Eur J Med Chem (1990) 25, 369–374

Short communication

Synthesis and biological activity of iodinated and photosensitive derivatives of tetrabenazine**

G Aranda[1]*, JP Beaucourt[2], M Ponchant[2], MF Isambert[3], JP Henry[3]

[1]*Laboratoire de Synthèse Organique, École Polytechnique, 91128 Palaiseau;*
[2]*Service des Molécules Marquées, Centre d'Énergie Nucléaire Saclay, 91191 Gif-sur-Yvette;*
[3]*Laboratoire de Neurobiologie Physico-chimique, Institut de Biologie Physico-chimique, 13, rue P et M Curie, 75005 Paris, France*

(Received 14 March 1989; accepted 26 October 1989)

Summary — The synthesis of a photosensitive iodinated derivative of tetrabenazine, which should be able to lead to the identification of the vesicular catecholamine transporter of adrenal medulla by photoaffinity, is described in detail. The biological activity of this iodinated ligand was found to be significantly lower than that of non iodinated ligands.

Résumé — Synthèse et activité biologique de dérivés iodés et photosensibles de la tétrabénazine. *La synthèse d'un dérivé de la tétrabénazine, photosensible et iodé, susceptible de conduire par photoaffinité à l'identification du transporteur vésiculaire des catécholamines de la médullo-surrénale, est exposée en détail. Une diminution importante de l'activité biologique du ligand iodé est observée comparativement à celle des ligands non iodés.*

neuroleptic tetrabenazine / catecholamines carrier / photoaffinity labelling / iodinated ligand

Introduction

Adrenaline and noradrenaline, the catecholamines of adrenal medulla, are stored in specialized organelles, the chromaffin granules, from which they are released in the bloodstream by exocytosis. The mechanism by which these granules accumulate monoamines is now well understood [1–3]. It is a two-step ATP-dependent process involving:
(i) inward translocation of protons by an electrogenic ATP-dependent H^+-pump of the granule membrane;
(ii) a monoamine/H^+ antiport catalyzed by a specific transporter located in the same membrane, but independent of the H^+-pump. The same mechanism operates in all monoamine storage vesicles, such as the dopamine, noradrenaline or serotonin presynaptic vesicles of the nervous system [4] or the serotonin dense granules of blood platelets [5–7]. The monoamine transporter is a minor component of these membranes, and, in spite of its interest, its purification has not as yet been possible. In an effort to achieve this goal, tritiated ligands were developed to label the transporter, using known uptake inhibitors [8–11]. Tetrabenazine is such an inhibitor [12, 13], from which a high affinity ligand was derived, [^{3}H]dihydrotetrabenazine, characterized by an equilibrium dissociation constant of 3 nM [8].

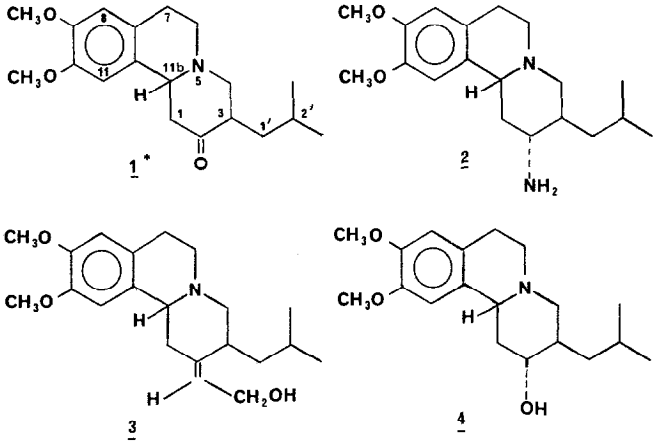
Various tritiated azidoderivatives of tetrabenazine were also synthesized to identify the transporter by the photoaffinity technique [14, 15]. Though interesting results have been obtained [14], these derivatives were difficult to use for the following reasons:
(i) the affinity of the probe for its binding site was decreased by the derivatization used, the dissociation constant increasing to 50 nM after introduction of an amide link;
(ii) the low specific activity (2 Ci/mmol) of the derivative resulted in high non specific labelling;
(iii) because of the low energy of tritium radiation and of some instability of the covalently bound probe, the electrophoresed material had to be analyzed by slicing the gels and measuring the radioactivity by liquid scintillation. Derivatives of higher specific activity were subsequently synthesized [15] which improved specific labelling, but they were still difficult to use for fluorographic detection of the labelled material after electrophoresis on sodium dodecylsulfate/polyacrylamide slab gels. For these

*Correspondence and reprints
**This work was supported in part by the CNRS (ARI No 902622)

reasons, we initiated the synthesis of a new series of iodinated derivatives, which, to our mind, should be easier to use because of their higher specific activity.

