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Discovery of Orally Bioavailable NK_1 Receptor Antagonists

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Abstract—Benzyloxyphenethylpiperazines are a new class of high affinity NK_1 receptor antagonists. Oral bioavailability and selectivity can be fine tuned by the nature of the substituents on the basic nitrogen atom. Addition of substituents with a carboxylic acid group led to very selective and orally active NK_1 antagonists free of interaction with L-type calcium channels.

The endogenous undecapeptide Substance P (SP) elicits a wide range of physiological responses both centrally and peripherally. Through binding to NK_1 receptors, SP has been implicated in the induction of neurogenic inflammation, in the transmission of nociceptive stimulus, in the control of vomiting reflex and in affective disorders.[1] Thus, NK_1 receptor antagonists are potentially useful for the treatment of a wide range of clinical diseases such as asthma, chronic pain, emesis, anxiety and depression. The disclosure by Pfizer of the first two non peptide NK_1 antagonists, CP-96,345 and CP-99,994 (**1**)[2] (Fig. 1), has spurred intensive research in this field. During the last few years, several other NK_1 receptor antagonists have been reported including benzyloxyaminopiperidines such as L-733,060 **2**[3] (Fig. 1). However, clinical development of the early NK_1 antagonists has been hampered by poor bioavailability and/or cardiovascular side effects resulting from interaction with L-type calcium channels. Subsequent efforts have been devoted to the conception of NK_1 antagonists with improved in vivo activity and reduced interaction with calcium channels such as MK-869 **3**[4] and CP-122,721 **5**.[5]

To date, only two NK_1 antagonists have reached phase III clinical trials. A prodrug of MK-869 **4**[6] is currently under development for the treatment of emesis whereas CP-122,721 has shown robust antidepressant effect in humans and is now undergoing further evaluation.

Herein, we would like to report our own efforts directed towards the discovery of orally bioavailable NK_1 antagonists free of interaction with calcium channels. Our starting point **6** suffered from several drawbacks

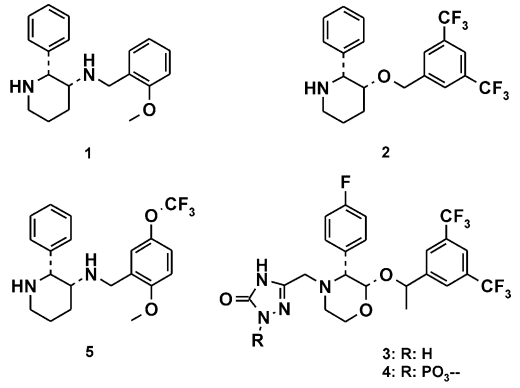

Figure 1. Selected NK_1 antagonists.

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(Fig. 2). In addition to its modest affinity for the NK_1 receptor, absorption issues were anticipated due to the poor aqueous solubility (s: 0.6 μg/mL, pH: 7.4) and high lipophilicity (log $D > 5.0$) of the compound. Sequential removal of the benzyl and trimethoxybenzyl groups on the piperazine ring led to **7**, a molecule with a much better affinity for the NK_1 receptor and lower lipophilicity (log D: 2.40). These results bear out the currently established pharmacophoric model consisting of two aromatic rings, a hydrogen bond acceptor and a nitrogen atom.[7] However, the presence of the second nitrogen of the piperazine greatly improved solubility (s: 0.2 mg/mL for **7**) and gave us the opportunity to further modulate the physicochemical and ADME properties of the molecule (vide infra).

Chemistry

Preparation of the benzyloxyphenethylpiperazines (**9**–**23**) started from 2-phenyl-2-piperazinylethanol (**8**) which was easily obtained by reaction of the *N*-protected piperazine with bromophenylacetate followed by reduction of the ester (Scheme 1). Enantiomerically pure **8** was obtained by gently heating the *N*-protected piperazine with the chiral styrene epoxide in ethanol. The nucleophilic attack on the epoxide gave a mixture of two regioisomers that were readily separated by chromatography. Synthesis of substituted-phenyl or heteroarylpiperazinylether (**24**–**39**) relies on the recently reported arylboronic acid Mannich reaction.[8] This elegant three-component coupling reaction provided a straightforward access to alcohol intermediates by simply stirring at room temperature in methylene chloride the commercially available arylboronic acid, the *N*-Boc piperazine and the hydroxyacetaldehyde. Alkylation of the alcohols with benzyl bromides under standard conditions followed by cleavage of the carbamate group gave the target compounds **24**.

