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Synthesis of a Novel Class of Non-Peptide NK-2 Receptor Ligand, Derived from 1-Phenyl-3-pyrrol-1-ylindan-2-carboxamides

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Abstract—A series of *trans,trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide derivatives has been synthesized in eight steps starting from cinnamic acid or 3,3-diphenylpropionic acid. The *trans,trans* configuration of these carboxamides has been established by X-ray analysis and by NOE experiments in NMR. These new compounds were evaluated for their potential NK-1, NK-2 and NK-3 receptors binding affinity. The *N,N*-disubstituted carboxamides bound selectively on NK-2 receptors.

Introduction

The tachykinins,[1] a group of small peptides which are released from sensory nerves, are implicated in a wide range of pathophysiological conditions (including nociceptive, inflammatory, and immunoregulatory processes, airway obstruction and asthma, skin disorders, inflammatory bowel disease, emesis, and various CNS disorders).[2–6] The three main endogenous tachykinins identified to date, substance P, neurokinin A (NKA), and neurokinin B (NKB), interact with three neurokinin receptors (NK-1, NK-2 and NK-3). These receptors, widely distributed in both the central nervous system (CNS) and periphery,[7] belong to the seven transmembrane G-protein-coupled receptors superfamily (7TM-GPCR).[2] Since the discovery in 1991 of CP-96,345,[8] the first potent non-peptide human neurokinin-1 (NK-1) receptor antagonist from Pfizer, and of RP-67,580,[9] another potent NK-1 receptor antagonist identified from random screening by Rhône-Poulenc in 1992, interest in the tachykinin area has widely increased and many research groups dedicated efforts to the identification of non-peptide antagonists selective for the three neurokinin receptors. Among the most interesting described antagonists,[10] CP-99,994,[11] SB-223412,[12–14] SR-48968[15,16] and some phenylpiperonylindan-2-carboxamides **1**,[17] are representative of the large structural diversity found in this class of compounds (Fig. 1). Taking into account all the recent SAR studies realized on theses various series,[10–17] we designed a number of chemical models which could offer, in principle, realistic opportunities to be potent NK-1, NK-2 or NK-3 receptor antagonists. In this report, we described the synthesis and the first preliminary in vitro evaluation of new *trans,trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxamides **2**, a novel chemical class of potential non-peptide antagonists for the NK-2 receptors (Fig. 2).

Chemistry

The general methodology adopted for the synthesis of carboxamides **2** is summarized in Scheme 1.[18] Condensation between benzene and cinnamic acid in the presence of $AlCl_3$ or cyclization of 3,3-diphenylpropionic acid with polyphosphoric acid (PPA) afforded the 3-phenylindan-1-one **4**. The reaction of **4** with ethyl carbonate gave the cetoester **5**, subsequently functionalized on the 1-position with ammonium acetate to afford the enaminoester **6**. A mixture of the isomers **7** and **8** was obtained from **6** through a Clauson–Kaas reaction involving probably a thermal [1,3] sigmatropic rearrangement. The hydrogenation of the indenes **7** and **8** by using $NaBH_4$–$NiCl_2$, $6H_2O$ yielded a mixture of the all-

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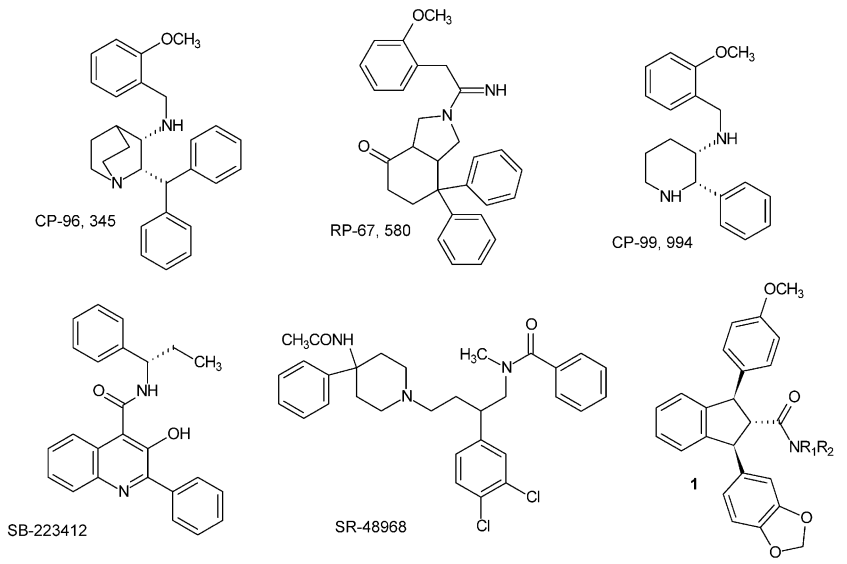


Figure 1. Structures of CP-96,345, RP-67,580, CP-99,994, SB-223412, SR 48968 and compounds **1**.

trans **9** and all-cis **10** epimers. Finally the saponification of the two diastereomers **9** and **10** afforded the *trans–trans* acid **3** via an epimerization at C-2. The *trans–trans* configuration of **3** was established by X-ray crystallography (Fig. 3, Table 1). The crystal structure for **3** revealed a particular spatial conformation of the phenyl and pyrrole rings allowing an easy and free access to the acid function.

Acid **3** treated by triethylamine and then by ethyl chloroformate gave in situ the carbonic mixed anhydride **11** which was reacted with various primary or secondary amines to afford the *trans,trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxamides **2a**–**h** purified by crystallization from diethyl ether or by chromatography on silica gel (Scheme 1). Assignment of the relative configuration of carboxamides **2** was made on the basis of NOE experiments. Specifically, irradiation of H-2 in **2** led to an NOE with H-2′ and H-6′ of the 1-phenyl group and H-α of the pyrrole. These observations were consistent with a *trans* stereochemical relationship between H-2 and the H-1 and H-3 in **2**. For **2d**, this all-*trans* configuration was confirmed from the X-ray analysis data (Fig. 4, Table 1).