Chemistry

The ligands liable to effectively lead to the binding of the transporter correspond to the derivatives **2, 3** and **4** of tetrabenazine (TBZO) **1**.



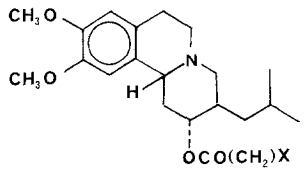
*The adopted numeration corresponds to that described earlier [16].

The necessary photosensitive function can be introduced through synthons **2, 3** and **4**, which show a high affinity for the monoamine transporter (table I). Dihydrotetrabenazine (TBZOH) **4** is the easiest to obtain [8]. In order to avoid the interaction of the photosensitive function with the TBZ moiety, these 2 functions must not be close to one another. Among the possible derivatives of alcohols **3** and **4**, only the esters of alcohol **4** were obtained. Because of spontaneous intramolecular cyclisation observed during the synthesis of various esters, a caproic chain was preferred to a valeric or a butyric one.

Esterification with ω-azido caproic acid chloride [17] gave the corresponding ester **5** in 98% yield after chromatography. The amino ligand **6** was obtained quantitatively from **5** by the Staudinger method [18] in boiling tetrahydrofurane.

Table I. Affinity of the synthesized derivatives for the monoamine transporter.

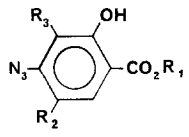
Compound	*EC_{50} (nM)*	
1	3.0 ± 0.5	(n = 8)
2	116 ± 14	(n = 6)
3	14 ± 8	(n = 5)
4	6.7 ± 1.1	(n = 7)
6	8.1 ± 3.3	(n = 32)
12	53 ± 17	(n = 16)
13	428 ± 226	(n = 20)



X = N_3, n = 5 **5**

X = NH_2, n = 5 **6**

4-Azido salicylic acid **7** was chosen as a photosensitive molecule to be coupled with the ω-amino caproic ester **6**. **7** was obtained from the corresponding amine by diazotization by NO_2Na in the presence of sulfuric acid followed by treatment with N_3Na in water. A high specific radioactivity obtainable with ^{125}I seemed to be necessary for the further use of the photosensitive ligand at a very low concentration [19, 20].



$R_1 = R_2 = R_3 = H$ **7**

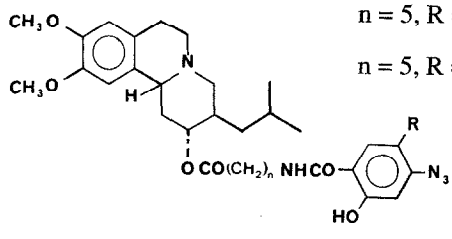
$R_1 = CH_3$, $R_2 = R_3 = H$ **8**

$R_1 = CH_3$, $R_2 = I$, $R_3 = H$ **9**

$R_1 = H$, $R_2 = I$, $R_3 = H$ **10**

$R_1 = CH_3$, $R_2 = R_3 = I$ **11**

The validity of the techniques of radioiodinations [21, 22] was assessed by the iodination of **8**. The first method [21] only gave decarboxylated compounds and the second one [22] mainly gave the diiodoester **11** in DMF or acetonitrile, contrary to previous reported results [22, 23]. Finally, monoiodoester **9** was obtained in 80% yield as a mixture with starting ester **8** and diiodoester 11 according to the method of Ji and Ji [24]. **9** was then saponified to **10** by a methanolic hydroxide solution. Amides **12** and **13** were obtained by condensation of the amine **6** with the succinimidyl esters of **7** and **10** [25]. They were isolated crude with a purity of 97–98% as determined by ^{13}C-NMR and were purified by HPLC.



n = 5, R = H **12**

n = 5, R = I **13**

Pharmacology

The affinity of the tetrabenazine derivatives for the monoamine transporter of chromaffin granule membranes was measured by testing their efficiency

to displace bound [^{3}H] TBZOH [8]. The results are given in the table as EC_{50} values (concentration displacing 50% of the bound ligand).

