resulting crude product was subjected to flash chromatography to yield 82 mg of trans-9.

Conversion of cis-9 to trans-9

The ester cis-9 (90 mg, 0.26 mmol) was dissolved in dry THF (1 mL), and dry potassium carbonate (7.18 mg, 0.052 mmol) was added. The mixture was stirred at r.t. for 24 h and the progress of the reaction was monitored by TLC. After 12 h, according to TLC, the ratio between cis-9 and trans-9 was estimated to be 1:1. After 24 h, the solvent was evaporated under reduced pressure and the resulting product was subjected to flash chromatography to give 82 mg of trans-9.

General procedure for the synthesis of alcohols trans-10 and cis-10

To a stirred suspension of potassium borohydride (1.2 g) and lithium chloride (0.9 g) in dry tetrahydrofuran (15 mL), ester (0.30 g, 0.88 mmol) trans-9 or cis-9, dissolved in tetrahydrofuran (5 mL), was added dropwise over a period of 30 min. The reaction mixture was refluxed for 2 h, concentrated under vacuum, poured into water (100 mL) and extracted with ethyl acetate (4 × 80 mL). The combined organic layers were dried with sodium sulfate and evaporated under vacuum to afford the crude alcohol, which after flash purification gave the corresponding pure alcohol.

Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.22 g (82%). M. p. 126 – 127 °C. – 1H NMR: δ = 2.28 – 2.30 (m, 1H, 2-H), 2.79 (d, 1H, 11-H, J = 10 Hz), 3.00 (d, 1H, 11-H, J = 10 Hz), 3.75 – 3.80 (m, 3H, 2-H, 3-H), 4.35 (s, 1H, 10-H), 6.48 (m, 1H, 7-H), 6.93 – 7.53 (m, 7H, 8-H, 9-H, Ph), 8.00 (d, 1H, 6-H, J = 8.2 Hz). – Anal. for C19H19NO4: calcd. C 73.33, H 6.19, N 4.53; found C 73.30, H 6.18, N 4.50.

Flash chromatography: ethyl acetate/petroleum ether. Yield: 0.20 g (75%). M. p. 137 – 139 °C. – 1H NMR: δ = 2.68 (d, 1H, 11-H, J = 10 Hz), 2.90 (d, 1H, 11-H, J = 10 Hz),
2.85 – 2.98, 1H, 2-H), 3.80 – 3.89 (m, 3H, 2-H, 3-H), 4.03 (1H, 10-H), 6.72 (m, 1H, 7-H), 6.50 – 7.43 (m, 7H, 8-H, 9-H, Ph), 8.03 (d, 1H, 6-H, J = 8.2 Hz). – Anal. for C19H19NO3: calcd. C 72.41, H 6.28, N 8.44; found C 72.40, H 6.27, N 8.43.

Flash chromatography: ethyl acetate/petroleum ether.
NuH: 1-(3-trifluoromethyl)phenylpiperazine. Yield: 1.06 g (60 %). M. p. 180 – 181 °C. – 1H NMR: δ = 2.00 – 2.10 (m, 1H, 2-H), 2.76 (d, 1H, 11-H, J = 12 Hz), 3.23 – 3.26 (m, 5H, 12-H, 13-H), 3.35 – 3.50 (m, 2H, 3-H), 4.00 – 4.36 (m, 5H, 2-H, 3-H, 13-H), 4.39 (s, 1H, 10-H), 6.96 (m, 1H, 7-H), 7.03 – 7.63 (m, 1H, 8-H, 9-H, Ph, Ph-CH3), 8.18 (d, 1H, 6-H, J = 6.8 Hz). – Anal. for C23H21F3N3O2: calcd. C 57.27, H 5.78; found C 57.23, H 5.55, N 7.91.

Flash chromatography: ethyl acetate/petroleum ether.
NuH: 1-(3-trifluoromethyl)phenylpiperazine. Yield: 0.79 g (45 %). M. p. 192 – 194 °C. – 1H NMR: δ = 2.62 (d, 1H, 11-H, J = 11 Hz), 2.89 (d, 1H, 11-H, J = 11 Hz), 3.00 (m, 1H, 2-H, 3-H), 3.30 – 3.38 (m, 2H, 12-H), 3.70 – 3.75 (m, 3H, 2-H, 12-H), 3.85 – 3.95 (m, 2H, 3-H), 4.10 (s, 1H, 10-H), 4.15 – 4.25 (m, 4H, 13-H), 7.09 (m, 1H, 7-H), 7.31 – 7.80 (m, 11H, 8-H, 9-H, Ph, Ph-CH3), 8.10 (d, 1H, 6-H, J = 7.5 Hz). – Anal. for C30H29F3N3O2: calcd. C 67.28, H 5.27, N 7.85; found C 67.25, H 5.29, N 7.88.

Flash chromatography: ethyl acetate/petroleum ether.
NuH: 1-(3-methoxyphenyl)phenylpiperazine. Yield: 0.9 g (56 %). M. p. 213 – 215 °C. – 1H NMR: δ = 2.75 (d, 1H, 11-H, J = 12 Hz), 2.89 (d, 1H, 11-H, J = 10 Hz). 3.02 – 3.32 (m, 5H, 2-H, 12-H), 3.68 (m, 1H, 2-H), 3.80 – 3.89 (m, 2H, 3-H), 4.00 – 4.20 (m, 5H, 2-H, 12-H, 13-H, OCH3), 7.10 (m, 1H, 7-H), 7.32 – 7.85 (m, 11H, 8-H, 9-H, Ph, Ph-CH3), 8.03 (d, 1H, 6-H, J = 7.8 Hz). – Anal. for C29H21NO3: calcd. C 74.41, H 5.92, N 8.44; found C 74.39, H 6.28, N 8.42.

Flash chromatography: ethyl acetate/petroleum ether.
NuH: 1-(2-methylthiophenyl)phenylpiperazine. Yield: 0.82 g (50 %). M. p. 190 – 192 °C. – 1H NMR: δ = 2.27 – 2.33 (m, 1H, 2-H), 3.01 (d, 1H, 11-H, J = 12 Hz), 3.00 – 3.28 (m, 4H, 12-H), 3.42 (d, 1H, 11-H, J = 12 Hz), 3.82 – 4.13 (m, 10H, 2-H, 3-H, 13-H, OCH3), 4.62 (s, 1H, 10-H), 6.89 – 7.57 (m, 12H, 7-H, 8-H, 9-H, Ph, Ph-CH3), 8.11 (d, 1H, 6-H, J = 8 Hz). – Anal. for C30H21N3O2: calcd. C 74.21, H 5.68, N 8.44; found C 74.23, H 6.30, N 8.43.
\[ \text{H NMR: } \delta = 2.80 \text{ (d, 1H, 11-H, } J = 12 \text{ Hz)}, 3.00 \text{ (d, 1H, 11-H, } J = 12 \text{ Hz)}, 3.25 \text{ (m, 1H, 2-H)}, 3.52 - 3.94 \text{ (m, 11H, 2-H, 3-H, 12-H, 13-H), 4.10 \text{ (s, 1H, 10-H)}, 7.05 \text{ (m, 1H, 7-H), 7.00 - 7.65 \text{ (m, 7H, 8-H, 9-H, Ph)}, 8.17 \text{ (d, 1H, 6-H, } J = 7.3 \text{ Hz).} \]
