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Synthesis of 2-(4-Biphenylyl)quinoline-4-carboxylate and Carboxamide Analogs. New Human Neurokinin-3 (hNK-3) Receptor Antagonists*

The 2-phenylquinoline-4-carboxamide **1** (Chart 1) has been found to possess moderate affinity for human neurokinin-3 (hNK-3) receptor. In the present work, and in a trial to investigate the effect of the lipophilic moiety at C-2 of the quinoline ring on the antagonistic activity, an enlargement of the aromatic area at this position was suggested. In this respect, two series of 2-(4-biphenylyl)quinoline-4-carboxylates and carboxamides have been synthesized with certain modifications at the quinoline-2 and 4-position in order to study their effect on the anticipated hNK-3 receptor antagonistic activity. Fifteen compounds were screened for such activity using guinea-pig isolated ileum longitudinal muscle preparation and senktide as selective hNK-3 receptor agonist. Some compounds showed considerable antagonistic effect. Compound **7b**, 6-bromo-2-(4-biphenylyl)quinoline-4-carboxylic acid, was the most prominent hNK-3 receptor antagonist in this study. Unexpectedly, some compounds were agonists.

Key words: 2-(4-Biphenylyl)quinoline-4-carboxylates and carboxamides; Human neurokinin-3 (hNK-3) receptor antagonists; Senktide

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Introduction

The last few years have witnessed a growing interest in the pharmacology of human tachykinins and the identification and characterization of their human neurokinin (hNK) receptor subtypes. It has been well documented that there are at least three distinct seven-transmembrane G protein-coupled receptors named human neurokinin-1 (hNK-1), human neurokinin-2 (hNK-2), and human neurokinin-3 (hNK-3) receptors [1]. Their endogenous neurotransmitters have been shown to constitute a family of small neuropeptides (tachykinins or neurokinins) which share a common carboxy terminal region and are present in the central and the peripheral nervous systems [2]. The main mammalian tachykinins; substance P (SP), neurokinin A (NKA), and neurokinin B (NKB); have been demonstrated to interact with the three hNK receptors in a certain rank order of potency [3]. Tachykinins were known to be implicated in a wide range of patho-physiological conditions such as nociceptive, inflammatory, and immunoregulatory processes, airway obstruction and asthma, skin disorders, inflammatory bowel disease, emesis, and various CNS disorders [1, 3]. Initially, efforts in the research area of tachykinins have been directed towards the production of potent and selective non-peptide hNK-1 and hNK-2 receptors antagonists [4–6]. Over the past few years, much concern has been given to the synthesis and identification of potent and selective "peptoid" and non-peptide hNK-3 receptor antagonists derived from diverse chemical classes [7–15]. Such compounds provided improved reagents to assist in the clarification of the physiological and pathophysiological role of hNK-3 receptors and the potential therapeutic utility of their selective antagonists. Evidence from pharmacological studies using selective peptide hNK-3 receptor agonists revealed that the hNK-3 receptor exerts a neuromodulatory role in the central nervous system (CNS) and the periphery [16]. Among the family of hNK-3 receptor antagonists, the 2-phenylquinoline-4-carboxamide derivatives have been found to possess variable degrees of affinity towards the hNK-3 receptor [17].

In a trial to deduce a putative pharmacophoric model of selective non-peptide hNK-3 receptor antagonists, Giardina et al. have studied various quinoline derivatives where they identified the importance of the 2-phenylquinoline-4-carboxamide framework for hNK-3 receptor antagonistic activity **1** (Chart 1). Their lead compound **2**, *N*-benzyl-7-methoxy-2-phenylquinoline-4-carboxamide (Chart 1), proved to be highly selective for hNK-3 receptor whereas no significant affinity for hNK-1 receptor was

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Full Paper

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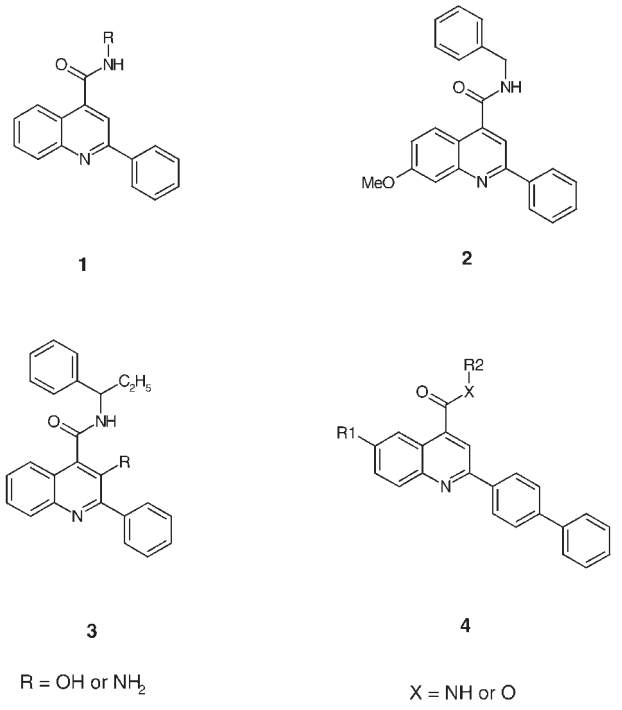


Chart 1. Structures of **1**, **2**, **3**, and **4**.

noticed [17]. The proposed pharmacophore has demonstrated the significance of the lipophilic 2-phenyl moiety of the carboxyquinoline skeleton and the role of the exocyclic nitrogen as a hydrophilic hydrogen-bond acceptor center [18]. Recently, they proved that the 3-substituted-2-phenylquinoline-4-carboxamides **3** (Chart 1) were the most potent hNK-3 receptor antagonists [19]. Furthermore, they explored the effect of replacing the quinoline nucleus with a naphthalene ring, which appeared to be suitable for further modifications as it offers the option of introducing an electron-withdrawing group at position 2 or 4, conferring on the ring an overall electron-deficiency similar to that of quinoline [20].

