A Synthesis of Potential New Antiarrhythmic Agents

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N-Ethylation of substituted ethyl 1*H*-indole-2-carboxylates with iodoethane and potassium carbonate gave substituted ethyl 1-ethyl-1*H*-indole-2-carboxylates. The later compounds on treatment with a range of aryl amines with varying structural complexity, gave the desired ethyl 1*H*-indole-2-carboxamide analogues.

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In the search for new potential and safer antiarrhythmic agents, the present study focuses on the synthesis of selected novel ethyl 1*H*-indole-2-carboxamide analogues. A variety of antiarrhyhtmic agents (*e.g*. procainamide, disopyramide, lidocaine, tocainide, and flecanide) [1-13], containing amide functional groups have shown interesting antiarrhythmic activity [14-21].

In view of the wide range of structural diversity of compounds possessing antiarrhythmic activity, efforts to determine a definitive structure have not been too successful. Even some of the more common antiarrhythmic drugs were synthesized for different purposes, when interestingly; upon routine pharmacological screening and clinical trials their antiarrhythmic activity was revealed.

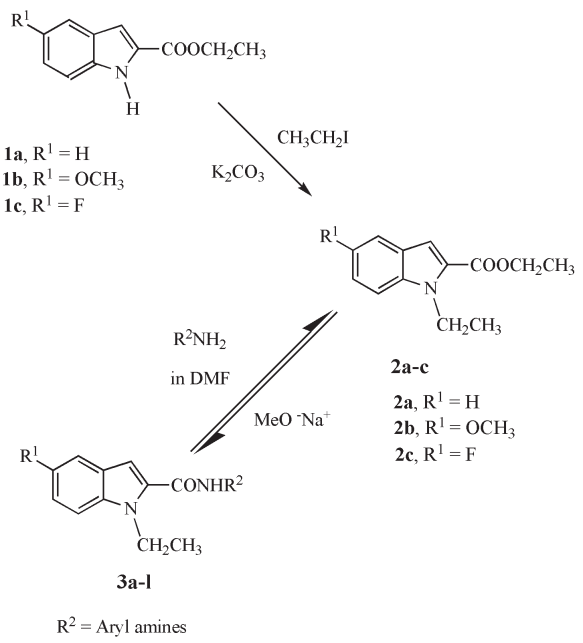
The first extensive reviews on the structure activity relationships of antiarrhythmic drugs were by Conn [22]. These investigations indicated that most antiarrhythmic drugs possess a tertiary amine group that appears to be a key component for activity. The aromatic ring system is important and this moiety, is usually connected to the tertiary amine *via* a hydroxy substituted alkyl chain typically an ester or an amide group, although methoxy groups substituted on the aromatic ring may enhance activity [23-24].

Our approach into a new series of some selected analogues is based on the synthesis, chemistry and pharmacological activity of a variety of ethyl 1-ethyl-1*H*-indole-2-carboxamide analogues. Since the interest in amides have been growing steadily over the years for more targeted biological action [25-29]. This prompted us to design and evaluate a series of novel amides. Scheme 1 illustrates the synthetic approach chosen for the preparation of the amides.

The first step involved the reaction of substituted ethyl 1*H*-indole-2-carboxylates (**1a-c**, Scheme 1) with iodoethane in the presence of potassium carbonate for the preparation of the desired substituted ethyl 1-ethyl-1*H*-indole-2-carboxylates (**2a-c**, Scheme 1). This reaction was exploited following initial experiments to ascertain whether it was necessary to protect the nitrogen atom. It became obvious during these studies in view of the very low yields, that protection of the nitrogen atom in the ring was most probably required to prevent any interaction during the synthesis of the desired amides.

Surprisingly, there was no precedence found for this kind of reaction especially with the indole nucleus and the substituents adopted herein. However, the reaction was found to proceed smoothly and afforded the corresponding ethyl 1-ethyl-1*H*-indole-2-carboxylates (**2a-c** Scheme 1) albeit in low yields (39% - 44%). Attempts to modify and improve these yields were met with little success (see Table).

