Tetrahedron 68 (2012) 1427–1435

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Convenient synthesis of 3-unsubstituted oxindole-1-carboxamides

Márta Porcs-Makkay [a,*], Balázs Volk [a], Eszter Kókai [b], Gyula Simig [a]

[a] EGIS Pharmaceuticals Plc., Chemical Research Division, PO Box 100, H-1475 Budapest, Hungary
[b] Budapest University of Technology and Economics, Faculty of Chemical Engineering, PO Box 91, 1521 Budapest, Hungary

ARTICLE INFO

Article history:
Received 5 July 2011
Received in revised form 22 November 2011
Accepted 12 December 2011
Available online 16 December 2011

Dedicated to the memory of Professor István Hermecz

Keywords:
Oxindole
Amidation
Dephenoxycarbonylation
4-*N*,*N*-Dimethylaminopyridinum (DMAP) salt

ABSTRACT

The multiple reactivity of the mesomeric anion formed by *N*- or *C*(3)-deprotonation of 3-unsubstituted oxindoles hampers the selective introduction of substituents onto the nitrogen atom. A conveniently applicable reaction sequence has been elaborated for the synthesis of 3-unsubstituted oxindole-1-carboxamides starting from the easily available 1,3-bis(phenoxycarbonyl)oxindoles. Selective amidation of the *N*-phenoxycarbonyl moiety and subsequent removal of the *C*(3)-phenoxycarbonyl moiety furnished the title compounds, which are useful building blocks for further functionalization. Besides the novel methodologies, several new representatives of this valuable compound family and their intermediates are also described below.

1. Introduction

The occurrence of 2-oxo-2,3-dihydroindole-1-carboxamides (1,3-dihydro-2*H*-indol-2-one-1-carboxamides, oxindole-1-carboxamides, **1**, Fig. 1) exhibiting various substituents at the 3-position is scarce in scientific journals.[1–7] On the contrary, the patent literature of these compounds is rich due to the interest aroused by the therapeutic efficacy of some members of this compound family.[8–12] An outstanding example of this type of oxindole derivatives is (*Z*)-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (tenidap, **1a**, Fig. 1)[11,13,14] exhibiting anxiolytic and antirheumatic activity, which was finally not launched because of serious side-effects. The development of ilonidap (**1b**, Fig. 1),[6] a successor of tenidap, was also abandoned.

Earlier activity of our research group ranged from the synthesis of 3-acyloxindole-1-carboxamides (**1**, R^3=H, R^4=acyl)[15–18] to oxindole-1,3-dicarboxamides (**2**).[19] Next, we aimed at elaborating a practical synthesis of 3-unsubstituted oxindole-1-carboxamides (**3**), which are appropriate building blocks for further functionalization.

According to the described procedures, the 1-carbamoyl moiety of 3-unsubstituted (**3**),[20–22] 3-acyl (**1**, R^3=H, R^4=acyl)[11,12,23] or 3,3-dialkyl (**1**, R^3,R^4=alkyl)[24–26] substituted oxindoles can be introduced using isocyanates. Nevertheless, the use of isocyanates for the introduction of the 1-carbamoyl group does not make the direct synthesis of *N*,*N*-disubstituted oxindole-1-carboxamides possible. Moreover, the applicability of this method is further limited by the fact that relatively few organic isocyanates are commercially available.[14]

3-Unsubstituted 1-alkoxy(aryloxy)carbonyl-oxindoles (**4**, Fig. 1) seemed to be appropriate starting compounds for the synthesis of 3-unsubstituted oxindole-1-carboxamides (**3**). However, our earlier experiments showed that treatment of 5-chloro-1-phenoxycarbonyloxindole (**4a**) with ammonium carbonate (1 equiv) in DMF at 25 °C for 3 h resulted in a mixture of the desired 5-chlorooxindole-1-carboxamide (**3a**) and by-product 5-chlorooxindole (**5a**) in a 2:1 ratio (Scheme 1),[16] and the use of various amines instead of ammonium carbonate also furnished similar mixtures in a ratio depending on the character of the amine applied.[27]

The use of the 1-(4-nitrophenoxy)carbonyl group seemed to eliminate this problem (i.e., N-desaryloxycarbonylation), as described in the only paper published in this field,[28] and in a patent application[29] for the transformation of **4b** to the 1-carbamoyl derivative **3b**. The 1-(4-nitrophenoxy)carbonyl moiety has also been applied to a similar reaction of 3,3-dialkylated oxindoles.[24] Nevertheless, (4-nitrophenoxy)chloroformate is an expensive reagent and it has earlier been demonstrated that preparation of the starting compound **4b** via selective N(1)-

* Corresponding author. Fax: +36 1 2655613; e-mail address: porcs-makkay.marta@egis.hu (M. Porcs-Makkay).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.12.027

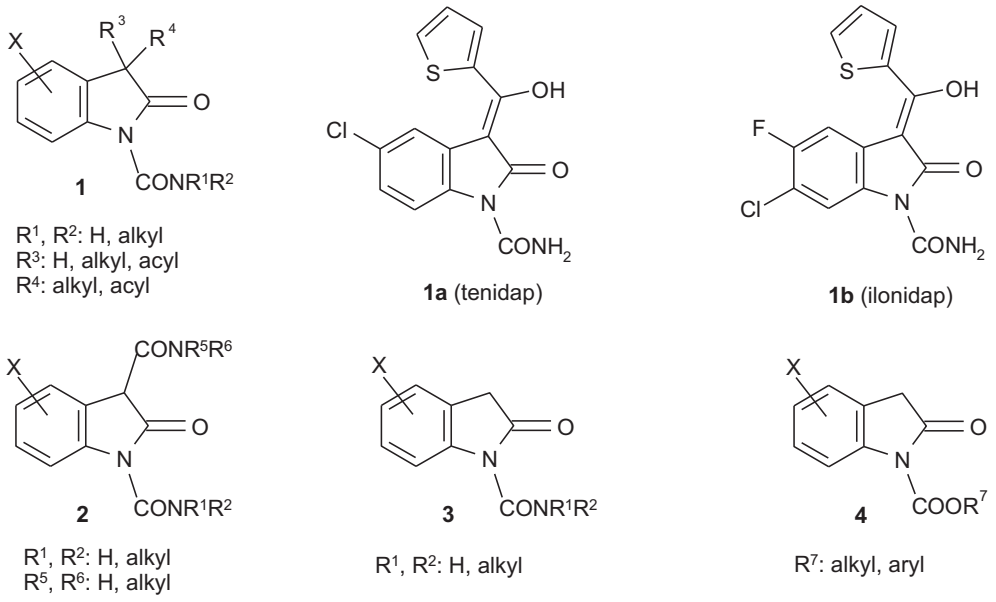
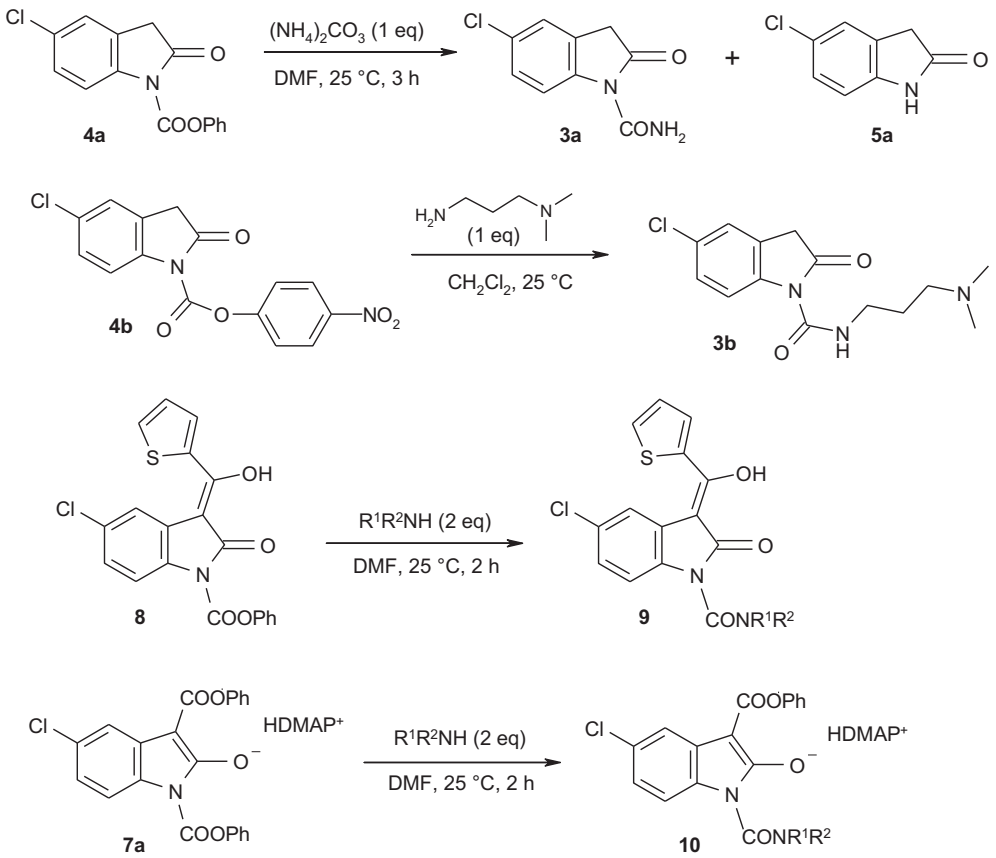


Fig. 1. Structure of various oxindole-1-carboxamides (**1**, **3**), 1,3-dicarboxamides (**2**) and intermediates thereof (**4**).