Discussion and Conclusion

In the design of a new tetrabenazine-derived photosensitive probe of the monoamine transporter, 2 changes were tried:
(i) introduction of an ester link of the tetrabenazine nucleus and;
(ii) iodination of the acylazido moiety.

Apparently, amine or azido derivatization of the tetrabenazine nucleus did not dramatically affect its affinity for the monoamine transporter. In fact, valeric derivatives had affinities similar to that of caproic ones, characterized by EC_{50} of 17, 27 and 450 nM for the amino, azido and iodoazido derivatives, respectively. This result is consistent with a previous study from our laboratory where the relation between the length of the lipophilic chain and the biological activity has been similarly studied [26]. It is also consistent with the observation that the affinity of a series of tetrabenazine derivatives increased with their hydrophobicity, estimated from the apparent octanol-water partition coefficient [27].

On the other hand, the iodinated ligand has a much lower affinity than the non iodinated one. This important decrease is certainly related to the high Van Der Waals radius and polarisability of the iodine atom, which introduce numerous interactions near the receptor. This observation is surprising, since the photosensitive function which has been iodinated is distant from the biological moiety. It might be of general interest for the application of the technique of photoaffinity, since in this technique, active ligands are often directly radioiodinated without any test of the activity of the iodinated derivative. Furthermore, it seems necessary to also check the photolysis of the iodinated arylazido moiety, since photo–diiodination process has been recently described [28]. Though the use of another ligand and/or a different photosensitive function is possible in our case, it is probably more interesting to attempt the isolation of the transporter by affinity chromatography through the already described amine **6**.

Experimental protocols

Biological methods

The affinity of tetrabenazine derivatives for the monoamine transporter of chromaffin granule membranes was measured by testing their efficiency to displace bound [^{3}H] TBZOH [8].

Bovine chromaffin granule membranes were purified as described [29]. [^{3}H] TBZOH (15 Ci/mmol) and tetrabenazine were obtained from CEA (Gif-sur-Yvette, France) and Fluka (Buchs, Switzerland), respectively.

Membranes (19 μg of protein/ml) in 0.3 M sucrose/10 mM Hepes buffer, pH 7.5 were incubated for 2 h at 30°C with 1 nM [^{3}H] TBZOH and the studied compound at various concentrations. Bound [^{3}H] TBZOH was determined by filtration through GF/B glass fiber filters (Whatman, Clifton, NJ) preincubated in 0.3% polyethyleneimine [30]. Nonspecific binding, determined by addition of 2 μM tetrabenazine to the incubation mixture, was subtracted. The drug concentration corresponding to half-inhibition of [^{3}H] TBZOH binding (EC_{50}) was derived from the inhibition curve obtained by fitting the data to the theoretical curve by non-linear regression analysis (n, number of experimental points used for the determination of the curve).

Chemical synthesis

Melting points were determined on a heating stage under microscope and were uncorrected. Chromatographic analyses on silica gel HF 254 were performed by successive elutions. IR spectra were recorded on a Perkin Elmer 257 spectrometer, in carbon tetrachloride or chloroform solution. ^{13}C NMR spectra were recorded on a Bruker AC 200 FT spectrometer in deuterated chloroform. ^{13}C chemical shifts are given in ppm with TMS as standard with a sensitivity of ± 0.10 ppm·δ $(CH_3)_4Si$ = δ $(CDCl_3)$–77.1 ppm (see table II). ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer in deuterated chloroform. Chemical shifts were given in ppm with TMS as standard. Analysis of new photosensitive compounds were carried out and recorded on a Finnigan Mat 4006 spectrometer. All syntheses related to photosensitive aromatic compounds were achieved in a darkroom. NMR spectra of these compounds were carried out using a tube made of inactinic glass. Methylene chloride was distilled on P_2O_5, acetone and acetonitrile on K_2CO_3, tetrahydrofuran on sodium in the presence of benzophenone. Chromatography under pressure was achieved on a Jobin-Yvon chromatograph.