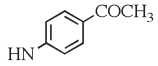
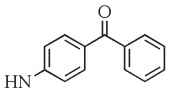
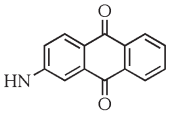
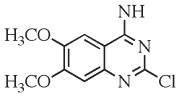
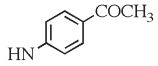
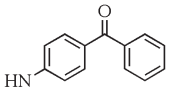
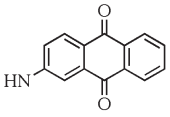
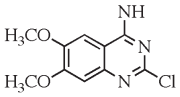
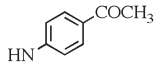
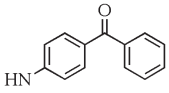
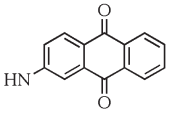
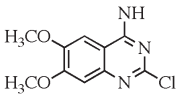
Scheme 1



The substituted ethyl 1-ethyl-1*H*-indole-2-carboxylates (**2a-c**, Scheme 1) were then treated with a range of aryl amines with varying structural complexity in *N*,*N*-dimethylformamide to furnish the desired novel amides (**3a-l**) in high yields (69-78%). The outcome of these reactions was most encouraging since normally with such large bulky groups in the ring systems employed, a considerable amount of steric hindrance for the reaction to occur would be expected. These new series of compounds were pharmacologically evaluated on experimental adult Wistar rats

Table

Synthesis of Amides

Compound	R^1	R^2	Yield %	m.p (ºC)
2a	H	H	44	135
2b	OCH_3	H	42	166
2c	F	H	39	154
3a	H		77	244
3b	H		70	257
3c	H		70	290
3d	H		72	284
3e	OCH_3		75	248
3f	OCH_3		72	261
3g	OCH_3		72	293
3h	OCH_3		70	288
3i	F		78	246
3j	F		69	259
3k	F		70	289
3l	F		74	282

(300-400g body weight) and were notably found to exhibit good antiarrhythmic activity during our preliminary screening. Further biological evaluation is now ongoing in our laboratories.

In conclusion, our synthesis of a series of novel amides has been accomplished in two short steps from relatively simple, inexpensive and commercially available starting materials in an efficient manner in high yields despite their complexity.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Bruker 250 MHz instrument in an appropriate deuterated solvent (deuteriochloroform) with tetramethylsilane as the internal standard. Mass spectra were recorded on a Varian Saturn 3 GC/MS spectrometer. Infrared spectra were recorded on a Nicolet 205 FT-IR sepectrometer. Microanalysis was performed on an elemental analyzer Perkin-Elmer 2400 CHN by Butterworth Laboratories, UK.

General Procedure for the Preparation of Ethyl 1-Ethyl (or 5-methoxy or 5-fluoro)-1*H*-indole-2-carboxylate (**2a-c**).

A mixture of the appropriately substituted ethyl (or 5-methoxy or 5-fluoro)-1*H*-indole-2-carboxylate (**1a-c**, 5 g, 0.023 mol), potassium carbonate (6.4 g, 0.046 mol), iodoethane (17.94 g, 0.115 mol) and *N*,*N*-dimethylformamide (30 ml) was heated at 80-90 ºC with stirring. After 10 hours, the mixture was evaporated to dryness and extracted with dichloromethane (3x50 ml). The dichloromethane was washed with H_2O (50 ml), dried and filtered by using magnesium sulphate and evaporated to dryness to give a white solid. Recrystallization from ethanol gave the title compounds.

General Procedure for the Preparation of Ethyl 1*H*-Indole-2-carboxamide Derivatives (**3a-l**).

A mixture of the appropriately substituted ethyl 1-ethyl (or 5-methoxy or 5-fluoro)-1*H*-indole-2-carboxylate (**2a-c**, 1g, 4.5 mmol), sodium methoxide (1 mol equivalent), the appropriate substituted amine (3 mol equivalent) and *N*,*N*-dimethylformamide (10 ml) were refluxed for 4 hr. The mixture was cooled (ice bath) and the resultant solid was collected by filtration and washed with H_2O (2x25 ml), dried and recrystallized from *N*,*N*-dimethylformamide to furnish the desired compounds.

Ethyl 1-Ethyl-1*H*-indole-2-carboxylate (**2a**) [30-31]**.**

This compound was obtained by *N*-ethylation of ethyl 1*H*-indole-2-carboxylate (**1a**) with iodoethane in the presence of potassium carbonate to yield 4.4 g (44%) of (**2a**) as white crystals (ethanol), mp 135º; ir: (potassium bromide): C=O 1735, C-O 1105 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.30(m, 3H), 1.51(t, 3H), 3.89(q, 2H), 4.29(m, 2H), 6.87(d, 1H), 7.25(s, 1H), 7.36(d, 1H), 7.59-7.67(m, 2H); ms: m/z: 217 (M^+).

Anal. Calcd. for $C_{13}H_{15}NO_2$ (217.26): C, 71.87; H, 6.96; N, 6.45. Found C, 71.81; H, 6.99; N, 6.47.

