Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 7, pp. 799-804, 1997
© 1997 Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00109-1

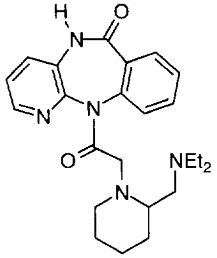
SYNTHESIS AND EVALUATION OF HALOGENATED DIBENZODIAZEPINES AS MUSCARINIC RECEPTOR LIGANDS

Michael Kassiou,[a] Roger W. Read,[b,*] and Xue-qin Shi[b]

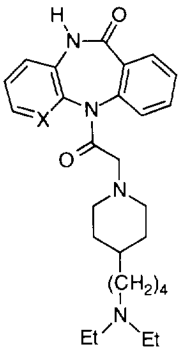
[a]*Radiopharmaceuticals Division, ANSTO, PMB 1, Menai NSW 2234, Australia*
[b]*School of Chemistry, The University of New South Wales, Sydney NSW 2052, Australia*

Abstract: Syntheses of four novel amide analogues of the muscarinic M_2 receptor antagonists, DIBA and BIBN 140, are described from a common intermediate. Pharmacological evaluation through in vitro assays reveals high muscarinic receptor affinity in each of the compounds, but variable subtype selectivity, primarily M_2 but in one case M_3. © 1997 Elsevier Science Ltd.

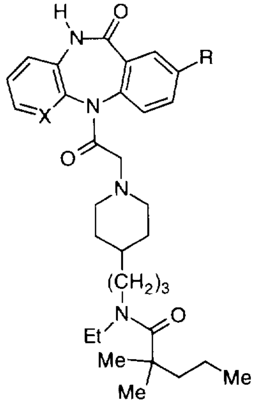
Clinical studies of Alzheimer's disease and other age-related illnesses have been restricted largely to subjects that are in advanced stages of dementia. In those demented patients, presynaptic M_2 muscarinic receptors are depleted.[1] It is possible that the decrease in M_2 receptors begins at an earlier stage and that detection of this decrease might be used to diagnose the onset of dementia.