Substituents on the basic nitrogen were introduced through alkylation or acylation with the appropriate reagents. Compounds bearing either a carboxylic acid or a tetrazole were prepared from the corresponding amide or nitrile following experimental procedures described in the literature (Scheme 2). The Williamson reaction could not be used for the preparation of the α-methylsubstitutedbenzylethers (**58**–**61**) since rapid decomposition of the benzylbromides took place. Therefore condensation of the (*R*) or (*S*) alcohol **8** with benzoic acid and methylenation of the resulting ester with dimethyltitanocene[9] yielded the enol ethers (Scheme 3). Homogeneous hydrogenation with Wilkinson's catalyst and deprotection of the nitrogen afforded the expected products as a mixture of two diastereoisomers that were separated by chromatography. Absolute configuration of the second chiral center was determined by X-ray diffraction analysis on the hydrochloride salt of **59a** (Fig. 3).

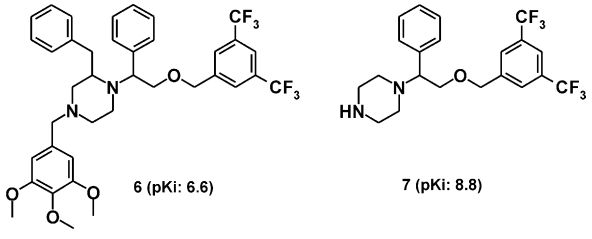
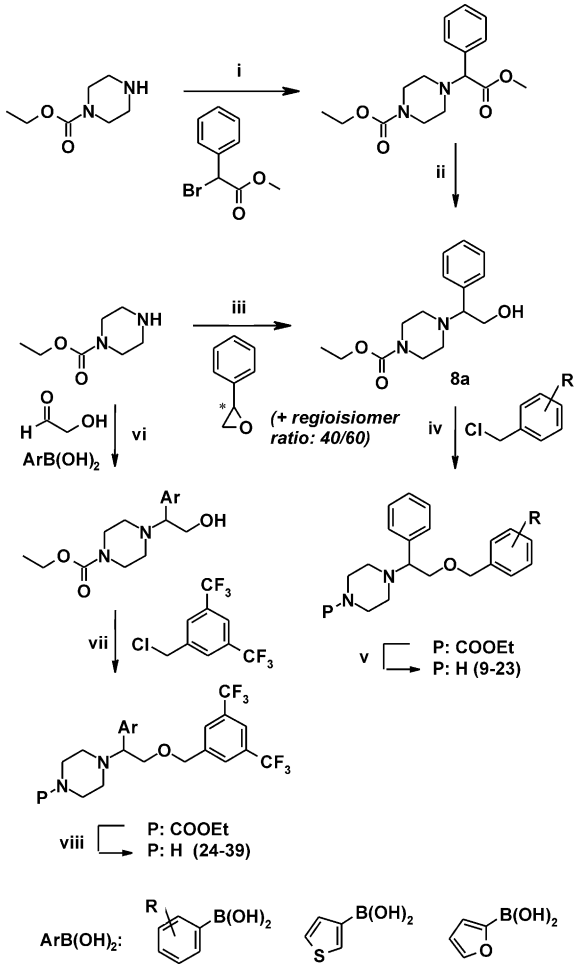


Figure 2.