Trans-*2 hydroxy-3 isobutyl-9,10 dimethoxy-1,2,3,4,6,7 hexahydro-11bH-benzo(a)quinolizine* ***4***
It was obtained by reduction of tetrabenazine according to a known method [31]. The mixture of *cis/trans* alcohols was chromatographed on silica gel H60. The *trans* isomer (75%) was first eluted and then characterized. Mp = 167–170°C. IR ($CHCl_3$, cm^{-1}): 3600, 3350, 2950, 1620, 1470, 1370, 1150, 1010.
^{1}H NMR: 0.91 (3H, d, J = 6.20 Hz, CH_3); 0.93 (3H, d, J = 6.20 Hz, CH_3); 3.63 (6H, s, 2 OCH_3); 6.57 and 6.66 (2H, 2s, C_6H_2).

Trans-*2 (6-azidohexanoyloxy)-3 isobutyl-9,10 dimethoxy-1,2,3,4,6,7 hexahydro-11bH-benzo(a)quinolizine* ***5***
ω-Azido caproic acid chloride was obtained as already described (17). Bp = 62–64°C under 10^{-2} torr. Alcohol **4** was esterified in methylene chloride under N_2, in the presence of DMPA at the ice bath temperature. After usual work-up, the ester **6** was chromatographed and purified as an oil, turning yellow at room temperature. Yield 97% from **4**.
IR (CCl_4, cm^{-1}): 2940, 2100, 1735, 1610, 1470, 1270, 1170, 1025.
^{1}H NMR: 0.90 (3H, d, J = 6.40 Hz, CH_3); 0.913 (3H, d, J = 6.40 Hz, CH_3); 3.27 (1H, t, J = 7.0 Hz, CH in position 11b); 3.83 (6H, s, 2 OCH_3); 4.67 (1H, dt, $J_{1,2}$ = 10 Hz, $J_{2,3}$ = 4.5 Hz, H in position 2); 6.58 and 6.62 (2H, s, C_6H_2).

Trans-2 (6-aminohexanoyloxy)-3 isobutyl-9,10 dimethoxy-1,2,3,4,6,7 hexahydro-11bH-benzo(a)quinolizine ***6***

The azido ester **5** was transformed into amine **6** by the Staudinger method in boiling tetrahydrofurane with triphenylphosphine during 17 h then with H_2O. A colorless oil was obtained rapidly yellowing at room temperature. Recrystallization in acetone/hexane was tedious. PF = 102–104°C. The corresponding stable hydrochloride was easily obtained by dissolving the oil in cold dilute hydrochloric methanol. Recrystallisation of this hydrochloride was achieved in the mixture acetone/ethyl ether and a few drops of methanol. Mp = 204–206°C.

Amine **6**: $C_{25}H_{40}N_2O_4$, m = 432.60. Mass spectrometry by chemical ionization (NH_3): 432.2. IR (CCl_4, cm^{-1}): 3300, 2960, 2940, 1735, 1610, 1470, 1370, 1250. ^1H NMR: 0.83 (3H, d, J = 6.40 Hz, CH_3); 0.86 (3H, d, J = 6.40 Hz, CH_3); 3.76 (6H, s, $2OCH_3$); 4.60 (1H, dt, $J_{1,2}$ = 10.2 Hz, $J_{2,3}$ = 4.2 Hz, H in position 2); 6.50 and 6.55 (1H, s, C_6H_2).

4-Azido-5 iodo methylsalicylate ***9***

4-Aminosalicylic acid was diazotized in 25% H_2SO_4 solution by NO_2Na and N_3Na in water, to give 4-azidosalicylic acid, which was filtered off, dissolved in an excess of CH_2Cl_2 and then washed with a 10% hydrochloric acid solution. **7** was obtained with a 54% global yield as a pink crystallized powder (mp = 214.5–215.5°C). TLC on silica 60 F_{254}. Eluent: methanol/CH_2Cl_2 (1/3). Rf = 0.40.

7 was hardly soluble in usual solvents, especially in chloroform. By reaction with diazomethane, methyl ester **8** was obtained and recrystallized first in pentane and then in aqueous ethanol. Mp = 63–64°C. IR (CCl_4, cm^{-1}): 2980, 2120, 1685, 1445, 1345, 1270, 1145, 955, 940. ^1H NMR: 3.92 (s, 3H, OCH_3); 6.47–7.78 (m, 3H, C_6H_3); 10.92 (s, 1H, OH). ^{13}C NMR: 52.3, OCH_3; 107.2, CH in position 5; 109.3, C in position 1; 110.5, CH in position 3; 131.6, CH in position 6; 147.3, C in position 2; 162.9, C in position 4; 169.95, CO_2.