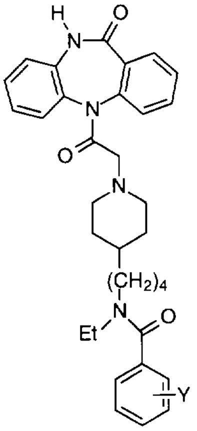
1 AF-DX 116



2 X=N AQ-RA 741
3 X=CH DIBA



4 X = N, R = Cl BIBN 99
5 X = CH, R = H BIBN 140



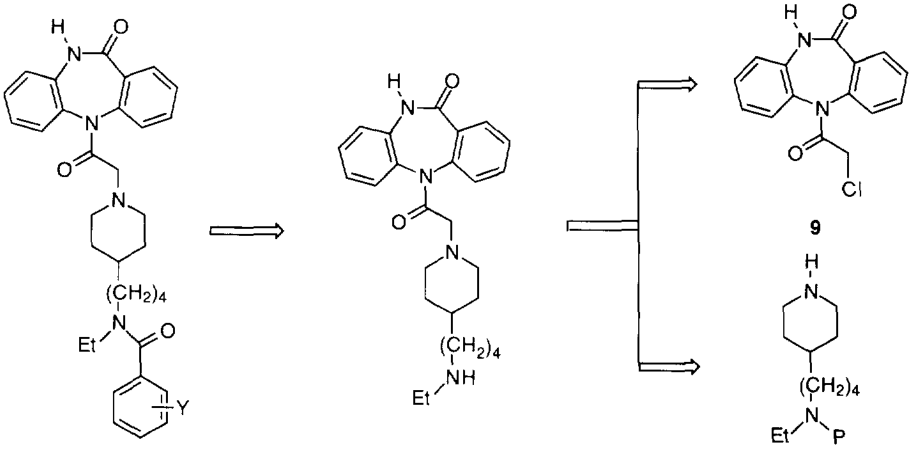
6 Y = 3-iodo
7 Y = 4-fluoro

Until now muscarinic M_2 receptor antagonists have been designed with the aim of developing compounds that could be used for the treatment of cognitive disorders.[2] Dibenzodiazepines have evolved from the prototype, AF-DX 116 **1**, to related compounds with improved affinity and higher M_2 selectivity (e.g., AQ-RA 741 **2**[3] and DIBA **3**[4,5]), which are potent at M_2 receptors but do not cross the blood-brain barrier sufficiently to be useful. Two antagonists that are permeable to the central nervous system and yet show high receptor affinity and a pronounced M_2 versus M_1 selectivity ratio are BIBN 99 **4** and BIBN 140 **5**,[6] in which the side-chain basic nitrogen of earlier compounds is replaced by an amide group. This amide character therefore imparts lipophilicity to the molecules without unduly affecting antagonist activity and is considered an important design element.

In this paper is described a convergent synthesis of analogues **6** and **7** (see Scheme 1) of BIBN 140 **5**, in which the *N*-acyl group is replaced with 3-iodobenzoyl and 4-fluorobenzoyl groups, and an assessment of their muscarinic receptor affinities. These specific halogenated derivatives have been selected because their radiolabelled analogues (with I-123, a γ emitter with $t_{1/2}$ = 13.5 h, and F-18, a β^+ emitter with $t_{1/2}$ = 109.6 min) are particularly suited for use in sensitive but noninvasive techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET), respectively.[7]

Synthesis

A convergent synthesis of the aroyl derivatives **6** and **7** was envisaged as outlined in Scheme 1. The chloroamide **9** is readily available by literature methods,[4,8] therefore our synthetic efforts were directed towards the substituted piperidine portion. Key to the success of this general route was the early protection of the side chain nitrogen as its ethoxycarbonyl derivative **10**.



6 Y = 3-iodo
7 Y = 4-fluoro

11

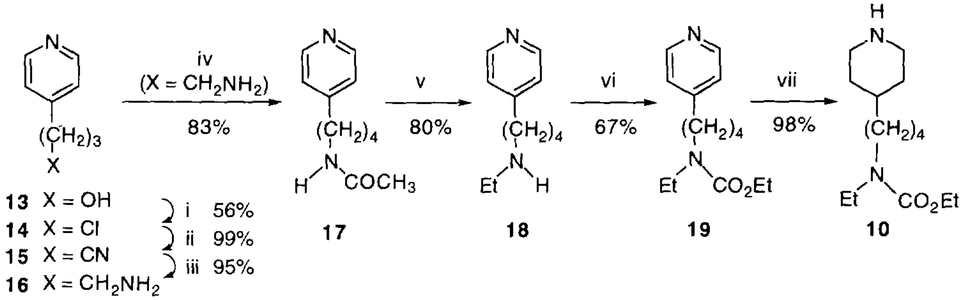
12 P = H
10 P = CO_2Et

Scheme 1

Existing approaches to the synthesis of dibenzodiazepinone-containing muscarinic antagonists and their analogues (e.g., **2** and **3**) follow a common strategy.[4,9,10] This approach cannot be adopted directly for the synthesis of **11** because problems of selectivity between two secondary amine groups, as in **12** (P = H), would be experienced in the latter substitution reaction. Use of a selectively protected aminoalkylpiperidine, **12** (P ≠ H), was required for a successful outcome.

Compound **10** was ultimately readily prepared from commercially available and inexpensive pyridine-4-propanol **13**, as outlined in Scheme 2. Treatment of **13** with the Lucas reagent provided clean access to chloride **14**, which underwent nucleophilic displacement with NaCN in warm dimethyl sulfoxide,[11] to give the nitrile **15** in excellent yield. Nitriles have been reduced to primary amines using a wide variety of reagents, however, at this stage it was also important to retain the pyridine ring in its nonreduced form. Selective reduction of the nitrile group of **15** was achieved using a small excess (2 mol equiv) of $LiAlH_4$ in diethyl ether. 4-(4-Pyridyl)butanamine **16** was obtained in 95% yield in a form suitable for further use without any further purification.

