SYNTHESIS AND DETERMINATION OF THE ABSOLUTE STEREOCHEMISTRY OF THE ENANTIOMERS OF 3-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES RELATED TO THE CALCIUM ANTAGONIST VERAPAMIL

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Abstract - The four stereoisomers of 3-[4-cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (2) were prepared. The stereochemistry of the side chain quaternary carbon was derived from iodide 4 of known absolute configuration. The absolute stereochemistry at the 3-position of the tetrahydroisoquinoline was determined by correlation with L-DOPA. These compounds are related to the calcium antagonist verapamil and the calcium antagonist activity was greatest for the (S,S,R,S) isomer.

Structure-activity relationship (SAR) studies to date on the Group II calcium antagonist verapamil (1)2-4 have dealt with substitutions in the aromatic rings5,6 or modifications at the quaternary carbon atom.7-9 Our interest in the SAR of verapamil prompted us to prepare and evaluate a number of rigid phenethylamine analogs and preliminary results of these investigations indicated that compound 2 had interesting pharmacological activity. In this structure, the [4-cyano-(3,4-dimethoxyphenyl)-5-methylhex-1-yl] component of verapamil is attached to the 3-position of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (THIQ). Additional interest in 2 arose from the fact that remarkably few 3-substituted THIQ derivatives have been reported. This is in contrast to numerous examples of pharmacologically active 1, 2, and 4 substituted THIQ compounds.10 Since compound 2 contains two asymmetric centers, it was of interest to prepare the four isomers inherent in this structure. Reported herein are the synthesis and establishment of the absolute stereochemistry of these four stereoisomers.

The preparation of 2 from 3-(3,4-dimethoxyphenyl)propionic acid (3) is outlined in Scheme I. Alkylation of the dianion of 3 with iodide 4 (prepared from the corresponding chloride11 with NaI-acetone) gave a mixture of diastereomeric acids 5. Treatment of 5 with diphenylphosphoryl azide (DPPA)12 gave isocyanate 6 which, without isolation, was reduced with NaBH₄ to an
approximately 1:1 mixture of formamides 7 as determined by tlc and $^1$H NMR analysis. Bischler-Napieralski cyclization of 7 followed by NaBH$_4$ reduction gave THIQ 8 which was subjected to Eschweiler-Clarke methylation to afford 2. Compound 2 thus obtained was an approximately 1:1 mixture of diastereomers as determined by $^1$H NMR and hplc analysis.

**Scheme 1**

![Scheme 1](image)

The four isomers of 2 were obtained by the same basic route as was used for the parent compound (Schemes II and III). The (S)-iodide 4 was obtained from the known optically active chloride which had been used to prepare the enantiomers of verapamil.$^{11}$ Alkylation of 3 with (S)-4 followed by DPPA treatment and NaBH$_4$ reduction as before gave diastereomeric formamides (−)-9 and (−)-10 which were separated by chromatography on silica gel. The pure diastereomers thus obtained were converted to the THIQ final products as previously described to afford (−)-(3R,4S)-11 and (+)-(3S,4S)-12. The stereochemical assignments for position 3 of the THIQ are made in a following section.

The other two isomers, (−)-(3S,4R)-11 and (−)-(3R,4R)-12, were obtained by an analogous series of reactions (and chromatographic separation) from (R)-4 which was obtained from the corresponding known (R)-chloride$^{11}$ (Scheme III). The physical data obtained for these four isomers (Table I) is in accord with the assignment of 11 and 12 as enantiomeric pairs. Compounds (−)-11 and (+)-12, both of which were derived from (S)-4, are assigned enantiomer excesses (ee) of >98% based on the optical purity (>98% ee) of (S)-4 (experimental section). Compounds (+)-11 and (−)-12 are assigned ee of >96% based on the purity of (R)-4 (>96% ee).
Scheme II

3

(3S,7R) - 9

(3S,7S) - 10

(3S,4S) - 11

(3S,4S) - 12
Scheme III

\[
\begin{align*}
\text{MeO-} & \text{MeO-} \quad \text{COOH} \\
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
3 & \\
(\text{B}) & -4 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO-} & \text{NHCHO} \\
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
(3R, 7S) & -9 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO-} & \text{NHCHO} \\
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
(3R, 7R) & -10 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
(3S, 4R) & -11 \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
\text{MeO-} & \text{MeO-} \\
(3R, 4R) & -12 \\
\end{align*}
\]
TABLE I
PHYSICAL DATA FOR THlQ DERIVATIVES

