Synthesis and Biological Evaluation of Phenylacetyl Derivatives Having Low Central Nervous System Permeability as Potent and Selective M_2 Muscarinic Receptor Antagonists[1)]

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A series of phenylacetyl derivatives containing the 5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one or 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one skeleton was prepared and evaluated for their binding affinities to muscarinic receptors *in vitro* and for antagonism of bradycardia, salivation and tremor *in vivo*. Among them, compounds 56 and 66 had high affinity for M_2 muscarinic receptors in the heart ($pK_i = 8.7$ and 8.9, respectively) with low affinity for M_3 muscarinic receptors in the submandibular gland. A structure–activity relationship (SAR) study suggested that the high M_2 selectivity over the M_3 muscarinic receptors of 56 may be attributed to the direction of the carboxamide carbonyl group. In *in vivo* studies, 56 and 66 antagonized oxotremorine-induced bradycardia in rats on both intravenous and oral administration, and their heart rate increasing effect in dogs with nocturnal bradycardia was about 3-fold greater than that of AF-DX 116. Furthermore, they had almost no influence on oxotremorine-induced tremor in mice, presenting no evidence of central transfer.

Key words phenylacetyl derivative; M_2 muscarinic receptor; antagonism; M_2 selectivity; bradycardia

Activation of muscarinic receptors by the neurotransmitter acetylcholine produces a variety of responses because various receptor subtypes exist in different tissues. M_2 muscarinic receptors are abundant in peripheral effector organs, *e.g.*, heart and smooth muscle, and play an important role in the control of heart rate mediated by the vagus nerve.[2)] The overactivation of M_2 muscarinic receptors, that is, an increase in parasympathetic tone, is thought to be a significant factor in sick sinus syndrome and atrioventricular block, and this indicates that M_2 muscarinic receptor antagonists may be useful in the treatment of functional sinus disorders caused by vagotonia. In fact, administration of atropine, a non-selective muscarinic receptor antagonist, was effective in increasing the heart rate for 60% of patients with sinus nodal dysfunction in clinical trials.[3)] However, its use is limited by the short duration of action and the occurrence of undesirable side effects, such as dry mouth, mydriasis, decreased sweating, constipation and urinary retention, caused by antagonism of other subtypes.

Moreover, M_2 muscarinic receptors are also located presynaptically in the cortex and hippocampus and upon stimulation inhibit the release of acetylcholine.[4)] Due to blockade of presynaptical receptors, selective M_2 muscarinic receptor antagonists may improve memory and learning. Based on this hypothesis, new M_2 muscarinic receptor antagonists, such as BIBN 99 (**2**),[5)] 5-[[4-[4-(diisobutylamino)butyl]-1-phenyl]acetyl]-10,11-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (DIBD) (**3**)[6)] and its derivative **4**, able to cross the blood-brain barrier (BBB) have been developed as candidates for the treatment of Alzheimer's disease. These compounds were generated by increasing the lipophilicity of known M_2 muscarinic receptor antagonists.

We recently discovered novel selective M_2 muscarinic receptor antagonists containing a succinamide skeleton and a tricyclic ring system by modification of AF-DX 116 (**1**).[1,7)] YM-47244 (**5**) showed high affinity ($pK_i = 9.2$) and selectivity (M_3/M_2 ratio = 79) for M_2 muscarinic receptors in the heart and it appeared that the alkyl-bearing N atom of the piperazine ring was important for these properties. As a next step, we looked at DIBD, which is structurally quite different from the succinamide skeleton. As it is undesirable for an antibradycardiac agent to act on the central nervous system (CNS), we envisaged the structural modifications depicted in Fig. 2. First, a heteroatom was

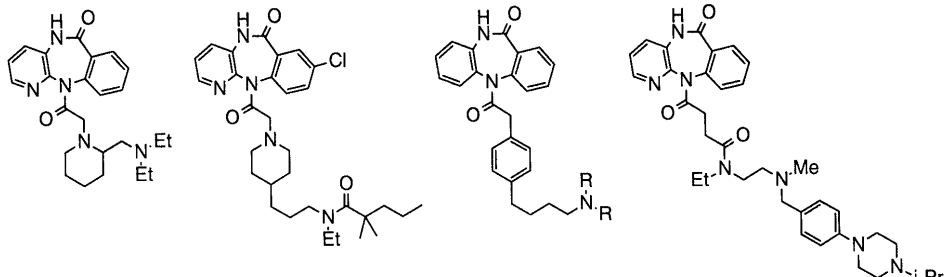

Fig. 1

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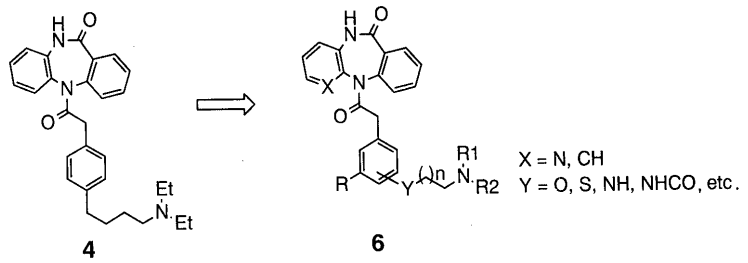
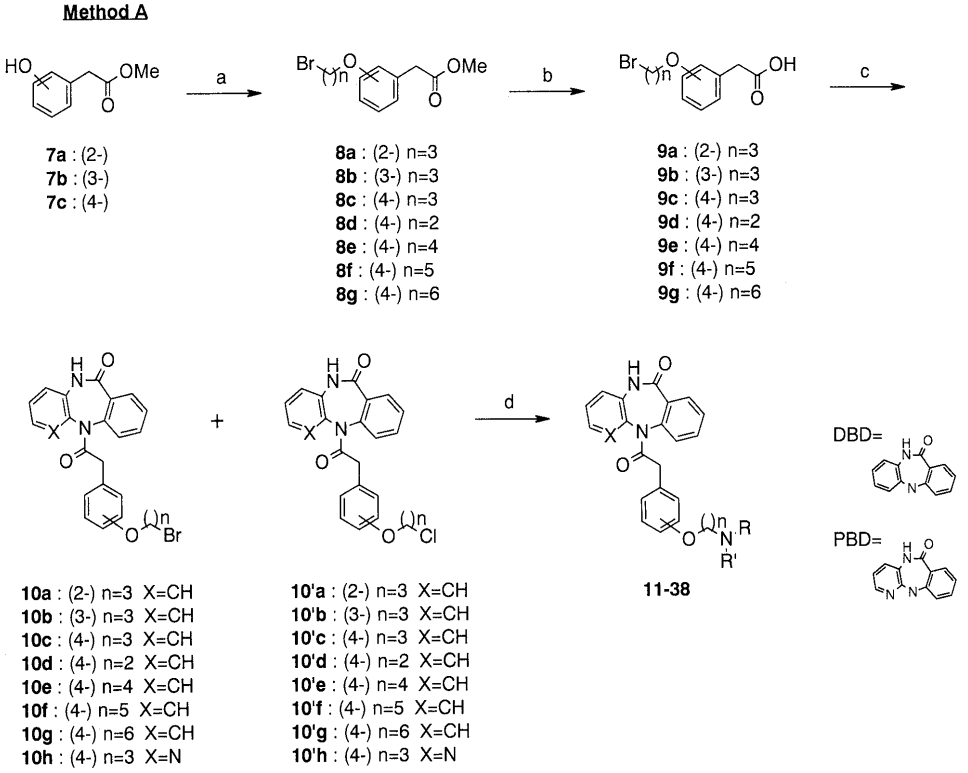


Fig. 2



Reagents: (a)Br(CH2)nBr (n=2-6),K2CO3,DMF or CH3CN; (b)aq.NaOH,MeOH then H3O+; (c)(i)SOCl2,cat.DMF,dioxane, (ii)DBD or PBD,*N,N*-dimethylaniline,THF; (d)RR'NH,EtOH.

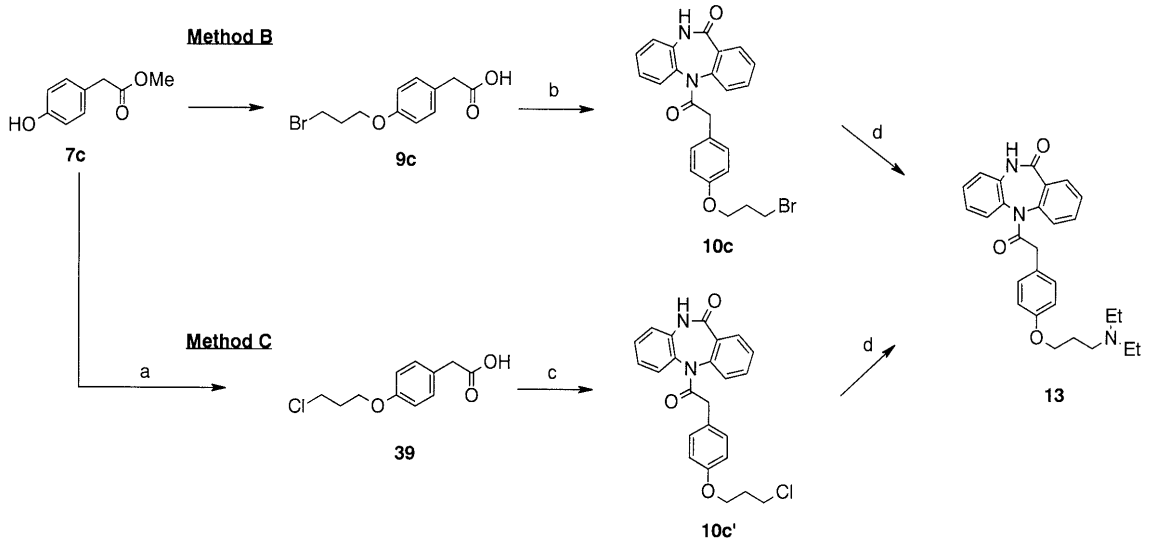
Chart 1

inserted into the benzyl position to reduce the lipophilicity. The calculated logP (c-logP) values of compounds **2** and **4** were 4.90 and 4.35, respectively, and as expected, the replacement of the carbon atom on the benzyl position of **4** by O, S, or N decreased the c-logP value (3.24, 3.88 and 2.82, respectively).[8] Second, a substituent was introduced at the 3-position on the phenyl ring of the phenylacetyl moiety, where a functional group is easily introduced. To our knowledge, there has been no report discussing the effect of this substituent on the affinities for muscarinic receptor subtypes. We expected that the affinity and selectivity for M_2 muscarinic receptors would be modified.

In this paper, we describe the results of our work on the synthesis, structure–activity relationships (SAR) and biological activities of compounds **6**.

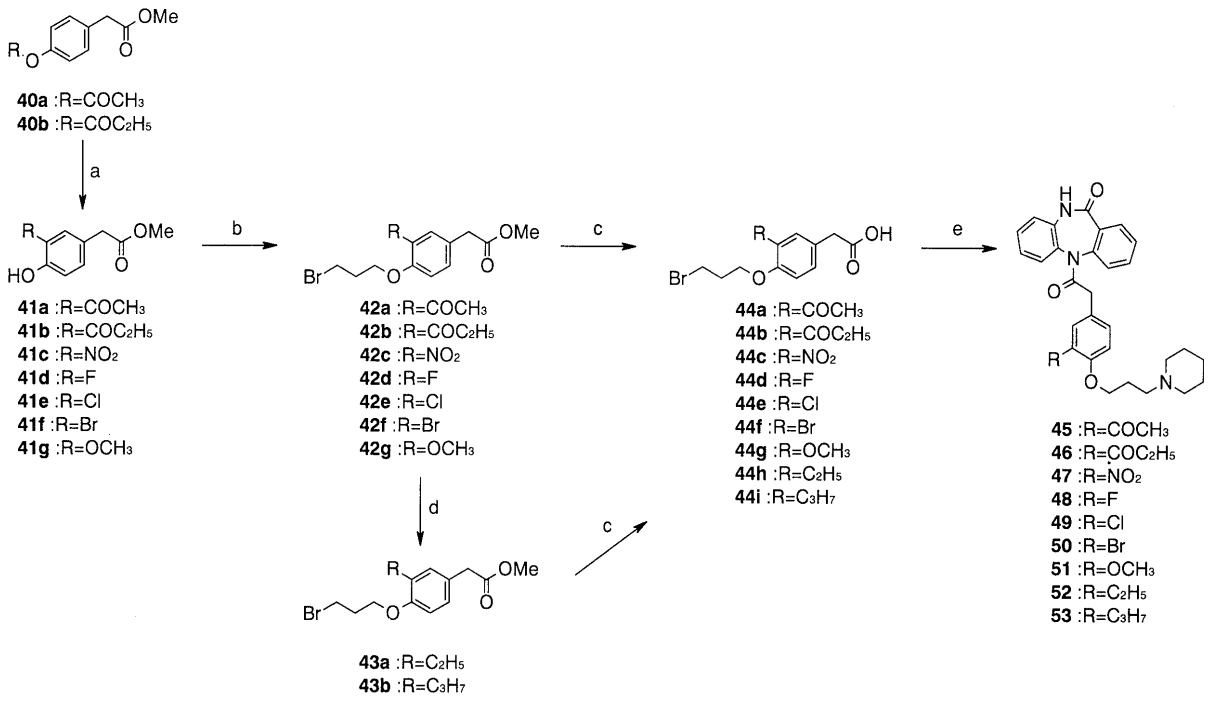
Chemistry

3-Unsubstituted target compounds **11**—**38** were synthesized from methyl 2-, 3-, or 4-hydroxyphenylacetate **7a**—**c**, as shown in Chart 1. Treatment of **7a**—**c** with an excess amount (5 eq) of dibromoalkanes with different methylene chain lengths ($n=2$—6) in *N,N*-dimethylformamide (DMF) or acetonitrile in the presence of potassium carbonate afforded *O*-alkyl compounds **8a**—**g**. Alkaline hydrolysis of **8a**—**g** produced the corresponding acids **9a**—**g** in good yields. Reaction of acid chlorides obtained from **9a**—**g**, thionyl chloride and a catalytic amount of DMF with 10,11-dihydro-5*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (DBD)[9] or 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]-benzodiazepin-6-one (PBD)[10] in the presence of *N,N*-dimethylaniline in tetrahydrofuran (THF) under reflux, afforded mixtures of (bromoalkyloxy)phenylacetyl analogues **10a**—**h** and (chloroalkyloxy)phenylacetyl analogues **10'a**—**h** which could not be separated by silica gel column chromatography. Our results in the condensation reaction were different from those in the report by Cohen *et al.*, who found that only 4-(bromoalkyl)phenylacetyl derivatives were produced from 4-(bromoalkyl)phenylacetic acid under the same conditions.[6b] Mixtures of **10** and **10'** were continuously treated with several amines in EtOH to give the target compounds **11**—**38** (method A).



Reagents: (a)(i)Cl(CH2)3Cl,K2CO3,CH3CN,(ii)aq.NaOH,MeOH then H3O+; (b)(i)SOBr2,cat.DMF,dioxane,(ii)DBD,*N,N*-dimethylaniline,THF; (c)(i)SOCl2,cat.DMF,dioxane,(ii)DBD,*N,N*-dimethylaniline,THF; (d)Et2NH,EtOH.

