Synthesis of Novel Succinamide Derivatives Having the 5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one Skeleton as Potent and Selective M_2 Muscarinic Receptor Antagonists. I

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A series of 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one derivatives containing the succinamide skeleton has been synthesized and evaluated for M_1, M_2 and M_3 muscarinic receptor binding affinities (*in vitro*) and M_2 and M_3 muscarinic receptor antagonistic activities (*in vivo*). Some of them showed higher and more selective binding affinities for M_2 muscarinic receptors than that of AF-DX 116. Among them, 11-[3-[*N*-[2-(*N*-benzyl-*N*-methylamino)ethyl]-*N*-ethylcarbamoyl]propionyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (68) was found to be the most potent and selective M_2 muscarinic receptor antagonist *in vitro*. This compound also strongly inhibited the oxotremorine-induced bradycardia after intravenous administration and showed 130-fold selectivity for M_2 muscarinic receptors over M_3 muscarinic receptors *in vivo*.

Key words selective M_2 muscarinic receptor antagonist; succinamide; AF-DX 116; bradycardia

Muscarinic cholinergic receptors can be biologically categorized into at least five subtypes (m_1—m_5), which share about 70% identity in terms of amino acid sequences.[1-5] They can be pharmacologically divided into three subtypes (M_1—M_3) in terms of the effects of different selective antagonists, and the m_1, m_2 and m_3 receptors correlate to the M_1, M_2 and M_3 muscarinic receptors, respectively.[6,7] The M_2 muscarinic receptors are located in the heart, smooth muscle and glands, and play a crucial role in the regulation of the heart rate in the sinus node. The heart rate is reduced by stimulation of M_2 muscarinic receptors, coupled preferentially to the inhibition of adenylate cyclase.[8] Clinical trials have been reported involving administration of atropine, a potent non-specific muscarinic receptor antagonist, which was effective in increasing the heart rate for 60% of patients with sinus nodal dysfunction.[9] Although these data demonstrated that an M_2 antagonist may be a useful drug for bradycardiac disorders, the use of atropine is limited due to the short duration of action and the occurrence of several unwanted side effects such as dryness of the mouth, mydriasis and gastrointestinal and urinary events caused by antagonism of other subtypes. This is the reason why selective M_2 antagonists are required.

Three distinct types of selective M_2 antagonists, himbacine,[10] methoctramine[11] and AF-DX 116, are known, and derivatives of methoctramine[12-14] and AF-DX 116[15-17] have been reported by several researchers. Methoctramine derivatives have been used as a tool in muscarinic receptor subtype characterization. AF-DX 116 (11-[[2-[(diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one) (otenzepad) (**2**) which includes a tricyclic ring system[18] is now entering the clinical development stage. This compound was found by modification of pirenzepine (**1**), a selective M_1 muscarinic receptor antagonist that contains the same tricyclic system, by moving the most basic nitrogen of the piperazine ring to a location attached to the piperidine ring *via* a methylene bridge. This modification brought about a drastic change in the selectivity for muscarinic receptor subtypes. This result indicated that the influence of the side chain of the piperidine ring, especially the spatial orientation of the protonated nitrogen atom in relation to the tricyclic ring system, is critical for the selectivity.[19,20]

We selected AF-DX 116 as a lead compound and tried to find more potent and selective antagonists for the M_2 muscarinic receptor subtype. Our strategy was based on the assumption that cleavage of the piperidine ring of **2** would give compounds greater flexibility for interacting with M_2 muscarinic receptors. In addition, compounds thus modified need not to be chiral. Overall, we found that succinamide derivatives **3** had more potent and selective M_2 antagonistic activities *in vitro* and *in vivo* than AF-DX 116 (Fig. 1). In this paper, we describe the synthesis of these compounds (**3**) as well as their biological activities.

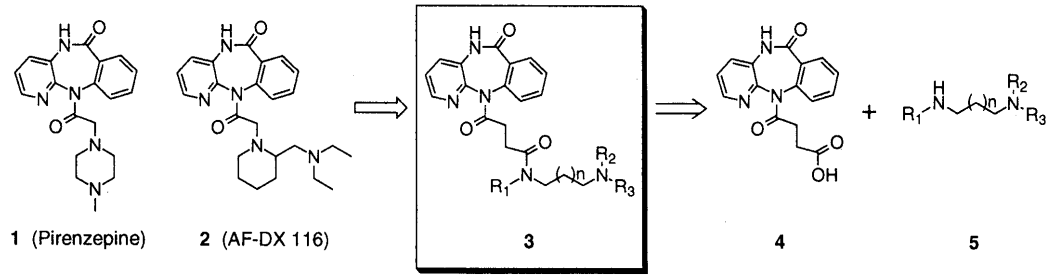

Fig. 1

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Chemistry

Our general synthetic route was a condensation reaction between carboxylic acid (**4**) and diamines (**5**) (Fig. 1). Commercially unavailable diamines (**10**—**38**) were prepared by a variety of methods as outlined in Chart 1 and Table 4. *N*,*N*-Dialkylaminoethyl chlorides (**6a**—**c**) were treated with excess amounts of amines in EtOH under reflux to yield **10**—**14** (method A).[21] The diamines **7a**—**c** were transformed to **15**—**17** by reductive alkylation with corresponding aldehydes in the presence of sodium triacetoxyborohydride ($NaB(OAc)_3H$) and acetic acid (method B) or by acylation using acid anhydride followed by reduction with lithium aluminum hydride ($LiAlH_4$) (method C).[22] The diamines **18**—**29** were synthesized from *N*,*N*′-diethylethylenediamine (**8**) according to method B or C, or by alkylation with the respective arylmethyl halides (method D). Reductive alkylation of secondary amines (**9a**—**i**) with chloroacetaldehyde followed by heating with ethylamine gave the diamines **30**—**38** (method E).

The synthesis of compounds **41**—**73**, **75** and **78** is shown in Chart 2 and Table 5. A starting tricyclic compound, 5,11-dihydro-6-oxo-6*H*-pyrido[2,3-*b*][1,4]benzodiazepine (**39**), was prepared according to the method reported by Schmidt.[23] It was acylated with ethyl succinyl chloride and triethylamine to afford **40**, which was easily hydrolyzed with ethanolic NaOH to the carboxylic acid (**4**). Compound **4**, which was used without any purification, was coupled with substituted diamines **5** in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (WSCD) and 1-hydroxybenzotriazole (HOBT) in *N*,*N*-dimethylformamide (DMF) to give compounds **41**—**73**. The alcohol **74**, obtained by the condensation reaction between **4** and 2-ethylaminoethanol, was converted to the aldehyde by Swern oxidation.[24] This intermediate, which was not isolated, was treated with benzylamine in the presence of $NaB(OAc)_3H$ and acetic acid to yield the terminal mono-substituted derivative **75**.

The diamino compound **78** was prepared as follows. Reaction of **4** with *N*,*O*-dimethylhydroxylamine using the WSCD–HOBT method afforded **76** and was followed by reduction with LAH in tetrahydrofuran (THF) at −10 °C to yield the aldehyde **77**.[25] Compound **77** was reacted with the amine **19** using the above-mentioned reductive amination procedure to give the desired compound **78**.

NMR measurements demonstrated that compounds **42**—**73** and **75** exist as mixtures of rotamers about the amide bond in dimethyl sulfoxide-d_6 (DMSO-d_6). The free energy of activation ($\Delta G^{\neq}$) of **68** as a representative of this series was measured by variable-temperature studies in DMSO-d_6 (25—140 °C).[26] On warming, the peaks of the methylene bond in the benzyl position coalesced (coalescence temperature; $T_c = 71$ °C). From the coalescence temperature and the separation of the benzyl signals ($\Delta\nu = 17.6$ Hz), $\Delta G^{\neq}_{344°}$ was found to be 15.7 kcal mol^{-1}, a value that allows free rotation at room temperature (25 °C). Additionally, the fact that **41** and **78** each exist as a single isomer proved that the amide bond on the side chain participates in controlling the conformational equilibria of the rotamers.

Pharmacological Results and Discussion

***In Vitro* Tests** The muscarinic receptor binding affinity and selectivity were assessed by employing receptor-binding assays as reported previously.[27] The binding affinities for synthesized compounds were obtained by using rat cerebral cortex (M_1), heart (M_2) and submandibular gland (M_3), and measuring the displacement of [^{3}H]pirenzepine (PZ), [^{3}H]quinuclidinyl benzilate (QNB) and [^{3}H]*N*-methylscopolamine (NMS), respectively. The results, expressed as pK_i values, and the selectivity ratios for M_2 muscarinic receptors to M_1 and M_3 muscarinic receptors (M_1/M_2, M_3/M_2, respectively) are presented in Tables 1 and 2. AF-DX 116 (**2**) was used as the reference compound.

First, we investigated the effect of amide substituents in compounds possessing a terminal diethylamino group (Table 1). Introduction of small alkyl groups dramatically increased the binding affinity for all the receptor subtypes (iso-Pr **45** > Pr **44** = Et **43** > Me **42** > H **41**). The presence of a larger alkyl group (*e.g.*, cyclohexyl **46**) resulted in a reduction of the affinity but imparted the same M_1/M_2 and M_3/M_2 selectivity as in the case of AF-DX 116. The

