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Synthesis, Electrophysiological Properties and Analysis of Structural Requirements of a Novel Class of Antiarrhythmic Agents with Potassium and Calcium Channel Blocking Properties

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Abstract—Class III antiarrhythmic agents have been shown to prevent reentrant arrhythmias but also to be responsible for initiating arrhythmias characterised by afterdepolarizations and triggered activities. By combining potassium and calcium channel antagonistic actions, as with BRL-32872[1,2] (**1**), it might be possible to reduce the incidence of proarrhythmias albeit retaining antiarrhythmic efficacy. In the present study we synthesised and tested for their electrophysiological activity in guinea pig papillary muscle a wide panel of analogues of BRL-32872. Some qualitative relationships between compound structure and the inhibitory effect on the rapidly activating component of the delayed rectifier potassium current and/or the L-type calcium current will be presented. New derivatives depicting bell-shaped dose–response curves on action potential duration may therefore represent novel agents for improved antiarrhythmic therapy.

Introduction

The search for antiarrhythmic drugs has been focused for the last decade on agents that prolong cardiac action potential and refractoriness (Class III antiarrhythmic action).[3] Selective inhibition of the rapid component of the cardiac delayed rectifier potassium current constitutes the main mechanism of action of compounds that have been developed to prolong cardiac action potential duration in a dose-dependent manner[4] and thereby inhibit reentry circuits.[5] However, these agents have also been found to promote afterdepolarizations and to exhibit a reverse-frequency dependent increase in action potential duration (APD). As a consequence K channel blockers have been suggested to favour the occurrence of torsade de pointes (TdP) and to have a reduced efficacy at high frequency. TdP have been observed with most class III antiarrhythmic agents during both experimental studies[6] and clinical investigations.[7] In contrast, compounds with multiple electrophysiological activities, as evidenced with amiodarone,[8,9] appear to have less proarrhythmic effects than class III antiarrhythmic agents and their ability to increase APD is not reverse-frequency dependent.

BRL-32872 **1** (Fig. 1) is a novel antiarrhythmic agent that has been shown in guinea-pig ventricular myocytes[1] to exhibit a dual electrophysiological mechanism of action (Fig. 1B and 1C): At low concentrations, BRL-32872 inhibits the rapidly activating component of the delayed rectifier potassium current (I_{Kr}; EC_{50}: 0.028 μM) and consequently prolongs cardiac action potential. When the concentration is increased further, BRL-32872 shows an additional L-type calcium current inhibitory effect (I_{Ca}; EC_{50}: 2.8 μM) which limits action potential prolongation. This dual activity (i.e. potassium and calcium current inhibitions) provides BRL-32872

Key words: Antiarrhythmic; class III; class IV; potassium channel; calcium channel.

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with a combined class III and class IV antiarrhythmic profile.[1] BRL-32872 has been shown to prevent cardiac arrhythmias and to be associated with a reduced incidence of experimentally-induced TdP.[2] Furthermore, BRL-32872 did not show evidence of reverse use-dependent effect on APD, both in isolated cardiac preparations and in humans.[10,11]

The aim of the present study was to determine whether chemical structure modifications of BRL-32872 could lead to specific alterations of class III and/or class IV activities. For this purpose, we synthesised a panel of BRL-32872 analogues and characterized their effect on APD to evaluate class III versus class IV activity ratio. A secondary objective was to determine whether structural requirements favouring the effect either on the K channel or on the Ca channel could be identified.

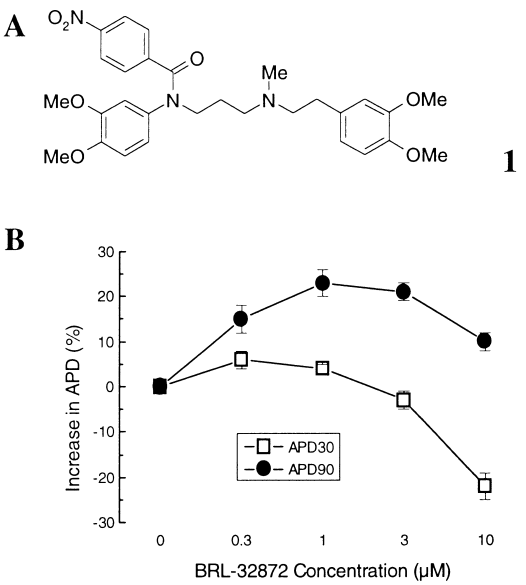


Figure 1. (A) Structure of BRL-32872. (B) Action potential duration recorded on guinea-pig papillary muscle at 30% and 90% of repolarization using standard microelectrode technique. (C) Isolated L-type calcium (circles) and delayed rectifier potassium (squares) currents.

Results and Discussion

The chemical modifications that have been performed on BRL-32872 structure are illustrated in Figure 2 and a selection of representative compounds synthesized to obtain a broad structural diversity around BRL-32872 structure is listed in Tables 1–3. In these tables, structural characteristics of the compounds are displayed together with their biological activity measured on guinea-pig papillary muscles. This activity has been assessed by the microelectrode technique to follow electrophysiological characteristics of guinea pig papillary muscles in the absence and in the presence of increasing concentrations of tested compounds (0.3, 1.0, 3.0, and 10.0 μM). The principal electrophysiological parameter which has been analysed for this study was the action potential duration measured at 30 and 90 percent of repolarization (APD_{30} and APD_{90}, respectively). An increase of APD_{90} usually obtained with low concentrations of tested compounds was considered as an index of class III antiarrhythmic effect and a decrease of APD_{30} noted at higher concentrations was considered as an index of class IV antiarrhythmic activity.

The selected graphs of Figure 3 exemplify that the strategies followed to synthesize BRL-32872 analogues gave rise to compounds eliciting clearly distinct balances between the activity on the potassium and the calcium channels. From the upper left graph showing the electrophysiological profile of a pure class III antiarrhythmic

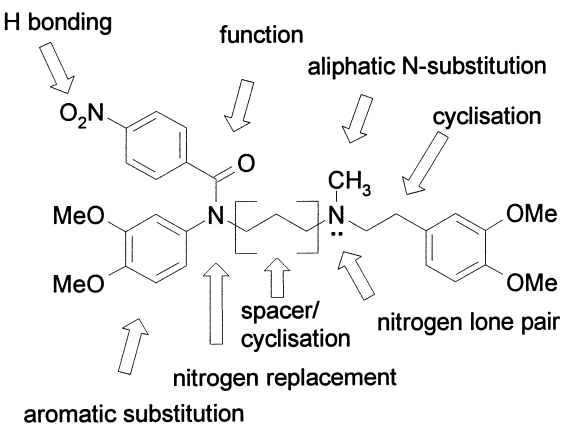
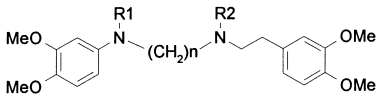


Figure 2. Summary of the different structural modifications performed on **1** for the structure–activity studies.

Table 1. Action potential of 'linear' analogues of **1**, recorded on guinea-pig papillary muscle at 30% and 90% of repolarization using standard microlectrode technique

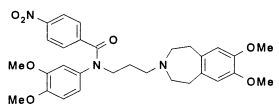
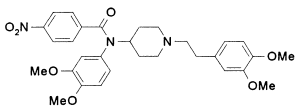
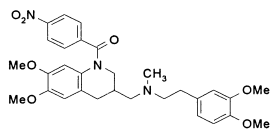
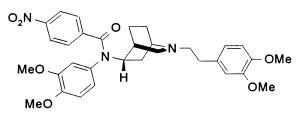
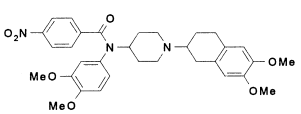
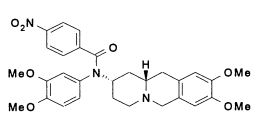
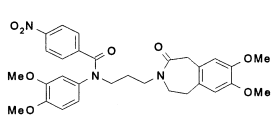


Entry	R1	R2	n	Variation (%)	0.3 μM	1 μM	3 mM	10 mM
1	$CO(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	15 ± 3	23 ± 3	21 ± 2	10 ± 2
				APD30	*6 ± 2*	*4 ± 1*	*−3 ± 2*	*−22 ± 3*
25	$CO(C_6H_4\text{-}4\text{-}CN)$	CH_3	3	APD90	8 ± 2	18 ± 5	24 ± 6	23 ± 2
				APD30	*3 ± 0*	*11 ± 1*	*11 ± 3*	*4 ± 3*
26	$CO(C_6H_4\text{-}4\text{-}NH_2)$	CH_3	3	APD90	7 ± 1	17 ± 3	25 ± 4	25 ± 4
				APD30	*4 ± 2*	*7 ± 3*	*7 ± 4*	*1 ± 6*
27	COC_6H_5	CH_3	3	APD90	6 ± 0	12 ± 0	18 ± 0	20 ± 5
				APD30	*4 ± 1*	*4 ± 2*	*1 ± 1*	*−7 ± 8*
28	$CO[C_6H_4\text{-}4(\text{imidazol-1-yl})]$	CH_3	3	APD90	4 ± 2	9 ± 3	13 ± 1	11 ± 3
				APD30	*3 ± 5*	*9 ± 4*	*8 ± 3*	*−1 ± 4*
29	$CO(C_6H_4\text{-}4\text{-}NHSO_2CH_3)$	CH_3	3	APD90	3 ± 0	8 ± 2	18 ± 4	28 ± 1
				APD30	*4 ± 0*	*5 ± 1*	*8 ± 0*	*9 ± 2*
30	$CO(C_6H_4\text{-}4\text{-}NHCOCH_3)$	CH_3	3	APD90	1 ± 2	5 ± 1	15 ± 3	26 ± 5
				APD30	*−3 ± 1*	*0 ± 2*	*2 ± 4*	*2 ± 8*
31	$CO(C_6H_4\text{-}4\text{-}CF_3)$	CH_3	3	APD90	1 ± 0	0 ± 1	0 ± 1	−3 ± 0
				APD30	*−2 ± 0*	*−7 ± 5*	*−11 ± 1*	*−19 ± 3*
32	$COCH_3$	CH_3	3	APD90	3 ± 1	10 ± 1	18 ± 1	23 ± 1
				APD30	*2 ± 1*	*4 ± 0*	*5 ± 1*	*1 ± 1*
6	H	CH_3	3	APD90	3 ± 0	7 ± 1	14 ± 2	18 ± 2
				APD30	*3 ± 1*	*3 ± 2*	*4 ± 2*	*0 ± 3*
33	$CH_2(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	6 ± 2	10 ± 4	11 ± 4	11 ± 6
				APD30	*3 ± 3*	*2 ± 5*	*−4 ± 7*	*−11 ± 8*
34	$PO(OEt)(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	2 ± 0	5 ± 2	7 ± 4	3 ± 7
				APD30	*2 ± 1*	*0 ± 2*	*−7 ± 1*	*−22 ± 3*
35	$CONH(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	3 ± 0	5 ± 1	4 ± 1	−3 ± 5
				APD30	*1 ± 2*	*−1 ± 2*	*−11 ± 2*	*−25 ± 8*
36	$SO_2(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	3 ± 1	2 ± 4	1 ± 7	−10 ± 6
				APD30	*−1 ± 3*	*−4 ± 3*	*−18 ± 7*	*−33 ± 6*
37	$COCH_2(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	3	APD90	1 ± 2	3 ± 3	3 ± 3	−4 ± 4
				APD30	*−3 ± 3*	*−7 ± 3*	*−17 ± 4*	*−30 ± 5*
38	$CO(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	2	APD90	9 ± 1	15 ± 2	16 ± 1	7 ± 1
				APD30	*3 ± 1*	*4 ± 2*	*0 ± 1*	*−13 ± 1*
39	$CO(C_6H_4\text{-}4\text{-}NO_2)$	CH_3	4	APD90	4 ± 1	9 ± 1	12 ± 1	12 ± 2
				APD30	*1 ± 1*	*1 ± 1*	*−3 ± 1*	*−10 ± 2*
40	$CO(C_6H_4\text{-}4\text{-}NO_2)$	H	3	APD90	8 ± 1	17 ± 3	21 ± 3	15 ± 2
				APD30	*3 ± 1*	*3 ± 1*	*−4 ± 1*	*−16 ± 2*
41	$CO(C_6H_4\text{-}4\text{-}NO_2)$	$CH(CH_3)_2$	3	APD90	11 ± 2	16 ± 1	15 ± 3	5 ± 1
				APD30	*5 ± 0*	*−1 ± 3*	*−9 ± 3*	*−26 ± 3*
42	$CO(C_6H_4\text{-}4\text{-}NO_2)$	$CH_2CH=CH_2$	3	APD90	9 ± 2	15 ± 2	15 ± 1	8 ± 2
				APD30	*3 ± 3*	*3 ± 2*	*−3 ± 2*	*−15 ± 0*
43	$CO(C_6H_4\text{-}4\text{-}NO_2)$	$(CH_3)_2^+$	3	APD90	−1 ± 0	−2 ± 1	−1 ± 1	3 ± 1
				APD30	*−2 ± 1*	*−4 ± 1*	*−4 ± 1*	*−3 ± 1*

agent (**29**) to the lower right panel depicting activity of a compound with predominant class IV activity (**37**), all intermediate profiles have been obtained (**48, 46, 58, 34**).