Results and Discussion

The synthesized compounds **2a**–**h** were tested for their in vitro binding affinity on tachykinin NK-1, NK-2 and NK-3 receptors.[19–21] The results expressed as IC_{50} and K_i are reported in Table 2. Although **2a**, **2b** and **2g** bound selectively on NK-2 receptors with K_i varying from 0.633 (**2b**) to 0.733 μM (**2g**), none of the test compounds exerted affinity against NK-1 and NK-3 receptors. From a structure–activity relationship point of view, these results seem to indicate that the disubstitution of the carboxamide nitrogen atom was essential for a selective NK-2 binding affinity. These results could be related to the X-ray crystallography data established for a secondary amide (**2d**). The oxygen atom of the amide group O(22) pointed away from the pyrrole and phenyl rings. The crystalline cohesion was ensured by one intermolecular H-bond between N(23) of molecule I (x, y, z) and O(22) of molecule II ($1+x$, y, z): N(23, I) ... O(22, II) = 2.866(4) Å, H(123, I) ... O(22, II) = 2.04 Å, N(23, I) − H(123, I) ... O(22, II) = 162.4°. This H-bond, only defined for the secondary carboxamides **2c**–**f**,**h**, seems to be the necessary cohesion factor for obtaining a solid form. Inversely, the tertiary amides **2a**–**b**,**g** were always isolated as oily compounds. Moreover, the lack of such a H-bond in tertiary carboxamides **2a**–**b**,**g** could offer a better flexibility than for the secondary ones. This structural discrimination could have some consequences on the pharmacological activity of **2a**–**b**,**g** via their possible fixation on NK-2 receptor versus the inability for establishing such fixation for the pharmacological inactive secondary amides **2c**–**f**,**h**. Evaluation of the antagonistic potency of **2a**–**b**,**g** on specific isolated organs as well as their in vivo activity are currently under investigation.

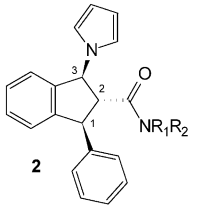
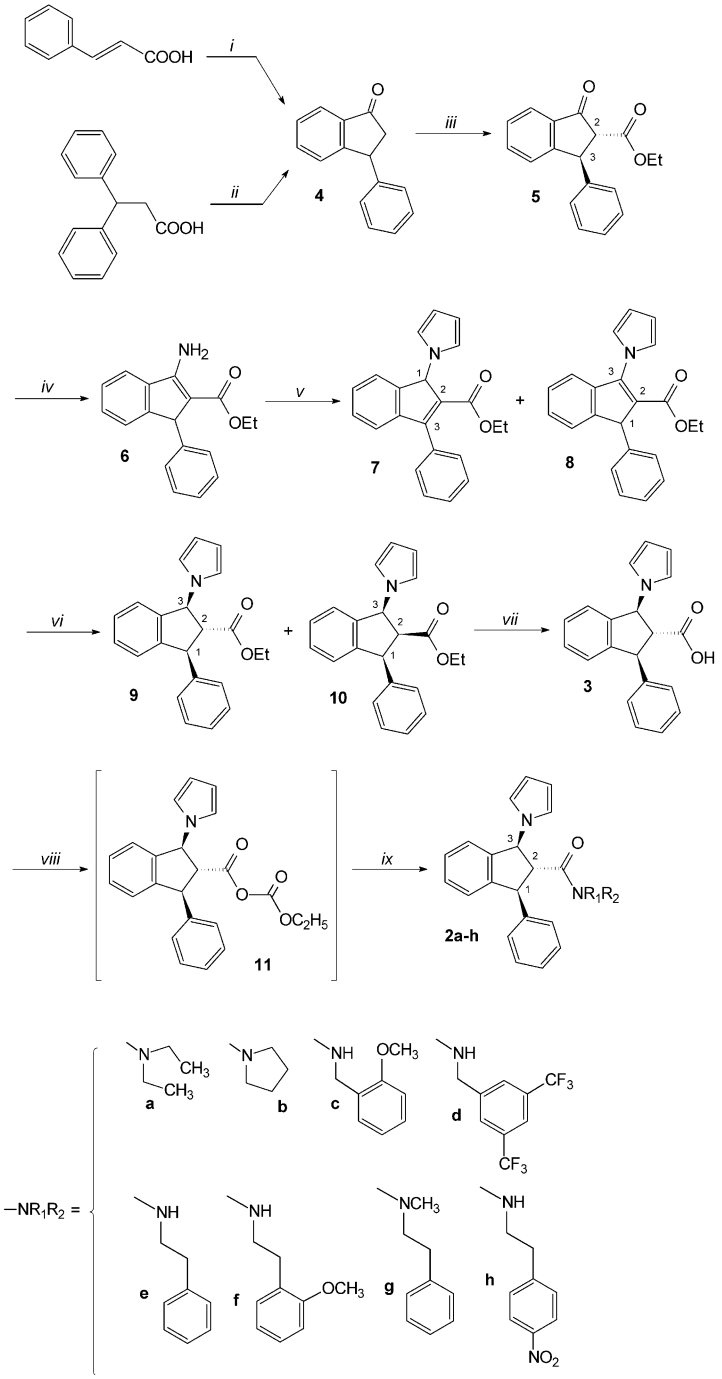


Figure 2. Identification of the *trans,trans*-1-phenyl-3-pyrrol-1-ylindan-2-carboxamides **2**.

