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Replacement of the quinoline system in 2-phenyl-4-quinolinecarboxamide NK-3 receptor antagonists

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Abstract

Results from a medicinal chemistry approach aimed at replacing the quinoline ring system in the potent and selective human neurokinin-3 (hNK-3) receptor antagonists **1**–**4** of general formula **I** are discussed. The data give further insight upon the potential NK-3 pharmacophore. In particular, it is highlighted that both the benzene-condensed ring and the quinoline nitrogen are crucial determinants for optimal binding affinity to the hNK-3 receptor. Some novel compounds maintained part of the binding affinity to the receptor (**5**, **6**, **10** and **13**) and compound **5**, featuring the naphthalene ring system, appears to be suitable for further modifications; it offers the option to introduce electron-withdrawing groups at position 2 and 4, conferring on the ring an overall electron-deficiency similar to that of the quinoline.

Keywords: Tachykinins; Neurokinin B; Neurokinin-3 receptor antagonists; 2-Phenyl-4-quinolinecarboxamides

1. Introduction

At least three distinct seven transmembrane G protein-coupled receptors, named neurokinin-1 (NK-1), neurokinin-2 (NK-2) and neurokinin-3 (NK-3), mediate the pharmacological actions of tachykinins [1]. These small neuropeptides share the common carboxy-terminal sequence (Phe–X–Gly–Leu–Met–NH_2) and are present in the CNS and peripheral nervous system; in the latter, a prominent source of the tachykinins are sensory nerves. The main mammalian tachykinins are substance P (SP), neurokinin A (NKA) and neurokinin B (NKB) and, although they interact with all three neurokinin receptors, SP is more selective for NK-1, NKA for NK-2 and NKB for NK-3 receptors [2]. The initial focus of the research in this area was mainly on NK-1 and NK-2 receptors for which potent and selective non-peptide antagonists have been available since 1991 [3,4]. Only recently, potent and selective 'peptoid' and non-peptide NK-3 receptor antagonists from diverse chemical classes [5–11] appeared in the literature and provided improved reagents to assist in the clarification of the physiological and pathophysiological role of NK-3 receptors and the potential therapeutic utility of selective NK-3 receptor antagonists [12,13]. Our group recently described 2-phenyl-4-quinolinecarboxamides **1**–**4** of general formula **I** in Table 1 as potent and selective hNK-3 receptor antagonists [10] and outlined the medicinal chemistry strategy employed to generate the prototype leads from modifications of potent NK-1 receptor antagonists [10,11].

One of the strategies utilized in the lead optimization process was the replacement of the quinoline system in compounds **1**–**4** by other aromatic (hetero)cycles com-

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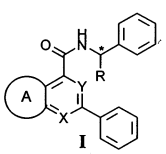
prising one or two fused rings, resulting in compounds **5**–**17** (Tables 1 and 2). The present paper describes chemical syntheses and structure–activity relationships (SARs) of compounds **5**–**17**, utilizing the radioligand binding affinity to the hNK-3 receptors stably expressed in CHO cell lines, as an index of biological activity (displacement of [^{125}I]–MePhe^7–NKB binding).

Table 1
Chemical structures and radioligand binding affinities to the human neurokinin-3 receptor expressed in CHO cells (hNK-3-CHO) of compounds **1**–**14** of general formula **I** [a,b]



I

Compd	A	X	Y	R	*	Formula	hNK-3-CHO binding[a] $K_i \pm$ SEM (nM)[b]
1		N	C	COOMe	(R,S)	$C_{25}H_{20}N_2O_3$	30.7 ± 3.8
2		N	C	COOMe	(R)	$C_{25}H_{20}N_2O_3$	13.3 ± 2.7
3		N	C	Et	(R,S)	$C_{25}H_{22}N_2O$	42.5 ± 2.6
4		N	C	Et	(S)	$C_{25}H_{22}N_2O$	18.0 ± 1.0
5		C	C	COOMe	(R,S)	$C_{26}H_{21}NO_3$	1202 (2)
6		N	N	COOMe	(R,S)	$C_{24}H_{19}N_3O_3$	883 (2)
7		C	N	COOMe	(R,S)	$C_{25}H_{20}N_2O_3$	> 10000 (1)
8	--	N	C	COOMe	(R,S)	$C_{21}H_{18}N_2O_3$	> 10000 (1)
9		N	C	Et	(R,S)	$C_{27}H_{24}N_2O$	> 10000 (1)
10		N	C	Et	(S)	$C_{23}H_{20}N_4O$	1674 (2)
11		N	C	Et	(S)	$C_{22}H_{20}N_4O$	5842 (1)
12		N	C	Et	(S)	$C_{23}H_{22}N_4O$	> 10000 (1)
13		N	C	Et	(S)	$C_{25}H_{26}N_2O$	1476 (1)
14		N	C	Et	(R,S)	$C_{23}H_{20}N_4O_3$	> 10000 (2)

[a] Inhibition of [^{125}I]MePhe^7–NKB binding in hNK-3-CHO cell membranes [24,25].

[b] Average of three to eight independent determinations ($n = 3$–8), unless otherwise indicated in parentheses.

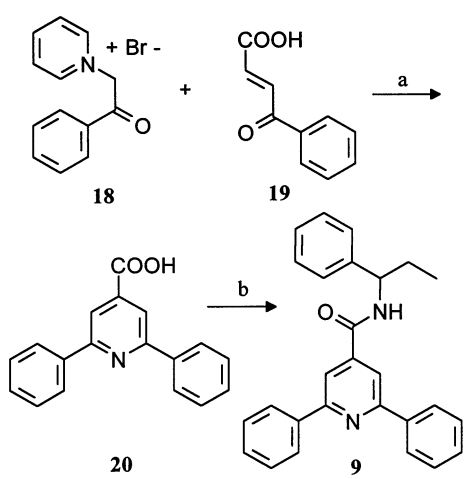
2. Chemistry

Synthetic procedures for compounds **1**–**8** in Table 1 have already been reported [11]. Compound **9** was prepared according to Scheme 1. Commercially available *N*-phenacylpyridinium bromide (**18**) and 3-benzoyl acrylic acid (**19**) were refluxed in a 10:1 mixture of acetic acid and acetic anhydride in the presence of a large excess of $AcONH_4$, as described by Blumbergs et al. [14], to produce 2,6-diphenylpyridine-4-carboxylic acid (**20**) which was coupled with 1-phenylpropylamine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) to yield the desired secondary amide **9**.

Compound **10** was prepared as shown in Scheme 2. Thus, Guareschi condensation of nitroacetamidine (**21**) [15,16] with ethyl 2,4-dioxo-4-phenylbutanoate (**22**) in refluxing EtOH resulted in high yields of ethyl 2-amino-3-nitro-6-phenylpyridine-4-carboxylate (**23**), which was transformed into the diamine **24** by catalytic hydrogenation of the nitro function.