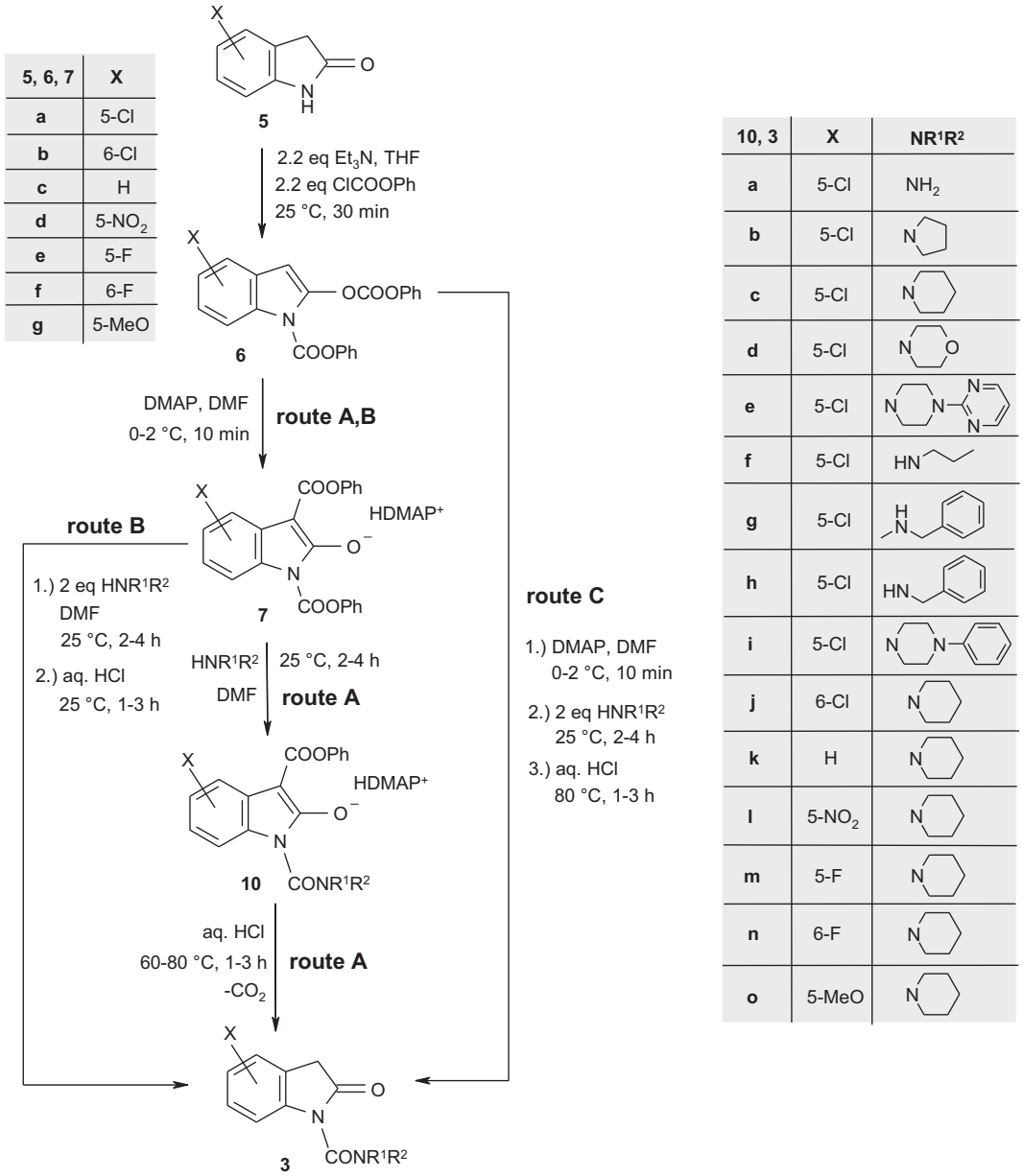


Scheme 1. Literature procedures for the preparation of oxindole-1-carboxamides.

aryloxycarbonylation could not be carried out due to the facile formation of *N*(1),*O*- and *N*(1),*C*(3)-bis(aryloxycarbonyl) derivatives (types **6** and **7**, respectively, see Scheme 2)[15,16] Thus, **4b** did not seem an ideal starting material for our purpose, either.

Our earlier studies demonstrated, although for 3-substituted congeners, that the 1-phenoxycarbonyl moiety took part in aminolysis under mild conditions. 5-Chloro-1-phenoxycarbonyl-3-thenoyloxindole (**8**, Scheme 1), which exists in the *Z* enol structure,[16] and the 4-*N*,*N*-dimethylaminopyridinum (DMAP) salt of 5-chloro-1,3-diphenoxycarbonyloxindole (**7a**)[30] could easily be amidated with various primary, secondary aliphatic and cyclic amines to form the corresponding 1-carbamoyl derivatives **9**[17] and **10**,[19] respectively, in good yields (Scheme 1).

Based on the above, and supposing that removal of the 3-phenoxycarbonyl group is viable, we decided to investigate



Scheme 2. New synthesis of oxindole-1-carboxamides.

a general synthesis of oxindole-1-carboxamides (**3**) starting from the easily available[30] 1,3-bis(phenoxycarbonyl)oxindole DMAP salts **7** (Scheme 2).

2. Results and discussion

We describe here a convenient, widely applicable synthesis of 3-unsubstituted oxindole-1-carboxamides (**3**). The synthetic route applied is depicted in Scheme 2.

The synthesis of diester salts **7a**–**d** has been described in our earlier publication[30] by *N*,*O*-bis(phenoxycarbonylation) of oxindoles **5a**–**d** to **6a**–**d** and their subsequent rearrangement (Scheme 2). New derivatives **6e**–**g** and **7e**–**g** were now obtained by using the same protocol.

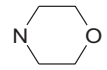
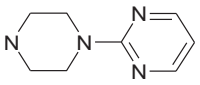
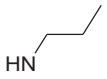
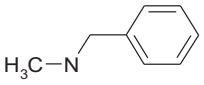
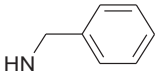
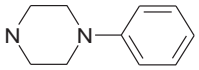
Selective amidation of diester DMAP salt **7a** to form 1-carboxamido-3-phenoxycarbonyl compounds **10b**–**g** (Scheme 2) has been described earlier.[19] New compounds **10a** and **10h**–**o** were now prepared by an analogous procedure. Treatment of compounds **10** with aqueous hydrochloric acid for 0.5–3 h at room temperature or at 60–80 °C resulted in the removal of the 3-phenoxycarbonyl group via hydrolysis and decarboxylation, leading to 3-unsubstituted oxindole-1-carboxamides **3** (Scheme 2, route A). Carrying out the amidation and the subsequent dephenoxycarbonylation in one-pot (route B) was also viable, as shown by the transformation of diesters **7b** and **7c** to target compounds **3j** and **3k**.

Considering the reaction conditions of the single synthetic steps leading from diesters **6** to 3-unsubstituted amides **3**, the opportunity arose to carry out the transformations in one-pot (Scheme 2, route C). Thus, compounds **3a**–**o** were prepared in most cases in good yields in one-pot, by treatment of the corresponding *N*,*O*-bis(phenoxycarbonyl) derivatives **6** with DMAP in DMF, followed by amidation of the resulting 1,3-diester salts **7**, without isolation of intermediates **10**, and subsequent removal of the 3-phenoxycarbonyl group on acidic treatment of the reaction mixture.