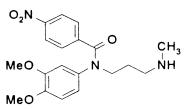
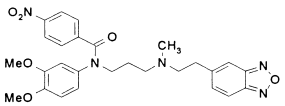
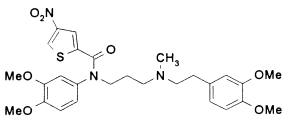
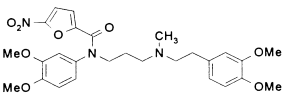
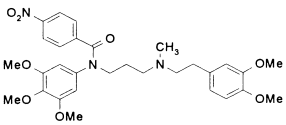
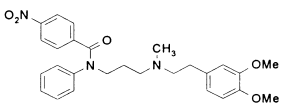
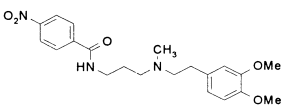
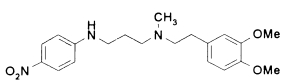
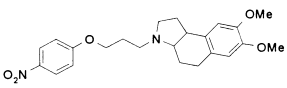
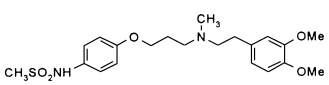
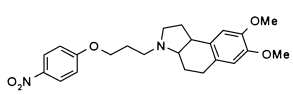
In the present experiments, action potential measurements were used as indexes of class III and class IV activities. It is noteworthy that these parameters do not allow quantitative analysis of the effectiveness of tested compounds on calcium and potassium channels for three main reasons. First, APD_{30} and APD_{90} are not independent parameters and the modulation of one of them may affect the other. Second, inhibition of an ionic current involved in action potential process, as potassium current, not only influences action potential shape

Table 2. Action potential duration of cyclized analogues of **1**, recorded on guinea-pig papillary muscle at 30% and 90% repolarization using microelectrode technique

Entry	Structure	Variation (%)	0.3 μM	1 μM	3 μM	10 μM
44		APD90 *APD30*	14 ± 3 *6 ± 3*	24 ± 2 *7 ± 3*	25 ± 2 *3 ± 3′*	14 ± 2 *−10 ± 4*
45		APD90 *APD30*	19 ± 9 *5 ± 3*	35 ± 13 *12 ± 1*	34 ± 8 *11 ± 1*	19 ± 7 *−3 ± 3*
46		APD90 *APD30*	8 ± 2 *5 ± 2*	20 ± 4 *11 ± 3*	24 ± 5 *10 ± 3*	19 ± 5 *−2 ± 3*
47		APD90 *APD30*	6 ± 1 *2 ± 1*	14 ± 1 *5 ± 1*	21 ± *5 ± 2*	22 ± 3 *−1 ± 3*
48		APD90 *APD30*	10 ± 3 *4 ± 1*	22 ± 6 *9 ± 4*	28 ± 7 *9 ± 4*	28 ± 5 *7 ± 3*
49		APD90 *APD30*	5 ± 2 *3 ± 3*	12 ± 1 *6 ± 0*	23 ± 3 *11 ± 0*	32 ± 4 *11 ± 0*
50		APD90 *APD30*	−1 ± 1 *−3 ± 2*	−1 ± 1 *−4 ± 2*	3 ± 1 *−3 ± 2*	11 ± 0 *−1 ± 1*

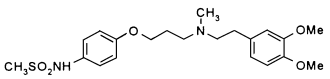
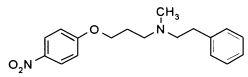
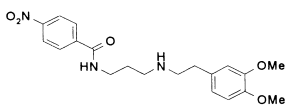
but also increases passive membrane resistance of the preparation. It is established that the consequence of Ca current inhibition on action potential duration is more marked at high than at low membrane resistance; in compounds combining K current inhibition at low concentration and Ca current blocking activity at high concentration, the action potential shortening due to the inhibition of the calcium current will be influenced by the previous potassium blocking effect. Third, a potent calcium blocking activity can completely mask the effect of potassium current inhibition on action potential duration. This is illustrated by the results obtained with compound **37** which displays an electrophysiological profile typical for pure class IV antiarrhythmic activity (Fig. 3). Patch-clamp analysis (Fig. 4) revealed that compound **37** induces a total inhibition of the calcium current in the presence of a marked inhibition of the potassium current. The latter effect was entirely masked by calcium current inhibition when considering APD parameters. On the opposite, compound **29** which profile is typical for pure class III antiarrhythmic agents (Fig. 3) was indeed found to be a selective inhibitor of the delayed rectifier potassium current (Fig. 4). The present results confirm, with compounds having a dual mechanism of action, the observation that Hirosama et al. made with a combination of specific K and Ca blockers.[12] In their study, Hirosama et al. showed that no APD prolongation could be induced by *d*-sotalol

Table 3. Action potential duration of miscellaneous analogues of **1**, recorded on guinea-pig papillary muscle at 30% and 90% of repolarization using standard microelectrode technique

Entry	Structure	Variation (%)	0.3 μM	1 μM	3 μM	10 μM
51		APD90 *APD30*	5 ± 1 *3 ± 1*	13 ± 2 *5 ± 2*	23 ± 2 *6 ± 2*	30 ± 3 *4 ± 3*
52		APD90 *APD30*	6 ± 1 *2 ± 2*	9 ± 2 *1 ± 2*	8 ± 2 *−6 ± 1*	4 ± 2 *−15 ± 1*
53		APD90 *APD30*	18 ± 3 *8 ± 1*	23 ± 5 *7 ± 0*	22 ± 7 *2 ± 3*	20 ± 9 *−6 ± 3*
54		APD90 *APD30*	6 ± 0 *3 ± 2*	13 ± 2 *6 ± 1*	21 ± 0 *8 ± 0*	19 ± 5 *−4 ± 4*
55		APD90 *APD30*	7 ± 1 *5 ± 2*	16 ± 2 *9 ± 3*	22 ± 3 *6 ± 3*	18 ± 4 *−4 ± 2*
56		APD90 *APD30*	9 ± 1 *4 ± 1*	15 ± 1 *3 ± 1*	12 ± 2 *−7 ± 2*	−2 ± 5 *−28 ± 3*
57		APD90 *APD30*	39 ± 4 *18 ± 3*	47 ± 4 *18 ± 3*	41 ± 2 *9 ± 1*	25 ± 1 *−8 ± 2*
58		APD90 *APD30*	17 ± 3 *9 ± 2*	25 ± 5 *9 ± 2*	21 ± 5 *1 ± 1*	4 ± 2 *−19 ± 2*
59		APD90 *APD30*	19 ± 3 *7 ± 1*	22 ± 2 *7 ± 1*	15 ± 0 *−2 ± 2*	−5 ± 2 *−25 ± 3*
60		APD90 *APD30*	23 ± 2 *8 ± 1*	37 ± 3 *13 ± 5*	32 ± 3 *4 ± 5*	12 ± 2 *−17 ± 3*
61		APD90 *APD30*	23 ± 2 *12 ± 2*	31 ± 2 *11 ± 3*	24 ± 2 *4 ± 4*	6 ± 3 *−18 ± 4*

(continued)

Table 3—*contd*

Entry	Structure	Variation (%)	0.3 μM	1 μM	3 μM	10 μM
62		APD90 *APD30*	24 ± 4 *9 ± 2*	42 ± 7 *10 ± 4*	50 ± 8 *8 ± 3*	39 ± 6 *−1 ± 2*
63		APD90 *APD30*	22 ± 8 *10 ± 2*	30 ± 7 *11 ± 2*	26 ± 5 *2 ± 3*	12 ± 4 *−22 ± 4*
64		APD90 *APD30*	15 ± 3 *10 ± 1*	26 ± 5 *11 ± 2*	30 ± 4 *7 ± 2*	16 ± 2 *−10 ± 1*

when a pure calcium channel blocker, verapamil, was perfused before *d*-sotalol. In contrast, when verapamil was added after *d*-sotalol-induced APD prolongation, decrease of APD could be observed.

Consequently, QSAR could not be envisaged using action potential duration as the critical biological parameter. QSAR would require patch-clamp analysis of tested compounds on both the delayed rectifier potassium and the calcium currents. Therefore, the impact of the principal chemical modifications on action potential duration was taken as a semi-quantitative indicator of calcium and potassium channels inhibition and led to the following analysis.

Hydrogen bonding ability

Decreasing the hydrogen bonding ability could account for the decreased rank order of activity to prolong action potential duration between **1, 25, 26**, and **27**, this

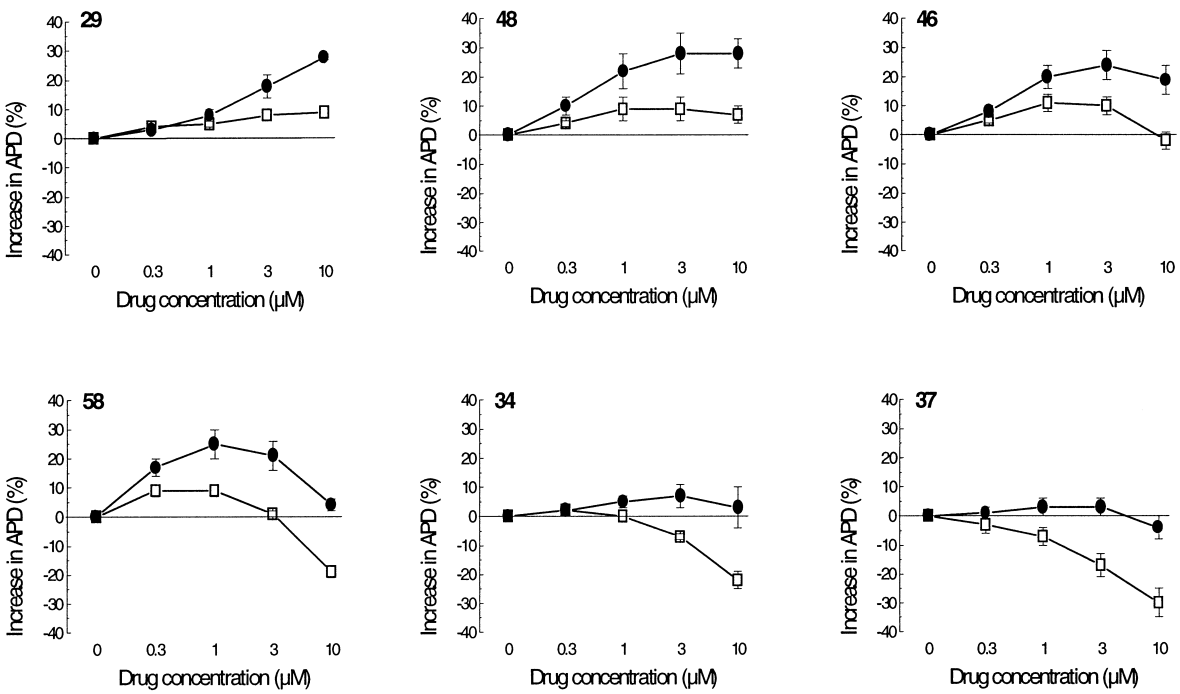


Figure 3. Action potential duration (recorded on guinea-pig papillary muscle at 30% and 90% of repolarization using standard microelectrode technique) of a set of compounds varying from a pure class III agent (**29**) to a compound with predominant class IV activity (**37**).

