Eur J Med Chem (1997) 32, 843–868

Pharmacological profile of a novel series of NK_1 antagonists. In vitro and in vivo potency of benzimidazolone derivatives

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(Received 20 March 1997; accepted 25 June 1997)

Summary — By low throughput examination of our chemical library, compound **7** was selected as a lead NK_1 antagonist with a K_i of 7.1 nM. Modifications of its structure led to the finding that the in vitro potency could be markedly enhanced by disubstituting the anilino phenyl ring as in compounds **13** or **22**. Human binding data correlated rather well with results obtained with in vitro animal smooth muscle preparations. Several agents proved to possess antinociceptive properties as exemplified in the hot-plate test in mice; compound **13** was the most active with ED_{50} of 0.001 and 0.3 mg/kg after iv and po administration respectively. Furthermore, antagonist **71** was found to be a potent inhibitor of SP-induced bronchoconstriction in guinea-pigs with an ED_{50} between 0.1 and 0.03 mg/kg iv. Furthermore, upon oral administration, **71** was observed to be active in a model of SP-induced bronchial hypersensitivity in mice, with an ID_{50} of around 3 mg/kg.

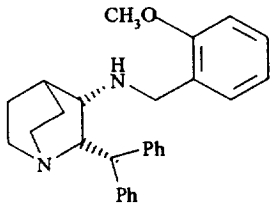
benzimidazolone / tachykinin / NK_1 / antinociceptive / bronchoconstriction

Introduction

Under physiological conditions, specific processing endopeptidases are responsible for the release of substance P, as well as neurokinin A and B. These tachykinins interact with three G-protein coupled receptors NK_1, NK_2 and NK_3 [1]. The first member of this triad has been shown to be involved in processes of neurogenic inflammation and nociception: the release of tachykinins at the central nervous system level is part of the transmission of nociceptive signals in the spinal cord from the periphery, especially in dorsal horn neurons [2]. Since SP antagonists can block behaviour elicited by peripheral noxious stimuli, it has been hypothesized that selective antagonists for the neurokinin receptors could be of interest in the treatment of pain [3]. At the periphery, release of neurokinins causes vasodilation, plasma extravasation, salivary gland secretion, activation of the immune system, and mast-cell degranulation [4]. Besides potential treatment of gastrointestinal disorders, migraine, emesis, or lesions of the urinary system, it has been suggested that NK_1 receptor antagonists would offer advantages in the treatment of various inflammatory diseases of the airways and in asthma: actually, the release of tachykinins from lung sensory nerve endings (C-fibers) has been implicated in non-adrenergic non-cholinergic (NANC) bronchoconstriction, neurogenic mucosal plasma extravasation and mucus hypersecretion in the airways [5, 6].

The structures of a great number of tachykinin antagonists, peptidic or not, have been disclosed in the recent years [7]. Among the most interesting non-peptidergic antagonists described, CP-96345 **1** [8] and CP-99994 **2** [9], SR 140333 **3** [10], RPR 100893 **4** [11], L-737488 **5** [12], or LY 303870 **6** [13] are representative of the large structural diversity found in this class of compounds. We report herein our efforts toward the discovery of a novel structural family of potent tachykinin antagonists as well as their in vivo potency, first in a classical pain assay and second in a model of SP-induced bronchoconstriction.

*Correspondence and reprints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Ph

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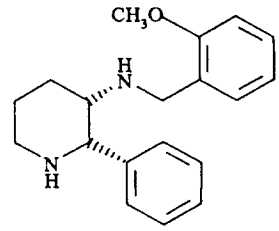
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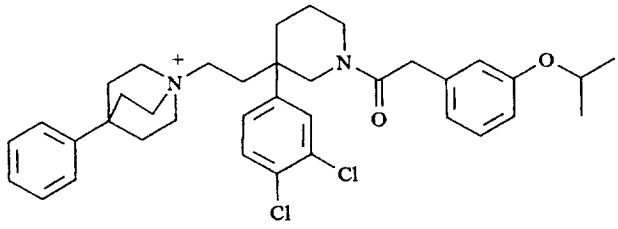
2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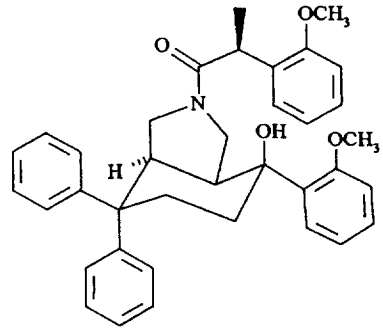
3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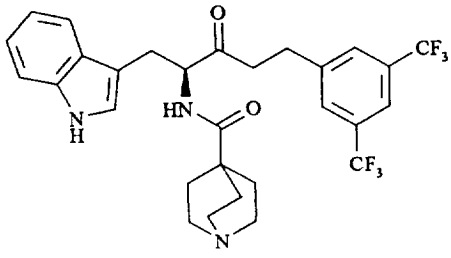
OH
OCH3
H

4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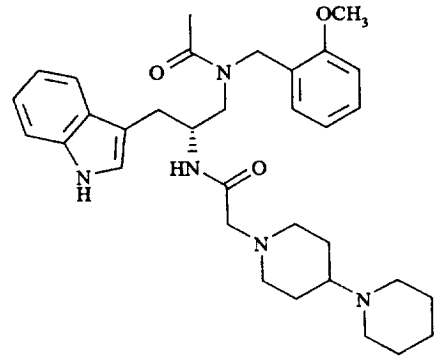
HN
O
N
H
CF3
N

5


OCH3
O
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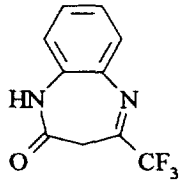
N
N

6

Chemistry

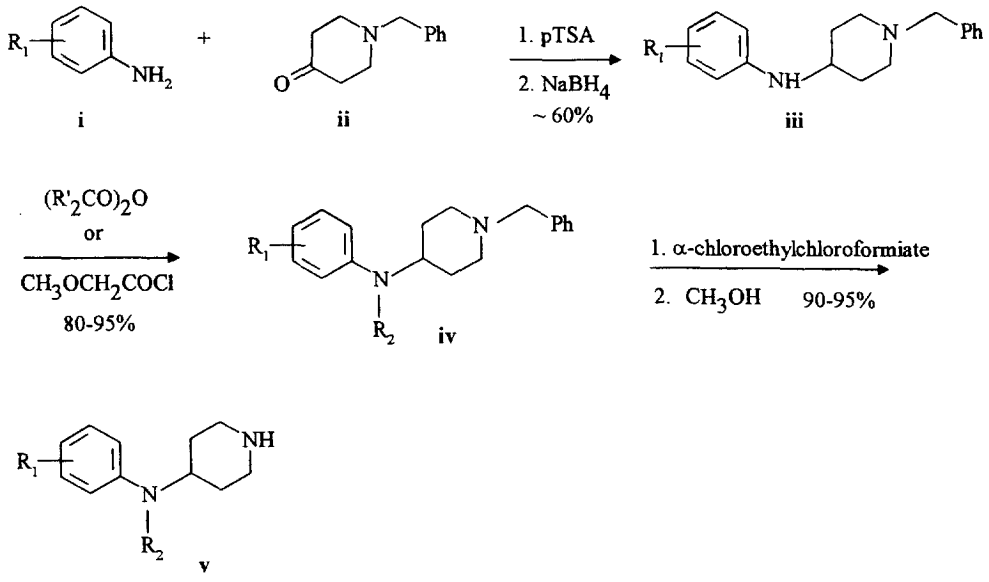
The compounds described in tables I–IV were prepared by the methods oulined in schemes 1 and 2. A conveniently substituted aniline **i** was first condensed with 1-benzyl-4-piperidinone **ii** under classical reductive amination conditions (pTSA, toluene, then $NaBH_4$ in methanol). Acylation of **iii** was then performed, using either an anhydride or an acid chloride to yield intermediate **iv** after crystallization. Debenzylation of the piperidine ring using hydrogen and Pd–C was used when no halogen atom was present on the aromatic ring; this catalytic method was replaced by α-chloroethylchloroformate in dichloromethane, followed by methanolic hydrolysis when R_1 was a fluorine or a chlorine atom. In both cases, yields of intermediate **v** were found to be superior to 90% without any purification.

The preparation of the second half of the molecules started with the condensation of properly substituted orthophenylene diamines **vi** with a keto ester derivative **vii** in xylene as illustrated in scheme 2; this reaction went through a 2,3-dihydro-(1*H*)-1,5-benzoazepin-2-one intermediate **viii**, which reacted via a [1,3]-sigmatropic thermic rearrangement to afford the benzimidazolone **ix** [14, 15]. In one case only, this intermediate could be isolated after crystallization and caracterized as **viii-a**.

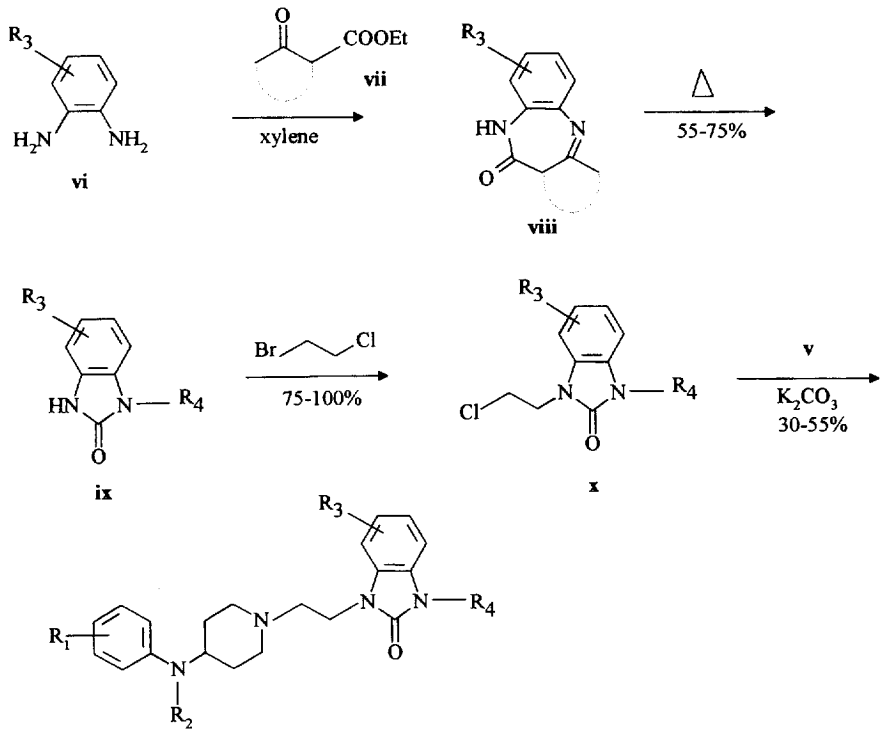


viii-a

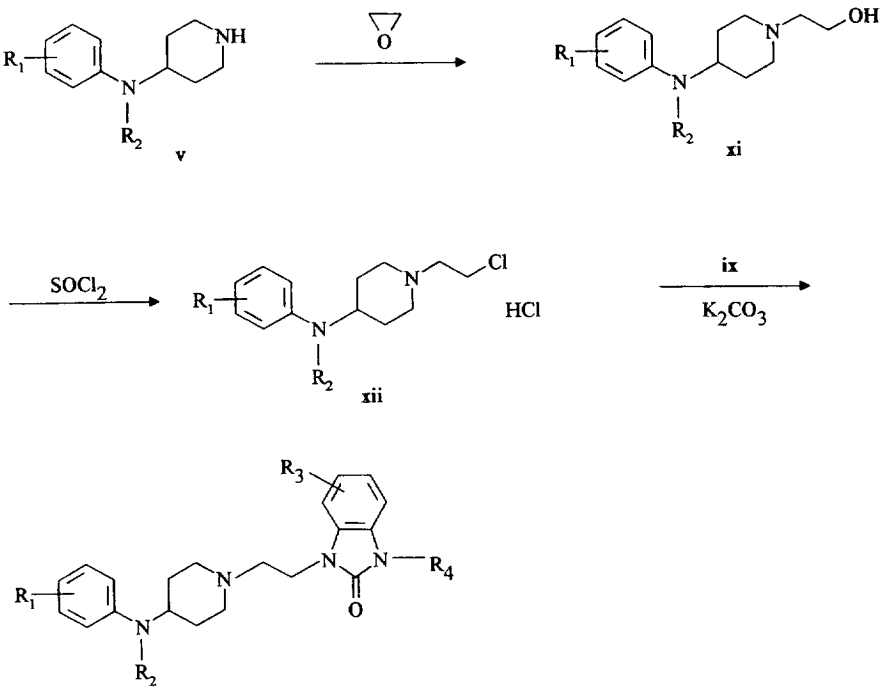
The chloroethyl side chain was introduced by reacting intermediate **ix** with $BrCH_2CH_2Cl$ and K_2CO_3 in DMF: the crude resulting compound **x** was alkylated with appropriate **v**, previously obtained in scheme 1, again in the presence of K_2CO_3 in DMF, to give the desired final antagonists which were purified by silica gel chromatography. The major drawback of this chemical approach was the formation of a large amount (20–50%) of a side product at the very last step of the synthesis: this unwanted compound was isolated and caracterized as the corresponding carbamate [16] of the piperidino tertiary amine (compound **45** vs compound **25**). In order to avoid the formation of this undesired by-product, a second approach was studied (scheme 3) in which intermediate **v** was condensed with ethylene oxide to give **xi** in high yield. Chlorination of the side chain was performed using thionyl chloride in toluene to give **xii** as the



Scheme 1.



Scheme 2.

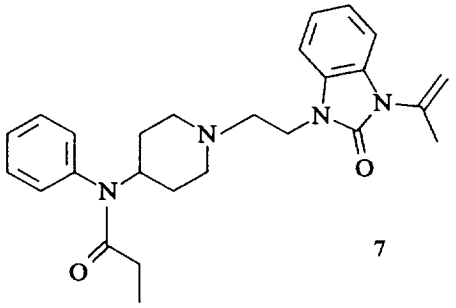


Scheme 3.

hydrochloride; chlorine displacement with intermediate **ix** obtained in scheme 2 yielded under K_2CO_3/DMF conditions the final desired antagonists after silica gel chromatography. Unfortunately, the global yield for this alternative route was not improved as compared to the previous one, probably due to the purifications of the intermediate and final derivatives which proved to be much more tedious than in the first pathway.

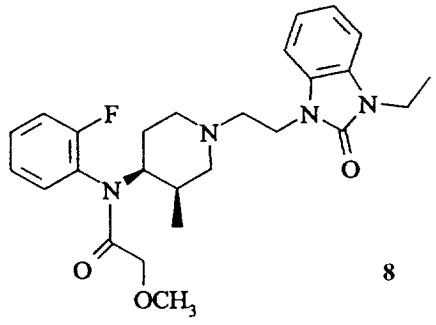
In vitro studies

Screening was based on binding affinity studies both on NK_1 and NK_2 receptors. For most of the compounds, this work was paralelled by evaluation of their antagonistic potency on specific isolated organs: rabbit *vena cava* (RVC) for NK_1 receptor, rabbit pulmonary artery (RPA) for NK_2 receptor and rat portal vein (RPV) for NK_3 receptor [17, 18]. Low-volume screening of our chemical library (100 compounds) on NK_1 and NK_2 receptor binding assays led to the identification of **7** as a relatively potent and selective NK_1 antagonist, with a K_i of 7.1 and 6300 nM respectively:



7

The only structurally related compounds described in the literature are ethyl benzimidazolones, exemplified by derivative **8**, which are claimed to be potent analgesics in the hot-plate mouse assay [19]. No interaction with the tachykinin receptors was reported, and we were delighted to find that compound **8** possessed only micromolar affinity for NK_1 receptor and no affinity at all for the NK_2 receptor:



8

In order to improve the potency of lead compound **7**, classical structural modifications were undertaken to investigate the role of the different functionalities present in the molecule.