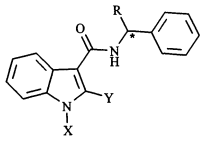
The six-membered fused pyrazine ring was incorporated by condensation of **24** with a masked dialdehyde, the 2,3-dihydroxy-1,4-dioxane, producing ethyl 6-phenylpyrido[2,3-*b*]pyrazine-8-carboxylate (**25**) [17]. Subsequent hydrolysis of the ester function under basic conditions and coupling reaction with (*S*)-(−)-1-phenylpropylamine afforded the desired secondary amide **10**.

Compounds **11** and **12** were prepared as shown in Scheme 3. The five-membered fused imidazole ring was incorporated by refluxing **24** (Scheme 2) in triethylorthoformate [15,18]. Acidic hydrolysis of the ester **27** produced 5-phenyl-3H-imidazo[4,5-*b*]pyridine-7-carboxylic acid, which was transformed into the final amide **11** under the usual condensation conditions.



Scheme 1. (a) AcOH/Ac_2O, (10:1), $AcONH_4$, 100°C, 5 h; (b) DCC, HOBT, (±)-Ph(Et)$CHNH_2$, THF/MeCN (1:1), r.t., 20 h.

Table 2
Chemical structures and radioligand binding affinities to the human neurokinin-3 receptor expressed in CHO cells (hNK-3-CHO) of compounds **15–17** of general formula **II**



II

Compd.	X	Y	R	*	Formula	hNK-3-CHO binding [a] $K_i \pm$ SEM (nM) [b]
15	H	Ph	COOMe	(*R*,*S*)	$C_{24}H_{20}N_2O_3$	>10000 (1)
16	H	CH_2Ph	Et	(*R*,*S*)	$C_{25}H_{24}N_2O$	3079 ± 55
17	Ph	H	Et	(*R*,*S*)	$C_{24}H_{22}N_2O$	>10000 (1)

[a] Inhibition of [^{125}I]MePhe^7–NKB binding in hNK-3-CHO cell membranes [24,25].
[b] Average of three to eight independent determinations ($n = 3$–8), unless otherwise indicated in parentheses.

Finally, regioselective methylation [19] of **11** with MeI and NaH in DMF afforded the 3-Me analogue **12**.

Compound **13** was prepared according to the synthetic procedure described in Scheme 4. The α,β-unsaturated ester **30** was obtained through the condensation of acetophenone **28** with glyoxylic acid, esterification and subsequent dehydration by *p*-toluenesulfonic acid in toluene at reflux. Reaction of compound **30** with cyclohexanone and $AcONH_4$ in refluxing toluene afforded the 5,6,7,8-tetrahydroquinoline (**31**) which, after basic hydrolysis, was condensed with (*S*)-(−)-1-phenylpropylamine to give compound **13**.

Condensation of ethyl benzoylpiruvate and 4-aminouracil (**33**) in refluxing acetic acid afforded ethyl 2,4-dioxo-7-phenyl-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-5-carboxylate (**34**) as shown in Scheme 5. Basic hydrolysis and coupling with (*R*,*S*)-1-phenylpropylamine provided compound **14**.

Chemical structures and binding affinities of the indole derivatives **15–17** of general formula **II** are reported in Table 2.

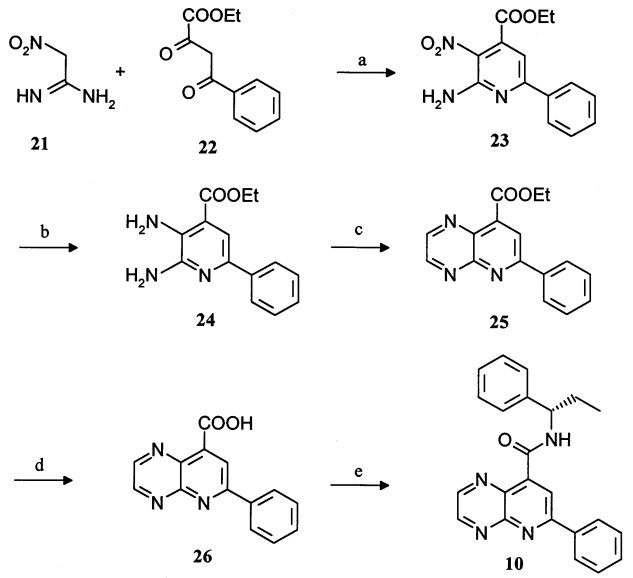
The 2-phenylindole derivative **15** was obtained in low yield by stirring 2-phenylindole (**35**) with trichloromethyl chloroformate in toluene in the presence of a stoichiometric amount of pyridine [20]; the non-isolated acyl chloride intermediate was then treated with a DMF solution of methyl phenylglycinate and Et_3N, as shown in Scheme 6.

A slightly modified procedure (Scheme 7), entailing the use of triphosgene [bis(trichloromethyl)carbonate] in a mixture of pyridine and CH_2Cl_2 as the solvent, was employed in the case of 2-benzylindole (**36**), in turn prepared by following the procedure of Burger and Bringhen [21]. The carboxylic acid derivative **37** was isolated in 48% yield by stirring the acyl chloride intermediate with 5% $NaHCO_3$ and Et_2O overnight and then transforming the sodium salt into the corresponding free acid. In the final coupling reaction, *N*-(3-dimethylaminopropyl) - *N*′ - ethylcarbodiimide hydrochloride (WSC) was used as the condensing agent to produce compound **16**.

1-Phenylindole (**39**) was prepared in quantitative yield by a modified Ullmann reaction, featuring the Cu_2Br_2-promoted indole *N*-arylation in *N*-methylpyrrolidone (NMP) and PhI at 170°C, as described in Scheme 8 [22]. Analogously to Scheme 7, the introduction of the 3-carboxylic function was achieved by the use of triphosgene. A standard coupling reaction produced compound **17**.

3. Pharmacology

Cloning and expression of the hNK-3 receptor in CHO stable cell line were performed as described by Buell et al. [23] and recently modified by Sarau and co-workers [24]. Receptor binding assay was performed with crude membranes. For NK-3 receptor competition binding studies, [^{125}I]–[MePhe^7]–NKB binding to hNK-3-CHO membranes was performed using the procedure of Sadowski and co-workers [25]. Concentration–response curves for compounds **1–17** were run using duplicate samples; among them, compounds which gave an IC_{50} binding affinity lower than 1000 nM in the first experiment were run in three to eight independent experiments ($n = 3$–8). Specific binding was determined by subtracting total binding from non-specific binding, which was assessed as the binding in the presence of 0.5 μM cold [MePhe^7]–NKB. Percent inhibition of specific binding was determined for each concentration of the compounds and the IC_{50}, defined as the concentration required to inhibit 50% of the specific binding, obtained from concentration–response



Scheme 2. (a) 95% EtOH, reflux, 20 h; (b) H_2, 10% Pd/C, 95% EtOH/THF, (1:1), 22 h; (c) 2,3-dihydroxy-1,4-dioxane, 95% EtOH, 30 h; (d) KOH, EtOH/H_2O (1:1), reflux, 3 h; then 1 N HCl; (e) DCC, HOBT, (*S*)-(−)-Ph(Et)CHNH$_2$, THF/MeCN (1:1), r.t., 15 h.