Table 1 summarizes the yields of transformations **6**→**3** carried out with isolation of intermediates **7** and **10** (route A), with isolation of **10** alone (route B), and in one-pot (route C). In cases where the total yield of the first two steps (**6**→**7** and **7**→**10**) was lower than the yield of the one-pot reaction (**6**→**3**), acidic hydrolysis of intermediates **10** to compounds **3** was not performed. The data demonstrate that the one-pot procedure (route C) is in most cases superior to routes A and B, in terms of yield and synthetic simplicity. However, for a few derivatives (**3a**, **3i**–**k**), the stepwise approach resulted in a higher overall yield.

At the beginning, 5-chlorooxindole derivatives were used as model compounds (see **3a**–**i**). Later on, we inquired whether this methodology could be generalised by varying the character and the position of the substituent on the aromatic nucleus. Thus, we investigated the analogous synthesis of 6-chloro (**3j**), 5-nitro (**3l**), 5-methoxy (**3o**), 5-fluoro (**3m**), 6-fluoro (**3n**) and unsubstituted (**3k**) oxindole derivatives, using piperidine as the amine reagent. It was concluded that in each case the desired oxindole-1-carboxamides (**3**) could be prepared using the one-pot procedure, in medium to good yield.

Table 1
Comparison of the total yields of transformations **6**→**3** carried out with isolation of intermediates **7** and **10** (route A), with isolation of **10** alone (route B), and in one-pot (route C)

6,**7**	X	**10**,**3**	NR^1R^2	Yield (%)	Yield (%)	Yield (%)	Total yield (%) of sequential steps (route A[a])	Total yield (%) via route [a]	One-pot yield (%) via route C[a]
				6→**7**	**7**→**10**	**10**→**3**	**6**→**7**→**10**→**3**	**6**→**7**→**3**	**6**→**3**
a	5-Cl	**a**	NH_2	93[b]	93	95	82		49
a	5-Cl	**b**		93[b]	63[c]				71
a	5-Cl	**c**		93[b]	83[c]				86
a	5-Cl	**d**		93[b]	77[c]	65	47		51
a	5-Cl	**e**		93[b]	94[c]	67	59		68
a	5-Cl	**f**		93[b]	80[c]	99	74		97
a	5-Cl	**g**		93[b]	50[c]	40	19		34
a	5-Cl	**h**		93[b]	43	67	27		93
a	5-Cl	**i**		93[b]	86	99	79		46
b	6-Cl	**j**		97[b]	90			88	86
c	H	**k**		96[b]	95	74	67	41	46
d	5-NO_2	**l**		94[b]	48	99	46		86
e	5-F	**m**		92	72				73
f	6-F	**n**		66	57				75
g	5-MeO	**o**		96	34				88

[a] Yield of product **3** is calculated for **6** as the starting compound.
[b] See Ref. 30.
[c] See Ref. 19.

3. Conclusions

Various procedures have been developed at our laboratory for the practical synthesis of 3-unsubstituted oxindole-1-carboxamides (**3**). The most convenient one-pot approach applies the easily available *N*(1),*O*-bis(phenoxycarbonyl) derivatives (**6**) as starting materials, and involves (i) *O*→*C*(3) migration of the phenoxycarbonyl moiety (**6**→**7**); (ii) amidation in position 1 (**7**→**10**); and (iii) hydrolysis and decarboxylation of the 3-phenoxycarbonyl group upon acidic treatment, furnishing oxindole-1-carboxamides (**3**) in medium to high overall yields. The methodology described above is applicable for oxindole derivatives with various substituents on the aromatic nucleus and offers a convenient approach to a wide range of new oxindole-1-carboxamides, which are only circuitously or, in the case of *N*,*N*-disubstituted carboxamides, not at all available by other procedures.

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 spectra were recorded on a Varian Gemini 200 (200 MHz), Bruker Avance III (400 MHz) or a Varian Unity Inova 500 (500 MHz) spectrometer. $CDCl_3$ or DMSO-d_6 was used as solvent and tetramethylsilane (TMS) as 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. Compounds **6a**–**d**,[30] **7a**–**d**[30] and **10b**–**g**[19] were described in our earlier papers. New intermediates and final products are described below in detail.

4.2. General procedure I for the synthesis of *N*,*O*-diacylated oxindoles 6[30]

To a solution of the corresponding substituted oxindole (**5**, 40 mmol) and triethylamine (88 mmol) in THF (140 mL) was added phenyl chloroformate (13.76 g, 11.0 mL, 88 mmol) dropwise. The temperature was kept below 30 °C during the addition. After stirring for 30 min at room temperature, the solvent was evaporated. Water (40 mL) was added to the residue and the mixture was stirred for 2 h at 0–5 °C. The crystalline product was filtered and recrystallized from ethyl acetate to give compounds **6**.

*4.2.1. Phenyl 5-fluoro-2-[(phenoxycarbonyl)oxy]-1H-indole-1-carboxylate (**6e**).* This compound was prepared according to the general procedure I using 5-fluorooxindole (**5e**) to give **6e** (5.90 g, 38%) as colourless crystals, mp 95–98 °C (ethyl acetate). IR (KBr, cm^{-1}): 1785, 1749, 1615, 1475. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (1H, dd, J=9.1, 4.5 Hz), 7.47 (2H, m), 7.37–7.23 (6H, m), 7.31 (1H, d, J=8.2 Hz), 7.09 (2H, m), 7.07 (1H, dd, J=7.8, 2.6 Hz), 6.48 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.8 (d, J=241.3 Hz), 151.0, 150.8, 149.8, 148.3, 142.1, 129.8, 129.6, 129.1 (d, J=1.3 Hz), 127.6 (d, J=10.2 Hz), 126.8, 126.6, 121.5, 120.7, 117.0 (d, J=9.1 Hz), 112.9 (d, J=24.9 Hz), 106.6 (d, J=24.4 Hz), 98.3 (d, J=3.7 Hz). Anal. Calcd for $C_{22}H_{14}FNO_5$ (391.36): C 67.52, H 3.61, N 3.58%. Found: C 67.40, H 3.63, N 3.58%.

*4.2.2. Phenyl 6-fluoro-2-[(phenoxycarbonyl)oxy]-1H-indole-1-carboxylate (**6f**).* This compound was prepared according to the general procedure I using 6-fluorooxindole (**5f**) to give **6f** (11.3 g, 73%) as colourless crystals, mp 125–128 °C (ethyl acetate). IR (KBr, cm^{-1}): 1784, 1757, 1613, 1497. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (1H, dd, J=10.2, 2.3 Hz), 7.51 (1H, d, J=8.7 Hz), 7.30 (10H, m), 7.06 (1H, dd, J=8.8, 2.4 Hz), 6.48 (1H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0 (d, J=241.2 Hz), 151.1, 150.8, 149.8, 148.3, 141.1 (d, J=3.4 Hz), 133.0 (d, J=13.3 Hz), 129.8, 129.6, 126.9, 126.6, 122.7, 121.8 (d, J=9.6 Hz), 121.4, 120.7, 112.2 (d, J=24.0 Hz), 103.4 (d, J=29.3 Hz), 98.0. Anal. Calcd for $C_{22}H_{14}FNO_5$ (391.36): C 67.52, H 3.61, N 3.58%. Found: C 67.09, H 3.69, N 3.55%.

*4.2.3. Phenyl 5-methoxy-2-[(phenoxycarbonyl)oxy]-1H-indole-1-carboxylate (**6g**).* This compound was prepared according to the general procedure I using 5-methoxyoxindole (**5g**) to give **6g** (14.0 g, 87%) as colourless crystals, mp 117–121 °C (ethyl acetate). IR (KBr, cm^{-1}): 1787, 1758, 1604, 1481. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (1H, d, J=9.1 Hz), 7.40–7.09 (10H, m), 7.03 (1H, d, J=2.3 Hz), 6.95 (1H, dd, J=9.1, 2.3 Hz), 6.43 (1H, s), 3.85 (3H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.7, 151.1, 150.9, 149.9, 148.4, 141.5, 129.7, 129.5, 127.5, 127.2, 126.7, 121.5, 120.7, 116.6, 113.3, 104.1, 98.4, 55.7. Anal. Calcd for $C_{23}H_{17}NO_6$ (403.40): C 68.48, H 4.25, N 3.47%. Found: C 68.13, H 4.33, N 3.44%.

4.3. General procedure II for the synthesis of 1,3-diacylated oxindole DMAP salts 7[30]

To a solution of **6** (10 mmol) in DMF (10 mL) was added a solution of DMAP (10 mmol) in DMF (10 mL) at 0–2 °C. The mixture was stirred for 10 min and ice-water (40 g) was added. The crude product was filtered and washed with water to give compounds **7**. An analytical sample was recrystallized from the solvent indicated.