Ethyl 1-Ethyl-5-methoxy-1*H*-indole-2-carboxylate (2b).

This compound was obtained by *N*-ethylation of ethyl 5-methoxy-1*H*-indole-2-carboxylate (**1b**) with iodoethane in the presence of potassium carbonate to yield 4.8 g (42%) of (**2b**) as white crystals (ethanol), mp 166º; ir: (potassium bromide): C-O 1155, 1210, C=O 1744 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.30 (m, 3H), 1.51 (t, 3H), 3.73 (s, 3H), 3.89 (q, 2H), 4.29 (m, 2H), 6.76 (d, 1H), 6.87 (s, 1H), 7.10 (d, 1H), 7.25 (s, 1H); ms: m/z: 247, 248 (M^+).

Anal. Calcd. for $C_{14}H_{17}NO_3$ (247.12): C, 68.00; H, 6.93; N, 5.66. Found C, 68.03; H, 6.98; N, 5.70.

Ethyl 1-Ethyl-5-fluoro-1*H*-indole-2-carboxylate (2c).

This compound was obtained by *N*-ethylation of ethyl 5-fluoro-1*H*-indole-2-carboxylate (**1c**) with iodoethane in the presence of potassium carbonate to yield 4.2 g (39%) of (**2c**) as white crystals (ethanol), mp 154º; ir: (potassium bromide): C-F 1215, C=O 1732, C-O 1150 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.30 (m, 3H), 1.51 (t, 3H), 3.89 (q, 2H), 4.29 (m, 2H), 6.85 (m, 1H), 7.07 (d, 1H), 7.25-7.30 (m, 2H); ms: m/z: 235 (M^+).

Anal. Calcd. for $C_{13}H_{14}FNO_2$ (235.25): C, 66.37; H, 6.00; N, 5.95. Found C, 66.41; H, 6.04; N, 5.96.

N-(4-Acetylphenyl)-1-ethyl-1*H*-indole-2-carboxamide (**3a**).

This compound was obtained by amidation of ethyl 1-ethyl-1*H*-indole-2-carboxylate (**2a**) with 4-aminoacetophenone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.08 g (77%) of (**3a**) as brown crystals (*N*,*N*-dimethylformamide), mp 244º; ir: (potassium bromide): C=O 1680, 1720, NH 3426 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 2.55 (s, 3H) 3.89 (q, 2H) 7.17 (s, 4H), 7.41 (s, 1H), 7.75 (d, 2H), 7.84 (d, 2H), 8.0 (br.s, 1H); ms: m/z: 306 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$ (306.36): C, 74.49; H, 5.92; N, 9.14. Found C, 74.53; H, 5.95; N, 9.16.

N-(4-Benzoylphenyl)-1-ethyl-1*H*-indole-2-carboxamide (**3b**).

This compound was obtained by amidation of ethyl 1-ethyl-1*H*-indole-2-carboxylate (**2a**) with 4-aminobenzophenone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.16 g 70% of (**3b**) as brown crystals (*N*,*N*-dimethylformamide), mp 257º; ir: (potassium bromide): C=O 1722, 1694, NH 3422 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.89 (q, 2H), 7.17 (s, 4H), 7.36-7.45 (m, 4H), 7.68-7.74 (m, 6H), 8.0 (br.s, 1H); ms: m/z: 368 (M^+).

Anal. Calcd. for $C_{24}H_{20}N_2O_2$ (368.43): C, 78.24; H, 5.47; N, 7.60. Found C, 78.29; H, 5.48; N, 7.61.

1-Ethyl-*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-1*H*-indole-2-carboxamide (**3c**).

This compound was obtained by amidation of ethyl 1-ethyl-1*H*-indole-2-carboxylate (**2a**) with 4-aminoanthraquinone in sodium methoxide and *N*,*N*-dimethylformamide to yield 3.01 g (70%) of (**3b**) as green crystals (*N*,*N*-dimethylformamide), mp 290º; ir: (potassium bromide): C=O 1715, 1665, NH 3445 cm^{-1} . ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.89 (q, 2H), 7.17 (s, 4H), 7.41 (s, 1H), 7.55 (m, 2H), 7.78-7.80 (m, 3H), 7.93 (d, 1H), 8.0 (br.s, 1H), 8.18 (s, 1H); ms: m/z: 395 (M^+).

Anal. Calcd. for $C_{25}H_{18}N_2O_3$ (394.42): C, 76.13; H, 4.60; N, 7.10. Found C, 76.16; H, 4.63; N, 7.12.