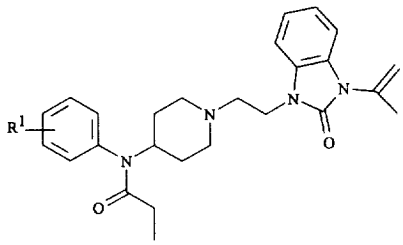
Modifications on the anilino phenyl ring (table I)

Substitution by a halogen atom (chloro or fluoro) had virtually no influence both on affinity and NK_1 antagonist activity (compounds **9**, **10**, **15**). Other monosubstitutions (CH_3, OCH_3) were also without influence or even rather deleterious for in vitro binding activity. Disubstitution gave dramatically different results according to the position of the substituting group: 2,4- and 2,5-substitutions of the phenyl ring proved to be very deleterious for NK_1 affinity (compounds **11** and **12**). In contrast, the 3,4-dichloro substitution was found to be very beneficial for NK_1 antagonist activity and proved to be superior to the corresponding 3,5-substitution (0.99 nM for compound **13** and 6 nM for compound **14**). The other 3,4-disubstitutions gave compounds with K_i varying from 1.1 (**19**: 3,4-di CH_3) to 17 nM (**22**: 3,4-di OCH_3). In spite of this moderate affinity value obtained with **22**, a strong pA2 value was found on the rabbit *vena cava* (9.7); actually, **22** proved to be one of the most potent compounds screened on this isolated organ assay, but all the 3,4- and 3,5-substituted derivatives had pA2 > 8.5. The phenyl ring could also be replaced by a naphthyl ring without loss in binding affinity (compound **24**); in contrast, a reduced potency was noted for the pyridine ring containing derivative **25**. Furthermore, all these compounds were selective NK_1 antagonists, since a much lower activity was found on NK_2 and NK_3 specific isolated organs (respectively RPA and RPV), with pA2 < 6.

Modifications on the anilino nitrogen atom (table II)

When the propionyl side chain was replaced by a butyryl side chain, the NK_1 antagonist activity was conserved (pA2 = 8.25 for **26** as compared to 7.6–8.0 for **7**). Replacement of the amide group by a urea as in **27** and **32** resulted in a 20- to 50-fold decrease in K_i. Compound **28** in which the side chain was cyclized on the anilino phenyl ring to give a tetrahydroquinolinone was less effective than its corresponding opened analog. Suppressing completely the side chain (compound **29**) proved to be very deleterious for affinity; other modifications on this side chain (acetyl: compounds **30** and **35**, benzoyl: **31**, aminoacetyl: **33** and **36**, methoxyacetyl: **34**) gave very potent and selective NK_1 antagonists, with K_i around 1 nM and pA2's culminating at 9.71. The bulky phthalimidoacetyl containing derivative **37** was less potent with a K_i of 23 nM.

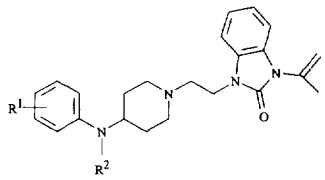
Table I. Physical data and in vitro results for compounds **7–25**.

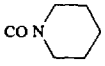
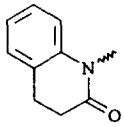
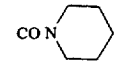


Compound	*R[1]*	*Formula analysis*[a]	*Mp (°C) recryst solv*	*NK_1*		*NK_2*		*NK_3*
				K_i (nM)	*pA 2*[k]	*K_i (nM)*	*pA 2*	*pA 2*
7	H	$C_{26}H_{32}N_4O_2$ C[b], H, N	136 cyclohexane	7.1	7.6–8.0	6300	5.64	4.60
9	3-Cl	$C_{26}H_{31}ClN_4O_22$ C, H, N, Cl	128 pentane	2.8	7.97	2600	in[l]	in
10	4-Cl	$C_{26}H_{31}ClN_4O_2$ C, H, N, Cl	128 pentane	12	8.67	480	in	in
11	2,4-diCl	$C_{26}H_{30}Cl_2N_4O_2$ C[c], H, N[d], Cl[e]	amorphous	85		2000		
12	2,5-diCl	$C_{26}H_{30}Cl_2N_4O_2$ C, H, N, Cl	148 pentane	220		2000		
13	3,4-diCl	$C_{26}H_{30}Cl_2N_4O_2$ C[f], H, N, Cl	156 pentane	0.99	9.3	> 1000	5.10	5.40
14	3,5-diCl	$C_{26}H_{30}Cl_2N_4O_2$ C[g], H, N, Cl[h]	170 pentane	6	9.3	> 10000	in	5.3–5.7
15	4-F	$C_{26}H_{31}FN_4O_2$ C, H, N	114 pentane	1.7	8.65	820	in	in
16	3,4-diF	$C_{26}H_{30}F_2N_4O_2$ C[i], H, N	166 pentane	6.1	8.67	1300	5.98	5.67
17	3-Cl-4-F	$C_{26}H_{30}ClFN_4O_2$ C, H, N, Cl	130–132 pentane	2.3	< 8.70	3000	5.3	5.30–5.38
18	4-CH_3	$C_{27}H_{34}N_4O_2$ C, H, N	110 pentane	9.6		> 10000		
19	3,4-diCH_3	$C_{28}H_{36}N_4O_2$ C, H, N	138 pentane	1.1	8.66	1100	6.12	5.66
20	3-Cl-4-CH_3	$C_{27}H_{33}ClN_4O_2$ C, H, N, Cl	138–140 pentane	4.4	9.68	970	5.98	5.68
21	3-OCH_3	$C_{27}H_{34}N_4O_3$ C, H, N	110–112 pentane	26		3800		
22	3,4-diOCH_3	$C_{28}H_{36}N_4O_4$ C, H, N	145 pentane	17	9.70	> 10000	in	5.69–5.99
23	3-Cl-4-OCH_3	$C_{27}H_{33}ClN_4O_3$ C, H, N, Cl	150–152 pentane	5	< 9.3	> 1000	5.00	5.22–5.69
24	Naphth-2-yl	$C_{30}H_{34}N_4O_2$ C[j], H, N	118–120 pentane	4.8		> 10000		
25	Pyridin-4-yl	$C_{25}H_{31}N_5O_2$ C, H, N	106 pentane	240	7.24	> 10000	5.46	in

[a]Compounds gave satisfactory analyses (± 0.4%) unless otherwise indicated. [b]C: found, 72.19; calc, 71.74. [c]C: found, 61.59; calc, 62.28. [d]N: found, 10.88; calc, 11.47. [e]Cl: found, 14.69; calc, 14.14. [f]C: found, 61.79; calc, 62.28. [g]C: found, 61.83; calc, 62.28. [h]Cl: found, 14.41; calc, 11.14. [i]C: found, 66.18; calc, 66.65. [j]C: found, 74.13; calc, 74.66. [k]pA2 represents the concentration of antagonist that reduces the effect of a double dose of agonist to that of a single dose. [l]in: inactive.

Table II. Physical data and in vitro results for compounds **26–37**.



Compound	R^1	R^2	*Formula analysis*[a]	*Mp (°C) recryst solv*	NK_1		NK_2		NK_3
					K_i *(nM)*	*pA 2*	K_i *(nM)*	*pA 2*	*pA 2*
7	H	COEt	$C_{26}H_{32}N_4O_2$ C, H, N	136 cyclohexane	7.1	7.6–8.0	6300	5.64	4.60
26	H	COPr	$C_{27}H_{34}N_4O_2$ C, H, N	202 CH_2Cl_2–CH_3OH	11	8.25	> 1000	5.00	5.95
27	H		$C_{29}H_{37}N_5O_2$ C, H, N[b]	amorphous	350	7.69	1200	in	in
28			$C_{26}H_{30}N_4O_2$ C, H, N	175–182 iPr_2O	180	6.63	1700	in	in
13	3,4-diCl	COEt	$C_{26}H_{30}Cl_2N_4O_2$ C[c], H, N, Cl	156 pentane	0.99	9.3	> 1000	5.10	5.40
29	3,4-diCl	H	$C_{23}H_{26}Cl_2N_4O$ C, H, N[d], Cl	amorphous	250	6.65	7000	in	5.20–5.55
30	3,4-diCl	$COCH_3$	$C_{25}H_{28}Cl_2N_4O_2$ C, H, N, Cl	175 CH_2Cl_2–C_2H_5OH	1.2	8.69	3900	in	5.68
31	3,4-diCl	COPh	$C_{30}H_{30}Cl_2N_4O_2$ C, H, N, Cl	158 pentane	0.87	8.86	10000	in	5.34–6.34
32	3,4-diCl		$C_{29}H_{35}Cl_2N_5O_2$ C, H, N[e], Cl	amorphous	19	7.60	800	in	5.74–6.70
33	3,4-diCl	$COCH_2NH_2$	$C_{25}H_{29}Cl_2N_5O_2$ ND[f]	162 $iPrO_2$	0.46	9.4	4700	in	5.30–5.70
34	3,4-diCl	$COCH_2OCH_3$	$C_{26}H_{30}Cl_2N_4O_3$ ND	amorphous	0.85	9.71	1300	in	5.71
20	3-Cl-4-CH_3	COEt	$C_{27}H_{33}ClN_4O_2$ C, H, N, Cl	138–140 pentane	4.4	9.68	970	5.98	5.68
35	3-Cl-4-CH_3	$COCH_3$	$C_{26}H_{31}ClN_4O_2$ C, H, N, Cl	146 pentane	2.8		3000		
36	3-Cl-4-CH_3	$COCH_2NH_2$	$C_{26}H_{32}ClN_5O_2$ C[g], H, N, Cl	134 pentane	0.2	9.3	10000	in	5.38–6.29
37	3-Cl-4-CH_3	$COCH_2Pht$	$C_{34}H_{34}ClN_5O_4$ C, H, N[h], Cl	amorphous	23		800		

[a]Compounds gave satisfactory analyses (± 0.4%) unless otherwise indicated. [b]N: found, 13.64; calc, 14.36. [c]C: found, 61.79; calc, 62.28. [d]N: found, 12.03; calc, 12.58. [e]N: found, 11.87; calc, 12.58. [f]ND: not determined, but satisfactory results by high-resolution MS analysis were obtained. [g]C: found, 63.67; calc, 64.79. [h]N: found, 10.70; calc, 11.44.

Table III illustrates representative examples of atypical structures: the propionyl amino moiety was completely suppressed (**38**), extruded to give a secondary acetamide (**39**), cyclized to give a spiro-imidazolinone (**40**), or phenyl and methyl were exchanged (**41**): these four compounds gave a K_i higher than 10 nM.

Modifications on the piperidino ethyl moiety (table IV)

As illustrated by compounds **42** and **43**, quaternization of the nitrogen on the piperidine ring resulted in a 4- to 7-fold decrease in NK_1 binding affinity, although activity was conserved at the isolated organ level. The dichloro-substituted analog **43** was found to be more potent than its non-substituted counterpart on binding affinity. Furthermore, using a 3-carbon chain between the piperidine ring and the benzimidazolone moiety (compound **44**) decreased the binding affinity value, but not the pA2 value. Inserting a carbamoyl function within this chain gave compound **45** which was completely devoid of affinity for NK_1 receptor as compared to its *N*-alkyl counterpart **25**.

Modifications on the benzimidazolone phenyl ring (table V)

Introducing a methyl group in position 7 (compound **46**) or two chlorine atoms in positions 5 and 6 (compound **48**) proved to be favourable for in vitro NK_1 binding affinity. This was particularly confirmed by isolated-organ studies for compound **48** which gave a pA2 of 9.3. The 4-nitro group of compound **47** caused a major decrease in potency, but a trifluoromethyl group, either in position 5, 6 or 7 (compounds **50**, **51**, **52**, respectively), appeared to be only slightly detrimental for activity when compared to the non-substituted compound **13**. Replacing the phenyl ring by naphthyl (**49** and **55**) was virtually without effect on activity, as well as introducing a nitrogen atom in the phenyl ring to give both imidazopyridin-2-ones **53** and **54**. Again, all the derivatives of this group were shown to be selective NK_1 antagonists.

Modifications on the benzimidazolone 3-nitrogen (table VI)

Curiously, the non-substituted analog **56** was completely devoid of affinity for the NK_1 binding site, while its dichloro counterpart **65** retained some potency on RVC (pA2 = 8.70). Modifications of the isopropylidene moiety to give derivatives **57–62**, **64** and **70** resulted in a significant loss of potency. The level of activity on isolated RVC was maintained in the same range as for the reference derivatives **7** and **13** when the isopropylidene was substituted by a methyl or a trifluoromethyl group to give compounds **66**, **67** and **68**. Interestingly, this was the same when the double bond of the isopropylidene moiety was included into a five-membered ring to give compounds **63**, **69** and **71**. Again, no significant NK_2 or NK_3 antagonist activities were detected for the compounds of this group. Three atypical derivatives are described at the bottom of table VI; in **72**, an imidazolinic ring was built using an imino function in place of the carbonyl group of the benzimidazolone [20]: this compound was found to be moderately active in the binding assay. Compounds **73** and **74**, in which the nitrogen in position 3 was respectively replaced by an oxygen atom or a carbonyl function were also poorly active.

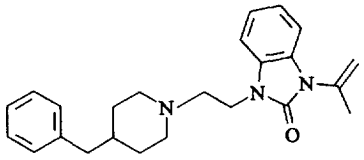
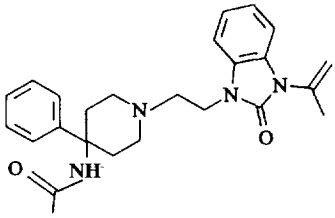
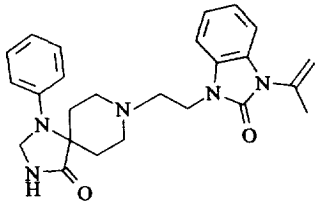
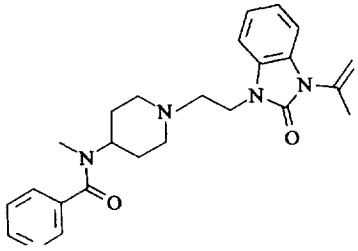
Selectivity

An extensive specificity analysis was performed with antagonist **13** on a panel of 14 receptors [21] where K_i values were higher than 10^{-6} M, except on the 5HT1A site (1.3×10^{-7} M). Affinities for sodium (Veratridine) and calcium (Nifedipine) channels were found to be 2.5 and 1.0 μM, respectively.

Affinity studies for the μ opioid receptor subtype were performed for some of the most promising derivatives and results are summarized in table VII. Compound **7** clearly exemplifies how vital the isopropylidene group is to decreasing the μ binding potency compared to the ethyl group in reference derivative **8**. Their respective K_i for this receptor subtype was 250 nM and 0.37 nM. Generally, a monosubstitution on the anilino phenyl ring of lead compound **7** proved to be slightly favourable to μ affinity. In contrast, disubstitution resulted in a loss of μ affinity (compounds **13**, **22**). Increasing the size of the side chain on the nitrogen atom was detrimental for affinity (compounds **32**, **33**, **34**, **37**). Substitution on the aromatic ring of the benzimidazolone had little effect with the exception of the $5\text{-}CF_3$ in compound **50** which resulted in a dramatic decrease of the μ affinity. A notable diminution in μ affinity was also seen upon introduction of a heteroatom in the aromatic ring as in **54** and **55**. Finally, replacing the isopropylidene moiety by another small group (acetyl in **57** or cyclopropyl in **58**) improved the affinity for the μ opioid receptor. In contrast, increasing the size of this substituent (1-phenylvinyl in **70** or cyclopentenyl in **69** and **71**) resulted in a 10-fold decrease in μ affinity.

As a summary of these in vitro investigations, it is interesting to note that several compounds described above reach the same level of potency as the reference antagonists: in our hands, CP 99994 (**2**), SR 140333

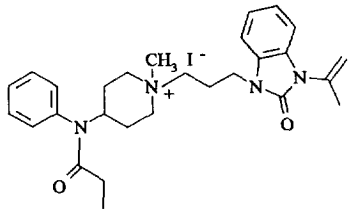
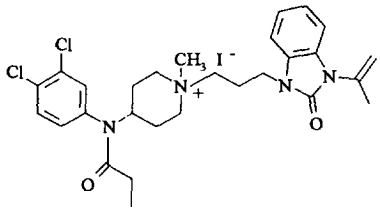
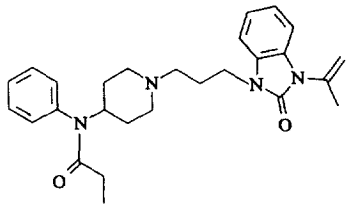
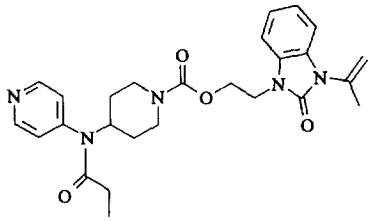
Table III. Physical data and in vitro results for compounds **38–41**.