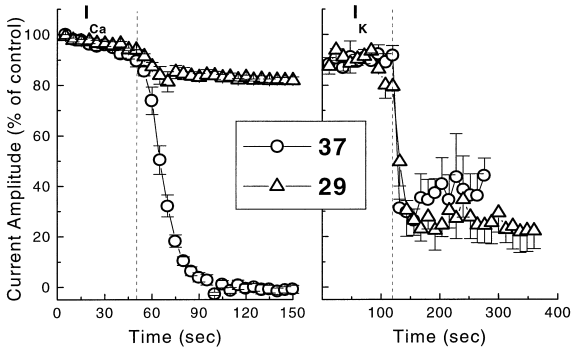


Figure 4. Isolated L-type calcium (left) and delayed rectifier potassium (right) currents for a class III agent (**29**) and a compound (**37**) where the class III effect on APD is masked by a strong class IV effect.

parameter correlating fairly well with the variation of potency whereas hydrophobicity, for example, does not. Because compounds **28** to **31** are less potent than the unsubstituted phenyl **27**, a steric restriction was thought to play a role in the reduced class III activity. The conjunction of both hypotheses might explain why compounds **32** and **6** have still a moderate activity whereas **31** is completely devoid of class III activity. The replacement of the nitro substituent by a sulfonamido as illustrated by compound **29** completely abolished the class IV activity and slightly reduced the class III activity of the molecule.

Similarly, the replacement of the nitrophenyl group by other nitroaromatic residues (**53** and **54**) led to a reduction of the class IV activity but had various influences on the class III activity. The nitro substituent was therefore maintained, with rare exceptions, in the further studies.

Amide function

Compound **33** was also only very marginally effective, suggesting the possible involvement of hydrogen bonding in the amide region. Surprisingly compounds **34** to **37**, wherein the amide function is replaced by a longer/bulkier function, were completely devoid of class III activity but displayed significant reductions in APD_{30}. As a consequence the 4-nitrobenzamide was maintained as the standard substituent of the 1,3-propanediamine derivatives, with the exception of compound **58**.

Spacer

To investigate the role of the distance between the two nitrogen atoms, analogues of **1** with a two- and a four-carbon link have been synthesized (**38** and **39**). These two compounds (**38** and **39**) exhibited a markedly reduced activity when compared to compound **1** (Table 1), suggesting that the optimal spacer length to maintain both activities might be of 3 carbons. Although this observation needs to be confirmed using a larger range of spacer length, all the other compounds synthesized in this study were performed with a three-carbon chain length.

Aliphatic N-substitution

The removal of the aliphatic N-substitution (**40**) or the increase in size of the substituent (**41** and **42**) resulted in a decrease of class III potency and quaternarization of the amine resulted in an inactive compound (**43**). Most studies have therefore been performed on tertiary amines. Nevertheless this methyl being removed by metabolization of BRL-32872 (data not shown), the synthesis and the study of a desmethyl derivative like **64** was justified by the expectation of a potentially improved metabolic profile. Removal of the dimethoxyphenethyl residue (**51**) led to a threefold decrease in class III potency, and a complete loss of class IV activity. Replacement of the dimethoxyphenethyl group by another related residue (**52**, Table 3) reduced significantly both activities.

Cyclization of the chain

The inclusion of either the propanediamine segment or the phenethylamine in a saturated cycle, while maintaining a three-carbon spacer between the two nitrogen atoms, seems to have either no influence (**44** versus **1**) or a slightly positive one on class III potency (**45**). Nevertheless a partial reduction of the class III potency could be observed at the low concentrations with the less flexible compounds **46, 47, 48**, and especially **49**. It is noteworthy that this increased rigidity almost completely suppressed the class IV activity as illustrated by decreased potency from **1**, to **46, 47, 48**, and **49**.

Nitrogen lone pair

The availability of the electron lone pair on the basic nitrogen appeared to be essential for activity as demonstrated by the complete loss of both calcium and potassium inhibitory actions with the quaternarized derivative **43** or the lactam **50**. This may suggest either a critical hydrogen bonding in this part of the molecule or, that at the physiological pH used in our tests, this amine has to be protonated. This lone pair availability has therefore been maintained in the subsequent studies.

The fact that the amide **50** is inactive although hydrogen bonding is still possible via the oxygen atom may support this last hypothesis.

Aromatic N-substitution

Changing the number of substituents of the N-aryl residue (**55** and **56**) reduced the class III activity in comparison with **1**. In addition, an increase in the number of substituents (**55**) resulted in a dramatic drop in the class IV effect. In contrast the complete removal of the N-aromatic residue led to a significant increase in class III activity as illustrated by the results obtained with **57** compared to **1** or **64** compared to **40**.

Nitrogen replacement

With the exception of **58** and **59** which are equipotent to **1**, the other aminopropanol derivatives **60–63** are more potent than BRL-32872 (**1**) in terms of class III activity. The main difference with the first structural type is that the replacement of the nitro by a sulfonamido residue (**62**) boosts the class III activity in contradiction with the data observed for **29**, without removing completely the class IV activity. Despite their nearly systematically improved potency these compounds have not been further developed because they demonstrated unwanted side effects in vivo after oral administration, like reduced locomotor activity and piloerection in the rat and, for **60**, excessive salivation, tremor and panic signs in the dog suggesting a central nervous action (data not shown).

Conclusion

A significant number of structural modifications have been performed around BRL-32872 (**1**) and led to a wide panel of Class III versus Class IV potency ratio as deduced from their electrophysiological properties on isolated guinea-pig papillary muscles. The results obtained in the present study suggest that some structural features markedly affect compound activity like the availability of the nitrogen lone pair and a relative overall flexibility in the molecular structure. These conclusions are in line with the results by Souchet et al. who studied conformationally constrained analogues of BRL-32872.[13] The hydrogen bonding capability of the benzamide substituent as well as the number and size of the substituents of the basic nitrogen proved also to be important mainly for the class III activity. Importantly, we have been able to modulate class III versus class IV activities by specific chemical modifications. It has been shown recently that advantages over specific class III antiarrhythmic drugs of compounds combining class III and class IV activities highly depend on the balance between these two activities.[10] Azimilide, for example, is able to induce a bell-shaped dose-dependent increase in action potential duration and this effect is proposed to result from a dual potassium and calcium currents inhibition.[14] Azimilide is thus comparable to BRL-32872 in its electrophysiological profile. However, BRL-32872 shows a marked advantage over azimilide in its ability to prolong action potential independently of stimulation frequency whereas azimilide effects are reverse-rate dependent.[10] A difference in potassium and calcium current inhibition balance is likely to be responsible for this advantage of BRL-32872 over azimilide.[10] Controlling this balance may thus be of critical importance in the design of new antiarrhythmic compounds combining class III and class IV activities.

The simultaneous occurrence of these two activities in the same molecule leads to a dose-related self-limitation of the prolongation of the action potential duration in contrast with the effect of pure class III antiarrhythmic agents. This property has already been shown to limit the proarrhythmic potential of these antiarrhythmic agents and is believed to generate safer drugs.[15] The different structural modifications performed in the present study allowed the generation of a panel of different profiles varying from mainly class III to predominantly class IV agents via different types of balanced actions and suggested that chemical modifications based on the lead structure could produce a group of compounds with improved antiarrhythmic profile.

Experimental

Electrophysiological experiments

Methods used to record action potential parameters with the microelectrode technique and ionic currents with the patch-clamp technique have been described previously.[1]

Intracellular microelectrode technique in guinea-pig papillary muscles

Guinea-pigs were anaesthetized with sodium pentobarbital (60 mg/kg). The hearts were rapidly removed and placed in a modified Tyrode solution (mM: NaCl 125, KCl 4, $CaCl_2$ 1.8, $MgCl_2$ 1, NaH_2PO_4 0.9, $NaHCO_3$ 24, glucose 11, pH 7.4) gassed with 95%O_2/5%CO_2. Thin papillary muscles were excised from either right or left ventricle, fixed to the silastic bottom of an organ bath and superfused with Tyrode solution maintained at 37 °C. After a 2 h stabilization period, transmembrane potentials were recorded by conventional glass microelectrodes filled with 3 M KCl and connected to a high input impedance amplifier. External stimuli (2 msec; twice threshold) were delivered upon bipolar platinum electrodes applied at the base of the preparation. The basic cycle length of stimulation was 1000 msec. Measurements were made of the following: resting membrane potential, action potential amplitude,

maximum upstroke velocity (Vmax) and action potential duration measured at 30% and 90% of repolarization (APD_{30} and APD_{90}, respectively).

Patch-clamp technique

The technique of cell dissociation used was derived from the method described by Mitra and Morad.[16] Whole-cell configuration of the patch-clamp technique was used for this study.[17] For potassium current experiments, external solution contained (mM): NaCl 140, KCl 5, HEPES 10, glucose 10. Either $CaCl_2$ 2 mM and $MgCl_2$ 1 mM or $MgCl_2$ 2 mM alone to avoid calcium current activation were added to this solution. Results obtained in both conditions were similar. The pH was adjusted to 7.4 with NaOH. The internal medium contained (mM): K-asp 80, KCl 60, MgATP 2, $MgCl_2$ 2, EGTA 2, HEPES 10, glucose 10, and the pH was adjusted to 7.2 with KOH. For calcium current experiments, external solution contained (mM): NaCl 120, CsCl 20, $CaCl_2$ 2, $MgCl_2$ 1, HEPES 10, glucose 10. The pH was adjusted to 7.4 with NaOH. The internal medium contained (mM): K-asp 100, CsCl 40, MgATP 2, $MgCl_2$ 2, EGTA 2, HEPES 10, glucose 10, and the pH was adjusted to 7.2 with KOH. Pipettes were made from borosilicate capillary tubing and had resistances of 2 to 4 MΩ when filled with the internal solution. Experiments were performed at 33 ± 2 °C. Series resistance was compensated and currents were low-pass filtered at a cut-off frequency of 1 kHz (5 pole Tchebyschev filter).

Chemistry

General

Melting points (uncorrected) were determined with a Gallenkamp melting point apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AC 200 MHz spectrometer. Microanalytical data were provided by the Physical and Analytical Service Unit of the SmithKline Beecham Pharmaceutical Research Laboratories at Great Burgh, Great Britain; only symbols of analyzed elements are given, and data were within 0.4% of theoretical values unless indicated.