*4.3.1. 4-(Dimethylamino)pyridinium 5-fluoro-1,3-bis(phenoxycarbonyl)-1H-indol-2-olate (**7e**).* This compound was prepared according to the general procedure II using **6e** (3.91 g, 10 mmol) to give **7e** (4.70 g, 92%) as colourless crystals, mp 184–186 °C (acetonitrile). IR (KBr, cm^{-1}): 2795, 1715, 1628, 1570. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.18 (1H, s), 8.20 (2H, d, J=7.7 Hz), 7.60 (1H, d, J=9.0 Hz), 7.48–7.08 (10H, m), 7.32 (1H, d, J=2.4 Hz), 6.96 (2H, d, J=7.7 Hz), 6.49 (1H, d, J=9.6, 2.8 Hz), 3.17 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.3, 161.5 (d, J=248.0 Hz), 158.3, 157.5, 157.1, 152.2, 150.7 (d, J=9.3 Hz), 139.4, 129.7 (d, J=22.8 Hz), 129.5, 129.0, 126.4, 125.8, 124.0, 122.5, 122.0, 121.4, 115.4, 113.2 (d, J=9.3 Hz), 107.0, 103.4 (d, J=23.4 Hz), 102.9 (d, J=25.4 Hz), 80.4, 24.1. Anal. Calcd for $C_{29}H_{24}FN_3O_5$ (513.53): C 67.83, H 4.71, N 8.18%. Found: C 67.53, H 4.75, N 8.09%.

*4.3.2. 4-(Dimethylamino)pyridinium 6-fluoro-1,3-bis(phenoxycarbonyl)-1H-indol-2-olate (**7f**).* This compound was prepared according to the general procedure II using **6f** (3.93 g, 10 mmol) to give **7f** (3.41 g, 66%) as colourless crystals, mp 210–214 °C (ethanol). IR (KBr, cm^{-1}): 2776, 1732, 1672, 1621. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.19 (1H, s), 8.19 (2H, d, J=7.7 Hz), 7.53 (1H, td, J=6.0, 2.4 Hz), 7.40 (10H, m), 7.08 (1H, d, J=8.6 Hz), 6.97 (2H, d, J=7.7 Hz), 6.77 (1H, td, J=8.5, 2.6 Hz), 3.17 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.2, 162.8, 157.0, 156.8 (d, J=230.0 Hz), 152.4, 150.7 (d, J=10.3 Hz), 139.3, 130.3 (d, J=11.7 Hz), 129.6, 129.0, 125.8, 123.8, 122.5, 122.0, 116.5, 108.7 (d, J=21.0 Hz), 107.1, 100.7 (d, J=28.8 Hz), 78.8. Anal. Calcd for $C_{29}H_{24}FN_3O_5$ (513.53): C 67.83, H 4.71, N 8.18%. Found: C 67.56, H 4.69, N 8.39%.

*4.3.3. 4-(Dimethylamino)pyridinium 5-methoxy-1,3-bis(phenoxycarbonyl)-1H-indol-2-olate (**7g**).* This compound was prepared according to the general procedure II using **6g** (4.03 g, 10 mmol) to give **7g** (5.05 g, 96%) as colourless crystals, mp 189–190 °C (toluene). IR (KBr, cm^{-1}): 2814, 1715, 1674, 1622, 1584. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.18 (1H, s), 8.18 (2H, d, J=7.5 Hz), 7.54 (1H, d, J=8.6 Hz), 7.31 (10H, m), 7.24 (1H, d, J=2.6 Hz), 6.92 (2H, d,

J=7.4 Hz), 6.32 (1H, dd, J=8.6, 2.7 Hz), 3.76 (3H, s), 3.14 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.4, 156.9, 155.9, 152.4, 150.9, 150.6, 139.9, 132.6, 129.8, 129.6, 129.5, 129.0, 125.6, 124.4, 123.8, 122.5, 122.1, 121.8, 115.5, 113.0, 107.0, 103.6, 102.6, 80.2, 55.0. Anal. Calcd for $C_{30}H_{27}N_3O_6$ (525.57): C 68.56, H 5.18, N 8.00%. Found: C 68.70, H 5.23, N 8.06%.

4.4. General procedure III for the synthesis of compounds 10[19]

A solution of the DMAP salt of the 1,3-bis(phenoxycarbonyl)-1*H*-indol-2-olate (**7**, 4.0 mmol) and the corresponding amine (8.0 mmol) in DMF (10 mL) was stirred at room temperature for 2–4 h. The reaction mixture was poured onto ice-water (20 g) and stirred for 1 h. The crystalline product was filtered and washed with water to give compound compounds **10**. The compounds obtained could be used in the next step without further purification. An analytical sample was recrystallized from the solvent indicated.

*4.4.1. 4-(Dimethylamino)pyridinium 1-carbamoyl-5-chloro-3-(phenoxycarbonyl)-1H-indol-2-olate (**10a**).* A solution of the DMAP salt of the 1,3-bis(phenoxycarbonyl)-1*H*-indol-2-olate **7a** (2.12 g, 4.0 mmol) and ammonium carbonate (1.36 g, NH_3 content 10%, 8.0 mmol) in DMF (10 mL) was stirred at 45 °C for 2 h. The reaction mixture was poured onto ice-water (20 g) and stirred for 1 h. The crystalline product was filtered and washed with water to give **10a** (1.69 g, 93%) as colourless crystals, mp 186–187 °C (acetonitrile). IR (KBr, cm^{-1}): 3316, 1704, 1557, 1436. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.18 (1H, br s), 9.44 (1H, br s), 8.18 (2H, d, J=7.6 Hz), 7.99 (1H, d, J=8.5 Hz), 7.53 (1H, d, J=2.2 Hz), 7.37 (2H, m), 7.15 (1H, m), 7.09 (2H, d, J=7.6 Hz), 6.98 (1H, s), 6.96 (2H, J=7.6 Hz), 6.71 (1H, dd, J=8.5, 2.2 Hz), 3.16 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.7, 163.1, 157.1, 154.9, 152.1, 139.3, 131.5, 129.6, 129.0, 126.1, 124.1, 122.6, 117.4, 115.6, 114.3, 80.8. Anal. Calcd for $C_{23}H_{21}N_4O_4$ (452.90): C 61.00, H 4.67, Cl 7.83, N 12.37%. Found: C 60.92, H 4.66, Cl 7.81, N 12.44%.

*4.4.2. 4-(Dimethylamino)pyridinium 1-(benzylcarbamoyl)-5-chloro-3-(phenoxycarbonyl)-1H-indol-2-olate (**10h**).* This compound was prepared according to the general procedure III using **7a** and benzylamine to give **10h** (0.90 g, 43%) as colourless crystals, mp 202–205 °C (acetonitrile). IR (KBr, cm^{-1}): 3058, 1701, 1647, 1538, 1398. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.21 (1H, t, J=5.4 Hz), 8.24 (1H, d, J=8.8 Hz), 7.87 (2H, d, J=7.5 Hz), 7.73 (1H, d, J=2.2 Hz), 7.31 (11H, m), 6.94 (1H, dd, J=8.7, 2.4 Hz), 6.39 (2H, d, J=7.6 Hz), 4.60 (2H, d, J=5.4 Hz), 3.05 (6H, s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 163.0, 157.0, 154.5, 152.1, 139.7, 139.6, 131.4, 129.5, 129.1, 128.6, 127.4, 127.3, 127.0, 126.2, 124.1, 122.5, 117.5, 115.7, 114.2, 107.1, 80.9, 42.6. Anal. Calcd for $C_{30}H_{27}ClN_4O_4$ (543.03): C 66.36, H 5.01, Cl 6.53, N 10.32%. Found: C 66.08, H 5.13, Cl 6.51, N 10.48%.

*4.4.3. 4-(Dimethylamino)pyridinium 1-[(4-phenylpiperazin-1-yl)carbonyl]-5-chloro-3-(phenoxycarbonyl)-1H-indol-2-olate (**10i**).* This compound was prepared according to the general procedure III using **7a** and 1-phenylpiperazine to give **10i** (2.06 g, 86%) as colourless crystals, mp 160–163 °C (acetonitrile). IR (KBr, cm^{-1}): 3064, 1733, 1647, 1558, 1394. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.27 (1H, br s), 8.19 (2H, d, J=7.3 Hz), 7.45 (1H, d, J=1.5 Hz), 7.36 (2H, t, J=7.8 Hz), 7.22 (2H, t, J=7.8 Hz), 7.14 (1H, m), 7.08 (2H, d, J=7.8 Hz), 6.95 (2H, d J=7.3 Hz), 6.94 (2H, d, J=7.1 Hz), 6.84 (1H, d, J=8.2 Hz), 6.79 (1H, m), 6.66 (1H, dd, J=8.2, 2.1 Hz), 3.79 (2H, br s), 3.56 (2H, br s), 3.27 (4H, m), 3.16 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.7, 157.4, 152.5, 152.3, 151.0, 149.6, 140.7, 139.8, 130.3, 129.5, 129.1, 129.0, 128.9, 127.5, 127.4, 127.3, 125.0, 124.7, 123.8, 122.6, 119.6, 119.4, 116.7, 116.1, 116.0, 115.8, 115.3, 113.3, 113.2, 110.0, 107.1, 79.5, 35.9. Anal. Calcd for $C_{33}H_{32}ClN_5O_4$ (598,11): C 66.27, H 5.39, Cl 5.93, N 11.71%. Found: C 66.10, H 5.57, Cl 6.19, N 11.48%.