Compound		*Formula analysis*[a]	*Mp (°C) recryst solv*	*NK_1*		*NK_2*		*NK_3*
				K_i (nM)	*pA 2*	*K_i (nM)*	*pA 2*	*pA 2*
38		$C_{24}H_{29}N_3O$ C, H, N	amorphous	750		> 10000	4.60	5.57
39		$C_{25}H_{30}N_4O_2$ C, H, N	amorphous	720	5.69	> 100000	< 4.7	6.00
40		$C_{25}H_{29}N_5O_2$ C[b], H, N[c]	146–148 pentane	15		> 100000		
41		$C_{25}H_{30}N_4O_2$ C[d], H, N	120–122 pentane	41	6.62	8000	in	5.22

[a]Compounds gave satisfactory analyses (± 0.4%). [b]C: found, 69.58; calc, 69.15. [c]N: found, 16.23; calc, 15.65. [d]C: found, 71.74; calc, 70.92.

(**3**) and RPR 100893 (**4**) gave K_i of 0.25, 0.2 and 25.1 nM on the NK_1 receptor respectively. Within our series, 3,4-substitution on the anilino phenyl ring was found to be very beneficial for obtaining a strong antagonistic activity at the NK_1 receptor: **13** (3,4-dichloro), **20** (3-Cl-4-CH_3), **22** (3,4-diOCH_3) and **23** (3-Cl-4-OCH_3) were among the most potent antagonists prepared. The substitution pattern on the anilino nitrogen played a major role as well: increasing too much the size of the chain was found to be deleterious for activity; the best compromise was found with the methoxyacetyl (compounds **34** and **71**), the aminoacetyl (compounds **33** and **36**) and of course the propionyl (compound **13**) side chains. Except for the 7-CH_3 and the 5,6-dichloro substitutions (compounds **46** and **48**), modifications on the benzimidazolone phenyl ring proved to be of little interest. Similar conclusions could be drawn from the variations performed in order to replace the isopropylidene moiety: only the cyclopentene-containing derivative **71** was found to be as active as its counterpart. Furthermore, as the reference derivatives **2**, **3** and **4**, our most active NK_1 antagonists were virtually devoid of NK_2 and μ opioid binding affinity.

Table IV. Physical data and in vitro results for compounds **42–45**.

Compound	*Formula analysis*[a]	*Mp (°C) recryst solv*	*NK$_1$*		*NK$_2$*		*NK$_3$*
			K_i (nM)	*pA 2*	*K_i (nM)*	*pA 2*	*pA 2*
42 	$C_{27}H_{35}N_4O_2$, I C, H, N	216 (dec) acetone	50	7.06	> 10000		
43 	$C_{27}H_{33}Cl_2N_4O_2$,I ND[b]	amorphous	4.6		1000		
44 	$C_{27}H_{34}N_4O_2$ C[c], H, N	150–152 diethyl ether	170	8.26	> 1000		
45 	$C_{26}H_{31}N_5O_4$ C[d], H, N[e]	amorphous	5000		> 10000		

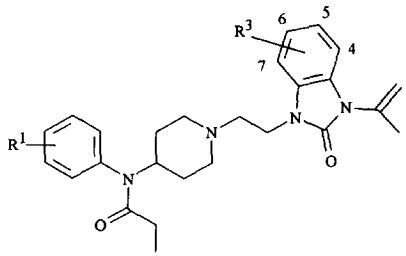
[a]Compounds gave satisfactory analyses (± 0.4%) unless otherwise indicated. [b]ND: not determined, but satisfactory results by high-resolution MS analysis were obtained. [c]C: found, 67.13; calc, 66.41. [d]C: found, 65.39; calc, 65.89. [e]N: found, 14.66; calc, 14.13.

In vivo studies

Antinociceptive potency (table VIII)

In order to address the issue of in vivo antinociceptive potency of our most promising antagonists, we tested them on the hot-plate model in mice, using the method described by Eddy and Leimbach [22]. In our hands, the reference antagonists **2** and **3** behave as potent antinociceptive substances, with ED_{50} of 0.006 and 1.5 mg/kg respectively after iv administration. Lead compound **7** was also found to be active, but the most interesting finding was the dramatic enhancement of potency which accompanied the 3,4-dichloro-substitution on the anilino phenyl ring in compound **13**: ED_{50} culminated at 0.001 mg/kg iv. In comparison, morphine gave an ED_{50} of 0.3 mg/kg. Further-

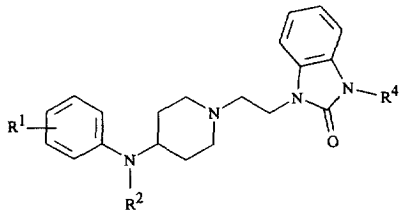
Table V. Physical data and in vitro results for compounds **46–55**.



Compound	R^1	R^3	*Formula analysis*[a]	*Mp (°C) recryst solv*	NK_1		NK_2		NK_3
					K_i (nM)	pA 2	K_i (nM)	pA 2	pA 2
7	H	H	$C_{26}H_{32}N_4O_2$ C, H, N	136 cyclohexane	7.1	7.6–8.0	6300	5.64	4.60
46	H	7-CH_3	$C_{27}H_{34}N_4O_2$ C[b], H, N	150–152 ethanol	0.69	8.25	> 1000	5.30	6.75
47	H	4-NO_2	$C_{26}H_{31}N_5O_4$ ND[c]	162 CH_2Cl_2–C_2H_5OH	1300		> 10000		
48	H	5,6-diCl	$C_{26}H_{30}Cl_2N_4O_2$ C, H, N[d], Cl	amorphous	0.69	9.3	340	5.00	5.10
49	H	naphth[2,3-*d*] imidazol-2-one	$C_{30}H_{34}N_4O_2$ C, H, N	173–175 CH_2Cl_2–C_2H_5OH	5.2		> 100000		
13	3,4-diCl	H	$C_{26}H_{30}Cl_2N_4O_2$ C[e], H, N, Cl	156 pentane	0.99	9.3	> 1000	5.10	5.40
50	3,4-diCl	5-CF_3	$C_{27}H_{29}Cl_2F_3N_4O_2$ ND	amorphous	7.3	8.76	3000	in	5.66–5.80
51	3,4-diCl	6-CF_3	$C_{27}H_{29}Cl_2F_3N_4O_2$ ND	amorphous	15	8.40	3000	in	5.75–5.80
52	3,4-diCl	7-CF_3	$C_{27}H_{29}Cl_2F_3N_4O_2$ C, H, N, Cl	amorphous	4.4	8.36	> 1000	5.35	in
53	3,4-diCl	imidazo[4,5-*b*] pyridin-2-one	$C_{25}H_{29}Cl_2N_5O_2$ ND	amorphous	3.8	8.70	580	in	in
54	3,4-diCl	imidazo[4,5-*e*] pyridin-2-one	$C_{25}H_{29}Cl_2N_5O_2$ C[f], H, N[g], Cl	amorphous	0.65	9.00	1500	in	5.82
55	3,4-diCl	napht[2,3-*d*] imidazol-2-one	$C_{30}H_{32}Cl_2N_4O_2$ C[h], H, N, Cl[i]	185-190 $iPrO_2$	5.7	8.74	4400	in	in

[a]Compounds gave satisfactory analyses (± 0.4%) unless otherwise indicated. [b]C: found, 71.85; calc, 72.62. [c]ND: not determined, but satisfactory results by high-resolution MS analysis were obtained. [d]N: found, 10.66; calc, 11.17. [e]C: found, 61.79; calc, 62.28. [f]C: found, 59.19; calc, 59.76. [g]N: found, 13.28; calc, 13.85. [h]C: found, 64.72; calc, 65.33. [i]Cl: found, 13.62; calc, 12.86.

Table VI. Physical data and in vitro results for compounds **56–74**.



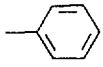
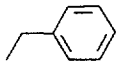
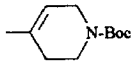
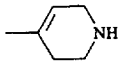
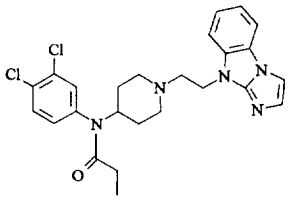
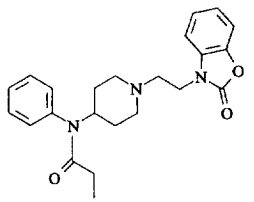
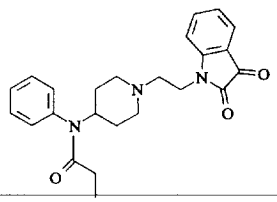
Compound	*R¹*	*R²*	*R⁴*	*Formula analysis*[a]	*Mp (°C) recryst solv*	*NK₁*		*NK₂*		*NK₃*
						K_i (nM)	*pA 2*	*K_i (nM)*	*pA 2*	*pA 2*
7	H	COEt		$C_{26}H_{32}N_4O_2$ C, H, N	136 cyclohexane	7.1		6300	5.64	4.60
56	H	COEt	H	$C_{23}H_{28}N_4O_2$ C, H, N[b]	205 H_2O	3300		> 100000		
57	H	COEt		$C_{25}H_{30}N_4O_3$ ND[c]	175–177 CH_2Cl_2	3900		> 10000		
58	H	COEt		$C_{26}H_{32}N_4O_2$ C, H, N	98–100 hexane	120		> 10000		
59	H	COEt		$C_{29}H_{32}N_4O_2$ C, H, N	176–180 H_2O	37	6.7	2400	5.0	5.71–6.00
60	H	COEt		$C_{30}H_{34}N_4O_2$ C[d], H, N	amorphous	550		1800		
61	H	COEt		$C_{33}H_{43}N_4O_2$ C, H, N	amorphous	510	7.76	200	in	in
62	H	COEt		$C_{29}H_{32}N_5O_4$ ND	amorphous	5700		> 10000		
63	H	COEt		$C_{28}H_{34}N_4O_2$ C[e], H, N	amorphous	49	8.66	> 100000	in	in
64	H	COEt		$C_{31}H_{34}N_4O_2$ C[f], H, N	amorphous	690		1500		
13	3,4-diCl	COEt		$C_{26}H_{30}Cl_2N_4O_2$ C[g], H, N, Cl	156 pentane	0.99	9.30	> 1000	5.10	5.40

Table VI. *Continued.*

65	3,4-diCl	COEt	H	$C_{23}H_{26}Cl_2N_4O_2$ C, H, N[h], Cl[i]	amorphous	100	8.70	> 1000	in	5.70
66	3,4-diCl	COEt		$C_{26}H_{27}Cl_2F_3N_4O_2$ ND	amorphous	14	< 8.34	> 1000		
67	3,4-diCl	COEt		$C_{27}H_{32}Cl_2N_4O_2$ ND	amorphous	3.3	8.71	290	5.31	in
68	3,4-diCl	COEt		$C_{27}H_{32}Cl_2N_4O_2$ C, H, N[k], Cl	131 iPrOH	7.9	8.71	830	in	in
69	3,4-diCl	COEt		$C_{28}H_{32}Cl_2N_4O_2$ Cl, H, N[m], Cl	155–157 EtOAc–AcOH	3.6	9.02	1000	in	5.72
70	3,4-diCl	COEt		$C_{31}H_{32}Cl_2N_4O_2$ C[n], H, N[o], Cl	amorphous	110		1000		
34	3,4-diCl	$COCH_2$-OCH_3		$C_{26}H_{30}Cl_2N_4O_3$ ND	amorphous	0.85	9.71	1300	in	5.71
71	3,4-diCl	$COCH_2$-OCH_3		$C_{28}H_{32}Cl_2N_4O_3$ C, H, N, Cl	144–145 AcOEt	0.25	9.4	2000	in	5.75–6.73
72				$C_{25}H_{27}Cl_2N_5O$ C, H, N, Cl	170 pentane	76		> 1000		
73				$C_{25}H_{27}Cl_2N_5O$ C, H, N, Cl	119 iPr_2O	310		> 1000		
74				$C_{24}H_{27}N_3O_3$ C, H, N	129 EtOAc–CH_2Cl_2	2600		> 100000		

[a]Compounds gave satisfactory analyses (± 0.4%) unless otherwise indicated. [b]N: found, 14.28; calc, 13.58. [c]ND: not determined, but satisfactory results by high-resolution MS analysis were obtained. [d]C: found, 74.17; calc, 74.92. [e]C: found, 72.86; calc, 73.33. [f]C: found, 74.45; calc, 75.28. [g]C: found, 61.79; calc, 62.28. [h]N: found, 10.72; calc, 11.25. [i]Cl: found, 21.93; calc, 21.36. [j]C: found, 62.19; calc, 62.91. [k]N: found, 10.35; calc, 10.87. [l]C: found, 63.29; calc, 63.76. [m]N: found, 10.17; calc, 10.62. [n]C: found, 65.30; calc, 66.07. [o]N: found, 9.34; calc, 9.94.

Table VII. μ binding affinities.

Compound	*K_i (nM)*	*Compound*	*K_i (nM)*
2	30000	**33**	6700
3	1100	**34**	1000
4	10000	**37**	> 100000
7	250	**50**	8100
8	0.37	**54**	1600
9	37	**55**	1900
12	19	**57**	9.2
13	540	**58**	2.8
22	6000	**69**	2300
32	1700	**70**	1000
		71	2800

Table VIII. Hot-plate test in mice. Results after iv administration.

Compound	*ED_{50} (mg/kg)*
2	0.006
3	1.5
4	0.01
7	0.025
13	0.001
30	0.01–0.1
34	0.01–0.1
36	0.01
54	0.1–1
69	0.1–1
71	0.4
Morphine	0.3

more, compound **13** was found to be active after oral administration with an ED_{50} of 0.3 mg/kg. CP 99994 **2** was also orally active with an ED_{50} of 1 mg/kg. Replacement of the propionyl side chain on the anilino nitrogen atom by an acetyl, methoxy acetyl or aminoacetyl side chain decreased the activity at least by one order of magnitude (compounds **30**, **34**, **36**). Introduction of a heteroatom in the aromatic ring of the benzimidazolone (in **54**), as well as replacing the isopropylidene moiety by a cyclopentene ring (**69**, **71**) were also found to be deleterious modifications for activity.

SP-induced bronchoconstriction in guinea-pigs

Again, the most potent in vitro candidates were further evaluated on the SP-induced bronchoconstriction model, first by the iv route. Inhibitions obtained at different doses are reported in table IX.

Table IX. SP-induced bronchoconstriction in the guinea-pig. Results after iv administration.

Compound	*1 mg/kg (%)*	*0.3 mg/kg (%)*	*0.1 mg/kg (%)*	*0.03 mg/kg (%)*
9	82	35		
12	in			
13	87	55	in	
15	83	57	in	
19	62	in		
22	20			
31	in			
32	27	66	in	
34	97	88	85	46
35	–	88	80	in
36	–	53	10	
42	30	in		
46	83	43	in	
48	75	63	28	in
50	94	62	in	
54	–	84	61	in
55	58			
59	in			
71	89		79	29

The substitution on the anilino phenyl ring was found to be of prime importance in order to obtain a strong activity in this assay: actually, the 3,4-dichloro substitution was superior to every other disubstitution tested (compare **13** with **12**, **19** or **22**); however, the 3-chloro or 4-fluorophenyl containing antagonists **9** and **15** disclosed similar potency as their dichloro counterpart. The preferred substitutions on the anilino nitrogen atom were again the acetyl, the propionyl and the methoxymethylcarbonyl side chains (compounds **35**, **13**, **34** and **71**). Substitution on the phenyl ring of the benzimidazolone gave rather potent derivatives, especially when the modification took place at position 7 (compounds **46**: 7-CH_3 and **54**: imidazo[4,5-*e*]-pyridin-2-one). Finally, in order to obtain a potent activity and a long duration of action, the best substitutions on the benzimidazolone nitrogen atom were found to be the isopropylidene itself or the cyclopentene ring (compounds **34** and **71**).