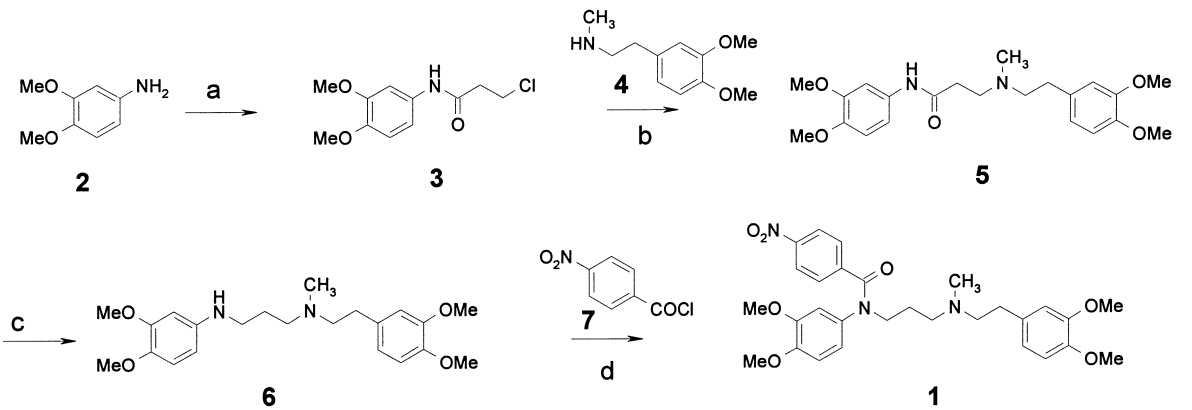
Unless noted, a standard work-up and purification procedure was used for isolation of the products. This involved filtration or extensive extraction with a solvent (washing of extract with aqueous solutions, when mentioned), drying over $MgSO_4$ and evaporation under reduced pressure. Chromatographic purifications were performed using E. Merck Silicagel 60 (70–230 mesh) and all solvents were of Carlo Erba RPE grade; nature and ratio of the solvent mixtures used will be reported each time. Salification was performed in methanol by addition of a 5.5 N solution of anhydrous HCl in diethyl ether.

Structures with a chiral atom have been isolated and tested as racemates.

Methods

Eight different general methods were used to generate the compounds described in this study and they will be described below.

The compounds of Table 1 (with exception of compounds **39** and **40**), compound **44** of Table 2 and compounds **52** to **56** of Table 3 were prepared using the method A exemplified in Scheme 1. 3-Chloropropionyl chloride was condensed on 4-aminoveratrole **2** to give the benzamide **3** which was then condensed on N-methyl-2-(3,4-dimethoxyphenyl)ethylamine 4 to afford the amide **5** and subsequently reduced by lithium aluminum

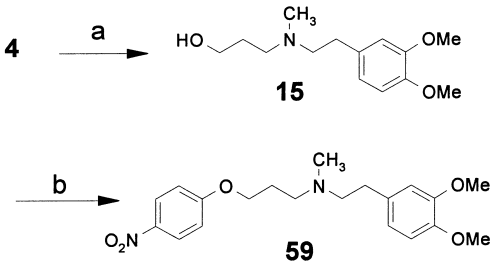


Scheme 1. Method A: (a) Cl-$(CH_2)_2$-COCl, $CHCl_3$, NEt_3, 0 °C, 55%; (b) **4**, CH_3CN, NEt_3, reflux, 78%; (c) $LiAlH_4$, THF, reflux, 89%; (d) **7**, $CHCl_3$, NEt_3, rt, 93%.

hydride (LAH) to afford **6**. This diamine was then acylated with 4-nitrobenzoyl chloride **7**. For compound **39** method A gave too low overall yield and another method (method B, Scheme 2) was therefore developed. In this method **4** was condensed with succinic anhydride to give **8**. Subsequent transformation in acid chloride followed by reaction on **2** afforded the diamide **9** which was reduced to the diamine **10**. Acylation was performed as in method A.

Compounds **45, 47, 48**, and **49** of Table 2 were prepared by method C, as illustrated in Scheme 3 with compound **48**. The diamine **14** was obtained by reductive amination of the ketone **13** with the primary amine **2**. Then the acylation step was performed by using **7** as in Scheme 1.

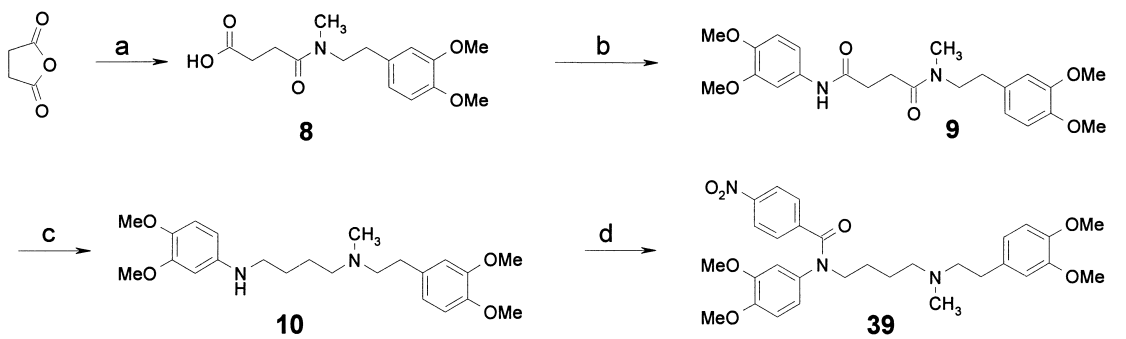
The aminopropanol derivatives **59** to **63** of Table 3 were prepared following method D by the condensation of 3-chloropropanol on the appropriate substituted amine followed by the condensation of 1-fluoro-4-nitrobenzene as illustrated in Scheme 4 with compound **59**. Compound **62** was obtained by reduction of the nitro group of compound **59**, the resulting amino residue was then further functionalized with methanesulfonyl chloride.



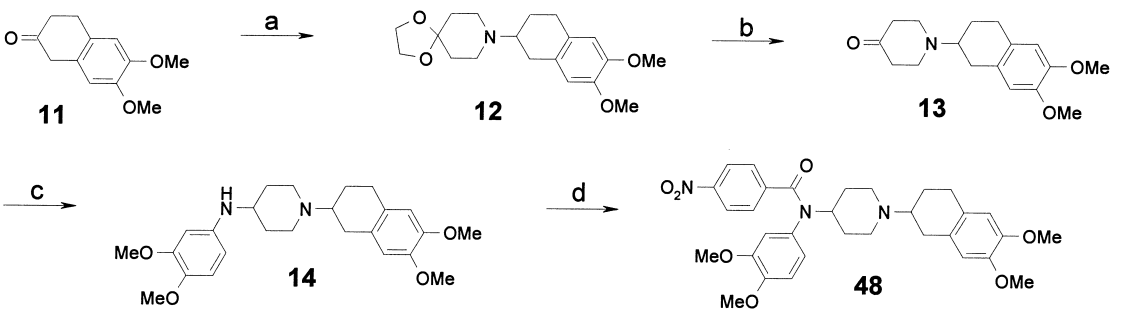
Scheme 4. Method D: (a) Cl-$(CH_2)_3$-OH, KF/celite® (or NEt_3), CH_3CN, 85 °C, 56%; (b) 1-fluoro-4-nitrobenzene, DMSO, rt, 76%.

1,3-diaminopropane derivatives **57** and **64** were preferably prepared by condensation of **7** on 3-chloropropanamine followed by condensation on **4** to generate **57** or 3,4-dimethoxybenzeneethanamine to generate **64** (method E, Scheme 5).

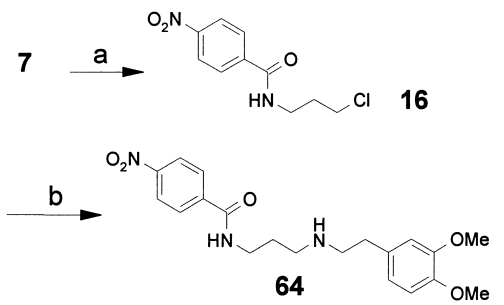
Compound **46** (method F, Scheme 6) was synthesized from 6,7-dimethoxy-3-quinolinecarboxylic acid **17**.[18] The acid chloride derivative was reacted with **4** to give the corresponding amide **18**. Reduction with $NaBH_4$ and acetic acid in dioxane afforded simultaneous reduction of



Scheme 2. Method B: (a) **4**, 60 °C, 16% (b) i. $(COCl)_2$, CH_2Cl_2, DMF cat., rt, ii. **2**, CH_2Cl_2, NEt_3, rt, 37%; (c) $LiAlH_4$, THF/ether, reflux, 13%; (d) **7**, $CHCl_3$, NEt_3, rt, 61%.



Scheme 3. Method C: (a) i. 1,4-dioxa-8-azaspiro[4,5]decane, TsOH, toluene, reflux; ii. H_2, PtO_2, 10 bars, rt 58%. (b) HCl, reflux, 78%; (c) i. **2**, toluene, reflux; ii. $NaBH_4$, AcOH/EtOH, rt, 69%; (d) **7**, CH_2Cl_2, NEt_3, rt, 59%.



Scheme 5. Method E: (a) Cl-$(CH_2)_3$-NH_2, NEt_3, CH_2Cl_2, 5 °C, 92%; (b) 3,4-dimethoxy benzeneethanamine, NEt_3, CH_3CN, 50 °C, 60%.

the amide and of the quinoline to **19**. Acylation was performed as above with **7**.

The secondary amines **40** and **51**, were synthesized following method G (Scheme 7). The compound resulting from the reaction of 3-chloro-1-bromopropane with **20** was transformed by phase transfer catalysis into the more reactive bromo derivative **21**.

The lactam of **50** being not compatible with the LAH reduction step of method A, method H (Scheme 8) was used.

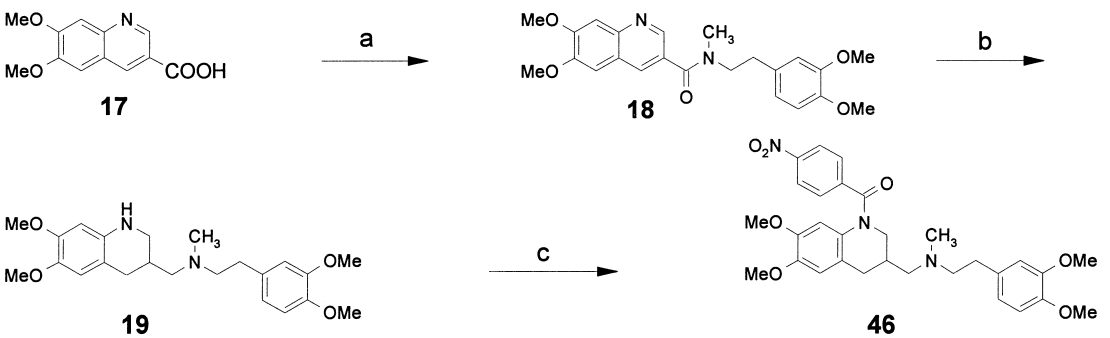
Table 4 will mention for each compound the method used, the formula and the literature reference if the compound has been previously reported.

General method A (Scheme 1)

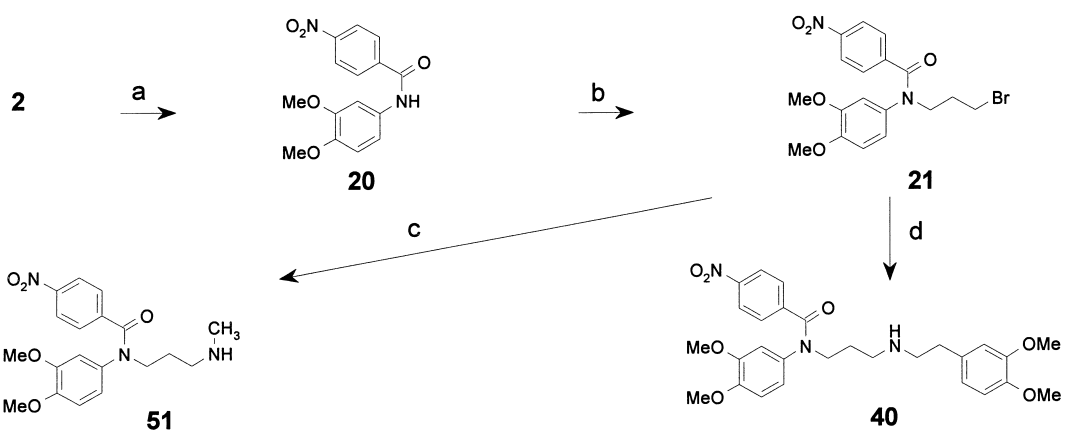
This method is illustrated by the synthesis of compound **1**.