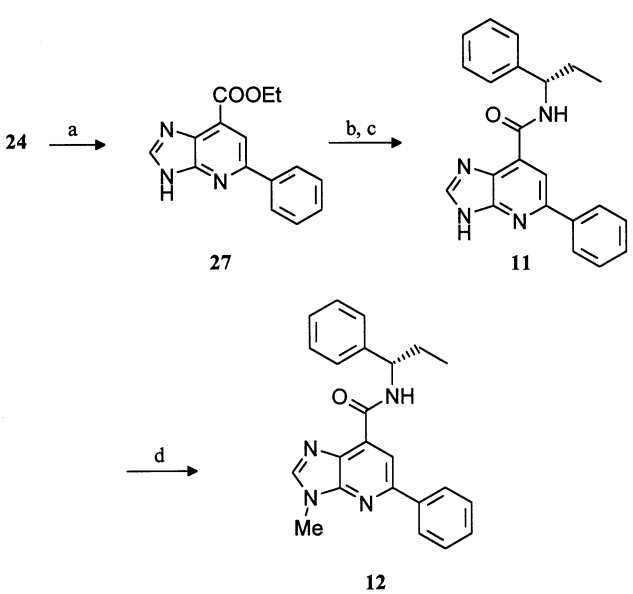
curves. Values reported in Tables 1 and 2 are the apparent inhibition constant (K_i), which was calculated from the IC_{50} as described by Cheng and Prusoff [26].

4. Results and discussion

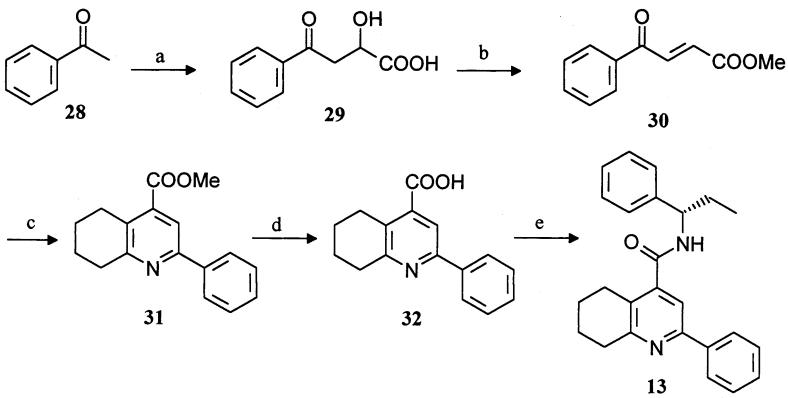
Following the discovery of compounds **1**–**4** possessing the 2-phenylquinoline backbone as potent and selective hNK-3 receptor antagonists [10], we decided to explore in more detail the bicyclic quinoline scaffold as part of an expanded chemical program for lead optimization. The aromatic nuclei that were investigated first were those having a (6,6) membered ring system featuring the benzene condensed ring (in Table 1, A = benzene, compounds **5**–**7**). The naphthalene derivative **5** and the quinazoline **6** showed a 28–40-fold lower affinity for hNK-3 receptors compared to the quinoline corresponding compound, whereas the isoquinoline **7** was far less potent (> 320-fold lower affinity). Thus, the presence of the quinoline nitrogen appears to be necessary for high hNK-3 binding affinity, whereas the extra nitrogen in position 3 of the aromatic system is clearly detrimental; this latter effect might be due to a negative interaction with the receptor or to the stabilization of an unfavored conformation of the 4-carboxamide side chain.

Then, we investigated the role of the condensed benzene ring (A) by three major approaches: elimination of this moiety, which gave rise to unsubstituted pyridines (e.g. **8**); benzene-substitution, which produced the phenyl-substituted pyridine **9**, and replacement of the condensed benzene by various (heteroaromatic)-cycles (compounds **10**–**14**). The substantial decrease in hNK-3 binding affinity observed with the pyridines **8** and **9** might indicate that a ring fused to the pyridine nucleus is crucial for affinity. Since incorporation of either electron-deficient (i.e. pyrazine) or electron-rich (i.e. imidazole) rings resulted in the poorly active compounds **10**–**12**, it is possible that the presence of the basic aromatic nitrogen(s) is responsible for the marked decrease observed in hNK-3 binding affinity. The importance of the aromatic character of ring A was assessed through the synthesis of the tetrahydro derivative **13**, which showed an 80-fold reduced binding affinity. Also, other polar heterocyclic rings, such as the 2,4-dioxo-1,2,3,4-tetrahydropyrimidine, are not tolerated (see compound **14**).

Another approach investigated was the replacement of the (6,6) by a (6,5) aromatic system, and the indole ring was chosen as the most suitable substitute for the quinoline (compounds **15**–**17**, Table 2). However, either the most immediate modification **15** or the introduction of a methylene spacer between the indole and the 2-phenyl ring **16**, or the 1-phenyl substitution **17** (both maintaining the same number of atoms between the phenyl substituent and the amidic carbonyl as in the quinoline) failed to produce compounds with maintained hNK-3 binding affinity. The low affinity of all the indole derivatives in Table 2 might be due either to: (i) the presence of the five-membered ring that alters the relative geometry of the 2-phenyl substituent in respect to the 4-carboxamide side chain and/or (ii) the absence of a basic nitrogen that was demonstrated to be of particular importance in the (6,6) series.



Scheme 3. (a) HC(OEt)$_3$, reflux, 24 h; (b) 6 N HCl, reflux, 5 h; (c) DCC, HOBT, Et$_3$N, (*S*)-(−)-Ph(Et)CHNH$_2$, THF/MeCN (1:1), r.t., 9 h; (d) MeI, 60% NaH, DMF, 2 h.



Scheme 4. (a) Glyoxylic acid, NaOH, MeOH/H_2O (1:1), r.t., 24 h; (b) 1. $NaHCO_3$, MeI, DMF, 18 h; 2. PTSA, PhMe, reflux, 1 h; (c) cyclohexanone, $AcONH_4$, PhMe, reflux, 4 h; (d) NaOH, 95% EtOH, overnight; (e) DCC, HOBT, (*S*)-(−)-Ph(Et)$CHNH_2$, THF/MeCN (1:1), r.t., 16 h.