Chart 2

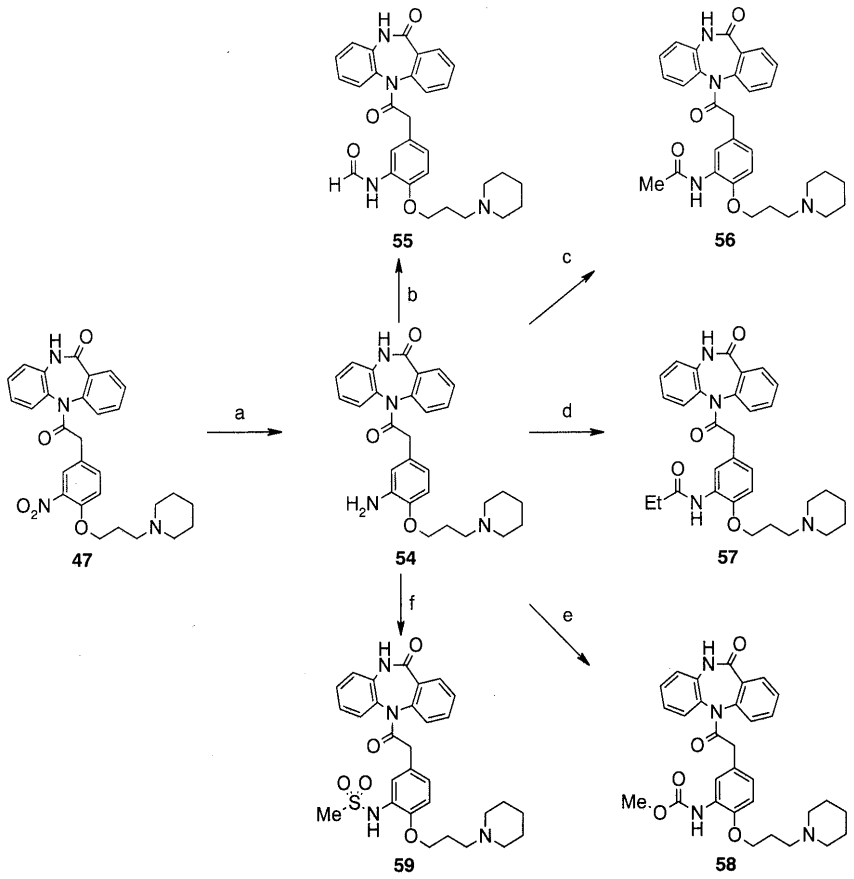


Reagents: (a)(i)AlCl3,trichlorobenzene,(ii)SOCl2,MeOH; (b)Br(CH2)3Br,K2CO3,CH3CN; (c)aq.NaOH,MeOH; (d)(i)NaBH4,MeOH,(ii)Et3SiH,TFA; (e)(i)SOCl2,cat.DMF,dioxane,(ii)DBD,*N,N*-dimethylaniline,THF,(iii)piperidine,EtOH.

Chart 3

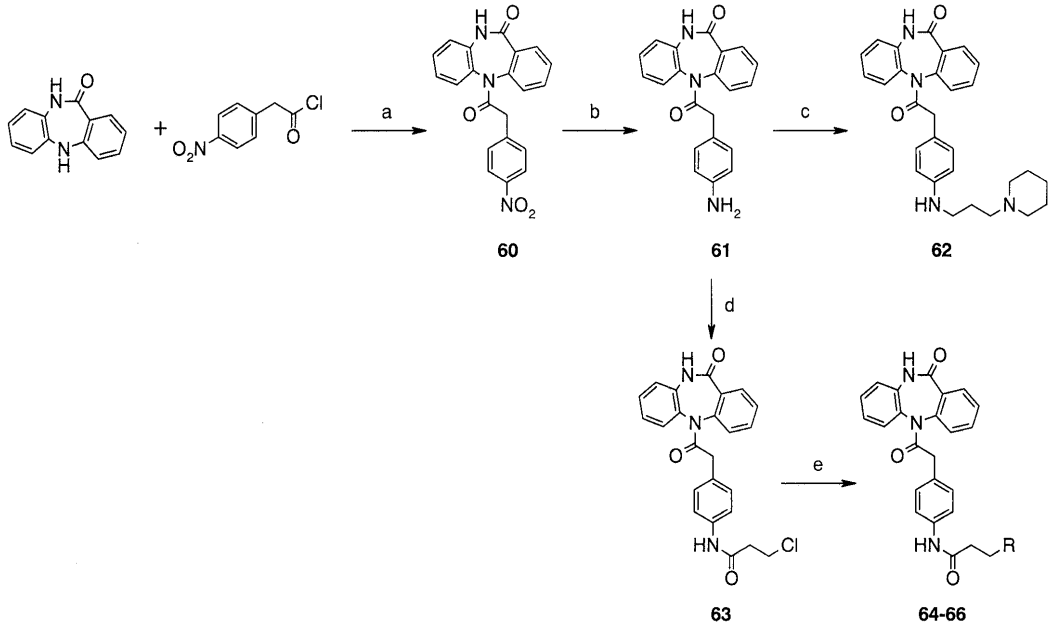
The synthetic routes using **10c** and **10′c** are shown in Chart 2 (method B and C). Reaction of **9c** with thionyl bromide, followed by condensation with DBD in the presence of *N,N*-dimethylaniline, gave **10c** in 9% yield. Phenylacetic acid (**39**) was prepared from **7c** and 1,3-dichloropropane under the same conditions as in the synthesis of **9c**, and the acid chloride obtained from **39** and thionyl chloride was coupled with DBD to give **10′c** in 75% yield. Compounds **10c** and **10′c** were treated with an excess (10 eq) of diethylamine to give **13** in 85% and 73% yields, respectively. Because we confirmed that the identical product **13** was obtained from each of the intermediates **10c** and **10′c**, we used the mixture of halide compounds for the synthesis of **6**.

Synthetic routes for [3-substituted-4-(3-piperidinopropoxy)]phenylacetyl derivatives **45**—**53** are illustrated in Chart 3. Compounds **41a** and **41b** were obtained by Fries rearrangement[11] of methyl 4-acetoxy and 4-propionyloxy phenylacetate **40a** and **40b**, respectively. Compounds **41a**—**g** were transformed to methyl [3-substituted-4-(3-bromopropoxy)]phenylacetate **42a**—**g** and reduction of the ketone of **42a** and **42b** with sodium borohydride in MeOH followed the treatment with triethylsilane (Et_3SiH) in trifluoroacetic acid afforded **43a** and **43b**, respectively.



Reagents: (a)H_2,Pd/C,MeOH; (b)HCO_2H-Ac_2O,dioxane; (c)Ac_2O,pyridine; (d)C_2H_5COCl,pyridine; (e)$ClCO_2CH_3$,pyridine; (f)CH_3SO_2Cl,pyridine.

Chart 4

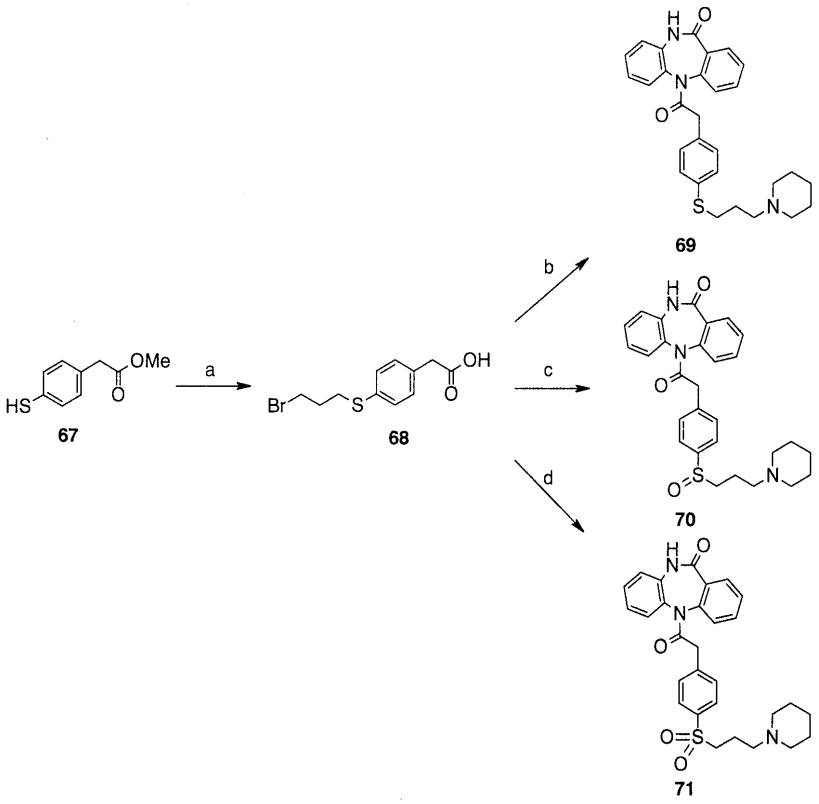


Reagents: (a) *N,N*-dimethylaniline THF; (b) Raney-Ni, DMF; (c) (i) 1,3-dibromopropane, HMPA, (ii) piperidine; (d) 3-chloropropionyl chloride, CH_3CN; (e) amine, *n*-Bu_4NBr, CH_3CN.

Chart 5

Starting from **42a**—**g** and **43a**—**b**, the desired compounds **45**—**53** were obtained by the previous method.

The 3-aminophenylacetate derivative **54** was prepared by catalytic hydrogenation of **47** over 10% Pd–C (Chart 4). Formylation of **54** with HCO_2H–Ac_2O gave compound **55**, and acylation with Ac_2O or propionyl chloride in



Reagents: (a)(i)Br(CH2)3Br,K2CO3,CH3CN,(ii)aq.NaOH,MeOH then H3O+; (b)(i)SOCl2,cat.DMF,dioxane,(ii)DBD,*N*,*N*-dimethylaniline,THF; (iii)piperidine,EtOH-CH3CN; (c)(i)SOCl2,cat.DMF,dioxane,(ii)DBD,*N*,*N*-dimethylaniline,THF,(iii)0.9eq.*m*CPBA,CH2Cl2, (iv)piperidine,CH3CN;(d)(i)SOCl2,cat.DMF,dioxane,(ii)DBD,*N*,*N*-dimethylaniline,THF,(iii)2.2eq. *m*CPBA,CH2Cl2,(iv)piperidine,CH3CN.

Chart 6

pyridine afforded **56** and **57**, respectively. The carbamate **58** and the sulfonamide **59** were obtained by the reaction of **54** with methyl chloroformate or methanesulfonyl chloride, respectively, in pyridine.

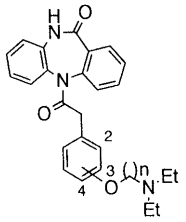
Synthesis of 4-propionamide phenylacetate derivatives **64**—**66** is illustrated in Chart 5. The 4-nitrophenylacetamide **60** obtained from DBD and 4-nitrophenylacetyl chloride was hydrogenated over Raney-Ni to afford the 4-aminophenylacetamide **61**. The resulting **61** was treated with 1,3-dibromopropane or 3-chloropropionyl chloride followed by heating with an excess of secondary amine in acetonitrile to yield the desired compounds **62** and **64**—**66**, respectively.

The thiophenoxy derivative **69** was obtained from methyl 4-mercaptophenylacetate **67**[12] under the same conditions as used for preparing compounds **11**—**38**. The sulfoxide **70** and the sulfone **71** were prepared by oxidation using 0.9 and 2.2 eq of *m*-chloroperoxybenzoic acid, respectively (Chart 6).

Pharmacological Results and Discussion

***In Vitro* Tests** The muscarinic receptor binding affinity and selectivity were assessed by employing receptor-binding assays as reported previously.[13] The binding affinities for test 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 over M_1 and M_3 muscarinic receptors (M_1/M_2, M_3/M_2, respectively) are presented in Tables 1—5. AF-DX 116 (**1**), **4** and YM-47244 (**5**) were used as reference compounds.

Table 1. The Binding Affinities of Compounds **11**—**17** for M_1, M_2 and M_3 Muscarinic Receptors

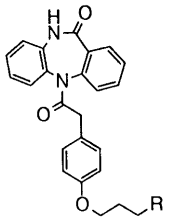


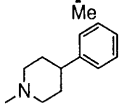
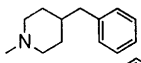
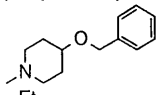
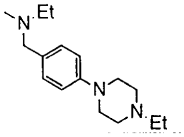
Compd.	*n*	Position	Binding affinity, pK_i[a]			Selectivity ratio	
			M_1[b]	M_2[c]	M_3[d]	M_1/M_2	M_3/M_2
11	3	2	6.0	6.3	5.6	2.0	5.0
12	3	3	7.7	7.7	7.3	1.0	2.5
13	3	4	8.1	8.7	7.7	4.0	10
14	2	4	7.4	7.9	7.2	3.2	5.0
15	4	4	8.4	8.6	7.7	1.6	7.9
16	5	4	8.1	8.5	7.5	2.5	10
17	6	4	7.5	7.8	6.7	2.0	13

a) pK_i values each represent an average of two or more determinations from separate assays. *b*) pK_i for [^{3}H]PZ binding; rat cerebral cortex. *c*) pK_i for [^{3}H]QNB binding; rat heart. *d*) pK_i for [^{3}H]NMS binding; rat submandibular gland.

Initially, the effects of substituted position and the alkyl length of the side chain on 5-phenylacethyl-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one were investigated (Table 1). A comparison of **11**—**17** demonstrated that

Table 2. The Binding Affinities of Compounds **18**—**36** for M_1, M_2 and M_3 Muscarinic Receptors



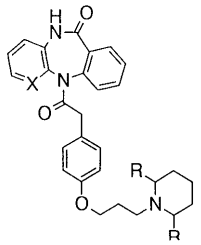
Compd.	R	Binding affinity, pK_i[a]			Selectivity ratio	
		M_1	M_2	M_3	M_1/M_2	M_3/M_2
18	NMe_2	7.6	7.9	7.0	2.0	7.9
19	N*n*-Pr_2	8.1	8.4	7.7	2.0	5.0
20	N iso-Pr_2	8.1	8.7	7.8	4.0	7.9
21	N iso-Bu_2	7.6	8.2	7.3	4.0	7.9
23		7.8	8.5	7.3	5.0	16
22		8.3	8.8	7.9	3.2	7.9
24		8.2	8.6	7.7	2.5	7.9
25		8.4	9.0	7.9	4.0	13
26		8.6	9.3	8.0	5.0	20
27		8.5	9.2	7.8	5.0	25
28		7.6	8.0	7.0	2.5	10
29		7.6	8.0	7.0	2.5	10
30		8.1	8.7	7.6	4.0	13
31	 (mixture of *cis* and *trans*)	8.5	9.0	7.8	3.2	16
32		8.5	9.0	7.9	3.2	13
33		7.8	8.1	7.0	2.0	13
34		7.8	8.3	7.1	3.2	16
35		8.2	8.7	7.5	3.2	16
36		8.6	9.4	7.8	6.3	40

a) See Table 1.

4-(3-diethylaminopropoxy) analog **13** showed a 10- to 250-fold higher affinity for M_2 muscarinic receptors than the 2 or 3-substituted compounds **11** and **12**, and the adequate alkyl chain length was **3**—**5**. We chose $n=3$ as the alkyl chain length to investigate further SAR.

We next studied the influence of the terminal amino moiety on **13** (Table 2). Comparing compounds **13** and **18**—**21** with an approximate ranking of dimethyl < di-isobutyl < di-*n*-propyl < diethyl = di-isopropyl in terms of the affinity for M_2 muscarinic receptors, it appears that the highest M_2 affinity is obtained when the alkyl length is 2. In addition, the finding that the bulkier cyclohexylethylamino analog **22** was equipotent to **13** indicated that at least one alkyl substituent should be of an appropriate size to obtain high M_2 affinity. On the other hand, the M_2 affinity was enhanced by increasing the ring size of the cyclic amine (5-membered **24** < 6-**25** < 7-**26** = 8-**27**). Morpholine **28** and *N*-methylpiperazine **29** analogs were found to have one-tenth of the potency of the piperidine derivative **25**, probably due to a reduction in basicity. 4-Methyl, 3,5-dimethyl or *cis*-2,6-dimethylpiperidine analogs **30**—**32** displayed comparable or slightly less M_2 affinity relative to **25**, though they are bulkier compounds. These results may indicate that the affinity for M_2 muscarinic receptors depends more on the basicity of the tertiary amine than on the bulkiness in the cyclic amino analog series.

