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Received August 24, 2000

A new synthesis of oxindole-1-carboxamides was elaborated by the reaction of oxindole-1-phenylcarboxylate with various amines. This method also permitted the preparation of *N,N*-disubstituted oxindole-1-carboxamides.

J. Heterocyclic Chem., **38**, 451 (2001).

Oxindole-1-carboxamides **1** are a new class of analgesic, anti-inflammatory and antiarthritic agents [1,2,3]. An outstanding member of this group is tenidap (**2**) [4,5]. The compounds of formula **1** were prepared from oxindoles **3** by attaching the appropriate substituents to the 1- and 3-position in either order [6,7]. The 1-carbamoyl moiety was introduced exclusively by treating an *N*-unsubstituted oxindole **3** with an alkyl, aryl or acyl isocyanate. Thus, the 1-carbamoyl moiety of tenidap (**2**) was introduced by reacting the corresponding *N*-unsubstituted oxindole with chlorosulfonyl isocyanate followed by hydrolysis of the *N*-chlorosulfonyl group [4].

The use of isocyanates for the introduction of the 1-carbamoyl moiety has two major disadvantages: relatively few organic isocyanates are commercially available and *N,N*-disubstituted oxindole-1-carboxamides can not be synthesised by this method.

Recently we elaborated a new practical synthesis of tenidap (**2**) [8,9]. We were able to prepare the key-intermediate **4** in high yield [10,11] and introduce the 1-carbamoyl group by ammonolysis of the phenoxycarbonyl moiety, thus avoiding the use of chlorosulfonyl isocyanate. Here we report the reactions of 5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-phenoxycarbonyl-2,3-

Scheme 1

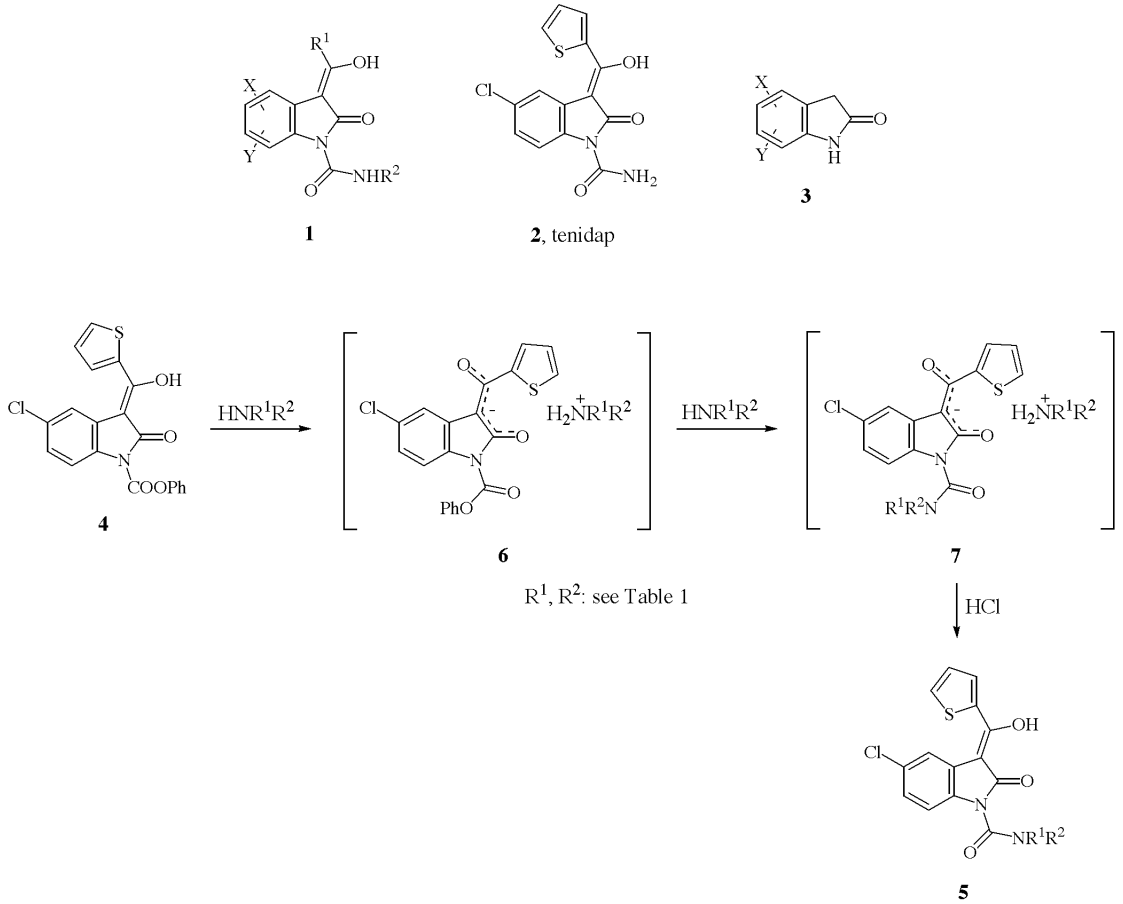
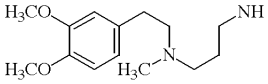
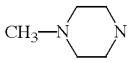
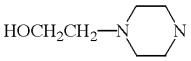
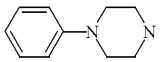
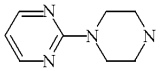
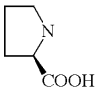