5. Conclusions

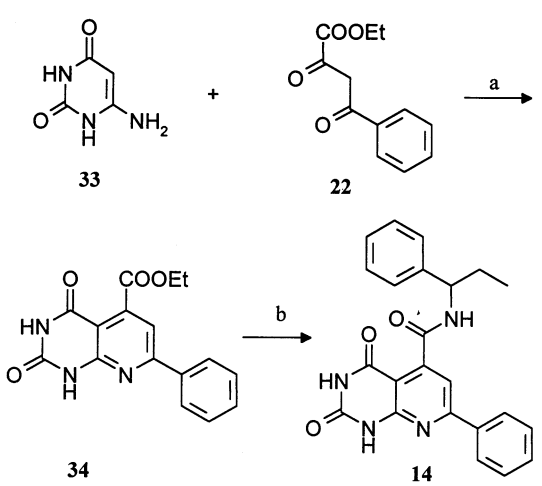
In conclusion, these data indicate that the quinoline ring, far from being a mere scaffold for spacing and correctly orienting the 2-phenyl and the 4-carboxamido substituents, is an essential moiety for optimal binding affinity to the hNK-3 receptor. In fact, although some novel compounds maintained part of the binding affinity to the hNK-3 receptor (**5**, **6**, **10** and **13**), none of the 13 aromatic nuclei exploited resulted in similar potency to that of the quinoline corresponding compounds. However, the naphthalene ring system (compound **5**) appears to be the most promising and workable framework; it offers the option for further substitution at the carbons in position 2 and 4, particularly with electron-withdrawing groups able to mimic the electron-deficiency of the quinoline ring. In addition, investigation of the optimal substitution pattern of the benzene-condensed ring (A) offers room for further improvement in hNK-3 binding affinity.

Taken collectively, these and previously published data [13] further refine an hypothesis of the NK-3 pharmacophore, helpful in the design of novel potent compounds from diverse chemical classes.

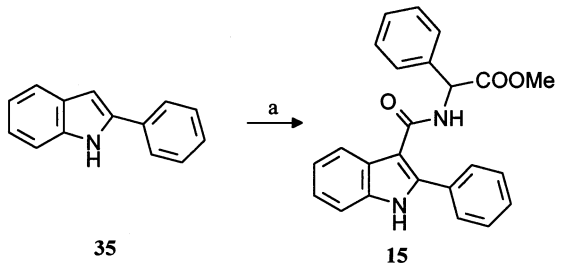
6. Experimental

6.1. Chemistry

Melting points were determined with a Büchi 530 hot stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker ARX 300 spectrometer at 303 K unless otherwise indicated. Chemical shifts were recorded in parts per million (δ units) downfield from tetramethylsilane (TMS); NMR spectral data are reported as a list. IR spectra were recorded in Nujol mull on sodium chloride disks or in KBr with a Perkin–Elmer 1420 spectrophotometer; mass spectra were obtained on a Finnegan MAT TSQ-700 spectrometer. Optical rotations were determined in MeOH solution at the indicated concentration with a Perkin–Elmer 341 polarimeter at the sodium D-line. Silica gel used for flash column chromatography was Kiesegel 60 (230–400 mesh) (E. Merck AG, Darmstadt, Germany). Evaporations were performed at reduced pressure, and all oily products were dried at 0.1 mbar for 16 h. Combustion elemental analyses were performed at Redox snc, Milan, Italy. Analyses indicated by the symbols of the elements were within $\pm 0.4\%$ of theoretical values. Syntheses of compounds **1**–**8** are reported elsewhere [11]. Methyl 3-benzoylacrylate (**30**) was prepared following the same procedure described by Bennet and Mason [27] for methyl 3-pivaloylacrylate. Ethyl benzoylpyruvate (**22**) was prepared according to Batt and Houghton [28].



Scheme 5. (a) AcOH reflux, 20 h; (b) 1. KOH, 95% EtOH, 3 h; 2. (±)-Ph(Et)$CHNH_2$, Et_3N, HBTU, CH_2Cl_2/CH_3CN (1:1), 4 h.



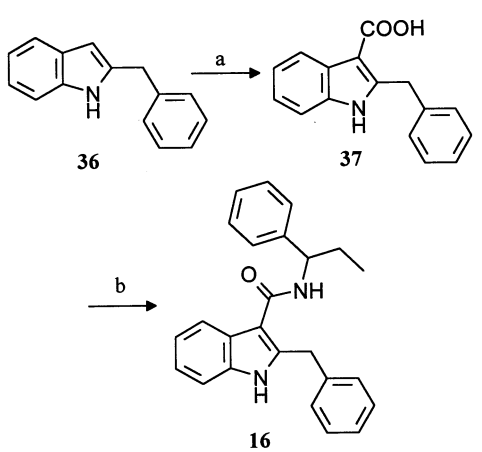
Scheme 6. (a) 1. $ClCOOCCl_3$, pyridine, PhMe, r.t., 4 h; 2. (*R*,*S*)-methyl phenyl glycinate, Et_3N, DMF, 0°C to r.t., overnight.

*6.1.1. 2,6-Diphenylpyridine-4-carboxylic acid (**20**)*

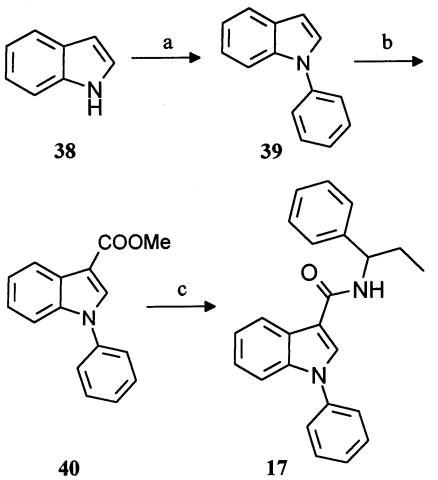
A stirred mixture of *N*-phenacylpyridinum bromide (**18**, 6 g, 20.0 mmol), benzoylacrylic acid (**19**, 11.1 g, 20.0 mmol), AcOH (40 ml), Ac_2O (4 ml), and NH_4OAc (24.0 g, 310 mmol) was refluxed for 5 h. The hot mixture was then diluted with water (150 ml), allowed to cool, and filtered. The solid was washed with water and dissolved in a warm aqueous solution of K_2CO_3 (200 ml, 0.14 M). The brown solution was extracted with CH_2Cl_2 (3 × 20 ml) and Et_2O (2 × 50 ml) and then acidified with 37% HCl to pH 2 and filtered. The solid product was washed with water and evaporated to dryness to obtain the crude acid **20**, which was crystallized from EtOH (2.9 g, 50%), m.p. 279–281°C. IR (KBr): 3448, 3280–2690, 2658, 2598, 2534, 1700, 1564 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.80 (s br, 1H), 8.27 (m, 4H), 8.24 (m, 2H), 7.60–7.48 (m, 6H).

*6.1.2. Ethyl 2-amino-3-nitro-6-phenyl-4-pyridincarboxylate (**23**)*

To a solution of nitroacetamidine [15,16] (**21**, 1.24 g, 12 mmol) in 95% EtOH (50 ml), ethyl benzoylpyruvate [28] (**22**, 2.23 g, 10 mmol) was added; the mixture was refluxed for 20 h and then evaporated to dryness. The residue was purified by flash column chromatography



Scheme 7. (a) Triphosgene, pyridine, CH_2Cl_2, 3 h; then 5% $NaHCO_3$, Et_2O, overnight; (b) WSC, HOBT, (±)-Ph(Et)$CHNH_2$, THF/CH_3CN (1:1), r.t., overnight.