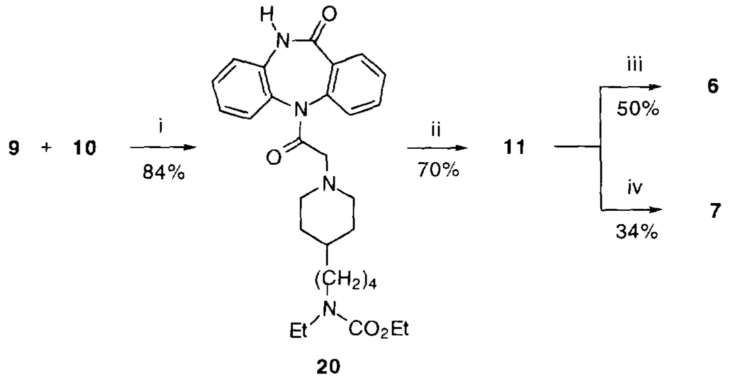
A sequence involving ethoxycarbonylation of the primary amino group of **16** followed by ethylation failed in the latter step due to inactivity of the ethoxycarbonylamino group. Therefore, primary amine **16** was acetylated and the intermediate amide **17** reduced[12] with $LiAlH_4$ in tetrahydrofuran to give the secondary amine **18** as a pale-yellow oil. Treatment of **18** with $ClCO_2Et$ under basic conditions then yielded carbamate **19** without difficulty.



Reagents: i. $ZnCl_2$, conc. HCl, reflux, 24 h; ii. NaCN, DMSO, reflux, 2 h; iii. $LiAlH_4$, ether, rt, 3 h; iv. Ac_2O, ambient temp.; v. $LiAlH_4$, THF, reflux, 2 h; vi. $ClCO_2Et$, NaOH, pH 9, 0 °C, 30 min; vii. H_2, PtO_2, HCl, MeOH.

Scheme 2

It was noted that many of the signals for protons and carbons in the vicinity of the carbamate nitrogen were broadened in carbamate **19**. At elevated temperature (380 K) the previously broad (almost undetectable) carbon signals at δ 13.8, 28.6, 42.2, 46.8, and 156.0 became sharp and could be assigned to $NCH_2\underline{C}H_3$, C3', C4', $N\underline{C}H_2CH_3$, and CO, respectively, indicating that broadening was due to restricted rotation about the amide bond. Localisation of the broadening phenomenon confirmed that ethoxycarbonylation had occurred at the expected secondary amine position.



Reagents: i. CH_3CN, K_2CO_3, reflux, 5 h; ii. $(CH_3)_3SiI$, $CHCl_3$, reflux; iii. 3-iodobenzoyl chloride, *n*-Bu_4NHSO_4, 5% aq. NaOH, CH_2Cl_2, reflux, 2 h; iv. 4-fluorobenzoyl chloride, *n*-Bu_4NHSO_4, 5% aq. NaOH, CH_2Cl_2, 0 °C, 10 min.

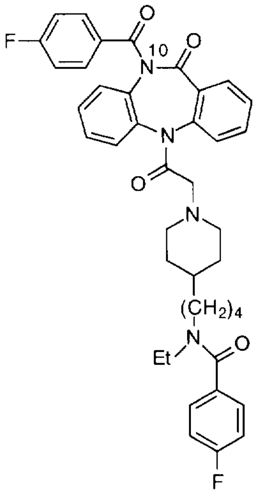
Scheme 3

Finally, hydrogenation[4] of carbamate **19** at atmospheric pressure under acidic conditions over PtO_2 gave the desired, appropriately substituted piperidine reactant **10** in satisfactory yield. Attachment of this lower portion **10** to chloroamide **9**[4] then afforded the advanced carbamate intermediate **20**[13] (Scheme 3).

