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Versatile synthesis of oxindole-1,3-dicarboxamides

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Dedicated to Professor Károly Lempert on the occasion of his 85th birthday

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ABSTRACT

A new, high-yielding synthesis of oxindole-1,3-dicarboxamides was elaborated starting from 1-phenoxycarbonyl-3-ethoxycarbonyl-2-oxindole and 1,3-diphenoxycarbonyl-2-oxindole. This method permits also the preparation of *N*,*N*,*N*′-tri- and *N*,*N*,*N*′,*N*′-tetrasubstituted oxidole-1,3-dicarboxamides, families of compounds that are unknown in the literature. The scope and limitations of the methodology have also been investigated, and a remarkable selectivity has been observed among the amines used in the amidation steps.

1. Introduction

The occurrence of 3-unsubstituted 2-oxo-2,3-dihydroindole (oxindole) 1-carboxamides,[1,2] oxindole-1,3-dicarboxamides,[2] 1-acyloxindole-3-carboxamides,[3] 1-alkyloxindole-3-carboxamides,[4–7] and 1-aryloxindole-3-carboxamides[8] is very scarce in the scientific literature. In the patent literature, there is somewhat more published information on these families of compounds, nonetheless the chemistry of these derivatives is still far from being completely revealed. Several 2-oxo-2,3-dihydroindole (oxindole) 1-carboxamides,[9] 1,3-dicarboxamides,[10] 1-acyl-3-carboxamides,[11] and 1-alkyl-3-carboxamides[12] were published by researchers at Pfizer as potential analgesic, anti-inflammatory, and antiarthritic agents. All these compounds contained *N*-monoalkylated carboxamide moieties. According to the literature, 3-substituted oxindole-1-carboxamides can act as inhibitors of interleukin-1 biosynthesis,[13] and they are effective in the treatment of autoimmune disorders[14] or in the prevention of virus infections.[15] An outstanding example of this type of oxindole derivatives was (*Z*)-5-chloro-3-[1-hydroxy-1-(2-thienyl) methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (tenidap, **1**, Fig. 1).[16–18] The sodium salt of **1**[19,20] exhibiting anxiolytic and antirheumatic activity, was granted regulatory approval in several countries.[21] In spite of the very high market expectations,[22] it was finally not launched because of serious side-effects.[23] The development of ilonidap (**2**),[24] a successor of tenidap or its corresponding lysine salt,[25] with the aim of eliminating the undesired side-effects, was abandoned, as well.

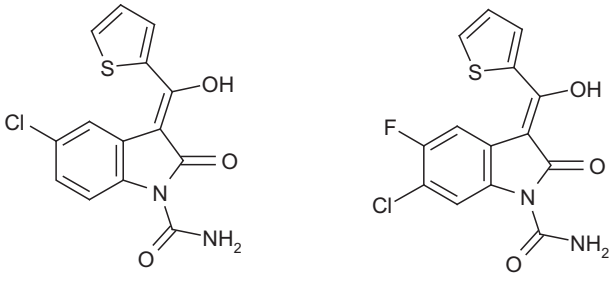

Figure 1. Structure of tenidap (**1**) and ilonidap (**2**).

According to the described procedures for the preparation of oxindole-1,3-dicarboxamides,[9,10] the two carbamoyl moieties were introduced successively into the oxindole molecule using alkyl, aryl or acyl isocyanates (Scheme 1). First, the 1-carbamoyl function was formed by refluxing the starting oxindole derivative **3** with the appropriate isocyanate in an aprotic solvent, preferably in toluene at reflux temperature,[9,18] but this step was also described in diethyl ether,

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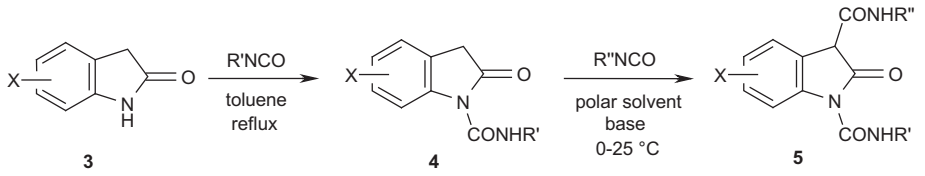


Scheme 1. Literature procedures for the preparation of oxindole-1-carboxamides and oxindole-1,3-dicarboxamides.

THF or acetonitrile at room temperature.[18] In the second step, the oxindole-1-carboxamide **4** thus obtained was converted into 1,3-dicarboxamide **5** by treatment with a further isocyanate in a polar solvent (DMF, diethylformamide or DMSO, preferably DMF) at 0–25 °C, in the presence of a base (TEA or NaH). The use of isocyanates for the introduction of the carbamoyl moieties has three major disadvantages: (i) relatively few organic isocyanates are commercially available,[20] (ii) 1-unsubstituted oxindole-3-carboxamides can not be prepared by this method, (iii) *N*,*N*-disubstituted oxindole-1-carboxamides, *N*,*N*,*N*′-tri- and *N*,*N*,*N*′,*N*′-tetrasubstituted oxindole-1,3-dicarboxamides can not be synthesized, either.

Earlier several papers have dealt with the reactions of 3-substituted-2-oxindole derivatives and alkylchloroformates under various conditions, encountering the formation of product mixtures and a low yield of the required regioisomer.[26–30] In the most instructive paper in this field, Beccalli et al. described the reactions of 3-aroylmethyl-2-oxo-2,3-dihydroindoles with ethyl chloroformate[31] and the *O–C(3)* acyl migrations were carried out in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP). As a part of our research program on the novel synthesis of tenidap (**1**),[32] we have elaborated two protocols for the synthesis of 1,3-di[alkoxy(aryloxy) carbonyl]-oxindoles (oxindole-1,3-dicarboxylates) with identical or different acyl groups in the two positions.[33] These compounds could be easily isolated as 4-dimethylaminopyridinium (DMAP) salts of the enolates (**6**, Fig. 2). On treatment of salts **6** (R^2=R^3) with aqueous acid, 3-aryl- and 3-benzyloxycarbonyl groups underwent hydrolysis and decarboxylation. However, compounds **7** containing an alkoxycarbonyl moiety in position 3 were isolated in good yield. The ^{1}H NMR spectra of compounds **7** indicated an equilibrium between the keto and enol forms in solution (Scheme 2), while single crystal X-ray analysis of compound **7** (R^1=H, R^2=R^3=Et) exhibited the presence of the enol form in crystalline state.[33] In a subsequent paper it was demonstrated that 3-(thiophen-2-ylcarbonyl) derivatives bearing a phenoxycarbonyl moiety in position 1 could be reacted with various primary and secondary amines.[34]

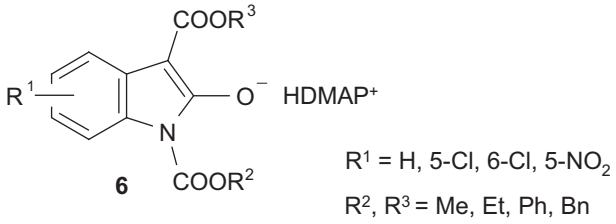
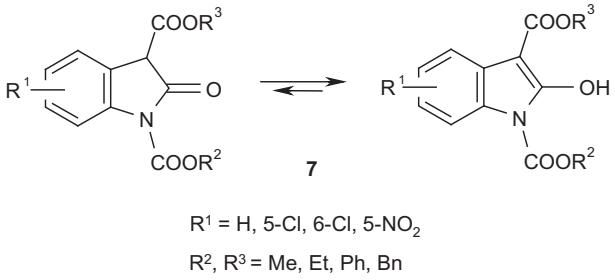


Figure 2. 4-Dimethylaminopyridinium (DMAP) salts of oxindole-1,3-dicarboxylates.

2. Results and discussion

Now we describe the synthesis of a wide variety of new oxindole-1,3-dicarboxamides **8** by reacting dicarboxylates **9** or **10** successively with various amines (Scheme 3). The new methodology, in contrast to the literature procedures, also allows the synthesis of *N*,*N*-disubstituted diamides.

Treatment of 3-ethoxycarbonyl-1-phenoxycarbonyl derivative **9** with 2 equiv of secondary aliphatic amines (pyrrolidine, piperidine, and morpholine) in DMF at ambient temperature afforded



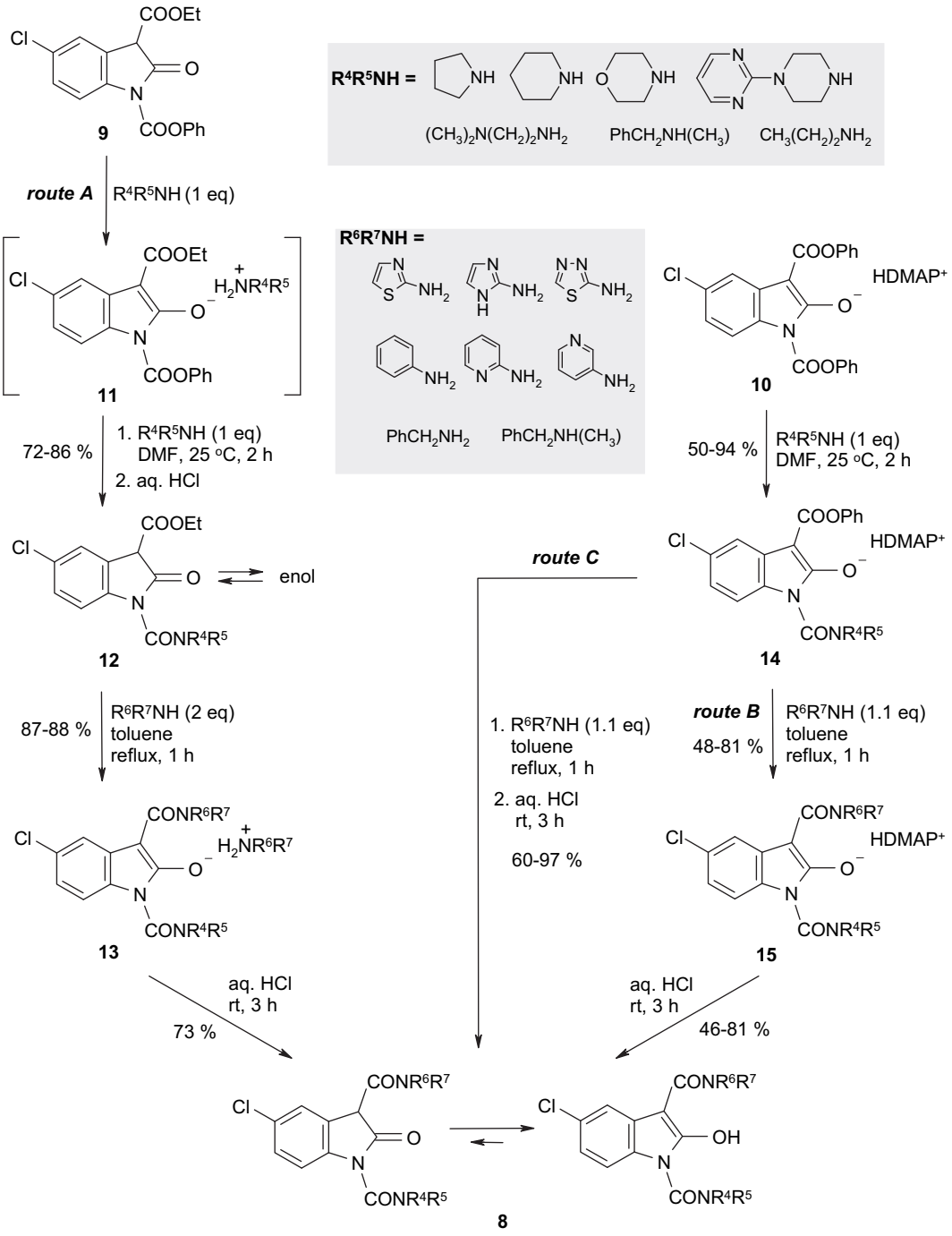
Scheme 2. Keto/enol equilibrium of oxindole-1,3-dicarboxylates.