Table 3. The Binding Affinities of Compounds **37** and **38** or M_1, M_2 and M_3 Muscarinic Receptors

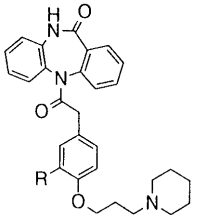


Compd.	X	R	Binding affinity, pK_i[a]			Selectivity ratio	
			M_1	M_2	M_3	M_1/M_2	M_3/M_2
25	CH	H	8.4	9.0	7.9	4.0	13
32	CH	Me	8.5	9.0	7.9	3.2	13
37	N	H	7.4	8.2	6.8	6.3	25
38	N	Me	7.5	8.3	6.9	6.3	25

a) See Table 1.

We reported that the introduction of a benzyl group into the terminal amine of succinamide derivatives was effective in increasing the affinity for M_2 muscarinic receptors.[1b] Unfortunately, compound **23** having an *N*-ethylbenzylamino group displayed an M_2 affinity similar to that of the corresponding diethylamino analog **13**. The introduction of a phenyl group into the piperidine ring of **25** with or without a linker failed to improve the M_2 affinity (**33**—**35**). On the other hand, 4-(4-ethylpiperazin-1-yl)benzylamino analog **36** showed a higher affinity for M_2 muscarinic receptors ($pK_i=9.4$) than **13**, with an enhanced M_2 selectivity over M_3 muscarinic receptors ($M_3/M_2=40$), and this finding parallels that observed in succinamide derivatives. It was speculated that the phenyl ring acts as a linker connecting two amino moieties, those of benzylamine and ethylpiperazine, which are likely to interact with different anionic groups located on the M_2 muscarinic receptors. We could not improve the M_2 selectivity over M_1 and M_3 muscarinic receptors sufficiently except for **36** by optimization of the terminal amino moiety even though high affinity for M_2 muscarinic

Table 4. The Binding Affinities of Compounds **45**—**59** for M_1, M_2 and M_3 Muscarinic Receptors



Compd.	R	Binding affinity, pK_i[a]			Selectivity ratio	
		M_1	M_2	M_3	M_1/M_2	M_3/M_2
25	H	8.4	9.0	7.9	4.0	13
45	$COCH_3$	6.9	7.9	6.2	10	50
46	COC_2H_5	6.8	7.5	6.1	5.0	25
47	NO_2	7.6	8.6	6.8	10	63
48	F	8.1	8.7	7.4	4.0	20
49	Cl	7.8	8.4	7.0	4.0	25
50	Br	7.6	8.2	6.7	4.0	32
51	OCH_3	6.9	7.9	6.2	10	50
52	C_2H_5	7.4	8.1	6.7	5.0	25
53	C_3H_7	7.2	7.8	6.4	6.3	25
54	NH_2	7.5	8.2	6.7	5.0	32
55	NHCHO	7.8	8.9	6.5	13	250
56	$NHCOCH_3$	8.1	8.7	6.9	4.0	63
57	$NHCOC_2H_5$	7.5	8.5	6.4	10	126
58	$NHCO_2CH_3$	7.2	8.2	5.9	10	200
59	$NHSO_2CH_3$	6.4	7.4	5.5	10	79
1 (AF-DX 116)		6.1	6.9	5.7	6.3	16
5 (YM-47244)		8.2	9.2	7.3	10	79

a) See Table 1.

receptors was achieved. We changed the DBD of compounds **25** and **32** to the PBD skeleton used in YM-47244 and AF-DX 116, but the binding affinity of **37** and **38** for M_2 muscarinic receptors was approximately one-fifth of that of the corresponding **25** and **32** (Table 3).

We next focused on the effects of the 3-substituent on the phenyl ring of **25** (Table 4). Unfortunately, introduction of a substituent onto the 3-position of the phenyl ring resulted in decreased affinity for all muscarinic receptor subtypes, except for the formamide analog **55**, which showed an M_2 affinity similar to that of **25**. It seems that the affinity for each subtype is in reverse order to the size of the substituent: H **25**>fluoro **48**>chloro **49**>bromo **50**>ethyl **52**>acetyl **45**>*n*-propyl **53**>propionyl **46**. Therefore, we analyzed the relationship between the pK_i value and the size of the 3-substituent as measured by molecular refractivity (MR)[14] (using the Oxford molecular program TSAR); the results are shown in Fig. 3. Though a good linear regression was not obtained between the pK_i of M_2 muscarinic receptors and MR values for the compounds in Table 4 due to a large scatter ($r=0.499$, $p=0.048$) (Fig. 3(a)), linear regression analysis reveals a significant trend ($r=0.911$, $p<0.001$) of decreasing M_2 affinity with increasing MR value after the exclusion of the formamide **55**, acetamide **56**, propionamide **57** and methoxycarbonylamino **58** analogs (Fig. 3(b)). On the other hand, a more significant linear regression was obtained between the pK_i of M_3 muscarinic receptors and the MR values for the compounds in Table

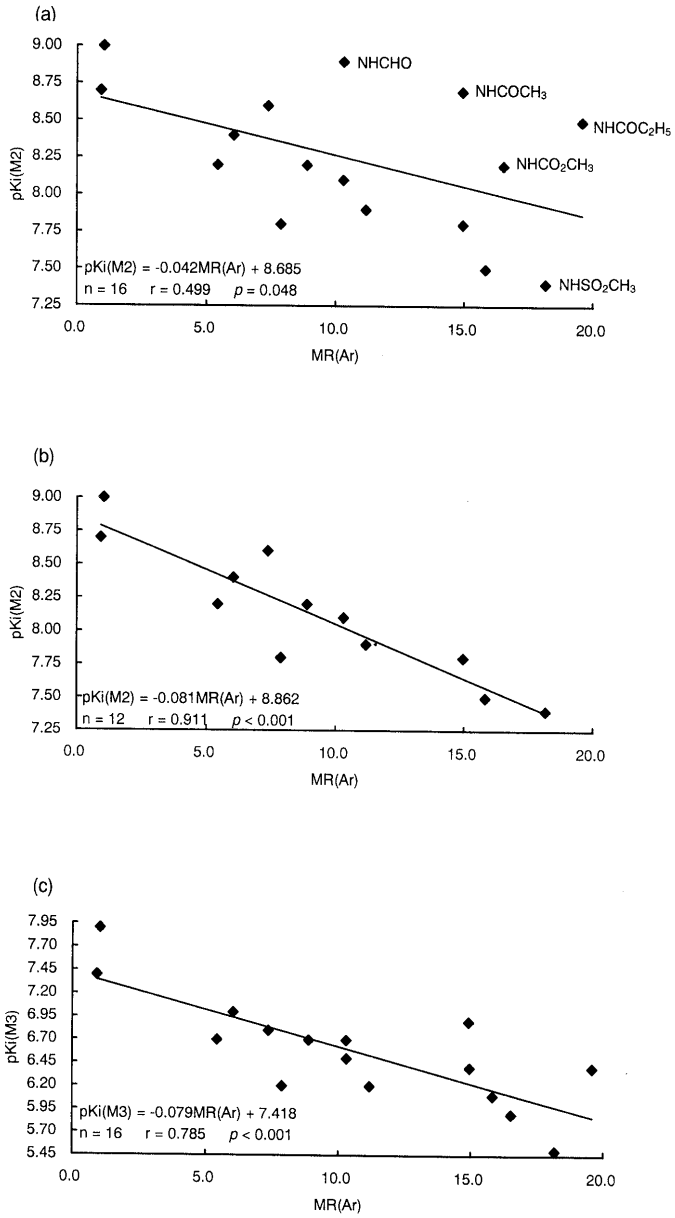
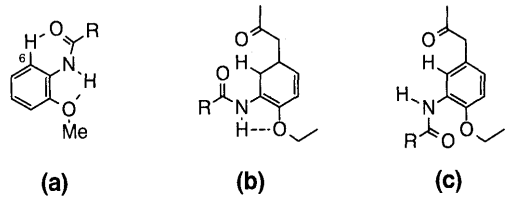


Fig. 3. Plot of MR Values *vs.* the Affinity for M_2 Muscarinic Receptors ((a) and (b)) or M_3 Muscarinic Receptors ((c)).

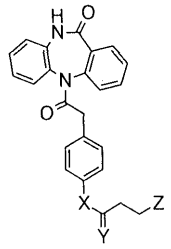
4 than in the case of M_2 muscarinic receptors ($r=0.785$, $p<0.001$) (Fig. 3(c)). These results indicate that the size of the 3-substituent may participate in determining the affinity for both M_2 and M_3 muscarinic receptors, and the carboxamide carbonyl group of **55**—**58** may contribute to the M_2 affinity probably by hydrogen-bonding interaction with muscarinic receptors, overcoming the effect of their molecular size. Additionally, the observation that the methanesulfonamide **59** was 13-fold less potent than **57** in spite of its smaller MR value suggests that the oxygen atom of the sulfonamide group was not located in an appropriate direction for this interaction. As a result, the carboxamide derivatives **55**—**58** displayed 20—100 times greater M_2 affinity than **1** with an improved M_2 selectivity over M_3 muscarinic receptors, and in particular, the formamide **55** was found to have affinity and selectivity for M_2 muscarinic receptors ($pK_i(M_2)=8.9$, $M_3/M_2=320$) comparable to those of YM-47244. A similar relationship between M_1 affinity and MR value to that of M_2 mus-



(a) (b) (c)

Fig. 4

Table 5. The Binding Affinities of Compounds **62**, **64**—**66** and **69**—**71** for M_1, M_2 and M_3 Muscarinic Receptors



Compd.	X	Y	Z	Binding affinity, pK_i[a]			Selectivity ratio	
				M_1	M_2	M_3	M_1/M_2	M_3/M_2
25	O	H_2	Piperidine	8.4	9.0	7.9	4.0	13
62	NH	H_2	Piperidine	8.5	8.7	7.5	2.0	16
64	NH	O	Piperidine	8.0	8.7	7.1	5.0	40
65	NH	O	Pyrrolidine	8.2	8.7	7.1	3.2	40
66	NH	O	NEt_2	8.1	8.9	7.3	6.3	40
69	S	H_2	Piperidine	9.0	9.5	8.1	3.2	25
70	S(O)	H_2	Piperidine	6.4	7.1	6.2	5.0	7.9
71	$S(O)_2$	H_2	Piperidine	6.3	6.6	5.9	2.0	5.0
4	CH_2	H_2	NEt_2	8.7	9.2	8.4	3.2	6.2

a) See Table 1.

carinic receptors was observed.[15]

The 2-methoxyphenylanilide moiety is generally known to adopt a planar conformation owing to intramolecular hydrogen bonding, and the signal of the hydrogen atom at the 6-position of the benzene ring in the ^{1}H-NMR spectrum is observed to be shifted downfield due to the influence of the carbonyl group (Fig. 4(a)).[16] Regarding **55**—**58**, the δ value of the *o*-proton in dimethyl sulfoxide-d_6 (DMSO-d_6) was observed to be shifted downfield at 7.42—7.70, while that of **59** was not (δ=7.04) (Table 6).[17] This finding is consistent with the above discussion on SAR of carboxamide derivatives. We further speculate that the configuration of the -NHCO- bond as illustrated in Fig. 4(b) not (c) is essential for the binding with M_2 muscarinic receptors.

Table 5 shows the results of replacement of the phenoxy moiety with anilino **62**, anilido **64**—**66**, thiophenoxy **69**, sulfoxide **70** and sulfone **71** analogs in comparison with the reported compound **4**. Though the anilino analog **62** was not improved in either M_2 affinity or selectivity, the anilido analogs **64**—**66** showed better M_2 selectivity over M_3 muscarinic receptors, and in particular, the 3-diethylaminopropionamide derivative **66** exhibited higher M_2 affinity and M_2 selectivity over M_3 muscarinic receptors ($pK_i(M_2)=8.9$, $M_3/M_2=40$) than the corresponding phenoxy analog **13**. The thiophenoxy analog **69** displayed the highest M_2 affinity ($pK_i(M_2)=9.5$) in this series and its oxides **70** and **71** were found to have 100-fold

Table 6. δ Value of the H Proton on the *o*-Position of Compounds **55**—**59** in DMSO-d_6

Compd.	δ Value of the proton
55	7.70
56	7.58
57	7.42
58	7.60
59	7.04

weaker affinity for M_2 muscarinic receptors than **69**. On the other hand, the reported compound **4** showed poor selectivity for M_2 muscarinic receptors over M_3 muscarinic receptors though it possessed a high M_2 affinity.

***In Vivo* Tests** Among these compounds, **55**, **56**, **66** and **69** were evaluated *in vivo*. From the viewpoint of side effects, we have to pay attention to M_3 receptor antagonistic activities, which are the main problem in the administration of atropine. Initially, we studied the oxotremorine-induced bradycardia in pithed rats and the oxotremorine-induced salivation in urethane-anesthetized rats to assess the M_2 and M_3 muscarinic receptor antagonistic activities in comparison with those of **1**, **5** and atropine. Test compounds were given by intravenous (i.v.) or oral (*p.o.*) administration, and the data are presented as pDR_{10} values against bradycardia and pID_{50} values against salivation as described in Experimental. In this oxotremorine-induced bradycardia model, these compounds behaved as noncompetitive-like antagonists in the same manner as **5**; 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 **1**, which exhibited competitive antagonism. The pDR_{10} values of these compounds were calculated from the ED_{30} values. In Table 7, the M_2 and M_3 antagonistic activities and M_2 selectivity over M_3 muscarinic receptors 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 relative to atropine (selectivity ratio=1).

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

The i.v. experiments showed that compound **56** possessed the highest M_2 muscarinic receptor antagonistic activity among the four compounds ($pDR_{10}=7.16$), with pronounced selectivity (M_3/M_2 ratio=288); this activity was 34-fold greater than that of **1** and equal to that of atropine. On the other hand, compound **66** was found to be more potent than **56** after *p.o.* administration. Compound **55**, which exhibited a marked effect *in vitro*, could not be evaluated in the *p.o.* experiment due to the large scatter of the data. Individual differences in metabolism in the formamide group may be responsible for this result. Thus, compounds **56** and **66** can be regarded as surrogates of atropine, which has the desired attributes of oral activity and M_2 selectivity over M_3 muscarinic receptors.

In the same dogs, nocturnal bradycardia was monitored under non-restricted conditions using a Holter electrocardiograph after oral administration of compounds **56** and **66** in comparison to **1**. The activity in oral

Table 7. Muscarinic Receptor Antagonistic Activities and Selectivity Ratio for *in Vivo* Experiments in Rats

Compd.	Inhibitory effects in oxotremorine-induced bradycardia (M_2)				Inhibitory effects in oxotremorine-induced salivation (M_3)		Selectivity ratio (M_3/M_2)
	i.v.		*p.o.*		i.v.		
	pDR_{10}[a]	*n*	pDR_{10}[a]	*n*	pID_{50}[a]	*n*	
55	6.76[b] (6.56—6.90)	9	—		N.T.[c]		—
56	7.16[b] (7.01—7.36)	8	5.21[b] (5.03—5.44)	12	5.00 (4.70—5.01)	16	288
66	6.90[b] (6.83—6.98)	11	5.41[b] (5.24—5.55)	12	5.29 (5.19—5.33)	15	81
69	6.92[b] (6.73—7.08)	6	5.33[b] (5.24—5.42)	8	5.54 (5.45—5.63)	16	48
1	5.63 (5.56—5.70)	32	4.90 (3.68—6.02)	36	4.60 (4.52—4.69)	24	21
5	7.67[b] (7.51—7.89)	8	5.79[b] (5.71—5.86)	5	5.32 (5.25—5.38)	9	447
Atropine	6.94 (6.88—7.01)	21	N.T.[c]		7.24 (7.21—7.28)	14	1

a) Values are the means of the indicated number of experiments (*n*). Figures in parentheses represent 95% confidence limits. *b*) Values are calculated from EC_{30} values. See Experimental. *c*) N.T.: Not tested.