Scheme 8. (a) PhI, Cu_2Br_2, Na_2CO_3, NMP, 170°C, 6 h; (b) triphosgene, pyridine, DCM, 2 h, then MeOH, r.t., 2 h; (c) 1. 40% KOH, MeOH, 100°C, 0.5 h, 2. WSC, HOBT, (±)-Ph(Et)$CHNH_2$, THF/CH_3CN (1:1), r.t., overnight.

(eluting with EtOAc/*n*-hexane, 15:85) to give the title compound **23** (1.9 g, 66%). IR (KBr): 3461, 3308, 1729, 1615, 1562, 1453, 1373, 1351, 1252, 1211, 1033, 840, 773, 703 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.19–8.11 (m, 2H), 8.01 (s br, 2H), 7.59–7.49 (m, 3H), 7.41 (s, 1H), 4.35 (q, $J = 6.8$ Hz, 2H), 1.31 (t, $J = 6.8$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 287 (M^+), 140, 104, 65.

*6.1.3. Ethyl 2,3-diamino-6-phenyl-4-pyridincarboxylate (**24**)*

The nitropyridine **23** (2.9 g, 10 mmol) was dissolved in a mixture of 95% EtOH (100 ml) and THF (100 ml) and hydrogenated with 10% Pd/C (210 mg) at 60 psi for 22 h at room temperature (r.t.). The solution was filtered through a Celite pad, and the solid was washed with additional THF. The filtrate was concentrated to provide the diaminopyridine **24** (2.5 g, quantitative), which was used without any further purification. IR (KBr): 3402, 1640, 1620, 1610, 1430, 1213, 775, 698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 7.85 (d, $J = 6.7$ Hz, 2H), 7.38 (s, 1H), 7.37 (dd, $J = 6.7$, 6.7 Hz, 2H), 7.24 (dd, $J = 6.7$, 6.7 Hz, 1H), 6.55 (s br, 2H), 6.10 (s br, 2H), 4.30 (q, $J = 6.8$ Hz, 2H), 1.31 (t, $J = 6.8$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 257 (M^+), 183, 155, 140.

*6.1.4. Ethyl 6-phenylpyrido[2,3-b]pyrazine-8-carboxylate (**25**)*

To a solution of diaminopyridine **24** (2.22 g, 8.6 mmol) in 95% EtOH (90 ml), 2,3-dihydroxy-1,4-dioxane (1.0 g, 8.3 mmol) was added and the mixture was stirred for 36 h at r.t. The suspension thus obtained was filtered and the solid was crystallized from EtOAc/*n*-hexane to give the pyrazine derivative as a light green

powder (0.94 g, 40%), m.p. 171–172°C. IR (KBr): 2990, 1728, 1604, 1374, 1246 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.20 (d, $J = 2.5$ Hz, 1H), 9.07 (d, $J = 2.5$ Hz, 1H), 8.69 (s, 1H), 8.39 (m, 2H), 7.60 (m, 3H), 4.49 (q, $J = 6.8$ Hz, 2H), 1.40 (t, $J = 6.8$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 279 (M^+), 207.

6.1.5. 6-Phenylpyrido[2,3-b]pyrazine-8-carboxylic acid (26)

The pyrazine ester **25** was suspended in water (10 ml) and 85% KOH (0.3 g, 4.55 mmol) was added. The mixture was heated at 80°C for 2 h, the basic solution was then acidified with 1 N HCl (7 ml) and the solid thus obtained was filtered, dried and utilized without any further purification (1.12 g, 97%). IR (KBr): 3824–3452, 1730, 1608, 1551, 1473, 1389, 1328, 1204, 1048, 875, 760, 630 cm^{-1}; ^1H NMR (DMSO-d_6): δ 14.10 (s br, 1H), 9.21 (d, $J = 2.5$ Hz, 1H), 9.08 (d, $J = 2.5$ Hz, 1H), 8.66 (s, 1H), 8.42–8.36 (m, 2H), 7.65–7.58 (m, 3H).

6.1.6. Ethyl 5-phenyl-3H-imidazo[4,5-b]pyridine-7-carboxylate (27)

A mixture of crude diamine **24** (2.57 g, 10 mmol) and triethylorthoformate (100 ml) was heated under reflux for 18 h and then evaporated to dryness. The residue was purified by flash column chromatography (eluting with a gradient mixture of CH_2Cl_2/*i*-PrOH) to give the imidazole derivative **27** (0.94 g, 66%). IR (KBr): 3336, 3084, 2984, 1730, 1695, 1636, 1584, 1480, 1465, 1372, 1177, 1128, 930, 755 cm^{-1}; ^1H NMR (DMSO-d_6): δ 12.89 (s br, 1H), 8.61 (s, 1H), 8.19 (s, 1H), 8.15 (d, $J = 7.2$ Hz, 2H), 7.53 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.45 (dd, $J = 7.2$, 7.2 Hz, 1H), 4.51 (q, $J = 7.2$ Hz, 2H), 1.42 (t, $J = 7.2$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 267 (M^+), 195, 166, 140.

6.1.7. General procedure for the synthesis of amides (9–11)

To a solution of the corresponding carboxylic acid in THF/MeCN (1:1, 10 ml/mmol of substrate) DCC (1.5 eq), Et_3N (2 eq) and HOBT (1.5 eq) were added. After 1 h at r.t., 1-phenylpropylamine (2 eq) was added and the reaction mixture stirred overnight. The residue was evaporated to dryness, dissolved in EtOAc (15 ml/mmol), washed with 10% HCl, brine, dried over anhydrous Na_2SO_4 and finally evaporated to dryness. The light brown oil thus obtained was purified by flash column chromatography. Elution solvents, yields, crystallization solvents and physico–chemical data for compounds **9**–**11** are reported below.

6.1.8. N-(α-Ethylbenzyl)-2,6-diphenylpyridine-4-carboxamide (9)

Eluent EtOAc/*n*-hexane (10:90); 20% yield; white powder, m.p. 217–218°C. IR (KBr): 3450, 3290, 1634, 1582, 1536, 1460, 1294, 1030, 766, 692 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.15 (d, $J = 8.2$ Hz, 1H), 8.28 (s, 2H), 8.26 (d, $J = 6.6$ Hz, 4H), 7.60–7.49 (m, 6H), 7.44 (d, $J = 7.4$ Hz, 2H), 7.36 (dd, $J = 7.4$, 7.4 Hz, 2H), 7.25 (dd, $J = 7.4$, 7.4 Hz, 1H), 5.20 (dt, $J = 8.2$, 8.2 Hz, 1H), 1.91 (dq, $J = 8.2$, 7.4 Hz, 2H), 0.96 (t, $J = 7.4$ Hz, 3H); ESI POS-MS (solvent MeOH, spray 4.5 kV, skimmer 60 eV, capillary 220°C): m/z 393 (MH^+), 415 (MNa^+); *Anal.* ($C_{27}H_{24}N_2O$): C, H, N.