Table 1

	R^1R^2N
5a	CH_3NH
5b	C_2H_5NH
5c	$(CH_3)_2NCH_2CH_2NH$
5d	
5e	$(CH_3)_2N$
5f	$C_6H_5CH_2NCH_3$
5g	
5h	
5i	
5j	
5k	
5l	
5m	
5n	
5o	$HOOCCH_2NH$
5p	CH_3OOCCH_2NH
5r	

dihydro-indole (**4**) with various primary and secondary amines providing the corresponding 1-carbamoyl derivatives **5**. *N*,*N*-Disubstituted-oxindole-1-carboxamides are also available by our method.

We demonstrated, that in the course of the ammonolysis of compound **4** to tenidap (**2**) intermediate salt **6** (R^1 = R^2 = H) is formed in the first step (Scheme 1) [9], therefore two equivalents of ammonia were required for the transformation and the product was obtained after acidic treatment of enolate salt **7** (R^1 = R^2 = H). Aminolysis of compound **4** with various amines is expected to follow a similar pathway: aminolysis of the ester group is preceded by the formation of enolate salt **6** and final product **5** is obtained by acidification of enolate salt **7**. Therefore at least two equivalents of the amine have to be used in the reactions (compounds **5a-c**, **5e-n**, see experimental). However, enolate salt **6** can also be prepared in a separate step by addition of one equivalent of triethylamine (compounds **5f** and **5p**) or sodium hydride (compounds **5d**, **5o** and **5r**) prior to the amine used for the aminolysis of the ester group, in the same pot. The *Z* enol structure was assigned to compounds **5** based on nmr studies with compound **5e**. The absence of oxindole C(3)-H signal in the ^{1}H nmr spectrum together with the oxindole C(3) signal at 99.9 ppm in the ^{13}C nmr indicate the enol structure. Significant NOE detected between oxindole C(4) and thiophene C(3) hydrogens proves the *Z* enol configuration.

Ammonolysis of compound **4** to tenidap (**2**) was accomplished by heating at 80-90 °C for several hours. Similar reaction conditions were required in the reaction of **4** with methylamine, dimethylamine and amino acid derivatives. However, aminolysis with other amines listed in Table 1 took place smoothly at ambient temperature during 2 hours. The yields of recrystallized products (varying from 38% to 85%) are not optimized. Amino acid derivatives **5o** and **5r** were obtained in lower yields, 39% and 38%, respectively. It is interesting to mention that aniline and 3-amino-pyridine did not react with compound **4** even under vigorous conditions (starting material was recovered quantitatively after stirring at 110 °C for 1 hour).

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and are not corrected. The ir spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer, using potassium bromide pellets. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer, at 200 or 400 MHz and at 50.3 or 101 MHz, respectively. Chemical shifts were reported as δ values (ppm) down field from internal tetramethylsilane.

N-Methyl-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (**5a**).