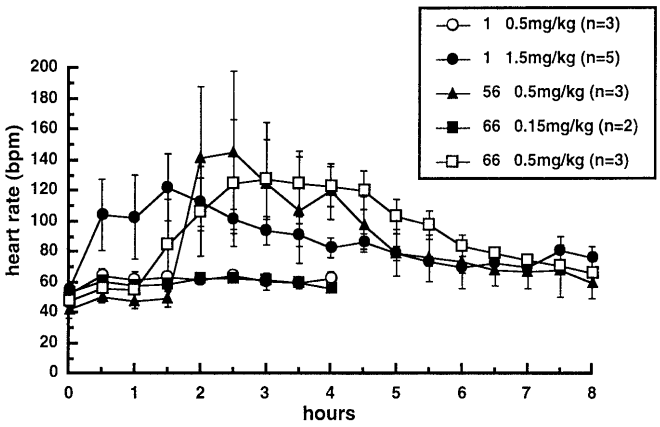


Fig. 5. Heart Rate-Increasing Effects of **56**, **66** and **1** on Nocturnal Bradycardia in Conscious Dogs

administration was determined based on the inhibitory effect on nocturnal bradycardia. Figure 5 shows the results obtained with the administration of **56** (0.5 mg/kg) and **66** (0.15 and 0.5 mg/kg), compared with doses of 0.5 and 1.5 mg/kg of **1**. The control heart rate was between 50 and 70 beats per minute, and 0.5 mg/kg of **56** and **66** produced a smooth response, giving a maximal heart rate from 120 to 140 beats per minute; this effect was the same as that of 1.5 mg/kg of **1**. The effect of **66** lasted for a longer period of time, compared with that of **1**, and its action was similar to that of **5**.[1b] On the other hand, neither 0.15 mg/kg of **56** or **66**, nor 0.5 mg/kg of **1** produced any effect. These results indicate that compounds **56** and **66** are 3-fold more potent than **1** in the inhibition of nocturnal bradycardia in conscious, unrestrained dogs after oral dosing.

The CNS activity of compounds **56** and **66** was evaluated by inhibitory effects on oxotremorine-induced tremor in mice reported by Noronha-Blob compared to those of atropine and **4**.[18] Compounds were administered intravenously *via* the tail vein, and the mice were scored

Table 8. Inhibition of Oxotremorine-Induced Tremor in Mice

Compd.	Dose (mg/kg)	Mean±S.E.	*n*
56	10	2.0±0.0	4
	30	2.0±0.0	4
66	30	1.75±0.25	4
	100	2.0±0.0	4
4	10	1.5±0.342	6
	30	0.667±0.307	6
Atropine	0.3	1.75±0.164	8
	1	0.813±0.282	8
	3	0.125±0.125	8

into 5 grades using a point system as described in Experimental. The data were presented as the mean of the total score in each dosage group (Table 8). Both 3 mg/kg of atropine and 30 mg/kg of **4** distinctly inhibited the tremor (mean = 0.125 and 0.667, respectively). In contrast, **56** and **66** had almost no influence up to fatal doses (100 and 300 mg/kg, respectively). Moreover, the respective c-logP values of **56** and **66** are 2.28 and 2.77, *i.e.*, their lipophilicity is lower than that of **4** (4.35), because of the insertion of a hetero atom into the benzyl position. Judging from these results, we speculate that the low CNS activity of **56** and **66** is a consequence of poor BBB permeation due to reduced lipophilicity.

Conclusions

A series of phenylacetyl derivatives having a tricyclic ring system was synthesized on the basis of SAR results for our succinamide-type M_2 muscarinic receptor antagonists. Among them, compounds **56** (YM-59981) and **66** (YM-55758) were found to be potent M_2 muscarinic receptor antagonists with high oral activity and poor BBB penetration. Substituents at the 3-position on the benzene ring of 4-(3-piperidinopropoxy)phenylacetyl derivatives had a marked influence on the affinity and selectivity for muscarinic receptors. Though the affinities for all subtypes

Table 9. Physical Data for Intermediate Phenylacetic Acid Derivatives

Compd.	^{1}H-NMR δ (in $CDCl_3$, J in Hz)	mp[a]	FAB-MS ($M^+ + 1$)
9a	2.24—2.43 (2H, m), 3.59 (2H, t, J=6.3), 3.65 (2H, s), 4.13 (2H, t, J=6.3), 6.85—7.02 (2H, m), 7.17—7.35 (2H, m)	Oil	273
9b	2.24—2.38 (2H, m), 3.60 (2H, t, J=6.2), 3.62 (2H, s), 4.10 (2H, t, J=6.2), 6.80—6.92 (3H, m), 7.16—7.35 (1H, m)	81—83 (E)	273
9d	3.59 (2H, s), 3.62 (2H, t, J=6.1), 4.28 (2H, t, J=6.1), 6.82—6.95 (2H, m), 7.16—7.26 (2H, m)	107—108 (E)	259
9e	1.89—1.96 (2H, m), 2.02—2.10 (2H, m), 3.47 (2H, t, J=6.4), 3.57 (2H, s), 3.97 (2H, t, J=6.0), 6.84 (2H, d, J=8.0), 7.17 (2H, d, J=8.0)	89—90 (E)	288
9f	1.56—1.68 (2H, m), 1.76—1.86 (2H, m), 1.88—1.98 (2H, m), 3.44 (2H, t, J=6.6), 3.58 (2H, s), 3.95 (2H, t, J=6.6), 6.85 (2H, d, J=8.7), 7.12 (2H, d, J=8.7)	72—73 (E-H)	302
9g	1.46—1.53 (4H, m), 1.73—1.82 (2H, m), 1.84—1.94 (2H, m), 3.42 (2H, t, J=6.6), 3.58 (2H, s), 3.94 (2H, t, J=6.6), 6.85 (2H, d, J=8.7), 7.18 (2H, d, J=8.7)	74—75 (E-H)	316
44a	2.36—2.41 (2H, m), 2.60 (3H, s), 3.59—3.62 (4H, m), 4.22 (2H, t, J=6.0), 6.96 (1H, d, J=8.5), 7.39 (1H, dd, J=8.5, 2.0), 7.63 (1H, d, J=2.0)	99—101 (E)	316
44b	1.17 (3H, t, J=7.5), 2.34—2.40 (2H, m), 2.95 (2H, q, J=7.5), 3.60 (2H, t, J=7.0), 3.62 (2H, s), 4.21 (2H, t, J=6.5), 6.95 (1H, d, J=8.5), 7.36 (1H, dd, J=8.5, 2.0), 7.56 (1H, d, J=2.0)	99—100 (E)	329
44c	2.22—2.49 (2H, m), 3.65 (2H, t, J=6.2), 3.66 (2H, s), 4.25 (2H, t, J=5.8), 7.07 (1H, d, J=8.6), 7.47 (1H, dd, J=8.6, 2.3), 7.80 (1H, d, J=2.2)	76—77 (E-H)	318
44d	2.20—2.47 (2H, m), 3.58 (2H, s), 3.62 (2H, t, J=6.2), 4.16 (2H, t, J=6.0), 6.92—7.10 (3H, m)	72—73 (E-H)	291
44e	2.22—2.49 (2H, m), 3.57 (2H, s), 3.65 (2H, t, J=6.4), 4.16 (2H, t, J=5.8), 6.89 (1H, d, J=8.4), 7.13 (1H, dd, J=8.4, 2.0), 7.31 (1H, d, J=2.0)	82—83 (E)	307
44f	2.22—2.49 (2H, m), 3.57 (2H, s), 3.67 (2H, t, J=6.4), 4.15 (2H, t, J=5.9), 6.86 (1H, d, J=8.5), 7.17 (1H, dd, J=8.5, 2.2), 7.47 (1H, d, J=2.3)	82—83 (E-H)	351
44g	2.21—2.48 (2H, m), 3.59 (2H, s), 3.62 (2H, t, J=6.4), 3.85 (3H, s), 4.14 (2H, t, J=6.0), 6.80—6.86 (3H, m)	102—103 (E)	303
44i	0.94 (3H, t, J=7.0), 1.55—1.62 (2H, m), 2.29—2.35 (2H, m), 2.55 (2H, t, J=8.0), 3.54 (2H, s), 3.61 (2H, t, J=6.0), 4.08 (2H, t, J=6.0), 6.79 (1H, d, J=8.5), 7.00—7.07 (2H, m)	Oil	315

a) Solvents for recrystallization: E, diethyl ether; H, *n*-hexane.

decreased in proportion to the size of the substituent, the M_2 affinity of compounds **55—58** containing an anilido moiety was comparable to or slightly less than that of unsubstituted compound **25**, with improved M_2 selectivity over M_3 muscarinic receptors.

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 a Hitachi M-80 spectrometer. High-resolution mass spectra (HRMS) were recorded on VG ZAB-VSE mass spectrometers. Column chromatography on silica gel was performed with Kieselgel 60 (E. Merck).

4-(3-Bromopropoxy)phenylacetic Acid (9c) 1) A mixture of methyl 4-hydroxyphenylacetate (**7c**, 16.6 g, 100 mmol), 1,3-dibromopropane (50.8 ml, 500 mmol) and potassium carbonate (16.6 g, 120 mmol) in acetonitrile (200 ml) was stirred for 7 h at 80 °C, then filtered. The filtrate was concentrated *in vacuo* and the residue was purified on a silica gel column (*n*-hexane : AcOEt, 9 : 1, v/v) to give 20.9 g of **8c** as a yellow oil in 73% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.27—2.35 (2H, m), 3.58 (2H, t, J=6.0 Hz), 3.59 (2H, s), 3.67 (3H, s), 4.09 (2H, t, J=6.0 Hz), 6.87 (2H, d, J=8.7 Hz), 7.20 (2H, d, J=8.7 Hz). FAB-MS m/z: 288 ($M^+ + 1$).

2) A solution of **8c** (20.9 g, 72.8 mmol), 1 N aqueous NaOH (109 ml, 109 mmol) and MeOH (100 ml) was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure, the residue was dissolved in H_2O (60 ml). The solution was treated with 1 N aqueous HCl (120 ml), and extracted with $CHCl_3$ (100 ml × 2). The combined extract was washed with brine, dried over $MgSO_4$ and concentrated to afford a solid residue. This residue was recrystallized from ether to give 18.3 g of **9c** as a white solid in 67% yield, mp 90—93 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.24—2.44 (2H, m), 3.58 (2H, t, J=6.0 Hz), 3.59 (2H, s), 4.09 (2H, t, J=5.8 Hz), 6.86 (2H, d, J=8.6 Hz), 7.20 (2H, d, J=8.6 Hz). GC-MS m/z: 272 (M^+). *Anal.* Calcd for $C_{11}H_{13}BrO_5$: C, 48.37; H, 4.80; Br, 29.26. Found: C, 48.54; H, 4.76; Br, 28.86.

4-(3-Chloropropoxy)phenylacetic Acid (39) The title compound was prepared in the same manner as **9c** using 1,3-dichloropropane instead of 1,3-dibromopropane in 47% yield, mp 87—89 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.18—2.24 (2H, m), 3.57 (2H, s), 3.72 (2H, t, J=6.4 Hz), 4.09 (2H, t, J=6.0 Hz), 6.85 (2H, d, J=8.4 Hz), 7.18 (2H, d, J=8.4 Hz). GC-MS m/z: 228 (M^+). *Anal.* Calcd for $C_{11}H_{13}ClO_5$: C, 57.78; H, 5.73; Cl, 15.50. Found: C, 57.86; H, 5.77; Br, 15.82.

5-[[4-(3-Diethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (13) (Method A) 1) Thionyl chloride (0.18 ml, 2.40 mmol) was added dropwise to a solution of **9c** (330 mg, 1.20 mmol) and DMF (1 drop) in 1,4-dioxane (10 ml) was added at room temperature, and the reaction mixture was stirred at 70 °C for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. The resulting oil was dissolved in THF (10 ml), then DBD (210 mg, 1.00 mmol) and *N*,*N*-dimethylaniline (120 mg, 1.00 mmol) were added, and the reaction mixture was stirred at reflux for 8 h. After cooling to room temperature, the reaction mixture was poured into water, acidified with 0.1 N hydrochloride acid, and extracted with $CHCl_3$ (20 ml × 2). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified on a silica gel column (*n*-hexane–AcOEt, 1 : 2, v/v) to give 340 mg of a mixture of 5-[[4-(3-bromopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (**10c**) and 5-[[4-(3-chloropropoxy)-phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (**10′c**) as colorless needles. The ratio of **10c** and **10′c** was about 6 : 4 as judged from the NMR data. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.27 (2H, m), 3.50—3.61 (1.6H, m), 3.63—3.80 (0.4H, m), 4.01—4.07 (2H, m), 6.81 (2H, d, J=8.4 Hz), 6.89 (2H, d, J=8.4 Hz), 7.16—7.56 (5H, m), 7.60—7.71 (2H, m), 7.72—7.81 (1H, m), 10.58 (1H, s). FAB-MS m/z: 466 ($M^+ + 1$, **10c**), 421 ($M^+ + 1$, **10′c**).

2) A mixture of **10c** and **10′c** (340 mg) was treated with diethylamine (70% in H_2O) (535 mg, 7.31 mmol) in EtOH (15 ml) at 80 °C for 8 h.

The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue obtained was diluted with 0.2 N aqueous NaOH and extracted with $CHCl_3$ (20 ml × 2). 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 hydrochloride salt was precipitated from EtOH with 4 N hydrochloric acid in AcOEt to give 210 mg of **13** as colorless needles in 43% yield from DBD, mp 148—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.22 (6H, t, J=7.2 Hz), 2.06—2.13 (2H, m), 3.10—3.21 (6H, m), 3.40—3.63 (2H, m), 4.03 (2H, t, J=6.0 Hz), 6.81 (2H, d, J=8.0 Hz), 6.91 (2H, d, J=8.0 Hz), 7.16—7.56 (5H, m). 7.60—7.71 (2H, m), 7.73—7.81 (1H, m), 9.97 (1H, br s), 10.58 (1H, s). FAB-MS m/z: 458 (M^++1). *Anal.* Calcd for $C_{28}H_{31}N_3O_3 \cdot HCl \cdot 0.5H_2O$: C, 66.86; H, 6.61; Cl, 7.05; N, 8.35. Found: C, 66.95; H, 6.61; Cl, 7.26; N, 8.28.

5-[[2-(3-Diethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (11) The title compound was prepared according to method A using **9a** instead of **9c** in 49% yield, mp 142—144 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, t, J=7.2 Hz), 1.08—1.14 (3H, m), 1.95—2.10 (2H, m), 2.85—3.02 (6H, m), 3.64 (2H, dd, J=16.4, 9.2 Hz), 3.90—3.98 (1H, m), 4.05—4.12 (1H, m), 6.70—6.77 (1H, m), 6.86—7.00 (2H, m), 7.15 (1H, d, J=7.6 Hz), 7.20—7.26 (2H, m), 7.30 (1H, t, J=7.6 Hz), 7.42—7.50 (2H, m), 7.62—7.77 (3H, m), 9.91 (1H, br s), 10.59—10.77 (1H, m). FAB-MS m/z: 458 (M^++1). *Anal.* Calcd for $C_{28}H_{31}N_3O_3 \cdot HCl \cdot 1.3H_2O$: C, 64.54; H, 6.77; Cl, 6.80; N, 8.06. Found: C, 64.50; H, 6.81; Cl, 6.86; N, 7.97.