*4.4.4. 4-(Dimethylamino)pyridinium 6-chloro-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10j**).* This compound was prepared according to the general procedure III using **7b** and piperidine to give **10j** (1.88 g, 90%) as colourless crystals, mp 183–185 °C (acetonitrile). IR (KBr, cm^{-1}): 3066, 2942, 1700, 1493. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 13.21 (1H, br s), 8.19 (2H, d, J=7.3 Hz), 7.48 (1H, d, J=7.9 Hz), 7.36 (2H, t, J=7.8 Hz), 7.15 (1H, t, J=7.3 Hz), 7.07 (2H, d, J=7.8Hz), 6.98 (2H, d, J=7.3 Hz), 6.69 (2H, d, J=8.4 Hz), 3.55 (2H, br s), 3.29 (2H, br s), 3.15 (6H, s), 1.59 (6H, br s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.0, 154.0, 140.0, 128.9, 123.7, 122.5, 119.8, 115.3, 108.5, 107.1, 24.0. 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 64.29, H 5.61, Cl 6.89, N 10.42%.

*4.4.5. 4-(Dimethylamino)pyridinium 3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10k**).* This compound was prepared according to the general procedure III using **7c** and piperidine to give **10k** (1.85 g, 95%) as colourless crystals, mp 174–176 °C (acetonitrile). IR (KBr, cm^{-1}): 2931, 1696, 1646, 1546. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 13.33 (1H, br s), 8.18 (2H, d, J=7.2 Hz), 7.48 (1H, d, J=7.6 Hz), 7.34 (2H, t, J=7.7 Hz), 7.12 (1H, m), 7.07 (2H, d, J=7.6 Hz), 6.92 (2H, d, J=7.2 Hz), 6.76 (2H, m), 6.67 (1H, t, J=7.6Hz), 3.70 (2H, br s), 3.40 (2H, br s), 3.15 (6H, s), 1.61 (6H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.4, 154.0, 142.0, 141.0, 129.5, 128.9, 127.6, 123.6, 122.5, 120.2, 118.9, 117.6, 115.3, 108.5, 107.0, 44.4, 26.1, 25.4, 24.1. Anal. Calcd for $C_{28}H_{30}N_4O_4$ (486.58): C 69.12, H 6.21, N 11.51%. Found: C 69.13, H 6.42, N 11.14%.

*4.4.6. 4-(Dimethylamino)pyridinium 5-nitro-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10l**).* This compound was prepared in a one-pot procedure starting from **6d** (1.67 g, 4.0 mmol), treated in a solution of DMF (10 mL) with DMAP (0.49 g, 4.0 mmol) at 0–2 °C. The mixture was stirred for 10 min, then piperidine (0.68 g, 0.79 mL, 8.0 mmol) was added and stirred for 1 h at room temperature. It was poured onto a mixture of ice and water (20 g) and stirred for 1 h. The crystalline product was filtered and washed with water to give **10l** (1.02 g, 48%) as yellow crystals, mp 205–206 °C (acetonitrile). IR (KBr, cm^{-1}): 3058, 2946, 1691, 1515. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.34 (1H, d, J=2.4 Hz), 8.18 (2H, d, J=7.6 Hz), 7.66 (1H, dd, J=8.4, 2.4 Hz), 7.41 (2H, m), 7.16 (3H, m), 6.94 (3H, d, J=8.6 Hz), 3.70 (2H, br s), 3.40 (2H, br s), 3.15 (6H, s), 1.90–1.30 (6H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.3, 163.1, 157.0, 152.1, 151.6, 141.7, 139.3, 136.7, 130.3, 129.1, 124.2, 122.6, 114.6, 111.1, 107.7, 107.1, 79.7, 47.8, 44.4, 26.3, 25.5, 24.0. Anal. Calcd for $C_{28}H_{29}N_5O_6$ (531.55): C 63.23, H 5.50, N 13.18%. Found: C 63.07, H 5.52, N 13.16%.

*4.4.7. 4-(Dimethylamino)pyridinium 5-fluoro-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10m**).* This compound was prepared according to the general procedure III using **7e** and piperidine to give **10m** (1.45 g, 72%) as colourless crystals, mp 179–180 °C (acetonitrile). IR (KBr, cm^{-1}): 2937, 1698, 1648, 1558, 1398. ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.33 (1H, br s), 8.19 (2H, d, J=7.6 Hz), 7.34 (2H, t, J=7.7 Hz), 7.19 (1H, dd, J=10.7, 2.6 Hz), 7.14 (1H, t, J=7.7 Hz), 7.08 (2H, d, J=7.6 Hz), 6.96 (2H, d, J=7.6 Hz), 6.76 (1H, dd, J=8.2, 5.0 Hz), 6.41 (1H, td, J=8.3, 2.7 Hz), 3.52 (4H, br s), 3.17 (6H, s), 1.55 (6H, br s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.3, 158.3 (d, J=230.3 Hz), 156.8, 152.4 (d, J=22.6 Hz), 140.1, 129.0, 128.0, 123.9, 122.5, 108.8, 107.1, 103.2 (d, J=24.0 Hz), 24.0. Anal. Calcd for $C_{28}H_{29}FN_4O_4$ (504.57): C 66.65, H 5.79, N 11.10%. Found: C 66.40, H 5.58, N 10.84%.

*4.4.8. 4-(Dimethylamino)pyridinium 6-fluoro-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10n**).* This compound

was prepared according to the general procedure III using **7f** (2.06 g, 4.0 mmol) and piperidine (0.68 g, 0.8 mL, 8.0 mmol) to give **10n** (1.15 g, 57%) as colourless crystals, mp 173–176 °C (acetonitrile). IR (KBr, cm^{-1}): 2945, 1707, 1655, 1632, 1481. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.34 (1H, s), 8.19 (2H, d, J=7.6 Hz), 7.40 (1H, dd, J=8.8, 6.0 Hz), 7.34 (2H, m), 7.10 (3H, m), 6.96 (2H, d, J=7.6 Hz), 6.58 (2H, m), 3.39 (4H, br s), 3.17 (6H, s), 1.59 (6H, br s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.9, 156.7 (d, J=230.2 Hz), 155.6, 152.4 (d, J=16.3 Hz), 139.9, 129.5, 128.9, 123.6, 122.5, 107.1, 106.1 (d, J=21.0 Hz), 96.5 (d, J=27.0 Hz), 78.6, 58.0, 34.0, 24.1. Anal. Calcd for $C_{28}H_{29}FN_4O_4$ (504.57): C 66.65, H 5.79, N 11.10%. Found: C 66.55, H 5.59, N 10.98%.

*4.4.9. 4-(Dimethylamino)pyridinium 5-methoxy-3-(phenoxycarbonyl)-1-(piperidin-1-ylcarbonyl)-1H-indol-2-olate (**10o**).* This compound was prepared according to the general procedure III using **7g** and piperidine to give **10o** (0.70 g, 34%) as colourless crystals, mp 136–138 °C (ethyl acetate). IR (KBr, cm^{-1}): 2939, 1693, 1644, 1561, 1398. ^1H NMR (DMSO-d_6, 400 MHz) δ 13.30 (1H, br s), 8.19 (2H, d, J=7.6 Hz), 7.36 (2H, m), 7.11 (4H, m), 6.96 (2H, d, J=7.6 Hz), 6.67 (1H, d, J=8.3 Hz), 6.25 (1H, dd, J=8.3, 2.6 Hz), 3.65 (3H, s), 3.39 (4H, br s), 3.17 (6H, s), 1.59 (6H, br s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.2, 157.5, 156.8, 154.5, 152.9, 152.6, 140.2, 129.5, 128.9, 126.4, 123.6, 122.5, 118.9, 115.4, 80.1, 59.9, 55.2, 25.9, 24.1, 23.8, 20.9, 14.2. Anal. Calcd for $C_{29}H_{32}N_4O_5$ (516.6): C 67.43, H 6.24, N 10.85%. Found: C 67.38, H 6.34, N 10.53%.