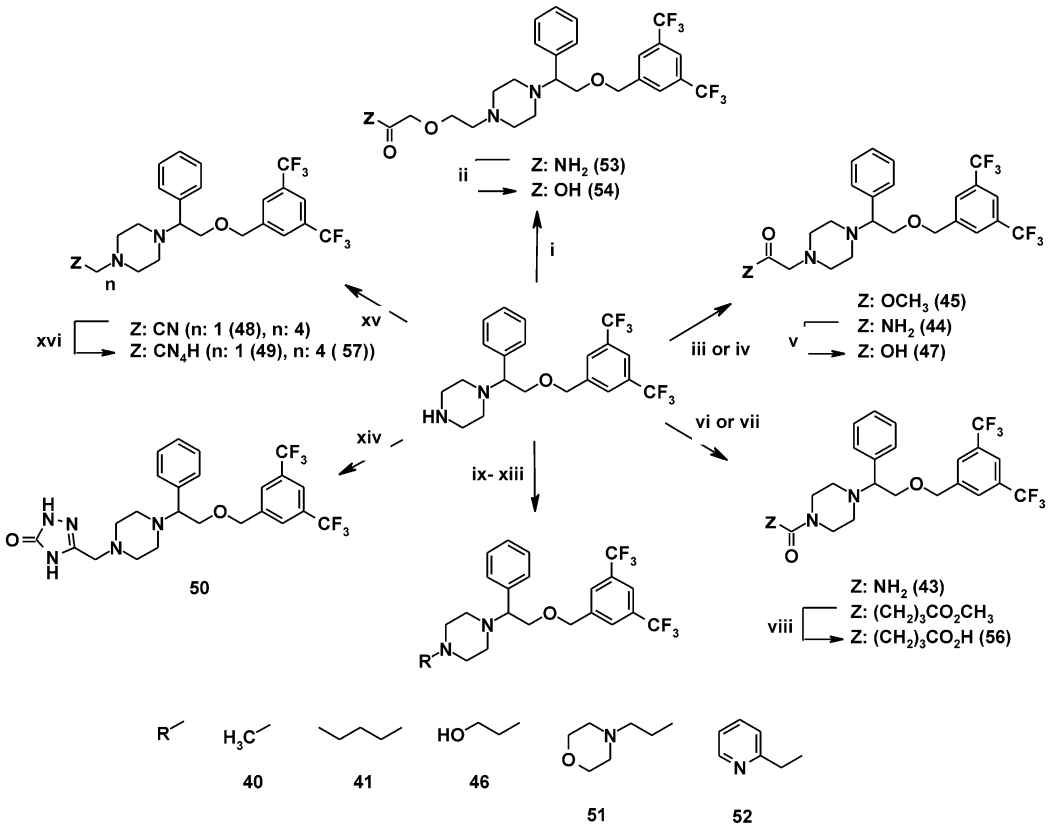
Biology

As can be seen in Table 1, introduction of substituents other than CF_3 on the distal aromatic ring led to a loss of affinity for the NK_1 receptor. The drop was moderate when chlorine or bromine atoms were used instead of CF_3 and was much more severe when fluorine or alkyl groups (Me, tBu) were introduced instead of CF_3. Attempts to modify the position of the substituents was unconvincing, for example when the CF_3 groups were shifted to the 2,5-position, a 100-fold loss of affinity was observed (**21**). Hence, CF_3 substituents in 3,5-position appear to be optimal for high affinity.

Introduction of substituents in the *para* position of the proximal phenyl was detrimental to the interaction with the NK_1 receptor (Table 2). Surprisingly, even a fluorine



Scheme 1. (i) K_2CO_3, DMF, rt, 84%; (ii) LAH, THF, −10 °C, 93%; (iii) EtOH, reflux, 92%; (iv) NaH, NaI, THF, rt; (v) KOH, EtOH, 80 °C; (vi) CH_2Cl_2, 50 °C; (vii) NaH, NaI, THF, rt; (viii) KOH, EtOH, 80 °C.



Scheme 2. (i) $Cl(CH_2)_2OCH_2CONH_2$, K_2CO_3, DMF; (ii) HCl 1 N, reflux; (iii) $BrCH_2CONH_2$, Na_2CO_3, MeOH, reflux; (iv) $BrCH_2CO_2Me$, K_2CO_3, DMF; (v) HCl 1 N, reflux; (vi) Me_3SiNCO, THF; (vii) $ClCO(CH_2)_3CO_2Me$, CH_2Cl_2/NaOH aq; (viii) KOH, MeOH, rt; (ix) HCHO, $NaBH_3CN$, AcOH, MeOH; (x) $Br(CH_2)_3CH_3$, KI, $NaHCO_3$, EtOH; (xi) $Cl(CH_2)_2OH$, Na_2CO_3, MeOH, reflux; (xii) $Cl(CH_2)_2$morpholine, NaI, $NaHCO_3$, EtOH; (xiii) 2-pyridinecarboxaldehyde, $NaBH_3CN$, AcOH, MeOH; (xiv) $ClCH_2CN$, $H_2NNHCO_2CH_3$, MeOH then K_2CO_3, DMF, 140 °C; (xv) $Br(CH_2)_4CN$, K_2CO_3, DMF; (xvi) Me_3SiN_3, Bu_2SnO, toluene, reflux.