1-carboxamido compounds **12** (Scheme 3, route A, Table 1). The primarily formed diester enolate salts **11**, the formation of which has already been demonstrated in our earlier studies,[32–34] underwent a selective amidation at the 1-position and after acidic work-up compounds **12** were obtained. An equilibrium between the keto and enol forms of compounds **12** in solution has been indicated by the ^{1}H NMR spectra. The simultaneous presence of the keto and the enol form induced the duplication of several signals in the ^{13}C spectra, the signal for *C(3)* appeared at $\delta \sim 85$ ppm for the enolic form and at $\delta \sim 52$ ppm for the keto form.

Surprisingly, amide-ester **12a** (NR^4R^5: 1-pyrrolidinyl) failed to react with piperidine, when refluxed in toluene for 11 h. Conversely, the reaction of amide-esters **12a**,**c** with a primary aromatic amine, 2-aminothiazole in refluxing toluene afforded diamide enolate salts **13a**,**b** in good yield (Scheme 3, route A, Table 2). This seemingly inconsistent behavior of the 3-ethoxycarbonyl group of **12a** toward the two amines will be discussed later. Treatment of the salts **13a**,**b** with diluted aqueous hydrochloric acid solution resulted in compounds **8a**,**b** (Scheme 3, route A, Table 5). In dimethyl sulfoxide-d_6 solution of compounds **8a**,**b**, exclusively the signals of the enol form were detected by ^{1}H NMR. The absence of the keto tautomer was also shown by ^{13}C NMR technique, which did not exhibit any sp^3 signal for the oxindole skeleton.

The above mentioned studies carried out starting from 'mixed' diester **9** have shown that the two ester groups can be selectively amidated. Because of the different character of the two ester groups (phenylcarbamate vs ethyl acetoacetate), the selective amidation in position 1 can not be explained simply with the higher reactivity of the phenyl ester. The formation of enolate salts **11** in the course of the amidation reactions decreases much more the reactivity of the ester group at the 3-position due to delocalization of the negative charge than at the 1-position.

With knowledge of the above results, it seemed to be reasonable to test also the DMAP salt of 1,3-diphenoxycarbonyl derivative (**10**) as the starting compound of the amidation reactions, since this compound is easier to prepare than the derivatives bearing different alkoxy or aryloxy moieties in the two positions.[32] In line with the above observed regioselectivity, the reactions of enolate salt **10** with an equivalent amount of various primary and secondary aliphatic amines in DMF at ambient temperature resulted in selective amidation at the 1-position, affording DMAP salts **14a**–**g** (Scheme 3, Table 3). However, primary aromatic amines (e.g., aniline, 3-aminopyridine) failed to react with **10** under the same conditions.



Scheme 3. Synthesis of new oxindole-1,3-dicarboxamides from oxindole-1,3-dicarboxylates.

Table 1
Compounds **12**

	NR^4R^5	Yield (%)
a		79
b		86
c		72

Table 2
Compounds **13**

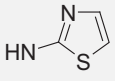
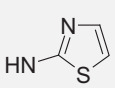
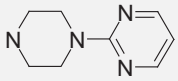
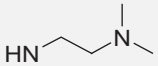
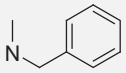
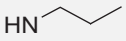
	NR^4R^5	NR^6R^7	Yield (%)
a			87
b			88

Table 3
Compounds **14**

	NR^4R^5	Yield (%)
a		63
b		83
c		77
d		94
e		94
f		50
g		80

Amidation of the 3-phenoxycarbonyl group of **14a**,**b**,**d**,**g** with an equivalent amount of primary aromatic amines was carried out in refluxing toluene to give the DMAP salts of diamides **15a**–**e** (Scheme 3, route B, Table 4). Cyclic secondary amines (piperidine, morpholine) resisted again to react not only under these conditions, but even when the reaction was carried out in DMF at 110 °C. Compounds **15a**–**e** were then transformed to the corresponding diamides **8a**,**e**,**g**,**i**,**o** (Scheme 3, route B, Table 5) by treatment with aqueous hydrochloric acid. The second amidation reaction of derivative **14** could be performed in good yield also without the isolation of intermediate **15**, by subsequent treatment with a primary or secondary aliphatic or primary aromatic amine and aqueous hydrochloric acid solution, as demonstrated by the synthesis of diamides **8c**,**d**,**f**,**h**,**j**–**n** (Scheme 3, route C, Table 5).

We were looking for an explanation of the anomalous reactivity of primary aromatic amines in position 1 and cyclic secondary amines in

Table 4
Compounds **15**

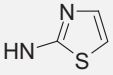
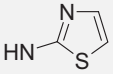
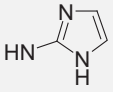
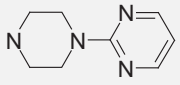
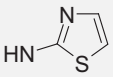
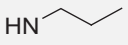
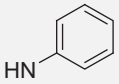
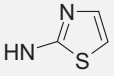
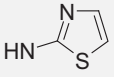
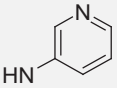
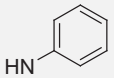
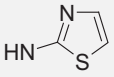
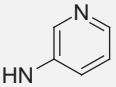
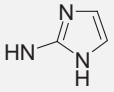
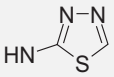
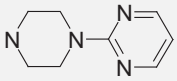
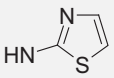
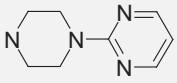
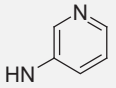
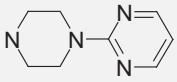
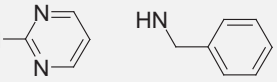
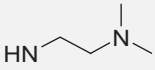
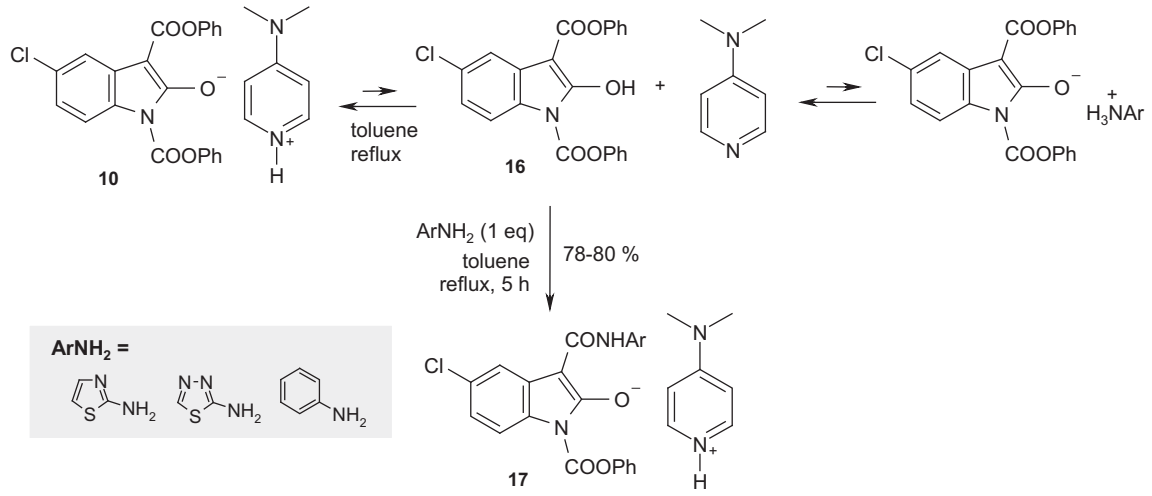
	NR^4R^5	NR^6R^7	Yield (%)
a			81
b			63
c			67
d			48
e			65

Table 5
Compounds **8**

	NR^4R^5	NR^6R^7	Yield[a,b] (%)	Route
a			73 (31) 81 (41)	A B
b			73 (46)	A
c			76 (59)	C
d			73 (61) 79 (62)	C D
e			61 (31)	B
f			84 (70)	C
g			67 (37)	B
h			67 (56)	C
i			46 (21)	B
j			60 (56)	C
k			64 (60)	C
l			97 (91)	C
m			71 (67)	C
n			87 (82)	C
o			99 (65)	B

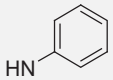
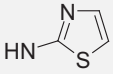
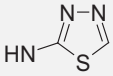
[a] Yields are calculated for compounds **12** (route A), **15** (route B), **14** (route C) or **17** (route D).
[b] Yields in parenthesis are overall yields, calculated for compounds **9** (route A) or **10** (routes B, C or D).