4.5. General procedures IV/A–IV/C for the synthesis of compounds 3

General procedure IV/A (route A). A suspension of compound **10** in a mixture of water (2 mL/mmol **10**) and concentrated HCl (82 μL/mmol **10**) was stirred for 0.5–3 h at room temperature or at 60–80 °C. The crystalline product was filtered and washed with water to give compound **3**. An analytical sample was recrystallized from the solvent indicated.

General procedure IV/B (route B). To a solution of 4-(dimethylamino)pyridinium 1,3-bis(phenoxycarbonyl)-1*H*-indol-2-olate (**7**) in DMF (2 mL/mmol **7**) the corresponding amine (2.0 equiv) was added and the solution thus obtained was stirred at room temperature for 2–4 h. It was poured onto a mixture of ice-water (2 g/mmol **7**) and concentrated HCl (82 μL/mmol **7**), and stirred for 2 h at room temperature. The crystalline product was filtered and washed with water to give compound **3**. An analytical sample was recrystallized from the solvent indicated.

General procedure IV/C (route C). To a solution of 1-phenoxycarbonyl-2-(phenoxycarbonyloxy)indole (**6**) in DMF (1 mL/mmol **6**) was added a solution of DMAP (1.0 equiv) in DMF (1 mL/mmol **6**) at 0–2 °C. The mixture was stirred for 10 min, the corresponding amine (2.0 equiv) was added and the solution thus obtained was stirred at room temperature for 2–4 h. It was poured onto a mixture of ice-water (200 g) and concentrated HCl (82 μL/mmol **6**), and stirred for 1–3 h at room temperature or at 50–100 °C. The crystalline product was filtered and washed with water to give compound **3**. An analytical sample was recrystallized from the solvent indicated.

*4.5.1. 5-Chloro-2-oxo-2,3-dihydro-1H-indole-1-carboxamide (**3a**). Method 1.* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and ammonium carbonate (3.40 g, NH_3 content 10%, 20 mmol), and stirred with aqueous HCl at 60 °C for 3 h to give **3a** (1.03 g, 49%) as colourless crystals, mp 206–209 °C (acetonitrile) (lit.[12] mp 211 °C). IR (KBr, cm^{-1}): 3368, 1740, 1716, 1584, 1470, 1375. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.03 (1H, d, J=8.7 Hz), 7.97 (1H, br s), 7.77 (1H, br s), 7.39 (1H, s), 7.34 (1H, dd, J=8.7, 2.2 Hz), 3.85 (2H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.6, 152.0, 140.5, 128.0, 127.4, 126.8, 124.3, 116.8, 36.6. Anal. Calcd for $C_9H_7ClN_2O_2$ (210.62): C 51.32, H 3.35, Cl 16.83, N 13.30%. Found: C 51.29, H 3.37, Cl 16.69, N 13.37%. *Method 2.* This compound was also prepared according to the general procedure IV/A using **10a** (0.91 g, 2 mmol), and stirred with aqueous HCl at 55–60 °C for 3 h to give **3a** (0.40 g, 95%) as colourless crystals, identical with compound obtained by *Method 1.*

*4.5.2. 5-Chloro-1-(pyrrolidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3b**).* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and pyrrolidine (1.44 g, 1.7 mL, 20 mmol), and stirred with aqueous HCl at room temperature for 1 h to give **3b** (1.88 g, 71%) as colourless crystals, mp 159–162 °C (ethyl acetate/hexane). IR (KBr, cm^{-1}): 2942, 1736, 1688, 1588. ^1H NMR (DMSO-d_6, 500 MHz) δ 7.27 (1H, d, J=2.1 Hz), 7.18 (2H, m), 3.65 (2H, t, J=6.4 Hz), 3.61 (2H, s), 3.53 (2H, t, J=6.4 Hz), 1.97 (4H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.0, 149.5, 140.3, 128.9, 128.0, 125.6, 124.6, 113.7, 47.7, 47.2, 36.0, 25.8, 24.5. Anal. Calcd for $C_{13}H_{13}ClN_2O_2$ (264.72): C 58.98, H 4.93, Cl 13.39, N 10.58%. Found: C 58.65, H 4.93, Cl 13.30, N 10.54%.

*4.5.3. 5-Chloro-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3c**).* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and piperidine (1.70 g, 2.0 mL, 20 mmol), and stirred with aqueous HCl at room temperature for 1 h to give **3c** (2.40 g, 86%) as colourless crystals, mp 112–114 °C (ethyl acetate). IR (KBr, cm^{-1}): 2949, 1744, 1684, 1608. ^1H NMR (DMSO-d_6, 500 MHz) δ 7.25 (2H, m), 7.05 (1H, d, J=8.1 Hz), 3.67 (2H, s), 3.61 (2H, s), 3.38 (2H, s), 1.69 (6H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.1, 150.0, 140.6, 128.5, 127.8, 125.6, 124.5, 113.2, 48.2, 45.0, 35.8, 26.2, 25.3, 24.0. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.75): C 60.32, H 5.42, Cl 12.72, N 10.05%. Found: C 60.13, H 5.39, Cl 12.65, N 9.93%.

*4.5.4. 5-Chloro-1-(morpholin-4-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3d**). Method 1.* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and morpholine (1.74 g, 1.70 mL, 20 mmol), and stirred with aqueous HCl at room temperature for 1 h to give **3d** (1.43 g, 51%) as colourless crystals, mp 149–150 °C (ethyl acetate). IR (KBr, cm^{-1}): 2930, 1733, 1681, 1613. ^1H NMR (DMSO-d_6, 500 MHz) δ 7.29 (1H, d, J=2.1 Hz), 7.26 (1H, m), 7.14 (1H, d, J=8.2 Hz), 3.78 (4H, s), 3.63 (2H, s), 3.50 (4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.3, 150.1, 140.4, 129.2, 128.2, 125.6, 124.7, 113.9, 66.6, 36.0. Anal. Calcd for $C_{13}H_{13}ClN_2O_3$ (280.72): C 55.62, H 4.67, Cl 12.63, N 9.98%. Found: C 55.31, H 4.70, Cl 12.41, N 9.71%. *Method 2.* This compound was also prepared according to the general procedure IV/A using **10d** (3.14 g, 6 mmol), and stirred with aqueous HCl at room temperature for 1 h to give **3d** (1.10 g, 65%) as colourless crystals, identical with compound obtained by *Method 1.*

*4.5.5. 5-Chloro-1-[(4-pyrimidin-2-ylpiperazin-1-yl)carbonyl]-1,3-dihydro-2H-indol-2-one (**3e**). Method 1.* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and 1-(pyrimidin-2-yl)piperazine (3.28 g, 20 mmol), and stirred with aqueous HCl at 70–80 °C for 2 h to give **3e** (2.43 g, 68%) as colourless crystals, mp 180–181 °C (ethyl acetate). IR (KBr, cm^{-1}): 2917, 1745, 1691, 1589, 1545. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.33 (2H, d, J=4.8 Hz), 7.28 (1H, d, J=1.8 Hz), 7.26 (1H, m), 7.13 (1H, d, J=8.8 Hz), 6.55 (1H, t, J=4.8 Hz), 3.96 (4H, s), 3.80 (2H, s), 3.65 (2H, s), 3.55 (2H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 190.4, 172.3, 161.4, 157.7, 150.2, 140.4, 129.0, 128.1, 125.7, 124.6, 113.9, 110.5, 43.5, 36.0. Anal. Calcd for $C_{17}H_{16}ClN_5O_2$ (357.80): C 57.07, H 4.51, Cl 9.91, N 19.57%. Found: C 57.17, H 4.53, Cl 9.67, N 19.21%. *Method 2.* This compound was also prepared according to the general procedure IV/A using **10e** (0.90 g, 1.5 mmol), and stirred with aqueous HCl at