Furthermore, inhibition of bronchoconstriction obtained at 3, 20 and 40 minutes after iv treatment with compound **34** is depicted on figure 1. This antagonist significantly inhibited responses of SP with an ID_{50} of approximatively 0.03 mg/kg at 3 min. A similar effect was obtained with CP 99994 at the same dosage. Moreover, in a model of SP-induced bronchial hyperreactivity adapted from Vargaftig's work [23], compound **71** was found to be orally active with an ID_{50} of approximatively 3 mg/kg when administered one hour before inhalation of SP, whereas CP 99994 was inactive under these experimental conditions.

Conclusion

NK_1 receptor antagonists have proven to be effective in blocking neurogenic inflammatory responses as well as nociception in several animal models. Thus, they may have important clinical utility, first as analgesic drugs, especially in the management of chronic pain, and second as antiinflammatory agents, particularly targeted to the bronchopulmonary system. Binding affinity studies led to the discovery of a novel structural series of NK_1 receptor antagonists of the benzimidazolone type. Data collected from isolated organ assays correlated rather well with binding results, and allowed the selection of several antagonists for in vivo studies. In the hot-plate test, compound **13** showed a potent antinociceptive activity orally, with an ED_{50} of 0.3 mg/kg. Moreover, compound **71** proved to be orally active in a model of SP-induced bronchial hypersensitivity in mice. These data clearly support the therapeutic use of such agents in the management of pain conditions, as well as under inflammatory conditions, especially at the pulmonary level.

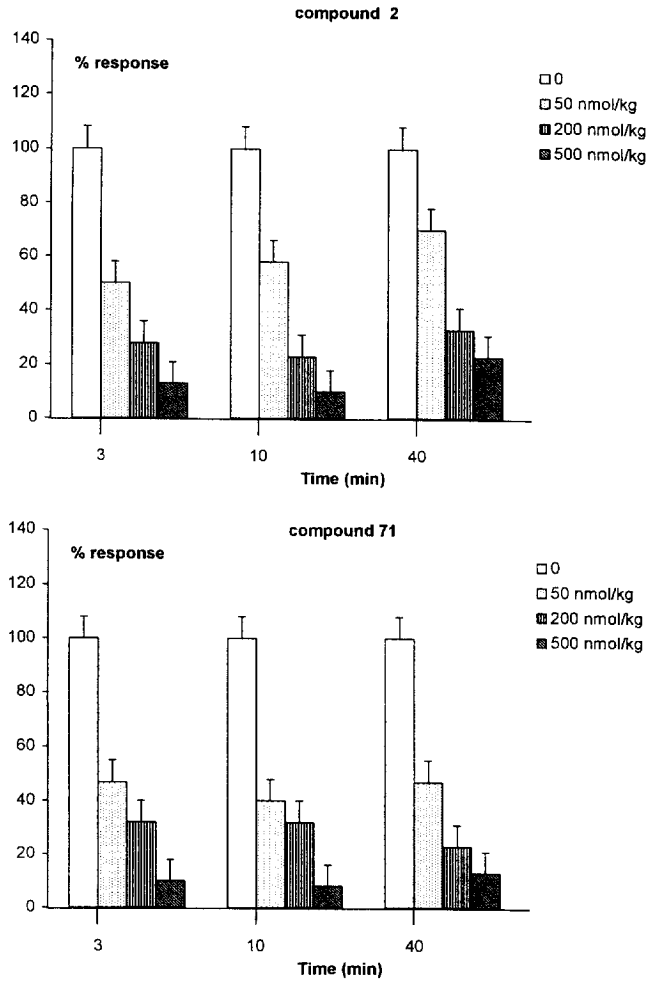


Fig 1. Effect of antagonists **2** (CP 99994) and **71** on SP-induced bronchoconstriction after iv administration.

Experimental protocols

Melting points were determined on a Tottoli apparatus and were not corrected. Elemental analyses were carried out by the analytical department of the Institut de Recherches Servier; results obtained for specified elements are within ± 0.4% of the theoretical values. IR spectra were recorded on a Bruker IFS 28 spectrophotometer. ^{1}H-NMR spectra of deuteriochloroform or DMSO-d_6 solutions were recorded on Bruker AC 200 or AM 300 spectrometers. Chemical shifts are given in ppm with TMS as the internal standard.

N-(3-Chlorophenyl)-1-benzylpiperidin-4-amine ***iii-a***

16 g (0.125 mol) of 3-chloroaniline and 23.65 g (0.125 mol) of 1-benzyl-piperidin-4-one was refluxed in 300 mL of toluene, and water was eliminated with a Dean-Stark apparatus. After

48 h, the solvent was evaporated. The crude solid (37 g) was disolved in 400 mL of methanol, and sodium borohydride (12 g, 0.312 mol) was added portionwise during 5 h (temperature rose to 40 °C). The reaction was stirred at room temperature overnight, then evaporated to dryness. The residue was taken up with water and ethyl acetate. The organic layer was extracted with 1 N HCl, and the resulting acidic layer was washed with ether. Alcalinisation with 1 N NaOH was followed by extraction with ethyl acetate. The organic layer was washed with water, brine, and dried over sodium sulfate. Filtration and evaporation gave 34 g (91%) of the desired intermediate as an amorphous solid: ^{1}H-NMR ($CDCl_3$) δ 1.5 (2H, m), 1.7 (1H, broad s), 2.05 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.25 (1H, m), 3.55 (2H, s), 6.35–6.70 and 7.05 (4H, 2m), 7.25 (5H, m).

N-(4-Chlorophenyl)-1-benzylpiperidin-4-amine ***iii-b***
Mp 90–92 °C; IR (nujol) 3622, 3390, 1597 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m), 1.65 (1H, broad s), 2.05 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.25 (1H, m), 3.50 (2H, s), 6.5 (2H, d), 7.1 (2H, d), 7.35 (5H, m).

N-(2,4-Dichlorophenyl)-1-benzylpiperidin-4-amine ***iii-c***
Mp 92 °C; IR (nujol) 3400, 3100, 3050, 2807–2764, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.53 (2H, m), 2.03 (2H, m), 2.18 (2H, m), 3.30 (1H, broad s), 3.52 (2H, s), 4.20 (1H, d), 6.58 (1H, d), 7.08 (1H, dd), 7.22 (1H, d), 7.30 (5H, m).

N-(2,5-Dichlorophenyl)-1-benzylpiperidin-4-amine ***iii-d***
IR (KBr) 3413 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (2H, m), 2.05 (2H, m), 2.2 (2H, m), 2.85 (2H, m), 3.3 (1H, m), 3.55 (2H, s), 4.3 (1H, d), 6.60 (2H, m), 7.15 (1H, d), 7.30 (5H, m).

N-(3,4-Dichlorophenyl)-1-benzylpiperidin-4-amine ***iii-e***
Mp 92–94 °C; IR (nujol) 3384, 1594 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.2 (1H, m), 3.55 (2H, s), 3.60 (1H, d), 6.4 (1H, dd), 6.6 (1H, d), 7.15 (1H, d), 7.3 (5H, m).

N-(3,5-Dichlorophenyl)-1-benzylpiperidin-4-amine ***iii-f***
IR (KBr) 3412 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.2 (1H, m), 3.5 (2H, s), 3.7 (1H, d), 6.4 (2H, s), 6.6 (1H, s), 7.3 (5H, m).

N-(4-Fluorophenyl)-1-benzylpiperidin-4-amine ***iii-g***
Mp 90–92 °C; IR (nujol) 3372 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m), 2.05 (2H, m), 2.15 (2H, m), 2.8 (2H, m), 3.2 (1H, m), 3.35 (1H, d), 3.55 (2H, s), 6.5 (2H, m), 6.85 (2H, m), 7.3 (5H, m).

N-(3,4-Difluorophenyl)-1-benzylpiperidin-4-amine ***iii-h***
Mp 78–80 °C; IR (nujol) 3377, 1627, 1603 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.8 (2H, m), 3.2 (1H, m), 3.45 (1H, broad s), 3.55 (2H, s), 6.2 (1H, m), 6.35 (1H, m), 6.9 (1H, m), 7.3 (5H, m).

N-(3-Chloro-4-fluorophenyl)-1-benzylpiperidin-4-amine ***iii-i***
Mp 82 °C; IR (nujol) 3388, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.2 (1H, m), 3.40 (1H, broad s), 3.50 (2H, s), 6.4 (1H, m), 6.55 (1H, m), 6.9 (1H, t), 7.3 (5H, m).

N-(4-Methylphenyl)-1-benzylpiperidin-4-amine ***iii-j***
Mp 102 °C; IR (nujol) 3400, 1616 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.01 (2H, m), 2.15 (2H, m), 2.3 (3H, s), 2.8 (2H, m), 3.3 (2H, m), 3.5 (2H, s), 6.5 (2H, d), 6.95 (2H, d), 7.3 (5H, m).

N-(3,4-Dimethylphenyl)-1-benzylpiperidin-4-amine ***iii-k***
Mp 74–76 °C; IR (nujol) 3377, 1612–1583, 735–700 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 1.3 (2H, m), 1.82 (2H, m), 2.05 (8H, m), 2.75 (2H, m), 3.10 (1H, m), 3.45 (2H, t), 5.0 (1H, d), 6.30 (1H, dd), 6.38 (1H, d), 6.79 (1H, d), 7.30 (5H, m).

N-(3-Chloro-4-methylphenyl)-1-benzylpiperidin-4-amine ***iii-l***
Mp 70 °C; IR (nujol) 3380, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m), 1.9–2.2 (4H, m), 2.25 (3H, s), 2.8 (2H, m), 3.2 (1H, m), 3.4 (1H, broad s), 3.5 (2H, s), 6.35 (1H, dd), 6.55 (1H, d), 6.95 (1H, d), 7.3 (5H, m).

N-(3-Methoxyphenyl)-1-benzylpiperidin-4-amine **iii-m**
IR (KBr) 3396, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (2H, m), 1.9–2.2 (4H, m), 2.85 (2H, m), 3.25 (1H, m), 3.4–3.6 (1H, broad s), 3.55 (2H, s), 3.75 (3H, s), 6.1–6.3 (3H, m), 7.05 (1H, m), 7.3 (5H, m).

N-(3,4-Dimethoxyphenyl)-1-benzylpiperidin-4-amine ***iii-n***
IR (KBr) 3400, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.45 (2H, m), 2.05 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.2 (1H, m), 3.5 (2H, s), 3.8 (6H, 2s), 6.15 (1H, dd), 6.2 (1H, d), 6.7 (1H, d), 7.3 (5H, m).

N-(3-Chloro-4-methoxyphenyl)-1-benzylpiperidin-4-amine ***iii-o***
Mp 95 °C; IR (nujol) 3377, 2855 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.2 (1H, m), 3.3 (1H, broad s), 3.5 (2H, s), 3.8 (3H, s), 6.45 (1H, dd), 6.65 (1H, d), 6.8 (1H, d), 7.3 (5H, m).

N-(Naphth-2-yl)-1-benzylpiperidin-4-amine ***iii-p***
Mp 120 °C; IR (nujol) 3387, 1628 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (2H, m), 2.0–2.3 (4H, m), 2.85 (2H, m), 3.4 (1H, m), 3.55 (2H, s), 3.65 (1H, d), 6.8 (2H, m), 7.1–7.4 (7H, m), 7.65 (3H, m).

N-(Pyridin-4-yl)-1-benzylpiperidin-4-amine ***iii-q***
IR (nujol) 3213, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (2H, m), 2.0 (2H, m), 2.15 (2H, m), 2.85 (2H, m), 3.35 (1H, m), 3.55 (2H, s), 4.15 (1H, d), 6.4 (2H, d), 7.3 (5H, m), 8.15 (2H, d).

N-(1-Benzylpiperidin-4-yl)-N-(3-chlorophenyl)propionamide ***iv-a***

16.5 g (0.0575 mol) of intermediate **iii-a** was dissolved in 300 mL of toluene. 15 mL (0.115 mol) of propionic anhydride was added at room temperature and the reaction mixture was refluxed overnight. After cooling to room temperature, 200 mL of 10% NaOH was added and the resulting mixture was stirred for one hour with occasional ice cooling. The organic layer was washed with water until pH 7 was achieved, dried over sodium sulfate and evaporated. The crude residue (19.5 g) was purified on a column of 70/230 mesh silicagel column chromatography by sequential elution with methylene chloride and by methylene chloride–ethanol, 98:2 to give 17 g (85%) of the desired intermediate. IR (KBr) 1662 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.3–1.5 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.9 (2H, m), 3.4 (2H, s), 4.5–4.7 (1H, m), 6.95 (1H, m), 7.1 (1H, d), 7.2–7.4 (7H, m).

N-(1-Benzylpiperidin-4-yl)-N-(4-chlorophenyl)propionamide ***iv-b***
Mp 110–112 °C; IR (nujol) 1658, 1601 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.35 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.45 (2H, s), 4.5–4.7 (1H, m), 6.95 (2H, d), 7.25 (5H, m), 7.4 (2H, d).

N-(1-Benzylpiperidin-4-yl)-N-(2,4-dichlorophenyl)propionamide ***iv-c***
IR (KBr) 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.1–1.6 (2H, m), 1.7–2.0 (4H, m), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 4.6 (1H, m), 7.1 (1H, d), 7.3 (6H, m), 7.5 (1H, d).

N-(1-Benzylpiperidin-4-yl)-N-(2,5-dichlorophenyl)propionamide ***iv-d***
IR (nujol) 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.8–2.05 (4H, m), 2.1 (2H, m), 2.85 (2H, m), 3.45 (2H, s), 4.65 (1H, m), 7.25 (1H, d), 7.3 (6H, m), 7.45 (1H, d).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dichlorophenyl)propionamide ***iv-e***
IR (nujol) 1664 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 4.6 (1H, m), 6.9 (1H, dd), 7.25 (6H, m), 7.5 (1H, d).

N-(1-Benzylpiperidin-4-yl)-N-(3,5-dichlorophenyl)propionamide ***iv-f***
IR (nujol) 1666 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.35 (2H, m), 1.75 (2H, m), 1.95 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.45 (2H, s), 4.6 (1H, m), 7.0 (2H, dd), 7.25 (5H, m), 7.4 (1H, s).

N-(1-Benzylpiperidin-4-yl)-N-(4-fluorophenyl)propionamide ***iv-g***
IR (nujol) 1657 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.85 (3H, t), 1.2 (2H, m), 1.7 (2H, m), 1.8 (2H, q), 2.0 (2H, m), 2.8 (2H, m), 3.4 (2H, s), 4.4 (1H, m), 7.2–7.4 (9H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-difluorophenyl)propionamide ***iv-h***
IR (nujol) 1660, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.3 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 4.6 (1H, m), 6.8–7.35 (7H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3-chloro-4-fluorophenyl)propionamide ***iv-i***
IR (nujol) 1662 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.45 (2H, s), 4.6 (1H, m), 6.9–7.8 (8H, m).

N-(1-Benzylpiperidin-4-yl)-N-(4-methylphenyl)propionamide ***iv-j***
IR (nujol) 1654, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.4 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.4 (3H, s), 2.85 (2H, m), 3.4 (2H, s), 4.65 (1H, m), 6.90 (2H, d), 7.25 (7H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dimethylphenyl)propionamide ***iv-k***
Mp 146 °C; IR (nujol) 1650, 1603 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.85 (3H, t), 1.2 (2H, m), 1.7 (2H, m), 1.85 (2H, q), 2.0 (2H, m), 2.25 (6H, s), 2.75 (2H, m), 3.4 (2H, s), 4.40(1H, m), 6.90 (1H, dd), 6.95 (1H, d), 7.30 (6H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3-chloro-4-methylphenyl)-propionamide ***iv-l***
Mp 130–131 °C; IR (nujol) 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2–1.55 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.4 (3H, s), 2.85 (2H, m), 3.45 (2H, s), 4.65 (1H, m), 6.85 (1H, dd), 7.1 (1H, d), 7.25 (6H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dimethoxyphenyl)propionamide ***iv-m***
IR (nujol) 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.4 (2H, m), 1.75 (2H, m), 1.95 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 3.85 (6H, 2s), 4.6 (1H, m), 6.55 (1H, d), 6.65 (1H, dd), 6.85 (1H, d), 7.25 (5H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3-chloro-4-methoxyphenyl)-propionamide ***iv-n***
Mp 130–132 °C; IR (nujol) 1663 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.35 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 3.9 (3H, s), 4.6 (1H, m), 6.9 (2H, m), 7.1 (1H, d), 7.25 (5H, m).