Attempts to remove the ethoxycarbonyl group by hydrolysis under alkaline (25% aqueous KOH) or acid (48% HBr in water) conditions were unsuccessful. However, iodotrimethylsilane in $CHCl_3$[14] proved satisfactory and gave the secondary amine **11**[13] in 70% yield.

The advanced secondary amine **11** was intended as a key substance from which a wide range of derivatives might later be prepared. It was subjected in turn to acylation with 3-iodobenzoyl chloride and 4-fluorobenzoyl chloride, in order to prepare the model halogenated amide derivatives **6** and **7**. Surprisingly the reactions occurred at remarkably different rates.

The secondary amine **11** reacted with a slight excess (1.5 mol equiv) of 3-iodobenzoyl chloride in CH_2Cl_2 under basic phase transfer conditions at reflux for 2 h to yield the first target molecule, 3-iodobenzamide **6**, as an amorphous powder (mp 74-75 °C).[13] The substance was characterised by elemental analysis, mass spectrometry, and ^{1}H and ^{13}C NMR spectroscopy. Its ^{1}H NMR spectrum was complex due to broadening caused by the two noncyclic amide groups, but the essential features were as expected and very similar to those of carbamate **20**. Isomers about the amide group attached to the dibenzodiazepinone ring system were evident from the appearance of two equal intensity broad N-H singlets at δ 9.06 and 9.60 in the ^{1}H NMR spectrum. Many of the ^{13}C NMR signals associated with this part of the molecule were broad but the majority of the remaining aromatic signals and the ethyl signals were sharp and appeared as duplicate peaks. It appeared from this observation that rotation about the amide group at the dibenzodiazepinone terminus was relatively slow on the NMR timescale but that rotation about the amide in the side chain was an even slower process thereby giving the duplication of signals.



21

In contrast, secondary amine **11** reacted with 4-fluorobenzoyl chloride (1.5 mol equiv) under the conditions used for the preparation of 3-iodobenzamide **6** to give in moderate yield a product that was not the desired amide **7**. The substance showed a molecular ion at *m/z* 679 (M+H) in its electrospray mass spectrum. Microanalytical results were slightly ambiguous but were most consistent with a formula $C_{40}H_{40}N_4O_4F_2$, indicative of a diacylation product, probably **21**.[13]

Repetition of the reaction under milder conditions (a stoichiometric amount of 4-fluorobenzoyl chloride in CH_2Cl_2 under basic phase transfer conditions in ice) gave complete reaction within 5 min. Three components were evident by TLC analysis immediately after addition. They were, in decreasing R_f value: the diacylation product **21**, the desired monoamide **7**, and the starting amine **11**. The 4-fluorobenzamide **7**[13] was isolated as a colourless foam in 79% yield. Its electron impact mass spectrum showed a trace (M-1) molecular ion at *m/z* 555 and a base peak at *m/z* 123 corresponding to the 4-fluorobenzoyl ion. Elemental analysis results were consistent with a hemihydrate of the expected substance, $C_{33}H_{37}N_4O_3F$, and matrix assisted laser desorption ionisation (MALDI) mass spectrometry showed an intense molecular ion at *m/z* 557.47. The structure of the 4-fluorobenzamide **7** was therefore confirmed. Its ^{1}H NMR spectrum contained very broad signals, similar to those of the 3-iodobenzamide **6**, but integration of the aromatic region showed the presence of twelve protons, eight from the dibenzodiazepinone rings and four from the new fluorobenzoyl protons. Two broad equal intensity signals at δ 8.95 and 9.55 were also observed, again corresponding to the isomeric amide N-H protons attached at position 10 in the dibenzodiazepinone ring.