70–80 °C for 2 h to give **3e** (0.36 g, 67%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.6. 5-Chloro-2-oxo-N-propyl-2,3-dihydro-1H-indole-1-carboxamide (**3f**). Method 1.* This compound was prepared according to the general procedure IV/A using **10f** (1.24 g, 2.5 mmol), and stirred with aqueous HCl at 80 °C for 2 h to give **3f** (0.63 g, 99%) as colourless crystals, mp 104–105 °C (ethanol). IR (KBr, cm^{-1}): 3314, 2967, 1750, 1703, 1534. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.51 (1H, t, J=5.5 Hz), 8.01 (1H, d, J=8.7 Hz), 7.39 (1H, d, J=2.3 Hz), 7.34 (1H, dd, J=8.8, 2.3 Hz), 3.85 (2H, s), 3.25 (2H, q, J=6.9 Hz), 1.55 (2H, sext, J=7.3 Hz), 0.90 (3H, t, J=7.3 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.7, 151.5, 140.5, 128.0, 127.3, 126.8, 124.3, 116.6, 41.1, 36.6, 22.4, 11.3. Anal. Calcd for $C_{12}H_{13}ClN_2O_2$ (252.70): C 57.04, H 5.19, Cl 14.03, N 11.09%. Found: C 56.83, H 5.04, Cl 14.16, N 11.00%. *Method 2*. This compound was also prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and propylamine (1.65 mL, 1.18 g, 20 mmol), and stirred with aqueous HCl at 80 °C for 2 h to give **3f** (2.5 g, 97%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.7. N-Benzyl-5-chloro-N-methyl-2-oxo-2,3-dihydro-1H-indole-1-carboxamide (**3g**). Method 1.* This compound was prepared according to the general procedure IV/C using **6a** (0.82 g, 2.0 mmol) and *N*-benzylmethylamine (0.48 g, 0.51 mL, 4.0 mmol), and stirred with aqueous HCl at 80–100 °C for 2 h to give **3g** (0.13 g, 34%) as yellow crystals, mp 130–132 °C (acetonitrile). IR (KBr, cm^{-1}): 2941, 1735, 1693, 1476. ^1H NMR (DMSO-d_6, 500 MHz) δ 7.44–7.18 (7H, m), 7.05 (1H, d, J=8.2 Hz), 4.70 (2H, br s), 3.81 (2H, br s), 2.94 (3H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.7, 151.6, 140.6, 136.5, 128.7, 127.5, 127.4, 127.3, 124.8, 113.1, 53.8, 51.8, 35.9. Anal. Calcd for $C_{17}H_{15}ClN_2O_2$ (314.77): C 64.87, H 4.80, Cl 11.26, N 8.90%. Found: C 64.53, H 4.94, Cl 11.16, N 8.97%. *Method 2*. This compound was also prepared according to the general procedure IV/A using **10g** (2.23 g, 4 mmol), and stirred with aqueous HCl at 70–80 °C for 2 h to give **3g** (0.50 g, 40%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.8. N-Benzyl-5-chloro-2-oxo-2,3-dihydro-1H-indole-1-carboxamide (**3h**). Method 1.* This compound was prepared according to the general procedure IV/A using **10h** (0.50 g, 0.9 mmol), and stirred with aqueous HCl at 60–80 °C for 2 h to give **3h** (0.18 g, 67%) as colourless crystals, mp 141–142 °C (acetonitrile). IR (KBr, cm^{-1}): 2944, 1742, 1730, 1689, 1472. ^1H NMR (DMSO-d_6, 500 MHz) δ 8.9 (1H, br s), 8.21 (1H, d, J=8.8 Hz), 7.37 (4H, m), 7.32–7.27 (2H, m), 7.24 (1H, m), 4.58 (2H, s), 3.71 (2H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.5, 151.9, 140.2, 137.8, 129.9, 128.7, 128.4, 127.6, 127.5, 124.6, 124.1, 117.6, 43.8, 36.7. Anal. Calcd for $C_{16}H_{13}ClN_2O_2$ (300.75): C 63.90, H 4.36, Cl 11.79, N 9.31%. Found: C 63.65, H 4.41, Cl 11.86, N 9.34%. *Method 2*. This compound was also prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and benzylamine (2.14 g, 2.2 mL, 20 mmol), and stirred with aqueous HCl at 70–80 °C for 2 h to give **3h** (2.80 g, 93%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.9. 5-Chloro-1-[(4-phenylpiperazin-1-yl)carbonyl]-1,3-dihydro-2H-indol-2-one (**3i**).* This compound was prepared according to the general procedure IV/C using **6a** (4.08 g, 10 mmol) and 1-phenylpiperazine (3.24 g, 3.0 mL, 20 mmol), and stirred with aqueous HCl at 70–80 °C for 2 h to give **3i** (1.64 g, 46%) as colourless crystals, mp 189–190 °C (ethyl acetate). IR (KBr, cm^{-1}): 2922, 2825, 1736, 1677, 1598. ^1H NMR (DMSO-d_6, 500 MHz) δ 7.26 (4H, m), 7.10 (1H, d, J=8.3 Hz), 6.92 (3H, m), 3.89 (4H, s), 3.65 (2H, s), 3.28 (4H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.5, 150.1, 140.5, 129.4, 129.2, 128.3, 125.7, 124.8, 117.0, 114.0, 36.0. Anal. Calcd for $C_{19}H_{18}ClN_3O_2$ (355.81): C 64.13, H 5.10, Cl 9.96, N 11.81%. Found: C 64.45, H 5.25, Cl 9.59, N 11.60%. *Method 2*. This compound was also prepared according to the general procedure IV/A using **10i** (0.60 g, 1 mmol), and stirred with aqueous HCl at 70–80 °C for 2 h to give **3i** (0.35 g, 99%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.10. 6-Chloro-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3j**). Method 1.* This compound was prepared according to the general procedure IV/B using **7b** (0.79 g, 1.5 mmol) and piperidine (0.26 g, 0.30 mL, 3.0 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3j** (0.38 g, 91%) as colourless crystals, mp 121–122 °C (ethanol). IR (KBr, cm^{-1}): 2941, 1741, 1685, 1610, 1437. ^1H NMR (DMSO-d_6, 200 MHz) δ 7.32 (1H, d, J=8.1 Hz), 7.13 (1H, dd, J=8.1, 1.8 Hz), 7.03 (1H, d, J=1.8 Hz), 3.73 (2H, br s), 3.57 (2H, br s), 3.36 (2H, br s), 1.65–1.40 (6H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 172.9, 149.3, 143.2, 131.9, 126.0, 124.2, 122.7, 111.7, 47.7, 44.5, 35.9, 26.2, 25.3, 23.7. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$ (278.74): C 60.33, H 5.42, Cl 12.72, N 10.05%. Found: C 60.06, H 5.50, Cl 12.75, N 10.03%. *Method 2*. This compound was also prepared according to the general procedure IV/C using **6b** (4.08 g, 10 mmol) and piperidine (1.70 g, 2.0 mL, 20 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3j** (2.40 g, 86%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.11. 1-(Piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3k**). Method 1.* This compound was prepared according to the general procedure IV/B using **7c** (1.0 g, 2.0 mmol) and piperidine (0.34 g, 0.4 mL, 4.0 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3k** (0.21 g, 43%) as colourless crystals, mp 117–122 °C (ethanol). IR (KBr, cm^{-1}): 2944, 1732, 1675, 1610, 1437. ^1H NMR (DMSO-d_6, 200 MHz) δ 7.30 (1H, d, J=7.0 Hz), 7.26 (1H, t, J=7.9 Hz), 7.07 (1H, t, J=7.5 Hz), 6.97 (1H, d, J=7.9 Hz), 3.80–3.50 (4H, m), 3.36 (2H, br s), 1.65–1.40 (6H, m). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 173.0, 149.7, 142.0, 127.6, 125.1, 124.6, 123.0, 111.3, 47.6, 44.4, 35.7, 26.3, 25.3, 23.8. Anal. Calcd for $C_{14}H_{16}N_2O_2$ (244.30): C 68.83, H 6.60, N 11.47%. Found: C 68.65, H 6.68, N 11.50%. *Method 2*. This compound was also prepared according to the general procedure IV/C using **6c** (1.87 g, 5 mmol) and piperidine (0.85 g, 1.0 mL, 10 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3k** (0.56 g, 46%) as colourless crystals, identical with compound obtained by *Method 1*. *Method 3*. This compound was also prepared according to the general procedure IV/A using **10k** (0.49 g, 1 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3k** (0.18 g, 74%) as colourless crystals, identical with compound obtained by *Method 1*.

*4.5.12. 5-Nitro-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3l**). Method 1.* This compound was prepared according to the general procedure IV/C using **6d** (8.37 g, 20 mmol) and piperidine (3.40 g, 4.0 mL, 40 mmol), and stirred with aqueous HCl at 50–55 °C for 1 h to give **3l** (5.0 g, 86%) as pale brown crystals, mp 160–162 °C (ethanol). IR (KBr, cm^{-1}): 2948, 1762, 1693. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.22 (1H, dd, J=8.8, 2.2 Hz), 8.16 (1H, br s), 7.25 (1H, d, J=8.8 Hz), 3.74 (4H, br s), 3.40 (2H, br s), 1.95–1.40 (6H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 149.1, 147.6, 143.8, 125.0, 124.8, 120.1, 112.2, 48.4, 45.3, 35.6, 26.3, 25.3, 24.0. Anal. Calcd for $C_{14}H_{15}N_3O_4$ (289.30): C 58.12, H 5.23, N 14.53%. Found: C 58.23, H 5.39, N 14.15%. *Method 2*. This compound was also prepared according to the general procedure IV/A using **10l** (11.15 g, 21 mmol), and stirred with aqueous HCl at 65 °C for 0.5 h to give **3l** (6.0 g, 99%) as yellow crystals, identical with compound obtained by *Method 1*.