N-(1-Benzylpiperidin-4-yl)-N-(naphth-2-yl)propionamide ***iv-o***
IR (KBr) 1657, 1630, 1597 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.3–1.6 (2H, m), 1.7–2.0 (4H, m), 2.1 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 4.75 (1H, m), 7.1–7.6 (9H, 2m), 7.85 (3H, m).

N-(1-Benzylpiperidin-4-yl)-N-(pyridin-4-yl)propionamide ***iv-p***
IR (nujol) 1664 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.35 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.05 (2H, m), 2.85 (2H, m), 3.4 (2H, s), 4.65 (1H, m), 7.05 (2H, d), 7.2 (5H, m), 8.7 (2H, d).

N-(1-Benzylpiperidin-4-yl)-N-(phenyl)butyramide ***iv-q***
IR (KBr) 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.8 (3H, t), 1.4 (2H, m), 1.55 (2H, m), 1.75 (2H, m), 1.85 (2H, t), 2.1 (2H, m), 2.85 (2H, m), 3.45 (3H, s), 4.6–4.8 (1H, m), 7.05 (2H, m), 7.25 (5H, m), 7.4 (3H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dichlorophenyl)ethanamide ***iv-r***
IR (nujol) 1652 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.7 (2H, m), 2.1 (2H, m), 2.3 (3H, s), 2.9 (2H, m), 3.45 (2H, s), 4.6 (1H, m), 6.95 (2H, m), 7.25 (5H, m), 7.5 (1H, d).

N-(1-Benzylpiperidin-4-yl)-N-(3-chloro-4-methylphenyl)ethanamide ***iv-s***
IR (nujol) 1650, 1602 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.7 (2H, m), 1.75 (3H, s), 2.1 (2H, m), 2.4 (3H, s), 2.85 (2H, m), 3.45 (2H, s), 4.6 (1H, m), 6.9 (1H, dd), 7.1 (1H, d), 7.25 (6H, m).

N-(1-Benzylpiperidin-4-yl)-N-(phenyl)-N-(piperidin-1-yl-carbonyl)amine ***iv-t***
Mp 95 °C; IR (nujol) 3059, 3030, 2763, 2723, 1639, 1597, 1581, 764, 744, 702 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.15 (4H, m), 1.38 (2H, m), 1.60 (2H, m), 1.80 (2H, m), 2.08 (2H, m), 2.88 (2H, m), 3.14 (4H, m), 3.43 (2H, s), 4.03 (1H, m), 7.05 (2H, d), 7.10–7.40 (7H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dichlorophenyl)-N-(piperidin-1-yl-carbonyl)amine ***iv-u***
Mp 210 °C (sublimation); IR (nujol) 1650 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.15–1.5 (6H, 2m), 1.6 (2H, m), 1.75 (2H, m), 2.05 (2H, m), 2.9 (2H, m), 3.15 (4H, m), 3.45 (2H, s), 4.0 (1H, m), 6.9 (1H, dd), 7.15 (1H, d), 7.25 (5H, m), 7.4 (1H, d).

N-(1-Benzylpiperidin-4-yl)-(1H)-quinolein-1-yl-2-one ***iv-v***
IR (KBr) 3020, 2940, 2801–2760, 1670, 1602, 755, 739, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.65 (2H, m), 2.12 (2H, m), 2.58 (4H, m), 2.80 (2H, m), 3.0 (2H, m), 3.55 (2H, s), 4.30 (1H, m), 6.90–7.40 (9H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dichlorophenyl)benzoylamine ***iv-w***
Mp 130 °C; IR (nujol) 3080–3050, 2803–2750, 1657, 1585, 741, 725, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.53 (2H, m), 1.86 (2H, m), 2.15 (2H, m), 2.95 (2H, m), 3.48 (2H, s), 4.70 (1H, m), 6.82 (1H, dd), 7.15 (1H, d), 7.20 (11H, m).

N-(1-Benzylpiperidin-4-yl)-N-(3,4-dichlorophenyl)-N-(methoxymethylcarbonyl)amine ***iv-x***
IR (nujol) 2700–2400, 1684 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.5–2.0 (4H, 2m), 3.1 (2H, m), 3.2 (3H, s), 3.3 (2H, m), 3.7 (2H, m), 4.2 (2H, dd), 4.65 (1H, m), 7.3 (1H, dd), 7.35–7.6 (5H, m), 7.65 (1H, s), 7.75 (1H, d).

N-(1-Benzylpiperidin-4-yl)-N-(3-chloro-4-methylphenyl)-N-(phthalimidomethylcarbo-nyl)amine ***iv-y***
IR (nujol) 1714, 1674 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 1.75 (2H, m), 2.05 (2H, m), 2.4 (3H, s), 2.85 (2H, m), 3.4 (2H, s), 4.0 (2H, s), 4.55 (1H, m), 7.1 (1H, dd), 7.3 (7H, m), 7.7–7.9 (4H, 2m).

N-(3-Chlorophenyl)-N-(piperidin-4-yl)propionamide ***v-a***

16 g (0.0448 mol) of the benzyl piperidine derivative **iv-a** was dissolved in 200 mL of methylene chloride, and this solution was cooled down to 0–5 °C. α-Chloroethylchloroformiate (0.0492 mol, 5.32 mL) was added dropwise in 50 mL of methylene chloride; the resulting solution was stirred at 0 °C for half an hour, then warmed to room temperature and stirred at this temperature for 3 h. The solvent was evaporated and the residue was taken up with 200 mL of anhydrous methanol. The reaction mixture was warmed at 50 °C for 1 h under nitrogen. After evaporation of the solvent, the resulting residue was taken up with water, and this aqueous solution was washed four times with diethyl ether. Alcalinisation with 10 mL of concentrated (35%) NaOH was followed by extraction with diethyl ether. The organic layer was washed with water and brine, dried over sodium sulfate, then filtered and evaporated to give 8.05 g (68%) of the deprotected piperidino intermediate **v-a**. IR (nujol) 3320, 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.25 (2H, m), 1.5 (1H, broad s), 1.75 (2H, m), 1.95 (2H, q), 2.7 (2H, m), 3.05 (2H, m), 4.6–4.8 (1H, m), 6.95 (1H, m), 7.15 (1H, d), 7.35 (2H, m).

N-(4-Chlorophenyl)-N-(piperidin-4-yl)propionamide ***v-b***
IR (KBr) 3305, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.1–1.3 (2H, m), 1.55 (1H, broad s), 1.75 (2H, m), 1.9 (2H, q), 2.7 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 7.0 (2H, d), 7.35 (2H, d).

N-(2,4-Dichlorophenyl)-N-(piperidin-4-yl)propionamide ***v-c***
IR (KBr) 3320, 1664 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.1 (1H, m), 1.4 (1H, m), 1.8–2.1 (4H, m), 2.3 (1H, broad s), 2.75 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 7.15 (1H, d), 7.3 (1H, dd), 7.55 (1H, d).

N-(2,5-Dichlorophenyl)-N-(piperidin-4-yl)propionamide ***v-d***
IR (nujol) 3300, 1652 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.1 (1H, m), 1.35 (1H, m), 1.4 (1H, m), 1.8–2.1 (4H, m), 2.75 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 7.25 (1H, d), 7.35 (1H, dd), 7.45 (1H, d).

N-(3,4-Dichlorophenyl)-N-(piperidin-4-yl)propionamide ***v-e***
IR (nujol) 3313, 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.8 (2H, m), 1.95 (2H, m), 2.75 (2H, m), 3.1 (2H, m), 4.75 (1H, m), 6.95 (1H, dd), 7.25 (1H, d), 7.5 (1H, d).

N-(3,5-Dichlorophenyl)-N-(piperidin-4-yl)propionamide ***v-f***
IR (nujol) 3289, 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.25 (2H, m), 1.45 (1H, broad s), 1.8 (2H, m), 1.95 (2H, m), 2.7 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 7.0 (2H, d), 7.4 (1H, m).

N-(4-Fluorophenyl)-N-(piperidin-4-yl)propionamide ***v-g***
IR (nujol) 3332, 1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.2 (2H, m), 1.4 (1H, broad s), 1.75 (2H, m), 1.9 (2H, q), 2.7 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 7.1 (4H, m); ^{19}F-NMR ($CDCl_3$) δ/$CFCl_3$ −116.

N-(3,4-Difluorophenyl)-N-(piperidin-4-yl)propionamide ***v-h***
IR (KBr) 3320, 1661, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2 (2H, m), 1.5 (1H, broad s), 1.8 (2H, m), 1.95 (2H, q), 2.7 (2H, m), 3.05 (2H, m), 4.6–4.8 (1H, m), 6.8–7.0 (2H, m), 7.2 (1H, m).

N-(3-Chloro-4-fluorophenyl)-N-(piperidin-4-yl)propionamide ***v-i***
IR (KBr) 3300, 1666 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2 (2H, m), 1.45 (1H, broad s), 1.75 (2H, m), 1.9 (2H, q), 2.7 (2H, m), 3.05 (2H, m), 4.7 (1H, m), 6.9–7.3 (3H, m).

N-(4-Methylphenyl)-N-(piperidin-4-yl)propionamide ***v-j***
IR (KBr) 3307, 1652, 1607 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.25 (2H, m), 1.45 (1H, broad s), 1.75 (2H, m), 1.9 (2H, q), 2.35 (3H, s), 2.7 (2H, m), 3.0 (2H, m), 4.7 (1H, m), 6.9 (2H, d), 7.2 (2H, d).

N-(3,4-Dimethylphenyl)-N-(piperidin-4-yl)propionamide ***v-k***
IR (KBr) 3320, 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.25 (2H, m), 1.55 (1H, broad s), 1.75 (2H, m), 1.95 (2H, q), 2.3 (6H, 2s), 2.7 (2H, m), 3.05 (2H, m), 4.7 (1H, m), 6.8 (2H, m), 7.15 (1H, d).

N-(3-Chloro-4-methylphenyl)-N-(piperidin-4-yl)propionamide ***v-l***
IR (KBr) 3312, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.25 (2H, m), 1.4 (1H, broad s), 1.75 (2H, m), 1.95 (2H, q), 2.4 (2H, s), 2.7 (2H, m), 3.1 (2H, m), 4.7 (1H, m), 6.85 (1H, dd), 7.10 (1H, d), 7.25 (1H, d).

N-(3,4-Dimethoxyphenyl)-N-(piperidin-4-yl)propionamide ***v-m***
IR (KBr) 3330, 2840, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.45 (1H, broad s), 1.75 (2H, m), 1.95 (2H, q), 2.7 (2H, m), 3.05 (2H, m), 3.9 (6H, 2s), 4.7 (1H, m), 6.55 (1H, d), 6.65 (1H, dd), 6.85 (1H, d).

N-(3-Chloro-4-methoxyphenyl)-N-(piperidin-4-yl)propionamide ***v-n***
IR (nujol) 3300, 1651 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.8 (2H, m), 1.95 (2H, q), 2.75 (2H, m), 3.15 (2H, m), 3.55 (1H, m), 3.9 (3H, s), 4.65 (1H, m), 6.95 (2H, m), 7.1 (1H, d).

N-(Naphth-2-yl)-N-(piperidin-4-yl)propionamide ***v-o***
IR (KBr) 3300, 1653–1629 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2–1.5 (2H, m), 1.8–2.05 (4H, m), 2.4 (1H, broad s), 2.75 (2H, m), 3.1 (2H, m), 4.8 (1H, m), 7.15 (1H, d), 7.55 (3H, m), 7.85 (3H, m).

N-(Pyridin-4-yl)-N-(piperidin-4-yl)propionamide ***v-p***
^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.8 (2H, m), 1.9 (2H, q), 2.6 (1H, broad s), 2.75 (2H, m), 3.15 (2H, m), 4.75 (1H, m), 7.05 (2H, d), 8.7 (2H, d).

N-Phenyl-N-(piperidin-4-yl)butyramide ***v-q***
IR (nujol) 3360, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.8 (3H, t), 1.2–1.4 (2H, m), 1.3 (1H, broad s), 1.6 (2H, m), 1.7–2.0 (4H, m), 2.75 (2H, m), 3.05 (2H, m), 4.65–4.85 (1H, m), 7.05 (2H, m), 7.4 (3H, m).

N-(3,4-Dichlorophenyl)-N-(piperidin-4-yl)ethanamide ***v-r***
IR (KBr) 3344, 2854–2807, 1660, 1583–1537, 820–729 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.32 (2H, m), 1.80 (2H, m), 1.80 (3H, s), 2.78 (2H, m), 3.15 (2H, m), 4.72 (1H, m), 6.98 (1H, dd),7.25 (1H, d), 7.50 (1H, d).

N-(3-Chloro-4-methylphenyl)-N-(piperidin-4-yl)ethanamide ***v-s***
IR (KBr) 3316, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (2H, m), 1.45 (1H, broad s), 1.75 (2H, m), 1.8 (3H, s), 2.4 (3H, s), 2.7 (2H, m), 3.05 (2H, m), 4.7 (1H, m), 6.85 (1H, dd), 7.05 (1H, d), 7.25 (1H, d).

N-Phenyl-N-(piperidin-4-yl)piperidinocarbonylamine ***v-t***
Mp 125 °C; IR (nujol) 1639, 1596, 764, 711 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0–1.7 (8H, m), 1.85 (2H, m), 2.68 (2H, m), 2.95–3.25 (6H, m), 4.10 (1H, m), 7.0–7.4 (5H, m).

N-(3,4-Dichlorophenyl)-N-(piperidin-4-yl)piperidinocarbonylamine ***v-u***
IR (KBr) 3320, 1652 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.1–1.4 (6H, m), 1.4 (2H, m), 1.65 (2H, m), 2.45 (2H, m), 2.9 (2H, m), 3.1 (4H, m), 3.8 (1H, m), 7.0 (1H, dd), 7.25 (1H, d), 7.55 (1H, d).

N-(Piperidin-4-yl)-(1H)-quinolein-1-yl-2-one ***v-v***
IR (KBr) 3320, 1667 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.6 (1H, broad s), 1.7 (2H, m), 2.4–2.9 (8H, m), 3.2 (2H, m), 4.3 (1H, m), 7.0 (1H, m), 7.2 (3H, m).

N-(3,4-Dichlorophenyl)-N-(piperidin-4-yl)benzoylamine ***v-w***
Mp 142–144 °C; IR (nujol) 3310, 1650 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 1.6 (1H, broad s), 1.9 (2H, m), 2.75 (2H, m), 3.1 (2H, m), 4.75 (1H, m), 6.85 (1H, dd), 7.3 (7H, m).

N-(3,4-Dichlorophenyl)-N-(piperidin-4-yl)methoxymethylcarbonylamine ***v-x***
IR (KBr) 3331, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3 (2H, m), 1.75 (2H, m), 1.9 (1H, broad s), 2.7 (2H, m), 3.1 (2H, m), 3.3 (3H, s), 3.65 (2H, s), 4.7 (1H, m), 6.95 (1H, dd), 7.25 (1H, d), 7.5 (1H, d).

N-(3-Chloro-4-methylphenyl)-N(piperidin-4-yl)phthalimidomethylcarbonyl amine ***v-y***
IR (nujol) 3600–2400, 1750–1642 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3–2.1 (4H, m), 2.4 (3H, s), 2.7–3.2 (4H, m), 3.7 (2H, s), 4.85 (1H, m), 7.2–-7.9 (7H, m).