To a saturated solution of methylamine in DMF (25 ml) was added **4** (3.98 g, 0.01 mole) at 0 °C and the reaction mixture was heated in a sealed vessel at 70-80 °C for 12 hours. A mixture of water (25 ml) and concentrated aqueous hydrochloric acid (2.5 ml) was added. The resulting crystalline precipitate was filtered and recrystallized from ethyl-acetate to give **5a** (1.77 g, 53%) as yellow crystals: mp 215-216 °C. ir (potassium bromide): *ν* 1714, 1644, 1606 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.49

(1H, bs), 8.34 (1H, d, *J* = 8.8 Hz), 7.92 (1H, dd, *J* = 3.8, 1.1 Hz), 7.78 (1H, dd, *J* = 5.0, 1.1 Hz), 7.62 (1H, d, *J* = 2.2 Hz), 7.29 (1H, dd, *J* = 5.0, 3.8 Hz), 7.24 (1H, dd, *J* = 8.8, 2.2 Hz), 3.04 + 3.02 (3H, s+s); ^{13}C nmr (deuteriochloroform): δ 172.8, 167.1, 152.2, 134.9, 134.2, 132.5, 131.9, 129.3, 127.9, 126.5, 122.6, 118.8, 117.2, 100.1, 26.4.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_3S$ (334.79): C, 53.82; H, 3.31; Cl, 10.59; N, 8.37; S, 9.58. Found: C, 53.54; H, 3.28; Cl, 10.49; N, 8.30; S, 9.49.

N-Propyl-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (**5b**).

To a solution of **4** (3.98 g, 0.01 mole) in DMF (25 ml) was added 1-propylamine (1.8 ml, 1.32 g, 0.022 mole) dropwise at 25 °C over a period of 5 minutes. After stirring for 2 hours at room temperature, a mixture of water (50 ml) and concentrated aqueous hydrochloric acid (2.5 ml) was added. The solid precipitate was filtered to give **5b** (1.81 g, 50%) as yellow crystals: mp 142-143 °C. ir (potassium bromide): *ν* 1715, 1650, 1612 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.60 (1H, s), 8.32 (1H, d, *J* = 8.9 Hz), 7.92 (1H, dd, *J* = 3.8, 1.1 Hz), 7.78 (1H, dd, *J* = 5.0, 1.1 Hz), 7.62 (1H, d, *J* = 2.2 Hz), 7.31 (1H, dd, *J* = 8.9, 2.2 Hz), 7.24 (1H, dd, *J* = 5.0, 3.8 Hz), 3.42 (2H, m), 1.70 (2H, q, *J* = 7.3 Hz), 1.02 (3H, t, *J* = 7.3 Hz); ^{13}C nmr (deuteriochloroform): δ 172.8, 167.0, 151.6, 135.0, 134.3, 132.5, 131.9, 129.2, 126.5, 122.6, 118.8, 117.3, 100.2, 41.8, 22.7, 11.4.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3S$ (362.85): C, 56.27; H, 4.17; Cl, 9.77; N, 7.72; S, 8.84. Found: C, 55.95; H, 4.05; Cl, 9.70; N, 7.64; S, 8.86.

N-[2-(Dimethylamino)ethyl]-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide hydrochloride (**5c**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and 2-(dimethylamino)ethylamine (1.94 g, 0.022 mole). Recrystallisation from acetonitrile gave **5c** (3.13 g, 73%) as yellow crystals: mp 192-193 °C. ir (potassium bromide): *ν* 1714, 1644, 1612 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.67 (2H, bs), 8.62 (1H, dd, *J* = 3.8, 1.1 Hz), 8.35 (1H, d, *J* = 2.4 Hz), 8.03 (1H, d, *J* = 8.5 Hz), 7.61 (1H, dd, *J* = 5.0, 1.1 = Hz), 7.06 (1H, dd, *J* = 5.0, 3.8 Hz), 6.82 (1H, dd, *J* = 8.5, 2.4 Hz), 3.65 (2H, q, *J* = 5.8 Hz), 3.19 (2H, t, *J* = 5.8 Hz), 2.93 (6H, s); ^{13}C nmr (deuteriochloroform): δ 177.3, 166.0, 155.2, 149.2, 132.4, 130.2, 129.9, 129.5, 127.1, 126.6, 118.7, 117.7, 114.1, 94.4, 56.9, 42.9, 34.4.