Taking into consideration all the features described above, we focussed our efforts in the present work on the design and synthesis of certain 2-(4-biphenylyl)-quinoline-4-carboxylate and carboxamide analogs **4** (Chart 1) containing the pharmacophoric atomic sequence **1** with special emphasis on the enlargement of the aromatic area at C-2. Further chemical modifications aimed at optimizing the selectivity towards the hNK-3 receptor involved incorporation of a variety of substituents at C-4 for the purpose of studying their effect on the anticipated biological activity. The proposed compounds were considered as biphenylyl analogs that could be bioisosterically correlated to the lead compounds **2** or **3**.

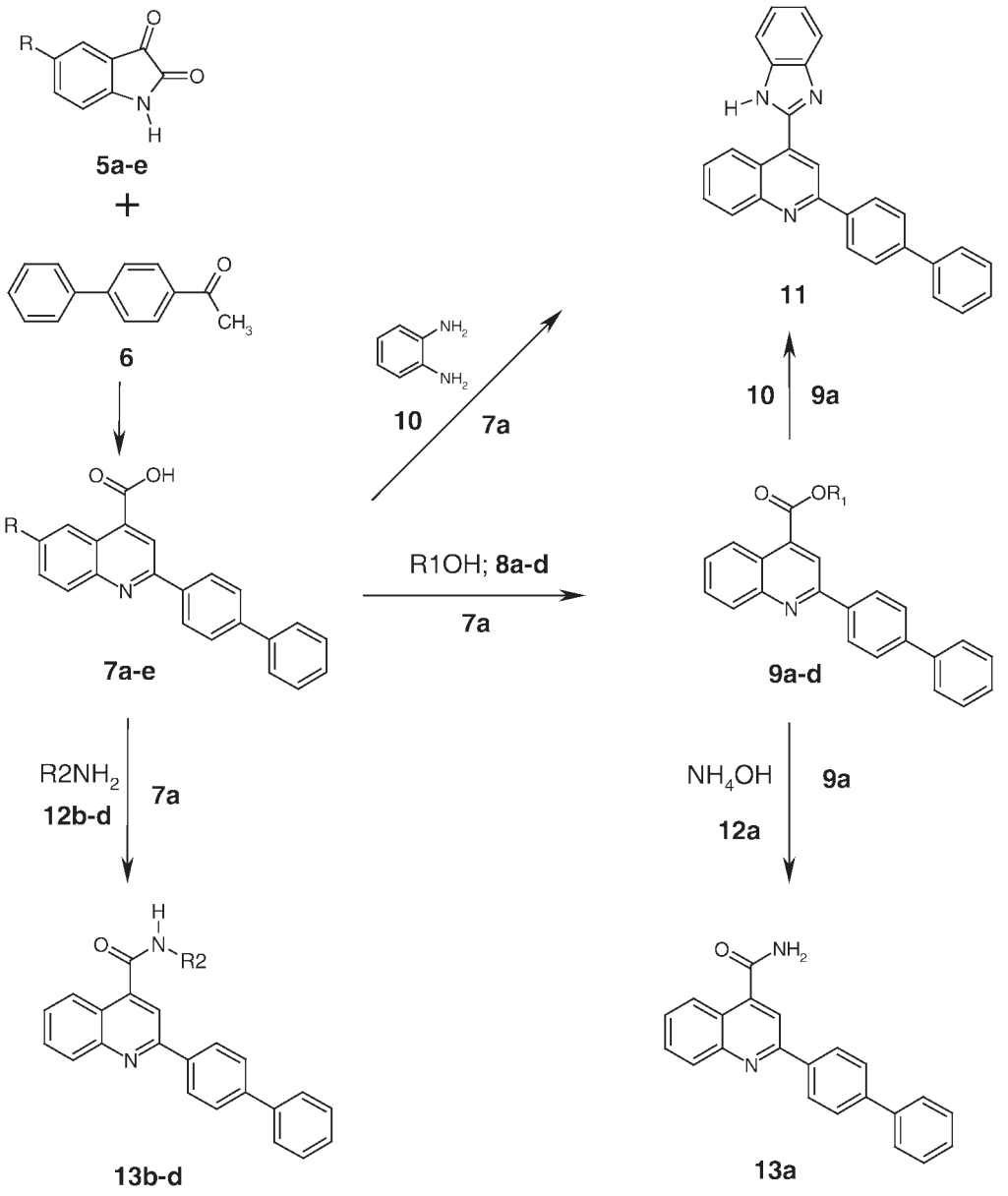
Results and discussion

Chemistry

The synthetic pathways adopted for the preparation of the newly synthesized compounds are outlined in Schemes 1–3. The parent compounds **7a–e** were obtained in high yields according to Pfitzinger reaction conditions [21]. It involved refluxing isatins **5a–e** with 4-acetylbiphenyl **6** in aqueous 30% NaOH. The carboxylate derivatives **9a–d** were prepared by stirring 2-(4-biphenylyl)quinoline-4-carboxylic acid **7a** with ethyl chloroformate in the presence of triethylamine in chloroform at 5–10 °C, followed by addition of the appropriate alcohol **8a–d**. The IR spectral data of these compounds showed the carbonyl absorption at 1722–1695 cm^{-1}, whereas compound **9d** showed an additional NH band at 3284 cm^{-1}. Compound **11**, 2-(4-biphenylyl)-4-(2-1*H*-benzimidazolyl)quinoline, could be obtained by either of the following two approaches: a) reacting the parent compound **7a** with 2-phenylenediamine **10** in the presence of orthophosphoric acid and phosphorus pentoxide; b) the desired compound was obtained in