1-(Prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-a***

54 g (0.5 mol) of orthophenylene diamine was suspended in 150 mL of anhydrous xylene and heated at 120 °C. When the mixture was homogenous, 1 mL of an aqueous 47% KOH solution was added, rapidly followed within 5–10 min by the addition of 61.5 g of methyl acetoacetate in 20 mL of xylene. Approximatively 25 mL of a water–methanol mixture was eliminated by using a Dean-Stark apparatus. The temperature progressively rose to the boiling point of xylene, and reflux was maintained for three more hours. After cooling to 40 °C, 82.5 mL of 47% KOH and 55 mL of water was added. The resulting aqueous layer was washed three times with xylene. When the basic aqueous layer was acidified with 60 mL of acetic acid, a solid precipitated; this residue was washed with water, then dried (P_2O_5), to give 68.5 g (78%) of a white solid. Mp 120 °C; IR (nujol) 3200–3000, 1697 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.2 (3H, s), 5.2–5.4 (2H, s), 7.1 (4H, m), 10.4 (1H, m).

1-(Prop-1-en-2-yl)-7-methyl-1,3-dihydro-2H-benzimidazol-2-one ***ix-b***
Mp 195 °C; IR (nujol) 3145, 3060, 1718, 1653, 889, 856, 760–761 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.26 (3H, s), 2.33 (3H, s), 5.22 (1H, s), 5.35 (1H, s), 6.80–7.10 (3H, m), 10.70 (1H, s).

1-(Prop-1-en-2-yl)-4-nitro-1,3-dihydro-2H-benzimidazol-2-one ***ix-c***
IR (nujol) 3250–2500, 1709, 1662, 1633, 1531, 1385 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.15 (3H, s), 4.70 (1H, s), 5.20 (1H, s), 7.20 (1H, t), 7.35 (1H, d), 7.60 (1H, d), 11.70 (1H, s).

1-(Prop-1-en-2-yl)-5,6-dichloro-1,3-dihydro-2H-benzimidazol-2-one ***ix-d***
Mp 235 °C (sublimation); IR (nujol) 3161, 2752, 1712, 1657, 1626–1595, 858 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.10 (3H, s), 5.20 (1H, s), 5.38 (1H, s), 7.20–7.25 (2H, 2s), 7.70 (1H, broad s).

1-(Prop-1-en-2-yl)-5-trifluoromethyl-1,3-dihydro-2H-benzimidazol-2-one ***ix-e*** *and 1-isopropenyl-6-trifluoromethyl-1,3-dihydro-2H-benzimidazol-2-one* ***ix-f***
^{1}H-NMR (DMSO-d_6) δ 2.15 (3H, s) or 2.55 (3H, s), 5.20 (1H, s) or 5.40 (1H, s), 7.40 (1H, d), 7.70 (1H, d), 7.90 (1H, s), 11.40 (1H, broad s) or 11.50 (1H, broad s).

1-(Prop-1-en-2-yl)-7-trifluoromethyl-1,3-dihydro-2H-benzimidazol-2-one ***ix-g***
Mp 190–192 °C (sublimation); IR (nujol) 3155–3079, 1702, 1660, 1628–1618, 1120, 883, 829, 789, 739 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.10 (3H, s), 5.25 (1H, s), 5.50 (1H, s), 7.15 (1H, s), 7.35 (1H, s), 7.40 (1H, s), 11.60 (1H, broad s).

1-(Prop-1-en-2-yl)-2H-naphth-[2,3-d]-imidazol-2-one ***ix-h***
Mp 200–203 °C; IR (nujol) 3200–2800, 1703, 1660, 1606 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.2 (3H, s), 5.45 (1H, s), 5.25 (1H, s), 7.35 (2H, m), 7.4–7.5 (2H, 2s), 7.8–8.0 (2H, m), 11.50 (1H, broad s).

1-(Prop-1-en-2-yl)-1,3-dihydroimidazo-[4,5-b]-pyridin-2-one ***ix-i***
IR (nujol) 3200–2600, 1713, 1658, 1618 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.15 (3H, s), 5.15–5.35 (2H, 2s), 7.05 (1H, m), 7.40 (1H, d), 7.95 (1H, d), 11.7 (1H, broad s).

3-(Prop-1-en-2-yl)-1,3-dihydroimidazo-[4,5-b]-pyridin-2-one ***ix-j***
IR (nujol) 3250–3000, 1710, 1655, 1633 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.15 (3H, s), 5.25–5.3 (2H, 2s), 7.05 (1H, dd), 7.3 (1H, d), 7.95 (1H, d).

1-(Cyclopenten-1-yl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-k***
Mp 158–160 °C; IR (nujol) 3200–3100, 1705, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.1 (2H, m), 2.6 (2H, m), 2.95 (2H, t), 6.0 (1H, t), 7.2 (4H, m).

2,3-Dihydro-4-trifluoromethyl-(1H)-1,5-benzoazepin-2-one ***viii-a***
Mp 180–183 °C (sublimation); IR (nujol) 3211–3134, 1689, 1662, 1603–1574, 1115, 760 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.45 (2H, s), 7.15–7.50 (4H, m).

1-(3,3,3-Trifluoroprop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-m***
Mp 158–160 °C; IR (nujol) 3100, 1712, 1323–1138 cm^{-1}; ^1H-NMR (DMSO–d_6) δ 6.3–6.6 (2H, s), 6.9 (1H, d), 7.0 (3H, m), 11.2 (1H, broad s).

1-(But-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-n***
Mp 95–97 °C; IR (nujol) 3200–3600, 1701, 1620 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.9 (3H, d), 2.1 (3H, s), 5.8 (1H, q), 6.9–7.2 (4H, m), 10.5 (1H, s).

1-(1-Ethylethene)-1,3-dihydro-2H-benzimidazol-2-one ***ix-o***
IR (nujol) 3136–3070, 1693, 1651, 1621, 910, 742 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.12 (3H, t), 2.62 (2H, q), 5.38 (1H, s), 5.46 (1H, s), 7.0–7.2 (4H, m), 10.6 (1H, broad s).

1-(Cyclopropyl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-p***
33.6 g (0.23 mol) of 2-cyclopropylaminoaniline and 27.6 g (0.46 mol) of urea was heated neat at 160 °C for 5 h. After cooling to room temperature, the reaction mixture was taken up with 200 mL of water and 200 mL of ethyl acetate and the aqueous layer was extracted with 2 N HCl then water. The organic layer was slowly concentrated, and a pale yellow solid crystallized (17 g). Recristallization from 50 mL of EtOH gave, after washing and drying, 6.45 g of white crystals. Mp 186–188 °C; IR (nujol) 3200–3000, 1711, 1666 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.1 (4H, m), 2.9 (1H, m), 7.0–7.3 (4H, m), 11.0 (1H, broad).

1-(Phenyl)-1,3-dihydro-2H-benzimidazol-2-one ***ix-q***
^1H-NMR (DMSO–d_6) δ 7.0 (4H, m), 7.5 (5H, m).

1-(Prop-1-en-2-yl)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-a***

26.13 g (0.15 mol) of 1-(prop-1-en-2-yl)-1,3-dihydro-2*H*-benzimidazol-2-one was reacted in 400 mL of anhydrous DMF with 22.8 g (0.65 mol) of dry K_2CO_3 and 50 mL (0.6 mol) of 1-bromo-2-chloroethane. The reaction was stirred at 52 °C for 18 h. After filtration of the solid, the solvent was evaporated and the resulting crude oil was taken up with water and ether. The organic layer was washed with water and 1 N NaOH then again water to neutrality. Drying over sodium sulfate and evaporation of the solvent gave 28 g (80%) of the chloro derivative. IR (KBr) 1709, 1657, 1614 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.2 (3H, s), 3.8 (2H, t), 4.2 (2H, t), 5.35–5.52 (2H, 2d), 7.15 (4H, m).

1-(Prop-1-en-2-yl)-3-(2-chloroethyl)-1,3-dihydroimidazo-[4,5-b]-pyridin-2-one ***x-b***
IR (nujol) 1709, 1655, 1608 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.25 (3H, s), 3.9 (2H, t), 4.35 (2H, t), 5.15 (1H, s), 5.3 (1H, s), 7.0 (1H, m), 7.3 (1H, d), 8.05 (1H, d).

1-(2-Chloroethyl)-3-(prop-1en-2-yl)-1,3-dihydroimidazo-[4,5-b]-pyridin-2-one ***x-c***
IR (KBr) 1720, 1659, 1619 cm^{-1}; ^1H-NMR (DMSO–d_6) δ 2.2 (3H, s), 3.95 (2H, t), 4.25 (2H, t), 5.3–5.4 (2H, 2s), 7.15 (1H, m), 7.7 (1H, d), 8.05 (1H, d).

1-(Cyclopenten-1-yl)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-d***
^1H-NMR ($CDCl_3$) δ 2.1 (2H, m), 2.6 (2H, m), 2.9 (2H, m), 3.65 (2H, t), 3.80 (2H, t), 4.25 (2H, t), 5.95 (1H, m), 7.0–7.25 (4H, m).

1-(1-Phenylethene)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-e***
IR (KBr) 3060, 2964, 2929, 1714, 1635, 1614, 1577, 910, 775, 752, 712, 696 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 3.88 (2H, t), 4.28 (2H, t), 5.60 (1H, s), 5.98 (1H, s), 6.70 (1H, d), 6.90–720 (3H, m), 7.32 (5H, m).

1-(3,3,3-Trifluoroprop-1-en-2-yl)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-f***
^1H-NMR ($CDCl_3$) δ 3.65 (1H, t), 3.85 (1H, t), 4.3–4.4 (2H, m), 6.0–6.5 (2H, 2s), 6.8–7.3 (5H, m).

1-(But-1-en-2-yl)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-g***
IR (KBr) 1710, 1614 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.85 (3H, d), 2.05 (3H, s), 3.85 (2H, t), 4.20 (2H, t), 5.75 (1H, q), 6.9–7.1 (4H, m).

1-(1-Ethylethene)-3-(2-chloroethyl)-1,3-dihydro-2H-benzimidazol-2-one ***x-h***
^1H-NMR ($CDCl_3$) δ 1.1 (3H, t), 2.6 (2H, q), 3.85 (2H, t), 4.25 (2H, t), 5.2–5.4 (2H, 2s), 7.1 (4H, m).

N-Phenyl-N-[1-(2-hydroxyethyl)piperidin-4-yl]propionamide ***xi-a***

4-(*N*-propionylanilino)-piperidine (23.2 g, 0.1 mol) was dissolved in anhydrous methanol (100 mL) and the solution was cooled down to 15 °C. A solution of ethylene oxide (13.2 g in 20 mL of toluene) was added within 10 min and the temperature was then allowed to rise to room temperature. Solvants were evaporated and the resulting residue was dried to give 27 g (98%) of the desired primary alcohol. IR (KBr) 3411, 1631 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.2–1.4 (2H, m), 1.8 (2H, m), 1.9 (2H, q), 2.2 (2H, m), 2.5 (2H, t), 2.7 (1H, broad s), 2.9 (2H, m), 3.55 (2H, t), 4.55–4.8 (1H, m), 7.05 (2H, m), 7.4 (3H, m).

N-Phenyl-N-[1-(2-hydroxyethyl)piperidin-4-yl]butyramide ***xi-b***
IR (KBr) 3438, 1651 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.8 (3H, t), 1.35 (2H, m), 1.6 (2H, m), 1.8 (2H, m), 1.85 (2H, t), 2.2 (2H, m), 2.45 (2H, t), 2.9 (2H, m), 3.5 (2H, t), 4.65 (1H, m), 7.1 (2H, m), 7.4 (3H, m).

N-Phenyl-N-[1-(2-chloroethyl)piperidin-4-yl]propionamide ***xii-a***

The hydroxyethyl derivative **xi-a** (28 g, 0.1 mol) was dissolved in 200 mL in toluene. 9 mL (0.125 mol) of thionyl chloride in 30 mL of toluene was slowly added. The temperature rose quickly to 40 °C. The reaction was refluxed for 2 h. After cooling the precipitate was filtered, washed with toluene and ether and finally dried over P_2O_5 to give 32 g (97%) of the chloro derivative. ^1H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.65 (2H, m), 1.9 (2H, q), 2.0 (2H, m), 3.2 (2H, m), 3.4 (2H, m), 3.5 (2H, m), 4.0 (2H, t), 4.7 (1H, m), 7.1–7.6 (5H, 2m).

N-Phenyl-N-[1-(3-bromopropyl)piperidin-4-yl]propionamide ***xii-b***
7 g (0.03 mol) of 4-(*N*-propionylanilino)piperidine was heated at 65 °C in 30 mL of 1,3-dibromopropane for 1 h. Ethyl acetate was added and the resulting solid was filtrated, rinced with ether and dried to give 10.4 g (80%) of the desired bromo derivative as the hydrobromide. Mp 240 °C (sublimation); IR (nujol) 2700–2500, 1635 cm^{-1}; ^1H-NMR (DMSO–d_6) δ 0.85

(3H, t), 1.5 (2H, m), 1.8 (2H, m), 1.9 (2H, m), 2.15 (2H, m), 3.1 (4H, m), 3.6 (4H, m), 4.7 (1H, m), 7.2–7.6 (5H, 2m), 9.0 (1H, broad s).

N-Phenyl-N-[1-(2-chloroethyl)piperidin-4-yl]butyramide ***xii-c***
IR (nujol) 2550–2300, 1651 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.75 (3H, t), 1.45 (2H, m), 1.65 (2H, m), 1.85 (2H, t), 1.95 (2H, m), 3.0–3.6 (6H, m), 3.95 (2H, t), 4.7 (1H, m), 7.2 (2H, m), 7.5 (3H, m).

N-Phenyl-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***7***

2.4 g (6.9 mmol) of the chloro derivative **x-a** and 1.2 g (6.9 mmol) of the benzimidazolone **ix-a** was reacted with 2.1 g (15 mmol) of K_2CO_3 in 60 mL of anhydrous DMF at 85 °C for 20 h. After cooling to room temperature, the solvent was evaporated and the semi-solid residue was taken up with ethyl acetate and water. Washing the organic layer with water was followed by drying over calcium sulfate and evaporation of the solvent. Purification was performed on a silicagel column of chromatography (CH_2Cl_2–EtOAc, 1:1) to give 1.7 g (57%) of the final antagonist. Mp 136 °C; IR (nujol) 1705, 1640 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.1 (2H, m), 1.65 (2H, m), 1.8 (2H, m), 2.0 (5H, m), 2.5 (2H, m), 2.9 (2H, m), 3.85 (2H, t), 4.3–4.5 (1H, m), 5.1 (1H, s), 5.3 (1H, s), 7.0–7.5 (9H, m).

N-(3-Chlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl] ethyl]piperidinyl)propionamide ***9***
Mp 128 °C; IR (nujol) 1706, 1650, 1612 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.05 (2H, m), 1.65 (2H, m), 1.8 (2H, q), 2.0 (3H, s), 1.9–2.1 (2H, m), 2.5 (2H, t), 2.85 (2H, m), 3.85 (2H, t), 4.4 (1H, m), 5.05, 5.35 (2H, 2s), 7.0–7.25 (5H, 2m), 7.3 (1H, s), 7.5 (2H, m).

N-(4-Chlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***10***
Mp 128 °C; IR (nujol) 1706, 1648, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2–1.4 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.20 (2H, m), 2.65 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 4.55–4.75 (1H, m), 5.1, 5.3 (2H, 2s), 6.9–7.15 (6H, m), 7.35 (2H, t).

N-(2,4-Dichlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***11***
IR (KBr) 3062, 2939, 2807, 1707, 1663, 1614, 813–754 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.1–1.6 (2H, 2m), 1.8–2.0 (4H, m), 2.2 (3H, s), 2.25 (2H, m), 2.65 (2H, t), 3.0 (2H, m), 3.95 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.35 (1H, s), 6.9–7.1 (4H, m), 7.1 (1H, d), 7.3 (1H, dd), 7.5 (1H, d).