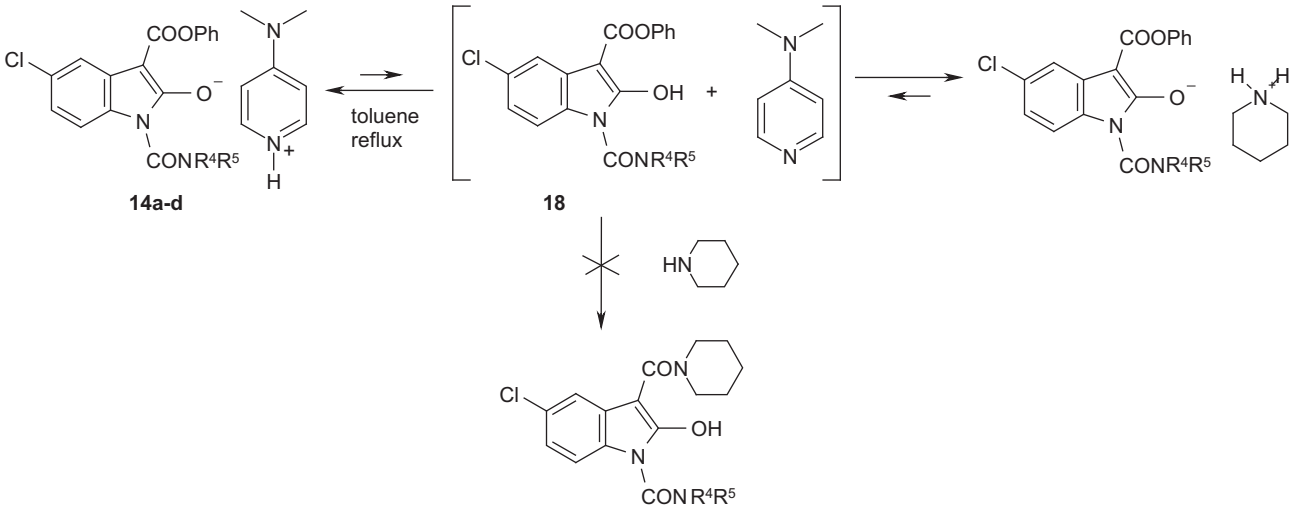
Scheme 4. Explanation of the selective 3-amidation with aromatic amines.

position 3. Surprisingly, the reaction of diester salt **10** with various primary aromatic amines in refluxing toluene resulted in amide salts **17**, i.e., in products selectively amidated at the 3-position (Scheme 4, Table 6). It is reasonable to assume that enolate salts (**10**,**14**) can not be the substrates of the 3-amidation reactions, because of the decreased reactivity of the 3-alkoxy(aryloxy)carbonyl group toward nucleophiles. We have to suppose that in the presence of a weak base (primary aromatic amine) enolate salt **10** is in equilibrium with its components, i.e., with the corresponding diester (**16**) and DMAP. Diester **16** is the substrate of the amidation reaction with primary aromatic amines. The 3-phenoxycarbonyl group of compound **16** is more reactive than the same moiety at the 1-position, as demonstrated also by the partial hydrolysis and decarboxylation of salt **10** in position 3 on treatment with aqueous acid.[32] Amidation of **16** occurs selectively at the 3-position indicating the particularly sluggish reactivity of the 1-phenoxycarbonyl group toward primary aromatic amines. Similar behavior of the 1-phenoxycarbonyl group of a related 3-acyl derivative has also been described.[34] It is presumable, of course that the equilibrium shown in Scheme 4 exists also in DMF at ambient temperature. However, no amidation with primary aromatic amines takes place under these mild conditions at all.

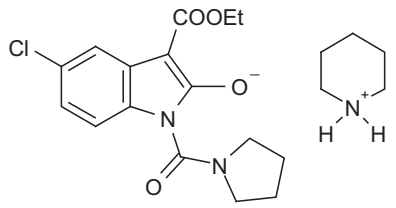
Table 6
Compounds **17**

	NHAr	Yield (%)
a		78
b		80
c		78

The failure of the 3-amidation reaction of amide-ester enolate salt **14a**–**d** with cyclic secondary amines might be explained on a similar basis (Scheme 5). The lack of reaction suggests the absence of 'free' amide-ester **18** in the reaction mixture, as a consequence of the salt formation with the two strongly basic amines (DMAP, piperidine). A similar formation of enolate salt **19** (Fig. 3) can explain the failure of 3-amidation in the reaction of amide-ester **12a** with piperidine.



Scheme 5. Explanation for the failure of 3-amidation with cyclic secondary amines.



19

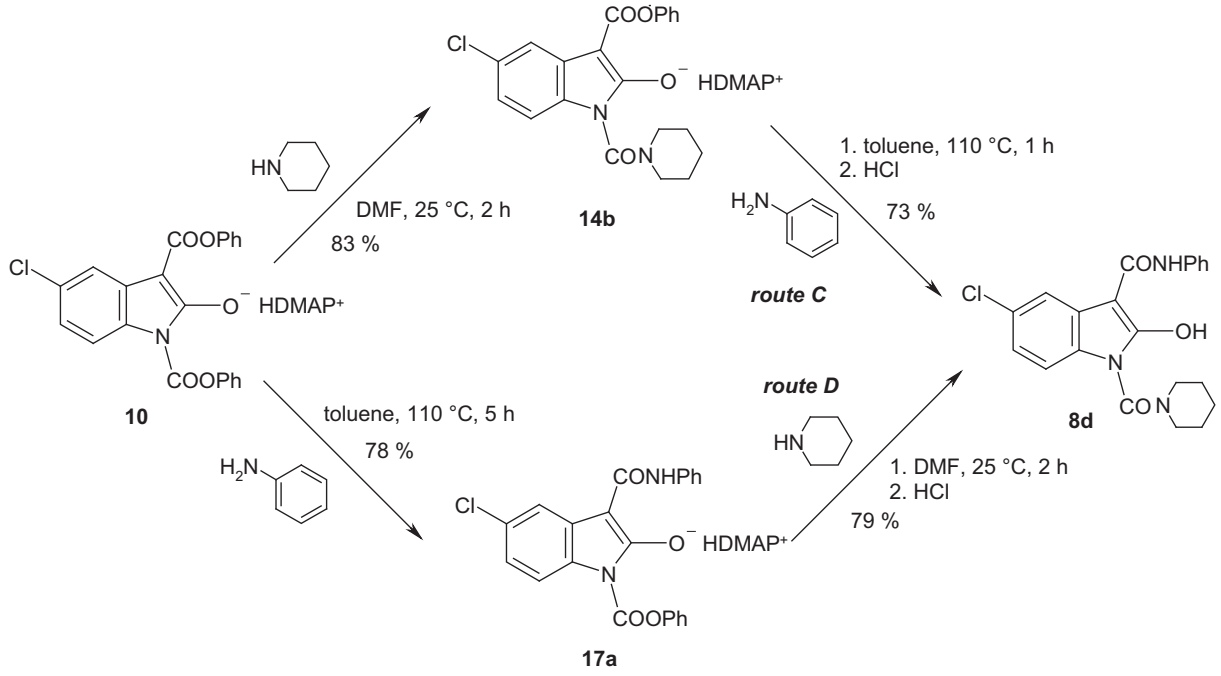
Figure 3. Enolate salt formed with piperidine.

The peculiar reactivity of primary aromatic and cyclic secondary aliphatic amines in the amidation reaction of diester enolate salt **10** is summarized in Scheme 6 (routes C and D), showing the two synthetic approaches to diamide **8d**.

4. Experimental section

4.1. General

All melting points were determined on a Büchi 535 capillary melting point apparatus. IR spectra were obtained on a Bruker IFS-113v FT spectrometer in KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 (200 and 50 MHz for ^{1}H and ^{13}C NMR spectra, respectively), Bruker Avance III (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) or a Varian Unity Inova 500 spectrometer (500 and 125 MHz for ^{1}H and ^{13}C NMR spectra, respectively). $CDCl_3$ or DMSO-d_6 was used as solvent and tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) and coupling constants (J) are given in parts per million and in hertz, respectively. Elemental analyses were performed on a Perkin/Elmer 2400 analyzer. The reactions were followed by analytical thin layer chromatography on silica gel 60 F_{254}. All unspecified reagents were purchased from commercial sources.



Scheme 6. Peculiar selective reactivity of oxindole-1,3-dicarboxylates with various amines.

3. Conclusion

In the present paper, a new, versatile method has been described for the preparation of oxindole-1,3-dicarboxamides starting from the corresponding 1,3-dicarboxylates. Amidation could be performed with a wide variety of primary and secondary aliphatic amines in position 1, and with aromatic and primary and secondary aliphatic amines in position 3. In the course of the systematic studies on the scope and limitations of the amidation reactions, we have revealed a plausible explanation for the unique reactivity of different types of amines. The methodology described above offers a convenient approach to a wide range of new oxindole-1,3-dicarboxamides, which are only circuitously or, in the case of *N*,*N*-disubstituted carboxamides, not at all available by other procedures. By benefiting from the complete regioselectivity of the amidation step, 1-carboxamido-oxindole-3-carboxylates and 3-carboxamido-oxindole-1-carboxylates, as useful synthetic building blocks, can also be synthesized using this novel procedure.

4.2. General procedure I for the synthesis of compounds 12

To a solution of 3-ethyl 1-phenyl 5-chloro-2-oxo-2,3-dihydro-1*H*-indole-1,3-dicarboxylate (**9**, 7.20 g, 0.02 mol) in DMF (50 mL) was added the corresponding amine (0.04 mol) drop wise, under vigorous stirring, at room temperature. The solution thus obtained was stirred for additional 2 h, then water (50 mL) and concd HCl (5 mL) were added. The precipitate was filtered off and recrystallized to give compound **12**.

*4.2.1. Ethyl 5-chloro-2-oxo-1-(pyrrolidin-1-ylcarbonyl)-2,3-dihydro-1H-indole-3-carboxylate (**12a**).* This compound was prepared according to the general procedure I using pyrrolidine (2.3 mL, 2.84 g, 0.04 mol) to give 5.32 g (79%) **12a** as colorless crystals, mp 98–100 °C (EtOAc/hexane). IR (KBr, cm^{-1}) 2985, 1762, 1726, 1684. ^{1}H NMR ($CDCl_3$, 400 MHz) enol/keto=1:2, *δ enol*: 7.67 (1H, d, *J*=1.8 Hz), 7.32 (1H, d, *J*=8.8 Hz), 7.15 (1H, dd, *J*=8.8, 2.0 Hz), 4.44 (2H, q, *J*=7.1 Hz), 3.60 (4H, m), 1.99 (4H, m), 1.46 (3H, t, *J*=7.1 Hz), *δ keto*: 7.35 (1H, d, *J*=2.0 Hz), 7.34 (1H, dd, *J*=8.8, 2.0 Hz), 7.30 (1H, d,

J=8.6 Hz), 4.48 (1H, s), 4.26 (2H, q, J=7.1 Hz), 3.60 (4H, m), 1.99 (4H, m), 1.30 (3H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 165.9, 148.8, 139.8, 129.4, 129.3, 124.7, 124.5, 122.4, 119.2, 114.0, 113.0, 85.7, 62.6, 60.9, 52.8, 47.7, 47.3, 25.8, 25.2, 24.5, 14.0. Anal. Calcd for $C_{16}H_{17}ClN_2O_4$ (336.78): C 57.06, H 5.09, Cl 10.53, N 8.32%. Found: C 56.61, H 5.13, Cl 10.38, N 8.14%.