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absolute Stereochem</th>
<th>Scheme</th>
<th>mp, °C</th>
<th>Solvent</th>
<th>[α]D25 (c, MeOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td>I</td>
<td>109-111</td>
<td>EtOH-Et2O</td>
<td></td>
</tr>
<tr>
<td>(+)-11</td>
<td>3S,4R</td>
<td>II</td>
<td>108-110</td>
<td>MeOH-Et2O</td>
<td>+25.8°(0.28)</td>
</tr>
<tr>
<td>(-)-11</td>
<td>3R,4S</td>
<td>II</td>
<td>108-110</td>
<td>EtOH-Et2O</td>
<td>-24.0°(0.34)</td>
</tr>
<tr>
<td>(+)-12</td>
<td>3S,4S</td>
<td>III</td>
<td>155-157</td>
<td>IPA-Et2O</td>
<td>+43.7°(0.32)</td>
</tr>
<tr>
<td>(-)-12</td>
<td>3R,4R</td>
<td>III</td>
<td>155-157</td>
<td>IPA-Et2O</td>
<td>-42.5°(0.28)</td>
</tr>
</tbody>
</table>

The assignment of the absolute stereochemistry of the 3 position of the THlQ was made by synthesis of (-)-(3R,4S)-11 from (S)-13 which was prepared from (-)-(S)-3,4-dihydroxyphenylalanine (L-DOPA)13 (Scheme IV). Amino alcohol 13 was converted to the BOC derivative 14 and then to tosylate 15. Treatment of 15 with vinylnimagnesium bromide and cuprous iodide afforded 16. Precedent for this useful conversion comes from the reported reaction of BOC-serine derivatives with organocuprates.14 Conversion of 16 to alcohol 17 and mesylate 18 proceeded without incident. However, attempted alkylation of 18 with the lithium salt of 2-(3,4-dimethoxyphenyl)-3-methylbutyronitrile (19) gave none of the desired product (21). The major side reaction which occurred under these conditions was intramolecular alkylation of the BOC nitrogen to form a BOC protected pyrrolidine. Fortunately, use of freshly prepared iodide 20, while an unstable material, did afford a modest yield of 21 as a mixture of two diastereomers. Deprotection of 21 followed by formylation gave the diastereomeric formamides which were separated by chromatography as before to afford (-)-(3S,7R)-9 and (+)-(3R,7R)-10.

The major formamide thus obtained, (-)-9, was cyclized, reduced, and N-methylated to afford (-)-11 identical in all respects to material obtained by the previous route (Scheme II). This sequence established the 3R configuration of the THlQ (-)-11 and, coupled with the known 4S configuration, established the complete absolute stereochemistry of (-)-11 as 3R,4S. The complete absolute stereochemistries of the other three isomers follow from the enantiomeric and diastereomeric relationships already established.
These isomers were tested for calcium antagonist activity as determined by their ability to relax the barium chloride contracted rat aortic strip (Table II). It was found that the majority of the calcium antagonist activity of the parent compound 2 resided in the (3S,4S)-12 enantiomer. This is consistent with the finding that the S enantiomer of verapamil is responsible for most of the parent compound's activity. In the THIQ derivatives, constraining the phenylethylamine moiety in the THIQ framework apparently introduces an additional stereochemical requirement in the binding of these compounds to the receptor which mediates the calcium antagonism in this series.
### TABLE II

**CALCIUM ANTAGONIST PROPERTIES OF THIQ DERIVATIVES**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$E_{D50}$ (mM)</th>
<th>Relative Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-(3S,4R)-11</td>
<td>4.0</td>
<td>0.08</td>
</tr>
<tr>
<td>(-)-(3S,4S)-11</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>(+)-(3S,4S)-12</td>
<td>0.1</td>
<td>3</td>
</tr>
<tr>
<td>(-)-(3R,4S)-12</td>
<td>2.0</td>
<td>0.15</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Verapamil (1)</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

*Determined by measuring the relaxation of BaCl$_2$ contracted rat aortic strips.

### EXPERIMENTAL

$^1$H NMR spectra were recorded with a Bruker WM 300 instrument and are reported in ppm $\delta$ downfield from an internal standard of TMS. Medium pressure (flash) chromatography was performed using 230-400 mesh Merck Kieselgel. Melting points are uncorrected. Elemental analyses were done by the Syntex analytical department.