5-[[3-(3-Diethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (12) The title compound was prepared according to method A using **9b** instead of **9c** in 69% yield. ^{1}H-NMR (DMSO-d_6) δ: 1.02 (6H, br s), 1.87 (2H, br s), 2.64 (6H, br s), 3.49—3.62 (2H, m), 3.94 (2H, t, J=6.1 Hz), 6.55 (2H, br s), 6.75—6.77 (1H, m), 7.12—7.53 (6H, m), 7.63—7.77 (3H, m), 10.55—10.58 (1H, m), 10.62 (1H, br s). HRMS (FAB) Found m/z=458.2452. $C_{28}H_{32}N_3O_3$ Calcd m/z=458.2444.

5-[[4-(2-Diethylaminoetoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-one Hydrochloride (14) The title compound was prepared according to method A using **9d** instead of **9c** in 59% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.98 (6H, br s), 2.56 (4H, br s), 2.78 (2H, br s), 3.43—3.61 (2H, m), 3.98 (2H, br s), 6.79 (2H, d, J=7.3 Hz), 6.89 (2H, d, J=7.3 Hz), 7.19—7.27 (3H, m), 7.37—7.78 (5H, m), 10.56 (1H, s), 10.62 (1H, br s). HRMS (FAB) Found m/z=444.2294. $C_{27}H_{30}N_3O_3$ Calcd m/z=444.2287.

5-[[4-(4-Diethylaminobuthoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (15) The title compound was prepared according to method A using **9e** instead of **9c** in 86% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.93 (6H, t, J=7.2 Hz), 1.46—1.53 (2H, m), 1.65—1.72 (2H, m), 2.37—2.46 (6H, m), 3.42—3.60 (2H, m), 3.92 (2H, t, J=6.4 Hz), 6.77 (2H, d, J=8.0 Hz), 6.87 (2H, d, J=8.0 Hz), 7.17—7.56 (5H, m), 7.62—7.70 (2H, m), 7.74—7.80 (1H, m), 10.56 (1H, br s), 10.62 (1H, br s). HRMS (FAB) Found m/z=472.2598. $C_{29}H_{34}N_3O_3$ Calcd m/z=472.2600.

5-[[4-(5-Diethylaminopentyloxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (16) The title compound was prepared according to method A using **9f** instead of **9c** in 88% yield. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, t, J=7.2 Hz), 1.38—1.50 (2H, m), 1.65—1.80 (2H, m), 2.94—3.11 (6H, m), 3.41—3.62 (2H, m), 3.94 (2H, t, J=6.3 Hz), 6.80 (2H, d, J=8.4 Hz), 6.90 (2H, d, J=8.4 Hz), 7.16—7.56 (5H, m), 7.63—7.71 (2H, m), 7.73—7.82 (1H, m), 10.57 (1H, br s), 10.62 (1H, br s). HRMS (FAB) Found m/z=486.2750. $C_{30}H_{36}N_3O_3$ Calcd m/z=486.2756.

5-[[4-(6-Diethylaminohexyloxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (17) The title compound was prepared according to method A using **9g** instead of **9c** in 91% yield. ^{1}H-NMR (DMSO-d_6) δ: 1.21 (6H, t, J=7.2 Hz), 1.30—1.48 (2H, m), 1.61—1.76 (4H, m), 2.91—3.11 (6H, m), 3.46—3.64 (2H, m), 3.92 (2H, t, J=6.3 Hz), 6.79 (2H, d, J=8.4 Hz), 6.98 (2H, d, J=8.4 Hz), 7.16—7.56 (5H, m), 7.64—7.71 (2H, m), 7.74—7.84 (1H, m), 10.56 (1H, br s), 10.62 (1H, br s). HRMS (FAB) Found m/z=500.2909. $C_{31}H_{38}N_3O_3$ Calcd m/z=500.2913.

5-[[4-(3-Dimethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (18) The title compound was prepared according to method A using dimethylamine instead of diethylamine in 89% yield, mp 147—149 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.09—2.16 (2H, m), 2.76 (6H, s), 3.16—3.20 (2H, m), 3.42—3.63 (2H, m), 4.01 (2H, t, J=6.0 Hz), 6.81 (2H, d, J=8.4 Hz), 6.90 (2H, d, J=8.4 Hz), 7.15—7.46 (5H, m), 7.61—7.71 (2H, m), 7.75—7.80 (1H, m), 10.59 (1H, br s), 10.63 (1H, br s). FAB-MS m/z: 430 (M^++1). *Anal.* Calcd for $C_{26}H_{26}N_3O_3 \cdot HCl \cdot 1.2H_2O$: C, 64.18; H, 6.09; Cl, 7.29; N, 8.64. Found: C, 64.28; H, 6.09; Cl, 7.13; N, 8.56.

5-[[4-(3-Dipropylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (19) The title compound was prepared according to method A using dipropylamine instead of diethylamine in 77% yield, mp 162—164 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.91 (6H, t, J=7.2 Hz), 1.63—1.73 (4H, m), 2.09—2.16 (2H, m), 2.99—3.06 (4H, m), 3.14—3.22 (2H, m), 3.38—3.63 (2H, m), 4.02 (2H, t, J=5.6 Hz), 6.81 (2H, d, J=8.4 Hz), 6.91 (2H, d, J=8.4 Hz), 7.16—7.56 (5H, m), 7.60—7.72 (2H, m), 7.74—7.81 (1H, m), 10.16 (1H, br s), 10.59 (1H, s). FAB-MS m/z: 486 (M^++1). *Anal.* Calcd for $C_{30}H_{35}N_3O_3 \cdot HCl \cdot 0.2H_2O$: C, 68.54; H, 6.98; Cl, 6.74; N, 7.99. Found: C, 68.53; H, 6.95; Cl, 6.50; N, 7.92.

5-[[4-(3-Diisopropylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (20) The title compound was prepared according to method A using diisopropylamine instead of diethylamine in 35% yield, mp 153—156 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.29 (6H, t, J=6.4 Hz), 1.33 (6H, t, J=6.4 Hz), 2.10—2.20 (2H, m), 3.17—3.21 (2H, m), 3.44—3.65 (4H, m), 4.01—4.05 (2H, m), 6.81 (2H, d, J=7.6 Hz), 6.92 (2H, d, J=7.6 Hz), 7.19—7.56 (5H, m), 7.63—7.68 (2H, m), 7.74—7.76 (1H, m), 9.61 (1H, br s), 10.59 (1H, s). FAB-MS m/z: 486 (M^++1). *Anal.* Calcd for $C_{30}H_{35}N_3O_3 \cdot HCl \cdot H_2O$: C, 66.72; H, 7.09; Cl, 6.56; N, 7.78. Found: C, 66.87; H, 7.37; Cl, 6.26; N, 7.40.

5-[[4-(3-Diisobutylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (21) The title compound was prepared according to method A using diisobutylamine instead of diethylamine in 73% yield, mp 127—129 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.00 (6H, d, J=6.8 Hz), 1.01 (6H, d, J=6.8 Hz), 2.04—2.21 (4H, m), 2.94—2.98 (4H, m), 3.21—3.28 (2H, m), 3.39—3.63 (2H, m), 4.00—4.06 (2H, m), 6.81 (2H, d, J=8.0 Hz), 6.92 (2H, d, J=8.0 Hz), 7.18—7.56 (5H, m), 7.60—7.72 (2H, m), 7.74—7.80 (1H, m), 10.60 (1H, s). FAB-MS m/z: 514 (M^++1). *Anal.* Calcd for $C_{32}H_{35}N_3O_3 \cdot HCl \cdot 0.8H_2O$: C, 68.08; H, 7.43; Cl, 6.28; N, 7.44. Found: C, 68.15; H, 7.42; Cl, 6.31; N, 7.41.

5-[[4-[3-(*N*-Cyclohexyl-*N*-ethylamino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Monofumarate (22) The title compound was prepared according to method A using *N*-cyclohexyl-*N*-ethylamine instead of diethylamine in 25% yield, mp 114—118 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.04 (3H, t, J=7.0 Hz), 1.19—1.67 (6H, m), 1.70—1.77 (4H, m), 1.85—1.88 (2H, m), 2.65—2.80 (5H, m), 3.41—3.57 (2H, m), 3.97 (2H, t, J=6.0 Hz), 6.55 (2H, s), 6.78 (2H, d, J=8.0 Hz), 6.89 (2H, d, J=8.5 Hz), 7.18—7.53 (5H, m), 7.61—7.64 (1H, m), 7.74—7.77 (1H, m), 10.57 (1H, s). FAB-MS m/z: 512 (M^++1). *Anal.* Calcd for $C_{32}H_{37}N_3O_3 \cdot C_4H_4O_4 \cdot 0.7H_2O$: C, 67.53; H, 7.67; N, 6.56. Found: C, 67.47; H, 6.96; N, 6.35.

5-[[4-[3-(*N*-Benzyl-*N*-ethylamino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (23) The title compound was prepared according to method A using *N*-benzyl-*N*-ethylamine instead of diethylamine in 83% yield, mp 175—178 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.28 (3H, t, J=7.2 Hz), 2.11—2.21 (2H, m), 3.04—3.18 (4H, m), 3.35—3.62 (2H, m), 3.96—4.01 (2H, m), 4.34 (2H, d, J=5.2 Hz), 6.75 (2H, d, J=8.0 Hz), 6.90 (2H, d, J=8.0 Hz), 7.20—7.30 (2H, m), 7.35—7.55 (6H, m), 7.60—7.72 (4H, m), 7.74—7.80 (1H, m), 10.59 (1H, s). FAB-MS m/z: 520 (M^++1). *Anal.* Calcd for $C_{33}H_{33}N_3O_3 \cdot HCl \cdot 1.5H_2O$: C, 67.97; H, 6.40; Cl, 6.08; N, 7.21. Found: C, 68.08; H, 6.69; Cl, 6.28; N, 7.24.

5-[[4-[3-(1-Pyrrolidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (24) The title compound was prepared according to method A using pyrrolidine instead of diethylamine in 87% yield, mp 140—142 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.83—1.94 (2H, m), 1.96—2.04 (2H, m), 2.08—2.16 (2H, m), 2.95—3.04 (2H, m), 3.21—3.30 (2H, m), 3.40—3.64 (4H, m), 4.02 (2H, t, J=6.0 Hz), 6.80 (2H, d, J=8.0 Hz), 6.90 (2H, d, J=8.0 Hz), 7.16—7.56 (5H, m), 7.60—7.72 (2H, m), 7.73—7.81 (1H, m), 10.54 (1H, br s), 10.58 (1H, s). FAB-MS m/z: 456 (M^++1). *Anal.* Calcd for $C_{28}H_{29}N_3O_3 \cdot HCl \cdot 1.5H_2O$: C, 64.79; H, 6.41; Cl, 6.83; N, 8.10. Found: C, 64.52; H, 6.47; Cl, 6.44; N, 8.28.

5-[[4-(3-Piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-one Hydrochloride (25) The title compound was prepared according to method A using piperidine instead of diethylamine in 67% yield, mp 143—145 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33—1.44 (1H, m), 1.66—1.73 (1H, m), 1.75—1.84 (4H, m), 2.12—2.21 (2H, m),

2.80—2.92 (2H, m), 3.10—3.17 (2H, m), 3.39—3.63 (4H, m), 4.01 (2H, t, $J=5.6$ Hz), 6.80 (2H, d, $J=8.0$ Hz), 6.90 (2H, d, $J=8.0$ Hz), 7.16—7.57 (5H, m), 7.60—7.72 (2H, m), 7.74—7.81 (1H, m), 10.45 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 470 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{31}N_3O_3 \cdot HCl \cdot H_2O$: C, 66.47; H, 6.54; Cl, 6.77; N, 8.02. Found: C, 66.59; H, 6.94; Cl, 6.37; N, 8.04.

5-[[4-[3-(Hexahydro-1-azepinyl)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (26) The title compound was prepared according to method A using hexamethyleneimine instead of diethylamine in 69% yield, mp 169—173 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.52—1.72 (4H, m), 1.79—1.91 (4H, m), 2.10—2.22 (2H, m), 3.06—3.15 (2H, m), 3.15—3.23 (2H, m), 3.33—3.40 (2H, m), 3.41—3.63 (2H, m), 4.01 (2H, t, $J=6.0$ Hz), 6.81 (2H, d, $J=8.0$ Hz), 6.90 (2H, d, $J=8.0$ Hz), 7.16—7.57 (5H, m), 7.60—7.71 (2H, m), 7.74—7.81 (1H, m), 10.51 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 484 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{33}N_3O_3 \cdot HCl \cdot 0.2H_2O$: C, 68.81; H, 6.62; Cl, 6.77; N, 8.02. Found: C, 68.90; H, 6.64; Cl, 6.75; N, 8.00.

5-[[4-[3-(Octahydro-1-azocinyl)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (27) The title compound was prepared according to method A using heptamethyleneimine instead of diethylamine in 20% yield, mp 164—167 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.46—1.81 (8H, m), 1.84—1.95 (2H, m), 2.09—2.19 (2H, m), 3.13—3.25 (4H, m), 3.35—3.40 (2H, m), 3.43—3.63 (2H, m), 4.01 (2H, t, $J=5.6$ Hz), 6.81 (2H, d, $J=8.4$ Hz), 6.91 (2H, d, $J=8.4$ Hz), 7.16—7.57 (5H, m), 7.61—7.72 (2H, m), 7.74—7.81 (1H, m), 9.70 (1H, br s), 10.58 (1H, s). FAB-MS *m/z*: 498 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{35}N_3O_3 \cdot HCl$: C, 69.71; H, 6.79; Cl, 6.64; N, 7.87. Found: C, 69.49; H, 6.08; Cl, 6.73; N, 7.80.

5-[[4-(3-Morpholinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo-[*b*,*e*][1,4]diazepin-11-one Hydrochloride (28) The title compound was prepared according to method A using morpholine instead of diethylamine in 62% yield, mp 149—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.82—1.87 (2H, m), 2.30—2.36 (4H, m), 2.40 (2H, t, $J=7.3$ Hz), 3.43—3.57 (6H, m), 3.96 (2H, t, $J=6.1$ Hz), 6.78 (2H, d, $J=7.3$ Hz), 6.88 (2H, d, $J=7.3$ Hz), 7.19—7.56 (5H, m), 7.60—7.73 (2H, m), 7.74—7.80 (1H, m), 10.16 (1H, br s), 10.56 (1H, s). FAB-MS *m/z*: 472 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{29}N_3O_4 \cdot HCl \cdot 2.0H_2O$: C, 61.82; H, 6.30; Cl, 6.52; N, 7.72. Found: C, 61.56; H, 6.32; Cl, 6.78; N, 7.73.

5-[[4-[3-(4-Methyl-1-piperazinyl)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (29) The title compound was prepared according to method A using 4-methylpiperazine instead of diethylamine in 66% yield, mp 188—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.17—2.21 (2H, m), 2.83 (3H, s), 3.21—3.85 (12H, m), 4.04—4.06 (2H, m), 6.79—6.84 (2H, m), 6.90 (2H, d, $J=8.4$ Hz), 7.20—7.52 (5H, m), 7.60—7.72 (2H, m), 7.74—7.82 (1H, m), 10.59—10.61 (1H, m), 12.21 (1H, br s). FAB-MS *m/z*: 485 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{32}N_4O_3 \cdot 2HCl \cdot 1.2H_2O$: C, 60.14; H, 6.34; Cl, 12.24; N, 9.67. Found: C, 59.97; H, 6.29; Cl, 12.52; N, 9.55.

5-[[4-[3-(4-Methylpiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (30) The title compound was prepared according to method A using 4-methylpiperidine instead of diethylamine in 82% yield, mp 167—171 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.92 (3H, t, $J=6.4$ Hz), 1.03—1.40 (2H, m), 1.50—1.65 (1H, m), 1.77—1.84 (2H, m), 2.85—2.95 (2H, m), 3.16—3.20 (2H, m), 3.40—3.60 (4H, m), 3.98—4.04 (2H, m), 6.77—6.84 (2H, m), 6.92 (2H, d, $J=8.4$ Hz), 7.16—7.56 (5H, m), 7.60—7.73 (2H, m), 7.75—7.81 (1H, m), 9.10 (1H, br s), 10.58 (1H, s). FAB-MS *m/z*: 484 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{30}N_3O_3 \cdot HCl \cdot 0.6H_2O$: C, 67.87; H, 6.68; Cl, 6.68; N, 7.92. Found: C, 67.87; H, 6.97; Cl, 6.46; N, 7.66.