*4.2.2. Ethyl 5-chloro-2-oxo-1-(piperidin-1-ylcarbonyl)-2,3-dihydro-1H-indole-3-carboxylate (**12b**).* This compound was prepared according to the general procedure I using piperidine (4.0 mL, 3.40 g, 0.04 mol) to give 6.04 g (86%) **12b** as colorless crystals, mp 96–97 °C (EtOH). IR (KBr, cm^{-1}) 2945, 2857, 1701, 1656. ^{1}H NMR ($CDCl_3$, 200 MHz) enol/keto=1.0:1.1, δ *enol*: 7.68 (1H, d, J=1.8 Hz), 7.32 (1H, d, J=8.8 Hz), 7.15 (1H, dd, J=8.8, 2.0 Hz), 4.44 (2H, q, J=7.1 Hz), 3.51 (4H, m), 1.46 (6H, s), 1.46 (3H, t, J=7.1 Hz), δ *keto*: 7.35 (1H, d, J=2.0 Hz), 7.30 (1H, d, J=8.8 Hz), 7.15 (1H, dd, J=8.8, 2.0 Hz), 4.48 (1H, s), 4.26 (2H, q, J=7.1 Hz), 3.82–3.35 (4H, m), 1.46 (6H, s), 1.30 (3H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.6, 167.9, 159.1, 149.0, 148.4, 140.1, 129.1, 128.9, 128.6, 124.7, 124.5, 122.1, 119.0, 113.6, 113.6, 112.6, 85.5, 62.4, 60.6, 52.5, 56.9, 25.6, 23.9, 13.8. Anal. Calcd for $C_{17}H_{19}ClN_2O_4$ (350.81): C 58.20, H 5.46, Cl 10.11, N 7.99%. Found: C 58.26, H 5.52, Cl 10.01, N 8.01%.

*4.2.3. Ethyl 5-chloro-1-(morpholin-4-ylcarbonyl)-2-oxo-2,3-dihydro-1H-indole-3-carboxylate (**12c**).* This compound was prepared according to the general procedure I using morpholine (3.50 mL, 3.50 g, 0.04 mol) to give 5.08 g (72%) **12c** as colorless crystals, mp 96–99 °C (EtOH). IR (KBr, cm^{-1}) 2973, 1763, 1730, 1682. ^{1}H NMR ($CDCl_3$, 400 MHz) enol/keto=1:2, δ *enol*: 7.67 (1H, d, J=2.0 Hz), 7.32 (1H, d, J=8.8 Hz), 7.15 (1H, dd, J=8.8, 2.0 Hz), 4.44 (2H, q, J=7.1 Hz), 3.90–3.30 (8H, m), 1.46 (3H, t, J=7.1 Hz), δ *keto*: 7.35 (1H, d, J=2.0 Hz), 7.34 (1H, dd, J=8.8, 2.0 Hz), 7.30 (1H, d, J=8.8 Hz), 4.48 (1H, s), 4.26 (2H, q, J=7.1 Hz), 3.90–3.30 (8H, m), 1.30 (3H, t, J=7.1 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 159.2, 149.5, 139.9, 129.6, 129.5, 129.3, 124.7, 124.5, 123.1, 122.6, 119.3, 115.9, 114.3, 113.1, 86.0, 66.6, 62.8, 61.0, 52.8, 37.0, 14.5, 14.0. Anal. Calcd for $C_{16}H_{17}ClN_2O_5$ (352.78): C 54.47, H 4.86, Cl 10.05, N 7.94%. Found: C 54.16, H 4.81, Cl 10.42, N 8.08%.

4.3. General procedure II for the synthesis of compounds 13

A mixture of compound **12** (0.015 mol) and the corresponding amine (0.030 mol) in toluene (80 mL) was refluxed for 1 h. The precipitate was filtered off to give compound **13**. Compounds were of high purity without recrystallization, as indicated by elemental analyses and ^{1}H NMR spectra.

*4.3.1. 1,3-Thiazol-2-aminium 5-chloro-1-(pyrrolidin-1-ylcarbonyl)-3-(1,3-thiazol-2-ylcarbamoyl)-1H-indol-2-olate (**13a**).* This compound was prepared according to the general procedure II using **12a** (5.05 g, 0.015 mol) and 2-aminothiazole (3.00 g, 0.03 mol) to give 6.41 g (87%) **13a** as colorless crystals, mp 258–260 °C. IR (KBr, cm^{-1}) 2976, 1670, 1599, 1524. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.10 (1H, s), 8.65 (2H, s), 7.62 (1H, d, J=2.2 Hz), 7.38 (1H, d, J=3.6 Hz), 7.21 (1H, d, J=4.4 Hz), 7.02 (1H, d, J=3.6 Hz), 6.94 (1H, d, J=8.3 Hz), 6.86 (1H, d, J=4.4 Hz), 6.74 (1H, dd, J=8.4, 2.2 Hz), 3.51 (4H, s), 1.86 (4H, s). Anal. Calcd for $C_{20}H_{19}ClN_6O_3S_2$ (491.01): C 48.92, H 3.90, Cl 7.22, N 17.12, S 13.06%. Found: C 48.82, H 3.87, Cl 7.09, N 16.82, S 12.90%.

*4.3.2. 1,3-Thiazol-2-aminium 5-chloro-1-(morpholin-4-ylcarbonyl)-3-(1,3-thiazol-2-ylcarbamoyl)-1H-indol-2-olate (**13b**).* This compound was prepared according to the general procedure II using **12c** (5.29 g, 0.015 mol) and 2-aminothiazole (3.00 g, 0.03 mol) to give 6.70 g (88%) **13b** as colorless crystals, mp 254–255 °C. IR (KBr, cm^{-1}) 3088, 1667, 1596, 1522. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.10 (1H, s), 8.65 (2H, s), 7.63 (1H, d, J=2.2 Hz), 7.37 (1H, d, J=3.7 Hz), 7.21 (1H, d, J=4.2 Hz), 7.02 (1H, d, J=3.7 Hz), 6.94 (1H, d, J=8.2 Hz), 6.84 (1H, d, J=4.2 Hz), 6.75 (1H, dd, J=8.4, 2.2 Hz), 3.66 (8H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.1, 165.1, 161.6, 159.6, 151.9, 135.1, 130.6, 128.4, 125.6, 117.4, 115.5, 111.8, 110.9, 108.1, 82.4, 66.4, 47.7, 44.1. Anal. Calcd for $C_{20}H_{19}ClN_6O_4S_2$ (507.01): C 47.38, H 3.78, Cl 6.99, N 16.58, S 12.65%. Found: C 47.50, H 3.81, Cl 7.02, N 16.15, S 12.66%.

4.4. General procedure III for the synthesis of compounds 14

A solution of 4-(dimethylamino)pyridinium 5-chloro-1,3-bis (phenoxycarbonyl)-1*H*-indol-2-olate (**10**, 21.20 g, 0.04 mol) and the corresponding amine (0.08 mol) in DMF (100 mL) was stirred at room temperature for 4 h. It was poured onto a mixture of ice-water (200 g) and stirred for 1 h. The crystalline product was filtered, washed with water to give compound **14**. Compounds were of high purity without recrystallization, as indicated by elemental analyses and ^{1}H NMR spectra.

*4.4.1. 4-(Dimethylamino)pyridinium 5-chloro-3-(phenoxycarbonyl)-1-(pyrrolidin-1-ylcarbonyl)-1H-indol-2-olate (**14a**).* This compound was prepared according to the general procedure III using pyrrolidine (6.70 mL, 5.77 g, 0.08 mol) to give 12.80 g (63%) **14a** as colorless crystals, mp 182–186 °C. IR (KBr, cm^{-1}) 2876, 1702, 1646, 1562. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.18 (2H, d, J=7.5 Hz), 7.41 (1H, d, J=2.0 Hz), 7.38 (2H, m), 7.14 (3H, m), 6.95 (2H, d, J=7.5 Hz), 6.85 (1H, d, J=8.2 Hz), 6.68 (1H, dd, J=8.2, 2.0 Hz), 3.46 (4H, m), 3.15 (6H, s), 1.83 (4H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 163.8, 157.1, 152.3, 152.05, 139.9, 139.7, 129.9, 129.4, 129.2, 125.2, 124.3, 122.8, 117.2, 116.4, 116.1, 110.1, 107.2, 107.1, 80.3, 47.4, 46.7, 25.4, 24.5. Anal. Calcd for $C_{27}H_{27}ClN_4O_4$ (507.00): C 63.96, H 5.37, Cl 7.00, N 11.05%. Found: C 63.70, H 5.25, Cl 7.32, N 10.57%.

*4.4.2. 4-(Dimethylamino)pyridinium 5-chloro-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**14b**).* This compound was prepared according to the general procedure III using piperidine (8.0 mL, 6.80 g, 0.08 mol) to give 17.30 g (83%) **14b** as colorless crystals, mp 165–167 °C. IR (KBr, cm^{-1}) 2944, 1695, 1647, 1596, 1561. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.12 (2H, d, J=7.5 Hz), 7.69 (1H, d, J=2.0 Hz), 7.36 (2H, m), 7.22 (3H, m), 6.95 (1H, d, J=8.3 Hz), 6.85 (1H, dd, J=8.2 Hz, J=2.0 Hz), 6.49 (2H, d, J=6.8 Hz), 3.50 (4H, br s), 3.05 (6H, s), 1.63 (6H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 164.4, 163.1, 152.2, 131.5, 130.3, 129.4, 128.9, 124.8, 123.8, 122.5, 118.8, 116.7, 115.9, 115.3, 109.4, 107.0, 79.7, 43.9, 25.8, 24.0, 22.2, 21.8. Anal. Calcd for $C_{28}H_{29}ClN_4O_4$ (521.03): C 64.55, H 5.61, Cl 6.81, N 10.75%. Found: C 64.60, H 5.73, Cl 6.73, N 10.40%.

*4.4.3. 4-(Dimethylamino)pyridinium 5-chloro-1-(morpholin-4-ylcarbonyl)-3-(phenoxycarbonyl)-1H-indol-2-olate (**14c**).* This compound was prepared according to the general procedure III using morpholine (6.97 g, 0.08 mol) to give 16.20 g (77%) **14c** as colorless crystals, mp 158–160 °C. IR (KBr, cm^{-1}) 3243, 2857, 1698, 1648, 1594. 1554. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.20 (2H, d, J=7.3 Hz), 7.43 (1H, d, J=2.0 Hz), 7.35 (1H, m), 7.18 (3H, m), 6.96 (2H, d, J=7.3 Hz), 6.84 (1H, d, J=8.2 Hz), 6.74 (1H, m), 6.66 (1H, dd, J=8.2 Hz, J=2.0 Hz), 3.67 (4H, s), 3.33 (4H, s), 3.17 (6H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 157.6, 152.8, 152.5, 139.8, 130.4, 129.6, 129.1, 125.1, 123.9, 122.8, 119.0, 116.8, 115.8, 115.4, 110.2, 107.2, 79.5, 56.2, 18.6. Anal. Calcd for $C_{27}H_{27}ClN_4O_5$ (523.00): C 62.01, H 5.20, Cl 6.78, N 10.71%. Found: C 62.57, H 5.14, Cl 6.46, N 10.22%.