*4.5.13. 5-Fluoro-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3m**).* This compound was prepared according to the general

procedure IV/C using **6e** (1.17 g, 3.0 mmol) and piperidine (0.51 g, 0.60 mL, 6.0 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3m** (0.58 g, 73%) as colourless crystals, mp 114–117 °C (obtained by chromatography on silica gel, eluent: hexane/ethyl acetate 7:3). IR (KBr, cm^{-1}): 2950, 1736, 1681, 1483, 1430, 1167. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.07 (1H, m), 6.98 (2H, m), 3.69 (2H, m), 3.61 (2H, s), 3.40 (2H, br s), 1.69 (6H, br s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4, 159.3 (d, J=241.6 Hz), 150.2, 138.1 (d, J=2.5 Hz), 125.6 (d, J=8.8 Hz), 114.5 (d, J=23.4 Hz), 113.3 (d, J=8.3 Hz), 111.9 (d, J=24.8 Hz), 48.3, 45.1, 36.3 (d, J=1.5 Hz), 26.3, 25.4, 24.1. Anal. Calcd for $C_{14}H_{15}FN_2O_2$ (262.29): C 64.11, H 5.76, N 10.68%. Found: C 63.75, H 5.78, N 10.65%.

*4.5.14. 6-Fluoro-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3n**).* This compound was prepared according to the general procedure IV/C using **6f** (1.61 g, 4.0 mmol) and piperidine (0.68 g, 0.80 mL, 8.0 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3n** (0.78 g, 75%) as colourless crystals, mp 139–142 °C (ethyl acetate/hexane). IR (KBr, cm^{-1}): 2927, 1737, 1679, 1434. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.18 (1H, dd, J=8.2, 5.4 Hz), 6.90 (1H, dd, J=9.2, 2.4 Hz), 6.78 (1H, td, J=9.4, 2.4 Hz), 3.70 (2H, m), 3.58 (2H, s), 3.40 (2H, br s), 1.69 (6H, br s). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 162.6 (d, J=245.1 Hz), 149.8, 143.3 (d, J=12.1 Hz), 125.2 (d, J=9.3 Hz), 119.3 (d, J=3.4 Hz), 109.9 (d, J=22.5 Hz), 101.0 (d, J=28.3 Hz), 48.4, 45.2, 35.5, 26.4, 25.4, 24.1. Anal. Calcd for $C_{14}H_{15}FN_2O_2$ (262.29): C 64.11, H 5.76, N 10.68%. Found: C 63.83, H 5.86, N 10.74%.

*4.5.15. 5-Methoxy-1-(piperidin-1-ylcarbonyl)-1,3-dihydro-2H-indol-2-one (**3o**).* This compound was prepared according to the general procedure IV/C using **6g** (1.57 g, 4.0 mmol) and piperidine (0.68 g, 0.80 mL, 8.0 mmol), and stirred with aqueous HCl at room temperature for 2 h to give **3o** (0.98 g, 88%) as colourless crystals, mp 81–84 °C (obtained by chromatography on silica gel, eluent: hexane/ethyl acetate 7:3). IR (KBr, cm^{-1}): 2941, 1736, 1718, 1700, 1487, 1425. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.05 (1H, d, J=8.6 Hz), 6.85 (1H, d, J=2.2 Hz), 6.81 (1H, dd, J=8.6, 2.2 Hz), 3.79 (3H, s), 3.68 (2H, m), 3.59 (2H, s), 3.40 (2H, br s), 1.68 (6H, m). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.8, 157.3, 151.3, 136.5, 126.1, 113.6, 111.8, 56.1, 48.6, 45.4, 36.8, 26.6, 25.7, 24.4. Anal. Calcd for $C_{15}H_{18}N_2O_3$ (274.32): C 65.68, H 6.61, N 10.21%. Found: C 65.45, H 6.59, N 10.24%.

References and notes

1. Andreani, A.; Rambaldi, M. *J. Heterocycl. Chem.* **1988**, *25*, 1519.
2. Oezcan, S.; Balci, M. *Tetrahedron* **2008**, *64*, 5531.
3. Blizzard, A. T.; Margiatto, G.; Mrozik, H.; Schaeffer, J. M.; Fisher, M. H. *Tetrahedron Lett.* **1991**, *32*, 2441.
4. Fulton, J. B.; Warkentin, J. *Can. J. Chem.* **1987**, *65*, 1177.
5. Becker, D. P.; Flynn, D. L.; Moormann, A. E.; Nosal, R.; Villamil, C. I.; Loeffler, R.; Gullikson, G. W.; Moummi, Ch.; Yang, D.-C. *J. Med. Chem.* **2006**, *49*, 1125.
6. 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.
7. Sun, L.; Tran, N.; Tang, F.; App, H.; Hirth, P.; McMahon, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588.
8. Kadin, S. B. EP 208510, 1986; *Chem. Abstr.* **1987**, *106*, 138254.
9. Kadin, S. B. U.S. Patent 4,725,616, 1987; *Chem. Abstr.* **1989**, *110*, 23728.
10. Kadin, S. B. U.S. Patent 4,730,004, 1988; *Chem. Abstr.* **1989**, *110*, 23729.
11. Kadin, S. B. EP 153818, 1985; *Chem. Abstr.* **1986**, *104*, 88427u.
12. Crawford, Th. Ch. EP 155828, 1985; *Chem. Abstr.* **1986**, *104*, 109466y.
13. (a) Robinson, C. *Drugs Future* **1990**, *15*, 898; (b) *Drugs Future* **1993**, *18*, 875.
14. Robinson, R. P.; Donahue, K. M. *J. Heterocycl. Chem.* **1994**, *31*, 1541.
15. Blaskó, G.; Lukács, Gy.; Reiter, J.; Flórián, E.; Porcs-Makkay, M.; Mezei, T.; Simig, Gy. WO 9736895, 1997; *Chem. Abstr.* **1997**, *127*, 318879.
16. Porcs-Makkay, M.; Simig, Gy *Org. Process Res. Dev.* **2000**, *4*, 10.
17. Porcs-Makkay, M.; Simig, Gy *J. Heterocycl. Chem.* **2001**, *38*, 451.
18. Porcs-Makkay, M.; Volk, B.; Kapiller-Dezsöfi, R.; Mezei, T.; Simig, Gy *Monatsh. Chem.* **2004**, *135*, 697.
19. Porcs-Makkay, M.; Volk, B.; Mucsi, Z.; Simig, Gy *Tetrahedron* **2010**, *66*, 7017.
20. Kadin, S. B. EP 156603, 1985; *Chem. Abstr.* **1986**, *104*, 109468a.
21. Kelly, S. E. U.S. Patent 4,952,703, 1989; *Chem. Abstr.* **1991**, *114*, 42571q.
22. Gruber, J. M. WO 9520574, 1994; *Chem. Abstr.* **1995**, *123*, 339735g.
23. DeMello, K. L.; Bronk, B. S.; Crosson, R. M. U.S. Patent 2003/0207897, 2003; *Chem. Abstr.* **2003**, *139*, 350756.
24. McConnel, D.; Steurer, S.; Krist, B.; Weyer-Czernilofsky, U.; Impagnatiello, M.; Treu, M.; Kauffmann-Hefner, I.; Garin-Chesa, P.; Schnapp, A. EP 1598353, 2005; *Chem. Abstr.* **2005**, *144*, 6787.
25. Nadler, G.; Martin, M.; Zimmermann, R. EP 381374, 1990; *Chem. Abstr.* **1991**, *114*, 62126.
26. Martin, M.; Nadler, G.; Zimmermann, R. EP 303418, 1989; *Chem. Abstr.* **1989**, *111*, 97293.
27. Porcs-Makkay, M.; Volk, B.; Simig, Gy.; unpublished results.
28. Giraud, I.; Rapp, M.; Dupuy, J.-M.; Maurizis, J.-C.; Madelmont, J.-C. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 297.
29. No yield given in: Madelmont, J. -C.; Giraud, I.; Nicolas, C.; Maurizis, J. -C.; Rapp, M.; Ollier, M.; Renard, P.; Caignard, D. -H. WO 2001000621, 2001; *Chem. Abstr.* **2001**, *134*, 71584.
30. Porcs-Makkay, M.; Kálmán, A.; Argay, Gy.; Simig, Gy *Tetrahedron* **2000**, *56*, 5893.