N-(3,4-Dimethoxyphenyl)-N-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-4-nitrobenzamide (1)

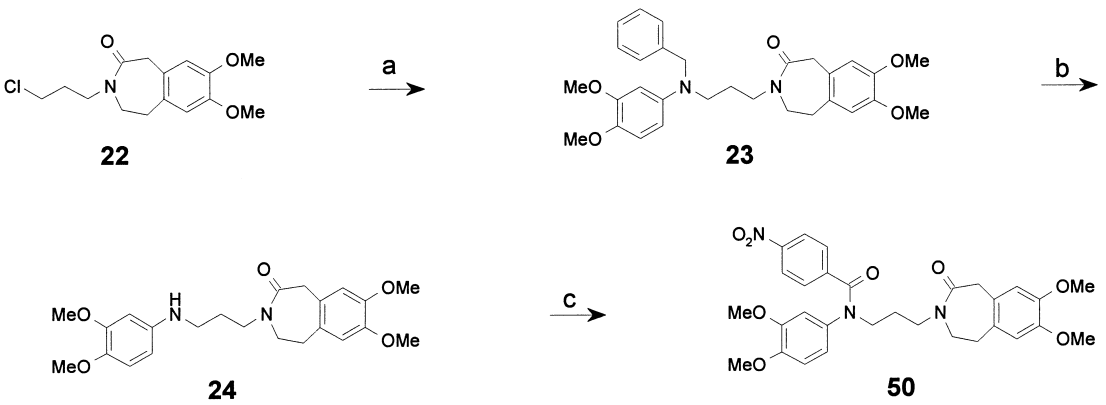
Step 1: 3-Chloro-N-(3,4-dimethoxyphenyl)propanamide (3). An ice cooled solution of 3-chloropropionyl chloride (24.4 g, 0.19 mol) in $CHCl_3$ (150 mL) was treated with 4-aminoveratrole (**2**) (21.5 g, 0.14 mol) and NEt_3 (15.5 g, 0.15 mol). The mixture was stirred for 1.5 h,



Scheme 6. Method F: (a) i. $(COCl)_2$, CH_2Cl_2, DMF cat., rt, ii. **4**, CH_2Cl_2, NEt_3, 0 °C then rt, 66%; (b) $NaBH_4$, AcOH/dioxane, 0 °C, 34%; (c) **7**, CH_3Cl, NEt_3, rt, 18%.



Scheme 7. Method G: (a) **7**, CH_2Cl_2, NEt_3, reflux, 83%; (b) i. Br-$(CH_2)_3$-Cl, NaOH, TBAB, H_2O, toluene, ii. LiBr, TBAB, reflux, 54%; (c) $MeNH_2$, EtOH, rt, 52%; (d) 3,4-dimethoxybenzeneethanamine, toluene, 80 °C, 70%.



Scheme 8. Method H: (a) N-benzyl-4-aminoveratrole, neat, 100 °C, 40%; (b) H_2, Pd/C, MeOH/AcOH, rt, room pressure, 93%; (c) **7**, $CHCl_3$, NEt_3, 0 °C, 61%.

allowed to warm gradually to room temperature (rt) then washed with water (200 mL), with 0.5 N aq HCl (200 mL), a saturated aqueous solution of $NaHCO_3$ (200 mL) and again with water until neutral. The organic solution was dried over $MgSO_4$, some SiO_2 (150 g) was then added and the mixture stirred a few minutes to remove polar impurities. After filtering off the solid the solvent was concentrated to dryness in vacuo and the residue was triturated in diisopropyl ether to afford **3** as off-white crystals (18.8 g, 55%, mp 137 °C) used without further purification in the next step. ^{1}H NMR ($CDCl_3$) δ 7.36 (d, 1H), 7.32 (s, 1H), 6.85 (dd, 1H), 6.82 (d, 1H), 3.90 (t, 2H), 3.88 (s, 3H), 3.86 (s, 3H), 2.80 (t, 2H).

Step 2: N-(3,4-Dimethoxyphenyl)-3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propanamide (5). A solution of **3** (10.7 g, 44 mmol), N-methyl-2-(3,4-dimethoxyphenyl)ethylamine (**4**)[19] (8.6 g, 44 mmol), and NEt_3 (5.3 g, 53 mmol) in acetonitrile (180 mL) was stirred 15 h at reflux temperature. The solvent was concentrated in vacuo, the residue was then dissolved in water (150 mL), the pH adjusted to 6 by means of diluted HCl and the solution was washed with diethylether (3×150 mL). The aqueous phase was made basic by means of aqueous 1 N NaOH, then extracted with CH_2Cl_2 (3×150 mL). The resulting organic phase was washed with water (150 mL), dried over $MgSO_4$ and concentrated to dryness. The residue (22.2 g) was purified by flash chromatography (SiO_2, first CH_2Cl_2:AcOEt: 8:2, then CH_2Cl_2:CH_3OH: 9:1). Crystallization in petroleum ether afforded **5** as a white solid (13.8 g, 78%, mp 101 °C). ^{1}H NMR ($CDCl_3$) δ 10.53 (s, 1H), 7.42 (d, 1H), 6.72 (m, 4H), 6.45 (dd, 1H), 3.87–3.80 (4s, 12H), 2.79 (m, 6H), 2.50 (t, 2H), 2.42 (s, 3H).

Step 3: N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N′-(3,4-dimethoxyphenyl)-1,3-propanediamine (6). A solution of **5** (13.5 g, 33.5 mmol) in THF (90 mL) was added dropwise to a solution of $LiAlH_4$ (1.95 g, 51 mmol) in anhydrous THF (70 mL), then heated to reflux for 3 h. The mixture was cooled with an ice bath and the excess of hydride was destroyed by careful addition of water (8 mL) followed by 10 N NaOH (2 mL). Diethylether (200 mL) was added and the mixture was filtered over Clarcel® to remove the hydrated lithium and aluminium salts. After drying over $MgSO_4$ the solution was concentrated in vacuo to afford crude **6** as an oily compound in a quantitative yield (13 g, ~90% purity estimated by ^{1}H NMR) which was used without further purification in the next step. An analytical sample was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 95:5) and salified affording **6** hydrochloride as white crystals (mp 165 °C). The E.A. corresponded to the dihydrochloride, monohydrate. ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 11 (broad s, 1H), 7.21–6.78 (m, 6H), 3.79–3.40 (4s, 12H), 3.36–3.26 (m, 6H), 3.02 (t, 2H), 2.79 (s, 3H), 2.20 (m, 2H).

Step 4: N-(3,4-Dimethoxyphenyl)-N-[3-[[2-(3,4-dimethoxypheny)ethyl]methylamino]propyl-4-nitrobenzamide (1). A solution of crude **6** (1.1 g corresponding to 2.5 mmol of pure compound) and NEt_3 (0.3 g, 3 mmol) in $CHCl_3$ (20 mL) was added dropwise to an ice cooled solution of 4-nitrobenzoyl chloride (**7**) (0.52 g, 2.8 mmol) in $CHCl_3$ (20 mL) and the mixture was stirred 3 h at rt. The solution was washed with water (50 mL), with a 2 N solution of $NaHCO_3$ (50 mL) and again with water (2×50 mL) then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2:CH_3OH, 9:1) affording **1** as white crystals (1.25 g, 93%). An analytical sample was salified affording **1**.HCl as white crystals (mp 129 °C). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 10.59 (broad s, 1H), 8.08 (d, 2H), 7.56 (d, 2H), 6.98–6.76 (m, 6H), 3.93 (t, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.66 (s, 6H), 3.23 (m, 4H), 2.95 (t, 2H), 2.78 (s, 3H), 1.99 (m, 2H).

Table 4. Synthetic methods, references and formulas of the cited compounds

no	(method)	Formulas[b]	Ref.
1	(A)[a]	$C_{29}H_{35}N_3O_7$[d]	19
6	(A)[a]	$C_{22}H_{32}N_2O_4$, 2HCl,H_2O	19
25	(A)	$C_{30}H_{35}N_3O_5$.HCl.$2H_2O$	19,26
26	(A)	$C_{29}H_{37}N_3O_5$[d]	27
27	(A)	$C_{29}H_{36}N_2O_5$.HCl.$2H_2O$	19
28	(A)	$C_{32}H_{38}N_4O_5$.[d]	27
29	(A)	$C_{30}H_{39}N_3O_7S$.HCl.H_2O	27
30	(A)	$C_{31}H_{39}N_3O_6$	27
31	(A)	$C_{30}H_{35}F_3N_2O_5$.HCl.H_2O	19
32	(A)	$C_{24}H_{34}N_2O_5$.HCl.$0.5H_2O$	26
33	(A)	$C_{29}H_{37}N_3O_6$.2HCl[c]	19
34	(A)	$C_{30}H_{40}N_3O_8P$,HCl	28
35	(A)	$C_{29}H_{36}N_4O_7$	19
36	(A)[a]	$C_{28}H_{35}N_3O_8S$.HCl.$0.5H_2O$	
37	(A)	$C_{30}H_{37}N_3O_7$.HCl.$2H_2O$	19
38	(A)[a]	$C_{28}H_{33}N_3O_7$.HCl	
39	(B)[a]	$C_{30}H_{37}N_3O_7$.HCl	
40	(G)[a]	$C_{28}H_{33}N_3O_7$,HCl	
41	(A)	$C_{31}H_{39}N_3O_7$.HCl	26
42	(A)	$C_{31}H_{37}N_3O_7$.HCl	26
43	(A)[a]	$C_{29}H_{35}N_3O_7$.ICH$_3$.$0.5H_2O$	
44	(A)[a]	$C_{30}H_{35}N_3O_7$.HCl	29
45	(C)	$C_{30}H_{35}N_3O_7$.HCl.H_2O	30
46	(F)[a]	$C_{30}H_{35}N_3O_7$.HCl.$0.5H_2O$	31
47	(C)	$C_{32}H_{37}N_3O_7$,HCl	13
48	(C)[a]	$C_{32}H_{37}N_3O_7$.HCl.H_2O	32
49	(C)[a]	$C_{30}H_{33}N_3O_7$. HCl[d]	
50	(H)	$C_{30}H_{33}N_3O_8$	29
51	(G)[a]	$C_{19}H_{23}N_3O_5$,HCl	
52	(A)	$C_{27}H_{29}N_5O_6$.HCl.$0.5H_2O$	33
53	(A)	$C_{27}H_{33}N_3O_7S$.[d]	34
54	(A)	$C_{27}H_{33}N_3O_8$.HCl	34
55	(A)	$C_{30}H_{37}N_3O_8$.HCl	26
56	(A)	$C_{27}H_{31}N_3O_5$.[d]	
57	(E)	$C_{21}H_{27}N_3O_5$.HCl.$0.5H_2O$	22
58	(D)[a]	$C_{20}H_{27}N_3O_4$.HCl.$0.5H_2O$	
59	(D)[a]	$C_{20}H_{26}N_2O_5$.HCl.$0.3H_2O$	
60	(D)[a]	$C_{20}H_{24}N_2O_5$.HCl	
61	(D)[a]	$C_{23}H_{28}N_2O_5$.[d]	
62	(D)[a]	$C_{21}H_{30}N_2O_5S$.HCl	
63	(D)[a]	$C_{18}H_{22}N_2O_3$.HCl	
64	(E)[a]	$C_{20}H_{25}N_3O_5$.HCl	22

[a]See experimental section.
[b]All compounds exhibited C, H, N analysis within 0.4% unless indicated.
[c]0.47 on H.
[d]High-resolution M.S.

N-(3,4-Dimethoxyphenyl)-N-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]propyl]-4-nitrobenzenesulfonamide (36). This compound was synthesized from **6** and 4-nitrobenzene sulfonylchloride using the same procedure. A sample was salified affording **36**.HCl as an amorphous yellow solid (mp 90–100 °C). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 10.61 (broad s, 1H), 8.43 (d, 2H), 7.87 (d, 2H), 6.94–6.87 (m, 3H), 6.76–6.67 (m, 3H), 3.75–3.62 (m, 14H), 3.36–3.18 (m, 4H), 2.95–2.87 (m, 2H), 2.74 (d, 3H), 1.79 (m, 2H).