*4.4.4. 4-(Dimethylamino)pyridinium 5-chloro-3-(phenoxycarbonyl)-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-1H-indol-2-olate (**14d**).* This compound was prepared according to the general procedure III using 1-(pyrimidin-2-yl)piperazine (13.12 g, 0.08 mol) to

give 22.60 g (94%) **14d** as colorless crystals, mp 145–150 °C. IR (KBr, cm^{-1}) 3058, 1690, 1647, 1588, 1551. ^1H NMR (DMSO-d_6, 200 MHz) δ 8.39 (2H, t, J=4.7 Hz), 8.18 (2H, d, J=7.5 Hz), 7.46 (1H, d, J=2.2 Hz), 7.36 (2H, m), 7.14 (3H, m), 6.92 (2H, d, J=7.5 Hz), 6.89 (1H, d, J=8.2 Hz), 6.70 (1H, dd, J=8.2, 2.2 Hz), 6.66 (1H, d, J=4.7 Hz), 3.83 (4H, s), 3.66 (4H, s), 3.15 (6H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 165.3, 162.3, 159.3, 151.9, 137.4, 130.8, 130.0, 125.3, 117.2, 115.5, 115.4, 111.3, 110.3, 82.4, 57.6, 24.0. Anal. Calcd for $C_{31}H_{30}ClN_7O_4$ (600.09): C 62.05, H 5.04, Cl 5.91, N 16.34%. Found: C 62.04, H 5.08, Cl 5.80, N 15.84%.

*4.4.5. 4-(Dimethylamino)pyridinium 5-chloro-1-{[2-(dimethylamino) ethyl]carbamoyl}-3-(phenoxycarbonyl)-1H-indol-2-olate (**14e**).* This compound was prepared according to the general procedure III using (2-dimethylamino)ethylamine (8.7 mL, 7.05 g, 0.08 mol) to give 19.70 g (94%) **14e** as colorless crystals, mp 184–185 °C. IR (KBr, cm^{-1}) 3056, 2939, 1710, 1644, 1618, 1596. 1511. ^1H NMR (DMSO-d_6, 400 MHz) δ 10.19 (1H, s), 8.14 (2H, dd, J=5.7, 1.5 Hz), 8.01 (1H, d, J=8.4 Hz), 7.52 (1H, d, J=2.2 Hz), 7.38 (2H, m), 7.14 (3H, m), 6.77 (2H, dd, J=5.7, 1.5 Hz), 6.75 (1H, dd, J=8.5, 2.2 Hz), 3.50 (2H, q, J=5.8 Hz), 3.05 (6H, s), 2.81 (2H, q, J=5.8 Hz), 2.49 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.0, 163.3, 155.6, 154.7, 152.2, 145.0, 144.9, 131.5, 129.6, 129.2, 126.3, 124.3, 122.7, 117.6, 115.9, 114.4, 107.0, 81.0, 57.9, 44.4, 44.3, 35.9. Anal. Calcd for $C_{27}H_{30}ClN_5O_4$ (524.02): C 61.89, H 5.77, Cl 6.77, N 13.36%. Found: C 61.70, H 5.83, Cl 6.67, N 13.13%.

*4.4.6. 4-(Dimethylamino)pyridinium 1-[benzyl(methyl)carbamoyl]-5-chloro-3-(phenoxycarbonyl)-1H-indol-2-olate (**14f**).* This compound was prepared according to the general procedure III using *N*-benzylmethylamine (10.28 mL, 9.68 g, 0.08 mol) to give 11.20 g (50%) **14f** as colorless crystals, mp 156–159 °C. IR (KBr, cm^{-1}) 3062, 2684, 1691, 1618, 1564. ^1H NMR (DMSO-d_6, 200 MHz) δ 13.10 (1H, br s), 8.20 (2H, d, J=7.6 Hz), 7.40 (6H, m), 7.15 (5H, m), 6.95 (2H, d, J=7.6 Hz), 6.82 (1H, d, J=8.2 Hz), 6.70 (1H, dd, J=8.2, 2.2 Hz), 4.68 (2H, s), 3.17 (6H, s), 2.91 (3H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 164.4, 163.1, 156.9, 154.3, 152.2, 139.6, 137.2, 132.0, 130.2, 129.4, 129.0, 128.6, 127.2, 125.0, 126.9, 122.5, 118.8, 116.8, 115.9, 115.3, 109.6, 107.0, 79.8, 51.6, 36.1. Anal. Calcd for $C_{31}H_{29}ClN_4O_4$ (557.06): C 66.84, H 5.25, Cl 6.36, N 10.06%. Found: C 66.64, H 5.22, Cl 6.28, N 9.99%.

*4.4.7. 4-(Dimethylamino)pyridinium 5-chloro-3-(phenoxycarbonyl)-1-(propylcarbamoyl)-1H-indol-2-olate monohydrate (**14g**).* This compound was prepared according to the general procedure III using propylamine (6.58 mL, 4.73 g, 0.08 mol) to give 16.40 g (80%) **14g** as colorless crystals, mp 209–211 °C. IR (KBr, cm^{-1}) 3057, 2961, 1712, 1647, 1618, 1564. ^1H NMR (DMSO-d_6, 500 MHz) δ 13.10 (1H, br s), 10.11 (1H, s), 8.20 (2H, d, J=7.6 Hz), 8.00 (1H, d, J=8.6 Hz), 7.53 (1H, d J=2.2 Hz), 7.37 (2H, m), 7.15 (3H, m), 6.95 (2H, d, J=7.6 Hz), 6.73 (1H, dd, J=8.6, 2.2 Hz), 3.34 (2H, q, J=7.2 Hz), 3.17 (6H, s), 1.54 (2H, q, J=7.2 Hz), 0.93 (3H, t, J=7.2 Hz). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 157.8, 154.4, 152.1, 139.3, 129.6, 126.0, 124.0, 123.3, 122.5, 117.4, 115.6, 114.1, 107.1, 40.5, 40.2, 22.8, 11.6. Anal. Calcd for $C_{26}H_{27}ClN_4O_4 \cdot H_2O$ (512.98): C 60.87, H 5.70, Cl 6.91, N 10.92%. Found: C 60.57, H 5.39, Cl 7.20, N 10.75%.

4.5. General procedure IV for the synthesis of compounds 15

A mixture of compound **14** (0.015 mol) and the corresponding amine (0.017 mol) in toluene (80 mL) was refluxed for 1 h. The precipitate was filtered off to give compound **15**. Compounds were of high purity without recrystallization, as indicated by elemental analyses and ^1H NMR spectra.

*4.5.1. 4-(Dimethylamino)pyridinium 5-chloro-1-(pyrrolidin-1-ylcarbonyl)-3-(1,3-thiazol-2-ylcarbamoyl)-1H-indol-2-olate (**15a**).* This compound was prepared according to the general procedure IV using **14a** (7.60 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 6.21 g (81%) **15a** as colorless crystals, mp 204–205 °C. IR (KBr, cm^{-1}) 2965, 1641, 1564, 1521. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.93 (1H, s), 8.19 (2H, d, J=7.7 Hz), 7.62 (1H, d, J=2.3 Hz), 7.32 (1H, d, J=3.5 Hz), 6.95 (1H, d, J=3.5 Hz), 6.94 (2H, d, J=7.6 Hz), 6.92 (1H, d, J=8.2 Hz), 6.70 (1H, dd, J=8.2, 2.3 Hz), 3.50 (4H, m), 3.17 (6H, s), 1.89 (4H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.0, 162.1, 159.1, 157.0, 151.5, 139.2, 137.3, 130.6, 129.4, 125.2, 116.9, 115.3, 111.3, 110.4, 107.0, 82.5, 47.4, 46.7, 25.4, 24.4. Anal. Calcd for $C_{24}H_{25}ClN_6O_3S$ (513.04): C 56.19, H 4.91, Cl 6.91, N 16.38, S 6.25%. Found: C 55.90, H 4.86, Cl 7.16, N 15.91, S 6.12%.

*4.5.2. 4-(Dimethylamino)pyridinium 5-chloro-1-(piperidin-1-ylcarbonyl)-3-(1,3-thiazol-2-ylcarbamoyl)-1H-indol-2-olate (**15b**).* This compound was prepared according to the general procedure IV using **14b** (7.81 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 5.00 g (63%) **15b** as colorless crystals, mp 210–212 °C. IR (KBr, cm^{-1}) 2932, 1642, 1608, 1564, 1519. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.95 (1H, s), 7.97 (2H, d, J=7.3 Hz), 7.95 (1H, s), 7.38 (1H, d, J=3.7 Hz), 6.88 (1H, d, J=8.3 Hz), 6.85 (1H, d, J=2.0 Hz), 6.83 (1H, dd, J=8.3, 2.0 Hz), 6.55 (2H, d, J=7.3 Hz), 3.82–3.35 (4H, m), 3.11 (6H, s), 1.63 (6H, s). Anal. Calcd for $C_{25}H_{27}ClN_6O_3S$ (527.06): C 56.97, H 5.16, Cl 6.73, N 15.95, S 6.08%. Found: C 56.63, H 5.13, Cl 6.53, N 15.63, S 6.10%.

*4.5.3. 4-(Dimethylamino)pyridinium 5-chloro-3-(1H-imidazol-2-ylcarbamoyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**15c**).* This compound was prepared according to the general procedure IV using **14b** (7.81 g, 0.015 mol) and 2-aminoimidazole (1.62 g, 0.017 mol) to give 5.15 g (67%) **15c** as colorless crystals, mp 221–225 °C. IR (KBr, cm^{-1}) 2935, 1648, 1571, 1511. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.36 (1H, s), 8.52 (2H, d, J=4.7 Hz), 8.18 (2H, dd, J=6.2, 1.2 Hz), 7.68 (1H, d, J=2.2 Hz), 6.94 (1H, t, J=4.7 Hz), 6.91 (2H, dd, J=6.2 Hz, J=1.2 Hz), 6.83 (1H, d, J=8.3 Hz), 6.66 (1H, dd, J=8.2, 2.2 Hz), 3.35 (4H, s), 3.14 (6H, s), 1.59 (6H, s). Anal. Calcd for $C_{25}H_{28}ClN_7O_3$ (510.01): C 58.88, H 5.53, Cl 6.95, N 19.23%. Found: C 58.55, H 5.37, Cl 6.69, N 18.80%.