Experimental

Chemistry

Melting points were determinated on a Kofler block and are uncorrected. IR spectra were recorded on a Unicam Mattson 1000 FTIR spectrophotometer. NMR spectra (^1H, ^{13}C, ^1H-COSY, NOE) were recorded at 400 or



Scheme 1. Reagents: (i) $AlCl_3$, C_6H_6, 38%; (ii) PPA, 30%; (iii) $(C_2H_5O)_2CO$, Na, 82%; (iv) CH_3COONH_4, C_2H_5OH, 94%; (v) 2,5-diMeOTHF, $C_5H_4ClN{\cdot}HCl$, 1,4-dioxane, 90% (**7**/**8**: 1/1); (vi) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, CH_3OH, 87% (**9**/**10**: 3/1); (vii) (a) NaOH, C_2H_5OH, H_2O; (b) HCl, H_2O, 79% from **9** and **10**; (viii) Et_3N, ClCOOEt; (ix) HNR_1R_2, 36–57%.

100 MHz with tetramethylsilane as an internal standard using a JEOL JNM-LA 400 spectrometer. Splitting patterns have been designated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; dd = double doublet; m = mutiplet. The samples used for NOE experiments were degassed by bubbling nitrogen through the solution. Mass spectra were recorded on a JEOL GC mate instrument using direct inlet system and electron impact ionisation. Analytical TLC was carried out on 0.25 precoated silica gel plates (Polygram SIL G/UV_{254}) with visualisation by irradiation with a UV lamp. Silica gel 60 (70–230 mesh) was used for column chromatography. Analyses indicated by the symbols of the elements were within ±0.3% of the theoretical values.

Ethyl 3-amino-1-phenyl-1*H*-inden-2-carboxylate (6). To a solution of **5** (0.043 mol) in 120 mL of ethanol were added portionwise ammonium acetate (1.07 mol). The reaction mixture was refluxed for 20 h then evaporated to dryness. The residue was triturated in water and made alkaline with sodium hydrogenocarbonate. The

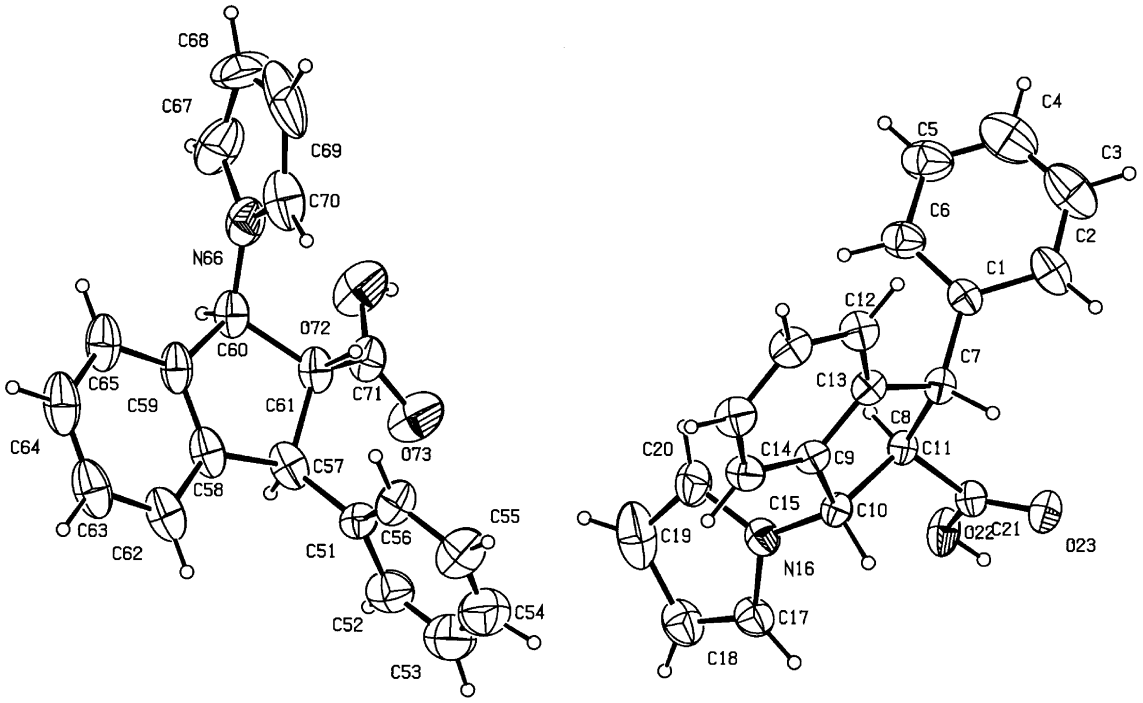


Figure 3. The ORTEP drawing of carboxylic acid **3** with thermal ellipsoids at 30% level.

Table 1. The crystallographic data of compounds **3** and **2d**

X-ray data		**3**	**2d**
Cryst syst		Triclinic	Monoclinic
Space group		P_{-1}	$P2_1/n$
Cell dimension	*a*	9.809(1) Å	5.018(2) Å
	b	11.113(1) Å	27.242(5) Å
	c	16.090(2) Å	18.977(5) Å
	β	95.14(1) °	96.33(3) °
V		1642.4(3) Å^3	2578.3(13) Å^3
Z		2	4
Dx		1.227 Mg m^{-3}	1.361 Mg m^{-3}
F(000)		640	1088
Crystal size		0.32×0.25×0.10 mm^3	0.70×0.20×0.05 mm^3
No. of unique refl. Meads		4776	3243
Refinement method		Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2		1.020	1.081
R[I > 2S(I)]		0.0748	0.0666
WR^2		0.1956	0.1751