N-(2,5-Dichlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***12***
Mp 148 °C; IR (nujol) 1703, 1666, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.20–1.55 (2H, 2m), 1.9 (4H, m), 2.2 (3H, s), 2.25 (2H, m), 2.7 (2H, t), 3.0 (2H, m), 3.95 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 7.0 (4H, m), 7.2 (1H, d), 7.3 (1H, dd), 7.45 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***13***
Mp 156 °C; IR (nujol) 3059, 1705, 1653, 1612, 1585, 756–754 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.88 (3H, t), 1.0 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.0 (3H, s), 2.08 (2H, m), 2.50 (2H, m), 2.85 (2H, m), 3.85 (2H, t), 4.38 (1H, m), 5.05 (1H, s), 5.32 (1H, s), 6.85–7.25 (5H, m), 7.52 (1H, d), 7.70 (1H, d).

N-(3,5-Dichlorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***14***
Mp 170 °C; IR (nujol) 1702, 1650, 1614 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.9 (3H, t), 1.1 (2H, m), 1.65 (2H, m), 1.85 (2H, q), 2.0 (2H, m), 2.05 (3H, s), 2.45 (2H, m), 2.85 (2H, m), 3.85 (2H, t), 4.35 (1H, m), 5.05 (1H, s), 1.3 (1H, s), 6.9–7.2 (4H, m), 7.35 (2H, s), 7.7 (1H, s).

N-(4-Fluorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***15***
Mp 114 °C; IR (nujol) 1707, 1660–1643, 1611 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.25 (2H, m), 2.6 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 4.6 (1H, m), 5.1 (1H, s), 5.3 (1H, s), 6.9–7.2 (8H, m).

N-(3,4-Difluorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***16***
Mp 166 °C; IR (nujol) 1699, 1655, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.25 (2H, m), 2.65 (2H, t), 2.95 (2H, m), 3.95 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.75–7.3 (7H, m).

N-(3-Chloro-4-fluorophenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***17***
Mp 130–132 °C; IR (nujol) 1708, 1651, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.25 (2H, m), 2.65 (2H, t), 3.0 (2H, m), 3.95 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.9–7.25 (7H, m).

N-(4-Methylphenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***18***
Mp 110 °C; IR (nujol) 1705, 1645, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.95 (3H, t), 1.35 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.2 (2H, m), 2.35 (3H, s), 2.65 (2H, m), 2.95 (2H, m), 3.9 (2H, m), 4.5–4.7 (1H, m), 5.1 (1H, s), 5.3 (1H, s), 6.9–7.1 (6H, 2m), 7.2 (2H, d).

N-(3,4-Dimethylphenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***19***
Mp 138 °C; IR (nujol) 1718, 1656, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.25–1.5 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.25 (2H, m), 2.3 (6H, 2s), 2.6 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.75 (2H, m), 6.9–7.2 (7H, m).

N-(3-Chloro-4-methylphenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***20***
Mp 138–140 °C; IR (nujol) 1708, 1651, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.35 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.2 (2H, m), 2.4 (3H, s), 2.65 (2H, t), 3.0 (2H, m), 3.9 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.85 (1H, dd), 6.9–7.15 (7H, m), 7.25 (1H, d).

N-(3-Methoxyphenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***21***
Mp 110–112 °C; IR (nujol) 2854, 1703, 1647, 1601 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.15 (2H, m), 1.65 (2H, m), 1.85 (2H, q), 2.0 (2H, m), 2.05 (3H, s), 2.4 (2H, m), 2.9 (2H, m), 3.8 (3H, s), 3.85 (2H, t), 4.4 (1H, m), 5.05 (1H, s), 5.35 (1H, s), 6.7 (2H, m), 7.0–7.2 (5H, 2m), 7.35 (1H, m).

N-(3,4-Dimethoxyphenyl)-N-(1-[2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl]piperidinyl)propionamide ***22***
Mp 145 °C; IR (nujol) 1712, 1642, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.4 (2H, m), 1.75 (2H, m), 1.95 (2H, q),

2.15 (3H, s), 2.25 (2H, m), 2.65 (2H, t), 3.0 (2H, m), 3.9 (6H, 2s), 3.95 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.55 (1H, d), 6.65 (1H, dd), 6.85 (1H, d), 7.05 (4H, m).

N-(3-Chloro-4-methoxyphenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)-propionamide ***23***
Mp 150–152 °C; IR (nujol) 1700, 1650, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.95 (2H, q), 2.15 (3H, s), 2.2 (2H, m), 2.6 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 3.95 (3H, s), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 7.0 (7H, m).

N-(Naphth-2-yl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***24***
Mp 118–120 °C; IR (nujol) 1708, 1650, 1629 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.85 (3H, t), 1.0–1.4 (2H, m), 1.6–1.9 (4H, m), 1.85 (3H, s), 2.05 (2H, m), 2.45 (2H, m), 2.9 (2H, m), 3.8 (3H, t), 4.5 (1H, m), 4.95 (1H, s), 5.2 (1H, s), 6.9–7.15 (4H, 2m), 7.3 (1H, d), 7.6 (2h, m), 7.75 (1H, s), 8.0 (3H, m).

N-(Pyridin-4-yl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***25***
Mp 106 °C; IR (nujol) 1705, 1652, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.2 (2H, m), 2.6 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 4.65 (1H, m), 5.1 (1H, s), 5.3 (1H, s), 6.9–7.15 (6H, m), 8.7 (2H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl} piperidinyl)butyramide ***26***
Mp 202 °C; IR (KBr) 3060, 2956, 2808, 1709, 1653, 1614, 1595, 754, 735, 708 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.7 (3H, t), 1.10 (2H, m), 1.42 (2H, m), 1.63 (2H, m), 1.78 (2H, t), 2.05 (5H, s + m), 2.50 (2H, m), 2.90 (2H, m), 3.86 (2H, t), 4.40 (1H, m), 5.05 (1H, s), 5.32 (1H, s), 7.02 (3H, m), 7.15 (3H, m), 7.45 (3H, m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)-N-(1-piperidinylcarbonyl)amine ***27***
IR (KBr) 3050, 2935–2853, 1714, 1645, 1595–1580, 756–704 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0–1.75 (6H, m), 1.52 (2H, m), 1.85 (2H, m), 2.18 (3H, s), 2.20 (2H, m), 2.62 (2H, m), 2.98 (2H, m), 3.13 (4H, m), 3.95 (2H, m), 4.05 (1H, m), 5.15 (1H, s), 5.32 (1H, s), 6.90–7.40 (9H, m).

1-{2-[3-(Prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}-4-[(1H)-quinolin-2-one]-piperidine ***28***
Mp 175–182 °C; IR (nujol) 1700, 1666, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.7 (2H, m), 2.2 (3H, s), 2.3 (2H, m), 2.5–2.9 (8H, m), 3.1 (2H, m), 4.0 (2H, t), 4.3 (1H, m), 5.2 (1H, s), 5.35 (1H, s), 7.0–7.3 (8H, m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)amine ***29***
IR (nujol) 3358, 1702, 1661, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m), 2.0 (2H, m), 2.2 (3H, s), 2.3 (2H, m), 2.75 (2H, t), 2.9 (2H, m), 3.2 (1H, m), 3.6 (1H, broad s), 4.0 (2H, t), 5.2 (1H, s), 5.35 (1H, s), 6.40 (1H, dd), 6.65 (1H, d), 7.10 (4H, m), 7.15 (1H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)acetamide ***30***
Mp 175 °C; IR (nujol) 1705, 1652, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.3 (2H, m), 1.7 (2H, m), 1.85 (3H, s), 2.15 (3H, s), 2.20 (2H, m), 2.65 (2H, t), 2.95 (2H, m), 3.9 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.30 (1H, s), 6.8–7.15 (5H, m), 7.2 (1H, d), 7.5 (1H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)benzamide ***31***
Mp 158 °C; IR (nujol) 1702, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.5 (2H, m), 1.9 (2H, m), 2.2 (3H, s), 2.3 (2H, m), 2.7 (2H, t), 3.05 (2H, m), 3.95 (2H, t), 4.7 (1H, m), 5.15 (1H, s), 5.35 (1H, s), 6.85 (1H, dd), 6.9–7.3 (11H, m).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)-N-(1-piperidinylcarbonyl)amine ***32***
IR (KBr) 2933–2953, 1705, 1651, 1614, 1586–1556, 755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.10–1.65 (8H, m), 1.80 (2H, m), 2.20 (5H, m + s), 2.65 (2H, m), 3.02 (2H, m), 3.15 (4H, m), 3.95 (3H, m), 5.15 (1H, s), 5.32 (1H, d), 5.90 (1H, dd), 6.95–7.10 (4H, m), 7.18 (1H, d), 7.40 (1H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)glycinamide ***33***
Mp 162 °C; IR (nujol) 3400, 3050, 1704, 1654, 1613, 1583, 810–755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.68 (2H, broad s), 1.70 (2H, m), 2.18 (3H, s), 2.25 (2H, m), 2.66 (2H, t), 2.98 (4H, m), 3.93 (2H, t), 4.60 (1H, m), 5.15 (1H, s), 5.32 (1H, s), 6.85–7.15 (5H, m), 7.20 (1H, d), 7.50 (1H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)methoxyacetamide ***34***
IR (nujol) 2855, 1701, 1669 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.38 (2H, m), 1.75 (2H, m), 2.17 (3H, s), 2.25 (2H, m), 2.62 (2H, t), 3.0 (2H, m), 3.30 (3H, s), 3.60 (3H, s), 3.92 (2H, t), 1.60 (1H, m), 5.11 (1H, s), 5.31 (1H, s), 6.85–7.12 (5H, m), 7.22 (1H, d), 7.50 (1H, d).

N-(3-Chloro-4-methylphenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)acetamide ***35***
Mp 146 °C; IR (nujol) 1709, 1649, 1599, 756–746 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.75 (5H, s + m), 2.17 (3H, s), 2.22 (3H, s), 2.40 (3H, s), 2.65 (2H, t), 3.0 (3H, m), 3.92 (2H, t), 4.62 (1H, m), 5.15 (1H, s), 5.30 (1H, d), 6.80–7.15 (6H, m), 7.25 (1H, d).

N-(3-Chloro-4-methylphenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)glycinamide ***36***
Mp 134 °C; IR (nujol) 3600–3200, 1705, 1651, 1613, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.8 (4H, m + broad s), 2.15 (3H, s), 2.25 (2H, m), 2.4 (3H, s), 2.65 (2H, t), 2.95 (2H, m), 3.05 (2H, s), 3.9 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.85 (1H, dd), 6.9–7.15 (5H, m), 7.3 (1H, d).

N-(3-Chloro-4-methylphenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)phthalimidoacetamide ***37***
IR (nujol) 1774, 1719, 1673, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.4 (2H, m),1.75 (2H, m), 2.15 (3H, s), 2.2 (2H, m), 2.4 (3H, s), 2.65 (2H, t), 3.0 (2H, m), 3.9 (2H, t), 4.05 (2H, s), 4.5 (1H, m), 5.15 (1H, s), 5.3 (1H, s), 6.9–7.15 (5H, m), 7.3 (2H, m), 7.65–7.9 (4H, 2m).

N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}-4-benzyl)piperidine ***38***
IR (KBr) 1709, 1657, 1614 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 1.1 (2H, m), 1.3–1.55 (3H, m), 1.85 (2H, m), 2.15 (3H, s), 2.4–2.6

(4H, m), 2.85 (2H, m), 3.9 (2H, t), 5.15 (1H, s), 5.35 (1H, d), 7.0–7.3 (9H, m).

N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}-4-acetamido-4-phenyl)piperidine ***39***
IR (nujol) 3469–2300, 1712, 1660, 1616 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 1.8–2.5 (4H, 2m), 1.8 (3H, s), 2.15 (3H, s), 2.7–3.7 (6H, m), 4.1 (2H, m), 5.15 (1H, s), 5.4 (1H, s), 6.0 (1H, s), 6.9–7.5 (9H, m), 7.95 (1H, broad s).

N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}-1-phenyl-1,3,8-triazaspiro[4,5])decan-4-one ***40***
Mp 146–148 °C; IR (nujol) 3300–3000, 1701, 1655, 1610 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 1.55 (2H, m), 2.15 (3H, s), 2.4 (2H, m), 2.65 (2H, t), 2.85 (4H, m), 3.95 (2H, t), 4.55 (2H, s), 5.15 (1H, s), 5.35 (1H, s), 6.7 (3H, m), 7.0–7.35 (6H, m), 8.65 (1H, broad s).

N-Methyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)benzamide ***41***
Mp 120–122 °C; IR (nujol) 1704, 1659, 1630 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 1.5–1.8 (4H, 2m), 2.0 (2H, m), 2.15 (3H, s), 2.65 (2H, t), 2.8 (3H, s), 2.95 (2H, m), 3.8 (1H, m), 3.9 (2H, t), 5.15 (1H, s), 5.35 (1H, s), 7.0–7.2 (4H, d + m), 7.4 (5H, 2m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinium iodide)propionamide ***42***
Mp 216 °C (decomposition); IR (nujol) 1728, 1705, 1647, 1612 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, m), 1.6–2.0 (6H, m), 2.15 (3H, s), 3.0 + 3.2 (3H, 2s), 3.3–3.75 (6H, m), 4.3 (2H, t), 4.6 (1H, m), 5.15 (1H, s), 5.4 (1H, s), 7.1–7.6 (9H, m).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinium iodide)propionamide ***43***
^{1}H-NMR (DMSO–d_6) δ 0.9 (3H, t), 1.7–2.05 (6H, m), 2.15 (3H, s), 3.05 + 3.2 (3H, 2s), 3.7 (6H, m), 4.25 + 4.24 (1H, 2t), 4.65 (1H, m), 5.2 (1H, s) 5.4 (1H, s), 7.1–7.8 (7H, m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]propyl}piperidinyl)propionamide ***44***
Mp 150–152 °C; IR (nujol) 2750–2400, 1707, 1649 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 1.5–1.7 (2H, m), 1.75–2.1 (6H, m), 2.15 (3H, s), 3.0–3.2 (4H, m), 3.4 (2H, m), 3.85 (2H, t), 4.7 (1H, m), 5.15 (1H, d), 5.35 (1H, d), 7.0–7.55 (9H, 3m), 9.8 (1H, broad s).

N-(4-Pyridyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyloxycarbonyl}piperidinyl)propionamide ***45***
IR (nujol) 1705, 1658, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.2 (3H, s), 2.75 (2H, m), 4.0–4.3 (2H, m), 4.1 (2H, t), 4.3 (2H, t), 4.75 (1H, m), 5.2 (1H, s), 5.35 (1H, s), 6.9–7.2 (6H, m), 8.75 (2H, d).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-7-methyl-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***46***
Mp 150–152 °C; IR (nujol) 1699, 1647, 1612 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.88 (3H, t), 1.10 (2H, m), 1.65 (2H, m), 1.80 (2H, q), 1.98 (3H, s), 2.08 (2H, m), 2.45 (2H, t), 2.48 (3H, s), 2.85 (2H, m), 4.02 (2H, t), 4.43 (1H, m), 5.02 (1H, s), 5.32 (1H, s), 6.75–6.95 (3H, m), 7.16 (2H, m), 7.45 (3H, m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-4-nitro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***47***
Mp 162 °C; IR (nujol) 1728, 1653, 1626, 1533, 1388 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.0 (2H, m), 1.6 (2H, m), 1.75 (2H, q), 1.95 (3H, s), 2.05 (2H, m), 2.55 (2H, m), 2.85 (2H, m), 3.9 (2H, t), 4.4 (1H, m), 4.65 (1H, s), 5.1 (1H, s), 7.0–7.2 (4H, m), 7.4 (2H, m), 7.55 (2H, m).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-5,6-dichloro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***48***
IR (nujol) 3000, 1714, 1660, 1595, 860, 702 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.86 (3H, t), 1.10 (2H, m), 1.65 (2H, m), 1.80 (2H, m), 2.06 (2H, m), 2.45 (5H, s + m), 2.85 (2H, m), 4.20 (2H, m), 4.40 (1H, m), 7.15 (2H, m), 7.45 (3H, m), 7.70 (2H, s), 12.5 (1H, broad s).