better yield by fusion of the methyl carboxylate ester **9a** with 2-phenylenediamine **10**. Furthermore, stirring of the same ester **9a** with conc. ammonia solution **12a** at room temp. afforded the 2-(4-biphenylyl)quinoline-4-carboxamide **13a**. The other carboxamide analogs were prepared by applying the method described for the synthesis of carboxylate derivatives **9a–d**, replacing the alcohols **8a–d** by either hydrazine hydrate **12b** to obtain the 2-(4-biphenylyl)quinoline-4-acid hydrazide **13b**, or by the appropriate amine **12c**,**d** to prepare the amides **13c** and **13d**, respectively (Scheme 1). Condensation of 4-(2-aminoethyl)-2-(4-biphenylyl)quinoline-4-carboxylate **9d** with benzaldehyde **14a**, 3-(4-nitrophenyl)-1*H*-pyrazol-4-aldehyde **14b**, and 3-acetylpyridine **14c** in acidic medium, to obtain the corresponding 2-(4-biphenylyl)-4-(2-arylideneaminoethyl)quinoline-4-carboxylates **15a–c**, has revealed that the structure of **9a** is a carboxylate ester rather than a carboxamide (Scheme 2). Starting from 2-(4-biphenylyl)quinoline-4-acid hydrazide **13b**, the azide analog; 2-(4-biphenylyl)quinoline-4-acid azide **16** could be prepared using sodium nitrite in the presence of acetic acid. The IR spectrum of compound **16** showed the N3 band at 2160 cm^{-1}. The same acid hydrazide **13b** was utilized to synthesize some arylidenehydrazinocarbonyl derivatives **17a–d** by condensation with some selected ketones **14b–e** (Scheme 3).

Biological results

Fifteen compounds, namely; **7a–c**, **9a**,**c**,**d**, **13b–d**, **15b**, **16**, and **17a–d** were screened for their *in vitro* effect on hNK-3 receptor using senktide-induced contrac-

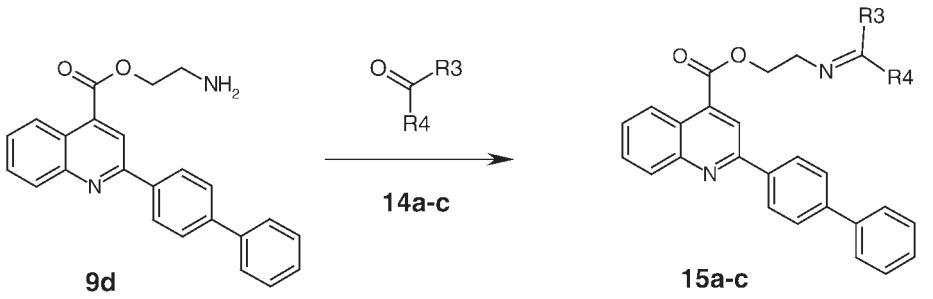


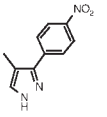
5,7: R = a: H; b: Br; c: Cl; d: CH_3; e: OCH_3