precipitate was filtered, washed with water and dissolved in dichloromethane. The organic layer was washed with a saturated aqueous sodium hydrogenocarbonate solution, dried over calcium chloride, filtered and evaporated to dryness to yield compound **6** as white crystals (94%); mp 118 °C. IR (KBr) 3460, 3360 (NH), 1655 (CO); ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 1H, H-4), 7.30 (m, 2H, ArH), 7.27–7.14 (m, 4H, ArH), 7.09 (m, 2H, ArH), 6.12 (bs, 2H, NH_2), 4.78 (s, 1H, H-1), 4.04 (m, 2H, CH_2), 1.05 (t, 3H, J = 7.05 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.5 (CO), 156.7 (C-3), 149.3 (C-1′), 141.5 (C-7a), 136.9 (C-3a), 129.3 (C-3′ and C-5′), 127.9 (C-2′ and C-6′), 127.7 (C-7), 126.6 (C-6), 126.1 (C-4), 124.8 (C-4′), 118.8 (C-5), 102.9 (C-2), 58.7 (CH_2), 52.1 (C-1), 14.1 (CH_3); MS (EI): *m*/*z* 280 ($M^+ + 1$, 24), 279 (M^+, 100), 234 (17), 206 (100), 128 (30). Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.37; H, 6.02; N, 4.95.

General procedure for ethyl phenyl-pyrrolyl-1*H*-inden-2-carboxylate (7) and (8)

To a solution of **6** (0.045 mol) in 170 mL of dioxane were added 2,5-dimethoxytetrahydrofuran (0.045 mol) and then 4-chloropyridine hydrochloride (0.045 mol). The reaction mixture was refluxed for 3 h then evaporated to dryness under reduced pressure. After cooling, the residue was extracted with diethyl ether and filtered. The organic layer was washed with a 1 N hydrochloric acid solution then with a saturated aqueous solution of sodium hydrogenocarbonate, dried over magnesium sulfate and evaporated to dryness to give an orange oil (90%) which was purified by chromatography on silica gel with methylene chloride as eluant.

Ethyl 3-phenyl-1-pyrrolyl-1*H*-inden-2-carboxylate (7). Orange oil (44%); R_f = 0.66. IR (KBr) 1725 (CO); ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 5H, ArH), 7.28 (m, 2H, ArH),

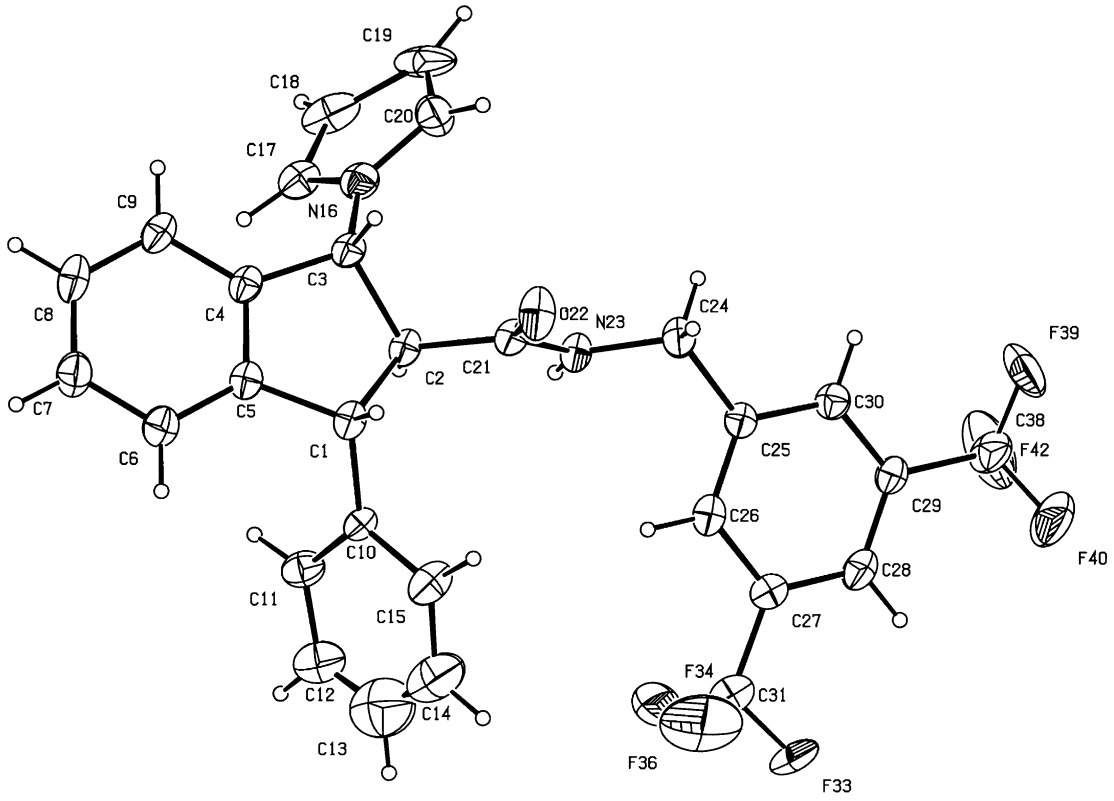


Figure 4. The ORTEP drawing of carboxamide **2d** with thermal ellipsoids at 30% level.

Table 2. Binding affinities for compounds **2a–h**

Compound	NK_1	NK_2			NK_3
	IC_{50} (μM)	IC_{50} (μM)	K_i (μM)	nH	IC_{50} (μM)
2a	> 10	2.0	0.667	0.66	> 10
2b	> 10	1.9	0.633	1.18	> 10
2c	> 10	> 10	—	—	> 10
2d	> 10	> 10	—	—	> 10
2e	> 10	> 10	—	—	> 10
2f	> 10	> 10	—	—	> 10
2g	> 10	2.2	0.733	0.67	> 10
2h	> 10	> 10	—	—	> 10

7.19 (m, 2H, ArH), 6.64 (dd, 2H, $J = 1.96$, 1.96 Hz, H-α), 6.08 (dd, 2H, $J = 1.96$, 1.96 Hz, H-β), 5.97 (s, 1H, H-1), 4.04–3.85 (m, 2H, CH_2), 0.93 (t, 3H, $J = 7.30$ Hz, CH_3). Anal. calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 79.91; H, 5.77; N, 4.21.