Anal. Calcd. for $C_{18}H_{19}Cl_2N_3O_3S$ (428.35): C, 50.47; H, 4.47; Cl, 16.55; N, 9.81; S, 7.49. Found: C, 50.71; H, 4.56; Cl, 16.15; N, 9.84; S, 7.70.

N-{3-[*N*-(3,4-Dimethoxyphenyl)ethyl-*N*-methylamino]propyl}-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide hydrochloride (**5d**).

To a suspension of sodium hydride 50% (0.48 g, 0.01 mole) in DMF (5 ml) was added a solution of **4** (3.98 g, 0.01 mole) in DMF (20 ml) dropwise over a period of 15 minutes maintaining the temperature below 25 °C. 3-[*N*-(3,4-Dimethoxyphenyl)ethyl-*N*-methylamino]propylamine (3.09 g, 0.011 mole) was added and the mixture was stirred for 6 hours at room temperature. A mixture of water (50 ml) and concentrated aqueous hydrochloric acid (5 ml) was added. The precipitate was filtered and recrystallized from methanol to give **5d** (5.03 g, 85%) as yellow crystals: mp 187-188 °C. ir (potassium bromide): *ν* 1713, 1647, 1609 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.20 (1H, bs), 9.59 (1H, bs), 8.22 (1H, dd, *J* = 3.7, 1.1 Hz), 8.05 (1H, d, *J* = 1.1 Hz), 8.01 (1H, bs), 7.76 (1H, dd, *J* = 5.0, 1.1 Hz), 7.15 (1H, t, *J* = 4.7 Hz), 7.04 (1H, m), 6.87 (2H, m), 6.78 (1H, dd, *J* = 8.4, 1.8 Hz), 3.74 (3H, s), 3.72 (3H, s), 3.40-3.10 (6H, m), 2.95 (2H, m), 2.80 (3H, d, *J* = 4.7 Hz), 1.98 (2H, m); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 154.4, 149.8, 149.1, 148.0, 138,4, 137.5, 135.8, 132.1, 131.0, 130.6, 130.1, 129.9, 129.7, 129.4, 129.3, 128.9, 127.7, 127.0, 120.9, 112.8, 112.4, 56.1, 55.8, 53.1, 52.8, 29.2, 24.3, 23.5.

Anal. Calcd. for $C_{28}H_{31}Cl_2N_3O_5S$ (592.56): C, 56.76; H, 5.27; Cl, 11.97; N, 7.09; S, 5.41. Found: C, 56.43; H, 5.30; Cl, 11.75; N, 7.14; S, 5.55.

N,*N*-Dimethyl-5-chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (**5e**).

This compound was prepared analogously to **5a** starting from **4** (3.98 g, 0.01 mole) and a saturated solution of dimethylamine in DMF (25 ml). The resulting crystalline product was recrystallized from ethanol to give **5e** (2.66 g, 76%) as yellow crystals: mp 162-163 °C. ir (potassium bromide): *ν* 1706, 1650, 1620 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.88 (1H, dd, *J* = 3.7, 1.1 Hz), 7.73 (1H, d, *J* = 5.3, 1.1 Hz), 7.64 (1H, dd, *J* = 1.7, 0.8 Hz), 7.28 (1H, dd, *J* = 5.3, 3.7 Hz), 7.19 (2H, m), 3.16 (6H, m); ^{13}C nmr (deuteriochloroform): δ 170.6, 166.6, 151.0, 135.5, 134.5, 132.2, 131.6, 128.8, 128.0, 126.3, 123.5, 119.6, 113.7, 99.9, 38.5, 36.9.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3S$ (348.82): C, 55.10; H, 3.76; Cl, 10.16; N, 8.03; S, 9.19. Found: C, 55.38; H, 3.77; Cl, 9.96; N, 7.84; S, 9.24.