5-[[4-[3-(3,5-Dimethylpiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (31) The title compound was prepared according to method A using 3,5-dimethylpiperidine instead of diethylamine in 85% yield, mp 235—237 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.81—0.91 (6H, m), 1.23—2.00 (6H, m), 2.36—2.80 (6H, m), 3.42—3.60 (2H, m), 3.94 (2H, s), 6.77 (2H, d, $J=7.9$ Hz), 6.88 (2H, d, $J=7.9$ Hz), 7.19—7.52 (5H, m), 7.61—7.73 (2H, m), 7.74—7.80 (1H, m), 10.56 (1H, s). FAB-MS *m/z*: 498 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{35}N_3O_3 \cdot HCl$: C, 69.71; H, 6.79; Cl, 6.64; N, 7.87. Found: C, 69.71; H, 6.92; Cl, 6.59; N, 7.83.

5-[[4-[3-(2,6-Dimethylpiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (32) The title compound was prepared according to method A using 2,6-dimethylpiperidine instead of diethylamine in 37% yield, mp 168—170 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (6H, d, $J=6.1$ Hz), 1.50—1.70 (4H, m), 1.81—1.85 (2H, m), 2.01—2.17 (2H, m), 3.26—3.31 (2H, m), 3.37—3.62 (4H, m), 4.03—4.06 (2H, m), 6.81 (2H, d, $J=7.3$ Hz), 6.91 (2H, d, $J=7.3$ Hz), 7.12—7.56 (5H, m), 7.62—7.69 (2H, m), 7.74—7.78 (1H, m), 9.94 (1H, br s), 10.57 (1H, s). FAB-MS *m/z*:498 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{35}N_3O_3 \cdot HCl \cdot H_2O$: C, 67.44; H, 6.94; Cl, 6.41; N, 7.61. Found: C, 67.46; H, 6.69; Cl, 6.21; N, 7.44.

5-[[4-[3-(4-Phenylpiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (33) The title compound was prepared according to method A using 4-phenylpiperidine instead of diethylamine in 60% yield, mp 177—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.98—2.02 (4H, m), 2.15—2.22(2H, m), 2.81—2.85 (1H, m), 3.00—3.11 (2H, m), 3.20—3.27 (2H, m), 3.41—3.63 (4H, m), 4.01—4.07 (2H, m), 6.80—6.84 (2H, m), 6.92 (2H, d, $J=8.4$ Hz), 7.16—7.46 (10H, m), 7.61—7.71 (2H, m), 7.72—7.79 (1H, m), 10.09 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 456 ($M^+ + 1$). *Anal.* Calcd for $C_{35}H_{35}N_3O_3 \cdot HCl \cdot 0.4H_2O$: C, 71.33; H, 6.29; Cl, 6.02; N, 7.13. Found: C, 71.23; H, 6.35; Cl, 6.04; N, 7.15.

5-[[4-[3-(4-Benzylpiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (34) The title compound was prepared according to method A using 4-benzylpiperidine instead of diethylamine in 56% yield, mp 200—202 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.45—1.58 (2H, m), 1.68—1.78 (3H, m), 2.09—2.16 (2H, m), 2.53 (2H, d, $J=6.4$ Hz), 2.84 (2H, q, $J=10.8$ Hz), 3.10—3.17 (2H, m), 3.40—3.63 (4H, m), 4.00 (2H, t, $J=5.6$ Hz), 6.79 (2H, d, $J=8.0$ Hz), 6.90 (2H, d, $J=8.0$ Hz), 7.17—7.56 (10H, m), 7.60—7.71 (2H, m), 7.72—7.80 (1H, m), 10.07 (1H, br s), 10.58 (1H, s). FAB-MS *m/z*: 560 ($M^+ + 1$). *Anal.* Calcd for $C_{36}H_{37}N_3O_3 \cdot HCl \cdot 0.7H_2O$: C, 71.03; H, 6.52; Cl, 5.82; N, 6.90. Found: C, 70.94; H, 6.55; Cl, 5.81; N, 6.83.

5-[[4-[3-(4-Benzyloxypiperidino)propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (35) The title compound was prepared according to method A using 4-benzyloxypiperidine instead of diethylamine in 35% yield, mp 149—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.49—1.52 (2H, m), 1.79—1.87 (4H, m), 2.07—2.70 (6H, m), 3.29—3.60 (3H, m), 3.94 (2H, t, $J=6.1$ Hz), 4.49 (2H, s), 6.77 (2H, d, $J=7.3$ Hz), 6.87 (2H, d, $J=7.3$ Hz), 7.19—7.58 (10H, m), 7.60—7.71 (2H, m), 7.72—7.81 (1H, m), 10.09 (1H, br s), 10.56 (1H, s). FAB-MS *m/z*: 576 ($M^+ + 1$). *Anal.* Calcd for $C_{36}H_{37}N_3O_4 \cdot HCl \cdot 0.3H_2O$: C, 70.02; H, 6.30; Cl, 5.74; N, 6.80. Found: C, 70.06; H, 6.22; Cl, 5.81; N, 6.76.

5-[[4-[3-[4-*N*-Ethyl-*N*-[4-(4-isopropyl-1-piperazinyl)benzyl]amino]-propoxy]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (36) The title compound was prepared according to method A using 4-*N*-ethyl-*N*-[4-(4-isopropyl-1-piperazinyl)benzyl]amine instead of diethylamine in 71% yield. ^{1}H-NMR (DMSO-d_6) δ: 0.95 (3H, t, $J=7.2$ Hz), 1.02 (3H, t, $J=7.2$ Hz), 1.81 (2H, t, $J=6.4$ Hz), 2.35 (2H, q, $J=7.2$ Hz), 2.39—2.48 (8H, m), 3.04—3.09 (4H, m), 3.43 (2H, s), 3.45—3.63 (4H, m), 3.92 (2H, t, $J=6.4$ Hz), 6.73 (2H, d, $J=8.0$ Hz), 6.82 (2H, d, $J=8.4$ Hz), 6.87 (2H, d, $J=8.0$ Hz), 7.10 (2H, d, $J=8.4$ Hz), 7.15—7.55 (5H, m), 7.60—7.71 (2H, m), 7.74—7.81 (1H, m), 10.58 (1H, s). HRMS (FAB) Found *m/z*=632.3604. $C_{39}H_{46}N_5O_3$ Calcd *m/z*=632.3601.

11-[[4-(3-Piperidinopropoxy)phenyl]acetyl]-5,11-dihydro-6*H*-pyrido-[2,3-*b*][1,4]benzodiazepin-6-one (37) The title compound was prepared according to method A using PBD and piperidine instead of DBD and diethylamine respectively in 76% yield, mp 172—177 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.42—1.57 (6H, m), 1.80—2.00 (2H, m), 2.20—2.80 (6H, m), 3.50—3.65 (2H, m), 3.96 (2H, t, $J=6.1$ Hz), 6.77 (2H, d, $J=8.7$ Hz), 6.87 (2H, d, $J=8.7$ Hz), 7.40—7.55 (4H, m), 7.61—7.63 (1H, m), 7.77—7.78 (1H, m), 8.35 (1H, s), 10.62 (1H, br s). FAB-MS *m/z*: 471 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{30}N_4O_3 \cdot 1.3H_2O$: C, 68.08; H, 6.65; N, 11.34. Found: C, 68.00; H, 6.35; N, 11.43.

11-[[4-[3-(2,6-Dimethylpiperidino)propoxy]phenyl]acetyl]-5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]benzodiazepin-6-one (38) The title compound was prepared according to method A using PBD and 2,6-dimethylpiperidine instead of DBD and diethylamine, respectively, in 43% yield, mp 161—165 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.27—1.99 (14H, m), 3.10—3.32 (4H, m), 3.57—3.62 (2H, m), 3.98—4.07 (2H, m), 6.78 (2H, d, $J=8.4$ Hz), 6.88 (2H, d, $J=8.4$ Hz), 7.40—7.52 (3H, m), 7.60—7.71 (2H, m), 7.76—7.80 (1H, m), 8.33—8.37 (1H, m), 10.64 (1H, s). HRMS(FAB) Found *m/z*=499.2708. $C_{30}H_{35}N_4O_3$ Calcd *m/z*=499.2709.

5-[[3-Acetyl-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (45) The title compound was prepared according to method A using 3-acetyl-4-(3-bromopropoxy)phenylacetic acid and piperidine instead of 4-(3-bromo-

propoxy)phenylacetic acid and diethylamine, respectively, in 58% yield, mp 216—219 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.35—1.43 (1H, m), 1.71—1.83 (5H, m), 2.20—2.30 (2H, m), 2.54 (3H, s), 2.84—2.92 (2H, m), 3.14—3.20 (2H, m), 3.42—3.71 (4H, m), 4.10—4.20 (2H, m), 6.98—7.04 (1H, m), 7.10—7.55 (7H, m), 7.61—7.77 (3H, m), 10.52—10.56 (1H, m), 10.69 (1H, br s). FAB-MS *m/z*: 512 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{33}N_3O_4 \cdot HCl \cdot H_2O$: C, 65.77; H, 6.41; Cl, 6.26; N, 7.42. Found: C, 65.51; H, 6.19; Cl, 6.80; N, 7.70.

5-[[4-(3-Piperidinopropoxy)-3-propionylphenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (46) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-propionylphenylacetic acid and piperidine instead of 4-(3-bromopropoxy)phenylacetic acid and diethylamine, respectively, in 48% yield, mp 203—206 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, t, J=7.0 Hz), 1.35—1.45 (1H, m), 1.85—1.92 (5H, m), 2.20—2.30 (2H, m), 2.80—2.95 (4H, m), 3.10—3.20 (2H, m), 3.40—3.75 (4H, m), 4.08—4.20 (2H, m), 7.01 (1H, t, J=10.0 Hz), 7.10—7.58 (7H, m), 7.62—7.78 (3H, m), 10.39 (1H, br s), 10.52—10.55 (1H, m). FAB-MS *m/z*: 526 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{35}N_3O_4 \cdot HCl \cdot 1.5H_2O$: C, 65.24; H, 6.67; Cl, 6.02; N, 7.13. Found: C, 65.07; H, 6.47; Cl, 5.93; N, 7.28.

5-[[3-Nitro-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (47) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-nitrophenylacetic acid and piperidine instead of 4-(3-bromopropoxy)-phenylacetic acid and diethylamine, respectively, in 44% yield, mp 192—195 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.75—1.84 (4H, m), 2.12—2.21 (2H, m), 2.80—2.92 (2H, m), 3.10—3.17 (2H, m), 3.39—3.63 (4H, m), 4.01 (2H, t, J=5.6 Hz), 6.80 (2H, d, J=8.0 Hz), 6.90 (2H, d, J=8.0 Hz), 7.16—7.57 (5H, m), 7.60—7.72 (2H, m), 7.74—7.81 (1H, m), 10.45 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 515 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{30}N_4O_5 \cdot HCl \cdot 1.3H_2O$: C, 60.63; H, 5.90; Cl, 6.17; N, 9.75. Found: C, 60.78; H, 6.03; Cl, 6.38; N, 9.77.

5-[[3-Fluoro-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (48) The title compound was prepared according to the method A using 4-(3-bromopropoxy)-3-fluorophenylacetic acid and piperidine instead of 4-(3-bromopropoxy)phenylacetic acid and diethylamine, respectively, in 50% yield, mp 143—146 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.30—1.44 (1H, m), 1.65—1.85 (5H, m), 2.16—2.26 (2H, m), 2.80—2.94 (2H, m), 3.10—3.20 (2H, m), 3.40—3.68 (4H, m), 4.06—4.14 (2H, m), 6.70—6.76 (1H, m), 6.78—6.86 (1H, m), 6.98—7.08 (1H, m), 7.16—7.56 (5H, m), 7.61—7.80 (3H, m), 10.40 (1H, br s), 10.60 (1H, s). FAB-MS *m/z*: 488 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{30}N_3O_3F \cdot HCl \cdot 1.1H_2O$: C, 64.05; H, 6.15; Cl, 6.52; F, 3.49; N, 7.73. Found: C, 63.92; H, 6.16; Cl, 6.73; F, 3.76; N, 7.71.

5-[[3-Chloro-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (49) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-chlorophenylacetic acid and piperidine instead of 4-(3-bromopropoxy)-phenylacetic acid and diethylamine, respectively, in 53% yield, mp 150—152 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32—1.46(1H, m), 1.66—1.82 (5H, m), 2.16—2.26 (2H, m), 2.81—2.93 (2H, m), 3.12—3.20 (2H, m), 3.40—3.50 (3H, m), 3.52—3.58 (1H, m), 3.61—3.70 (2H, m), 6.91 (1H, d, J=8.0 Hz), 6.99—7.06 (2H, m), 7.16—7.52 (5H, m), 7.60—7.80 (3H, m), 10.24 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 505 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{30}ClN_3O_3 \cdot HCl \cdot 1.5H_2O$: C, 61.38; H, 6.04; Cl, 12.49; N, 7.40. Found: C, 61.30; H, 5.65; Cl, 12.82; N, 7.36.

5-[[3-Bromo-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (50) The title compound was prepared according to method A using 3-bromo-4-(3-bromopropoxy)phenylacetic acid and piperidine instead of 4-(3-bromopropoxy)phenylacetic acid and diethylamine, respectively, in 49% yield, mp 166—169 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.30—1.46 (1H, m), 1.68—1.82 (5H, m), 2.09—2.25 (2H, m), 2.82—2.96 (2H, m), 3.06—3.24 (2H, m), 3.38—3.53 (3H, m), 3.62—3.68 (1H, m), 4.07—4.14 (2H, m), 6.94—7.03 (1H, m), 7.06—7.55 (6H, m), 7.60—7.80 (3H, m), 10.02 (1H, br s), 10.59 (1H, s). FAB-MS *m/z*: 549 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{30}N_3BrO_3 \cdot HCl \cdot 0.9H_2O$: C, 57.94; H, 5.50; Cl, 5.90; Br, 13.29; N, 6.99. Found: C, 58.00; H, 5.63; Cl, 5.76; Br, 12.98; N, 6.82.

5-[[3-Methoxy-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (51) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-methoxyphenylacetic acid and piperidine instead of 4-(3-bromopropoxy)phenylacetic acid and diethylamine, respectively, in 45% yield, mp 149—151 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32—1.44 (1H, m), 1.66—1.82 (5H, m), 2.10—2.20 (2H, m), 2.81—2.92 (2H, m), 3.10—3.19 (2H, m), 3.42—3.48 (2H, m), 3.50—3.59 (2H, m), 3.68 (3H, s), 3.95—4.02 (2H, m), 6.46—6.53 (2H, m), 6.76—6.83 (1H, m), 7.16—7.53 (5H, m), 7.60—7.80 (3H, m), 9.88 (1H, br s), 10.56 (1H, s). FAB-MS *m/z*: 500 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{33}N_3O_4 \cdot HCl \cdot H_2O$: C, 65.03; H, 6.55; Cl, 6.40; N, 7.58. Found: C, 64.75; H, 6.56; Cl, 6.40; N, 7.56.