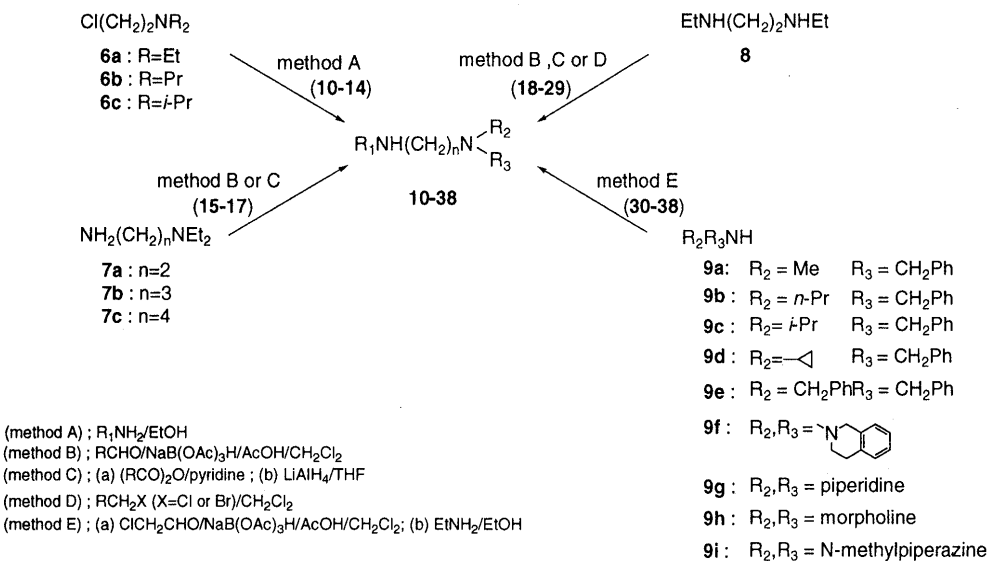


Chart 1. Preparation of the diamines **10**—**38**

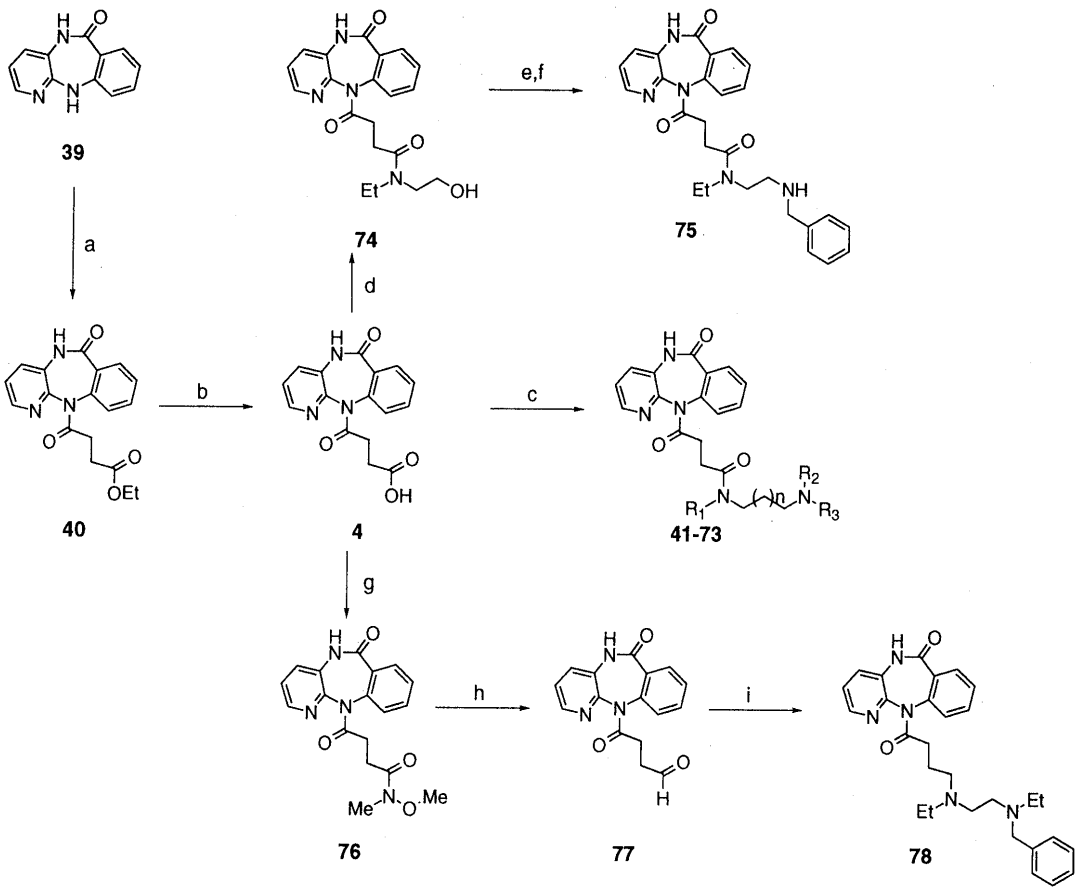
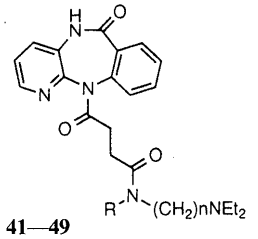


Chart 2. Preparation of the M_2 antagonists **41**—**73**, **75** and **78**

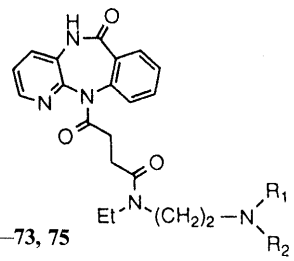
Table 1. The Binding Affinities of Compounds **41**—**49** for M_1, M_2 and M_3 Muscarinic Receptors



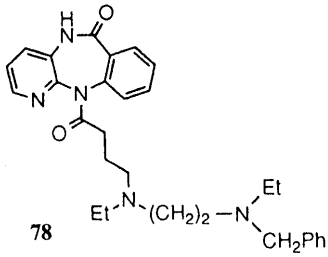
Compd. No.	R	*n*	Yield (%)	mp (°C) (Recryst. solvent)[a]	pK_i[b]			Selectivity ratio	
					M_1	M_2	M_3	M_1/M_2	M_3/M_2
2					6.1	6.9	5.7	6.3	16
41	H	2	74	114—115 (A–E)	5.3	5.6	5.2	2.0	2.5
42	Me	2	54	161—162 (C–E)	6.3	6.6	5.9	2.0	5.0
43	Et	2	78	153—154 (A–E)	6.7	7.6	6.5	7.9	13
44	Pr	2	51	133—134 (C–I)	6.6	7.6	6.5	10	13
45	iso-Pr	2	30	125—126 (C–I)	7.1	7.9	7.0	6.3	8.0
46	cyclo-Hex	2	39	124—125 (C–I)	6.2	7.2	5.7	10	32
47	CH_2Ph	2	53	104—105 (C–I)	6.1	7.1	6.0	10	13
48	Et	3	40	141—142 (A–E)	6.7	7.5	6.7	6.3	6.3
49	Et	4	73	155—156 (A–E)	6.9	7.2	7.0	2.0	1.6

a) The symbols are as follows: A, ethyl acetate; C, chloroform; E, diethyl ether; I, isopropyl ether. *b*) pK_i values each represent an aveage of two or more determinations from separate assays.

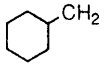
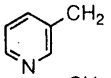
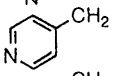
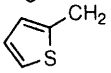
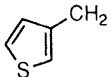
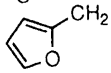
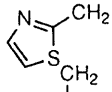
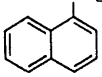
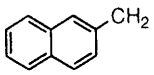
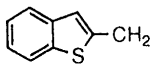
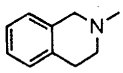
Table 2. The Binding Affinities of Compounds **50**—**73**, **75** and **78** for M_1, M_2 and M_3 Muscarinic Receptors



50—**73**, **75**



78

Compd. No.	R^1	R^2	Yield (%)	mp (°C) (Recryst. solvent)[a]	pK_i[b]			Selectivity ratio	
					M_1	M_2	M_3	M_1/M_2	M_3/M_2
50	Me	Me	77	144—145 (A–E)	6.4	7.2	6.3	6.3	7.9
51	Pr	Pr	56	73—76 (A–E)	6.3	7.3	6.6	10	5.0
52	iso-Pr	iso-Pr	88	161—162 (A–E)	7.3	8.3	7.0	10	20
53	Piperidine		72	174—176 (A)	7.2	8.2	7.2	10	10
54	Morpholine		75	174—175 (A–E)	5.1	6.1	5.0	10	13
55	4-Methylpiperazine		44	173—174 (A)	5.7	6.5	5.7	6.3	6.3
56	Et		65	176—177 (C–E)	7.0	7.9	6.6	7.9	20
57	Et	CH_2Ph	56	157—159 (C–E)	7.0	8.2	6.5	16	50
58	Et	CH_2CH_2Ph	82	160—162 (C–E)	6.8	7.9	6.3	13	40
59	Et		43	152—154 (A)	6.1	6.9	5.7	6.3	16
60	Et		55	152—154 (A–E)	6.1	7.1	5.5	10	40
61	Et		63	156—157 (C–E)	7.2	8.4	6.8	16	40
62	Et		54	160—161 (A)	7.2	8.4	6.8	16	40
63	Et		51	118—120 (A–E)	6.7	7.8	6.5	13	20
64	Et		76	123—125 (A–E)	5.4	6.5	5.3	13	16
65	Et		56	122—125 (A–E)	7.1	7.2	6.6	1.3	4.0
66	Et		71	102—105 (A–E)	7.3	8.0	6.9	5.0	13
67	Et		80	143—144 (A–E)	6.6	7.6	6.4	10	16
68	Me	CH_2Ph	78	164—165 (A)	7.6	8.6	7.0	10	40
69	Pr	CH_2Ph	67	152—153 (C–I)	6.5	7.7	6.5	16	16
70	iso-Pr	CH_2Ph	34	189—191 (A)	6.2	7.2	6.3	10	7.9
71	cyclo-Pr	CH_2Ph	63	153—154 (A–E)	6.2	7.4	5.9	16	32
72	CH_2Ph	CH_2Ph	65	73—76 (C–E)	5.4	6.1	5.3	5.0	6.3
73			59	142—144 (A–E)	7.2	8.5	7.0	20	32
75	H	CH_2Ph	33[c]	149—151 (A–E)	7.0	7.9	6.7	7.9	16
78					8.4	8.7	8.0	2.0	5.0

a) The symbols are as follows: A, ethyl acetate; C, chloroform; E, diethyl ether; I, isopropyl ether. *b*) pK_i values each represent an average of two or more determinations from separate assays. *c*) Overall yield from **12**.

introduction of an aryl group did not show a marked effect (**47**). These results suggest that a small alkyl moiety such as ethyl or isopropyl is adequate for muscarinic receptor binding around the amide substituent segment. The comparison of **43**, **48** and **49** demonstrated that an alkyl linker chain length of $n=2$ was appropriate. Because of the balance of affinity and selectivity for M_2 muscarinic receptors and the simplicity of the chemical synthesis, we chose an ethyl group as the appropriate amide substituent to investigate the structure–activity relationships (SAR)

of compounds containing different terminal amines.

Table 2 shows the influence of the amino element on the affinity and selectivity for muscarinic receptor subtypes. Although replacement of the diethylamino moiety with a dimethylamino or dipropylamino group (**50**, **51**) resulted in a slight reduction of the affinity for M_2 muscarinic receptors, conversion of **43** into the diisopropylamino analog (**52**) led to almost a 5-fold increase in the affinity for M_2 muscarinic receptors. Additionally, cyclization of the amine significantly influenced the affinity for muscarinic receptors. Although the piperidine derivative **53** showed a higher affinity than **43**, replacement of piperidine by morpholine (**54**) or 4-methylpiperazine (**55**) dramatically reduced the affinity for all subtypes, presumably due to a reduction in the pK_a of the basic nitrogen. This result indicates that sufficient basicity is necessary at the terminal amine part to permit forming a hydrogen bond with an acidic amino acid included in muscarinic receptors. A more dramatic improvement in both the affinity and selectivity for M_2 muscarinic receptors was observed with the introduction of an *N*-benzyl substituent (**57** *vs.* **43**). However, compound **56** containing a cyclohexylmethylamino group had a lower selectivity than **57**.