6.1.9. (S)-N-(α-Ethylbenzyl)-6-phenylpyrido[2,3-b]-pyrazine-8-carboxamide (10)

Eluent CH_2Cl_2/EtOAc (98:2); 94% yield; light brown needles, m.p. 126–127°C from *i*-Pr_2O/*i*-PrOH. $[\alpha]_D^{20} = -7$ ($c = 0.53$, MeOH). IR (KBr): 3060, 2930, 1666, 1598, 1542, 1486, 1456, 1376, 1184, 784, 696 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.81 (d, $J = 8.5$ Hz, 1H), 9.24 (d, $J = 2.2$ Hz, 1H), 9.12 (d, $J = 2.2$ Hz, 1H), 8.66 (s, 1H), 8.36 (m, 2H), 7.65–7.56 (m, 3H), 7.48 (d, $J = 7.8$ Hz, 2H), 7.37 (dd, $J = 7.8$, 7.8 Hz, 2H), 7.26 (dd, $J = 7.8$, 7.8 Hz, 1H), 5.10 (dd, $J = 8.2$, 7.3 Hz, 1H), 1.88 (dq, $J = 7.3$, 7.3 Hz, 2H), 0.99 (t, 7.3 Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 368 (M^+), 339, 234, 206, 179, 152, 134, 103; *Anal.* ($C_{23}H_{20}N_4O$): C, H, N.

6.1.10. (S)-N-(α-Ethylbenzyl)-2-phenyl-3H-imidazo-[4,5-b]pyridine-4-carboxamide (11)

The corresponding acid was easily obtained in quantitative yield by acidic hydrolysis (6 N HCl, reflux, 5 h) of the ester **27**; eluent PhMe/EtOAc (85:15); 50% yield, light brown powder, m.p. 166–168°C from PhMe/*n*-hexane. $[\alpha]_D^{20} = +3.8$ ($c = 0.56$, MeOH). IR (KBr): 3298, 2967, 2812, 1670, 1558, 1476, 1381, 1279, 929, 755, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 353 K): δ 13.3 (s br, 1H), 9.65 (s br, 1H), 8.60 (s br, 1H), 8.25 (s, 1H), 8.11 (d, $J = 7.7$ Hz, 2H), 7.52 (dd, $J = 7.7$, 7.7 Hz, 2H), 7.45 (d, $J = 7.7$ Hz, 2H), 7.43 (dd, $J = 7.7$, 7.7 Hz, 1H), 7.37 (dd, $J = 7.7$, 7.7 Hz, 2H), 7.26 (dd, $J = 7.7$, 7.7 Hz, 1H), 5.12 (dt, $J = 8.2$, 7.7 Hz, 1H), 1.98 (dq, $J = 7.7$, 7.7 Hz, 2H), 0.99 (t, $J = 7.7$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 356 (M^+), 327, 222, 194, 140, 134; *Anal.* ($C_{22}H_{20}N_4O$): C, H, N.

6.1.11. (S)-N-(α-Ethylbenzyl)-3-methyl-5-phenylimidazo[4,5-b]pyridine-7-carboxamide (12)

To a DMF solution (3 ml) of compound **11** (215 mg, 0.6 mmol), 60% NaH (27 mg, 0.67 mmol) was added. The homogeneous solution was stirred at r.t. under nitrogen for 2 h; MeI (0.06 ml, 0.96 mmol) was then added and the solution was stirred for additional 2 h. Solid NH_4Cl (1 g) was added and the solvent evaporated to dryness. The residue was taken-up in EtOAc and the suspension filtered; the light brown oil obtained after solvent evaporation was crystallized from *i*-Pr_2O to give the methyl derivative **12** (0.18 g, 78%), m.p.

162–163°C. $[\alpha]_D^{20} = +1.1$ ($c = 0.51$, MeOH). IR (KBr): 3304, 1666, 1586, 1504, 1426, 1358, 1260, 756, 644 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.85 (d, $J = 9.0$ Hz, 1H), 8.75 (s, 1H), 8.25 (s, 1H), 8.16 (d, $J = 7.8$ Hz, 2H), 7.54 (dd, $J = 7.8$, 7.8 Hz, 2H), 7.47 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.42 (d, $J = 7.3$ Hz, 2H), 7.37 (dd, $J = 7.3$, 7.3 Hz, 2H), 7.27 (dd, $J = 7.3$, 7.3 Hz, 1H), 5.12 (dt, $J = 9.0$, 7.3 Hz, 1H), 3.98 (s, 3H), 1.94 (dq, $J = 7.3$, 7.3 Hz, 2H), 0.95 (t, $J = 7.3$ Hz, 3H) [18]; ESI POS-MS (solvent MeOH, spray 4.5 kV, skimmer 60 eV, capillary 220°C): m/z 371 (MH^+), 393 (MNa^+); ESI DAU + 371 (collision gas: Argon): m/z 254, 226, 208; *Anal.* ($C_{23}H_{22}N_4O$): C, H, N.

6.1.12. 4-Methoxycarbonyl-2-phenyl-5,6,7,8-tetrahydroquinoline (31)

In a round bottomed flask provided with a Dean Stark apparatus, cyclohexanone (10 ml, 96.5 mmol), methyl 3-benzoylacrylate [27] (**30**, 1.9 g, 10 mmol), $AcONH_4$ (3.85 g, 50 mmol) were refluxed in toluene (50 ml) for 4 h, azeotroping water. After evaporation of the solvent, the residue was dissolved in Et_2O and washed with water; the organic phase was dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography (eluting with Et_2O/*n*-hexane, 2:8) yielding **31** as a dark oil which solidified on standing (0.6 g, 22%). IR (KBr): 2938, 2862, 1732, 1589, 1551 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.00 (d, $J = 6.7$ Hz, 2H), 7.89 (s, 1H), 7.50–7.34 (m, 3H), 3.92 (s, 3H), 3.05 (dd, $J = 6.3$, 6.3 Hz, 4H), 2.00–1.80 (m, 4H).

6.1.13. 4-Carboxy-2-phenyl-5,6,7,8-tetrahydroquinoline (32)

To a solution of **31** (2.5 g, 9.4 mmol) in 95% EtOH (100 ml), 80% pellets KOH (2.5 g, 35.6 mmol) was added and the solution was stirred for one night at r.t. The solvent was evaporated, the residue was dissolved in water and washed with Et_2O. The aqueous phase was acidified with 5 N HCl and extracted with CH_2Cl_2; the organic phase was dried over Na_2SO_4 and evaporated to dryness. Treatment of the crude product with Et_2O afforded **32** as a slightly pink powder (1.8 g, 75%), m.p. 182–186°C. IR (KBr): 3421, 2937, 1712, 1588, 1551 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.50 (s br, 1H), 8.05 (d, $J = 7.2$ Hz, 2H), 7.91 (s, 1H), 7.52–7.39 (m, 3H), 2.96 (dd, $J = 6.3$, 6.3 Hz, 4H), 1.90–1.74 (m, 4H); ESI NEG-MS (solvent MeOH, spray 4.5 kV, skimmer −60 eV, capillary 220°C): m/z 252 $(M-H)^-$; 505 $(2M-H)^-$; (CID Offset = 32 eV): m/z 252, 208.