8,9: R1 = a: CH_3; b: C_2H_5; c: n-C_4H_9; d: $(CH_2)_2NH_2$

12,13: R2 = b: NH_2; c: $CH_2CH(CH_3)_2$; d:cyclo-C_6H_{11}

Scheme 1



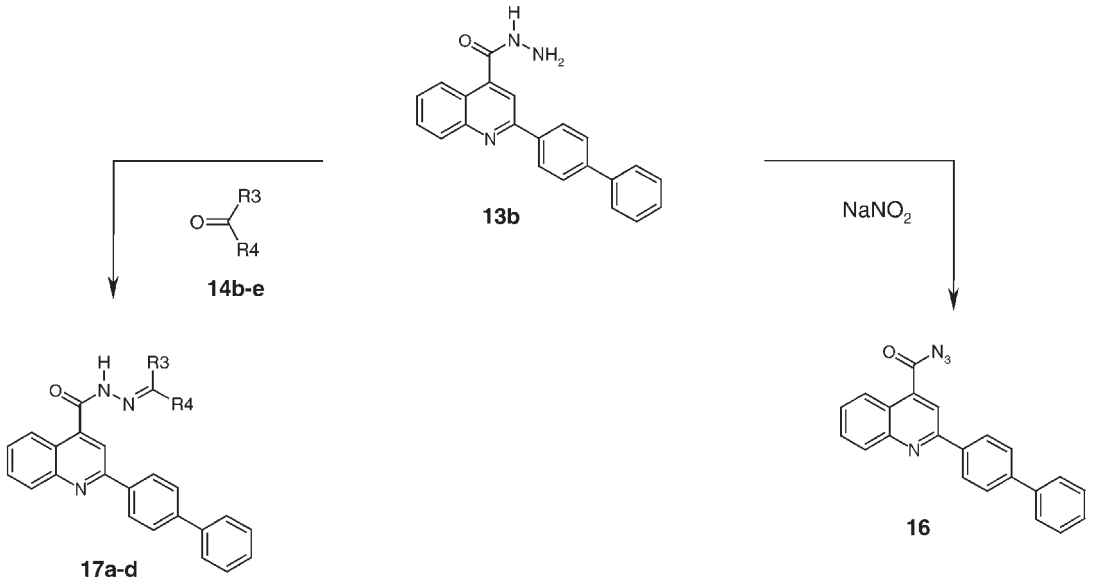
14,15	R3	R4
a	H	C_6H_5
b	H	
c	CH_3	3-pyridyl

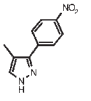
Scheme 2

tions in a guinea-pig ileum preparation [22]. Maggi et al. [23] have indicated that the hNK-3 receptor is especially abundant in the central nervous system while its expression in peripheral organs is much more limited. The guinea-pig ileum is a notable exception in this respect. Senktide, the synthetic and selective hNK-3 receptor agonist in the present study, is an oligopeptide of 8 amino acids having the sequence of Succ Asp Phe NMe Phe Gly Leu Met NH2 (MW: 842.88) [22]. Senktide is now widely accepted as a useful tool to probe the distribution and function of tachykinin hNK-3 receptor. The aim of this study was to determine the profile of action of the newly synthesized compounds at hNK-3 receptor, using a guinea-pig ileum preparation. The adopted method contributes to the contractile response of guinea-pig ileum smooth muscles in relation to the agonist (senktide) alone and the agonist in the presence of a specific concentration of the test compoun d. The percentage of changes in contractile response induced by senktide affected by the tested compounds are recorded in Table 1 and illustrated in Chart 2. The reported values are the average of 5 determinations ± standard error (SE).

the obtained data revealed that compounds **7b**, **9d**, and **15b** exhibited promising antagonistic activity towards the contractile response induced by senktide. Their percentage reduction of the senktide contractile response were 64.28 ± 2.9, 60.71 ± 4.3, and 55.28 ± 6.5, respectively. Compound **7a**, **9d**, and **16** showed moderate antagonistic effects with percentage reduction values of 32.84 ± 5.3, 26.75 ± 3.9, and 29.59 ± 11.6, respectively. The data also revealed that some tested compounds like **9c**, **13b**, and **13c** reduced the senktide contractile response by the percentage of 8.73 ± 0.7, 18.29 ± 1.1, and 14.12 ± 2.3, respectively, reflecting weak hNK-3 receptor antagonistic activity (Table 1). Unexpectedly, some of the tested compounds, namely, **7c**, **13d**, **17a–d** showed agonistic activity, increasing the senktide response by 18.39 ± 2.5, 52.24 ± 14.1, 16.67 ± 3.1, 36.36 ± 5.3, 13.26 ± 2.7, and 42.43 ± 4.32%, respectively (Table 1).

In the present work, the bromo derivative **7b**, namely, 6-bromo-2-(4-biphenylyl)quinoline-4-carboxylic acid, is the most active member in the newly synthesized series as it displayed a prominent antagonistic activity at the



14	17	R3	R4
b	a	H	
c	b	CH_3	3-pyridyl
d	c	H	4-Cl-C_6H_4
e	d	CH_3	4-Cl-C_6H_4

Scheme 3

Table 1. Percentage change in contractile response induced by senktide on the isolated guinea pig ileum

Comp. No.	% Change in contractile response ± SE[a]	Comp. No.	% Change in contractile respone ± SE[a]
7a	[b]– 32.84 ± 5.33	**13d**	+ 52.24 ± 14.11
7b	– 64.28 ± 2.91	**15b**	– 55.28 ± 6.59
7c	[c]+ 18.39 ± 2.58	**16**	– 29.59 ± 11.61
9a	– 26.75 ± 3.92	**17a**	+ 16.67 ± 3.10
9c	– 8.73 ± 0.77	**17b**	+ 36.36 ± 5.23
9d	– 60.7 ± 4.37	**17c**	+ 13.26 + 2.72
13b	– 18.29 ± 1.17	**17d**	+ 42.43 ± 4.32
13c	– 14.12 ± 2.32		

[a] The reported values are the average of 5 determinations ± standard error (SE). – [b] –ve: % of reduced action of senktide response (antagonistic activity). – [c] +v: % of increased action of senktide response (agonistic activity).