These results prompted us to examine the heteroaromatic analogues **59**—**64** and the bicyclic compounds **65**—**67** in order to establish the influence of the terminal aromatic ring. In a series of monocyclic systems, replacement of the phenyl ring of **57** by an electron-rich thiophene moiety produced analogues **61** and **62** having the same affinity as **57**, but the pyridine (**59** and **60**), furan (**63**) and thiazole (**64**) analogues were less potent. All of the bicyclic compounds **65**—**67** were less active than **57**. It might be speculated that the function of the terminal aromatic ring in binding with M_2 muscarinic receptors depends not only on steric, but also on electrical properties.

Further optimization was achieved by the substitution of alkylbenzylamine into **57**. Replacement of the ethyl group by a hydrogen atom (**75**) slightly decreased the affinity for the M_2 muscarinic receptor subtype, while maintaining the affinity for M_1 and M_3 muscarinic receptors, whereas introduction of a methyl group (**68**) resulted in an increase in the affinity for M_2 muscarinic receptors and the retention of both selectivities. *N*-Propyl (**69**), *N*-isopropyl (**70**) and *N*-cyclopropyl (**71**) compounds showed weaker affinity for M_2 muscarinic receptors than **57**. The result with **70** was especially unexpected, because the *N*,*N*-diisopropylamino compound **52** was more potent than the *N*,*N*-diethylamino analog **43**. The structurally restricted 1,2,3,4-tetrahydroisoquinoline derivative **73** was almost as potent as **68**, whereas the introduction of a larger substituent such as *N*,*N*-dibenzyl (**72**) resulted in a reduction of the affinity for all subtypes. These results indicate that the introduction of a more sterically hindered alkyl group such as isopropyl or cyclopropyl, or a benzyl group, would disturb the introduction of the terminal animo moiety with M_2 muscarinic receptors.

We synthesized the diamino analog **78** in order to confirm the hypothesis that high M_2-selectivity depends on the succinamide structure. Although the conversion of amide into amine unexpectedly resulted in a higher binding affinity, **78** was found to be 10-fold less selective for M_2 muscarinic receptors over M_1 and M_3 subtypes than **57**. This result indicated that the succinamide segment is associated with marked M_2 selectivity.

***In Vivo* Tests** AF-DX 116 shows no activity in the central nervous system after peripheral administration.[28] Our compounds might also have great difficulty in crossing the blood brain barrier due to their larger molecular size. As regards side effects, we have to pay attention to M_3 receptor-antagonistic activities because dryness of the mouth and mydriasis caused by the antagonism of M_3 muscarinic receptors were the main problems in the clinical trial of atropine.[9]

From the viewpoint of M_2 affinity and selectivity, **61**, **68** and **73** were selected and evaluated by *in vivo* assay in comparison with **2** and atropine. We studied the oxotremorine-induced bradycardia in pithed rats and the oxotremorine-induced salivation in anesthetized rats to assess M_2 and M_3 antagonistic activities, respectively.[27] All test compounds were given by intravenous injection, and antagonism for M_2 and M_3 muscarinic receptors was expressed as pDR_{10} and pID_{50} values, respectively, as described in Experimental. Among these compounds, **61** and **68** acted as noncompetitive-like antagonists in the oxotremorine-induced bradycardia model; the agonist dose-response curves were displaced to the right with a decrease in the maximum response of about 60%, and this behavior was different from that of **2** and **73**, which exhibited competitive antagonism. Therefore, the pDR_{10} values of these compounds were calculated from their ED_{30} values. In Table 3, M_2 and M_3 antagonistic activities and M_2 selectivity of the test compounds are given. The selectivity ratio (M_3/M_2) was calculated according to the following equation using the potencies of the compounds

Table 3. Muscarinic Receptor Antagonistic Activities and Selectivity Ratios of **61**, **68**, **73**, **2** and Atropine for *in Vivo* Experiments in Rats

Compd.[a]	Inhibitory effects in oxotremorine-induced bradycardia (M_2)		Inhibitory effects in oxotremorine-induced salivation (M_3)		Selectivity ratio (M_3/M_2)
	pDR_{10}[b]	*n*	pID_{50}[b]	*n*	
61	6.78[c] (6.61—7.07)	12	5.48 (5.41—5.56)	11	40
68	6.81[c] (6.73—6.89)	12	5.00 (4.95—5.06)	9	129
73	6.71 (6.61—6.84)	12	5.54 (5.43—5.68)	11	30
2	5.63 (5.56—5.70)	32	4.60 (4.52—4.69)	24	21
Atropine	6.94 (6.88—7.01)	21	7.24 (7.21—7.28)	14	1

a) Compounds were given by intravenous injection in both experiments. *b*) Values are the means of the indicated number of experiments (*n*). Figures in parentheses represent 95% confidence limits. *c*) Values are calculated from their ED_{30} values. See Experimental.

relative to atropine (selectivity ratio = 1).

$$M_3/M_2 = [ID_{50}(\text{compound})/ID_{50}(\text{atropine})]/[DR_{10}(\text{compound})/DR_{10}(\text{atropine})]$$

The experiments showed that **61**, **68** and **73** yielded respective pDR_{10} values of 6.78, 6.81 and 6.71 for antagonism of the oxotremorine-induced decrease in heart rate. These potencies are nearly 15-fold greater than that of **2**. In contrast, the inhibitory effect of **61**, **68** and **73** in the oxotremorine-induced salivation was 50- to 170-fold less than that of atropine. Consequently, these three compounds possessed selectivity for M_2 muscarinic receptors comparable to or higher than that of **2**. In particular, compound **68** was found to be 130-fold more selective than atropine, with the same degree of M_2 muscarinic receptor-antagonistic activity.

Conclusions

New potent and selective M_2 muscarinic receptor antagonists in the succinamide series were synthesized and their SAR evaluated. From their SAR, we obtained the following information. 1) The succinamide moiety is important for the appearance of selectivity for M_2 muscarinic receptors. 2) A substituent on the nitrogen atom in the amide bond had a marked influence on the affinity for muscarinic receptors. 3) Introduction of a benzyl group into the terminal amino element enhanced the affinity and selectivity for M_2 muscarinic receptors. Among this series, compound **68** showed the most potent M_2 antagonistic activity and marked M_2 selectivity both *in vitro* and *in vivo*. It is noteworthy that this compound includes a terminal benzylamine, which has not been reported so far in investigations of AF-DX 116 type M_2 selective antagonists.

Further research to establish in more detail the SAR of the substituents on the terminal phenyl ring to obtain M_2 muscarinic receptor antagonists possessing superior properties is in progress and will be the subject of a forthcoming paper.

Experimental

All melting points were measured with a Yanaco MP-500D melting point apparatus without correction. ^{1}H-NMR spectra were obtained on a JEOL JNM-EX90 or JNM-A500 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL JMS-DX300 or Hitachi M-80 spectrometer. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck).

General Procedure for the Preparation of Substituted Diamines 10—38 Physical data for compounds **10**—**38** are listed in Table 4.

N,*N*-Diethyl-*N'*-propylethylenediamine (**10**) [Method A]: A mixture of 2-diethylaminoethylene chloride **6a** (1.72 g, 10 mmol) and propylamine (2.96 g, 50 mmol) in EtOH (10 ml) was heated for 4 h at 70 °C. After the mixture had cooled, EtOH was distilled off under reduced pressure and the residue was basified with 1 N aqueous NaOH (10 ml). This mixture was extracted with $CHCl_3$ (10 ml × 2) and the combined extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated to give 1.52 g of **10** as a yellow oil in 96% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7.3 Hz), 1.01 (6H, t, J=7.3 Hz), 1.48—1.55 (2H, m), 1.81 (1H, br s), 2.51 (4H, q, J=7.3 Hz), 2.54—2.59 (4H, m), 2.66 (2H, t, J=6.1 Hz). GC-MS *m/z*: 158 (M^+).

N'-Cyclohexyl-*N*,*N*-diethylethylenediamine (**15**) [Method B]: A mixture of *N*,*N*-diethylethylenediamine (**7a**, 1.30 g, 11 mmol), cyclohexanone (1.00 g, 10 mmol), acetic acid (0.92 g, 15 mmol) and sodium triacetoxy borohydride ($NaB(OAc)_3H$) (3.20 g, 15 mmol) in CH_2Cl_2 (20 ml) was stirred for 2 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and extracted with CH_2Cl_2 (20 ml × 2). The combined extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified on a silica gel column ($CHCl_3$–MeOH, 100 : 1, v/v) to give 1.88 g of **15** as an oil in 93% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, t, J=7.3 Hz), 1.07—1.30 (5H, m), 1.60—1.63 (1H, m), 1.72—1.75 (2H, m), 1.88—1.90 (1H, m), 2.32 (1H, br s), 2.39—2.45 (1H, m), 2.51 (4H, t, J=7.3 Hz), 2.56 (2H, t, J=6.1 Hz), 2.70 (2H, t, J=6.1 Hz). GC-MS *m/z*: 198 (M^+).

N-Cyclohexylmethyl-*N*,*N'*-diethylethylenediamine (**18**) [Method B]: A mixture of *N*,*N'*-diethylethylenediamine (**8**, 5.00 g, 43 mmol), cyclohexylaldehyde (0.96 g, 8.6 mmol), acetic acid (7.4 g, 123 mmol) and $NaB(OAc)_3H$ (5.47 g, 25.8 mmol) in CH_2Cl_2 (50 ml) was stirred for 18 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH, then extracted with CH_2Cl_2 (20 ml × 2), and the combined extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 300 : 10 : 1, v/v/v) to give 0.74 g of **18** as an oil in 41% yield. ^{1}H-NMR ($CDCl_3$) δ: 0.78—0.83 (2H, m), 0.98 (3H, t, J=7.3 Hz), 1.14 (3H, t, J=7.3 Hz), 1.16—1.24 (2H, m), 1.37—1.43 (1H, m), 1.65—1.77 (6H, m), 2.15 (2H, d, J=7.3 Hz), 2.49 (2H, q, J=7.3 Hz), 2.53 (2H, t, J=6.1 Hz), 2.65—2.71 (4H, m), 3.47 (1H, br s). GC-MS *m/z*: 212 (M^+).