6.1.14. (S)-N-(α-Ethylbenzyl)-2-phenyl-5,6,7,8-tetrahydroquinoline-4-carboxamide (13)

To a solution of **32** (0.9 g, 3.1 mmol) in THF/MeCN (1:1, 10 ml), (*S*)-1-phenylpropylamine (0.84 g, 6.2 mmol) was added and the mixture was stirred at r.t. until complete dissolution of the reagents occurred. The solution was cooled to 0°C and DCC (0.64 g, 3.1 mmol) dissolved in CH_2Cl_2 (4 ml) was added. The mixture was stirred at r.t. for 15 min, then left overnight. Water (0.5 ml) was added under stirring and after 15 min the suspension was filtered off. The solution was evaporated to dryness. The residue was dissolved in EtOAc and washed with 5% NaOH and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated to dryness. Crystallization of the crude product from a mixture of *i*-Pr_2O/Me_2CO (1:1) yielded **13** as white crystals (0.4 g, 35%), m.p. 147–148°C. $[\alpha]_D^{20} = -6.8$ ($c = 0.56$, MeOH). IR (KBr): 3311, 1032, 2935, 1638, 1590, 1528 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.89 (d, $J = 8.4$ Hz, 1H), 8.04 (d, $J = 6.5$ Hz, 2H), 7.55 (s, 1H), 7.51–7.32 (m, 7H), 7.25 (m, 1H), 4.92 (dt, $J = 8.4$, 8.4 Hz, 1H), 2.92 (t, $J = 6.3$ Hz, 2H), 2.70 (t, $J = 6.3$ Hz, 2H), 1.89–1.69 (m, 6H), 0.92 (t, $J = 7.2$ Hz, 3H); ESI POS-MS (solvent MeOH, spray 4.5 kV, skimmer 60 eV, capillary 220°C): m/z 371 (MH^+); ESI DAU + 371 (collision gas: argon): m/z 371, 253, 208, 180; *Anal.* ($C_{25}H_{26}N_2O$): C, H, N.

6.1.15. Ethyl 2,4-dihydroxy-7-phenylpyrido[2,3-d]-pyrimidine-5-carboxylate (34)

A stirred mixture of ethyl benzoylpyruvate (**22**, 1.1 g, 5 mmol), 4-amino-2,6-dihydroxypyrimidine (**33**, 0.63 g, 5 mmol) and glacial AcOH (15 ml) was heated at 90°C for 20 h. The mixture was then evaporated to dryness and the residue triturated with Et_2O yielding **34** as a white powder (1.1 g, 70%), m.p. > 275°C. IR (KBr): 3168, 3052, 1728, 1674, 1578 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.83 (s br, 1H), 11.50 (s br, 1H), 8.20 (m, 2H), 7.85 (s, 1H), 7.55 (m, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H); ESI POS-MS (solvent MeOH, spray 4.5 kV, skimmer 60 eV, capillary 220°C): m/z 312 (MH^+), 334 (MNa^+); ESI DAU + 312 (collision gas: argon): m/z 311, 266, 248, 197, 168.

6.1.16. (R,S)-N-(α-Ethylbenzyl)-2,4-dihydroxy-7-phenylpyrido[2,3-d]pyrimidine-5-carboxamide (14)

To a solution of compound **34** (7.0 g, 22.5 mmol) in 95% EtOH (70 ml), 80% pellets KOH (1.0 g, 17.8 mmol) was added and the mixture was stirred at r.t. until complete dissolution of the reagents occurred. The solvent was evaporated, then the residue dissolved in water and the solution extracted twice with Et_2O. The aqueous phase was acidified to pH 4 with 6 N HCl and the precipitate was filtered, washed with water and dried, yielding a white powder (6.1 g, 95%). The crude carboxylic acid (2.85 g, 10 mmol) and Et_3N (2.8 ml, 20 mmol) were dissolved in a mixture of MeCN/CH_2Cl_2 (1:1) (200 ml). HBTU (4.55 g, 12 mmol) and (*R,S*)-1-phenylpropylamine (1.35 g, 10 mmol) were added and the mixture was stirred at r.t. for 6 h. The solvent was

evaporated and the residue dissolved in EtOAc. The organic phase was washed with water, 5% $NaHCO_3$, brine, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash column chromatography (eluting with EtOAc) and crystallized from *i*-PrOH yielding **14** as a white powder (0.7 g, 17%), m.p. 301–302°C. IR (KBr): 3344, 3184, 3060, 1724, 1656, 1570, 1532 cm^{-1}; ^1H NMR (DMSO-d_6): δ 11.30 (s br, 2H), 8.41 (d br, $J = 8.0$ Hz, 1H), 8.12 (m, 2H), 7.53 (m, 3H), 7.46 (s, 1H), 7.41 (d, $J = 7.1$ Hz, 2H), 7.34 (dd, $J = 7.1$, 7.1 Hz, 2H), 7.23 (dd, $J = 7.1$, 7.1 Hz, 1H), 5.00 (dt, $J = 8.0$, 8.0 Hz, 1H), 1.98–1.74 (m, 2H), 0.92 (t, $J = 7.1$ Hz, 3H); ESI POS-MS (solvent MeOH, spray 4.5 kV, skimmer −60 eV, capillary 220°C): *m*/*z* 401 (MH^+), 423 (MNa^+), 439 (MK^+); *Anal.* ($C_{23}H_{20}N_4O_3$): C, H, N.

6.1.17. (R,S)-N-[α-(Methoxycarbonyl)benzyl]-2-phenylindole-3-carboxamide (15)

To a solution of 2-phenylindole (**35**, 1.0 g, 5.1 mmol) in toluene (20 ml) under nitrogen atmosphere, pyridine (0.42 ml, 5.2 mmol) and trichloromethyl chloroformate (0.5 ml, 4.1 mmol) were added. The reaction mixture was stirred at r.t. for 4 h, then was cooled at 0°C and (*R*,*S*)-methyl 2-phenylglycinate (1.6 g, 9.9 mmol), dissolved in DMF (40 ml) and TEA (1.4 ml, 10.2 mmol), was added dropwise. After stirring at r.t. overnight, the mixture was evaporated to dryness, dissolved in CH_2Cl_2, washed with 1 N HCl, 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated again. The residue was purified by flash column chromatography (two columns were necessary, in the first column the eluent was Et_2O/*n*-hexane/28% NH_4OH, 75:25:0.25; in the second EtOAc/*n*-hexane/28% NH_4OH, 50:50:0.5) to yield **15** (0.27 g, 14%) as a white solid. IR (KBr): 3460–3120, 3060, 3030, 2920, 1750, 1630, 1580, 1550, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.38 (s br, 1H), 8.23 (m, 1H), 7.66 (m, 2H), 7.50 (m, 3H), 7.42–7.19 (m, 8H), 6.50 (d br, $J = 7.4$ Hz, 1H), 5.77 (d, $J = 7.4$ Hz, 1H), 3.70 (s, 3H); EI-MS (source 180°C, 70 eV, 200 mA): *m*/*z* 384 (M^+), 325, 220; *Anal.* ($C_{24}H_{20}N_2O_3$): C, H, N.