(S) and (R)-3-Cyano-3-(3,4-dimethoxyphenyl)-6-iodo-2-methylhexane ((S)-4 and (R)-4)

Resolution of 4-(3,4-dimethoxyphenyl)-4-(2-propyl)-4-pentenoic acid using (-)-cinchonidine was carried out as described in the literature. The optical purities of the (S)-(−)-acid and (R)-(−)-acid thus obtained were determined by $^1$H NMR analysis of the diastereomeric amides derived from the acid chlorides (oxalyl chloride, benzene) and (S)-(−)-α-methylbenzylamine. In the $^1$H NMR spectrum of the amide from the (S)-(−)-acid, resonances for the methoxy groups were at $\delta$ 3.63 and $\delta$ 3.87 while in the amide from the (R)-(−)-acid, resonances at $\delta$ 3.74 and $\delta$ 3.86 were observed. In the amide from the racemic acid, these four resonances appeared with equal intensities (thus ruling out any differences in the rates of formation of the diastereomeric amides). The amide from the (S)-(−)-acid was determined to have a diastereomeric ratio of >94:<6 by integration of the methoxy resonances at $\delta$ 3.63 and $\delta$ 3.74 respectively. Thus, an ee of >88% was assigned to the (S)-(−)-acid. The amide from the (R)-(−)-acid was pure (>98%) by $^1$H NMR analysis and the (R)-(−)-acid was therefore assigned an ee of >95%.

These acids were converted into the (S)-iodide 4 and (R)-iodide 4 by conversion to the corresponding chlorides as described, followed by treatment with NaI in acetone. They were obtained as thick oils which were used without purification in the next step.

(3S,7R) and (3S,7S)-7-Formamido-3,8-di-(3,4-dimethoxyphenyl)-2-methyl-3-octanenitrile ((S)-9 and (−)-10)

To a solution of 21 ml (0.15 mol) of diisopropylamine in 480 ml of THF at −50°C was added 91.8 ml (0.147 mol) of 1.6M n-butyllithium in hexane. HMPT (56 ml) was added followed by a solution of 15.1 g (0.072 mol) of 3-(3,4-dimethoxyphenyl)propionic acid (3) in 75 ml of THF. The
This compound was prepared from \((-\)-\)3-\(\text{S}\)-4-\(\text{S}\)-methylisoquinoline hydrochloride ((S,S)-12) for

\[\text{(S,S)-3-\(\text{S}\)-4-\(\text{S}\)-cyanomethylhex-1-yl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((S,S)-12)}\]

To a solution of 5.67 g (0.012 mol) of \((-\)-\)10 in 100 ml of MeCN was added 2.8 ml (0.03 mol) of POC\(_1\). The resulting solution was stirred 3 h at room temperature, concentrated at reduced pressure, and partitioned between Et\(_2\)O and aqueous \(\text{NaOH}\). The Et\(_2\)O layer was evaporated and the residue was dissolved in 100 ml of EtOH, cooled in an ice bath, and treated with 1.0 g of NaBH\(_4\). The mixture was stirred for 30 min and then added to water and acidified with HCl. The solution was washed with Et\(_2\)O and the aqueous layer was basified with \(\text{NH}_4\text{OH}\) and extracted with Et\(_2\)O. The Et\(_2\)O extract was evaporated and the residue was dissolved in 30 ml of formic acid and 30 ml of 37% aqueous formaldehyde. This solution was stirred at 100°C for 1 h and then added to ice-water which was subsequently basified with \(\text{NH}_4\text{OH}\). Et\(_2\)O extraction followed by drying (Na\(_2\)SO\(_4\)) and evaporation afforded the crude free base as an oil. This was dissolved in a small amount of EtOH-HCl and crystallization was induced by adding Et\(_2\)O. The yield of \((3S,4S)-12\) was 4.5 g (74%): \(^1\text{H NMR (DMSO-d}_6\) 0.71 (d, 3H), 1.13 (d, 3H), 2.65 and 2.70 (broad s, 3H, pseudo axial, equatorial \(\text{NCH}_3\)), 3.73 (s, 6H), 3.78 (s, 6H), 6.74 (s, 2H), 6.91 (s, 1H), 6.96 (s, 2H). \(^1\text{H NMR (CDCl}_3\) 3.85 (m, 1H), 3.90 (s, 3H), 6.00-6.30 (m, 3H), 6.74 (d, 2H), 6.96 (s, 2H). \(^1\text{H NMR (MeOH-d}_4\) 3.85 (m, 1H), 3.90 (s, 3H), 6.00-6.30 (m, 3H), 6.74 (d, 2H), 6.96 (s, 2H). Anal. Calcd for \(\text{C}_{27}\text{H}_{38}\text{N}_2\text{O}_4\cdot\text{HCl}: C, 66.90; H, 7.74; N, 5.98. Found: C, 66.89; H, 7.80; N, 5.81.