N,*N*,*N'*-Triethylpropylenediamine (**16**) [Method C]: Acetyl anhydride (3.06 g, 30 mmol) was added to a solution of *N*,*N*-diethylpropylenediamine **7b** (3.91 g, 30 mmol) in pyridine (40 ml) at 5 °C. The mixture was stirred for 18 h at room temperature, then concentrated. The residue obtained was dissolved in $CHCl_3$ (30 ml) and the solution was washed with 1 N aqueous NaOH and brine. The combined extract was dried over $MgSO_4$ and evaporated to give 5.10 g (99%) of 3-diethylaminopropyl-1-acetamide as an oil. [GC-MS *m/z*: 172(M^+)].

A solution of 3-diethylaminopropyl-1-acetamide (2.00 g, 11.6 mmol) in anhydrous THF (9 ml) was added dropwise to a suspension of $LiAlH_4$ (1.32 g, 35 mmol) in anhydrous THF (15 ml), while maintaining the reaction temperature below 20 °C. The mixture was stirred for 1 h at 80 °C, cooled to 0 °C, and then hydrolyzed by addition of 1 N NaOH (10 ml). The resulting suspension was filtered and the filtrate evaporated to give 1.69 g of **16** as an oil in 92% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, t, J=7.3 Hz), 1.10 (3H, t, J=7.3 Hz), 1.93 (1H, s), 1.60—1.68 (2H, m), 2.43—2.66 (8H, m), 3.31—3.37 (2H, m). GC-MS *m/z*: 158 (M^+).

N-Benzyl-*N*,*N'*-diethylethylenediamine (**19**) [Method D]: Benzyl bromide (1.47 g, 8.6 mmol) was added to a mixture of *N*,*N'*-diethylethylenediamine (**8**, 5.00 g, 43 mmol) and CH_2Cl_2 (50 ml) at below 10 °C. The mixture was stirred for 15 h at room temperature, and made alkaline with 1 N aqueous NaOH. The separated organic layer was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 100 : 1, v/v) to give 1.36 g of **19** as a yellow oil in 77% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.3 Hz), 1.07 (3H, t, J=7.3 Hz), 2.24 (1H, br s), 2.51—2.57 (4H, m), 2.60 (2H, q, J=7.3 Hz), 2.66 (2H, q, J=7.3 Hz), 3.57 (2H, s), 7.31 (5H, s). GC-MS *m/z*: 206 (M^+).

N-Benzyl-*N'*-ethyl-*N*-methylethylenediamine (**30**) [Method E]: i) A mixture of *N*-methylbenzylamine (**9a**, 1.21 g, 10 mmol), chloroacetaldehyde (40% in H_2O) (1.96 g, 10 mmol), acetic acid (0.66 g, 11 mmol) and $NaB(OAc)_3H$ (3.35 g, 15 mmol) in CH_2Cl_2 (20 ml) was stirred for 2 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and extracted with CH_2Cl_2 (20 ml × 3). The combined extract was washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column ($CHCl_3$) to give 1.38 g of *N*-benzyl-(2-chloroethyl)methylamine as an oil in 75% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.01 (6H, t, J=7.3 Hz), 1.10 (3H, t, J=7.3 Hz), 1.93 (1H, s), 1.60—1.68 (2H, m), 2.43—2.66 (8H, m), 3.31—3.37 (2H, m). GC-MS *m/z*: 158 (M^+).

ii) A solution of *N*-benzyl-(2-chloroethyl)methylamine (920 mg, 5 mmol) in EtOH (10 ml) was treated with $EtNH_2$ (70% in H_2O) (1.60 g, 25 mmol) and the mixture was heated for 3 h at 70 °C. The solvent was evaporated, and the residue was crystallized from EtOH–Et_2O to obtain 980 mg of **30** in 86% yield, mp 96—98 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.3 Hz), 2.31 (3H, s), 2.85—2.91 (4H, m), 3.00 (2H, q, J=6.4 Hz), 3.60 (2H, s), 7.27—7.34 (5H, m). GC-MS *m/z*: 193 (M^+).

4-Oxo-4-(6-oxo-5,6-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-11-yl)butyric Acid Ethyl Ester (**40**): Ethyl succinyl chloride (2.5 g, 15 mmol) and triethylamine (1.5 g, 15 mmol) were simultaneously added dropwise

Table 4. Physical Data for Substituted Diamines **10**—**38**

$$R_1NH(CH_2)_nN\langle^{R_2}_{R_3}$$

Compd. No.	R_1	R_2	R_3	n	Method	Yield (%)	^{1}H-NMR δ (in $CDCl_3$, J in Hz)	MS m/z	Ref.
10	Pr	Et	Et	2	A	96	0.92 (3H, t, J=7.3), 1.01 (6H, t, J=7.3), 1.48—1.55 (2H, m), 1.81 (1H, br s), 2.51 (4H, q, J=7.3), 2.54—2.59 (4H, m), 2.66 (2H, t, J=6.1)	158 (M^+)	21)
11	iso-Pr	Et	Et	2	A	99	1.16 (6H, t, J=7.2), 1.43 (6H, d, J=6.4), 2.71 (4H, q, J=7.2), 2.95—2.98 (4H, m), 3.20—3.49 (1H, m)	158 (M^+)	32)
12	CH_2Ph	Et	Et	2	A	72	0.99 (6H, t, J=7.1), 1.95 (1H, s), 2.37—2.73 (8H, m), 3.79 (2H, s), 7.22—7.35 (5H, m)	206 (M^+)	33)
13	Et	Pr	Pr	2	A	76	0.87 (3H, t, J=7.3), 1.11 (3H, t, J=7.3), 1.44 (4H, tq, J=7.3), 2.35—2.39 (4H, m), 2.53 (2H, t, J=6.1), 2.63—2.69 (4H, m)	172 (M^+)	
14	Et	iso-Pr	iso-Pr	2	A	44	1.02 (12H, t, J=7.3), 1.12 (3H, t, J=7.3), 1.98 (1H, br s), 2.58—2.62 (4H, m), 2.66 (2H, q, J=7.3), 2.97—3.03 (2H, m)	172 (M^+)	
15	cyclo-Hex	Et	Et	2	B	93	1.01 (6H, t, J=7.3), 1.07—1.30 (5H, m), 1.60—1.63 (1H, m), 1.72—1.75 (2H, m), 1.88—1.90 (1H, m), 2.32 (1H, br s), 2.39—2.45 (1H, m), 2.51 (4H, t, J=7.3), 2.56 (2H, t, J=6.1), 2.70 (2H, t, J=6.1)	198 (M^+)	34)
16	Et	Et	Et	3	C	91[a]	1.01 (6H, t, J=7.3), 1.10 (3H, t, J=7.3), 1.93 (1H, s), 1.60—1.68 (2H, m), 2.43—2.66 (8H, m), 3.31—3.37 (2H, m)	158 (M^+)	35)
17	Et	Et	Et	4	C	68[a]	1.01 (6H, t, J=7.2), 1.10 (3H, t, J=7.2), 1.45—1.52 (4H, m), 2.22 (1H, br s), 2.40—2.45 (2H, m), 2.49 (4H, q, J=7.2), 2.64 (2H, q, J=7.2)	172 (M^+)	32)
18	Et	Et	Cyclohexylmethyl	2	B	41	0.78—0.83 (2H, m), 0.98 (3H, t, J=7.3), 1.14 (3H, t, J=7.3), 1.16—1.24 (2H, m), 1.37—1.43 (1H, m), 1.65—1.77 (6H, m), 2.15 (2H, d, J=7.3), 2.49 (2H, q, J=7.3), 2.53 (2H, t, J=6.1), 2.65—2.71 (4H, m), 3.47 (1H, br s)	212 (M^+)	
19	Et	Et	CH_2Ph	2	D	77	1.04 (3H, t, J=7.3), 1.07 (3H, t, J=7.3), 2.24 (1H, br s), 2.51—2.57 (4H, m), 2.60 (2H, q, J=7.3), 2.66 (2H, q, J=7.3), 3.57 (2H, s), 7.31 (5H, s)	206 (M^+)	22)
20	Et	Et	CH_2CH_2Ph	2	C	67[a]	1.04 (3H, t, J=7.3), 1.06 (3H, t, J=7.3), 1.89 (1H, br s), 2.55 (2H, t, J=7.3), 2.60 (2H, t, J=7.3), 2.62 (2H, s), 2.64—2.67 (2H, m), 2.68—2.75 (4H, m), 7.17—7.20 (3H, m), 7.26—7.29 (2H, m)	221 (M^++1)	36)
21	Et	Et	3-CH_2Py	2	D	49	1.06 (3H, t, J=7.3), 1.08 (3H, t, J=7.3), 1.63 (1H, br s), 2.51—2.67 (8H, m), 3.59 (2H, s), 7.23—7.27 (1H, m), 7.64 (1H, d, J=7.3), 8.49 (1H, d, J=3.0), 8.54 (1H, s)	207 (M^+)	
22	Et	Et	4-CH_2Py	2	D	64	1.00 (3H, t, J=7.3), 1.12 (3H, t, J=7.3), 1.63 (1H, br s), 2.40—2.70 (8H, m), 3.58 (2H, s), 7.25 (2H, dd, J=4.4, 1.5), 7.64 (1H, d, J=7.3), 8.52 (2H, dd, J=4.4, 1.5)	207 (M^+)	
23	Et	Et	2-CH_2-thiophene	2	B	59	1.06 (3H, t, J=7.3), 1.12 (3H, t, J=7.3), 2.49 (1H, br s), 2.56 (2H, q, J=7.3), 2.60—2.66 (4H, m), 2.69 (2H, t, J=5.5), 3.80 (2H, s), 6.88 (1H, d, J=3.7), 6.92 (1H, dd, J=4.9, 3.7), 7.20 (1H, d, J=4.9)	213 (M^++1)	
24	Et	Et	3-CH_2-thiophene	2	B	60	1.06 (3H, t, J=7.3), 1.12 (3H, t, J=7.3), 2.06 (1H, br s), 2.55 (2H, q, J=7.3), 2.58—2.64 (4H, m), 2.70 (2H, t, J=6.1), 3.62 (2H, s), 7.03 (1H, d, J=5.0), 7.09 (1H, d, J=1.8), 7.27—7.28 (1H, m)	212 (M^+)	
25	Et	Et	2-CH_2-furan	2	B	48	1.08 (3H, t, J=7.3), 1.19 (3H, t, J=7.3), 2.57 (2H, q, J=7.3), 2.61—2.76 (5H, m), 3.66 (2H, s), 3.69 (2H, br s), 6.18 (1H, d, J=3.1), 6.32 (1H, dd, J=3.1, 1.2), 7.36 (1H, d, J=1.2)	197 (M^++1)	
26	Et	Et	2-CH_2-thiazole	2	D	67	1.09 (3H, t, J=7.3), 1.13 (3H, t, J=7.3), 2.32 (1H, br s), 2.63—2.68 (4H, m), 2.71—2.76 (4H, m), 3.95 (2H, s), 7.26 (1H, d, J=3.1), 7.70 (1H, d, J=3.1)	213 (M^+)	
27	Et	Et	1-CH_2-naphthalene	2	D	72	0.86 (3H, t, J=7.3), 1.11 (3H, t, J=7.3), 1.85 (1H, br s), 2.29 (2H, q, J=7.3), 2.56 (2H, t, J=5.5), 2.63 (2H, t, J=7.3), 2.66 (2H, t, J=5.5), 4.00 (2H, s), 7.39 (1H, t, J=7.9), 7.43—7.45 (1H, m), 7.47—7.51 (2H, m), 7.76 (1H, d, J=7.9), 7.84 (1H, d, J=7.9), 8.28 (1H, d, J=7.9)	256 (M^+)	

a) Overall yield from **7b**—**c** or **8**.