*4.5.4. 4-(Dimethylamino)pyridinium 5-chloro-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-3-(1,3-thiazol-2-ylcarbamoyl)-1H-indol-2-olate monohydrate (**15d**).* This compound was prepared according to the general procedure IV using **14d** (9.00 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 4.50 g (48%) **15d** as colorless crystals, mp 231–233 °C. IR (KBr, cm^{-1}) 2911, 1676, 1647, 1587. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.87 (1H, s), 8.39 (2H, d, J=4.7 Hz), 8.20 (2H, d, J=7.8 Hz), 7.65 (1H, d, J=2.2 Hz), 7.31 (1H, d, J=3.5 Hz), 6.95 (4H, d, J=8.4 Hz), 6.70 (2H, m), 3.83 (4H, s), 3.66 (4H, s), 3.15 (6H, s). Anal. Calcd for $C_{28}H_{28}ClN_9O_3S \cdot H_2O$ (624.14): C 53.88, H 4.85, Cl 5.68, N 20.20, S 5.13%. Found: C 54.07, H 4.59, Cl 5.63, N 19.89, S 5.10%.

*4.5.5. 4-(Dimethylamino)pyridinium 5-chloro-3-(phenylcarbamoyl)-1-(propylcarbamoyl)-1H-indol-2-olate monohydrate (**15e**).* This compound was prepared according to the general procedure IV using **14g** (7.69 g, 0.015 mol) and aniline (1.37 mL, 1.40 g, 0.017 mol) to give 5.00 g (65%) **15e** as colorless crystals, mp 209–211 °C. IR (KBr, cm^{-1}) 3066, 2963, 1693, 1646, 1538. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.12 (1H, br s), 10.53 (1H, br s), 9.84 (1H, br s), 8.20 (2H, d, J=6.6 Hz), 7.95 (1H, d, J=8.3 Hz), 7.79 (1H, s), 7.59 (2H, d, J=7.6 Hz), 7.22 (2H, m), 6.94 (2H, d, J=6.6 Hz), 6.87 (1H, m), 6.69 (1H, d, J=7.8 Hz), 3.24 (2H, q, J=7.2 Hz), 3.15 (6H, s), 1.54 (2H, q, J=7.2 Hz), 0.91 (3H, t, J=7.2 Hz). Anal. Calcd for $C_{26}H_{28}ClN_5O_3 \cdot H_2O$ (512.01): C 60.99, H 5.91, Cl 6.91, N 13.68%. Found: C 60.87, H 5.90, Cl 7.04, N 13.56%.

4.6. General procedure V for the synthesis of compounds 17

A mixture of compound **10** (5.30 g, 0.01 mol) and the corresponding aromatic amine (0.0112 mol) in toluene (50 mL) was

refluxed for 5 h. The precipitate was filtered off to give compound **17**. Compounds were of high purity without recrystallization, as indicated by elemental analyses and ^{1}H NMR spectra.

*4.6.1. 4-(Dimethylamino)pyridinium 5-chloro-1-(phenoxycarbonyl)-3-(phenylcarbamoyl)-1H-indol-2-olate (**17a**).* This compound was prepared according to the general procedure V using aniline (1.04 g, 1.02 mL, 0.0112 mol) to give 4.12 g (78%) **17a** as colorless crystals, mp 196–197 °C. IR (KBr, cm^{-1}): 3051, 2996, 1758, 1648, 1592, 1561, 1525. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 13.15 (1H, s), 10.78 (1H, s), 8.20 (2H, d, J=7.6 Hz), 7.83 (1H, d, J=2.4 Hz), 7.63 (3H, d, J=8.2 Hz), 7.48 (2H, t, J=7.6 Hz), 7.26 (5H, m), 6.96 (2H, d, J=7.6 Hz), 6.90 (1H, t, J=7.6 Hz), 6.74 (1H, dd, J=8.2, 2.4 Hz), 3.17 (6H, s). Anal. Calcd for $C_{29}H_{25}ClN_4O_4$ (529.01): C 65.84, H 4.76, Cl 6.70, N 10.59%. Found: C 65.25, H 4.70, Cl 6.66, N 10.54%.

*4.6.2. 4-(Dimethylamino)pyridinium 5-chloro-1-(phenoxycarbonyl)-3-(1,3-thiazol-2–ylcarbamoyl)-1H-indol-2-olate (**17b**).* This compound was prepared according to the general procedure V using 2-aminothiazole (1.12 g, 0.0112 mol) to give 4.29 g (80%) **17b** a colorless crystals, mp 225–230 °C. IR (KBr, cm^{-1}) 3085, 2969, 1718, 1646, 1594, 1562. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.00 (1H, br s), 11.91 (1H, s), 8.98 (1H, s), 8.20 (2H, d, J=7.7 Hz), 7.77 (1H, d, J=2.2 Hz), 7.62 (1H, d, J=8.4 Hz), 7.48 (2H, m), 7.34 (1H, d, J=3.7 Hz), 7.32 (3H, m), 7.00 (1H, d, J=3.7 Hz), 6.97 (2H, d, J=7.7 Hz), 6.84 (1H, dd, J=8.4, 2.2 Hz), 3.17 (6H, s). Anal. Calcd for $C_{26}H_{22}ClN_5O_4S$ (536.01): C 58.26, H 4.14, Cl 6.61, N 13.07, S 5.98%. Found: C 58.36, H 4.04, Cl 7.09, N 13.21, S 6.25%.

*4.6.3. 4-(Dimethylamino)pyridinium 5-chloro-1-(phenoxycarbonyl)-3-(1,3,4-thiadiazol-2-yl-carbamoyl)-1H-indol-2-olate monohydrate (**17c**).* This compound was prepared according to the general procedure V using 2-amino-1,3,4-thiadiazole (1.13 g, 0.0112 mol) to give 4.33 g (78%) **17c** as colorless crystals, mp 190–195 °C. IR (KBr, cm^{-1}) 3069, 2936, 1755, 1646, 1562. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.14 (1H, br s), 12.20 (1H, s), 8.98 (1H, s), 8.20 (2H, d, J=7.7 Hz), 7.74 (1H, d, J=2.4 Hz), 7.68 (1H, d, J=8.4 Hz), 7.48 (2H, m), 7.33 (3H, m), 6.97 (2H, d, J=7.7 Hz), 6.84 (1H, dd, J=8.4, 2.2 Hz), 3.17 (6H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.0, 161.4, 158.7, 150.5, 150.2, 147.2, 139.3, 131.7, 129.7, 128.6, 127.7, 126.1, 122.0, 118.3, 115.6, 114.2, 107.1, 82.9, 40.2. Anal. Calcd for $C_{25}H_{21}ClN_6O_4S\cdot H_2O$ (555.00): C 54.10, H 4.17, Cl 6.39, N 15.14, S 5.78%. Found: C 54.06, H 4.19, Cl 6.48, N 15.11, S 5.74%.

4.7. General procedures for the synthesis of compounds 8

Route A: A mixture of compound **12** (0.015 mol) and the corresponding amine (0.030 mol) in toluene (80 mL) was refluxed for 30 min. The precipitate was filtered off to give compound **13**. A mixture of **13** thus obtained, water (50 mL) and concd HCl (1.0 mL) was stirred for 3 h at room temperature, then the precipitate was filtered off to give compound **8**.

Route B: A mixture of compound **14** (0.015 mol) and the corresponding amine (0.017 mol) in toluene (80 mL) was refluxed for 1 h. The precipitate was filtered off to give compound **15**. A mixture of **15** thus obtained, water (50 mL) and concd HCl (1.0 mL) was stirred for 3 h at room temperature, then the precipitate was filtered off to give compound **8**.

Route C: A mixture of compound **14** (0.015 mol) and the corresponding amine (0.017 mol) in toluene (80 mL) was refluxed for 1 h. After cooling to room temperature, water (50 mL) and concd HCl (1.0 mL) were added and the mixture was stirred for 3 h at room temperature, then filtered off to give compound **8**.

Route D: A mixture of compound **17** (2.5 mmol) and the corresponding amine (5.0 mmol) in DMF (6 mL) was stirred at ambient temperature for 2 h, water (6 mL) and concd HCl (0.6 mL) were added and the mixture was stirred for 2 h at room temperature, then filtered off to give compound **8.**

*4.7.1. 5-Chloro-2-hydroxy-1-(pyrrolidin-1-ylcarbonyl)-N-1,3-thiazol-2-yl-1H-indole-3-carboxamide hemihydrate (**8a**).*

(a) This compound was prepared according to *Route A* using **12a** (5.05 g, 0.015 mol) and 2-aminothiazole (3.00 g, 0.03 mol) to give 4.28 g (73%) **8a** as colorless crystals, mp >260 °C. IR (KBr, cm^{-1}): 3094, 2881, 1681, 1594. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.93 (1H, s), 7.64 (1H, d, J=4.0 Hz), 7.59 (1H, d, J=1.5 Hz), 7.26 (1H, d, J=4.0 Hz), 6.98 (1H, d, J=8.2 Hz), 6.82 (1H, dd, J=8.2, 1.5 Hz), 3.51 (4H, s), 1.87 (4H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.6, 161.4, 160.0, 150.9, 130.1, 129.5, 127.5, 125.7, 118.6, 115.9, 113.2, 111.1, 83.0, 47.3, 46.8, 25.4, 24.5. Anal. Calcd for $C_{17}H_{15}ClN_4O_3S\cdot\frac{1}{2}H_2O$ (399.87): C 51.06, H 4.03, Cl 8.86, N 14.01, S 8.03%. Found: C 50.92, H 3.91, Cl 8.84, N 13.87, S 8.06%.

(b) This compound was prepared according to the *Route B* using **14a** (7.60 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 4.85 g (81%) **8a** identical with the compound obtained via *Route A*.

*4.7.2. 5-Chloro-2-hydroxy-1-(morpholin-4-ylcarbonyl)-N-1,3-thiazol-2-yl-1H-indole-3-carboxamide hemihydrate (**8b**).* This compound was prepared according to *Route A* using **12c** (5.29 g, 0.015 mol) and 2-aminothiazole (3.00 g, 0.03 mol) to give 4.55 g (73%) **8b** as colorless crystals, mp >260 °C. IR (KBr, cm^{-1}): 3101, 2858, 1665, 1594. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.64 (1H, d, J=4.2 Hz), 7.61 (1H, d, J=2.0 Hz), 7.26 (1H, d, J=4.2 Hz), 6.99 (1H, d, J=8.4 Hz), 6.84 (1H, dd, J=8.4, 2.2 Hz), 3.66 (8H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.6, 161.4, 160.0, 151.5, 130.5, 130.5, 129.7, 127.6, 125.9, 118.7, 115.9, 113.3, 111.4, 82.6, 66.4, 47.7, 44.2. Anal. Calcd for $C_{17}H_{15}ClN_4O_4S\cdot\frac{1}{2}H_2O$ (415.86): C 49.10, H 3.88, Cl 8.53, N 13.47, S 7.71%. Found: C 49.02, H 3.92, Cl 8.66, N 13.35, S 7.56%.