\((R)-3-\(\text{S}\)-4-\(\text{S}\)-cyanomethylhex-1-yl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride ((R,S)-11)

This compound was prepared from \((-\)-\)2 in 67% yield using procedures analogous to those used for...
\((3S,4S)-12:\) \(^1\)H NMR \((\text{Me}_2\text{SO-d}_6)\) \& 0.72 (d, 3H), 1.14 (d, 3H), 2.64 and 2.78 (broad s, 3H, NCH\(_3\)), 3.73 (s, 3H), 3.74 (s, 6H), 6.74 (s, 2H), 6.93 (s, 1H), 6.96 (s, 2H).

Anal. Calcd for \(\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_4\cdot\text{HCl}\cdot\text{H}_2\text{O}:\) C, 65.54; H, 7.93; N, 5.38. Found: C, 64.10; H, 7.98; N, 5.30.

\((3R,7S)\) and \((3R,7R)-7\)-Formamido-3,8-di-(3,4-dimethoxyphenyl)-2-methyl-3-octanenitrile \((+)-9\) and \((+)-10\).

A mixture of \((+)-9\) and \((+)-10\) was obtained in 78% overall yield from acid 3. The pure compounds were obtained by medium pressure chromatography (10% hexane-EtOAc). The first component eluted was \((+)-9:\) \(^1\)H NMR identical to \((-)-9:\) \([\alpha]^{25}_D\) +8.07° (c 0.33, MeOH).

Anal. Calcd for \(\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_5:\) C, 69.20; H, 7.74; N, 5.98. Found: C, 69.09; H, 7.76; N, 5.93. The second component eluted was \((+)-10:\) \(^1\)H NMR identical to \((-)-10:\) \([\alpha]^{25}_D\) +3.84° (c 0.37, MeOH).

Anal. Calcd for \(\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_5:\) C, 69.20; H, 7.74; N, 5.98. Found: C, 69.00; H, 7.95; N, 5.74.

\((R)-3-[(R)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-y1]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride (3R,4R)-12\)

This compound was prepared from \((+)-10\) in 76% yield and was spectrally identical to \((3S,4S)-12\).

Anal. Calcd for \(\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_4\cdot\text{HCl}:\) C, 66.85; H, 7.81; N, 5.57. Found: C, 66.77; H, 7.86; N, 5.54.

\((S)-3-[(R)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-y1]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride (3S,4R)-11\)

This compound was prepared from \((+)-9\) in 66% yield and was spectrally identical to \((3R,4S)-11\).

Anal. Calcd for \(\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_4\cdot\text{HCl}:\) 0.5 H\(_2\)O: C, 66.57; H, 7.87; N, 5.47. Found: C, 66.59; H, 7.89; N, 5.46.

\((R,S)-3-(R,S)-4-Cyano-4-(3,4-dimethoxyphenyl)-5-methylhex-1-y1]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline hydrochloride (2)\)

This was prepared according to the procedures described for the synthesis of the isomers except that \((4)-4\) was used and the diastereomeric formamides were not separated. The final product was analyzed by HPLC using a Spherisorb 5 C8 column with a mobile phase of 0.1 M triethylamine adjusted to pH 5.0:MeOH:ACN, 60:35:10. The two diastereomers were cleanly separated with the \((R,S)/(S,R)\) pair eluting as the first peak followed by the \((R,R)/(S,S)\) pair as the second. The diastereomer ratio was determined to be -50:50.

Anal. Calcd for \(\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_4\cdot\text{HCl}:\) C, 66.85; H, 7.81; N, 5.57. Found: C, 66.92; H, 7.58; N, 5.60.

\((S)-2-(\text{tert}-\text{Butyloxycarbonylamino})-3-(3,4-dimethoxyphenyl) propanol (14)\)

To a solution of 23.3 g (0.11 mol) of \(\text{d}_4\)-\text{tert}-butyldicarbonate in 400 ml of THF was added 24.0 g (0.11 mol) of \(\text{d}_4\)-\text{tert}-butyldicarbonate and the resulting solution was heated at reflux for 1 h. The mixture was concentrated at reduced pressure and the residue was filtered through silica gel (EtOAc).

Evaporation afforded 32.4 g (95%) of \((S)-14:\) mp 92-93°C; \([\alpha]^{25}_D\) -19.6° (c 0.3, MeOH).