Table 4. (continued)

Compd. No.	R_1	R_2	R_3	n	Method	Yield (%)	^{1}H-NMR δ (in $CDCl_3$, J in Hz)	MS m/z	Ref.
28	Et	Et	2-CH_2-naphthalene	2	D	64	1.06 (3H, t, J=7.3), 1.07 (3H, t, J=7.3), 2.19 (1H, br s), 2.54 (2H, t, J=7.3), 2.58 (2H, t, J=7.3), 2.64—2.70 (4H, m), 3.72 (2H, s), 7.41—7.48 (3H, m), 7.71 (1H, s), 7.78—7.81 (3H, m)	256 (M^+)	
29	Et	Et	2-CH_2-benzthiazole	2	D	60	1.08 (3H, t, J=7.3), 1.12 (3H, t, J=7.3), 2.08 (1H, s), 2.60—2.65 (4H, m), 2.66—2.73 (4H, m), 3.87 (2H, s), 7.12 (1H, s), 7.25—7.32 (2H, m), 7.67 (1H, d, J=7.9), 7.87 (1H, d, J=7.9)	262 (M^+)	
30[a]	Et	Me	CH_2Ph	2	E	64[b]	1.37 (3H, t, J=7.3), 2.31 (3H, s), 2.85—2.91 (4H, m), 3.00 (2H, t, J=6.4), 3.60 (2H, s), 7.27—7.34 (5H, m)	192 (M^+)	
31	Et	Pr	CH_2Ph	2	E	55[b]	0.85 (3H, t, J=7.3), 1.05 (3H, t, J=7.3), 1.30—1.62 (2H, m), 1.86 (1H, br s), 2.32—2.60 (8H, m), 3.54 (2H, s), 7.22—7.33 (5H, m)	221 (M^++1)	
32[a]	Et	iso-Pr	CH_2Ph	2	E	49[b]	1.14 (6H, d, J=7.3), 1.19 (3H, t, J=7.3), 1.41 (1H, t, J=7.3), 2.55 (2H, q, J=7.3), 2.73 (2H, t, J=6.3), 2.93—2.96 (2H, m), 3.05—3.09 (2H, m), 3.61 (2H, s), 7.28—7.36 (5H, m)	220 (M^+)	
33[a]	Et	cyclo-Pr	CH_2Ph	2	E	72[b]	0.55—0.63 (4H, m), 1.27 (3H, t, J=7.3), 1.91—1.93 (1H, m), 2.71 (2H, q, J=7.3), 2.92 (2H, t, J=6.7), 3.02 (2H, t, J=6.7), 3.80 (2H, s), 7.27—7.35 (5H, m)	218 (M^+)	
34	Et	CH_2Ph	CH_2Ph	2	E	75[b]	1.20 (3H, t, J=7.3), 2.54 (2H, q, J=7.3), 2.75 (1H, br s), 2.86 (2H, t, J=6.1), 2.94 (2H, t, J=6.1), 3.66 (4H, s), 7.26—7.35 (10H, m)	269 (M^++1)	
35[a]	Et	Tetrahydroisoquinoline		2	E	68[b]	1.34 (3H, t, J=7.3), 2.79 (2H, t, J=5.8), 2.92—2.99 (4H, m), 3.02—3.10 (4H, m), 3.72 (2H, s), 7.00—7.27 (3H, m)	204 (M^+)	
36	Et	Piperidine		2	E	61[b]	1.25 (3H, t, J=7.3), 1.48—1.51 (2H, m), 1.63—1.69 (4H, m), 2.40—2.61 (4H, m), 2.84 (2H, t, J=6.4), 3.03—3.81 (4H, m)	156 (M^+)	21)
37[a]	Et	Morpholine		2	E	27[b]	1.48 (3H, t, J=7.3), 2.49—2.60 (4H, m), 2.74—2.88 (2H, m), 3.03—3.27 (4H, m), 3.69—3.79 (4H, m)	159 (M^++1)	32)
38	Et	4-Methylpiperazine		2	E	13[b]	1.11 (3H, t, J=7.3), 1.66 (1H, br s), 2.28 (3H, s), 2.46—2.60 (10H, m), 2.68—2.79 (4H, m)	171 (M^+)	

a) As HCl salt. *b*) Overall yield from **9a**—**i**.

to a suspension of 5,11-dihydro-6-oxo-6*H*-pyrido[2,3-*b*][1,4]benzodiazepine (**39**, 3.0 g, 14 mmol) in dioxane (60 ml) at 80 °C. The mixture was stirred for 4 h at 100 °C, cooled to room temperature, then concentrated *in vacuo*. The residue obtained was dissolved in $CHCl_3$ (50 ml) and H_2O (50 ml). After filtration to remove the precipitate, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (50 ml × 2). The combined extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 100 : 1, v/v), and the product was crystallized from MeOH to give 2.94 g of **40** in 61% yield. mp 219—221 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.3 Hz), 2.33 (1H, br s), 2.60—2.72 (2H, m), 3.03 (1H, br s), 4.07 (2H, q, J=7.3 Hz), 7.32—7.34 (1H, m), 7.44 (1H, br s), 7.61—7.65 (3H, m), 7.99 (1H, d, J=6.7 Hz), 8.35—8.37 (1H, m), 9.86 (1H, br s). *Anal.* Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.39; H, 5.12; N, 12.18. FAB-MS m/z: 340 (M^++1).

11-[3-[*N*-[2-(*N*-Benzyl-*N*-methylamino)ethyl]-*N*-ethylcarbamoyl]-propionyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**68**): A solution of **40** (340 mg, 1 mmol), 1 N aqueous NaOH (3.4 ml) and EtOH (5 ml) was stirred at room temperature for 30 min. The mixture was neutralized with 1 N aqueous HCl (3.4 ml) and concentrated under reduced pressure, then the residue was dissolved in DMF (10 ml) and the precipitate was filtered off. Compound **30** (230 mg, 1 mmol), WSCD (230 mg, 1.2 mmol) and HOBT (68 mg, 0.5 mmol) were added to the filtrate and the mixture was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure, the residue was diluted with 1 N aqueous NaOH and extracted with $CHCl_3$ (15 ml × 3). The combined extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 300 : 10 : 1, v/v/v), and the product was crystallized from Et_2O to give 378 mg of **68** in 78% yield. Recrystallization from AcOEt afforded pure **68** as colorless needles, mp 164—165 °C. ^{1}H-NMR (DMSO-d_6) (25 °C) δ: 0.91 (1.4H, t, J=7.3 Hz), 1.06 (1.6H, t, J=7.3 Hz), 2.11 (1.6H, s), 2.17 (1.4H, s), 2.30—2.77 (6H, m), 3.13—3.35 (4H, m), 3.45 (1.1H, s), 3.49 (0.9H, s), 7.20—7.29 (5H, m), 7.40—7.49 (3H, m), 7.64—7.66 (1H, m), 7.70—7.71 (1H, m), 7.78—7.90 (1H, m), 8.31 (1H, br s), 10.81 (1H, s). (140 °C) δ: 1.01 (3H, t, J=7.1 Hz), 2.20 (3H, s), 2.46—2.78 (6H, m), 3.25 (2H, q, J=7.1 Hz), 3.34 (2H, t, J=6.8 Hz), 3.52 (2H, s), 7.17—7.28 (5H, m), 7.35—7.46 (3H, m), 7.59 (1H, dt, J=8.3, 1.7 Hz), 7.69 (1H, dd, J=8.0, 1.7 Hz), 7.80 (1H, dd, J=7.6, 1.5 Hz), 8.25 (1H, dd, J=4.9, 1.7 Hz), 10.57 (1H, br s). *Anal.* Calcd for $C_{28}H_{31}N_5O_3 \cdot 0.2H_2O$: C, 68.75; H, 6.47; N, 14.32. Found: C, 68.47; H, 6.33; N, 14.19. FAB-MS m/z: 486 (M^++1).

Compounds **41**—**73** were prepared in the same fashion as described for **68**.