6.1.18. 2-Benzyl-3-indolecarboxylic acid (37)

To an ice-cooled solution of 2-benzylindole [21] (**36**, 1.46 g, 7.04 mmol) in CH_2Cl_2 (10 ml) under nitrogen atmosphere, pyridine (0.57 ml, 7.04 mmol) and triphosgene (bis(trichloromethyl)carbonate, 2.09 g, 7.04 mmol) were added. The reaction mixture was allowed to reach r.t. and stirred overnight. The residue was treated with 5% $NaHCO_3$ (10 ml), Et_2O (20 ml) and stirred at r.t. for 30 min. The organic layer was separated, washed with 10% HCl (10 ml), brine (10 ml), dried over Na_2SO_4 and evaporated to dryness, affording **37** (1.68 g, 6.68 mmol, 95%) as a white powder; m.p. 198–200°C (dec.). IR (Nujol): 3398, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.20 (d, $J = 8.5$ Hz, 1H), 8.08 (s br, 1H), 7.40–7.12 (m, 8H), 4.61 (s, 2H); EI-MS (source 180°C, 70 eV, 200 mA): *m*/*z* 251 (M^+), 233, 204, 102.

6.1.19. (R,S)-N-(α-Ethylbenzyl)-2-benzyl-3-indolecarboxamide (16)

To a solution of **37** (0.42 g, 1.67 mmol) in THF/MeCN (1:1, 10 ml), WSC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide) (0.32 g, 1.67 mmol) and HOBT (1-hydroxybenzotriazole) (0.23 g, 1.67 mmol) were added. After 1 h at r.t., (*R*,*S*)-1-phenylpropylamine (0.23 g, 1.67 mmol) was added and the reaction mixture was stirred overnight. The residue was evaporated to dryness, dissolved in EtOAc (15 ml), washed with 10% HCl (10 ml), saturated solution of K_2CO_3 (10 ml), brine (10 ml), dried over Na_2SO_4 and evaporated to dryness. Treatment with *n*-hexane and filtration afforded **16** (0.41 g, 1.11 mmol, 67%) as white powder; m.p. 105–107°C. IR (Nujol): 3400, 1640 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.01 (s br, 1H), 7.74 (d, $J = 7.7$, 1H), 7.40–7.15 (m, 13H), 6.24 (d br, $J = 7.0$ Hz, 1H), 5.19 (dt, $J = 7.0$, 7.0 Hz, 1H), 4.54 (s, 2H), 2.05–1.90 (m, 2H), 0.99 (t, $J = 7.9$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): *m*/*z* 368 (M^+), 249, 234, 204; *Anal.* ($C_{25}H_{24}N_2O$): C, H, N.

6.1.20. N-Phenylindole (39)

To a solution of indole (5 g, 42.68 mmol) in NMP (*N*-methylpyrrolidone) (88 ml), Cu_2Br_2 (13 g, 45.35 mmol), Na_2CO_3 (4.8 g, 45.35 mmol) and iodobenzene (16 ml, 144.04 mmol) were added and the mixture was heated at 170°C for 6 h. After cooling to r.t., 5% HCl (40 ml) and EtOAc (40 ml) were added, and the mixture was filtered on a Celite pad. The filtrate was separated and the organic layer was washed with brine (40 ml), dried over Na_2SO_4 and evaporated to dryness. The crude product was purified by flash column chromatography, eluting with EtOAc/*n*-hexane 9:1 to yield 8.2 g (45.35 mmol, quantitative) of compound **39**. IR (neat): 3056, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.71 (m, 2H), 7.59 (d, $J = 7.8$ Hz, 1H), 7.40–7.32 (m, 3H), 7.29–7.17 (m, 3H), 7.11 (dd, $J = 7.8$, 7.8 Hz, 1H), 6.70 (d, $J = 3.1$ Hz, 1H); EI-MS (source 180°C, 70 eV, 200 mA): *m*/*z* 193 (M^+).

6.1.21. Methyl N-phenyl-3-indolecarboxylate (40)

To an ice-cooled solution of **39** (1 g, 5.17 mmol) in CH_2Cl_2 (10 ml) under nitrogen atmosphere, pyridine (0.42 ml) and triphosgene (1.53 g, 5.15 mmol) were added. The reaction mixture was allowed to reach r.t. and MeOH (20 ml) was added. After stirring for 2 h, the solvent was evaporated and CH_2Cl_2 (20 ml) was added. After washing with 5% $NaHCO_3$ (10 ml) and brine (10 ml), the mixture was dried over Na_2SO_4 and evaporated to dryness, affording **40** (0.74 g, 2.9 mmol, 57%). IR (neat): 3056, 1700, 1600 cm^{-1}; EI-MS (source

180°C, 70 eV, 200 mA): m/z 251 (M^+), 220, 193. 165.

6.1.22. (R,S)-N-(α-Ethylbenzyl)-1-phenyl-3-indolecarboxamide (17)

A solution of **40** (0.223 g, 0.927 mmol) in MeOH (5 ml) and 40% aqueous KOH (5 ml) was refluxed for 0.5 h, evaporated to dryness, diluted with water (3 ml) and adjusted to pH 2 with 20% HCl. The precipitate was filtered and dried under vacuum at 40°C for 3 h, affording *N*-phenyl-3-indolecarboxylic acid (0.210 g, 0.885 mmol), which was dissolved in THF/MeCN (1:1, 10 ml) and treated with WSC (*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide) (0.170 g, 0.885 mmol) and HOBT (1-hydroxybenzotriazole) (0.12 g, 0.885 mmol). After 1 h at r.t., (*R,S*)-1-phenylpropylamine (0.12 g, 0.885 mmol) was added and the reaction mixture was stirred overnight. The residue was evaporated to dryness, dissolved in EtOAc (15 ml), washed with 10% HCl (10 ml), saturated solution of K_2CO_3 (10 ml), brine (10 ml), dried over Na_2SO_4 and evaporated. Treatment with *n*-hexane and filtration afforded **17** (0.22 g, 0.62 mmol, 70%) as a light brown powder; m.p. 173–175°C. IR (Nujol): 3350, 1620, 1600 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06–8.00 (m, 1H), 7.86 (s, 1H), 7.57–7.23 (m, 13H), 6.21 (d br, $J = 7.7$ Hz, 1H), 5.21 (dt, $J = 7.7$, 7.7 Hz, 1H), 2.11–1.91 (m, 2H), 1.01 (t, $J = 7.2$ Hz, 3H); EI-MS (source 180°C, 70 eV, 200 mA): m/z 354 (M^+), 325, 236, 220; *Anal.* ($C_{24}H_{22}N_2O$): C, H, N.

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