Ethyl 1-phenyl-3-pyrrolyl-1*H*-inden-2-carboxylate (8). Orange oil (46%); $R_f = 0.74$. IR (KBr) 1730 (CO); ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 1H, ArH), 7.25 (m, 3H, ArH), 7.16 (m, 3H, ArH), 7.10 (m, 2H, ArH), 7.03 (dd, 2H, $J = 1.96$, 1.96 Hz, H-α), 6.30 (dd, 2H, $J = 1.96$, 1.96 Hz, H-β), 4.94 (s, 1H, H-1), 4.03–3.84 (m, 2H, CH_2), 0.92 (t, 3H, $J = 7.07$ Hz, CH_3). Anal. calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.17; H, 5.76; N, 4.33.

General procedure for *trans,trans* and *cis,cis* ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylate (9) and (10)

A mixture of compounds **7** and **8** (0.038 mol) and $NiCl_2$, $6H_2O$ (0.114 mol) were dissolved in 240 mL of methanol and $NaBH_4$ (0.57 mol) was added in portions with stirring under cooling for 2 h. The stirring was continued for 48 h at room temperature. After the removal of methanol by distillation, the black precipitate was dissolved in 5% hydrochloric acid, the acidic solution was extracted with diethyl ether. The extracts were collected, washed with water, dried over magnesium sulfate and evaporated to dryness under reduced pressure to give **5** as a yellow oil (87%). A sample of the two diastereoisomers **9** and **10** was readily separated by chromatography using methylene chloride as eluant.

***trans,trans* Ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylate (9).** Yellow crystals (65%); mp 62 °C; $R_f = 0.84$. IR (KBr) 1730 (CO); ^{1}H NMR ($CDCl_3$) δ 7.35 (m, 2H, ArH), 7.27 (m, 5H, ArH), 7.12 (m, 1H, H-5), 6.95 (m, 1H, H-6), 6.77 (dd, 2H, $J = 1.90$, 1.90 Hz, H-α), 6.20 (dd, 2H, $J = 1.90$, 1.90 Hz, H-β), 5.94 (d, 1H, $J = 8.70$ Hz, H-3), 4.58 (d, 1H, $J = 9.80$ Hz, H-1), 4.21–4.02 (m, 2H, CH_2), 3.39 (dd, 1H, $J = 9.80$, 8.70 Hz, H-2), 1.13 (t, 3H, $J = 7.30$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 172.9 (CO), 143.7 (C-1′), 142.1 (C-7a), 140.5 (C-3a), 128.9 (C-3′ and C-5′), 128.7 (C-4), 128.5 (C-2′ and C-6′), 127.9 (C-7), 127.3 (C-6), 125.1 (C-4′), 124.4 (C-5), 119.8 (C-α), 108.7 (C-β), 66.1 (C-3), 64.0 (CH_2), 60.9 (C-2), 52.9 (C-1), 14.2 (CH_3); MS (EI): m/z 332 ($M^{+\cdot}+1$, 21), 331 (M^+, 100), 286 (6), 264 (28), 191 (65). Anal. calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 80.03; H, 6.35; N, 4.19.

***cis,cis* Ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylate (10).** Orange oil (22%); $R_f = 0.78$. IR (KBr) 1735 (CO); ^{1}H NMR ($CDCl_3$) δ 7.39–7.23 (m, 9H, ArH), 6.84 (dd,

2H, $J=2.20$, 2.20 Hz, H-α), 6.15 (dd, 2H, $J=2.20$, 2.20 Hz, H-β), 5.98 (d, 1H, $J=7.45$ Hz, H-3), 4.73 (d, 1H, $J=7.45$ Hz, H-1), 3.99 (t, 1H, $J=7.45$ Hz, H-2), 3.45 (q, 2H, $J=7.20$ Hz, CH_2), 0.68 (t, 3H, $J=7.20$ Hz, CH_3); MS (EI): m/z 332 ($M^{+\cdot}+1$, 10), 331 (M^+, 37), 266 (20), 192 (100), 115 (87). Anal. calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.69; H, 6.31; N, 4.38.

1-Phenyl-3-pyrrol-1-ylindan-2-carboxylic acid (3). To a solution of ethyl 1-phenyl-3-pyrrol-1-ylindan-2-carboxylate **9** and **10** (0.032 mol) in 110 mL of ethanol were added 85 mL of an 2 M aqueous sodium hydroxide solution and the reaction mixture was heated to reflux for 4 h. The solvent was eliminated in vacuo and the residue was dissolved in water. The aqueous layer was washed with diethyl ether. Acidification with 3 N HCl solution gave a precipitate which was extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure to give white crystals (79%); mp 66 °C.[18]

General procedure for *N,N*-alkyl-1-phenyl-3-pyrrol-1-ylindan-2-carboxamides (2a–h)

To a stirred solution of 1-phenyl-3-pyrrol-1-ylindan-2-carboxylic acid **3** (3.3 mmol) in 25 mL of anhydrous acetone at 0 °C was added dropwise triethylamine (3.3 mmol). After 30 min, ethyl chloroformate (3.3 mmol) was added dropwise at 0 °C. After an other 30 min, the amine (3.6 mmol) was added dropwise at 0 °C and then the reaction mixture was refluxed for 3 h. After cooling, the precipitate which formed was filtered and the filtrate was evaporated to dryness under reduced pressure. The oily residue was dissolved in diethyl ether (70 mL) and the solution was washed with a 2 N aqueous hydrochloric acid solution (2 × 70 mL) and then with a saturated aqueous sodium hydrogenocarbonate solution (2 × 70 mL). The organic layer was collected, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The residue was triturated in diethyl ether and the formed crystals were filtered and recrystallized in diethyl ether. In case of oil, the residue was purified by chromatographic column using methylene chloride/methanol (95/5 v/v) as eluant.