N-Benzyl-*N*-methyl-5-chloro-3-[1-hydroxy-1-(2-thienyl)-methylene]-2-oxo-2,3-dihydroindole-1-carboxamide (**5f**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and *N*-(benzyl)methylamine (2.67 g, 0.022 mole). The resulting crystalline product was recrystallized from ethyl acetate to give **5f** (2.25 g, 53%) as yellow crystals: mp 125-126 °C. ir (potassium bromide): *ν* 1704, 1644, 1608 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.89 (1H, dd, *J* = 3.8, 1.1 Hz), 7.73 (1H, dd, *J* = 5.1, 1.1 Hz), 7.64 (1H, bs), 7.60-7.10 (8H, m), 4.78 (2H, s), 3.03 (3H, s); ^{13}C nmr (deuteriochloroform): δ 170.5, 166.5, 151.3, 135.7, 135.3, 134.3, 132.0, 131.4, 128.8, 128.6, 127.8, 126.1, 123.3, 119.5, 113.3, 99.7, 52.7, 35.9.

Anal. Calcd. for $C_{22}H_{17}ClN_2O_3S$ (424.92): C, 62.19; H, 4.03; Cl, 8.34; N, 6.59; S, 7.55. Found: C, 62.50; H, 4.04, Cl, 8.25; N, 6.47; S, 7.51.

Compound **5f** was also prepared analogously to **5r** starting from **4** (3.98 g, 0.01 mole) and triethylamine (1.01 g, 0.01 mole) followed by the addition of *N*-(benzyl)methylamine (1.33 g, 0.011 mole) to give **5f** (1.91 g, 45%), mp 125-126 °C, a product identical with the sample obtained above.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(pyrrolidine-1-carbonyl)-2,3-dihydroindole (**5g**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and pyrrolidine (1.57 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5g** (3.04 g, 81%) as yellow crystals: mp 153-154 °C. ir (potassium bromide): *ν* 1699, 1642, 1623 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.88 (1H, dd, *J* = 3.8, 1.2 Hz), 7.73 (1H, dd, *J* = 5.0, 1.2 Hz), 7.65 (1H, d, *J* = 2.0 Hz), 7.28 (1H, dd,

J = 5.0, 3.8 Hz), 7.27 (1H, d, *J* = 8.5 Hz), 7.18 (1H, dd, *J* = 8.5, 2.0 Hz), 3.80-3.65 (4H, m), 3.65-3.50 (4H, bs); ^{13}C nmr (deuteriochloroform): δ 170.2, 166.3, 148.8, 135.4, 134.0, 132.0, 131.4, 128.5, 127.9, 126.0, 119.3, 113.6, 99.8, 47.9, 47.3, 25.8, 24.6.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_3S$ (374.86): C, 57.68; H, 4.03; Cl, 9.46; N, 7.47; S, 8.55. Found: C, 57.40; H, 4.15; Cl, 9.19; N, 7.16; S, 8.52.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(piperidine-1-carbonyl)-2,3-dihydroindole (**5h**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and piperidine (1.87 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5h** (2.53 g, 65%) as yellow crystals: mp 159-159.5 °C. ir (potassium bromide): *ν* 1698, 1644, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.85 (1H, dd, *J* = 3.8, 1.0 Hz), 7.69 (1H, dd, *J* = 5.0, 1.0 Hz), 7.60 (1H, s), 7.25 (1H, dd, *J* = 5.0, 3.8 Hz), 7.15 (2H, s), 3.80-3.20 (4H, bs), 1.90-1.50 (6H, bs); ^{13}C nmr (deuteriochloroform): δ 170.5, 166.4, 149.3, 135.5, 134.6, 131.9, 131.4, 128.5, 127.9, 126.1, 124.9, 119.5, 113.3, 99.8, 48.4, 45.4, 26.4, 25.6, 24.2.

Anal. Calcd. for $C_{19}H_{17}ClN_2O_3S$ (388.88): C, 58.69; H, 4.41; Cl, 9.12; N, 7.20; S, 8.25. Found: C, 59.08; H, 4.36; Cl, 9.09; N, 7.14; S, 8.19.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(hexamethyleneimine-1-carbonyl)-2,3-dihydroindole (**5i**)**.**