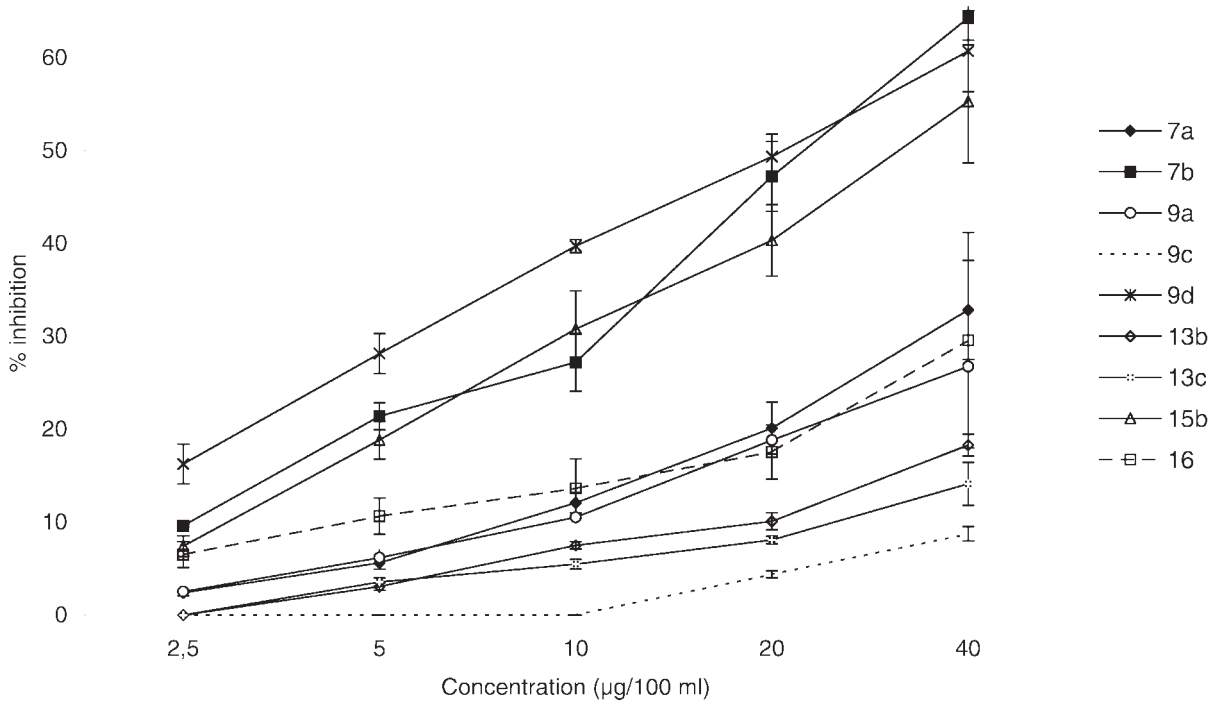


Chart 2. Mean concentration-response curves of the antagonists (**7a**, **7b**, **9a**, **9c**, **9d**, **13b**, **13c**, **15b**, 16) on the contractile response induced by senktide.

at the hNK-3 receptor with 64.28–2.9% response (Table 1). Its antagonistic activity was almost twice that exhibited by the unsubstituted analog **7a** (reduction in response 32.84–5.3%) (Table 1). In contrast, replacing the 6-bromo with a chloro atom as in **7c** directed the activity, unexpectedly, towards the agonistic side (increase in response 18.39–2.5%) (Table 1). The data also revealed that the carboxylate derivatives exerted appreciable antagonistic properties especially the aminoethyl carboxylate analog **9d** (reduction in response 60.7–4.3%) (Table 1).and its arylidene derivative **15b** (reduction in response 55.28–6.5%) (Table 1). Both the acid hydrazide **13b** and the acid azide **16** analogs exhibited weak antagonistic activity at the hNK-3 receptor (reduction in response 18.29–1.1 and 29.59–11.6%) (Table 1). In contrast to the arylidene derivative **15b,** substitution of the acid hydrazide **13b** with some ketonic compounds resulted in a change in the direction of activity towards the agonistic side, resulting in a series of hNK-3 receptor agonists **17a–d** with variable positive effects on senktide contractile response (increase in response 16.67–3.1, 36.36–5.3, 13.26–2.7 and 42.43–4.3%, respectively) (Table 1).

These findings coincided with those of Giardina et al. [18, 20], who suggested that the 2-arylquinoline backbone would be considered as an essential pharmacophore for optimal fitting to the hNK-3 receptor. Based on the results of the biological screening of the carboxamide and ester candidates, one can conclude that the occurrence of an acidic amide is not important for their activities. This conclusion contradicts the previous proposal of Giardina et al. [18] for analogous series. Introducing a large hydrophobic area at C-2 in the quinoline ring seemed to be irrelevant to the anticipated antagonistic activity of such types of compounds at the same receptor. Additionally, we suggest that the binding region of the antagonist may overlap with that of the agonist. The introduction of one bromine atom at C-6 of the quinoline ring would direct the bromo derivative (**7b**) towards the antagonistic region of the receptor and decrease the potency of senktide, whereas substituting the bromine with chlorine would direct the chloro compound (**7c**) towards the agonistic region and potentiate the potency of senktide via a synergistic mechanism. However, the aforementioned pharmacological data would strongly suggest further investigations in the area of 2-arylquinoline-4-carboxamides with the hope of finding more selective and potent non-peptide hNK-3 antagonists.

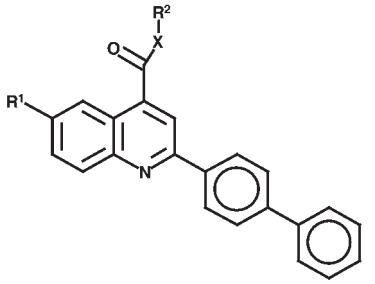


Table 2. Physical and analytical data of the newly synthesized compounds.