Pharmacological Evaluation

Compounds **6**, **7**, **11**, **20**, and **21** were evaluated in in vitro experiments to determine their neuroreceptor selectivity and affinity through the NIMH/NOVASCREEN® Drug Discovery and Development Program (Contract No. NIMH-2003).

Table 1. Binding affinities of compounds **6**, **7**, **11**, **20**, and **21** to muscarinic receptor subtypes.

Compound	(K_i, nM)		
	M_1	M_2	M_3
6	67.1	111	33.5
7	59.4	32.0	46.4
11	6.98	4.49	N/A*
20	70.0	37.1	39.2
21	129	46.9	79.1

* Accurate K_i could not be determined. IC_{50} <1.0 nM.

All compounds displayed selectivity and high affinity for muscarinic receptors when compared with other receptors screened, including subtypes of the dopaminergic, adrenergic, serotonergic, and sigma receptors (data not shown). Further, there was revealed a 2:1 and 3:1 selectivity towards the M_3 receptor compared with M_1 and M_2 binding, respectively, for compound **6**. In contrast, there was 2:1 and marginal selectivity towards the M_2 receptor compared with M_1 and M_3 binding, respectively, for compounds **7**, **20**, and **21**. Secondary amine **11** showed an order of magnitude higher affinity for muscarinic receptors than did its derivatives but marginal M_2 and undetermined M_3 selectivity. Retention of muscarinic selectivity is gratifying but the selectivity towards the M_3 receptor by the iodobenzoyl derivative **6** was unexpected and undesirable.

In summary, the synthesis of compound **11** has yielded a unique building block for design selective muscarinic binding ligands. However, comparison of the biological data for a wider range of compounds is needed before conclusions can be drawn about the reasons for the differences in muscarinic subtype selectivity. It is clear that all compounds prepared here have marked muscarinic receptor affinity and that relatively small changes at the nitrogen sidechain can dramatically influence subtype selectivity.

Acknowledgment. We wish to thank Dr A. Katsifis for assistance in organizing the pharmacological evaluation of the amine and four amide analogues.

References and Notes

1. (a) Mash, D. C.; Flynn, D. D.; Potter, L. T. *Science* **1985**, *228*, 1115; (b) Iversen, L. L. *Trends Pharmacol. Sci. Suppl.* **1986**, 44; (c) McKinney, M.; Coyle, J. T. *Mayo Clinic Proceedings* **1991**, *66*, 1225.
2. Dörje, F.; Wess, J.; Lambrecht, G.; Tacke, R.; Mutschler, E.; Braun, M. R. *J. Pharm. Exp. Ther.* **1991**, *250*, 727.
3. Doods, H. N.; Quirion, R.; Mihm, G.; Engel, W.; Rudolf, K.; Entzeroth, M.; Schiavi, G. B.; Ladinsky, H.; Bechtel, W. D.; Ensinger, H. A.; Mendla, K. D.; Eberlein, W. *Life Sci.* **1993**, *52*, 497.
4. Cohen, V. I.; Baumgold, J.; Jin, B.; De La Cruz, R.; Rzeszotarski, W. J.; Reba, R. C. *J. Med. Chem.* **1993**, *36*, 162.
5. Gitler, M. S.; Reba, R. C.; Cohen, V. I.; Rzeszotarski, W. J.; Baumgold, J. *Brain Res.* **1992**, *582*, 253.
6. Doods, H.; Entzeroth, M.; Ziegler, H.; Schiavi, G.; Engel, W.; Mihm, G.; Rudolf, K.; Eberlein, W. *Eur. J. Pharmacol.* **1993**, *242*, 23.
7. Stöcklin, M. *Eur. J. Nucl. Med.* **1992**, *19*, 527.
8. Giani, R. P.; Borsa, M.; Parini, E.; Tonon, G. C. *Synth. Commun.* **1985**, 550.
9. Cohen, V. I.; Jin, B.; Gitler, M. S.; de la Cruz, R. A.; Boulay, S. F.; Sood, V. K.; Zeeberg, B. R.; Reba, R. C. *Eur. J. Med. Chem.* **1995**, *30*, 61.