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and hexamethyleneimine (2.18 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5i** (3.10 g, 77%) as yellow crystals: mp 137-138 °C. ir (potassium bromide): *ν* 1704, 1644, 1618 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.89 (1H, dd, *J* = 3.7, 1.2 Hz), 7.75 (1H, dd, *J* = 5.0, 1.2 Hz), 7.65 (1H, d, *J* = 2.0 Hz), 7.28 (1H, dd, *J* = 5.0, 3.7 Hz), 7.19 (1H, dd, *J* = 8.5, 2.0 Hz), 7.11 (1H, d, *J* = 8.5 Hz), 4.10-3.85 (1H, bs), 3.65-3.30 (3H, bs), 2.00-1.85 (2H, bs), 1.85-1.65 (5H, bs), 1.65-1.40 (1H, bs); ^{13}C nmr (deuteriochloroform): δ 170.2, 166.3, 150.5, 135.4, 134.5, 132.0, 131.4, 128.4, 127.9, 126.1, 123.2, 119.5, 112.6, 99.7, 49.1, 47.6, 28.6, 27.9, 27.3, 26.3.

Anal. Calcd. for $C_{20}H_{19}ClN_2O_3S$ (402.91): C, 59.62; H, 4.75; Cl, 8.80; N, 6.95; S, 7.96. Found: C, 59.70; H, 4.60; Cl, 8.54, N, 7.10; S, 7.77.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(morpholine-4-carbonyl)-2,3-dihydroindole (**5j**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and morpholine (1.91 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5j** (2.93 g, 75%) as yellow crystals: mp 183-185 °C. ir (potassium bromide): *ν* 1693, 1660, 1595 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.89 (1H, dd, *J* = 3.8, 1.1 Hz), 7.75 (1H, dd, *J* = 5.0, 1.1 Hz), 7.65 (1H, d, *J* = 1.9 Hz), 7.28 (1H, dd, *J* = 5.0, 3.8 Hz), 7.26 (1H, d, *J* = 8.6 Hz), 7.19 (1H, dd, *J* = 8.6, 1.9 Hz), 4.00-3.20 (8H, m); ^{13}C nmr (deuteriochloroform): δ 170.7, 166.8, 149.7, 135.4, 134.5, 132.4, 131.7, 128.5, 128.0, 126.3, 123.5, 119.6, 113.9, 99.8, 66.8, 47.9, 44.9.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_4S$ (390.86): C, 55.32; H, 3.87; Cl, 9.07; N, 7.17; S, 8.20. Found: C, 55.72; H, 3.88; Cl, 8.95; N, 7.12; S, 8.20.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(4-methylpiperazine-1-carbonyl)-2,3-dihydroindole hydrochloride (**5k**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and 1-methylpiperazine (2.20 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5k** (2.20 g, 49%) as yellow crystals: mp 224-225 °C. ir (potassium bromide): *ν* 1711, 1644, 1605 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.90 (1H, dd, *J* = 3.8, 1.1 Hz), 7.78 (1H, dd, *J* = 4.9, 1.1 Hz), 7.65 (1H, d, *J* = 1.9 Hz), 7.32 (1H, m), 7.18 (2H, m), 4.20-3.80 (4H, bs), 3.80-3.30 (4H, bs), 2.91 (3H, s); ^{13}C nmr (deuteriochloroform): δ 171.1, 167.3, 149.6, 135.0, 133.9, 132.9, 132.1, 129.6, 128.3, 126.7, 123.5, 119.7, 114.6, 99.6, 53.5, 43.6.

Anal. Calcd. for $C_{19}H_{19}Cl_2N_3O_3S$ (440.37): C, 51.82; H, 4.35; Cl, 16.10; N, 9.54; S, 7.28. Found: C, 51.47; H, 4.38; Cl, 15.76; N, 9.15; S, 7.16.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-[4-(2-hydroxyethyl)piperazine-1-carbonyl]-2,3-dihydroindole hydrochloride (**5l**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and 1-(2-hydroxyethyl)piperazine (2.87 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5l** (2.59 g, 55%) as yellow crystals: mp 190-195 °C. ir (potassium bromide): *ν* 1699, 1644, 1601 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 11.00 (1H, s), 8.06 (1H, s), 7.94 (1H, s), 7.82 (1H, s), 7.40-7.10 (3H, m), 5.49 (3H, bs), 4.00-3.00 (10H, m); ^{13}C nmr (deuteriochloroform): δ 167.0, 149.4, 133.9, 132.6, 131.9, 129.3, 128.0, 126.5, 123.4, 119.3, 114.3, 99.6, 61.8, 61.1, 56.5, 53.2.