N-(2-Chloro-6,7-dimethoxyquinazolin-4-yl)-1-ethyl-1*H*-indole-2-carboxamide (**3d**).

This compound was obtained by amidation of ethyl 1-ethyl-1*H*-indole-2-carboxylate (**2a**) with 4-amino-6,7-dimethoxyquinazoline in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.33 g (72%) of (**3d**) as green crystals (*N*,*N*-dimethylformamide), mp 284º; ir: (potassium bromide): C-Cl 720, C=O 1665, NH 3493, OMe 1110 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.73 (s, 6H), 3.89 (q, 2H), 7.17 (s, 4H), 7.24 (s, 1H), 7.41 (s, 2H), 8.0 (br.s, 1H); ms: m/z: 412 (M^+).

Anal. Calcd. for $C_{21}H_{19}ClN_4O_3$ (410.85): C, 61.39; H, 4.66; N, 13.64. Found C, 61.42; H, 4.67; N, 13.68.

N-(4-Acetylphenyl)-1-ethyl-5-methoxy-1*H*-indole-2-carboxamide (**3e**).

This compound was obtained by amidation of ethyl 1-ethyl-5-methoxy-1*H*-indole-2-carboxylate (**2b**) with 4-aminoacetophenone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.14 g (75%) of (**3d**) as brown crystals (*N*,*N*-dimethylformamide), mp 248º; ir: (potassium bromide): (C=O 1680, 1715, NH 3477, C-O 1090 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 2.55 (s, 3H), 3.73 (s, 3H), 3.89 (q, 2H), 6.68 (t, 2H), 7.06 (d, 1H), 7.41 (s, 1H), 7.75 (d, 2H), 7.84 (d, 2H), 8.0 (br.s, 1H); ms: m/z: 336, 337 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$ (336.38): C, 71.41; H, 5.99; N, 8.33. Found C, 71.45; H, 6.00; N, 8.39.

N-(4-Benzoylphenyl)-1-ethyl-5-methoxy-1*H*-indole-2-carboxamide (**3f**).

This compound was obtained by amidation of ethyl 1-ethyl-5-methoxy-1*H*-indole-2-carboxylate (**2b**) with 4-aminobenzophenone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.29 g (72%) of (**3f**) as brown crystals (*N*,*N*-dimethylformamide), mp 261º; ir: (potassium bromide): C=O 1655, 1715, NH 3465, C-O 1010 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.73 (s, 3H), 3.89 (q, 2H), 6.68 (t, 2H), 7.06 (d, 1H), 7.36-7.45 (m, 4H), 7.68-7.74 (m, 6H), 8.0 (br.s, 1H); ms: m/z: 399, 400 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2O_3$ (398.45): C, 75.36; H, 5.57; N, 7.03. Found C, 75.36; H, 5.59; N, 7.09.

1-Ethyl-*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5-methoxy-1*H*-indole-2-carboxamide (**3g**).

This compound was obtained by amidation of ethyl 1-ethyl-5-methoxy-1*H*-indole-2-carboxylate (**2b**) with 4-aminoanthraquinone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.38 g (72%) of (**3g**) as green crystals (*N*,*N*-dimethylformamide), mp 293º; ir: (potassium bromide): C=O 1695, 1712, NH 3488, C-O 1210 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.73 (s, 3H) 3.89 (q, 2H), 6.68 (m, 2H), 7.06 (d, 1H), 7.41 (s, 1H), 7.55 (m, 2H), 7.78-7.80 (m, 3H), 7.93 (d, 1H), 8.0 (br.s, 1H), 8.18 (s, 1H); ms: m/z: 425 (M^+).

Anal. Calcd. for $C_{26}H_{20}N_2O_4$ (424.45): C, 76.13; H, 4.60; N, 7.10. Found C, 76.18; H, 4.63; N, 7.11.

N-(2-Chloro-6,7-dimethoxyquinazolin-4-yl)-1-ethyl-5-methoxy-1*H*-indole-2-carboxamide (**3h**).

This compound was obtained by amidation of ethyl 1-ethyl-5-methoxy-1*H*-indole-2-carboxylate (**2b**) with 4-amino-6,7-dimethoxyquinazoline in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.39 g (70%) of (**3h**) as green crystals (*N*,*N*-dimethylformamide), mp 288º; ir: (potassium bromide): C-Cl 680, C=O 1675, 1715, NH 3475, C-O 1288 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.73 (s, 9H), 3.89 (q, 2H), 6.68 (t, 2H), 7.06 (d, 1H), 7.24 (s, 1H), 7.41 (s, 2H), 8.0 (br.s, 1H); ms: m/z: 440, 442 (M^+).