10. Cohen, V. I.; Jin, B.; Reba, R. C. *J. Heterocycl. Chem.* **1993**, *30*, 835.
11. Friedman, L.; Shechter, H. *J. Org. Chem.* **1960**, *25*, 877.
12. Moffett, R. B. *Org. Synth.* **1967**, 354.
13. Physical and spectroscopic data for **6**, **7**, **11**, **20**, and **21**: **6** mp 74-75 °C (Found: C, 59.36; H, 5.95; N, 8.00. $C_{33}H_{37}N_4O_3I$ requires: C, 59.64; H, 5.62; N, 8.43%). IR (KBr) 3430 br, 1655, 1625, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.86-0.93, brm, $(H1''')_2$, $H_{ax}3'' + H_{ax}5''$, H4"; 1.05, brd, 6H; 1.23, brd, 3.5H; 1.99, brs, 2H; 2.54-2.74, brm, 2H; 3.11 (minor), 3.18 (major), 2 x brm, 4.5H; 3.41-3.48, brm, 1.5H; 7.11, t, *J* 7.7 Hz, 1H; 7.19-7.32, m, 4H; 7.43, br d, *J* 6 Hz, 3H; 7.58, ddd, *J* 7.7, 7.7, 1.6 Hz 1H; 7.68 (major), 7.72 (minor), 2 x brs, 2H; 7.98, brd, *J* 7.2 Hz, H1; 9.06, 9.60, 2 x brs, NH. ^{13}C NMR ($CDCl_3$) δ 12.8, 14.1, $NCH_2\underline{C}H_3$; 23.7, 24.2, C2'''; 27.7, 28.9, C1'''; 32.0, C3" + C5"; 35.0, C4"; 35.8, 36.1, C3'''; 39.7, 43.6, $N\underline{C}H_2CH_3$; 44.5, 48.6, C4'''; 53.7, C2" + C6"; 60.3, C2'; 121.7, CH; 125.4, CH; 126.5, br; 128.0, br; 128.4, br; 129.1, br; 130.1, CH; 131.6, C; 133.2, CH; 134.2, CH; 134.5, br; 138.1, CH; 139.1, C; 142.4, CH; 167.8, br, C11; 169.3, $\underline{C}OCH_2$; 169.5, $\underline{C}OPh$. EIMS *m/z* 664 (M^+, 0.1%), 662 (0.5), 236 (11), 231 (22), 210 (17), 148 (15), 111 (28), 97 (55), 83 (63), 69 (96), 55 (92), 43 (100).
    7 mp 71-72 °C (Found: C, 70.00; H, 6.95; N, 9.36. $C_{33}H_{37}N_4O_3F \bullet 0.5H_2O$ requires: C, 70.06; H, 6.77; N, 9.90%). IR (KBr) 3440, 1665, 1630, 1605 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.82, m, $NCH_2C\underline{H}_3$; 0.90-1.35, brm, 9H; 1.35-1.62, brm, 3H; 1.85-2.05, brm, 3H; 2.40-2.82, 3 x brs, 2H; 2.97-3.27, brm, 3H; 3.35-3.57, 2 x brm, 1H; 7.06, t, *J* 8.7 Hz, 2H; 7.20, brt, *J* 7.2 Hz, 1H; 7.15-7.45, brm; 7.33, d, *J* 8.7 Hz, 1H; 7.35, d, J 8.2 Hz, 1H; 7.38-7.48, brm, 4H; 7.58, td, *J* 7.6, 1.0 Hz, H2; 7.97, d, *J* 7.7 Hz, H1; 8.95, 9.55, 2 x brs, NH. ^{13}C NMR ($CDCl_3$) δ 11.4, 12.8, br; 14.1, br; 14.3; 18.8; 19.4; 20.4; 20.7; 22.6, brm; 24.1, br; 25.3; 