Anal. Calcd. for $C_{20}H_{21}Cl_2N_3O_4S$ (470.39): C, 51.07; H, 4.50; Cl, 15.07; N, 8.93; S, 6.82. Found: C, 51.23; H, 4.61; Cl, 14.72; N, 8.79; S, 6.90.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-(4-phenylpiperazine-1-carbonyl)-2,3-dihydroindole (**5m**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and 1-phenylpiperazine (3.49 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5m** (3.03 g, 65%) as yellow crystals: mp 174-175 °C. ir (potassium bromide): *ν* 1696, 1644, 1602 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 7.89 (1H, dd, *J* = 3.8, 1.1 Hz), 7.74 (1H, dd, *J* = 5.1, 1.1 Hz), 7.65 (1H, d, *J* = 1.8 Hz), 7.34-7.12 (5H, m), 6.99-6.86 (3H, m), 4.10-3.50 (4H, m), 3.50-3.10 (4H, bs); ^{13}C nmr (deuteriochloroform): δ 170.5, 166.6, 150.7, 149.4, 135.2, 134.3, 132.1, 131.4, 129.2, 128.7, 127.8, 126.1, 123.3, 120.6, 119.4, 116.7, 113.6, 99.6, 49.3.

Anal. Calcd. for $C_{24}H_{20}ClN_3O_3S$ (465.97): C, 61.87; H, 4.33; Cl, 7.61; N, 9.02; S, 6.88. Found: C, 61.56; H, 4.35; Cl, 7.50; N, 9.13; S, 6.83.

5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-1-[4-(2-pyrimidinyl)piperazine-1-carbonyl)]-2,3-dihydroindole (**5n**).

This compound was prepared analogously to **5b** starting from **4** (3.98 g, 0.01 mole) and 1-(2-pyrimidinyl)piperazine (3.61 g, 0.022 mole). The resulting crystalline product was recrystallized from acetonitrile to give **5n** (3.60 g, 77%) as yellow crystals: mp 181-184 °C. ir (potassium bromide): *ν* 1699, 1648, 1608 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.34 (2H, d, *J* = 4.7 Hz), 7.90

(1H, dd, *J* = 3.7, 1.1 Hz), 7.74 (1H, dd, *J* = 4.8, 1.1 Hz), 7.66 (1H, d, *J* = 1.8 Hz), 7.34-7.24 (2H, m), 7.19 (1H, dd, *J* = 8.4, 1.8 Hz), 6.55 (1H, t, *J* = 4.7 Hz), 4.10-3.40 (8H, m); ^{13}C nmr (deuteriochloroform): δ 170.5, 166.6, 161.5, 157.8, 149.6, 135.2, 134.3, 132.1, 131.5, 129.4, 128.7, 127.8, 126.1, 123.3, 119.4, 113.7, 110.5, 99.6, 47.1, 43.5.

Anal. Calcd. for $C_{22}H_{18}ClN_5O_3S$ (467.95): C, 56.47; H, 3.88; Cl, 7.58; N, 14.97; S, 6.85. Found: C, 56.54; H, 3.98; Cl, 7.56; N, 14.61; S, 7.01.

N-{5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carbonyl}-glycine (**5o**).

This compound was prepared analogously to **5d** starting from a suspension of sodium hydride 50% (0.48 g, 0.01 mole), **4** (3.98 g, 0.01 mole) and glycine (0.83 g; 0.011 mole) and stirring the mixture for 6 hours at 70-80 °C. The resulting crystalline product was recrystallized from acetonitrile to give **5o** (1.48 g, 39%) as yellow crystals: mp 205.5-207.5 °C. ir (potassium bromide): *ν* 1699, 1651, 1599 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 9.49 (1H, bs), 8.13 (1H, dd, *J* = 3.8, 1.1 Hz), 8.07 (1H, d, *J* = 8.5 Hz), 7.97 (1H, bs), 7.85 (1H, dd, *J* = 5.1, 1.1 Hz), 7.20 (1H, m), 7.10 (1H, m), 4.00 (2H, d, *J* = 6.5 Hz); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 171.1, 169.1, 167.2, 152.9, 139.6, 132.6, 131.6, 130.9, 127.8, 127.3, 122.9, 119.8, 115.2, 99.0, 56.9, 41.4.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_5S$ (378.80): C, 50.73; H, 2.93; Cl, 9.36; N, 7.40; S, 8.46. Found: C, 50.87; H, 2.96; Cl, 9.34; N, 7.18; S, 8.43.