N-Phenyl-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-naphth[2,3-d]imidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***49***
Mp 173–175 °C; IR (nujol) 1716, 1651, 1600 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.1 (2H, m), 1.65 (2H, m), 1.8 (2H, q), 2.05 (3H, s), 2.1 (2H, m), 2.6 (2H, t), 2.9 (2H, m), 3.95 (2H, t), 4.4 (1H, m), 5.20 (1H, s), 5.45 (1H, s), 7.8 (1H, m), 7.9 (1H, m).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-5-trifluoromethyl-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***50***
IR (nujol) 1732, 1672, 1617, 1320, 1173, 1122 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.1 (3H, s), 2.25 (2H, m), 2.6 (2H, t), 2.95 (2H, m), 4.1 (2H, t), 4.6 (1H, m), 5.1 (1H, s), 5.4 (1H, s), 6.9 (1H, dd), 7.25 (3H, m), 7.35 (1H, d), 7.5 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-6-trifluoromethyl-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***51***
IR (nujol) 1710–1708, 1662, 1622, 1327, 1159, 1119 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.00 (2H, m), 1.65 (2H, m), 1.80 (2H, m), 2.05 (5H, m + s), 2.50 (2H, t), 2.65 (2H, m), 2.70 (2H, m), 3.90 (2H, t), 4.40 (1H, m), 5.10 (1H, broad s), 5.40 (1H, broad s), 7.10–7.25 (2H, d), 7.40 (2H, m), 7.60 (2H, broad s).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-7-trifluoromethyl-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***52***
Mp 161–163 °C; IR (nujol) 1720, 1659, 1631, 1321, 1163, 1118 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.83 (3H, t), 1.00 (2H, m), 1.65 (2H, m), 1.85 (2H, m), 2.00 (3H, s), 2.05 (2H, q), 2.30 (2H, t), 2.85 (2H, m), 3.90 (2H, t), 4.10 (1H, m), 5.15 (1H, broad s), 5.40 (1H, broad s), 7.20–7.70 (2H, d), 7.25 (1H, s), 7.40 (2H, m), 7.60 (1H, broad s).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-on-1-yl]ethyl}piperidinyl)propionamide ***53***
IR (nujol) 1724, 1659, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.25 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.2 (3H, s), 2.2 (2H, m), 2.7 (2H, t), 3.0 (2H, m), 4.05 (2H, t), 4.6 (1H, m), 1.1 (1H, s), 5.3 (1H, s), 6.95 (2H, m), 7.2 (1H, d), 7.25 (1H, dd), 7.45 (1H, d), 8.0 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-imidazo[4,5-e]pyridin-2-on-1-yl]ethyl}piperidinyl)propionamide ***54***
IR (KBr) 1714, 1660, 1651–1584 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.90 (3H, t), 0.98 (2H, m), 1.63 (2H, m), 1.85 (2H, m), 2.10 (5H, m), 2.50 (2H, m), 2.85 (2H, m), 3.90 (2H, t), 4.40 (1H, m), 5.15 (1H, s), 5.78 (1H, s), 7.0 (1H, dd), 7.20 (1H, dd), 7.50 (1H, dd), 7.57 (1H, d), 7.70 (1H, d), 7.92 (1H, dd).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(prop-1-en-2-yl)-1,3-dihydro-2H-naphth[2,3-d]imidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***55***
Mp 185–190 °C; IR (nujol) 1710, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.15 (3H, s), 2.20 (2H, m), 2.65 (2H, t), 3.05 (2H, m), 4.0 (2H, t), 4.65 (1H, m), 5.2 (1H, s), 5.4 (1H, s), 6.9 (1H, dd), 7.2 (1H, d), 7.25–7.35 (4H, m), 7.45 (1H, d), 7.75 (2H, m).

N-Phenyl-N-(1-{2-[1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl) propionamide ***56***
Mp 205 °C; IR (nujol) 3200–2500, 1700–1600, 1690, 1640 cm^{-1}.

N-Phenyl-N-(1-{2-[3-acetyl-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl) propionamide ***57***
Mp 175–177 °C; IR (nujol) 3449, 1738, 1714, 1643, 1612–1597, 762, 708 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.88 (3H, t), 1.10 (2H, m), 1.65 (2H, m), 1.80 (2H, q), 2.05 (2H, m), 2.50 (5H, s + m), 2.90 (2H, m), 3.85 (2H, t), 4.40 (1H, m), 7.0–7.50 (9H, m).

N-Phenyl-N-(1-{2-[3-cyclopropyl-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***58***
Mp 98–100 °C; IR (nujol) 3047, 1703, 1645, 1616, 1593, 754, 708 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (7H, t + m), 1.35 (2H, m), 1.78 (2H, m), 1.92 (2H, t), 2.22 (2H, m), 2.60 (2H, t), 2.80 (1H, m), 2.95 (2H, m), 3.90 (1H, m), 4.65 (1H, m), 6.90 (1H, m), 7.02 (4H, m), 7.18 (1H, m), 7.35 (3H, m).

N-Phenyl-N-(1-{2-[3-phenyl-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl) propionamide ***59***
Mp 176–180 °C; IR (nujol) 2500, 1705, 1657 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.9 (3H, t), 1.6 (2H, m), 1.8 (2H, q), 2.05 (2H, m), 3.25 (3H, m), 3.4 (2H, t), 3.7 (2H, m), 4.3 (2H, t), 4.8 (1H, m), 7.0–7.3 (4H, m), 7.5 (10H, m).

N-Phenyl-N-(1-{2-[3-benzyl-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***60***
IR (nujol) 1707, 1653 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.4 (2H, m), 1.8 (2H, m), 1.95 (2H, q), 2.3 (2H, m), 2.6 (2H, t), 3.0 (2H, m), 4.0 (2H, t), 4.6–4.7 (1H, m), 5.0 (2H, s), 6.8–7.5 (14H, m).

N-Phenyl-N-(1-{2-[3-(1-tertbutyloxycarbonyl-1,2,3,6-tetrahydropyridin-4-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}-piperidinyl)propionamide ***61***
IR (nujol) 3057, 1711, 1655, 1616, 1595 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.02 (3H, t), 1.35 (2H, m), 1.52 (9H, s), 1.78 (2H, m), 1.98 (2H, q), 2.25 (2H, m), 2.52 (2H, m), 2.65 (2H, t), 2.98 (2H, m), 3.70 (2H, t), 3.92 (2H, t), 4.12 (2H, m), 4.65 (1H, m), 5.85 (1H, m), 7.05 (6H, m), 7.40 (3H, m).

N-Phenyl-N-(1-{2-[3-(1,2,3,6-tetrahydropyridin-4-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***62***
IR (nujol) 3500–3300, 1705, 1649, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.35 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.2 (2H, m), 2.5 (2H, m), 2.65 (2H, t), 2.95 (2H, m), 3.2 (2H, t), 3.65 (2H, m), 3.9 (2H, t), 4.65 (1H, m), 5.9 (1H, m), 7.0 (6H, m), 7.4 (3H, m).

N-Phenyl-N-(1-{2-[3-(cyclopenten-1-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***63***
IR (nujol) 3053, 1711, 1649, 1610, 1595, 756–702 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.36 (2H, m), 1.78 (2H, m), 1.92 (2H, m), 2.08 (2H, q), 2.22 (2H, m), 2.55 (2H, m), 2.65 (2H, t), 2.85 (2H, m), 3.0 (2H, m), 3.92 (2H, t), 4.68 (1H, m), 5.90 (1H, t), 6.90–7.20 (6H, m), 7.40 (3H, m).

N-Phenyl-N-(1-{2-[3-(2-phenylethyl-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***64***
IR (nujol) 1717, 1653, 1615, 1595, 774, 751, 707 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.35 (2H, m), 1.80 (2H, m), 1.92 (2H, q), 2.25 (2H, m), 2.70 (2H, t), 3.0 (2H, m), 4.0 (2H, t), 4.70 (1H, m), 5.50 (1H, s), 5.90 (1H, s), 6.65 (1H, d), 6.85–7.15 (8H, m), 7.20–750 (6H, m).

N-(3,4-Dichlorophenyl)-N-(1-{2-[1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl} piperidinyl)propionamide ***65***
IR (nujol) 3500–3100, 2800–2400, 1697–1620 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.9 (3H, t), 1.5 (2H, s), 1.85–2.1 (4H, m), 3.05–3.4 (4H, m), 3.70 (2H, m), 4.15 (3H, t), 4.7 (1H, m), 7.0 (3H, m), 7.25 (1H, m), 7.3 (1H,dd), 7.7 (1H, d), 7.75 (1H, d), 11.0 (1H, s).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(3,3,3-trifluoroprop-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***66***
IR (nujol) 3060, 1726, 1660, 1618, 1585–1558, 818–750, 733 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.25 (2H, m), 1.72 (2H, m),1.92 (2H, q), 2.20 (2H, m), 2.68 (2H, t), 2.98 (2H, m), 3.95 (2H, t), 4.63 (1H, m), 5.90 (1H, q), 6.45 (1H, s), 6.85–7.15 (5H, m), 7.18 (1H, d), 7.50 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(but-2-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***67***
IR (nujol) 1707, 1657, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.2–1.4 (2H, m), 1.7 (2H, m), 1.85 (3H, d), 1.9 (2H, m), 1.95 (3H, s), 2.20 (2H, m), 2.65 (2H, t), 3.0 (2H, m), 3.95 (2H, t), 4.6 (1H, m), 5.7 (1H, m), 6.85–7.15 (5H, m), 7.2 (1H, d), 7.5 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(but-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***68***
Mp 131 °C; IR (nujol) 1704, 1653, 1612 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (6H, m), 1.3 (2H, m), 1.7 (2H, m), 1.9 (2H, q), 2.2 (2H, m), 2.5–2.7 (4H, m), 3.0 (2H, m), 3.95 (2H, t), 4.65 (1H, m), 5.15 (1H, s), 5.35 (1H, s), 6.9–7.1 (5H, m), 7.2 (1H, d), 7.5 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(cyclopenten-1-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***69***
Mp 155–157 °C; IR (nujol) 1712, 1651, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.0 (3H, t), 1.35 (2H, m), 1.75 (2H, m), 1.85–2.15 (4H, m), 2.2 (2H, m), 2.55 (2H, m), 2.65 (2H, t), 2.8 (2H, m), 3.0 (2H, m), 3.9 (2H, t), 4.6 (1H, m), 5.9 (1H, m), 6.85–7.15 (5H, m), 7.2 (1H, d), 7.45 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(2-phenylethyl-1-en-2-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)propionamide ***70***
IR (nujol) 2855, 1701, 1669 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.38 (2H, m), 1.75 (2H, m), 2.17 (3H, s), 2.25 (2H, m), 2.62 (2H, t), 3.0 (2H, m), 3.30 (3H, s), 3.60 (3H, s), 3.92 (2H, t), 4.60 (1H, m), 5.11 (1H, s), 5.31 (1H, s), 6.85–7.12 (5H, m), 7.22 (1H, d), 7.50 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-{2-[3-(cyclopenten-1-yl)-1,3-dihydro-2H-benzimidazol-2-on-1-yl]ethyl}piperidinyl)methoxyacetamide ***71***
Mp 144–145 °C; IR (nujol) 1708, 1666, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.35 (2H, m), 1.75 (2H, m), 2.1 (2H, m), 2.25 (2H,

m), 2.55 (2H, m), 2.65 (2H, t), 2.85 (2H, m), 3.0 (2H, m), 3.3 (3H, s), 3.6 (2H, s), 3.9 (2H, t), 4.6 (1H, m), 5.85 (1H, m), 6.85–7.2 (6H, m), 7.2 (1H, d), 7.5 (1H, d).

N-(3,4-Dichlorophenyl)-N-(1-[2-[9H-imidazo[1,2-a]benzimidazole]ethyl]piperidinyl)propionamide ***72***
Mp 170 °C; IR (nujol) 1648, 1618–1590, 750 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 0.92 (2H, m), 1.60 (2H, m), 1.82 (2H, m), 2.02 (2H, m), 2.68 (2H, t), 2.85 (2H, m), 4.18 (2H, t), 4.35 (1H, m), 6.98 (1H, d), 7.03–7.25 (3H, m), 7.45 (1H, d), 7.52 (1H, s), 7.62 (1H, d), 7.68 (2H, d).

N-Phenyl-N-(2-[benzoxazoline-2-on-1-yl]ethylpiperidinyl)-propionamide ***73***
Mp 119 °C; IR (nujol) 1765, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (3H, t), 1.3 (2H, m), 1.75 (2H, m), 1.9 (2H, q), 2.25 (2H, m), 2.65 (2H, t), 2.9 (2H, m), 3.85 (2H, t), 4.65 (1H, m), 6.9 (1H, m), 7.05 (4H, m), 7.15 (1H, d), 7.35 (3H, m).

N-Phenyl-N-(2-[indolin-2,3-dion-1-yl]ethylpiperidinyl)propion-amide ***74***
Mp 129 °C; IR (nujol) 1734, 1643 cm^{-1}; ^{1}H-NMR (DMSO–d_6) δ 0.85 (3H, t), 1.15 (2H, m), 1.65 (2H, m), 1.8 (2H, q), 2.1 (2H, m), 2.4 (2H, m), 2.85 (2H, m), 3.65 (2H, t), 4.4 (1H, m), 7.15 (4H, m), 7.5 (5H, m).

Binding assays on human NK_1 and NK_2 receptors

Radioligand binding assays were performed with the IM9 human lymphoblastoma cell line which expressed NK_1 receptors [24] or with transfected Chinese hamster ovary (CHO) cells, a cell line expressing a single class of high-affinity human NK_2 receptor sites (about 600 000 binding sites/cell) with an apparent K_D of 2.1 nM for Neurokinin A [25]. Cells were incubated for 45 min at 23 °C with [^{3}H][Sar^{9}Met(O_2)^{11}] substance P or [^{3}H]Neurokinin A (approximately 0.1 nM) to label NK_1 and NK_2 sites, respectively. Binding in the presence of defined concentrations of the test compound was then estimated with a conventional filtration assay. Receptor selectivity with respect to opiate μ-receptors was assessed in a classical binding assay on rat brain membranes using tritiated DAGO as the μ-selective ligand [26]. Results were expressed in terms of K_i.

Isolated-organ studies

Experiments were carried out as described by Regoli et al [17, 18] on the rabbit *vena cava*, the rabbit pulmonary artery, and the rat portal vein for NK_1, NK_2, and NK_3 receptors, with SP, Neurokinin A and [MePhe^7]Neurokinin B as agonists respectively. The results were expressed in terms of pA2.

Hot-plate test

This assay was carried out in mice (male CD 1, 26–30 g) randomly assigned to groups of 12 animals using the method described by Eddy and Leimbach [22]. Compounds were administered iv 5 min or po 10 min before the test respectively. Results were expressed as an ED_{50} value, corresponding to the dose required to increase the reaction time by 50% (determined by simple linear regression with replications).

SP-induced bronchoconstriction

Male Hartley guinea-pigs (360–460 g, Charles River) were anaesthetized with urethane (1.5 g/kg ip) and anaesthesia was monitored in a classical way using clinical criteria. The trachea, left jugular vein and right carotid artery were cannulated. Body temperature was maintained at 37 ± 1 °C using a blanket control unit. The animal was attached to a respiratory pump, artificially ventilated (60 breaths/min, tidal volume 10 mL/kg) and curarized (galamine triethiodide 2 mg/kg iv) to prevent interference from spontaneous respiration. Artificial ventilation was defined so as to keep both blood gases and pH in the normal range, as determined in preliminary experiments. Bronchoconstriction experiments were terminated by an overdose of pentobarbital. Pulmonary inflation pressure was recorded on a breath-by-breath basis using a Statham pressure transducer connected to a side arm of the tracheal cannula. Carotid blood pressure was measured with a similar transducer (Spectramed P23xL, Bilthoven, The Netherlands). Both transducers were connected to amplifiers and a recorder (Gould RS3400, Valley View, OH, USA). All animals were pretreated with mepyramine (1 mg/kg iv) to block the effects of histamine release that may be induced by tachykinins, and with propanolol (1 mg/kg iv). Substance P (2 nmol/kg iv) was injected 15 min before iv treatment either with the antagonists, CP99994 (50, 200 and 500 nmol/kg), or with saline. Results were expressed as percentages of the mean response in the control group.

Acknowledgments

The authors wish to thank Dr JP Volland and his group for analytical and spectral studies, Dr JL Peglion for the synthesis of CP 99994, and Mrs D Pommier and Mr A Benoist for expert technical assistance.

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