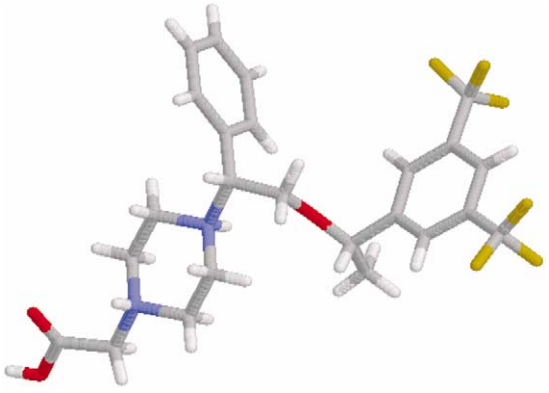
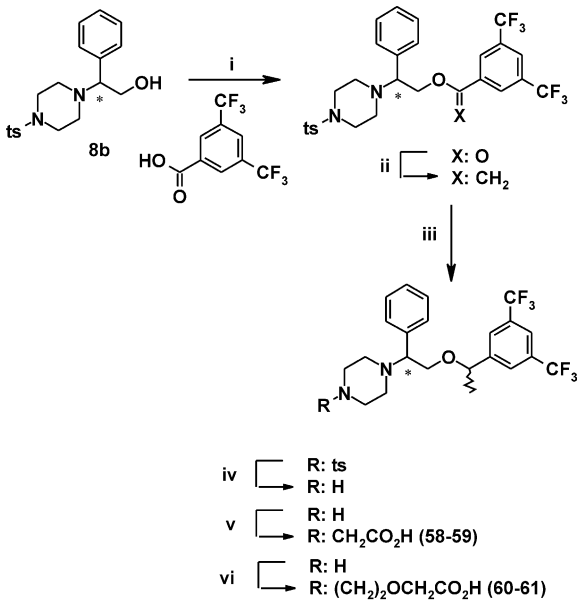


Figure 3. X-ray diffraction of **59a**.

atom in this position gave a compound with much weaker affinity than the unsubstituted analogue. Substitution in the *meta* or *ortho* position was well tolerated. Compound **36** with an α-naphthyl has similar affinity to **7** whereas the one with a β-naphthyl **37** has lower affinity. Replacement of phenyl with a heteroaryl nucleus revealed that thiophene but not furan could be used as a surrogate for phenyl. We then turned our attention to the introduction of substituents on the basic nitrogen of the piperazine nucleus (Table 3).

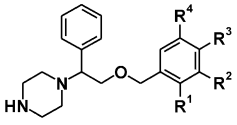
Introduction of alkyl groups (CH_3, $(CH_2)_3CH_3$) did not affect the affinity for the NK_1 receptor. However, we did observe subtle variations when the alkyl side chain contained polar functions such as alcohols and amides. Hence, compound **44** with an acetamide side chain displays a lower affinity than the parent compound whereas compounds with an ethanolamine side chain (**46**) or a longer amide (**53**) show similar affinity to **7**. The difference between **44** and **53** could lie in the pK_a of the basic nitrogen. pK_a values for compounds **44** and **53** (6.2 and 7.4, respectively) indicate that the nitrogen atom of **53** is half protonated at pH 7.4 whereas **44** is not. A protonated nitrogen seems to be favorable but not necessary for the interaction with the NK_1 receptor. This assumption is supported by the observation that acylation of the nitrogen further reduces the affinity. However, since compound **43** (urea) retains a reasonable affinity, the protonated nitrogen is not involved in an ionic interaction with the receptor but would rather act as a hydrogen bond donor. The interaction with the receptor is not stereoselective since we did not notice any difference between the two enantiomers **44a** and **44b**. Compounds with acidic functions also have a diminished binding affinity in comparison to simple alkyl derivatives.

The incorporation of a methyl group in the benzylic position next to the oxygen atom led to the creation of a second chiral center. The four were prepared and tested separately. The absolute configuration of the carbon atom next to the piperazine nucleus has only a



Scheme 3. (i) $(EtO)_3P(O)CH_2COOEt$, NaH, THF; (ii) Cp_2TiMe_2, toluene/THF, rt; (iii) H_2, $RhCl(PPh_3)_3$, EtOH; (iv) HCl aq 60 °C; (v) $BrCH_2CONH_2$, Na_2CO_3, MeOH, reflux then HCl 1 N reflux; (vi) $Cl(CH_2)_2OCH_2CONH_2$, K_2CO_3, DMF, then HCl 1 N, reflux.