Methyl-*N*-{5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carbonyl}-glycinate (**5p**).

To a solution of **4** (3.98 g; 0.01 mole) in DMF (25 ml) was added triethylamine (2.23 g, 0.022 mole) dropwise, maintaining the temperature below 30 °C. After stirring for 5 minutes at room temperature, glycine methyl ester hydrochloride (1.38 g, 0.011 mole) was added. The mixture was stirred for 5 hours at 60-70 °C. A mixture of water (50 ml) and concentrated aqueous hydrochloric acid (2.5 ml) was added. The precipitate was filtered and recrystallized from acetonitrile to give **5p** (2.20 g, 56%) as yellow crystals: mp 152.5-153.5 °C. ir (potassium bromide): *ν* 1757, 1728, 1648, 1602 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 13.8 (1H, bs), 9.08 (1H, t, *J* = 6.5 Hz), 8.29 (1H, d, *J* = 8.5 Hz) 7.89 (1H, dd, *J* = 3.8, 1.1 Hz), 7.77 (1H, dd, *J* = 5.1, 1.1 Hz), 7.62 (1H, d, *J* = 2.0 Hz), 7.28 (1H, dd, *J* = 5.1, 3.8 Hz), 7.20 (1H, dd, *J* = 8.5, 2.0 Hz), 4.10 (2H, d, *J* = 6.5 Hz), 3.80 (3H, s); ^{13}C nmr (deuteriochloroform): δ 197.4, 172.8, 169.8, 167.3, 151.6, 134.9, 133.9, 132.7, 132.0, 129.5, 127.9, 126.6, 122.7, 118.9, 117.2, 100.0, 52.5, 41.8.

Anal. Calcd. for $C_{17}H_{13}ClN_2O_5S$ (392.82): C, 51.98; H, 3.34; Cl, 9.03; N, 7.13; S, 8.16. Found: C, 51.61; H, 3.27; Cl, 8.91; N, 7.02; S, 8.08.

N-{5-Chloro-3-[1-hydroxy-1-(2-thienyl)methylene]-2-oxo-2,3-dihydroindole-1-carbonyl}-L-proline (**5r**).

To a suspension of sodium hydride 50% (0.48 g, 0.01 mole) in DMF (5 ml) was added a solution of **4** (3.98 g, 0.01 mole) in DMF (20 ml) dropwise over a period of 15 minutes maintaining the temperature below 25 °C. L-Proline (1.27 g; 0.011 mole) was added and the mixture was stirred for 12 hours at 70-80 °C. A mixture of water (50 ml) and concentrated aqueous hydrochloric acid (5 ml) was added and it was extracted with diethyl ether (3 x 25 ml). The solvent was evaporated, the residue was stirred with methanol (20 ml). The resulting crystalline product was recrystallized from acetonitrile to give **5r** (1.65 g, 38%) as yellow crystals: mp 173-174 °C. ir (potassium bromide): *ν* 1747, 1706, 1623, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 10.2 (1H, bs), 7.89 (1H, dd, *J* = 3.7, 1.1 Hz), 7.74 (1H, dd, *J* = 5.1, 1.1 Hz), 7.62 (1H, d, *J* = 1.8 Hz), 7.28 (2H, m), 7.18 (1H, dd, *J* = 8.4, 1.8 Hz), 4.73 (1H, bs), 3.80 (2H, bs), 2.45 (1H, m), 2.14 (3H, m); ^{13}C nmr (deuteriochloroform): δ 175.9, 170.2, 166.6, 149.8, 135.3, 133.9, 132.1, 131.6, 128.9, 127.9, 126.3, 123.3, 119.5, 113.9, 99.8, 59.9, 48.3.

Anal. Calcd. for $C_{19}H_{15}ClN_2O_5$ S (434.87): C, 54.48; H, 3.61; Cl, 8.46; N, 6.69; S, 7.66. Found: C, 54.73; H, 3.59; Cl, 8.67; N, 6.55; S, 7.42.

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