4-(3-Bromopropoxy)-3-ethylphenylacetic Acid (44h) 1) Sodium borohydride (340 mg, 9.12 mmol) was added to a mixture of methyl 3-acetyl-4-(3-bromopropoxy)phenylacetate (**42a**, 2.0 g, 6.08 mmol) and MeOH (10 ml) at room temperature and the whole was stirred for 20 min, then concentrated *in vacuo*. The residue obtained was dissolved in ether (20 ml) and H_2O (20 ml). The organic layer was separated and the aqueous layer was extracted with ether (20 ml × 2). The combined extract was dried over $MgSO_4$ and evaporated *in vacuo*. The residue obtained was dissolved in trifluoroacetic acid (14 ml) and triethylsilane (4.24 g, 36.5 mmol) was added dropwise at below 5 °C. The reaction mixture was stirred for 30 min at 5 °C. After removal of the solvent under reduced pressure, the residue was diluted with 1 N aqueous NaOH and extracted with $CHCl_3$ (20 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 (hexane–AcOEt, 10 : 1, v/v) to give 1.53 g of **43a** as an oil in 80% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.5 Hz), 2.30—2.35 (2H, m), 2.59—2.65 (2H, m), 3.55 (2H, s), 3.61 (2H, t, J=6.5 Hz), 3.68 (3H, s), 4.10 (2H, t, J=6.0 Hz), 6.79 (2H, d, J=9.0 Hz), 7.03—7.06 (1H, m). FAB-MS *m/z*: 316 ($M^+ + 1$).

2) A solution of **43a** (1.48 g, 4.70 mmol), 1 N aqueous NaOH (7.0 ml, 7.0 mmol) and EtOH (12 ml) was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in H_2O (20 ml). The solution was treated with 1 N aqueous HCl (10 ml), and extracted with $CHCl_3$ (20 ml × 2). The combined extract was washed with brine, dried over $MgSO_4$ and concentrated to a solid residue. This residue was recrystallized from ether to give 1.38 g of **44h** as a white solid in 98% yield, mp 85—86 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7.5 Hz), 2.30—2.35 (2H, m), 2.61 (2H, q, J=7.5 Hz), 3.56 (2H, s), 3.61 (2H, t, J=6.5 Hz), 4.09 (2H, t, J=6.0 Hz), 6.79 (2H, d, J=9.0 Hz), 7.05—7.07 (1H, m). GC-MS *m/z*: 300 (M^+). *Anal.* Calcd for $C_{13}H_{17}BrO_3$: C, 51.84; H, 5.69; Br, 26.53. Found: C, 51.94; H, 5.65; Br, 26.50.

5-[[3-Ethyl-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (52) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-ethylphenylacetic acid and piperidine instead of 4-(3-bromopropoxy)-phenylacetic acid and diethylamine, respectively, in 31% yield, mp 206—209 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, t, J=7.0 Hz), 1.35—1.40 (2H, m), 1.42—1.60 (4H, m), 1.80—1.90 (2H, m), 2.20—2.55 (8H, m), 3.40—3.58 (2H, m), 3.90—4.00 (2H, m), 6.67—6.69 (1H, m), 6.70—6.78 (2H, m), 7.15—7.55 (5H, m), 7.60—7.80 (3H, m), 9.88 (1H, br s), 10.52—10.56 (1H, m). FAB-MS *m/z*: 498 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{35}N_3O_3 \cdot HCl \cdot 0.6H_2O$: C, 68.33; H, 6.88; Cl, 6.51; N, 7.71. Found: C, 68.05; H, 6.82; Cl, 6.75; N, 7.74.

5-[[4-(3-Piperidinopropoxy)-3-propylphenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (53) The title compound was prepared according to method A using 4-(3-bromopropoxy)-3-propylphenylacetic acid and piperidine instead of 4-(3-bromopropoxy)-phenylacetic acid and diethylamine, respectively, in 21% yield, mp 201—203 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 0.88 (3H, t, J=7.0 Hz), 1.36—1.44 (1H, m), 1.56—1.62 (2H, m), 1.65—1.81 (5H, m), 2.15—2.20 (2H, m), 2.40—2.46 (2H, m), 2.82—2.92 (2H, m), 3.10—3.19 (2H, m), 3.42—3.60 (4H, m), 3.95—4.05 (2H, m), 6.72 (1H, d, J=15 Hz), 6.74—6.80 (2H, m), 7.16—7.58 (5H, m), 7.60—7.80 (3H, m), 9.94 (1H, br s), 10.53 (1H, s). FAB-MS *m/z*: 512 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{37}N_3O_3 \cdot HCl \cdot 0.3H_2O$: C, 69.44; H, 7.03; Cl, 6.40; N, 7.59. Found: C, 69.34; H, 6.97; Cl, 6.38; N, 7.63.

5-[[4-(3-Diethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (13) (Method B) 1) Thionyl bromide (1.30 ml, 16.8 mmol) was added dropwise to a solution of **9c** (2.30 g, 8.42 mmol) and DMF (1 drop) in 1,4-dioxane (10 ml) at room temperature, and the reaction mixture was stirred at 70 °C for 1 h. After cooling to room temperature, the solvent was removed at reduced pressure. The resulting oil was dissolved in THF (15 ml) was added DBD (1.48 mg, 7.00 mmol) and *N*,*N*-dimethylaniline (840 mg, 7.00 mmol), and the reaction mixture was stirred under reflux for 8 h. After cooling to

room temperature, the reaction mixture was poured into water, acidified with 0.1 N hydrochloride acid, and extracted with $CHCl_3$ (30 ml × 2). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified on a silica gel column (*n*-hexane–AcOEt, 1 : 2, v/v) to give 300 mg of 5-[[4-(3-bromopropoxy)-phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (**10c**) as colorless needles in 9.2% yield, mp 152—153 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.35 (2H, m), 3.42—3.60 (2H, m), 3.60 (2H, s), 3.90—4.08 (2H, m), 6.70—6.92 (2H, m), 6.95—7.15 (2H, m), 7.20—7.54 (6H, m), 7.56—7.62 (1H, m), 7.91—8.01 (1H, m), 8.70—8.92 (1H, m). FAB-MS *m*/*z*: 466 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{21}N_2BrO_5$: C, 61.95; H, 4.55; Br, 17.17; N, 6.02. Found: C, 62.15; H, 4.55; Br, 16.94; N, 5.93.

2) The title compound was prepared according to method A using **10c** instead of a mixture of **10c** and **10c′** in 85 % yield.

5-[[4-(3-Diethylaminopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (13) (Method C) 1) Thionyl chloride (0.35 ml, 4.80 mmol) was added dropwise to a solution of **39** (550 mg, 2.40 mmol) and DMF (1 drop) in 1,4-dioxane (5 ml) at room temperature, and the reaction mixture was stirred at 70 °C for 1 h. It was then cooled to room temperature, and the solvent was removed under reduced pressure. The resulting oil was dissolved in THF (10 ml), then DBD (420 mg, 2.00 mmol) and *N*,*N*-dimethylaniline (240 mg, 2.00 mmol) were added, and the reaction mixture was stirred under reflux for 8 h. After cooling to room temperature, the reaction mixture was poured into water, acidified with 0.1 N hydrochloric acid, and extracted with $CHCl_3$ (30 ml × 2). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified on a silica gel column (*n*-hexane–AcOEt, 1 : 2, v/v) to give 630 mg of 5-[[4-(3-chloropropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]-diazepin-11-one (**10′c**) as colorless needles in 75% yield, mp 160—161 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.06—2.25 (2H, m), 3.60 (2H, s), 3.63—3.75 (2H, m), 3.96—4.10 (2H, m), 6.70—6.82 (2H, m), 6.95—7.10 (2H, m), 7.20—7.52 (6H, m), 7.55—7.65 (1H, m), 7.90—8.00 (1H, m), 8.39 (1H, s). FAB-MS *m*/*z*: 421 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{21}N_2ClO_5$: C, 68.49; H, 5.03; Cl, 8.42; N, 6.66. Found: C, 68.34; H, 5.02; Cl, 8.40; N, 6.52.

2) The title compound was prepared according to method A using **10′c** instead of a mixture of **10c** and **10′c** in 73% yield.

5-[[3-Amino-4-(3-piperidinopropoxy)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (54) A suspension of **47** (3.62 g, 7.00 mmol) and 10% palladium on carbon (362 mg) in methanol (40 ml) was hydrogenated at atmospheric pressure for 20 h. The reaction mixture was filtered through Celite® and the solvent was evaporated off to afford 2.61 g of **52** as a yellow solid in 77% yield. ^{1}H-NMR (DMSO-d_6) δ: 1.37—1.38 (2H, m), 1.46—1.51 (4H, m), 1.81—1.87 (2H, m), 2.32 (4H, br s), 2.39 (2H, t, J = 7.3 Hz), 3.29—3.43 (2H, m), 3.90 (2H, t, J = 7.3 Hz), 4.63—4.65 (2H, m), 6.09 (1H, d, J = 7.3 Hz), 6.39 (1H, s), 6.62 (1H, d, J = 7.9 Hz), 7.19—7.81 (8H, m), 10.61 (1H, br s). FAB-MS *m*/*z*: 485 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{32}N_4O_5 \cdot 0.4H_2O$: C, 70.82; H, 6.72; N, 11.39. Found: C, 70.93; H, 6.70; N, 11.16.

2-(3-Piperidinopropoxy)-5-[[(11-oxo-5,10-dihydro-11*H*-dibenzo[*b*,*e*]-[1,4]diazepin-5-yl)carbonyl]methyl]formanilide (55) A mixture of acetic anhydride (0.62 ml, 7.00 mmol) and formic acid (0.62 ml, 16.5 mmol) was heated at 60 °C for 1 h. It was cooled to room temperature and then **54** (339 mg, 0.70 mmol) in 1,4-dioxane (5 ml) was added dropwise at below 10 °C, and the whole was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and basified with potassium carbonate. The resulting mixture was extracted with $CHCl_3$ (15 ml × 2), and the combined organic phases were dried over MgSO4, filtered, and concentrated. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 22 : 3, v/v) followed by crystallization from EtOH to give 248 mg of **53** as colorless needles in 69% yield, mp 220—221 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.33—1.41 (2H, m), 1.45—1.53 (4H, m), 1.83—1.94 (2H, m), 2.30—2.46 (6H, m), 3.34—3.62 (2H, m), 3.96—4.05 (2H, m), 6.62—6.90 (2H, m), 7.18—7.54(5H, m), 7.60—7.72 (2H, m), 7.74—7.80 (1H, m), 7.94 (1H, d, J = 1.6 Hz), 8.31 (1H, s). 9.43 (1H, br s), 10.56 (1H, s). FAB-MS *m*/*z*: 513 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{32}N_4O4 \cdot 0.3H_2O$: C, 69.56; H, 6.34; N, 10.82. Found: C, 69.55; H, 6.30; N, 10.79.

2-(3-Piperidinopropoxy)-5-[[(11-oxo-5,10-dihydro-11*H*-dibenzo[*b*,*e*]-[1,4]diazepin-5-yl)carbonyl]methyl]acetanilide Hydrochloride (56) A mixture of **54** (339 mg, 0.70 mmol) and acetic anhydride (0.10 ml, 1.10 mmol) in pyridine (5 ml) was stirred at room temperature for 3 h, and the solvent was evaporated off. Brine was added to the residue and the resulting mixture was extracted with $CHCl_3$ (10 ml × 2). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was purified on a silica gel column ($CHCl_3$–MeOH, 22 : 3, v/v) and the hydrochloride salt was precipitated from EtOH with 4 N hydrochloride in AcOEt to give 290 mg of **56** as colorless needles in 73% yield, mp 234—236 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.34—1.83 (6H, m), 2.12 (3H, s), 2.80—2.92 (2H, m), 3.15—3.24 (2H, m), 3.34—3.62 (4H, m), 4.02—4.08 (2H, m), 6.64—6.72 (1H, m), 6.84—6.92 (1H, m), 7.18—7.79 (9H, m), 8.95—9.00 (1H, m). 10.30 (1H, br s), 10.56—10.59 (1H, m). FAB-MS *m*/*z*: 527 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{34}N_4O_4 \cdot HCl \cdot 0.9H_2O$: C, 64.27; H, 6.40; Cl, 6.12; N, 9.67. Found: C, 64.30; H, 6.51; Cl, 6.19; N, 9.68.

2-(3-Piperidinopropoxy)-5-[[(11-oxo-5,10-dihydro-11*H*-dibenzo[*b*,*e*]-[1,4]diazepin-5-yl)carbonyl]methyl]propionanilide (57) The title compound was prepared according to the method described for **56**, using propionyl chloride instead of acetic anhydride, in 52% yield, mp 178—179 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.08 (3H, t, J = 7.3 Hz), 1.39—1.51 (6H, m), 1.91 (2H, br s), 2.36—2.38 (8H, m), 3.36—3.56 (2H, m), 4.01 (2H, br s), 6.67 (1H, br s), 6.87—6.90 (1H, m), 7.20—7.77 (9H, m), 8.76 (1H, br s). 10.54—10.57 (1H, m). FAB-MS *m*/*z*: 541 ($M^+ + 1$). *Anal.* Calcd for $C_{32}H_{36}N_4O_4 \cdot 0.8H_2O$: C, 69.24; H, 6.83; N, 10.09. Found: C, 69.01; H, 6.59; N, 10.11.

Methyl 2-(3-Piperidinopropoxy)-5-[[(11-oxo-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-5-yl)carbonyl]methyl]carbamate (58) The title compound was prepared according to the method described for **56**, using methyl chlorocarbonate instead of acetic anhydride, in 66% yield, mp 102—103 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36—1.42 (2H, m), 1.46—1.52 (4H, m), 1.83—1.90 (2H, m), 2.29—2.42 (6H, m), 3.35—3.61 (2H, m), 3.65 (3H, s), 3.97 (2H, t, J = 6.0 Hz), 6.63—6.68 (1H, m), 6.82—6.88 (1H, m), 7.16—7.56 (6H, m), 7.60—7.72 (2H, m), 7.74—7.80 (1H, m), 8.25 (1H, br s), 10.55—10.59 (1H, m). FAB-MS *m*/*z*: 543 ($M^+ + 1$). *Anal.* Calcd for $C_{31}H_{34}N_4O_5 \cdot 0.4H_2O$: C, 67.72; H, 6.38; N, 10.19. Found: C, 67.72; H, 6.40; N, 10.02.

2-(3-Piperidinopropoxy)-5-[[(11-oxo-5,10-dihydro-11*H*-dibenzo[*b*,*e*]-[1,4]diazepin-5-yl)carbonyl]methyl]methanesulfoanilide (59) The title compound was prepared according to the method described for **56**, using methanesulfonyl chloride instead of acetic anhydride, in 60% yield, mp 109—112 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.40—1.52 (6H, m), 1.93 (2H, br s), 2.36—2.38 (6H, m), 2.92 (3H, s), 3.37—3.60 (2H, m), 4.01 (2H, s), 6.79 (1H, br s), 6.94 (1H, t, J = 7.9 Hz), 7.00 (1H, s), 7.21—7.73 (9H, m), 10.57 (1H, br s). FAB-MS *m*/*z*: 563 ($M^+ + 1$). *Anal.* Calcd for $C_{30}H_{34}N_4O_5S \cdot 1.4H_2O$: C, 61.29; H, 6.31; N, 9.53; S, 5.45. Found: C, 61.24; H, 6.05; N, 9.25; S, 5.38.

5-[(4-Nitrophenyl)acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (60) A solution of 4-nitrophenylacetic acid (5.00 g, 27.6 mmol) and DMF (1 drop) in dichloromethane (50 ml) was treated dropwise with oxalyl chloride (3.60 ml, 41.4 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure. The resulting oil was dissolved in THF (15 ml), then a solution of DBD (4.64 g, 22.1 mmol) and *N*,*N*-dimethylaniline (3.83 ml, 30.4 mmol) in THF (50 ml) was added, and the reaction mixture was stirred at reflux for 5 h. The solvent was evaporated off, and the residue was dissolved in CH_2Cl_2 (50 ml). This solution was washed with 0.5 N aqueous HCl (50 ml × 2) and H_2O (50 ml), dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in refluxing MeOH (30 ml) and the resulting solution was gradually cooled to room temperature to precipitate undesired products. After removal of the precipitate, the filtrate was concentrated under reduced pressure and the resulting material was recrystallized from CH_3CN to yield 4.72 g of **60** as colorless needles in 46% yield, mp 255—256 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.70—3.95 (2H, m), 7.10—7.57 (7H, m), 7.61—7.78 (3H, m), 8.07 (2H, d, J = 8.4 Hz), 10.45—10.60 (1H, m). FAB-MS *m*/*z*: 374 ($M^+ + 1$). *Anal.* Calcd for $C_{21}H_{15}N_3O_4$: C, 67.56; H, 4.05; N, 11.25. Found: C, 67.44; H, 4.04; N, 11.34.