Iodination of ester **8** by chloramine T-sodium iodide in DMF or acetonitrile [23] gave a mixture of **9**/**11** in a ratio of 1/5 or 1/6. Diiodinated ester **11** was separated by recrystallization in CH_2Cl_2/pentane.

Iodination of **8** in an acetone/acetonitrile mixture provided a mixture of **8**/**9**. The amount of **9** decreases with increasing

Table II. ^{13}C chemical shifts of the indicated compounds as solutions in $CDCl_3$ (δ ppm).

Carbon	*Compound*							
	1	***4***	***5***	***6***	***12***		***13***	
1	47.5	40.7	36.8	36.9	36.7		36.7	
2	209.5	74.3	76.3	76.3	76.3		76.3	
3	47.5	41.6	38.3	38.4	38.2		38.2	
4	61.4	60.2	60.0	60.2	60.0		59.9	
6	50.4	51.9	51.7	51.7	51.7		51.7	
7	29.3	29.3	29.2	29.3	29.1		29.1	
8	111.7	111.4	111.4	112.0	111.6		111.8	
9	147.6	147.2	147.6	147.7	147.6		147.8	
10	147.7	147.4	147.3	147.6	147.3		147.4	
11	108.2	108.0	108.1	108.8	108.2		108.5	
11b	62.3	62.3	60.5	60.5	60.5		60.5	
12	126.1	126.1	126.4	126.7	126.4		126.5	
13	128.6	128.6	129.0	129.4	128.9		129.0	
1'	35.0	39.9	39.6	39.8	39.6		39.6	
2'	25.4	25.3	25.3	25.4	25.3		25.3	
3' (4')	23.1	24.1	23.9	24.0	23.9		23.9	
4' (3')	22.1	21.7	21.8	21.9	21.8		21.8	
			173.3	173.5	173.6	107.9 CH	173.7	73.7 CI
			34.0	34.5	34.3	109.7 CCO	34.2	107.8 CH
			28.6	26.4	26.3	111.6 CH	26.2	113.9 CCO
	side chain in 2		24.5	24.7	24.3	127.4 CH	24.1	137.1 CH
			29.2	31.6	29.0	146.1 COH	28.9	146.7 COH
			51.0	41.2	39.3	162.8 CN_3	39.5	162.8 CN_3
					169.3		168.1	

reaction time. Chromatography on silica gel 60 F_{254} with CH_2Cl_2/pentane (8/2) as eluent: Rf of **8**: 0.42; Rf of **9**: 0.47; Rf of **11**: 0.48.

Ester **9** was eventually obtained according to previous results [24]. 0.241 g (1.25 mmol) of **8** was dissolved in 10 ml of acetone redistilled over K_2CO_3 in the presence of 0.10 ml of a 0.1 N sodium hydroxide solution. 0.206 g (1.10 eq) of sodium iodide and 0.387 g (1.1 eq) of chloramine T where then added under vigorous stirring for more than 1 h. The solution was filtered, acetone removed *in vacuo* and CH_2Cl_2 added. The organic phase was washed with a sodium thiosulfate solution (10 ml) and water (2 x 10 ml), then dried over $MgSO_4$. After vacuum removal of the solvents, a whitish crystallized residue was obtained (0.40 g) which contained esters **8** and **9** (1/2) in the presence of 4-methyl-phenylsulfonamide. Mp = 135.5–136°C, as shown by ^1H NMR. By HPLC of **8** + **9**, pure iodinated ester **9** was obtained in 80% yield calculated according to the starting material, **8** recovered and recrystallized in 95% ethanol. Mp = 141–142.5°C. IR (CCl_4, cm^{-1}): 2980, 2110, 1680, 1615, 1475, 1443, 1330, 1285, 1105. ^1H NMR: 3.88 (s, 3H, OCH_3); 6.67 (s, 1H, CH in position 3); 8.12 (s, 1H, CH in position 6); 10.81 (s, 1H, OH). ^{13}C NMR: 52.07, OCH_3; 74.75, CI in 5; 107.0, CH in 3; 111.3, C in 1; 141.0, CH in 6; 148.5, C in 2; 162.7, C in 4; 168.8, CO_2.