11-[3-[*N*-Ethyl-*N*-(2-hydroxyethyl)carbamoyl]propionyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**74**): A solution of **40** (300 mg, 0.89 mmol), 1 N aqueous NaOH (3 ml) and EtOH (6 ml) was stirred for 30 min at room temperature, then neutralized with 1 N aqueous HCl (3 ml). Removal of the solvent under reduced pressure gave a residue, which was dissolved in DMF (10 ml). The precipitate was filtered off. 2-Ethylaminoethanol (79 mg, 0.89 mmol), WSCD (200 mg, 1.00 mmol) and HOBT (60 mg, 0.44 mmol) were added to the filtrate and the mixture was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure, the residue was diluted with water, and extracted with $CHCl_3$ (15 ml × 3). The organic solution was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 300 : 10 : 1, v/v/v), and the product was crystallized from AcOEt–Et_2O to give 310 mg of **74** in 92%

Table 5. Physical Data for Compounds **41**—**73**, **75**

Compd. No.	^{1}H-NMR δ (in DMSO-d_6, J in Hz)	MS m/z ($M^+ + 1$)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
41	0.90 (6H, t, J=7.3), 2.04—2.14 (1H, m), 2.33 (4H, q, J=7.3), 2.42 (4H, q, J=7.3), 2.72—2.82 (1H, m), 3.02 (2H, dd, J=14.4, 6.4), 7.40—7.49 (3H, m), 7.65—7.71 (2H, m), 7.78—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	410	$C_{22}H_{27}N_5O_3$	64.53 (64.43	6.65 6.88	17.10 16.96)
42	0.90 (3H, t, J=7.0), 0.91 (3H, t, J=7.0), 2.11—2.13 (1H, m), 2.41—2.59 (8H, m), 2.74—2.77 (1H, m), 2.94 (1.7H, s), 3.10 (1.3H, s), 3.24—3.28 (2H, m), 7.40—7.47 (3H, m), 7.64—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	424	$C_{23}H_{29}N_5O_3 \cdot 0.1H_2O$	64.95 (64.86	6.92 6.86	16.47 16.52)
43	0.89—0.96 (7.4H, m), 1.08 (1.6H, t, J=7.3), 2.07—2.20 (1H, m), 2.38—2.55 (8H, m), 2.70—2.81 (1H, m), 3.20—3.31 (4H, m), 7.39—7.48 (3H, m), 7.64—7.71 (2H, m), 7.78—7.80 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	438	$C_{24}H_{31}N_5O_3$	65.88 (65.60	7.14 7.17	16.01 15.93)
44	0.76 (1.5H, t, J=7.3), 0.83 (1.5H, t, J=7.3), 0.90 (6H, t, J=6.8), 1.39 (1H, q, J=7.3), 1.51 (1H, q, J=7.3), 2.12—2.15 (1H, m), 2.36—2.52 (8H, m), 2.73—2.76 (1H, m), 3.13—3.31 (4H, m), 7.40—7.48 (3H, m), 7.65—7.72 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	452	$C_{25}H_{33}N_5O_3 \cdot 0.2H_2O$	65.97 (65.87	7.40 7.29	15.39 15.38)
45	0.95 (6H, t, J=7.0), 1.03 (3H, t, J=7.3), 1.10 (3H, t, J=7.0), 2.12—2.15 (1H, m), 2.45—2.69 (8H, m), 2.74—2.77 (1H, m), 3.06—3.10 (1H, m), 3.17—3.21 (1H, m), 4.01—4.04 (0.53H, m), 4.37—4.41 (0.47H, m), 7.41—7.48 (3H, m), 7.64—7.71 (2H, m), 7.78—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	452	$C_{25}H_{33}N_5O_3 \cdot 0.2H_2O$	65.97 (65.92	7.40 7.32	15.39 15.29)
46	0.94 (13.4H, t, J=7.3), 1.08 (1.6H, t, J=7.3), 2.13—2.15 (1H, m), 2.37—2.60 (4H, m), 2.77—2.79 (1H, m), 2.88—2.98 (2H, m), 3.07—3.28 (4H, m), 7.40—7.48 (3H, m), 7.65—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	492	$C_{28}H_{37}N_5O_3 \cdot 0.4H_2O$	67.42 (67.33	7.64 7.75	14.04 13.98)
47	0.89 (6H, t, J=6.7), 2.36—2.69 (10H, m), 3.21—3.25 (2H, m), 4.47—4.52 (1H, m), 4.58—4.60 (1H, m), 7.15 (1H, d, J=7.3), 7.21—7.23 (1H, m), 7.26—7.29 (1H, m), 7.34 (1H, t, J=7.3), 7.40—7.48 (3H, m), 7.65—7.72 (2H, m), 7.80—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	500	$C_{29}H_{33}N_5O_3 \cdot 0.3H_2O$	68.97 (68.76	6.71 6.55	13.87 13.84)
48	0.90, 0.95 (7.4H, 2t, J=7.3), 1.07 (1.6H, t, J=7.3), 1.49 (1H, t, J=7.3), 1.60 (1H, t, J=7.3), 2.10—2.18 (1H, m), 2.26—2.50 (8H, m), 2.71—2.80 (1H, m), 3.15—3.30 (4H, m), 7.39—7.48 (3H, m), 7.63—7.70 (2H, m), 7.79—7.80 (1H, m), 8.30—8.31 (1H, m), 10.78 (1H, br s)	452	$C_{25}H_{33}N_5O_3$	66.50 (66.28	7.37 7.43	15.51 15.44)
49	0.88—0.96 (7.4H, m), 1.07 (1.6H, t, J=7.2), 1.26—1.48 (4H, m), 2.10—2.77 (10H, m), 3.17—3.33 (4H, m), 7.38—7.48 (3H, m), 7.64—7.73 (2H, m), 7.78—7.81 (1H, m), 8.30—8.31 (1H, m), 10.82 (1H, br s)	466	$C_{26}H_{35}N_5O_3 \cdot 0.2H_2O$	66.56 (66.43	7.60 7.55	14.93 14.85)
50	0.95 (1.5H, t, J=7.3), 1.08 (1.5H, t, J=7.3), 2.11 (3H, s), 2.15 (3H, s), 2.24 (1H, t, J=6.8), 2.35 (1H, t, J=6.8), 2.51—2.61 (3H, m), 2.75—2.85 (1H, m), 3.21—3.43 (4H, m), 7.40—7.47 (3H, m), 7.63—7.71 (2H, m), 7.80—7.82 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	410	$C_{22}H_{27}N_5O_3 \cdot 0.1H_2O$	64.25 (64.06	6.67 6.63	17.03 17.17)
51	0.81 (6H, t, J=7.3), 0.94 (1.4H, t, J=7.3), 1.07 (1.6H, t, J=7.3), 1.32—1.38 (4H, m), 2.12—2.15 (1H, m), 2.29—2.50 (8H, m), 2.75—2.78 (1H, m), 3.26—3.33 (4H, m), 7.40—7.49 (3H, m), 7.64—7.71 (2H, m), 7.79—7.80 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	466	$C_{26}H_{35}N_5O_3$	67.07 (66.89	7.58 7.78	15.04 14.96)
52	0.93 (13.4H, t, J=7.3), 1.08 (1.6H, t, J=7.3), 2.13—2.15 (1H, m), 2.37—2.60 (4H, m), 2.77—2.79 (1H, m), 2.88—2.98 (2H, m), 3.07—3.28 (4H, m), 7.40—7.48 (3H, m), 7.65—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	466	$C_{26}H_{35}N_5O_3$	67.07 (67.01	7.58 7.59	15.04 15.11)
53	0.95 (1.5H, t, J=7.3), 1.08 (1.5H, t, J=7.3), 1.33—1.36 (2H, m), 1.40—1.46 (4H, m), 2.12—2.15 (1H, m), 2.23—2.38 (6H, m), 2.50—2.52 (2H, m), 2.72—2.75 (1H, m), 3.22—3.26 (4H, m), 7.40—7.48 (3H, m), 7.64—7.71 (2H, m), 7.78—7.80 (1H, m), 8.30—8.31 (1H, m), 10.77 (1H, br s)	450	$C_{25}H_{31}N_5O_3 \cdot 0.4H_2O$	65.74 (65.71	7.02 6.82	15.33 15.30)
54	0.95 (1.4H, t, J=7.3), 1.80 (1.6H, t, J=7.3), 2.12—2.15 (1H, m), 2.29—2.58 (8H, m), 2.73—2.75 (1H, m), 3.21—3.34 (4H, m), 3.50—3.55 (4H, m), 7.41—7.48 (3H, m), 7.64—7.71 (2H, m), 7.80—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	452	$C_{24}H_{29}N_5O_4$	63.84 (63.63	6.47 6.53	15.51 15.61)
55	0.94 (1.5H, t, J=7.3), 1.07 (1.5H, t, J=7.3), 2.11, 2.12 (3H, 3s), 2.27—2.55 (13H, m), 2.72—2.75 (1H, m), 3.20—3.28 (4H, m), 7.40—7.48 (3H, m), 7.64—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	465	$C_{25}H_{32}N_6O_3 \cdot 0.3H_2O$	63.89 (63.97	6.99 6.96	17.88 17.85)
56	0.74—0.96 (6H, m), 1.05—1.12 (4H, m), 1.29—1.32 (1H, m), 1.60—1.69 (4H, m), 2.10—2.14 (3H, m), 2.34—2.55 (8H, m), 2.76—2.79 (1H, m), 3.17—3.30 (4H, m), 7.40—7.48 (3H, m), 7.65—7.72 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	506	$C_{29}H_{39}N_5O_3$	68.88 (68.65	7.77 7.77	13.85 13.74)
57	0.87 (1.6H, t, J=7.1), 0.94, 0.99, 1.03 (4.4H, 3t, J=7.1), 2.05—2.08 (1H, m), 2.38—2.50 (6H, m), 2.72—2.75 (1H, m), 3.10—3.31 (4H, m), 3.53 (1.1H, s), 3.56 (0.9H, s), 7.19—7.28 (5H, m), 7.40—7.48 (3H, m), 7.63—7.72 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	500	$C_{29}H_{33}N_5O_3$	69.72 (69.45	6.66 6.64	14.02 13.95)
58	0.91—0.95 (4.4H, m), 1.05 (1.6H, t, J=6.8), 2.12—2.15 (1H, m), 2.45—2.64 (10H, m), 2.75—2.78 (1H, m), 3.19—3.25 (4H, m), 7.13—7.27 (5H, m), 7.38—7.46 (3H, m), 7.63—7.72 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	514	$C_{30}H_{35}N_5O_3$	70.15 (70.24	6.87 7.02	13.63 13.50)

Table 5. (continued)