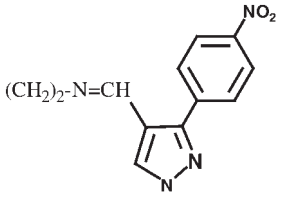
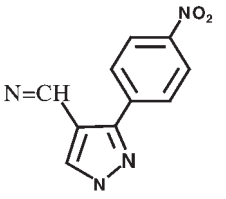
Comp.	X	R^1	R^2	Mp (°C) (cryst. sol.)[a]	Yield %	Mol. Form.[b] (MW)
7a	O	H	H	>300 (DMF)	90	$C_{22}H_{15}NO_2$ 325.37
7b	O	Br	H	>300 B/M	86	$C_{22}H_{14}BrNO_2$ 404.26
7c	O	Cl	H	170 B/M	88	$C_{22}H_{14}ClNO_2$ 359.81
7d	O	CH_3	H	167–168 M	78	$C_{23}H_{17}NO_2$ 339.40
7e	O	OCH_3	H	118–120 i-p	76	$C_{23}H_{17}NO_3$ 355.40
9a	O	H	CH_3	218–220 C	59	$C_{23}H_{17}NO_2$ 339.40
9b	O	H	C_2H_5	125–126 C/M	60	$C_{24}H_{19}NO_2$ 353.42
9c	O	H	*n*-$C_4H_9$91–92 M	58	$C_{26}H_{23}NO_2$ 381.48	
9d	O	H	$(CH_2)_2NH_2$	139–140 M	65	$C_{24}H_{20}N_2O_2$ 368.44
13a	NH	H	H	138–140 i-p	51	$C_{22}H_{16}N_2O$ 324.39
13b	NH	H	NH_2	238 C/M	48	$C_{22}H_{17}N_3O$ 339.40
13c	NH	H	$CH_2CH(CH_3)_2$	156–157 C	60	$C_{26}H_{24}N_2O$ 380.49
13d	NH	H	cyclo-C_6H_{11}	210–212 C/PE	65	$C_{28}H_{26}N_2O$ 406.55
15a	O	H	$(CH_2)_2$-N=CH-C_6H_5	196–197 M	69	$C_{31}H_{24}N_2O_2$ 456.55
15b				178–180 M	60	$C_{34}H_{25}N_5O_4$ 567.61
15c	O	H	(CH_2)-N=C (CH_3) (3-pyridyl)	156 E	45	$C_{31}H_{25}N_3O_2$ 471.57

Table 2. (continued)

Comp.	X	R^1	R^2	Mp (°C) (cryst. sol.)[a]	Yield %	Mol. Form.[b] (MW)
16	–	H	N_3	124–125 E	70	$C_{22}H_{14}N_4O$ 350.39
17a	NH	H		155–156 E	50	$C_{32}H_{22}N_6O_3$ 538.58
17b	NH	H	N=C(CH_3) (3-pyridyl)	213–215 B/PE	35	$C_{29}H_{22}N_4O$ 442.53
17c	NH	H	N=CH (4-ClC_6H_4)	228–230 i-p	55	$C_{29}H_{20}ClN_3O$ 461.95
17d	NH	H	N=C(CH_3) (4-ClC_6H_4)	240 i-p	42	$C_{30}H_{22}ClN_3O$ 475.98

[a] Crystallization solvents; B: b enzene; C: chloroform; DMF: dimethyl formamide; E: ethanol; i-p: isopropanol; M: methanol; PE: pet. ether. – [b] Analyzed for C, H, N; results are within 4% of the theoretical values of the formulae given.

Table 3. ^{1}H-NMR (DMSO-d_6) data of some of the newly synthesized compounds.