*4-Azido 3,5-diiodo methyl salicylate **11***
Mp = 99–100°C. IR ($CHCl_3$, cm^{-1}): 2115, 1680, 1612, 1335, 1160, 1100. ^1H NMR: 3.95 (s, 3H, OCH_3); 3.17 (s, 1H, CH in position 6); 11.73 (s, 1H, OH). ^{13}C NMR: 53.3, OCH_3; 77.9, CI in 5; 83.8, Cl in 3; 111.5, C in 1; 140.6, CH in 6; 147.9, C in 2; 161.7, C in 4; 168.4, CO_2.

*4-Azido 5-iodo salicylic acid **10***
By refluxing **9** in an ethanolic sodium hydroxide solution for 3 h, acid **10** was obtained as a crystallized residue, hardly soluble in usual solvents, especially in chloroform. (Mp with thermal decomposition not determined.) **10** was used without purification in the further steps.

*Amides **12** and **13***
General method. They were obtained by condensation in acetonitrile of the amine and succinimidyl ester of acid **7** or **10** [25].

Trans-*2 [6-[(4-azido-2 hydroxy)benzamido]hexanoyloxy]-3 isobutyl-9,10 dimethoxy-1,2,3,4,6,7 hexahydro-11bH-benzo-(a)quinolizine **12***
0.270 g (1.50 mmol) of 4-azidosalicylic acid **7** and 0.334 g (1.50 mmol) of disuccinimidyl carbonate were dissolved in acetonitrile/pyridine (5 ml/1 ml) under nitrogen and magnetic stirring at room temperature for 16 h. After addition of CH_2Cl_2 (60 ml), the organic phase was washed with a $NaHCO_3$ saturated solution (12 ml) and water (2 x 10 ml), then dried over K_2CO_3. After removal of the solvents *in vacuo*, 0.22 g (53%) of a crystallized compound was obtained. The aqueous phase contained unreacted **7**, which could be recovered after acidification. The crystallized succinimidyl ester was dissolved in acetonitrile/pyridine (2.50 ml/0.50 ml) under N_2 at room temperature. Amine **6** (0.282 g) in CH_3CN (4.50 ml) was added dropwise under magnetic stirring. After 16 h, the solvents were removed *in vacuo*. CH_2Cl_2 (75 ml) was added and the organic phase washed with a cold 2% sodium hydroxide solution (5 ml) and water (3 x 5 ml). After removal of the solvents, an homogeneous oil (0.37 g) was obtained (silica gel 60 F_{254}; eluent: ethyl acetate). The purity was 97–98% by ^{13}C NMR. The oil was purified by chromatography (silica gel H) but no crystals were obtained.

Amide **12**: $C_{32}H_{43}N_5O_6$, M = 593.73. MS (chemical ionization, NH_3): M = 593.9. IR ($CHCl_3$, cm^{-1}): 3300, 2980, 2950, 2135, 1740, 1725, 1660, 1465, 1375, 1100. ^1H NMR: 0.813 (3H, d, J = 6.5 Hz, CH_3); 0.83 (3H, d, J = 6.50 Hz, CH_3); 3.71 and 3.77 (6H, s, 2 OCH_3); 4.60 (1H, dt, $J_{1,2}$ = 10 Hz, $J_{2,3}$ = 4.5 Hz, H in position 2); 6.48 and 6.50 (2H, 2s, C_6H_2); 6.46, 6.47, 7.42 and 7.46 (3H, m, C_6H_3); 6.92 (1H, m, NH); 10.8 (1H, s, OH).