***trans,trans*-*N,N*-Diethyl-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2a).** Yellow oil (36%). IR (KBr) 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.26–7.21 (m, 4H, ArH), 7.20 (m, 1H, ArH), 7.17 (m, 1H, ArH), 7.15 (m, 1H, ArH), 7.11 (m, 1H, H-5), 6.95 (m, 1H, H-6), 6.67 (dd, 2H, $J=2.10$, 2.10 Hz, H-α), 6.09 (dd, 2H, $J=2.10$, 2.10 Hz, H-β), 5.88 (d, 1H, $J=8.90$ Hz, H-3), 4.63 (d, 1H, $J=9.85$ Hz, H-1), 3.35 (dd, 1H, $J=9.85$, 8.90 Hz, H-2), 3.22 (q, 2H, $J=7.10$ Hz, CH_2), 2.32 (m, 1H, CH_2), 2.22 (m, 1H, CH_2), 0.98 (t, 3H, $J=7.10$ Hz, CH_3), 0.25 (t, 3H, $J=7.10$ Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.0 (CO), 144.0 (C-1′), 142.0 (C-7a), 140.6 (C-3a), 128.7 (C-3′ and C-5′), 128.6 (C-4), 128.2 (C-2′ and C-6′), 127.6 (C-7), 127.2 (C-6), 125.1 (C-4′), 124.3 (C-5), 119.5 (C-α), 108.8 (C-β), 67.5 (C-3), 63.4 (C-2), 53.6 (C-1), 41.3 (CH_2), 40.9 (CH_2), 13.7 (CH_3), 13.0 (CH_3); MS (EI): m/z 359 ($M^{+\cdot}+1$, 8), 358 (M^+, 30), 258 (26), 191 (36), 100 (100), 72 (27). Anal. calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.22; H, 7.24; N, 7.71.

***trans,trans*-*N,N*-Pyrrolidinyl-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2b).** Yellow oil (52%). IR (KBr) 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 2H, ArH), 7.18 (m, 5H, ArH), 7.05 (m, 1H, H-5), 6.88 (m, 1H, H-6), 6.69 (dd, 2H, $J=2.10$, 2.10 Hz, H-α), 6.10 (dd, 2H, $J=2.10$, 2.10 Hz, H-β), 5.84 (d, 1H, $J=9.20$ Hz, H-3), 4.65 (d, 1H, $J=9.90$ Hz, H-1), 3.36 (m, 3H, H-2 and CH_2), 2.33 (m, 1H, CH_2), 2.16 (m, 1H, CH_2), 1.57 (m, 2H, CH_2), 1.41 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 169.9 (CO), 143.9 (C-1′), 141.9 (C-7a), 140.4 (C-3a), 128.6 (C-3′ and C-5′), 128.5 (C-4), 128.2 (C-2′ and C-6′), 127.5 (C-7), 127.1 (C-6), 124.9 (C-4′), 124.0 (C-5), 119.5 (C-α), 108.7 (C-β), 67.0 (C-3), 64.9 (C-2), 52.8 (CH_2), 45.8 (CH_2), 45.7 (C-1), 25.5 (CH_2), 24.0 (CH_2); MS (EI): m/z 356 (M^+, 15), 289 (7), 258 (10), 191 (22), 114 (69), 98 (100), 70 (72). Anal. calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.89; H, 6.71; N, 7.66.

***trans,trans*-*N*-(2-Methoxybenzyl)-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2c).** White crystals (42%); mp 142 °C. IR (KBr) 3270 (NH), 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 6H, ArH), 7.15 (m, 2H, ArH), 7.09 (m, 2H, ArH), 6.93 (m, 1H, ArH), 6.86 (m, 1H, ArH), 6.77 (m,1H, ArH), 6.71 (dd, 2H, $J=2.10$, 2.10 Hz, H-α), 6.16 (dd, 2H, $J=2.10$, 2.10 Hz, H-β), 5.96 (d, 1H, $J=8.90$ Hz, H-3), 5.52 (t, 1H, $J=6.00$ Hz, NH), 4.58 (d, 1H, $J=9.80$ Hz, H-1), 4.39 (dd, 1H, $J=14.40$, 6.00 Hz, CH_2), 4.30 (dd, 1H, $J=14.40$, 6.00 Hz, CH_2), 3.62 (s, 3H, OCH_3), 3.03 (dd, 1H, $J=9.80$, 8.90 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 170.6 (CO), 157.3 (C-2″), 143.8 (C-1′), 142.3 (C-7a), 140.6 (C-3a), 129.5 (C-6″), 128.7 (C-4), 128.5 (C-2′ and C-6′), 127.7 (C-7), 127.1 (C-4″), 125.8 (C-6), 125.1 (C-4′), 124.3 (C-5), 120.4 (C-1″), 119.7 (C-5″), 114.0 (C-3″), 109.9 (C-α), 108.6 (C-β), 67.0 (C-3), 66.0 (OCH_3), 54.9 (C-2), 52.6 (CH_2), 39.4 (C-1); MS (EI): m/z 423 ($M^+ + 1$, 29), 422 (M^+, 100), 355 (9), 258 (33), 192 (46), 121 (64). Anal. calcd for $C_{28}H_{26}N_2O_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.67; H, 6.17; N, 6.62.