Cpd. No.	^{1}H-NMR (δ ppm)
7a	7.38–8.66 (m, 14H, Ar.-*H*).
7b	7.43–8.53 (m, 13H, Ar.-*H*).
7c	7.31–8.46 (m, 13H, Ar.-H).
7d	2.83 (s, 3H, C*H*$_3$), 7.53–8.42 (m, 13H, Ar.-*H*).
7e	4.01 (s, 3H, OC*H*$_3$), 7.66–8.34 (m, 13H, Ar.-*H*).
9a	3.12 (s, 3H, C*H*$_3$), 7.24–8.74 (m, 14H, Ar.-*H*).
9b	1.52 (t, *J* = 6.9 Hz, 3H, ester -CH_2-C*H*$_3$), 4.57 (q, *J* = 6.9 Hz, 2H, ester-C*H*$_2$-CH_3), 7.26–8.77 (m, 14H, Ar.-*H*).
9c	1.23 (t, 3H, $(CH_2)_3$-*CH*$_3$), 2.60 (m, 2H, -$(CH_2)_2$-*CH*$_2$-CH_3), 2.81 (m, 2H, -CH_2-*CH*$_2$-CH_2-CH_3), 3.45 (t, 2H, -*CH*$_2$-$(CH_2)_2$-CH_3, 7.53–8.63 (m, 14H, Ar.-H).
11	7.39–8.66 (m,1 8H, Ar.-*H*), 9.1 (s, 1H, N*H*).
13a	7.61–8.12 (m, 14H, Ar.-*H*), 9.6 (s, 2H, N*H*$_2$).
13c	1.03 (d, 6 H, 2C*H*$_3$), 1.98 (m, 1H, -CH_2-C*H*$(CH_3)_2$, 3.39 (t, 2H, -C*H*$_2$-CH $(CH_3)_2$, 6.53 (t, 1H, N*H*), 7.26–8.22 (m, 14H, Ar.-*H*).
13d	1.24–1.89 (m, 10H, cyclohexyl), 4.12 (m, 1H, C_1-cyclohexyl-*H*), 6.14 (d, 1H, N*H*), 7.26–8.23 (m, 14H, Ar.-*H*).
15a	3.45 (t, *J* = 7 Hz, 2H, -C*H*$_2$-N=), 3.62 (t, *J* = 7 Hz, 2H, -C*H*$_2$-CH_2-N=), 7.39–8.66 (m, 20H, 19 Ar.-*H* and -C*H*=N).
15b	3.38 (t, *J* = 7.1 Hz, 2H, C*H*$_2$-N=), 3.59 (t, *J* = 7.1 Hz, 2H, -C*H*$_2$-CH_2-N=).
15c	2.93 (s, 3H, C*H*$_3$), 3.36 (t, *J* = 7.5 Hz, 2H, -C*H*$_2$-N=), 3.57 (t, *J* = 7.5 Hz, 2H, -C*H*$_2$-CH_2-N=), 7.39–8.66 (m, 18H, Ar.-*H*).
16	7.45–8.81 (m, 14H, Ar.-H).
17a	7.36–8.5 (m, 20H, 19 Ar.-*H* and pyrazole-N*H*), 8.9 (s, 1H, CO-N*H*).
17d	2.8 (s, 3H, C*H*$_3$), 7.41–8.32 (m, 18H, Ar.-*H*), 9.1 (s, 1H, CO-N*H*).

Experimental

Melting points were determined in open glass capillaries on a Stuart Melting Point apparatus and are uncorrected. The infrared spectra were recorded for KBr discs, using a Perkin-Elmer 421 spectrophotometer. The ^{1}H-NMR spectra were recorded on a varian EM-390 (200 MHz) spectrophotometer, using TMS as the internal standard and DMSO-d_6 as the solvent. Mircoanalytical data were performed at the Microanalytical Unit, Faculty of Science, University of Alexandria, A.R. Egypt, the values were within ±0.4% of the theoretical values. Follow up of the reactions and checking the homogeneity of the compounds were accomplished by TLC on silica gel-protected aluminum sheets (Type 60 F254, Merck) and the spots were detected by exposure to UV-lamp at λ 254 nm for a few seconds.

General procedure for the preparation of 2-(4-biphenylyl)-6-substituted-quinoline-4-carboxylic acids **(7a–e)**

A mixture of 4-acetylbiphenyl **6** (10 mmol) and the appropriate isatin **5a–e** (10 mmol) in 30% aqueous sodium hydroxide solution (50 mL) was refluxed for 4–6 h. The sodium salt of the title compound which partially separated out, was filtered off, and then acidified by stirring in glacial acetic acid (20 mL) for 30 min to liberate the free acid. The filtrate was also acidified till complete liberation of the acid from the dissolved sodium salt. The combined crops of the free acid were collected by filtration, dried, and crystallized from the appropriate solvent. Melting points, crystallization solvents, and percentage yields are listed in Table 2. The ^{1}H-NMR data are recorded in Table 3. IR (cm^{-1}): 3510–3340 (OH), 1680–1670 (C=O).

General procedure for the synthesis of alkyl 2-(4-biphenylyl)-quinoline-4-carboxylates (**9a–d**)

Ethyl chloroformate (1.1 mL, 10 mmol) was added, dropwise, to a stirred solution of 2-(4-biphenylyl)quinoline-4-carboxylic acid **7a** (3.25 g, 10 mmol) and triethylamine (2 mL, 20 mmol) in chloroform (20 mL) at 5–10 °C. Stirring was continued for 30 min then the appropriate alcohol **8a–d** (5 mL) was added. Stirring of the reaction mixture was maintained for a further 4 h at room temperature. The separated product was filtered off, dried, and crystallized from the appropriate solvent. Melting points, crystallization solvents, and percentage yields are listed in Table 2. The ^{1}H-NMR data are recorded in Table 3. IR (cm^{-1}): 1722–1695 (C=O) and for **9d**: 3284 (NH_2), 1694 (C=O).

2-(4-Biphenylyl)-4-(2-1H-benzimidazolyl)quinoline (**11**)

Method A

A well mixed powdered mixture of compound **7a** (0.33 g, 1 mmol) and 2-phenylenediamine **10** (0.11 g, 1 mmol) was added to a stirred mixture of orthophosphoric acid (2 mL) and phosphorus pentoxide (1 g). The reaction mixture was heated at 120 °C for 2 h. After being cooled to room temp., the mixture was poured on crushed ice and neutralized with solid sodium carbonate. The precipitated product was filtered off, dried, and crystallized from dimethyl formamide; mp > 300 °C; yield 60%.