*4.7.3. 5-Chloro-2-hydroxy-1-(morpholin-4-ylcarbonyl)-N-pyridin-3-yl-1H-indole-3-carboxamide dihydrate (**8c**).* This compound was prepared according to *Route C* using **14c** (7.85 g, 0.015 mol) and 3-aminopyridine (1.60 g, 0.017 mol) to give 5.00 g (76%) **8c** as colorless crystals, mp 194–196 °C. IR (KBr, cm^{-1}): 3451, 2935, 1671, 1600, 1554, 1526. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.30 (1H, s), 9.46 (1H, s), 8.44 (1H, d, J=7.5 Hz), 8.37 (1H, d, J=5.5 Hz), 7.87 (1H, d, J=5.5 Hz), 7.66 (1H, d, J=2.2 Hz), 6.94 (1H, J=8.4 Hz), 6.74 (1H, dd, J=8.4, 2.0 Hz), 3.65 (4H, s), 3.38 (4H, s). Anal. Calcd for $C_{19}H_{21}ClN_4O_6\cdot 2H_2O$ (436.87): C 52.23, H 4.84, Cl 8.11, N 12.82%. Found: C 52.17, H 4.44, Cl 8.15, N 12.80%.

*4.7.4. 5-Chloro-2-hydroxy-N-phenyl-1-(piperidin-1-ylcarbonyl)-1H-indole-3-carboxamide (**8d**).*

(a) This compound was prepared according to *Route C* using **14b** (7.81 g, 0.015 mol) and aniline (1.37 mL, 1.40 g, 0.017 mol) to give 4.36 g (73%) **8d** as colorless crystals, mp 181–183 °C. IR (KBr, cm^{-1}): 3290, 2945, 1744, 1684, 1664, 1600. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 10.70 (1H, br s), 7.62 (3H, m), 7.33 (3H, m), 7.07 (2H, m), 3.51 (4H, s), 1.87 (6H, s). Anal. Calcd for $C_{21}H_{20}ClN_3O_3$ (397.87): C 63.40, H 5.07, Cl 8.91, N 10.56%. Found: C 63.32, H 5.21, Cl 9.01, N 10.32%.

(b) This compound was prepared according to *Route D* using **17a** (1.32 g, 2.5 mmol) and piperidine (0.49 mL, 0.43 g, 5.0 mmol) to give 0.79 g (79%) **8d** identical with the compound obtained via *Route C*.

*4.7.5. 5-Chloro-2-hydroxy-1-(piperidin-1-ylcarbonyl)-N-1,3-thiazol-2-yl-1H-indole-3-carboxamide (**8e**).* This compound was prepared

according to *Route B* using **14b** (7.81 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 3.70 g (61%) **8e** as colorless crystals, mp >260 °C. IR (KBr, cm^{-1}): 2938, 1658, 1599, 1511. ^1H NMR (DMSO-d_6, 200 MHz) δ 12.90 (1H, s), 7.63 (1H, d, J=4.3 Hz), 7.59 (1H, d, J=2.0 Hz), 7.27 (1H, d, J=4.3 Hz), 6.96 (1H, J=8.2 Hz), 6.83 (1H, dd, J=8.2, 2.0 Hz), 3.44 (4H, s), 1.63 (6H, s). Anal. Calcd for $C_{18}H_{17}ClN_4O_3S$ (404.89): C 53.40, H 4.23, Cl 8.76, N 13.84, S 7.92%. Found: C 52.90, H 4.16, Cl 8.52, N 13.65, S 7.77%.

*4.7.6. 5-Chloro-2-hydroxy-1-(piperidin-1-ylcarbonyl)-N-pyridin-3-yl-1H-indole-3-carboxamide monohydrate (**8f**).* This compound was prepared according to *Route C* using **14b** (7.81 g, 0.015 mol) and 3-aminopyridine (1.60 g, 0.017 mol) to give 5.25 g, (84%) **8f** as colorless crystals, mp 257–258 °C. IR (KBr, cm^{-1}): 2935, 2855, 1685, 1543. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.38 (1H, s), 9.48 (1H, s), 8.44 (1H, d, J=8.8 Hz), 8.37 (1H, d, J=5.3 Hz), 7.86 (1H, dd, J=8.7, 5.5 Hz), 7.65 (1H, d, J=2.2 Hz), 6.85 (1H, J=8.2 Hz), 6.72 (1H, dd, J=8.2, 2.0 Hz), 3.82–3.35 (4H, s), 1.60 (6H, s). Anal. Calcd for $C_{20}H_{19}ClN_4O_3\cdot H_2O$ (416.88): C 57.62, H 5.08, Cl 8.51, N 13.44%. Found: C 57.25, H 4.76, Cl 8.78, N 13.38%.

*4.7.7. 5-Chloro-2-hydroxy-N-1H-imidazol-2-yl-1-(piperidin-1-ylcarbonyl)-1H-indole-3-carboxamide (**8g**).* This compound was prepared according to *Route B* using **14b** (7.81 g, 0.015 mol) and 2-aminoimidazole (1.62 g, 0.017 mol) to give 3.90 g (67%) **8g** as colorless crystals, mp 234–236 °C. IR (KBr, cm^{-1}): 2941, 2857, 1669, 1578. ^1H NMR (DMSO-d_6, 200 MHz) δ 12.53 (1H, s), 8.86 (2H, d, J=5.2 Hz), 7.63 (1H, d, J=2.2 Hz), 7.40 (1H, t, J=5.2 Hz), 6.91 (2H, m), 3.35 (4H, s), 1.59 (6H, s). Anal. Calcd for $C_{18}H_{18}ClN_5O_3$ (387.84): C 55.74, H 4.68, Cl 9.14, N 18.06%. Found: C 55.42, H 4.57, Cl 9.06, N 17.85%.

*4.7.8. 5-Chloro-2-hydroxy-1-(piperidin-1-ylcarbonyl)-N-1,3,4-thiadiazol-2-yl-1H-indole-3-carboxamide (**8h**).* This compound was prepared according to *Route C* using **14b** (7.81 g, 0.015 mol) and 2-amino-1,3,4-thiadiazole (1.72 g, 0.017 mol) to give 4.10 g (67%) **8h** as colorless crystals, mp 235–243 °C. IR (KBr, cm^{-1}): 2939, 1746, 1658, 15,925, 1531. ^1H NMR (DMSO-d_6, 200 MHz) δ 12.70 (1H, s), 9.08 (1H, s), 7.60 (1H, d, J=2.1 Hz), 7.00 (1H, s), 6.91 (1H, J=8.2 Hz), 6.81 (1H, dd, J=8.2, 2.0 Hz), 3.45 (4H, s), 1.59 (6H, s). Anal. Calcd for $C_{17}H_{16}ClN_5O_3S$ (405.88): C 50.30, H 3.97, Cl 8.74, N 17.25, S 7.90%. Found: C 50.50, H 3.59, Cl 8.52, N 16.88, S 7.96%.

*4.7.9. 5-Chloro-2-hydroxy-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-N-1,3-thiazol-2-yl-1H-indole-3-carboxamide monohydrate (**8i**).* This compound was prepared according to *Route B* using **14d** (9.00 g, 0.015 mol) and 2-aminothiazole (1.70 g, 0.017 mol) to give 3.46 g (46%) **8i** as colorless crystals, mp 200–202 °C. IR (KBr, cm^{-1}): 3455, 1648, 1589, 1550, 1502. ^1H NMR (DMSO-d_6, 200 MHz) δ 12.89 (1H, s), 8.39 (2H, d, J=4.5 Hz), 7.66 (1H, d, J=4.3 Hz), 7.62 (1H, d, J=2.2 Hz), 7.28 (1H, d, J=4.3 Hz), 7.01 (1H, d, J=8.5 Hz), 6.87 (1H, dd, J=8.3, 2.2 Hz), 6.68 (1H, d, J=4.6 Hz), 3.87 (4H, s), 3.63 (4H, s). Anal. Calcd for $C_{21}H_{18}ClN_7O_3S\cdot H_2O$ (501.97): C 50.25, H 4.02, Cl 7.06, N 19.53, S 6.39%. Found: C 50.38, H 3.98, Cl 6.82, N 18.87, S 6.15%.

*4.7.10. 5-Chloro-2-hydroxy-N-pyridin-3-yl-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-1H-indole-3-carboxamide (**8j**).* This compound was prepared according to *Route C* using **14d** (9.00 g, 0.015 mol) and 3-aminopyridine (1.60 g, 0.017 mol) to give 4.30 g (60%) **8j** as colorless crystals, mp 235–243 °C. IR (KBr, cm^{-1}): 2854, 1680, 1586, 1549. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.36 (1H, s), 9.50 (1H, s), 8.46 (1H, dd, J=8.4, 1.8 Hz), 8.39 (2H, d, J=4.8 Hz), 7.88 (1H, dd, J=8.4, 5.2 Hz), 7.69 (1H, d, J=2.1 Hz), 7.19 (1H, m), 6.91 (1H, d, J=8.2 Hz), 6.76 (1H, dd, J=8.4, 2.1 Hz), 6.68 (1H, t, J=4.8 Hz), 3.83 (4H, s), 3.66 (4H, s). Anal. Calcd for $C_{23}H_{20}ClN_7O_3$ (477.93): C 57.80, H 4.22, Cl 7.42, N 20.52%. Found: C 57.77, H 4.24, Cl 7.29, N 19.96%.

*4.7.11. N-Benzyl-5-chloro-2-hydroxy-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-1H-indole-3-carboxamide (**8k**).* This compound was prepared according to *Route C* using **14d** (9.00 g, 0.015 mol) and benzylamine (1.86 mL, 1.82 g, 0.017 mol) to give 4.71 g (64%) **8k** as colorless crystals, mp 205–206 °C. IR (KBr, cm^{-1}): 3307, 1745, 1691, 1663, 1588, 1552. ^1H NMR (DMSO-d_6, 200 MHz) δ 9.12 (1H, s), 8.40 (2H, d, J=4.7 Hz), 7.33 (7H, m), 7.14 (1H, d, J=8.8 Hz), 6.69 (1H, t, J=4.7 Hz), 4.80 (1H, s), 4.39 (2H, s), 3.69 (8H, m). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 165.4, 161.1, 158.1, 128.9, 128.4, 127.7, 127.3, 127.1, 125.0, 113.0, 110.7, 54.0, 43.3, 42.8. Anal. Calcd for $C_{25}H_{23}ClN_6O_3$ (490.96): C 61.16, H 4.72 Cl 7.22, N 17.12%. Found: C 61.32, H 4.69, Cl 7.17, N 17.00%.