Anal. Calcd for \(\text{C}_{16}\text{H}_{25}\text{NO}_3:\) C, 61.72; H, 8.09; N, 4.50. Found: C, 61.62; H, 8.13; N, 4.57.
A solution of 32.4 g (0.10 mol) of 14, 29.8 g (0.16 mol) of p-toluenesulfonyl chloride, and 0.63 g of DMAP in 100 ml of pyridine was stirred at room temperature for 48 h. The mixture was diluted with ether and washed with aqueous cupric sulfate and water. The ether was dried (MgSO₄) and evaporated to a residue that was purified by medium pressure chromatography (30% EtOAc-hexane) to afford 43.5 g (90%) of 15: mp 146-148°C; [α]D₂⁵ +15.4° (c 0.36, CHCl₃). Anal. Calcd for C₂₃H₃₁NO₇S: C 59.34; H 6.71; N 3.01. Found: C 59.37; H 6.73; N 2.98.

Vinylmagnesium bromide (37.3 ml, 0.60 mol, 1.6M in THF) was added to a -5°C suspension of 5.8 g (0.03 mol) of cuprous iodide in 75 ml of THF. The mixture was cooled to -70°C and a solution of 4.6 g (0.01 mol) of 15 in 80 ml of THF was added slowly. The resulting mixture was stirred at -70°C for 0.5 h and then allowed to warm to room temperature. The mixture was poured into aqueous NH₄Cl and extracted with Et₂O. The Et₂O was dried (MgSO₄) and evaporated. Purification of the residue by medium pressure chromatography (30% EtOAc-hexane) gave 2.0 g (63%) of 16: mp 91-92°C; 'H NMR (CDCl₃) 0.81 (s, 9H), 2.01-2.30 (m, 2H), 2.70 (m, 2H), 3.86 (s, 3H), 3.86 (m, 1H, CH₃), 3.87 (s, 3H), 5.10 (m, 2H), 5.80 (m, 1H), 6.70-6.82 (m, 3H); [α]D₂⁵ -20.9° (c 0.26, MeOH). Anal. Calcd for C₁₈H₂₇N0₄: C 67.26; H 8.47; N 4.36. Found: C, 67.33; H, 8.49; N, 4.36.

A solution of 1.6 g (0.005 mol) of 16 was added to a 0°C solution of diisamylborane (0.0075 mol, from 1.6 ml of 2-methyl-2-butene and 7.5 ml of 1.0M BH₃) in 25 ml of THF. The mixture was stirred at room temperature for 1 h, cooled to 0°C, and treated with 1.7 ml of 3M NaOH and 1.7 ml of 30% H₂O₂. The resulting solution was stirred 0.5 h at room temperature, diluted with ether, and washed with water and brine. Evaporation of the ether and crystallization of the residue from Et₂O-hexane gave 1.2 g (70%) of 17: mp 73-75°C; [α]D₂⁵ +0.89° (c 0.2, MeOH). Anal. Calcd for C₁₈H₂₇NO₅: C, 63.58; H, 8.64; N, 4.06.
purified by medium pressure chromatography (30% EtOAc-hexane) to afford 0.6 g (38%) of the diastereomeric mixture 21. This material was dissolved in 5 ml of formic acid and the resulting solution was heated at reflux for 15 min. The mixture was concentrated under reduced pressure and the residue was treated with 2 ml of formic-acetic anhydride. Et2O was added and the mixture was washed with water, aqueous NaHCO3, and brine. After drying (Na2SO4) the ether was evaporated and the residue was purified by medium pressure chromatography (EtOAc). The first component eluted was \((-\)-9, (0.18 g), identical by tlc and nmr analysis with material from the other route: \(\alpha_D^{25} -4.3^\circ\) (c 0.28, MeOH). The second component eluted was \((+)-10\) (0.04 g) identical by tlc and nmr analysis with material from the other route: \(\alpha_D^{25} +2.3^\circ\) (c 0.3, MeOH).

\((-\)-3R,4S)-11 from Scheme IV

This was prepared from formamide \((-\)-9, derived from 13 in Scheme IV, in 68% yield according to the previously described procedure. Anal. Calcd for C28H38N2O4.HCl.0.5H2O: C, 65.57; H, 7.89; N, 5.47. Found: C, 65.59; H, 7.89; N, 5.46.

ACKNOWLEDGEMENT

We thank Dr. David Lokensgard for the hplc determinations and Ms. Gina Costelli, Bertha Harris and Mary Kavanagh for preparing the manuscript.

REFERENCES

1. Contribution no. 728 from the Institute of Organic Chemistry. This paper is dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.


10. Examples would include such compounds as the $\beta$-agonists trimetoquinol and higenamine (1-substituted THIQ), the antidepressant nomifensin (2,4-disubstituted), and the tranquilizer butaclamol (1,2,4-trisubstituted) among others.


16. It is interesting to note that attaching the verapamil side chain to the 2-position of 6,7-dimethoxy-THIQ gave a compound with minimal calcium antagonist activity (ED$_{50}$ = 1 mM) (D. Repke, unpublished results).

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