26.9; 27.6; 27.8, br; 28.9, br; 29.0; 29.4; 30.9; 32.1, very br; 34.7; 35.1, br; 36.1, br; 39.8, br; 41.3; 43.7, br; 44.5, br; 48.8, br; 53.8, br; 60.4, br; 115.3; 125.6; 126.5, br; 128.0, br; 128.5; 128.6; 129.1 br; 131.6; 133.3; 134.3, br; 134.5; 135.5, br; 142.5; 161.3; 164.6, C4""; 167.7, br, C11; 169.5, $\underline{C}OCH_2$; 170.5, $\underline{C}OPh$. MALDI MS *m/z* 557.47 (95), 529.79 (42). EIMS *m/z* 555 (M-1, 0.1%), 319 (65), 305 (16), 210 (16), 181 (9), 123 (100), 95 (27), 84 (12).
    11 mp 58-60 °C (Found: C, 68.60; H, 7.63; N, 11.93. $C_{26}H_{34}N_4O_2 \bullet 1.2H_2O$ requires: C, 68.39; H, 7.45; N, 12.27%). IR (KBr) 3440 br, 1650, 1595 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.95-1.20, brm, $(H1''')_2$, $H_{ax}3''$, $H_{ax}5''$ and H4"; 1.16, t, *J* 7.3 Hz, $NCH_2C\underline{H}_3$; 1.27, quint, $(H2''')_2$; 1.49, m, $(H3''')_2$; 1.93, distorted t, *J* 11.0 Hz, $H_{ax}2''$ and $H_{ax}6''$; 2.5-2.8, brm, 1.5H; 2.63, t, *J* 7.5 Hz, $(H4''')_2$; 2.71, brq, *J* 6.8 Hz, $NC\underline{H}_2CH_3$; 3.13, m, 1.5H; 7.18, brm, H6; 7.20, brt, *J* 7.5 Hz, H8; 7.29, brt, *J* 7.0 Hz, H7; 7.41, brm, H2, H4 and H9; 7.57, td, *J* 7.5, 1.2 Hz, H3; 7.97, brd, *J* 7.9 Hz, H1. ^{13}C NMR ($CDCl_3$) δ 15.0, $CH_2\underline{C}H_3$; 24.4, C2'''; 30.0, C3'''; 32.0, C4"; 35.0, C3" and C5"; 36.2, C1'''; 43.9, $N\underline{C}H_2CH_3$; 49.6, C2" and C6"; 53.7, $CO\underline{C}H_2N$; 60.3, C4'''; 121.7, CH; 125.3, CH; 126.4, br, CH; 127.8, br, CH; 128.8, br, CH; 130.4, br, CH; 131.4, C; 132.9, CH; 134.3, C; 135.6, br, C; 142.4, C; 167.8, br, C11; 169.5, $\underline{C}OCH_2$. EIMS *m/z* 435 (M+1, 0.2%), 434 (M^+, 0.4), 433 (0.3), 210 (11), 197 (100), 183 (26), 152 (10), 96 (23), 58 (71).
    20 mp 54-55 °C (Found: C, 68.44; H, 7.36; N, 10.88. $C_{29}H_{38}N_4O_4$ requires: C, 68.74; H, 7.56; N, 11.06%). IR (KBr) 3460 br, 1660, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.90-1.20, brm, $(H1''')_2$, $H_{ax}3''$ and $H_{ax}5''$, H4"; 1.02, t, *J* 6.9 Hz, $NCH_2C\underline{H}_3$; 1.22, t, *J* 7.2 Hz, $OCH_2C\underline{H}_3$; 1.36, brm, $(H2''')_2$; 1.45, brm, $(H3''')_2$; 1.89, brt, *J ca.