***trans,trans*-*N*-(3,5-Bistrifluoromethylbenzyl)-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2d).** White crystals (57%); mp 204 °C. IR (KBr) 3290 (NH), 1645 (CO); ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H, H-4″), 7.57 (s, 2H, H-2″ and H-6″), 7.31 (m, 5H, ArH), 7.22 (m, 2H, ArH), 7.14 (m, 1H, H-5), 6.96 (m, 1H, H-6), 6.74 (dd, 2H, $J=2.10$, 2.10 Hz, H-α), 6.19 (dd, 2H, $J=2.10$, 2.10 Hz, H-β), 5.95 (d, 1H, $J=8.80$ Hz, H-3), 5.49 (t, 1H, $J=6.10$ Hz, NH), 4.62 (d, 1H, $J=9.65$ Hz, H-1), 4.45 (dd, 1H, $J=15.30$, 6.10 Hz, CH_2), 4.36 (dd, 1H, $J=15.30$, 6.10 Hz, CH_2), 3.11 (dd, 1H, $J=9.65$, 8.80 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 171.6 (CO), 143.5 (C-1′), 141.8 (C-7a), 140.6 (C-3a), 140.2 (C-1″), 131.8 (q, $J=36$ Hz, CF_3), 128.9 (C-3″ and C-5″), 128.4 (C-3′ and C-5′), 127.9 (C-4), 127.7 (C-2′ and C-6′), 127.6 (C-7), 125.1 (C-2″ and C-6″), 124.8 (C-6), 124.3 (C-4′), 124.1 (C-5), 121.4 (C-4″), 119.6 (C-α), 109.1 (C-β), 67.3 (C-3), 66.3 (NCH_2), 52.6 (C-2), 42.8 (C-1); MS (EI): m/z 529 ($M^+ + 1$, 33), 528

(M^+, 97), 461 (36), 258 (74), 227 (51), 191 (100). Anal. calcd for $C_{29}H_{22}F_6N_2O$: C, 65.89; H, 4.16; N, 5.30. Found: C, 65.77; H, 4.02; N, 5.22.

***trans,trans*-*N*-Phenethyl-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2e).** White crystals (45%); mp 143 °C. IR (KBr) 3350 (NH), 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.36–7.16 (m, 10H, ArH), 7.10 (m, 1H, ArH), 6.93 (m, 1H, ArH), 6.88 (m, 1H, ArH), 6.75 (dd, 2H, J = 2.10, 2.10 Hz, H-α), 6.20 (dd, 2H, J = 2.10, 2.10 Hz, H-β), 5.96 (d, 1H, J = 9.00 Hz, H-3), 4.99 (t, 1H, J = 5.30 Hz, NH), 4.61 (d, 1H, J = 9.90 Hz, H-1), 3.47 (m, 1H, CH_2), 3.36 (m, 1H, CH_2), 2.97 (dd, 1H, J = 9.90, 9.00 Hz, H-2), 2.64 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 170.9 (CO), 143.8 (C-1′), 142.1 (C-7a), 140.5 (C-1″), 138.5 (C-3a), 128.9 (C-3′ and C-5′), 128.8 (C-4), 128.6 (C-2′ and C-6′), 128.5 (C-3″ and C-5″), 128.4 (C-7), 127.8 (C-2″ and C-6″), 127.4 (C-6), 126.3 (C-4′), 125.0 (C-5), 124.2 (C-4″), 119.7 (C-α), 108.8 (C-β), 67.2 (C-3), 66.2 (C-2), 52.7 (CH_2), 40.7 (C-1), 35.6 (CH_2); MS (EI): m/z 407 ($M^+ + 1$, 16), 406 (M^+, 51), 339 (10), 258 (29), 192 (100), 105 (49). Anal. calcd for $C_{28}H_{26}N_2O$: C, 82.73; H, 6.45; N, 6.89. Found: C, 82.91; H, 6.46; N, 6.78.

***trans,trans*-*N*-[2-(2-Methoxyphenyl)ethyl)]-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2f).** White crystals (37%); mp 132 °C. IR (KBr) 3350 (NH), 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.35–7.22 (m, 7H, ArH), 7.21–7.09 (m, 2H, ArH), 6.93 (m, 1H, ArH), 6.75–6.69 (m, 5H, H-α and ArH), 6.19 (dd, 2H, J = 2.10, 2.10 Hz, H-β), 5.96 (d, 1H, J = 8.90 Hz, H-3), 5.13 (bs, 1H, NH), 4.61 (d, 1H, J = 9.70 Hz, H-1), 3.68 (s, 3H, OCH_3), 3.42 (m, 2H, CH_2), 2.95 (dd, 1H, J = 9.70, 8.90 Hz, H-2), 2.65 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ 171.0 (CO), 157.3 (C-2″), 143.8 (C-1′), 142.3 (C-7a), 140.6 (C-3a), 130.5 (C-3′ and C-5′), 128.8 (C-6″), 128.7 (C-4), 128.5 (C-2′ and C-6′), 127.7 (C-7), 127.3 (C-4″), 126.8 (C-6), 125.5 (C-1″), 125.1 (C-4′), 124.3 (C-5), 120.5 (C-5″), 119.7 (C-α), 110.2 (C-3″), 108.8 (C-β), 67.3 (C-3), 66.3 (OCH_3), 55.0 (C-2), 52.8 (CH_2), 39.5 (C-1), 30.3 (CH_2); MS (EI): m/z 437 ($M^+ + 1$, 21), 436 (M^+, 64), 369 (8), 258 (26), 192 (88), 135 (56), 91 (100). Anal. calcd for $C_{29}H_{28}N_2O_2$: C, 79.79; H, 6.46; N, 6.42. Found: C, 80.06; H, 6.70; N, 6.45.