N-(3,4-Dimethoxyphenyl-N-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl-4-nitrobenzamide (38). This compound was synthesized following method A, starting from **2** and chloroacetyl chloride. **38**.HCl, yellow crystals (mp 101 °C). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 10.72 (broad s, 1H), 8.08 (d, 2H), 7.66 (d, 2H), 7.20 (d, 1H), 6.92–6.78 (m, 5H), 4.26 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 3.40 (m, 2H), 3.25 (m, 2H), 3.01 (t, 2H), 2.91 (s, 3H).

N-(3,4-Dimethoxyphenyl-N-[3-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]butyl-4-nitrobenzamide (39). Method A provided only unidentified compounds in the reaction of the substituted chlorobutanamide on N-methyl-2-(3,4-dimethoxyphenyl)ethylamine. Thus another method (B) needed to be developed.

General method B (Scheme 2)

Step 1: N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-3-carboxypropionamide (8). A mixture of N-methyl-2-(3,4-dimethoxyphenyl)ethylamine (**4**) (3.9 g, 20 mmol) and succinic anhydride (2 g, 20 mmol) was stirred, neat, for 6 h at 60 °C. After cooling at rt, the oily mass was dissolved in CH_2Cl_2 (50 mL), washed twice with water (2×50 mL), with 1 N HCl (50 mL) and again with water. After drying over $MgSO_4$, the solvent was concentrated and the residue (0.93 g, 16%) used in the next step without further purification.

Step 2: N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N′-(3,4-dimethoxyphenyl)-1,4-butanediamide (9). To a solution of crude **8** (0.93 g, 3 mmol) and one drop of DMF in CH_2Cl_2 (15 mL), oxalyl chloride (0.41 g, 3 mmol) was added dropwise at rt and stirring was continued for 1.5 h. The solvent was concentrated in vacuo, the residue was dissolved in CH_2Cl_2 (15 mL) and added dropwise, at rt, to a solution of 4-aminoveratrole (**2**) (0.46 g, 3 mmol) and NEt_3 (0.3 g, 3 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred for one additional hour, then the solvent was concentrated in vacuo. The residue was dissolved in AcOEt (50 mL), washed with water (2×50 mL), 1 N HCl (50 mL), 1 N NaOH (50 mL) and again with water. The organic phase was dried over $MgSO_4$, concentrated in vacuo and the residue purified by flash chromatography (SiO_2, first AcOEt, then AcOEt:MeOH, 9:1) to afford **9** (0.5 g, 37%). ^{1}H NMR (DMSO-d_6) δ 9.81 and 9.77 (s, 0.5 H each, *syn* and *anti* forms), 7.33–6.69 (m, 6H), 4.37 (t, 2H), 3.07 (m, 12H), 3.44 (m, 2H), 2.94 and 2.80 (s, 1.5 each, *syn* and *anti*), 2.63–2.46 (m, 4H).

Step 3: N-[2-(3,4-Dimethoxypheny)ethyl]-N-methyl-N′-(3,4-dimethoxyphenyl)-1,4-butanediamine (10). The diamide **9** (0.5 g, 1.16 mmol) was dissolved in a 1:1 mixture of THF and diethylether (40 mL) then $LiAlH_4$ (0.38 g, 10 mmol) was added portionwise, and the mixture was heated one night at reflux. After cooling with an ice bath the mixture was carefully treated with water (0.3 mL), 15% NaOH (0.3 mL) again with water (0.9 mL) and the solid was filtered off. The organic solution was dried over $MgSO_4$, the solvent was concentrated in vacuo and the residue was purified by flash chromatography (SiO_2, CH_2Cl_2:MeOH, 9:1) to afford **10** (60 mg, 13%). ^{1}H NMR (DMSO-d_6) δ 6.86–6.68 (m, 4H), 6.26 (d, 1H), 6.02 (dd, 2H), 3.73 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H), 3.61 (s, 3H), 2.95 (t, 2H), 2.67 (m, 6H), 2.32 (s, 3H), 1.54 (m, 4H).

Step 4: N-(3,4-Dimethoxyphenyl-N-[4-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]butyl-4-nitrobenzamide (39). The last step was performed by a procedure similar to that described for **1**. The hydrochloride gave a vitreous mass. ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 10.36 (broad s, 1H), 8.06 (d, 2H), 7.55 (d, 2H), 6.92–6.70 (m, 6H), 3.89 (t, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 3.73 (s, 6H), 3.30–2.92 (m, 6H), 2.79 (s, 3H), 1.79 (m, 2H), 1.57 (m, 2H).

N,N-Dimethyl-N-[2-(3,4-dimethoxyphenyl)ethyl]-3-[(3,4-dimethoxyphenyl)-(4-nitrobenzoyl)amino]-propanaminium iodide (43). A solution of **1** (0.92 g, 1.7 mmol) in acetone (15 mL) was treated with iodomethane (0.71 g, 5 mmol) and refluxed for 24 h. The solution was concentrated in vacuo and the residue triturated with diethylether to afford **43** as an amorphous yellow solid (0.9 g, 92%, mp 100–110 °C, decomposition). ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 2H), 7.63 (d, 2H), 7.00 (s, 1H), 6.82–6.63 (m, 5H), 4.04 (t, 2H), 3.91–3.40 (m, 16H), 3.40 (s, 6H), 3.04 (m, 2H), 2.16 (m, 2H).

General method C (Scheme 3)

This method can be illustrated by the synthesis of compound **48**.

N-[1-(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-2-yl)-4-piperidinyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide (48)

Step 1: 8-(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-2-yl)-1,4-dioxa-8-azaspiro[4,5]decane (12). A solution of 6,7-dimethoxy-2-tetralone (**11**) (2.25 g, 11 mmol), 1,4-dioxa-8-azaspiro[4,5]decane (6.3 g, 44 mmol) and 4-methylbenzenesulfonic acid (0.21 g, 1.1 mmol) in toluene (60 mL) was heated under reflux for 1 h trapping the water with a Dean–Stark. Anhydrous ethanol (60 mL) was added and the resulting mixture was hydrogenated over PtO_2 (0.3 g) under 10 bars at rt. The catalyst was filtered off and the solvent concentrated. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2:CH_3OH, 95:5) then triturated in diisopropyl ether to afford **12** as brown crystals (2.15 g, 58%, mp 102–104 °C). ^{1}H NMR ($CDCl_3$) δ 6.57 (s, 2H), 3.97 (s, 4H), 3.83 (s, 6H), 2.98–2.65 (m, 8H), 2.26–2.07 (m, 1H), 2.00–2.78 (m, 4H), 1.78–1.43 (m, 2H).

Step 2: N-(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-2-yl)-4-piperidone (13). A solution of **12** (1.75 g, 5.25 mmol) in aq 1 N HCl (38 mL) was stirred at reflux for 2 h then cooled to rt. Aqueous 5 N NaOH (8 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue obtained was purified by chromatography (SiO2, AcOEt) to afford **13** as brown crystals (1.2 g, 78%, mp 98–100 °C). ^{1}H NMR ($CDCl_3$) δ 6.58 (s, 2H), 3.84 (s, 6H), 3.14–2.90 (m, 5H), 2.90–2.74 (m, 4H), 2.68–2.43 (m, 4H), 2.23–2.05 (m, 1H), 1.83–1.53 (m, 1H).

Step 3: 1-(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-2-yl)-N-(3,4-dimethoxyphenyl)-4-piperidineamine (14). A solution of **13** (1.2 g, 4.1 mmol), **2** (0.63 g, 4.1 mmol) and 4-methylbenzene sulfonic acid (0.1 g, 0.5 mmol) in toluene (30 mL) was stirred and heated at reflux for 2 h, trapping the water with a Dean–Stark. The reaction mixture was concentrated to dryness and the residue taken-up in an AcOH:EtOH (1:1) mixture (12 mL). After cooling with an ice-water bath, $NaBH_4$ (0.19 g, 5 mmol) was added portionwise. The mixture was stirred for 2 h at rt then poured onto ice-water. Concentrated aqueous NaOH was added to alkalize the aqueous phase which was then extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 96:4) to afford **14** as beige crystals (1.2 g, 68%, mp 121 °C). ^{1}H NMR (DMSO-d_6) δ 6.78–6.55 (m, 3H), 6.28 (s, 1H), 6.05 (d, 1H), 5.03 (d, 1H, exch. D_2O), 3.68 (s, 6H), 3.61 (s, 6H), 3.24–3.05 (m, 1H), 3.05–2.83 (m, 2H), 2.83–2.62 (m, 5H), 2.48–2.22 (m, 2H), 2.10–1.23 (m, 6H).

Step 4: N-[1-(1,2,3,4-Tetrahydro-6,7-dimethoxynaphthalen-2-yl)-4-piperidinyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide (48). A solution of 4-nitrobenzoyl chloride (**7**) (0.27 g 1.45 mmol) was added dropwise to an ice cooled stirred solution of **14** (0.51 g, 1.2 mmol) and NEt_3 (0.145 g 1.45 mmol) in CH_2Cl_2 (25 mL) and stirring was maintained for 2 h at rt. The reaction mixture was washed with aqueous 1 N NaOH, twice with water and dried over $MgSO_4$. The solvent was concentrated in vacuo, and the residue purified twice by chromatography (SiO_2, first CH_2Cl_2:CH_3OH, 96:4, then AcOEt) to afford **48** as white crystals (0.49 g, 59%, mp 201 °C).

A sample was salified to afford the hydrochloride as yellow crystals (mp 204 °C). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 10.18 (broad s, 1H), 8.06 (d, 2H), 7.57 (d, 2H), 6.94 (s, 1H), 6.87–6.57 (m, 4H), 5.00–4.75 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.67 (s, 3H), 3.81–3.32 (m, 3H), 3.23–2.51 (m, 6H), 2.43–1.56 (m, 6H).

(±)-*trans*-N-(3,4-Dimethoxyphenyl)-N-(8,9-dimethoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]-quinolizin-2-yl)-4-nitrobenzamide (49). This compound was synthesized by the same procedure starting from **2** and 8,9-dimethoxy-3,4,11,11a-tetrahydro-1*H*-benzo[*b*]quinolizin-2-6*H*-on.[20] The reductive amination gave predominantly the *trans* form.

Step 1: (±)-*trans*-N-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]-quinolizine-2-amine. ^{1}H NMR (DMSO-d_6) δ 6.70 (d, 1H), 6.62 (s, 2H), 6.29 (d, 1H), 6.08 (dd, 1H), 5.04 (d, 1H), 4.04–3.62 (m, 13H), 3.19–3.12 (m, 2H), 3.03–2.98 (m, 1H), 2.70–2.62 (m, 1H), 2.41–1.95 (m, 4H), 1.45–1.29 (m, 1H), 1.19–1.02 (m, 1H).

Step 2: (±)-*trans*-N-(3,4-Dimethoxyphenyl)-N-(8,9-dimethoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]-quinolizine-2-yl)-4-nitrobenzamide (49). Melting point 175 °C. ^{1}H NMR (DMSO-d_6) δ 8.05 (d, 2H), 7.56 (d, 2H), 6.88 (d, 1H), 6.75 (m, 2H), 6.61 (s, 2H), 4.62 (m, 1H), 3.85–3.66 (m, 13H), 3.44–3.33 (m, 2H), 3.20–3.02 (m, 1H), 2.73–2.65 (1H), 2.51–2.09 (m, 4H), 1.57–1.40 (m, 1H), 1.32–1.21 (m, 1H).