Table 1. Affinities[a] of compounds **9**–**23** for the NK_1 receptor



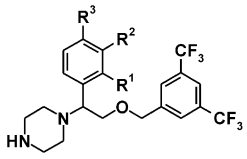
9-23

Compd	R^1	R^2	R^3	R^4	pK_i NK_1
7	H	CF_3	H	CF_3	8.8
9	H	H	H	H	+
10	OCH_3	H	H	H	+
11	OCF_3	H	H	H	++
12	Cl	H	H	H	++
13	H	Cl	H	H	6.4
14	H	Cl	Cl	H	7.0
15	H	Cl	H	Cl	8.5
16	H	Br	H	Br	8.3
17	H	F	H	F	6.7
18	H	F	H	CF_3	7.9
19	H	CH_3	H	CH_3	7.6
20	H	$C(CH_3)_3$	H	$C(CH_3)_3$	7.0
21	CF_3	H	CF3	H	7.8
22	H	OCH_3	OCH_3	OCH_3	6.9
23	OCH_3	Br	H	Br	8.1

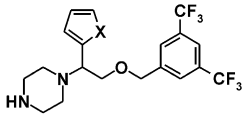
[a]Displacement of [^{3}H]-substance P from human NK_1 receptors expressed in CHO cells ($n=3$); +: <20% inhibition at 10^{-5} M; ++: 20–50% inhibition at 10^{-5} M.

marginal influence on the affinity (Table 4). However, it appears that the absolute configuration of the carbon atom bearing the methyl group has a marked effect on the affinity[10] with the (*S*) enantiomers being much more potent than the non-methylated derivatives while the (*R*) enantiomers are essentially inactive. The gain in affinity may be ascribed to a conformational effect and/or to an additional hydrophobic interaction with the NK_1 receptor.

Table 2. Affinities of compounds **24**–**39** for the NK_1 receptor[a]



24-37



38: X=S
39: X=O

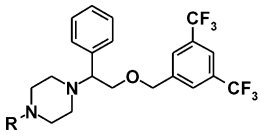
Compd	R^1	R^2	R^3	pK_i NK_1
7	H	H	H	8.8
24	F	H	H	8.3
25	Cl	H	H	8.8
26	CH_3	H	H	9.0
27	OCH_3	H	H	8.2
28	H	F	H	8.7
29	H	Cl	H	8.8
30	H	CH_3	H	8.5
31	H	OCH_3	H	9.0
32	H	H	F	7.1
33	H	H	OCH_3	7.3
34	F	F	H	8.5
35	H	Cl	Cl	8.2
36	CH=CH	CH=CH	H	8.8
37	H	CH=CH	CH=CH	7.5
38	—	—	—	8.1
39	—	—	—	6.8

[a]Displacement of [^{3}H]-substance P from human NK_1 receptors expressed in CHO cells ($n=3$).

In parallel to the binding assay, physicochemical and ADME properties of a selected set of compounds were investigated in order to detect possible flaws that might impair oral activity such as poor aqueous solubility, low membrane permeation and high first pass effect (Table 5). Solubility appears to be strongly influenced by the nature of the substituents on the basic nitrogen. Introduction of a butyl group on **7** (see **41**) markedly reduced solubility. Oddly enough, solubility at physiological pH was still low when an acetamide group was anchored to **7** (see **44**). This is likely to be due to the reduced pK_a value of the basic nitrogen. Compounds with acidic functions (**47**, **54**, **57**, **60b**) showed improved solubility with respect to **7**. The ability of the compounds to cross the intestinal membrane was evaluated with Caco-2 cells. Papps values ($>10^{-6}$ cm/s) indicate that permeability is not an issue for the compounds tested. Metabolic stability, assessed using guinea pig microsomes, varied widely. Addition of an acidic function considerably increases the metabolic stability of these compounds. On the other hand, it has already been shown that the introduction of a methyl group in the benzyloxy position is favorable.[11] As far as potential cardiovascular effects were concerned, we found that compounds with acidic side chains did not interact significantly with L-type calcium channels. Based on in vitro screening, compound **60b** was the most interesting.

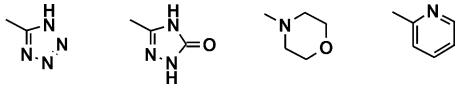
In vivo NK_1 antagonist activity of the selected compounds after oral administration was evaluated in the guinea-pig (Table 6). In agreement with the in vitro results, **60b** was the most potent compound to inhibit SP induced pulmonary edema. This compound displayed also a much longer duration of action being still active after 4 h at 1 mg/kg oral dose.