Trans-*2 [6-(4-azido 2-hydroxy 5-iodo)benzamido]hexanoyl-oxy]-3 isobutyl-9,10 dimethoxy-1,2,3,4,6,7 hexahydro-11bH-benzo-(a)quinolizine **13***
Similarly, 0.226 g of **10** and 0.235 g of **6** gave 0.36 g of **13** (92% yield) and 0.082 g of unreacted **10**. **13** was obtained as an homogeneous oil (silica gel HF_{254}, eluent: methanol/ethyl ether 5/95) with a purity of 97% (^{13}C NMR). This oil was dissolved in an acetone/pentane mixture and filtered on Celite to give orange crystals (non determined mp, due to thermal decomposition at about 140°C).
Amide **13**: $C_{32}H_{42}N_5O_6$, M = 719.63. MS (chemical ionization, NH_3): M = 719.4. IR (CCl_4, cm^{-1}): 3300, 2975, 2965, 2120, 1720, 1650, 1470, 1365, 1095. ^1H NMR: 0.94 (3H, d, J = 6.40 Hz, CH_3); 0.99 (3H, d, J = 6.40 Hz, CH_3); 3.74 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 4.82 (1H, dt, $J_{1,2}$ = 10 Hz, $J_{2,3}$ = 4.5 Hz, H in position 2); 6.40 and 6.58 (2H, s, C_6H_2); 6.75 and 8.10 (2H, s, $C_6H_2(OH)N_3$); 7.40 (1H, m, NH).

References

1 Njus D, Kelley PM, Harnadek GJ (1986) *Biochim Biophys Acta* 853, 237–265
2 Johnson RG (1988) *Physiol Rev* 68, 232–307
3 Kanner B, Schuldiner S (1987) *CRC Crit Rev Biochem* 22, 1–38
4 Toll L, Howard BD (1978) *Biochem* 17, 2517–2523
5 Carty SE, Johnson RG, Scarpa A (1981) *J Biol Chem* 256, 11244–11250
6 Wilkins JA, Saganicoff L (1981) *Biochem J* 198, 113–123
7 Fishkes H, Rudnick G (1982) *J Biol Chem* 257, 5671–5677
8 Scherman D, Jaudon P, Henry JP (1983) *Proc Natl Acad Sci USA* 80, 584–588
9 Scherman D, Henry JP (1984) *Mol Pharmacol* 25, 113–122
10 Deupree JD, Weaver JA (1984) *J Biol Chem* 259, 10907–10912
11 Darchen F, Scherman D, Laduron PM, Henry JP (1988) *Mol Pharmacol* 33, 672–677
12 Pletscher A (1977) *Br J Pharmacol* 59, 419–424
13 Scherman D, Henry JP (1980) *Biochem Pharmacol* 29, 1883–1890
14 Isambert MF, Henry JP (1985) *Biochemistry* 24, 3660–3667
15 Henry JP, Gasnier B, Isambert MF, Darchen F, Scherman D (1988) *In: Progress in Catecholamine Research* (Dahlström A, Belmaker PM, Sandler M, eds) A Liss, NY 141–147
16 Schwartz DE, Bruderer H, Rieder J, Brossi A (1966) *Biochem Pharmacol* 15, 645–655
17 Khoukhi N, Vaultier M, Carrié R (1987) *Tetrahedron* 43, 1811–1822
18 Vaultier M, Knouzi N, Carrié R (1983) *Tetrahedron Lett* 24, 763–764
19 Seevers RH, Counsell RE (1982) *Chem Rev* 82, 575–590

20 Ji I, Shin J, Ji Tae H (1985) *Anal Biochem* 151, 348–349
21 Escher EHF, Robert H, Guillemette G (1979) *Helv Chim Acta* 62, 1217–1222
22 Kometani T, Watt SD, Ji Tae H (1985) *Tetrahedron Lett* 26, 2043–2046
23 Kometani T, Watt SD, Ji Tae H, Fitz T (1985) *J Org Chem* 50, 5384–5387
24 Ji Tae H, Ji I (1982) *Anal Biochem* 121, 286–289
25 Ogura H, Kobayashi T, Shimizu K, Kawabe K, Takeda K (1979) *Tetrahedron Lett* 4745–4746
26 Aranda G, Gauvrit C (1987) *Phytochemistry* 26, 1909–1913
27 Scherman D, Gasnier B, Jaudon P, Henry JP (1988) *Mol Pharmacol* 33, 72–77
28 Watt DS, Kawada K, Leyva E, Platz MS (1989) *Tetrahedron Lett* 30, 899–902
29 Giraudat J, Roisin MP, Henry JP (1981) *Biochemistry* 19, 4499–4505
30 Bruns RF, Lawson-Wendling K, Pugsley TA (1983) *Anal Biochem* 132, 74–81
31 Brossi A, Chopart-Dit-Jean LH, Schnider O (1958) *Helv Chim Acta* 41, 1793–1805