Anal. Calcd. for $C_{22}H_{21}ClN_4O_4$ (440.88): C, 59.93; H, 4.80; N, 12.71. Found C, 59.98; H, 4.82; N, 12.74.

N-(4-Acetylphenyl)-1-ethyl-5-fluoro-1*H*-indole-2-carboxamide (**3i**).

This compound was obtained by amidation of ethyl 1-ethyl-5-fluoro-1*H*-indole-2-carboxylate (**2c**) with 4-aminoacetophenone

in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.14 g (78%) of (**3i**) as brown crystals (*N*,*N*-dimethylformamide), mp 246º; ir: (potassium bromide): C-F 1300, C=O 1650, 1708, NH 3473 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 2.55 (s, 3H), 3.89 (q, 2H), 6.88 (m, 2H), 7.15 (q, 1H), 7.41 (s, 1H), 7.75 (d, 2H), 7.84 (d, 2H), 8.0 (br.s, 1H); ms: m/z: 324(M^+).

Anal. Calcd. for $C_{19}H_{17}FN_2O_2$ (324.13): C, 70.36; H, 5.28; N, 8.64. Found C, 70.41; H, 5.30; N, 8.66.

N-(4-Benzoylphenyl)-1-ethyl-5-fluoro-1*H*-indole-2-carboxamide (**3j**)**.**

This compound was obtained by amidation of ethyl 1-ethyl-5-fluoro-1*H*-indole-2-carboxylate (**2c**) with 4-aminobenzophenone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.2 g (69%) of (**3j**) as brown crystals (*N*,*N*-dimethylformamide), mp 259º; ir: (potassium bromide): C-F 1300, C=O 1644, 1723, NH 3477 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.89 (q, 2H), 6.88 (m, 2H), 7.15 (q, 1H), 7.36-7.45 (m, 4H), 7.68-7.74 (m, 6H), 8.0 (br.s, 1H); ms: m/z: 387, 388 (M^+).

Anal. Calcd. for $C_{24}H_{19}FN_2O_2$ (386.14): C, 74.60; H, 4.96; N, 7.25. Found C, 74.64; H, 4.99; N, 7.28.

1-Ethyl-*N*-(9,10-dihydro-9,10-dioxoanthracen-2-yl)-5- fluoro-1*H*-indole-2-carboxamide (**3k**)**.**

This compound was obtained by amidation of ethyl 1-ethyl-5-fluoro-1*H*-indole-2-carboxylate (**2c**) with 4-aminoanthraquinone in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.31 g (70%) of (**3k**) as green crystals (*N*,*N*-dimethylformamide), mp 289º; ir: (potassium bromide): C-F 1350, C=O 1668, 1709, NH 3494 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.89 (q, 2H), 6.88 (m, 2H), 7.15 (q, 1H), 7.41 (s, 1H), 7.55 (m, 2H), 7.78-7.80 (m, 3H), 7.93 (d, 1H), 8.0 (br.s, 1H), 8.18 (s, 1H); ms: m/z: 412, 413 (M^+).

Anal. Calcd. for $C_{25}H_{17}FN_2O_3$ (412.41): C, 72.81; H, 4.15; N, 6.79. Found C, 72.84; H, 4.18; N, 6.82.

N-(2-Chloro-6,7-dimethoxyquinazolin-4-yl)-1-ethyl-5-fluoro-1*H*-indole-2-carboxamide (**3l**)**.**

This compound was obtained by amidation of ethyl 1-ethyl-5-fluoro-1*H*-indole-2-carboxylate (**2c**) with 4-amino-6,7-dimethoxyquinazoline in sodium methoxide and *N*,*N*-dimethylformamide to yield 1.43 g (74%) of (**3l**) as yellow crystals (*N*,*N*-dimethylformamide), mp 282º; ir: (potassium bromide): C-Cl 710, C-F 1250, C=O 1642, 1708, NH 3468 cm^{-1}. ^{1}H-nmr (deuteriochloroform): δ 1.51 (t, 3H), 3.73 (s, 6H), 3.89 (q, 2H), 6.88 (m, 2H), 7.15 (q, 1H), 7.24 (s, 1H), 7.41 (s, 2H), 8.0 (br.s, 1H); ms: m/z: 430 (M^+).

Anal. Calcd. for $C_{21}H_{18}ClFN_4O_3$ (428.11): C, 58.82; H, 4.23; N, 13.06. Found C, 58.83; H, 4.24; N, 13.11.

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