General method D (Scheme 4)

This method can be illustrated by the synthesis of compound **59**.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-3-(4-nitrophenoxy)propanamine (59)

Step 1: N-(3-Hydroxypropyl)-N-methyl-3,4-dimethoxybenzeneethanamine (15). A solution of **4** (1.0 g, 5 mmol), and 3-chloro-1-propranol (1.89 g, 20 mmol) was treated with potassium fluoride on Celite®[21] (2.75 g) in dry acetonitrile (30 mL) and the mixture was heated at 85 °C for 20 h under argon. After cooling, the mixture was filtered and the solid was washed with CH_2Cl_2 (150 mL). The organic solutions were combined, concentrated in vacuo and the residue was taken up in CH_2Cl_2 (50 mL), washed with water (50 mL), with 5% aqueous $NaHCO_3$ (50 mL) and again with water, then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 95:5) affording **15** (0.71 g, 56%) as a yellow oil. ^{1}H NMR (DMSO-d_6) δ 6.86–6.69 (m, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.43 (t, 2H), 3.37 (s, 1H), 2.69–2.52 (m, 4H), 2.43 (t, 2H), 2.22 (s, 3H), 1.56 (m, 2H). *Note*: This reaction can also be performed, in the same solvent and temperature conditions, by replacing KF on Celite® by NEt_3. Yields are usually slightly lower.

Step 2: N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-3-(4-nitrophenoxy)-propanamine (59). A suspension of NaH at 60% in oil (0.11 g, 2.7 mmol) was added to a solution of **15** (0.69 g, 2.7 mmol) in DMSO (5 mL) and the mixture was stirred for 2 h at rt. 1-Fluoro-4-nitrobenzene (0.43 g, 3 mmol) was added and the mixture was stirred for 1 h at rt then poured onto ice water (50 mL). The aqueous mixture was extracted with AcOEt, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 95:5) to afford **59** (0.77 g, 76%). A sample was salified as usual, affording **59**.HCl as an amorphous solid. ^{1}H NMR (hydrochloride) (DMSO-d_6) 10.82 (broad s, 1H), 8.23 (d, 2H), 7.16 (d, 2H), 6.92–6.78 (m, 3H), 4.24 (t, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.30 (m, 4H), 2.98 (t, 2H), 2.82 (s, 3H), 2.24 (m, 2H).

The following compounds have been obtained by this method:

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-N′-(4-nitrophenyl)-1,3-propanediamine (58). Starting from N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-1,3-propanediamine[22] and using K_2CO_3 instead of NaH, this method afforded **58**.HCl as an orange amorphous solid (mp 80–85 °C). Elemental analysis was consistent with the hemihydrate. ^{1}H NMR (hydrochloride) (DMSO-d_6) 10.63 (broad s, 1H), 8.00 (d, 2H), 7.52 (t, 1H), 6.91–6.67 (m, 5H), 3.75 (s, 3H), 3.72 (s, 3H), 3.28–3.15 (m, 6H), 3.01 (t, 2H), 2.80 (s, 3H), 2.03 (m, 2H).

N-[2-(3,4-Dimethoxyphenyl)ethyl]-N-methyl-1,3-propanediamine was obtained by reduction of N-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propanamide as described in method A. ^{1}H NMR ($CDCl_3$) δ 6.82–6.71 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.79–2.53 (m, 6H), 2.47 (t, 2H), 2.30 (s, 3H), 2.15 (broad s, 2H), 1.65 (m, 2H).

N-[[2-(3,4-Dimethoxyphenyl)ethyl]methylamino]propanamide was obtained by reaction of **4** on 3-chloropropanamide as described in method A. ^{1}H NMR ($CDCl_3$) δ 7.71 (broad s, 2H), 6.78–6.70 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.79–2.74 (m, 6H), 2.46 (t, 2H), 2.40 (s, 3H).

N-[4-[3-[2-[(3,4-Dimethoxyphenyl)ethyl]methylamino]-propyl]oxyphenyl] methanesulfonamide (62)

Step 1: 3-(4-Aminophenoxy)-N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-methylpropanamine. A mixture of **59** (2.78 g, 7.4 mmol) and $SnCl_2.2H_2O$ (10.05 g, 44.5 mmol) in

EtOH (150 mL) was stirred 2 h at reflux temperature and, after cooling to rt, neutralized by addition of a saturated solution of $NaHCO_3$. The mixture was concentrated in vacuo, the residue was taken-up in AcOEt, the organic solution was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2: CH_3OH, 98:2) to afford the title compound as a red oil (1.97 g, 77%). ^1H NMR (DMSO-d_6) 6.87–6.66 (m, 3H), 6.62 (d, 2H), 6.48 (d, 2H), 4.61 (broad s, 2H), 3.81 (t, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 2.70–2.40 (m, 6H), 2.21 (s, 3H), 1.77 (m, 2H).

Step 2: N-[4-[3-[2-[(3,4-Dimethoxyphenyl)ethyl]methylamino]propyl]oxyphenyl]methane sulfonamide (62). Methane sulfonyl chloride (0.8 g, 7.8 mmol) was added dropwise, at 0 °C, to a solution of 3-(4-aminophenoxy)-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methylpropanamine (2.25 g, 6.5 mmol) and NEt_3 (0.79 g, 7.8 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred for additional 3 h at rt then washed with water (3×100 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, CH_2Cl_2: CH_3OH, 95:5) and acidified by anhydrous HCl to afford **62**.HCl as white crystals (1.31 g, mp 157 °C). ^1H NMR (hydrochloride) (DMSO-d_6) δ 10.42 (broad s, 1H), 9.42 (s, 1H), 7.25–6.72 (m, 7H), 4.04 (t, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.30–3.20 (m, 4H), 2.96 (t, 2H), 2.88 (s, 3H), 2.82 (s, 3H), 2.17 (m, 2H).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-[3-[(4-nitrophenyl)-oxy]propyl] isoquinoline (60). Starting from 3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinoline this method afforded **60**.HCl, as yellow crystals (mp 230 °C). ^1H NMR (hydrochloride) (DMSO-d_6) δ 11.15 (broad s, 1H), 8.24 (d, 2H), 7.17 (d, 2H), 6.82 (s, 1H), 6.80 (s, 1H), 4.41–4.15 (m, 4H), 3.74–3.60 (m, 8H), 3.40–2.85 (m, 4H), 2.45–2.25 (m, 2H).

1,2,3,3a,4,5,9b-Hexahydro-7,8-dimethoxy-3-[3-[(4-nitrophenyl)oxy]propyl]-1*H*-benzo[*e*]indole 61. Starting from 1,2,3,3a,4,5,9b-hexahydro-7,8-dimethoxy-1*H*-benzo[*e*]indole-3-propanol[23] (0.5 g, 1.71 mmol, mixture of diastereomers) this method afforded **61** (0.39 g, 55%). The hydrochloride (**61**.HCl) was obtained as yellow crystals, (mp 215–216 °C). The diastereomers ratio observed by NMR was approximately 0.3/0.7. ^1H NMR (hydrochloride) (DMSO-d_6) 11.62 and 10.63 (2 broad s, 1H), 8.24 (d, 2H), 7.18 (d, 2H), 6.81 and 6.79 (2s, 1H), 6.73 and 6.71 (2s, 1H), 4.27 (t, 2H), 4.05–3.82 (m, 1H), 3.72 (s, 6H), 3.70–3.45 and 3.35–2.94 (2m, 5H), 2.94–1.58 (5m, 8H).

N-Methyl-3-(4-nitrophenoxy)-N-(2-phenylethyl)-propanamine (63). Starting from N-methyl-N-(2-phenylethyl)-propanamine this method afforded **63**.HCl as white crystals (mp 155 °C). ^1H NMR (hydrochloride) (DMSO-d_6) 10.86 (broad s, 1H), 8.23 (d, 2H), 7.39–7.21 (m, 5H), 7.17 (d, 2H), 4.24 (t, 2H), 3.40–3.15 (m, 4H), 3.06 (t, 2H), 2.84 (s, 3H), 2.25 (m, 2H).

General method E (Scheme 5)

This method is illustrated by the synthesis of compound **64**.

N-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]propyl]-4-nitrobenzamide (64)

Step 1: N-3-Chloropropyl-4-nitrobenzamide (16). To a solution of 3-chloro-1-propylamine hydrochloride (110 g, 0.85 mol) and NEt_3 (230 mL, 1.66 mol) in CH_2Cl_2 (1.5 L), 4-nitrobenzoyl chloride (**7**) (150 g, 0.81 mol) was added portionwise, under stirring and maintaining the temperature at 0–5 °C. Then, stirring was continued for additional 15 h at rt. The solution was washed with water (3×500 mL) and brine (500 mL) and dried over $MgSO_4$. After filtering-off the solid, the solution was partly concentrated in vacuo to a volume of 750 mL and a 1:1 mixture of diisopropylether and petroleum ether (1.5 L) was added and stirring was maintained for 18 h at rt. The resulting precipitate was filtered, washed with the above ether mixture (400 mL), then with petroleum ether (50 mL) and dried in vacuo at 60 °C to afford **16** as white crystals (180 g, 92%, mp 100 °C). ^1H NMR (DMSO-d_6) 8.87 (t, 1H), 8.31 (d, 2H), 8.07 (d, 2H), 3.71 (t, 2H), 3.41 (q, 2H), 2.00 (m, 2H).

Step 2: N-[3-[[2-(3,4-Dimethoxyphenyl)ethyl]amino]-propyl]-4-nitrobenzamide (64). A solution of **16** (120 g, 0.495 mol), 3,4-dimethoxy benzeneethanamine (896 g, 4.95 mol) and NEt_3 (55 g, 0.544 mol) in acetonitrile (420 mL) was stirred at 50 °C for 15 h. The solvent was concentrated in vacuo and the residue was taken up in CH_2Cl_2 (1.2 L), washed with water (3×600 mL) and brine (2×600 mL). The organic phase was dried and concentrated to afford a crude oil (756 g) containing, in addition to **64**, a large excess of 3,4-dimethoxy benzeneethanamine. This residue was dissolved in diethyl ether and acidified with 2 N aq HCl (2 L). The organic phase was discarded, the aqueous phase washed with diethyl ether (2×0.6 L) and then stirred for 18 h with diethyl ether (0.6 L). The slowly appearing precipitate was filtered, washed with ice water (250 mL) and ether (2×250 mL) to afford after drying crude hydrochloride as yellow crystals (194 g). Further purification, either by flash chromatography or recrystallization in acetonitrile afforded pure **64**.HCl (126 g, 60% based on **16**, mp 156 °C). ^1H NMR (hydrochloride) (DMSO-d_6) δ 9.10 (t, 1H), 8.92 (broad s, 1H), 8.32 (d, 2H), 8.11 (d, 2H), 6.88 (d, 1H), 6.86 (d, 1H), 6.76 (dd, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.42–3.35 (m, 2H), 3.16–3.08 (m, 2H), 3.02–2.84 (m, 4H), 1.95–1.88 (m, 2H). (*Note*: a large excess of

3,4-dimethoxy benzeneethanamine has been used to avoid di-substitution with **16** and is, of course, not required for the synthesis of N disubstituted compounds like **57**).

Method F (Scheme 6)
(1,2,3,4-Tetrahydro-6,7-dimethoxy-3-[[[2-(3,4-dimethoxyphenyl)ethyl]methylamino] methyl]-1-quinolinyl(-(4-nitrophenyl)-methanone (46)

Step 1: 6,7-Dimethoxy-N-[2-(3,4-dimethoxyphenyl)-ethyl]-N-methyl-3-quinolinecarboxamide (18). A suspension of **17**[18] (5 g, 18.5 mmol) in CH_2Cl_2 (60 mL) containing one drop of DMF was treated with oxalyl chloride (4.7 g, 37.1 mmol) whilst stirring at rt. The reaction mixture was stirred for two additional hours and the solvent was evaporated. The residue was taken-up in CH_2Cl_2 (50 mL) and a solution of N-methyl-2-(3,4-dimethoxyphenyl)ethylamine (**4**) (2.89 g, 14.8 mmol) and NEt_3 (3.37 g, 33.3 mmol) in CH_2Cl_2 (60 mL) was added at 0 °C. The mixture was allowed to warm to room temperature and stirring was maintained overnight. The solution was washed with water, with a saturated aqueous solution of $NaHCO_3$, again with water and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, first 99:1 then 97:3) to afford **18** as a yellow-brown oil (5.8 g, 66%). ^{1}H NMR (DMSO-d_6) 8.35 (s, 1H), 7.52–7.12 (m, 3H), 6.97–6.49 (m, 3H), 3.92 (s, 6H), 3.73 (s, 6H), 3.52–3.26 (m, 2H), 3.08 (s, 3H), 2.99–2.62 (m, 2H).