5-[(4-Aminophenyl)acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (61) A suspension of **60** (4.72 g, 11.8 mmol) and Raney-Ni (9 ml) in DMF (88 ml) was hydrogenated at atmospheric pressure for 1 h. The reaction mixture was filtered through Celite® and the solvent was evaporated off under reduced pressure. The residue was dissolved in $CHCl_3$ (50 ml) and the solvent was washed successively with 5% aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized from 2-propanol to yield 3.77 g of **61** as yellow needles in 93% yield, mp 181—182 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.34—3.42 (2H, m), 4.91 (2H, br s), 6.42 (2H, d, J =

8.1 Hz), 6.63 (2H, d, J=8.1 Hz), 7.16—7.52 (5H, m), 7.56—7.70 (2H, m), 7.71—7.82 (1H, m), 10.60 (1H, s). FAB-MS m/z: 344 ($M^+ + 1$). *Anal.* Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.25; H, 5.13; N, 12.13.

5-[[4-[(3-Piperidinopropyl)amino]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (62) A mixture of **61** (400 mg, 1.16 mmol) and 1,3-dibromopropane (0.13 ml, 1.28 mmol) in hexamethylphosphoramide (8 ml) was stirred at 100 °C for 2 h, then cooled to room temperature. Piperidine (0.83 ml, 8.40 mmol) was added, and the whole was stirred at 100 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with $CHCl_3$ (20 ml × 2). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, and the residue was purified on a silica gel column ($CHCl_3$–MeOH–28% aqueous NH_4OH, 150 : 10 : 1, v/v/v) to give 150 mg of **62** as an amorphous solid in 28% yield. ^{1}H-NMR (DMSO-d_6) δ: 1.36—1.42 (2H, m), 1.46—1.54 (4H, m), 1.59—1.70 (2H, m), 2.27—2.36 (6H, m), 2.93—3.02 (2H, m), 3.34—3.43 (2H, m), 5.52 (1H, br s), 6.40 (2H, d, J=8.1 Hz), 6.69 (2H, d, J=8.1 Hz), 7.16—7.55 (5H, m), 7.58—7.70 (2H, m), 7.72—7.81 (1H, m), 10.60 (1H, s). HRMS (FAB) Found m/z=469.2606. $C_{29}H_{33}N_4O_2$ Calcd m/z=469.2603.

5-[[4-(3-Chloropropionamido)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (63) A mixture of **61** (3.77 g, 11.0 mmol) and 3-chloropropionyl chloride (1.47 ml, 13.2 mmol) was heated at reflux for 30 min, then cooled to room temperature. The resulting precipitate was filtered off and washed with CH_3CN to yield 4.31 g of **63** as colorless needles in 91% yield, mp >230 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.80 (2H, t, J=6.4 Hz), 3.45—3.63 (2H, m), 3.87 (2H, t, J=6.4 Hz), 6.93 (2H, d, J=7.6 Hz), 7.17—7.28 (2H, m), 7.37—7.53 (4H, m), 7.62—7.81 (4H, m), 10.01 (1H, s), 10.60 (1H, s). FAB-MS m/z: 434 ($M^+ + 1$). *Anal.* Calcd for $C_{24}H_{20}N_3O_3Cl$: C, 66.44; H, 4.65; Cl, 8.17; N, 9.68. Found: C, 66.29; H, 4.87; Cl, 8.08; N, 9.86.

5-[[4-(3-Diethylaminopropionamido)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (66) A mixture of **63** (300 mg, 0.69 mmol) and sodium iodide (30 mg) was treated with diethylamine (70% in H_2O) (500 mg, 6.91 mmol) in CH_3CN (14 ml) at 80 °C for 8 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. The residue obtained was diluted with 1 N aqueous NaOH and extracted with $CHCl_3$ (20 ml × 2). 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 hydrochloride salt was precipitated from EtOH with 4 N hydrochloride in AcOEt to give 220 mg of **66** as colorless needles in 63% yield, mp 204—206 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.23 (6H, t, J=7.5 Hz), 2.81—2.85 (2H, m), 3.10—3.17 (4H, m), 3.34—3.38 (2H, m), 3.40—3.62 (2H, m), 6.90—7.00 (2H, m), 7.15—7.30 (2H, m), 7.35—7.69 (6H, m), 7.74—7.79 (2H, m), 9.50—9.60 (1H, m), 10.21 (1H, br s), 10.57—10.62 (1H, m). FAB-MS m/z: 471 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{30}N_4O_3 \cdot HCl \cdot H_2O$: C, 64.05; H, 6.33; Cl, 6.75; N, 10.67. Found: C, 63.92; H, 6.32; Cl, 6.94; N, 10.68.

5-[[4-(3-Piperidinopropionamido)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (64) The title compound was prepared as described for **66**, using piperidine instead of methyl diethylamine in 73% yield, mp 181—183 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.36—1.42 (1H, m), 1.60—1.73 (1H, m), 1.74—1.80 (4H, m), 2.84—2.96 (4H, m), 3.34—3.64 (6H, m), 6.94 (2H, d, J=8.0 Hz), 7.19—7.29 (2H, m), 7.36—7.82 (8H, m), 10.32—10.34 (1H, m), 10.42 (1H, br s), 10.58—10.61 (1H, m). FAB-MS m/z: 483 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{30}N_4O_3 \cdot HCl \cdot 2H_2O$: C, 62.75; H, 6.36; Cl, 6.39; N, 10.09. Found: C, 62.83; H, 6.07; Cl, 6.65; N, 10.12.

5-[[4-(3-Pyrrolidinopropionamido)phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (65) The title compound was prepared in the same manner as **66**, using pyrrolidine instead of methyl diethylamine in 64% yield, mp 169—171 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.82—1.93 (2H, m), 1.94—2.02 (2H, m), 2.84—2.88 (2H, m), 2.95—3.05 (2H, m), 3.40—3.64 (6H, m), 6.94 (2H, d, J=8.0 Hz), 7.18—7.29 (2H, m), 7.36—7.79 (8H, m), 10.26 (1H, br s), 10.46 (1H, br s), 10.58—10.61 (1H, m). FAB-MS m/z: 469 ($M^+ + 1$). *Anal.* Calcd for $C_{28}H_{28}N_4O_3 \cdot HCl \cdot 1.3H_2O$: C, 63.64; H, 6.03; Cl, 6.71; N, 10.60. Found: C, 63.44; H, 5.66; Cl, 7.07; N, 10.51.

4-(3-Bromopropyl)thiophenylacetic Acid (68) The title compound was prepared as described for **9c**, using methyl 4-mercaptophenylacetate instead of methyl 4-hydroxyphenylacetate in 61% yield, mp 70—72 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.12—2.17 (2H, m), 3.06 (2H, t, J=5.0 Hz), 3.52 (2H, t, J=5.0 Hz), 3.62 (2H, s), 7.21 (2H, d, J=5.0 Hz), 7.31 (2H, d, J=5.0 Hz). GC-MS m/z: 288 (M^+). *Anal.* Calcd for $C_{11}H_{13}BrSO_2$: C, 45.69; H, 4.53; Br, 27.63; S, 11.09. Found: C, 45.81; H, 4.46; Br, 27.98; S, 10.80.

5-[[4-[(3-Piperidinopropyl)thio]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (69) The title compound was prepared according to method A, using 4-(3-bromopropyl)thiophenylacetic acid and piperidine instead of 4-(3-bromopropoxy)phenylacetic acid and diethylamine, respectively, in 68% yield, mp 194—196 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.28—1.42 (1H, m), 1.62—1.86 (5H, m), 1.94—2.04 (2H, m), 2.76—2.84 (2H, m), 3.00 (2H, t, J=7.2 Hz), 3.04—3.12 (3H, m), 3.34—3.40 (1H, m), 3.46—3.70 (2H, m), 6.89—6.98 (2H, m), 7.18—7.57 (7H, m), 7.61—7.72 (2H, m), 7.74—7.79 (1H, m), 10.46 (1H, br s), 10.59—10.64 (1H, m). FAB-MS m/z: 486 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{31}N_3O_2S \cdot HCl$: C, 66.71; H, 6.18; N, 8.05; Cl, 6.79; S, 6.14. Found: C, 66.79; H, 6.26; N, 8.34; Cl, 6.80; S, 5.84.

5-[[4-[(3-Piperidinopropyl)sulfinyl]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (70) *m*-Chloroperoxybenzoic acid (295 mg, 1.71 mmol, 0.9 eq) was added to a solution of a roughly 1 : 1 mixture of 5-[[4-[(3-bromopropyl)thio]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one and 5-[[4-[(3-chloropropyl)thio]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one (600 mg, obtained from 600 mg (2.07 mmol) of 4-(3-bromopropyl)thiophenylacetic acid and 400 mg (1.90 mmol) of DBD) in CH_2Cl_2 (10 ml) at −70 °C, and the reaction mixture was stirred for 30 min. It was then poured into ice-water, basified with 5% aqueous $NaHCO_3$, and extracted with $CHCl_3$ (25 ml × 3). The combined extract was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue obtained was dissolved in CH_3CN (20 ml) and piperidine (290 mg, 3.40 mmol) was added. The reaction mixture was stirred for 8 h at 80 °C, cooled to room temperature, then concentrated *in vacuo*. The residue was diluted with 1 N aqueous NaOH and extracted with $CHCl_3$ (20 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 hydrochloride salt of **70** was precipitated from EtOH with 4 N hydrochloride in AcOEt to give 190 mg of **70** as colorless needles in 19% yield from DBD, mp 178—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.28—1.41 (1H, m), 1.62—1.84 (5H, m), 1.86—1.99 (1H, m), 2.02—2.14 (1H, m), 2.75—2.90 (3H, m), 3.02—3.15 (3H, m), 3.30—3.40 (2H, m), 3.58—3.85 (2H, m), 7.16—7.32 (4H, m), 7.35—7.80 (8H, m), 10.34 (1H, br s), 10.60—10.63 (1H, m). FAB-MS m/z: 502 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{31}N_3O_3S \cdot HCl \cdot 0.5H_2O$: C, 63.66; H, 6.08; Cl, 6.48; N, 7.68; S, 5.86. Found: C, 63.57; H, 6.18; Cl, 6.50; N, 7.82; S, 5.82.

5-[[4-[(3-Piperidinopropyl)sulfonyl]phenyl]acetyl]-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one Hydrochloride (71) The title compound was prepared in the same manner as **70**, using 2.2 eq of *m*-chloroperoxybenzoic acid instead of 0.9 eq, in 26% yield, mp 226—228 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 1.28—1.41 (1H, m), 1.60—1.80 (5H, m), 1.95—2.10 (2H, m), 2.75—2.90 (2H, m), 3.03—3.12 (2H, m), 3.30—3.40 (2H, m), 3.40—3.45 (2H, m), 3.64—3.88 (2H, m), 7.18—7.30 (4H, m), 7.35—7.82 (8H, m), 10.04 (1H, br s), 10.60—10.63 (1H, m). FAB-MS m/z: 518 ($M^+ + 1$). *Anal.* Calcd for $C_{29}H_{31}N_3O_4S \cdot HCl \cdot 0.3H_2O$: C, 62.25; H, 5.87; N, 7.51; Cl, 6.34; S, 5.73. Found: C, 62.22; H, 5.72; N, 7.54; Cl, 6.52; S, 5.72.

Biological Methods The following chemicals were commercially obtained: 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 each removed and homogenized in ice-cold HEPES buffer (20 mM 2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES), 100 mM NaCl, 10 mM $MgCl_2$, pH 7.5). The homogenates were filtered through two layers of cloth gauze and the filtrate was 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/kg (cerebral cortex), 1.0 mg/ml (heart) and 0.83 mg/kg (submandibular gland) as determined by the method of Bradford.[19] 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 the cerebral

cortex, 0.1 nM [^{3}H]QNB ($K_D = 0.128 \pm 0.004$ nM) for the heart and 0.3 nM [^{3}H]NMS ($K_D = 0.162 \pm 0.006$ nM) for the 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 immediately washed 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 TRI-CARB 2200 CA liquid scintillation counter. Competitive binding data were analyzed with the aid of the 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[20] 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 (Rat) General Procedure: 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 common carotid artery cannula was used for monitoring blood pressure, and the heart rate was measured with a tachometer triggered by the pulse wave of blood pressure. A femoral vein was also cannulated for i.v. administration of the drugs. Rats were pithed by introducing a blunt steel rod *via* the orbit into the spinal canal and then treated with atenolol (10 mg/kg i.v.) to exclude catecholamine-induced tachycardia. The pithed preparation were allowed to equilibrate for at least 15 min before experiments.

i.v. Study: After the general procedure, test compounds or saline were administered i.v. At 15 min after dosing, 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 then 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. On the other hand, in the case of compounds **55**, **56**, **66** and **69**, the maximum decrease in heart rate with oxotremorine was about 60%. Therefore, their dose-ratio was calculated from their ED_{30} values, the doses of oxotremorine required to produce a 30% decrease in heart rate.

p.o. Study: A test compound or 0.5% methylcellulose solution was administered *p.o.* 30 min before the assay, and the rats were treated as previously described. Three hours after the administration of a test compound, 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). Data were expressed as the negative logarithm of the DR_{10} value as described in the i.v. study.

Heart Rate (Conscious Dog) Experiments were performed on 2—6 male beagle dogs weighing 9 to 14 kg. Electrocardiogram (ECG) leads were attached to the shaved chest, and a zippered jacket was applied. An ambulatory ECG Holter monitor (SLB-90208, SpaceLabs Medical. Inc.) was placed in a pocket of the jacket, and the dog's activities were unrestricted. The ECG was recorded under conscious conditions for 24 h. Cassette tapes with two channels of ECG recordings were analyzed using a computer-assisted Holter analysis system (FT2000, SpaceLabs Medical. Inc.) to determine the heart rates. The test drugs were administered at 19 : 00. Measurements were performed at 30-min intervals during from 30 min before dosing to 8 h after dosing. Changes in heart rate after dosing were calculated with respect to the basal heart rate before dosing.

Salivation Male Wistar rats (300—350 g) were anesthetized with urethane (1.2 g/kg i.p.) and the femoral vein was cannulated for i.v. administration. After 10 min, a test compound or saline was administered i.v. 15 min after dosing, and 0.8 μmol/kg of oxotremorine was administered i.v. Saliva was collected for 5 min on filter paper according to Lavy and Mulder.[21] The average dose reducing salivary secretion to 50% of the control value was graphically determined (ID_{50} (moles per kilogram)) and the antagonism of the M_3 muscarinic receptors was expressed as the negative logarithm of the ID_{50} value, pID_{50}.

Tremor Test compounds or saline were administered intravenously *via* the tail vein to conscious male ICR mice (35—60 g). At 15 min thereafter, oxotremorine (1 mg/kg s.c.) was administered. After a 5-, 10-, or 15-min observation, mice were scored (using a point system) blind for the severity of the tremor response using 5 grades: 0, no apparent effect; 0.5, tremor was observed if mice were swung around by the tail; 1, tremor was observed if mice were lifted up by the tail; 1.5, intermittent or constant tremor; 2, constant severe tremor of the whole body. Points were summed up in each dosage group and divided by the number of animals per group to yield the mean value.

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