Method B

An equimolar mixture of 2-(4-biphenylyl)quinoline-4-methyl-carboxylate **9a** (0.34 g, 1 mmol) and 2-phenylenediamine **10** (0.11 g, 1 mmol) was heated in an oil bath at 200 °C for 1 h. After cooling to room temp., the solid product was treated with ethanol (5 mL), filtered off, dried and crystallized from dimethyl form, mp >300 °C; yield 76%. IR (cm^{-1}): 3335 (NH) and 1635 (C=N). ^{1}H-NMR: 7.39–8.66 (m, 18H, Ar-*H*), 9.1 (s, 1H, N*H*) Analysis for $C_{28}H_{19}N_3$ (397.48).

2-(4-biphenylyl)quinoline-4-carboxamide (**13a**)

To a stirred solution of 2-(4-biphenylyl)quinoline-4-methyl-carboxylate **9a** (0.34 g, 1 mmol) in methanol (10 mL) was added conc. ammonia solution **12a** (2 mL, 27%). Stirring was continued for 24 h at room temperature. The separated product was filtered off, dried, and crystallized. Melting point, crystallization solvent and percentage yield are listed in Table 2. IR (cm^{-1}): 3440 (NH_2), 1645 (C=O). ^{1}H-NMR: 7.61–8.12 (m, 14H, Ar-*H*), 9.6 (s, 2H, NH_2).

General procedure for the synthesis of 2-(4-biphenylyl)quinoline-4-substituted carboxamides (**13b–d**)

Ethyl chloroformate (1.1 mL, 10 mmol) was added, dropwise, to a stirred solution of 2-(4-biphenylyl)quinoline-4-carboxylic acid **7a** (3.25 g, 0.01 mmol) and triethylamine (2 mL, 20 mmol) in chloroform (20 mL) at 5–10 °C. Stirring was continued for 30 min, then hydrazine hydrate **12b** (10 mmol) or the appropriate amine (**12c** or **12d**) (10 mmol) was added. The reaction mixture was stirred for a further 4 h at room temperature and the separated product was filtered off, dried and crystallized from the appropriate solvent. Melting points, crystallization solvents and percentage yields are listed in Table 2. The ^{1}H-NMR data are recorded in Table 3. IR (cm^{-1}): 3320–3280 (NH), 1670–1655 (C=O).

General procedure for the synthesis of 2-(4-biphenylyl)-4-(2-arylideneaminoethyl)quinoline-4-carboxylates (**15a–c**)

A mixture of 4-(2-aminoethyl)-2-(4-biphenylyl)quinoline-4-carboxylate **9d** (0.37 g, 1 mmol) and the appropriate ketone **14a–c** (1 mmol) in ethanol (20 mL) containing 2 drops of concentrated sulfuric acid was heated under reflux for 1–2 h. The solvent was evaporated under vacuum and the residue was crystallized from the appropriate solvent. Melting points, crystallization solvents and percentage yields are listed in Table 2. The ^{1}H-NMR data are recorded in Table 3. IR (cm^{-1}): 1685–1675 (C=O), for **15b**: 3380 (NH), 1665 (C=O), 1630 (C=N).

2-(4-Biphenylyl)quinoline-4-carboxylicacid azide (**16**)

To a stirred solution of 2-(4-biphenylyl)quinoline-4-acid hydrazide **13b** (1.0 g, 3 mmol) in glacial acetic acid (10 mL), was added dropwise, a solution of sodium nitrite (0.7 g, 10 mmol) in water (2 mL). The reaction mixture was allowed to stand for 1 h at room temperature. The separated solid product was filtered off, dried and crystallized from ethanol; mp 124–25 °C; yield 70%. IR (cm^{-1}): 2160 (N_3), 1654 (C=O).

General procedure for the synthesis of 4-(arylidenehydrazinocarbonyl)-2-(4-biphenylyl)quinoline (**17a–d**)

A mixture of 2-(4-biphenylyl)quinoline-4-carboxylic acid hydrazide **13b** (0.34 g, 1 mmol) and the appropriate ketone **14b–e** (1 mmol) in ethanol (20 mL) containing 2 drops of concentrated sulfuric acid was heated under reflux for 1–2 h. The solvent was concentrated and the precipitated solid was filtered off, dried, and crystallized from the appropriate solvent. Melting points, crystallization solvents, and percentage yields are listed in Table 2. The ^{1}H-NMR data are recorded in Table 3. IR (cm^{-1}): 3360–3300 (NH), 1665–1650 (C=O).

In vitro pharmacology

Senktide-induced contractions in the guinea-pig ileum preparation

Male varicoloured guinea-pigs, weighing 350–400 g were stunned and bled. About 2-cm long segments of guinea pig whole ileum were suspended in 50 mL organ bath containing Tyrod's solution of the following composition (mM): NaCl

(136.9), KCl (2.7), $CaCl_2$ (1.0), $NaHCO_3$ (11.9), NaH_2PO_4 (0.4), and glucose (5.6), areated with 95% O_2 and 5% CO_2. Mechanical activity was recorded along the longitudinal axis. After an equilibration time of 15–20 min the tissues were challenged with Senktide, purchased from American Peptide Company, USA (2 µg/100 mL organ bath) for 20 min. Tissues were then thoroughly washed with fresh Tyrod's solution which was renewed every 5 min. After addition of the tested compounds (40 µg/100 mL organ bath), the tissues were rechallenged with senktide (2 µg/100 mL organ bath) after 20 min inoculation and the responses are recorded in Table 1 and illustrated in Chart 2 compared to the control (senktide, 100% contraction). The reported values are the average of 5 determinations ± standard error (SE).

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