Step 2: 1,2,3,4-Tetrahydro-6,7-dimethoxy-N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-3-quinoline methanamine (19). A solution of acetic acid (4.38 g, 73 mmol) in dioxane (10 mL) was added dropwise to an ice cooled mixture of **18** (2 g, 4.9 mmol) and $NaBH_4$ (2.76 g, 73 mmol) in dioxane (50 mL). The mixture was refluxed for 16 h then poured onto ice-water (50 mL). The mixture was extracted with AcOEt (4×50 mL) and the organic solution was washed with brine (3×50 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 99:1) to afford **19** as a yellow oil (0.66 g, 34%). ^{1}H NMR (DMSO-d_6) 6.88–6.75 (m, 2H), 6.70 (d, 1H), 6.45 (s, 1H), 6.11 (s, 1H), 5.19 (s, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 3.63 (s, 3H), 3.59 (s, 3H), 3.26–3.05 (m, 1H), 2.85–2.45 (m, 7H), 2.24 (s, 3H), 2.35–2.10 (m, 2H), 2.04–1.86 (m, 1H).

Step 3: [1,2,3,4-Tetrahydro-6,7-dimethoxy-3-[[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]methyl]-1-quinolinyl]-(4-nitrophenyl)-methanone (46). A solution of **7** (0.70 g, 3.8 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a solution of **19** (1.2 g, 3.0 mmol) and NEt_3 (0.385 g, 3.8 mmol) in CH_2Cl_2 (40 mL) cooled at 0 °C. Stirring was maintained for additional 16 h at rt. The reaction mixture was washed with water (2×20 mL) and the organic phase dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_8, first CH_2Cl_2:CH_3OH, 99:1, then CH_2Cl_2:CH_3OH:NEt_3, 99:0.5:0.5, finally: CH_2Cl_2:CH_3OH:NEt_3, 99.6:0.2:0.2). After concentration of the desired fractions the residue was salified to afford the hydrochloride of **46** as an orange amorphous solid (0.3 g, 18%, mp 110–120 °C). ^{1}H NMR (DMSO-d_6) δ 10.41 (broad s, 1H), 8.22 (d, 2H), 7.64 (d, 2H), 6.98–6,72 (m, 5H), 4.39–4.08 (m, 1H), 3.47 (s, 6H), 3.73 (s, 6 H), 3.73–3.62 (m, 1H), 3.43–2.93 (m, 7H), 2.87 (s, 3H), 2.78–2.58 (m, 2H).

General Method G (Scheme 7)
N-(3,4-Dimethoxyphenyl)-N-[3-[2-(3,4-dimethoxyphenyl)-ethyl]aminopropyl]-4-nitrobenzamide (40) and N-(3,4-Dimethoxyphenyl-3-methylaminopropyl)-4-nitrobenzamide (51)

Step 1: N-(3,4-Dimethoxyphenyl)-4-nitrobenzamide (20). A solution of **2** (100 g, 0.654 mol) and NEt_3 (72.8 g, 0.72 mol) in CH_2Cl_2 (400 mL) was treated dropwise with a solution of **7** in CH_2Cl_2 (400 mL) and the temperature allowed to reach the reflux of the solvent. After the addition was completed the mixture was stirred for an additional 1.5 h allowing the temperature to come back to ambient and another hour under ice cooling. The yellow solid which began to precipitate at the end of the addition was filtered, washed with CH_2Cl_2 (500 mL) and dried at rt to afford **20** (164 g, 83%) which was used without purification in the next step. ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 2H), 8.04 (d, 2H), 7.88 (s, 1H), 7.45 (d, 1H), 7.03 (dd, 1H), 6.87 (d, 1H), 3.91 (s, 3H), 3.89 (s, 3H).

Step 2: N-(3,4-Dimethoxyphenyl-3-bromopropyl)-4-nitrobenzamide (21). A stirred mixture of **20** (60.4 g, 0.2 mol), tetrabutylammonium bromide (TBAB) (6.44 g, 0.02 mol) in toluene (500 mL) and water (120 mL) was treated with NaOH (40 g, 1 mol) giving an exothermic reaction. Then 1-bromo-3-chloropropane (100 g, 0.635 mol) was added and the reaction mixture heated to reflux for 15 min. After cooling to rt the organic phase was washed with 5 N HCl (400 mL), H_2O (2×400 mL) and brine (400 mL), then added dropwise to 2.5 L of hexane with vigorous stirring. The resulting gummy solid was decanted off, resuspended in toluene (500 mL) and treated with LiBr (43.6 g, 0.5 mol) and TBAB (6.44 g, 0.02 mol) under vigorous stirring at 108 °C. The mixture was allowed to cool and H_2O (400 mL) and toluene (500 mL) were added. The organic phase was separated, washed with 5 N HCl (400 mL), water (2×400 mL) and brine (400 mL) and dried over Na_2SO_4. The solvent was concentrated in vacuo and the residue was crystallized from diethylether (800 mL) with gentle stirring overnight to afford **21** (45.8 g, 54%). This compound was used without further purification in the

next step (94% purity estimated by NMR). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 2H), 7.48 (d, 2H), 6.68 (d, 1H), 6.58 (d, 1H), 6.52 (dd, 1H), 4.04 (t, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.47 (t, 2H), 2.28 (m, 2H).

Step 3: N-(3,4-Dimethoxyphenyl)-N-[3-[2-(3,4-dimethoxyphenyl)ethyl]aminopropyl]-4-nitrobenzamide (40). A mixture of 3,4-dimethoxybenzeneethanamine (35.4 g, 0.195 mol) and NEt_3 (14.5 g, 0.143 mol) was heated neat to 80 °C. Then, a solution of **21** (6.4 g, 15 mmol) in toluene (50 mL) was added dropwise, and stirring was continued overnight at 80 °C. After cooling to rt, H_2O (320 mL), saturated Na_2CO_3 (40 mL) and AcOEt (320 mL) were added. The phases were separated, the aqueous phase was further extracted with AcOEt (250 mL), the organic phases were combined, washed with water (2×350 mL), dried over Na_2SO_4 and concentrated in vacuo to give an oil which was purified by chromatography (neutral Al_2O_3, first $CHCl_3$, then $CHCl_3$:CH_3OH, 99:1) affording **40** as a crude oil (8 g). The base was salified by anhydrous HCl in EtOH affording **40**.HCl (5.6 g, 70% based on pure **21**). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 8.96 (broad s, 2H); 8.08 (d, 2H), 7.57 (d, 2H), 6.95 (d, 1H), 6.92–6.87 (m, 2H), 6.80–6.70 (m, 3H), 3.92 (t, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 3.68 (s, 3H), 3.67 (s, 3H), 3.17–2.85 (m, 6H); 1.91 (m, 2H).

N-(3,4-Dimethoxyphenyl-3-methylaminopropyl)-4-nitrobenzamide (51). A 33% solution of CH_3NH_2 in EtOH (150 mL) was added to **21** (10 g, 24 mmol) and the mixture was stirred for 2.5 h at rt. The solvent was concentrated, the residue dissolved in CH_2Cl_2 and the solution washed with saturated $NaHCO_3$, then dried over Na_2SO_4. After concentration of the solvent, the residue was purified by chromatography (neutral Al_2O_3, $CHCl_3$:CH_3OH, from 99:1 stepwise to 8:2). The desired fractions were pooled, concentrated and salified by anhydrous HCl to afford **51**.HCl (4.6 g, 52% based on pure **21**). ^{1}H NMR (hydrochloride) (DMSO-d_6) δ 8.85 (broad s, 2H), 8.08 (d, 2H), 7.58 (d, 2H), 6.96 (d, 1H), 6.81–6.69 (m, 2H), 3.91 (t, 2H), 3.68 (s, 3H), 3.67 (s, 3H), 2.98 (t, 2H), 2.64 (s, 3H), 1.99–1.81 (m, 2H).

Method H (Scheme 8)
N-[3-(7,8-Dimethoxy-2,3,4,5-tetrahydro-2-oxo-1*H*-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide (50)

Step 1: N-[3-[N-(3,4-Dimethoxyphenyl)-N-phenylmethyl]-propylamino]-7,8-dimethoxy-2,3,4,5-tetrahydro-2-oxo-1*H*-3-benzazepin (23). A mixture of **22**[24] (0.42 g, 1.4 mmol) and N-benzyl-4-aminoveratrole[25] (1.02 g, 4.2 mmol) was heated neat at 100 °C for 1.5 h. After cooling the mixture was dissolved in AcOEt (50 mL) and the solution washed with water (2×20 mL). The organic phase was extracted with 1 N HCl (3×20 mL). The acidic aqueous phase was washed with AcOEt (20 mL), alkalized with 30% aqueous NaOH and then extracted with AcOEt (3×20 mL). The organic phase was washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (SiO_2, CH_2Cl_2:CH_3OH, 98:2) to afford **23** (0.28 g, 40%). ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5H), 6.73 (d, 1H), 6.59 (s, 1H), 6.52 (s, 1H), 6.34 (d, 1H), 6.24 (dd, 1H), 4.41 (s, 2H), 3.84–3.75 (m, 14H), 3.62 (m, 2H), 3.46 (t, 2H), 3.32 (t, 2H), 2.98 (m, 2H), 1.87 (m, 2H).

Step 2: N-[3-N-(3,4-Dimethoxyphenyl)-propylamino]-7,8-dimethoxy-2,3,4,5-tetrahydro-2-oxo-1*H*-3-benzazepin (24). A solution of **23** (1.6 g, 3.2 mmol) in a mixture of AcOH (6 mL) and CH_3OH (50 mL) was hydrogenated at rt and room presure over Pd/C (0.2 g). When the hydrogen absorption ceased the catalyst was filtered off and the solution was diluted with water. After alkalinization with 30% aq NaOH, the mixture was extracted with AcOEt (2×100 mL), the organic phase was washed with water (100 mL) and dried over $MgSO_4$. Concentration of the solvent afforded crude **24** (1.23 g, 93%), which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$) δ 6.72 (d, 1H), 6.60 (s, 1H), 6.55 (s, 1H), 6.25 (d, 1H), 6.13 (dd, 1H), 3.85–3.79 (m, 14H), 3.72 (t, 2H), 3.54 (t, 2H), 3.07 (m, 4H), 1.84 (m, 2H).

Step 3: N-[3-(7,8-Dimethoxy-2,3,4,5-tetrahydro-2-oxo-1*H*-3-benzazepin-3-yl)-propyl]-N-(3,4-dimethoxyphenyl)-4-nitrobenzamide (50). An ice cooled solution of **24** (1.18 g, 2.8 mmol) and NEt_3 (0.32 g, 3.1 mmol) in $CHCl_3$ (30 mL) was treated dropwise with a solution of **7** in $CHCl_3$ (5 mL) and stirring was maintained at rt for additional 4 h. The mixture was diluted with CH_2Cl_2 (100 mL) and washed successively with 1 N HCl (2×50 mL), 1 N NaOH (2×50 mL) and water (2×50 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The foamy residue was triturated in diethylether to afford an amorphous solid, which was dissolved in CH_3OH (5 mL) and re-precipitated by slow addition of diethylether (50 mL), to afford **50** as yellow crystals (mp 126 °C, 0.96 g, 61%). ^{1}H NMR (DMSO-d_6) δ 8.24 (d, 2H), 7.56 (d, 2H), 6.92–6.74 (m, 5H), 4.68 (s, 2H), 3.80–3.63 (m, 14H), 3.25–3.05 (m, 4H), 2.94 (t, 2H), 2.02 (m, 2H).

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