Compd. No.	^{1}H-NMR δ (in DMSO-d_6, J in Hz)	MS m/z ($M^+ + 1$)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
59	0.87 (1.1H, t, J=6.8), 0.93—1.05 (4.9H, m), 2.10—2.12 (1H, m), 2.42—2.49 (6H, m), 2.72—2.74 (1H, m), 3.11—3.26 (4H, m), 3.56 (1.1H, s), 3.60 (0.9H, s), 7.28 (1H, dd, J=7.8, 4.9), 7.40—7.49 (3H, m), 7.63—7.80 (4H, m), 8.31 (1H, br s), 8.40—8.47 (2H, m), 10.81 (1H, br s)	501	$C_{28}H_{32}N_6O_3 \cdot 0.2H_2O$	66.70 (66.55)	6.48 6.48	16.67 16.69)
60	0.89 (1.1H, t, J=6.8), 0.94, 0.98, 1.04 (4.9H, 3t, J=6.8), 2.10—2.12 (1H, m), 2,41—2.46 (6H, m), 2.72—2.76 (1H, m), 3.10—3.13 (1H, m), 3.21—3.24 (3H, m), 3.57 (1.1H, s), 3.60 (0.9H, s), 7.28 (2H, t, J=5.4), 7.31—7.48 (3H, m), 7.64—7.72 (2H, m), 7.81—7.83 (1H, m), 8.31 (1H, br s), 8.45 (2H, d, J=4.4), 10.79 (1H, br s)	501	$C_{28}H_{32}N_6O_3 \cdot 0.3H_2O$	66.46 (66.29	6.49 6.34	16.61 16.65)
61	0.88—1.00 (4.4H, m), 1.05 (1.6H, t, J=7.2), 2.10—2.12 (1H, m), 2.43—2.55 (6H, m), 2.73—2.76 (1H, m), 3.13—3.18 (1H, m), 3.24—3.32 (3H, m), 3.75 (1.6H, s), 3.79 (1.4H, s), 6.93 (2H, dd, J=7.6, 2.8), 7.35—7.46 (4H, m), 7.64—7.72 (2H, m), 7.78—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	506	$C_{27}H_{31}N_5O_3S \cdot 0.4H_2O$	63.23 (63.08	6.25 6.09	13.66 13.60)
62	0.89 (1.1H, t, J=6.8), 0.93, 0.98, 1.04 (4.9H, 3t, J=7.3, 7.3, 6.8), 2.09—2.11 (1H, m), 2.39—2.45 (6H, m), 3.12—3.15 (1H, m), 3.21—3.24 (3H, m), 3.55 (1.1H, s), 3.58 (0.9H, s), 7.00 (1H, d, J=4.9), 7.26 (1H, d, J=10.7), 7.42—7.47 (4H, m), 7.64—7.70 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.78 (1H, br s)	506	$C_{27}H_{31}N_5O_3S \cdot 0.4H_2O$	63.23 (63.16	6.25 6.16	13.66 13.62)
63	0.91—0.99 (4.4H, m), 1.05 (1.6H, t, J=7.0), 2.10—2.13 (1H, m), 2.39—2.50 (6H, m), 2.74—2.77 (1H, m), 3.17—3.31 (4H, m), 3.59 (1.1H, s), 3.62 (0.9H, s), 6.25 (1H, dd, J=12.8, 3.1), 6.36 (1H, dd, J=5.5, 3.1), 7.40—7.55 (4H, m), 7.63—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	490	$C_{27}H_{31}N_5O_4 \cdot 0.2H_2O$	65.76 (65.63	6.42 6.33	14.20 14.21)
64	0.92, 0.96, 1.00 (4.4H, 3t, J=6.8), 1.07 (1.6H, t, J=6.8), 2.10—2.13 (1H, m), 2.50—2.64 (6H, m), 2.73—2.76 (1H, m), 3.17—3.32 (4H, m), 3.88 (1.1H, s), 3.93 (0.9H, s), 7.40—7.46 (3H, m), 7.58 (1H, dd, J=10.8, 3.5), 7.64—7.70 (3H, m), 7.70—7.81 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	507	$C_{26}H_{30}N_6O_3S \cdot 0.2H_2O$	61.20 (61.06	6.01 5.83	16.47 16.45)
65	0.75 (1.2H, t, J=7.3), 0.89 (1.6H, t, J=7.3), 1.03, 1.07 (3.2H, 2t, J=7.3), 1.98—2.01 (1H, m), 2.18—2.31 (2H, m), 2.55—2.63 (5H, m), 2.96—3.04 (2H, m), 3.10—3.18 (2H, m), 3.94 (1.1H, s), 4.00 (0.9H, s), 7.37—7.51 (7H, m), 7.64—7.81 (4H, m), 7.86—7.89 (1H, m), 8.23 (1H, d, J=7.9), 8.30—8.31 (1H, m), 10.82 (1H, br s)	550	$C_{33}H_{35}N_5O_3$	72.11 (72.01	6.42 6.50	12.74 12.63)
66	0.84 (1.4H, t, J=6.8), 0.97 (1.6H, t, J=6.8), 1.03 (3H, t, J=6.8), 2.00—2.03 (1H, m), 2.50—2.58 (6H, m), 2.67—2.71 (1H, m), 3.06—3.11 (1H, m), 3.23—3.27 (3H, m), 3.69 (0.9H, s), 3.73 (1.1H, s), 7.32—7.47 (6H, m), 7.64—7.86 (7H, m), 8.28—7.29 (1H, m), 10.79 (1H, br s)	550	$C_{33}H_{35}N_5O_3$	72.11 (71.96	6.42 6.36	12.74 12.76)
67	0.90 (0.9H, t, J=7.3), 0.97, 1.01, 1.06 (5.1H, 3t, J=7.3), 2.04—2.06 (1H, m), 2.53—2.57 (6H, m), 2.61—2.63 (1H, m), 3.16—3.20 (1H, m), 3.28—3.30 (3H, m), 3.86 (1.1H, s), 3.90 (0.9H, s), 7.25—7.32 (3H, m), 7.38—7.47 (3H, m), 7.62—7.72 (3H, m), 7.79—7.83 (2H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	556	$C_{31}H_{33}N_5O_3S$	67.00 (66.99	5.99 5.91	12.60 12.33)
68	0.91 (1.4H, t, J=7.3), 1.06 (1.6H, t, J=7.3), 2.11 (1.6H, s), 2.17 (1.4H, s), 2.30—2.77 (6H, m), 3.13—3.35 (4H, m), 3.45 (1.1H, s), 3.49 (0.9H, s), 7.20—7.29 (5H, m), 7.40—7.49 (3H, m), 7.64—7.66 (1H, m), 7.70—7.71 (1H, m), 7.78—7.90 (1H, m), 8.30—8.31 (1H, m), 10.81 (1H, br s)	486	$C_{28}H_{31}N_5O_3 \cdot 0.2H_2O$	68.75 (68.47	6.47 6.33	14.32 14.19)
69	0.76—0.83 (3H, m), 0.87 (1.4H, t, J=6.8), 1.02 (1.6H, t, J=6.8), 1.36—1.46 (2H, m), 2.04—2.09 (1H, m), 2.30—2.50 (6H, m), 2.64—2.67 (1H, m), 3.10—3.31 (4H, m), 3.53 (1.6H, s), 3.56 (1.4H, s), 7.21—7.28 (5H, m), 7.38—7.47 (3H, m), 7.64—7.71 (2H, m), 7.77—7.79 (1H, m), 8.30—8.31 (1H, m), 10.80 (1H, br s)	514	$C_{30}H_{35}N_5O_3 \cdot 0.6H_2O$	68.71 (68.40	6.96 6.68	13.35 13.28)
70	0.83 (1H, t, J=7.2), 0.92 (3H, d, J=6.8), 0.95—0.99 (5H, m), 2.05—2.10 (1H, m), 2.28—2.50 (4H, m), 2.69—2.73 (1H, m), 2.78—2.91 (1H, m), 3.06—3.16 (3H, m), 3.18—3.20 (1H, m), 3.52 (1H, s), 3.55 (1H, s), 7.16—7.31 (5H, m), 7.42—7.48 (3H, m), 7.63—7.81 (3H, m), 8.30—8.31 (1H, m), 10.81 (1H, br s)	514	$C_{30}H_{35}N_5O_3 \cdot 0.3H_2O$	69.42 (69.39	6.91 6.81	13.49 13.47)
71	0.27 (1H, d, J=2.5), 0.32—0.34 (1H, m), 0.41—0.48 (2H, m), 0.86 (1.5H, t, J=7.2), 1.00 (1.5H, t, J=7.2), 1.80—1.82 (0.5H, m), 1.88—1.91 (0.5H, m), 2.06—2.12 (1H, m), 2.34—2.63 (4H, m), 2.70—2.75 (1H, m), 3.08—3.31 (4H, m), 3.68 (1H, s), 3.71 (1H, s), 7.20—7.30 (5H, m), 7.38—7.48 (3H, m), 7.65—7.72 (2H, m), 7.79—7.81 (1H, m), 8.31 (1H, m), 10.80 (1H, br s)	512	$C_{30}H_{33}N_5O_3 \cdot 0.3H_2O$	69.69 (69.65	6.55 6.54	13.55 13.59)
72	0.79 (1.3H, t, J=7.3), 0.97 (1.7H, t, J=7.3), 2.07—2.22 (1H, m), 2.40—2.50 (4H, m), 2.64—2.70 (1H, m), 3.00—3.30 (4H, m), 3.53 (2H, s), 3.60 (2H, s), 7.20—7.35 (10H, m), 7.39—7.48 (3H, m), 7.64—7.72 (2H, m), 7.80—7.81 (1H, m), 8.30—8.31 (1H, m), 10.81 (1H, br s)	562	$C_{34}H_{35}N_5O_3 \cdot 0.5H_2O$	71.56 (71.70	6.36 6.24	12.27 12.38)
73	0.97 (1.5H, t, J=7.3), 1.10 (1.5H, t, J=7.3), 2.11—2.13 (1H, m), 2.57—2.79 (7H, m), 3.24—3.45 (6H, m), 3.55 (1H, s), 3.60 (1H, s), 7.01—7.09 (3H, m), 7.40—7.48 (3H, m), 7.63—7.71 (2H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.79 (1H, br s)	498	$C_{29}H_{31}N_5O_3 \cdot 0.3H_2O$	69.25 (69.06	6.33 6.12	13.92 13.93)
75	0.92 (1.5H, t, J=6.7), 1.06 (1.5H, t, J=6.7), 2.55—2.76 (6H, m), 3.19—3.41 (4H, m), 3.64 (1H, s), 3.68 (1H, s), 7.19—7.29 (5H, m), 7.40—7.42 (1H, m), 7.45—7.47 (1H, m), 7.63—7.65 (1H, m), 7.69—7.71 (1H, m), 7.79—7.81 (1H, m), 8.30—8.31 (1H, m), 10.85 (1H, br s)	472	$C_{27}H_{29}N_5O_3 \cdot 0.3H_2O$	67.99 (67.88	6.26 6.23	14.68 14.56)

yield as colorless needles, mp 179—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (0.9H, t, J=7.3 Hz), 1.18 (2.1H, t, J=7.3 Hz), 2.42—2.69 (2H, m), 2.84—3.03 (2H, m), 3.34—3.40 (2H, m), 3.43—3.50 (2H, m), 3.68—3.73 (2H, m), 7.28—7.30 (1H, m), 7.40—7.47 (1H, m), 7.55—7.57 (2H, m), 7.61—7.62 (1H, m), 8.34 (1H, br s), 9.00 (1H, br s). *Anal.* Calcd for $C_{20}H_{22}N_4O \cdot 0.4H_2O$: C, 61.65; H, 5.90; N, 14.38. Found: C, 61.55; H, 5.61; N, 14.24. FAB-MS *m/z*: 383 ($M^+ + 1$).