Table 3. Affinties of compounds **40–57** for the NK_1 receptor[a]



40-57

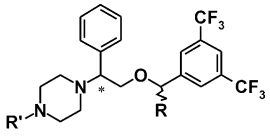
G1-G4



Compd	R	pK_i NK_1
7	H	8.8
40	CH_3	8.8
41	$(CH_2)_3CH_3$	8.6
42	$CO_2CH_2CH_3$	7.2
43	$CONH_2$	7.7
44a(*R*)	CH_2CONH_2	8.0
44b(*S*)	CH_2CONH_2	8.1
45	$CH_2CO_2CH_3$	7.4
46	CH_2CH_2OH	8.7
47	CH_2CO_2H	7.8
48	CH_2CN	8.1
49	CH_2G1	7.2
50	CH_2G2	7.8
51	$(CH_2)_2G3$	7.8
52	CH_2G4	8.7
53	$(CH_2)_2OCH_2CONH_2$	8.5
54	$(CH_2)_2OCH_2CO_2H$	7.8
55	$(CH_2)_4CO_2H$	8.0
56	$CO(CH_2)_3CO_2H$	+
57	$(CH_2)_4G1$	8.2

[a]Displacement of [^{3}H]-substance P from human NK_1 receptors expressed in CHO cells ($n=3$).

Table 4. Affinties of compounds **59–61** for the NK_1 receptor[a]



58-61

Compd	R	R′	pK_i NK_1
47	H	CH_2CO_2H	7.8
58a(*R*,*R*)	CH_3	CH_2CO_2H	+
58b(*S*,*S*)	CH_3	CH_2CO_2H	8.9
59a(*R*,*S*)	CH_3	CH_2CO_2H	8.5
59b(*S*,*R*)	CH_3	CH_2CO_2H	+
54	H	$(CH_2)_2OCH_2CO_2H$	7.8
60a(*R*,*R*)	CH_3	$(CH_2)_2OCH_2CO_2H$	+
60b(*S*,*S*)	CH_3	$(CH_2)_2OCH_2CO_2H$	8.9
61a(*R*,*S*)	CH_3	$(CH_2)_2OCH_2CO_2H$	8.6
61b(*S*,*R*)	CH_3	$(CH_2)_2OCH_2CO_2H$	+

[a]Displacement of [^{3}H]-substance P from human NK_1 receptors expressed in CHO cells ($n=3$).

In conclusion, we have described a series of benzyloxyphenethylpiperazines which are potent NK_1 antagonists. We found that the addition of an acidic function increases both solubility and metabolic stability of the compounds and that this translated in vivo into a better oral activity and longer duration of action. Pleasingly, acidic groups also reduced interaction with L-type calcium channels and gave much more selective compounds. Indeed, **60b** has been screened at 10 μM against a variety of G-protein coupled receptor and ion channels and no significant interactions have been identified.

Table 5. Physicochemical/in vitro ADME properties and calcium channel blocking effect of selected compounds

Cpds	Log D[a]	*S*[b]	Papps[c]	Clm[d]	pD′2[e]
6	5.20	0.0006	—	—	—
7	2.41	0.2	2.1	54	5.38
41	4.09	0.001	5.2	170	4.60
44	3.26	0.002	7.9	50	4.27
47	2.35	1.3	9.6	<10	<4.0
54	2.17	>2.0	4.2	<10	<4.0
57	2.71	0.2	2.6	<10	<4.0
60b	2.64	>2.0	8.7	<10	<4.0

[a]Log $D_{oct/w}$, buffer PBS, pH: 7.4.
[b]S: solubility (mg/mL, pH: 7.4).
[c]Papps, caco-2 permeability ($\times 10^{-6}$ cm/s).
[d]Clint, intrinsec clearance (μL/min/mg protein).
[e]Determined on isolated rat aorta [inhibition of contraction induced by KCl (100 mM)].

Table 6. Effect of orally administered compounds on SP-induced pulmonary oedema in guinea-pig[12]

Cpds	Dose[a]	30 min[b]	60 min[b]	120 min[b]	240 min[b]
41	10	62[c]	—	—	58[c]
43	10	15[c]	47[c]	26[c]	—
47	10	84[c]	76[c]	68[c]	53[c]
54	10	53[c]	61[c]	54[c]	29[c]
57	10	65[c]	99[c]	65[c]	20[c]
60b	**1**	**77**[c]	**75**[c]	—	**70**[c]

[a]mg/kg.
[b]Time of compound preadministration (before SP-induced extravasation).
[c]% of inhibition.

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