***trans,trans*-*N*-Methyl-*N*-phenethyl-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2g).** Yellow oil (41%). IR (KBr) 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 3H, ArH), 7.29 (m, 5H, ArH), 7.19 (m, 4H, ArH), 7.02 (m, 1H, H-5), 6.91 (m, 1H, H-6), 6.82 (dd, 2H, J = 1.85, 1.85 Hz, H-α), 6.12 (dd, 2H, J = 1.85, 1.85 Hz, H-β), 5.90 (d, 1H, J = 8.00 Hz, H-3), 4.64 (d, 1H, J = 8.90 Hz, H-1), 3.77 (m, 1H, CH_2), 3.46 (m, 1H, CH_2), 2.80 (m, 4H, H-2 and CH_3), 2.55 (m, 2H, CH_2); MS (EI): m/z 421 ($M^+ + 1$, 15), 420 (M^+, 44), 353 (7), 286 (11), 258 (27), 191 (45), 162 (100), 105 (74). Anal. calcd for $C_{29}H_{28}N_2O$: C, 82.82; H, 6.71; N, 6.66. Found: C, 82.67; H, 6.65; N, 6.61.

***trans,trans*-*N*-(4-Nitrophenethyl)-1-phenyl-3-pyrrol-1-ylindan-2-carboxamide (2h).** White crystals (43%); mp 171 °C. IR (KBr) 3345 (NH), 1650 (CO); ^{1}H NMR ($CDCl_3$) δ 7.99 (d, 2H, J = 8.70 Hz, H-2″ and H-6″), 7.36 (m, 3H, ArH), 7.31 (m, 2H, ArH), 7.23 (m, 2H, ArH), 7.10 (m, 1H, H-5), 7.01 (d, 2H, J = 8.70 Hz, H-3″ and H-5″), 6.92 (m, 1H, H-6), 6.77 (dd, 2H, J = 2.10, 2.10 Hz, H-α), 6.22 (dd, 2H, J = 2.10, 2.10′Hz, H-β), 5.94 (d, 1H, J = 9.10 Hz, H-3), 5.03 (t, 1H, J = 6.30 Hz, NH), 4.60 (d, 1H, J = 10.10 Hz, H-1), 3.44 (m, 2H, CH_2), 3.01 (dd, 1H, J = 10.10, 9.10 Hz, H-2), 2.77 (t, 2H, J = 6.30 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ 171.1 (CO), 146.6 (C-1″), 146.4 (C-4″), 143.6 (C-1′), 141.9 (C-7a), 140.4 (C-3a), 129.5 (C-3′ and C-5′), 128.9 (C-2″ and C-6″), 128.8 (C-4), 128.5 (C-2′ and C-6′), 127.8 (C-7), 127.4 (C-6), 125.0 (C-4′), 124.2 (C-5), 123.7 (C-3″ and C-5″), 119.7 (C-α), 108.9 (C-β), 67.3 (C-3), 66.2 (C-2), 52.6 (CH_2), 40.2 (C-1), 35.4 (CH_2); MS (EI): m/z 452 ($M^+ + 1$, 37), 451 (M^+, 100), 384 (13), 258 (25), 192 (57). Anal. calcd for $C_{28}H_{25}N_3O_3$: C, 74.48; H, 5.58; N, 9.31. Found: C, 74.59; H, 5.79; N, 9.24.

X-ray crystallography of 3 and 2d

Colorless single crystals were obtained from a chloroform/methanol (80/20) solution of **3** or **2d**. Diffraction data were collected using a Enraf-Nonius CAD-4 diffractometer. An empirical absorption correction was applied. The data were also corrected for Lorentz and polarization effect. The program PLATON[22,23] was used for analysis and drawing figures. The positions of non-H atoms were easily determined by the program SHELXS86[24] and the positions of the H atoms were deduced from coordinates of the non-H atoms and confirmed by Fourier synthesis. The non-H atoms were refined with anisotropic temperature parameters. H atoms were included for structure factor calculations but not refined. Full crystallographic results have been deposited at the Cambridge Crystallographic Data Centre (CCDC), UK, as Supplementary Material.[25]

Binding assays

The assays were performed using the following general procedures. For NK_1 receptors, human glioblastoma cells (U373MG) were used with [^{3}H][Sar^9, Met(O$_2$)^{11}]-SP as radiolabelled ligand (concentration 1.2 nM) and [Sar^9, Met(O$_2$)^{11}]-SP (concentration 1 μM) as non-specific ligand;[19] for NK_2 receptors, human recombinant (CHO cells) were used with [^{125}I]NKA as radiolabelled ligand (concentration 0.1 nM) and [Nle^{10}]-NKA(4-10) (concentration 10 μM) as non-specific ligand;[20] for NK_3, human recombinant (mammalian cells) were used with [^{3}H]Senktide as radiolabelled ligand and Senktide (1 μM) as non-specific ligand.[21] Following incubation, the membranes or cells in suspension were rapidly filtered under vaccum through glass fiber filters (GF/B or GF/C, Whatman or Packard). The filters were then washed several times with an ice-cold buffer using a cell harvester (Brandel, Packard). Bound radioactivity was measured with a scintillation counder (LS 6000, Beckman, Topcount, Packard) using a liquid scintillation cocktail (Formula 989, Microscint O, Packard).

The compounds were first tested in each assay at 10 μM. In the assays where compound inhibited the specific binding by more than 80% at this concentration, they

were further tested at eight concentrations ranging from 0.3 nM to 10 μM to obtain full competition curves. Each determination was made in duplicate.

In each experiment, a reference compound was tested at eight concentrations in duplicate to obtain a competition curve in order to validate this experiment. The specific radioligand binding to the receptors is defined as the difference between total binding and non-specific binding determined in the presence of an excess of unlabelled ligand. Results are expressed as a percent of control specific binding and as a percent inhibition of control specific binding obtained in the presence of the tested compounds. Individual data and mean data are presented in the Results section. IC_{50} values (concentration causing a half-maximal inhibition of control specific binding), and Hill coefficients (nH) were determined by non-linear regression analysis of the competition curves. These parameters were obtained by Hill equation curve fitting. The inhibition constants (K_i) were calculated from the Cheng Prusoff equation [$K_i 50/(1 + L/K_D)$, where L = concentration of radioligand in the assay, and K_D = affinity of the radioligand for the receptor).]

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