11-[3-[*N*-[2-(Benzylamino)ethyl]-*N*-ethylcarbamoyl]propionyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**75**): A solution of DMSO (90 mg, 1.2 mmol) in CH_2Cl_2 (2 ml) was added dropwise to a solution of $(COCl)_2$ (130 mg, 1 mmol) in CH_2Cl_2 (10 ml) at −60 °C. The mixture was stirred for 25 min at −60 °C, then a solution of **74** (260 mg, 0.7 mmol) in CH_2Cl_2 (8 ml) was added dropwise. Stirring was continued for 25 min at −60 °C, and Et_3N (240 mg, 2.4 mmol) in CH_2Cl_2 (2 ml) was then added dropwise. The reaction mixture was stirred for 2 h at room temperature, then cooled to 0 °C, and benzylamine (60 mg, 0.56 mmol), acetic acid (250 mg, 4.2 mmol) and $NaB(OAc)_3H$ (210 mg, 1 mmol) were added to it. The whole was stirred at room temperature for 1 h, and made alkaline with 1 N aqueous NaOH. The aqueous layer was extracted with $CHCl_3$ (15 ml × 2) and the combined extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 300 : 10 : 1, v/v/v), and the product was crystallized from Et_2O to give 105 mg of **75** in 33% yield. Recrystallization from AcOEt–Et_2O afforded pure **75** as colorless needles, mp 149—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (1.5H, t, J=6.7 Hz), 1.06 (1.5H, t, J=6.7 Hz), 2.55—2.76 (6H, m), 3.19—3.41 (4H, m), 3.64 (1H, s), 3.68 (1H, s), 7.19—7.29 (5H, m), 7.40—7.42 (1H, m), 7.45—7.47 (1H, m), 7.63—7.65 (1H, m), 7.69—7.71 (1H, m), 7.79—7.81 (1H, m), 8.31 (1H, br s), 10.85 (1H, br s). *Anal.* Calcd for $C_{27}H_{29}N_5O_3 \cdot 0.3H_2O$: C, 67.99; H, 6.26; N, 14.68. Found: C, 67.88; H, 6.23; N, 14.56. FAB-MS *m/z*: 472 ($M^+ + 1$).

11-[3-(*N*-Methoxy-*N*-methylcarbamoyl)propionyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**76**): A solution of **40** (600 mg, 1.77 mmol), 1 N aqueous NaOH (6 ml) and EtOH (10 ml) was stirred for 30 min at room temperature. After neutralization with 1 N aqueous HCl (6 ml) and removal of the solvent under reduced pressure, the residue was dissolved in DMF (10 ml) and the precipitate was filtered off. *N,O*-Dimethylhydroxylamine hydrochloride (190 mg, 1.95 mmol), Et_3N (200 mg, 1.98 mmol), WSCD (380 mg, 2.00 mmol) and HOBT (120 mg, 0.88 mmol) were added to the filtrate and the mixture was stirred for 4 h at room temperature. After removal of the solvent under reduced pressure, the residue was diluted with water, and extracted with $CHCl_3$ (15 ml × 3). The organic solution was dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 50 : 1, v/v), and the product was crystallized from AcOEt–Et_2O to give 560 mg of **76** in 89% yield as colorless needles, mp 194—196 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.71—2.77 (1H, m), 2.84—2.90 (1H, m), 3.13 (3H, s), 3.69 (3H, s), 7.29—7.33 (1H, m), 7.41—7.43 (1H, m), 7.60—7.64 (2H, m), 7.95—8.01 (1H, m), 8.56 (1H, br s), 9.49 (1H, br s). *Anal.* Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.12; N, 15.81. Found: C, 60.89; H, 5.20; N, 15.63. FAB-MS *m/z*: 355 ($M^+ + 1$).

4-(5,11-Dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one-11-yl)-4-oxo-butyraldehyde (**77**): A solution of **76** (540 mg, 1.52 mmol) in dry THF (20 ml) was treated with $LiAlH_4$ (60 mg, 1.58 mmol) at −10 °C. The reaction mixture was stirred for 15 min at the same temperature and then poured into 5% HCl in ethanol (10 ml) at −40 °C. The mixture was partitioned between brine (10 ml) and $CHCl_3$ (15 ml) and the organic solution was dried over $MgSO_4$, and evaporated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 50 : 1, v/v), and the product was crystallized from Et_2O to give 190 mg of **77** in 42% yield as colorless needles, mp 192—194 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.32—2.35 (1H, m), 2.99—3.02 (1H, m), 7.34—7.36 (1H, m), 7.42—7.45 (1H, m), 7.59—7.61 (1H, m), 7.62—7.66 (2H, m), 7.98—8.01 (1H, m), 8.35—8.38 (1H, m), 9.78 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}N_3O_3 \cdot 0.5H_2O$: C, 63.15; H, 4.64; N, 13.81. Found: C, 63.09; H, 4.62; N, 13.70. FAB-MS *m/z*: 296 ($M^+ + 1$).

11-[4-[*N*-[2-(*N*-Benzylethylamino)ethyl]ethylamino]butyryl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (**78**): A mixture of **77** (100 mg, 0.34 mmol), **19** (70 mg, 0.34 mmol), acetic acid (30 mg, 0.5 mmol) and $NaB(OAc)_3H$ (100 mg, 0.5 mmol) in CH_2Cl_2 (4 ml) was stirred for 1 h at room temperature. The mixture was made alkaline with 1 N aqueous NaOH and was extracted with CH_2Cl_2 (10 ml × 2). The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 300 : 10 : 1, v/v/v) and the product was crystallized from hexane to give 125 mg of **15** in 76% yield. Recrystallization from $CHCl_3$–hexane afforded pure **78** as colorless needles, mp 97—98 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.80 (3H, t, J=7.2 Hz), 0.93 (3H, t, J=7.2 Hz), 1.49—1.54 (2H, m), 1.98—2.00 (1H, m), 2.20—2.23 (2H, m), 2.26—2.44 (9H, m), 3.50 (2H, s), 7.17—7.22 (1H, m), 7.25—7.30 (4H, m), 7.45—7.47 (3H, m), 7.63—7.71 (2H, m), 7.80 (1H, d, J=3.2 Hz), 8.28 (1H, dd, J=4.8, 2.0 Hz), 10.79 (1H, s). *Anal.* Calcd for $C_{29}H_{35}N_5O_2$: C, 71.73; H, 7.26; N, 14.42. Found: C, 71.45; H, 7.35; N, 14.34. FAB-MS *m/z*: 486 ($M^+ + 1$).

Biological Methods The following chemicals were obtained commercially: oxotremorine (Sigma, U.S.A.), atropine sulfate (Tanabe, Japan), and [^{3}H]pirenzepine ([^{3}H]PZ), [^{3}H]quinuclidinyl benzilate ([^{3}H]QNB) and [^{3}H]*N*-methylscopolamine ([^{3}H]NMS) (Du Pont-New England Nuclear, U.K.).

Receptor Binding Assay Male Wistar rats (350—400 g) were decapitated, then the cerebral cortex, heart and submandibular gland were removed and homogenized in ice-cold HEPES buffer (20 mM HEPES, 100 mM NaCl, 10 mM $MgCl_2$; pH 7.5). The homogenates were filtered through two layers of cloth gauze and centrifuged at 50000 × ***g*** for 10 min. The pellets thus obtained were washed twice in HEPES buffer by resuspension and recentrifugation. The resulting pellets were resuspended in HEPES buffer to give final protein concentrations of approximately 0.47 mg/ml (cerebral cortex), 1.0 mg/ml (heart) and 0.83 mg/ml (submandibular gland) as determined by the method of Bradford.[29] Membrane suspensions were stored at −80 °C until required.

The membrane suspensions (volume of 150 ml) were incubated with approximately 1.0 nM [^{3}H]PZ (K_D=9.30±0.28 nM) for cerebral cortex, 0.1 nM [^{3}H]QNB (K_D=0.128±0.004 nM) for heart and 0.3 nM [^{3}H]NMS (K_D=0.162±0.006 nM) for submandibular gland at 25 °C for 45 min. In the displacement studies, the inhibition of the specific binding was examined in the presence of nonlabeled drugs in a total volume of 0.5 ml of HEPES buffer. Nonspecific binding was determined using 10 μM atropine. Assays were terminated by rapid filtration under vacuum through a Whatman GF/B filter. The filters were washed immediately three times with approximately 3 ml portions of ice-cold HEPES buffer, then solubilized in 5 ml of scintillation cocktail (Aquasol-2, Packard) and counted for radioactivity using a Packard TR1-CARB 2200 CA liquid scintillation counter. Competition binding data were analyzed with nonlinear least-squares program, "GraphPad PRISM ver. 1.0" (GraphPad Software) to obtain the IC_{50} values. The IC_{50} values were corrected for receptor occupancy by [^{3}H]PZ, [^{3}H]QNB and [^{3}H]NMS as described by Cheng and Prusoff[30] to give K_i values (concentrations of nonlabeled ligand that cause half-maximal receptor occupancy in the absence of [^{3}H]PZ, [^{3}H]QNB and [^{3}H]NMS, respectively).

Heart Rate Male Wistar rats (300—350 g) were anesthetized with pentobarbital (60 mg/kg i.p.). A tracheal cannula was inserted to allow artificial respiration with room air. A jugular vein was cannulated for i.v. administration of drugs. Rats were pithed by the introduction a blunt steel rod *via* the orbit into the spinal canal and were pretreated with atenolol (10 mg/kg i.v.) to exclude catecholamine-induced tachycardia. The test compound or saline was administered i.v. At 15 min thereafter, a cumulative administration of oxotremorine was carried out. Log dose–response curves were constructed by plotting the decrease in heart rate (percentage of the initial value) *vs.* the logarithm of the dose (moles per kilogram). The ED_{50} values, doses of oxotremorine required to produce a 50% decrease in heart rate, were calculated from the log dose–response curves, and the dose-ratio was calculated. The antagonism for M_2 muscarinic receptors was expressed as the pDR_{10} value, the negative logarithm of the DR_{10} value, which is the dose of the test compound required to produce the oxotremorine dose-ratio of 10. In the case of compounds **61** and **68**, the maximum decrease in heart rate of oxotremorine was about 60%. Therefore, their dose-ratio was calculated from their ED_{30} values, *i.e.*, the doses of oxotremorine required to produce a 30% decrease in heart rate.

Salivation Male Wistar rats (300—350 g) were anesthetized with urethane (1.2 g/kg i.p.). After 10 min, the test compound or saline was administered i.v. and at 15 min thereafter, administration of oxotremorine was carried out. Saliva was collected for 5 min on a filter paper according to Lavy and Mulder.[31] The average dose reducing salivary secretion to 50% of the control value was determined graphically (ID_{50} (moles per kilogram)) and the antagonism for M_3 muscarinic receptors was expressed as the negative logarithm of the ID_{50} value, pID_{50}.

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