*4.7.12. 5-Chloro-N^1-[2-(dimethylamino)ethyl]-2-hydroxy-N^3-pyridin-2-yl-1H-indole-1,3-dicarboxamide (**8l**).* This compound was prepared according to *Route C* using **14e** (7.86 g, 0.015 mol) and 2-aminopyridine (1.60 g, 0.017 mol) to give 5.85 g (97%) **8l** as colorless crystals, mp 188–190 °C. IR (KBr, cm^{-1}): 3026, 1687, 1594, 1543. ^1H NMR (DMSO-d_6, 200 MHz) δ 11.03 (1H, s), 10.04 (1H, t, J=5.5 Hz), 8.30 (1H, J=8.6 Hz), 8.19 (1H, m), 8.02 (1H, d, J=8.5 Hz), 7.84 (1H, d, J=2.4 Hz), 7.68 (1H, td, J=8.6, 1.8 Hz), 6.92 (1H, m), 6.78 (1H, dd, J=8.5, 2.4 Hz), 3.65 (2H, q, J=5.5 Hz), 3.12 (2H, t, J=5.5 Hz), 2.72 (6H, s). Anal. Calcd for $C_{19}H_{20}ClN_5O_3$ (401.87): C 56.79, H 5.02, Cl 8.82, N 17.43%. Found: C 56.48, H 4.88, Cl 8.50, N 17.49%.

*4.7.13. N^3-Benzyl-5-chloro-N^1-[2-(dimethylamino)ethyl]-2-hydroxy-N^3-methyl-1H-indole-1,3-dicarboxamide (**8m**).* This compound was prepared according to *Route C* using **14e** (7.86 g, 0.015 mol) and *N*-benzylmethylamine (2.2 mL, 2.06 g, 0.017 mol) to give 4.57 g (71%) **8m** as colorless crystals, mp 191–192 °C. IR (KBr, cm^{-1}): 3012, 1688, 1619, 1589, 1567, 1526. ^1H NMR (DMSO-d_6, 200 MHz) δ 10.58 (1H, t, J=5.5 Hz), 7.93 (1H, d, J=8.4 Hz), 7.35 (1H, d, J=2.2 Hz), 7.28 (5H, m), 6.59 (1H, dd, J=8.4, 2.2 Hz), 4.67 (2H, s), 3.65 (2H, q, J=6.0 Hz), 3.25 (2H, q, J=6.0 Hz), 2.89 (3H, s), 2.81 (6H, s). ^{13}C NMR (DMSO-d_6, 50 MHz) δ 168.5, 161.6, 155.6, 139.6, 134.1, 128.8, 124.4, 127.4, 126.7, 125.7, 115.5, 114.9, 84.6, 57.1, 51.7, 43.0, 35.3, 29.9, 27.0. Anal. Calcd for $C_{22}H_{25}ClN_4O_3$ (428.93): C 61.60, H 5.87, Cl 8.27, N 13.06%. Found: C 61.40, H 5.86, Cl 8.17, N 12.74%.

*4.7.14. 5-Chloro-N^1-[2-(dimethylamino)ethyl]-2-hydroxy-N^3-phenyl-1H-indole-1,3-dicarboxamide (**8n**).* This compound was prepared according to *Route C* using **14e** (7.86 g, 0.015 mol) and aniline (1.37 mL, 1.40 g, 0.017 mol) to give 5.25 g (87%) **8n** as colorless crystals, mp 228–229 °C. IR (KBr, cm^{-1}): 3191, 2401, 1693, 1612, 1594, 1538. ^1H NMR (DMSO-d_6, 200 MHz) δ 10.59 (1H, s), 10.05 (1H, t, J=5.8 Hz), 9.28(1H, br s), 8.00 (1H, d, J=8.5 Hz), 7.84 (1H, d, J=2.5 Hz), 7.60 (2H, m), 7.26 (2H, m), 6.91 (1H, m), 6.75 (1H, dd, J=8.5, 2.5 Hz), 3.68 (2H, m), 3.33 (2H, m), 2.85 (6H, s). ^{13}C NMR (DMSO-d_6, 125 MHz) δ 165.0, 164.4, 154.7, 140.9, 131.4, 128.9, 128.6, 126.4, 121.2, 118.1, 117.2, 115.7, 114.3, 85.0, 56.9, 42.9, 34.4. Anal. Calcd for $C_{20}H_{21}ClN_4O_3$ (400.88): C 59.93, H 5.28, Cl 8.84, N 13.98%. Found: C 59.78, H 5.32, Cl 8.77, N 14.02%.

*4.7.15. 5-Chloro-2-hydroxy-N^3-phenyl-N^1-propyl-1H-indole-1,3-dicarboxamide monohydrate (**8o**).* This compound was prepared according to *Route B* using **14g** (7.69 g, 0.015 mol) and aniline (1.37 mL, 1.40 g, 0.017 mol) to give 5.79 g (99%) **8o** as colorless crystals, mp 208–210 °C. IR (KBr, cm^{-1}): 3347, 3301, 2965, 1736, 1696, 1669, 1541. ^1H NMR (DMSO-d_6, 200 MHz) δ 10.57 (1H, br s), 9.85 (1H, br s), 8.00 (1H, d, J=8.4 Hz), 7.80 (1H, br s), 7.62 (2H, dd, J=8.6, 1.1 Hz), 7.25 (2H, t, J=8.6 Hz), 6.93 (1H, m), 6.76 (1H, br s), 3.26 (2H, br s), 1.55 (2H, q, J=7.2 Hz), 0.94 (3H, t, J=7.2 Hz). Anal.

Calcd for $C_{19}H_{18}ClN_3O_3 \cdot H_2O$ (389.83): C 58.54, H 5.17, Cl 9.10, N 10.78%. Found: C 58.14, H 5.38, Cl 9.10, N 10.66%.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.017.

References and notes

1. Andreani, A.; Rambaldi, M. *J. Heterocycl. Chem.* **1988**, *25*, 1519.
2. Oezcan, S.; Balci, M. *Tetrahedron* **2008**, *64*, 5531.
3. Esses-Reiter, K.; Reiter, J. *J. Heterocycl. Chem.* **2000**, *37*, 927.
4. Gallaschun, R. J.; Schnur, R. C. *J. Heterocycl. Chem.* **1992**, *29*, 369.
5. Deberly, A.; Bourdais, J. *J. Heterocycl. Chem.* **1977**, *14*, 781.
6. Gref, C.; Sabourault, B.; Bourdais, J. *Tetrahedron Lett.* **1972**, *19*, 1957.
7. Wiseman, E. H.; Chiaini, J.; McManus, J. M. *J. Med. Chem.* **1973**, *16*, 131.
8. Mylari, B. L.; Carty, T. J.; Moore, P. F.; Zembrowski, W. J. *J. Med. Chem.* **1990**, *33*, 2019.
9. Kadin, S. B. E.P. 208,510, 1986; *Chem. Abstr.* **1987**, *106*, 138254.
10. Kadin, S. B. U.S. 4,725,616, 1987; *Chem. Abstr.* **1989**, *110*, 23728.
11. Kadin, S. B. U.S. 4,730,004, 1988; *Chem. Abstr.* **1989**, *110*, 23729.
12. McManus, J. M., Kadin, S. B. D.E. 2,046,595, 1971; *Chem. Abstr.* **1971**, *75*, 448901.
13. Otterness, I. G. U.S. 4,861,794, 1988; *Chem. Abstr.* **1990**, *112*, 70013.
14. Showell, H. J. U.S. 4,853,409, 1988; *Chem. Abstr.* **1989**, *111*, 225312.
15. Silbermann, S. C.A. 2,156,120, 1994; *Chem. Abstr.* **1996**, *124*, 333055.
16. Kadin, S. B. E.P. 153,818, 1985; *Chem. Abstr.* **1986**, *104*, 88427.
17. Crawford, T. C. E.P. 155,828, 1985; *Chem. Abstr.* **1986**, *104*, 109466.
18. Kadin, S. B. E.P. 156,603, 1985; *Chem. Abstr.* **1986**, *104*, 109468.
19. (a) Robinson, C. *Drugs Future* **1990**, *15*, 898; (b) *Drugs Future* **1993**, *18*, 875.
20. Robinson, R. P.; Donahue, K. M. *J. Heterocycl. Chem.* **1994**, *31*, 1541.
21. *Drugs Future* **1995**, *20*, 972.
22. Scrip No. 1815, April 27 1993, p 29.
23. Scrip No. 2169, October 4 1996, p 24.
24. Robinson, R. P.; Reiter, L. A.; Barth, W. E.; Campeta, A. M.; Cooper, K.; Cronin, B. J.; Destito, R.; Donahue, K. M.; Falkner, F. C.; Fiese, E. F.; Johnson, D. L.; Kuperman, A. V.; Liston, T. E.; Malloy, D.; Martin, J. J.; Mitchell, D. Y.; Rusek, F. W.; Shamblin, S. L.; Wright, C. F. *J. Med. Chem.* **1996**, *39*, 10.
25. Cooper, K.; Crawford, T. C.; Littman, B. H.; Pazoles, C. J.; Ruggeri, S. G.; Wilner, K. D. W.O. 9416694, 1994; *Chem. Abstr.* **1994**, *121*, 587320.
26. Beccalli, E. M.; Marchesini, A. *Tetrahedron* **1995**, *51*, 2353.
27. Beccalli, E. M.; Marchesini, A. *Synth. Commun.* **1993**, *23*, 2945.
28. Beccalli, E. M.; Marchesini, A.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 579.
29. Beccalli, E. M.; Marchesini, A.; Pilati, T. *Tetrahedron* **1994**, *50*, 12697.
30. Beccalli, E. M.; Marchesini, A.; Pilati, T. *Synthesis* **1992**, 891.
31. Beccalli, E. M.; Marchesini, A. *Tetrahedron* **1993**, *49*, 4741.
32. Porcs-Makkay, M.; Simig, G. *Org. Process Res. Dev.* **2000**, *4*, 10.
33. Porcs-Makkay, M.; Kálmán, A.; Argay, G.; Simig, G. *Tetrahedron* **2000**, *56*, 5893.
34. Porcs-Makkay, M.; Simig, G. *J. Heterocycl. Chem.* **2001**, *38*, 451.