* 9 Hz, $H_{ax}2''$ and $H_{ax}6''$; 2.48 (minor), 2.68 (major), 2 x brm, 1.5H; 3.10 (major), 3.16 (minor), 2 x brm, 5.5H; 4.06, q, *J* 7.2 Hz, $COC\underline{H}_2CH_3$; 7.10-7.19, m, H6; 7.24, brm, H7 and H8; 7.31-7.42, brm, H2; 7.38, brd, J 7.7 Hz, H4 and H9; 7.52, ddd, *J* 7.7, 7.4, 1.5 Hz, H3; 7.94, br d, J 7.7 Hz, H1; 9.89 (minor), 10.33 (major), 2 x brs, NH. ^{13}C NMR ($CDCl_3$) δ 13.2, 13.6, br, $NCH_2\underline{C}H_3$; 14.0 (minor), 14.6 (major), $OCH_2\underline{C}H_3$; 20.8 (minor), 23.8 (major), C2'''; 28.5, br, C3'''; 32.0, C4"; 35.0, C3" and C5"; 36.0, C1'''; 41.5, br, $N\underline{C}H2CH3$; 46.2, 46.8, br, C4'''; 49.6, C2" and C6"; 53.7, $CO\underline{C}H_2N$; 60.2, 60.8, $O\underline{C}H_2CH_3$; 121.7, CH; 125.2, CH; 126.4, br, CH; 127.8, br, CH; 128.8, br, CH; 130.4, br, CH; 131.3, C; 132.9, CH; 134.3, C; 135.6, br, C; 142.4, C; 156.0, $\underline{C}O_2Et$; 168.0, br, C11; 169.4, $\underline{C}OCH_2$. EIMS *m/z* 506 (M^+, 0.3%), 269 (100), 255 (24), 210 (9), 181 (16), 130 (24), 96 (32), 58 (52), 44 (67).
    21 mp 56-57 °C (Found: C, 70.93; H, 6.22; N, 8.00. $C_{40}H_{40}O_4F_2$ requires: C, 70.78; H, 5.94; N, 8.25%). IR (KBr) 3440 br, 1680, 1640, 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.82, m, 3H; 0.91-1.65, m, 12H; 1.65-1.85, m, 2H; 1.97, brt, *J ca* 10 Hz, 1H; 2.50-2.85, br m, 3H; 2.90-3.60, brm, 9H; 7.06, t, *J* 8.7 Hz, 2H; 7.07, t, *J* 8.7 Hz, 2H; 7.33, d, *J* 8.2 Hz, 1H; 7.33-7.46, brm, 3H; 7.50, br d, *J* 9.2 Hz, 1H; 7.61, brm, 1H; 7.74, brm, 1H; 7.92, brm, 1H; 7.95, dd, J 7.7, 1.5 Hz, 1H. ^{13}C NMR ($CDCl_3$) δ 11.4; 12.8, br; 14.1, br; 14.3; 18.8; 19.4; 22.6; 24.0, br; 25.3; 27.7, br; 29.1; 29.9; 31.6; 31.7; 31.8; 34.7; 35.0; 36.0, br, 39.8, br; 43.8, br; 44.6, br; 48.8, br; 54.0; 54.3; 60.6; 115.3; 115.7; 115.9; 116.2; 127.9, br; 128.5; 128.6; 128.8; 129.0; 129.2, br m; 131.7, br; 133.0, br; 133.3; 133.4; 134.4, br; 139.0, br; 143.4, br; 161.4, C; 164.7, C; 167.0, br, C11; 169.3, $\underline{C}OCH_2$; 170.4, $\underline{C}OPh$; 170.5, $\underline{C}OPh$. Electrospray MS *m/z* 679 (M+H).
14. Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.

(*Received in USA* 23 *December* 1996; *accepted* 19 *February* 1997)