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SYNTHESIS AND REACTIONS OF 4-OXIRANYLMETHYLFURO-[3,2-*b*]PYRROLES AND THEIR BENZO DERIVATIVES*

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*Methyl 4-oxiranylmethyl-4H-furo[3,2-b]pyrrole-5-carboxylates **2a-c** and methyl 1-oxiranylmethyl-1H-benzo[4,5]furo[3,2-b]pyrrole-2-carboxylate (**2d**) were prepared by reaction of the appropriate starting compounds **1a-d** with excess chloromethyloxirane. The compounds **2a-d** undergo oxirane ring opening by heterocyclic amines (morpholine, pyrrolidine, piperidine or 4-methylpiperazine) giving N-2-hydroxy-3-heteroaminopropyl-substituted compounds **3a-f** or substituted 4,5-dihydrofuro[2',3':4,5]pyrrolo-[2,1-c][1,4]oxazin-8-ones **4a-e**.*

Keywords: benzo[4,5]furo[3,2-*b*]pyrroles, furo[3,2-*b*]pyrroles, furo[2',3':4,5]pyrrolo[2,1-*c*][1,4]-oxazines, oxirane ring opening.

Investigations of indole isosters (furopyrroles, thienopyrroles), in which the benzene ring is replaced by the furan or thiophene ring, resulted in the discovery of many biologically active compounds [1]. Therefore, efficient synthetic routes to these types of heterocycles are of great interest [1]. In continuation of our program aimed at developing efficient syntheses of fused oxygen-nitrogen containing heterocycles we have reported the use of substituted furo[3,2-*b*] and furo[2,3-*b*]pyrroles in organic synthesis [2-9]. In our previous studies [7], comparing the course of Diels–Alder reactions of furo[3,2-*b*]pyrroles with their [2,3-*b*] isomers, we concluded that the [2,3-*b*] system is a more reactive diene than its [3,2-*b*] isomer. This observation is supported by high-level *ab initio* calculations [9]. We have also reported [8] the results of the use of substituted furo[3,2-*b*]pyrrole and furo[2,3-*b*]pyrrole-type aldehydes in the synthesis [8]. Both systems with a formyl substituent at C(2) are comparable in their reactivity. The aim of this study was to synthesize some new 4-(2-oxiranylmethyl)furo-[3,2-*b*]pyrroles **2a-c** and their benzo derivatives **2d** and to follow up their reactions with heterocyclic amines.

An excess of chloromethyloxirane gave with **1a-d** [2, 3], under catalysis by trimethylbenzylammonium hydroxide, the compounds **2a-d**. We have used the procedure which was described in detail by Rybar and his co-workers [10-13]. Transformation of **2a-d** into the final **3** or **4** was effected by opening of the oxirane ring with the appropriate heterocyclic amines – morpholine, pyrrolidine, piperidine, or 4-methylpiperazine (Scheme 1).

* Dedicated to Prof. Dr. Edmunds Lukevics in honor of his 65th birthday.

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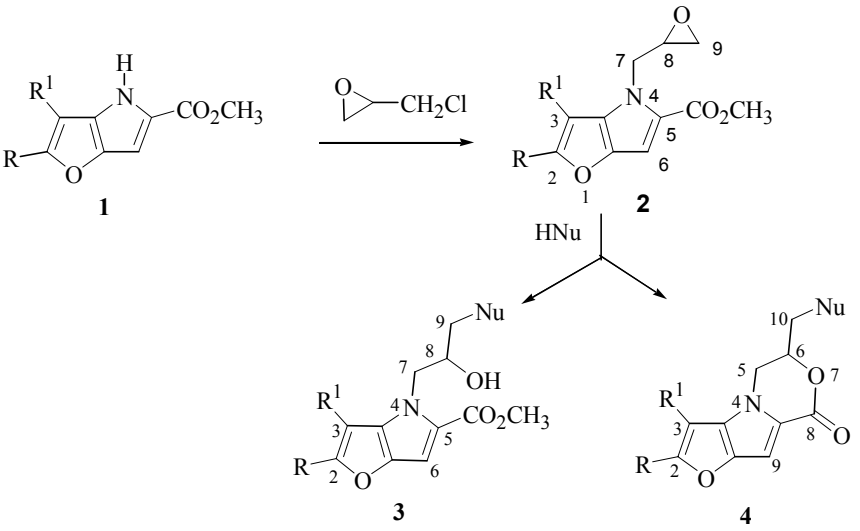
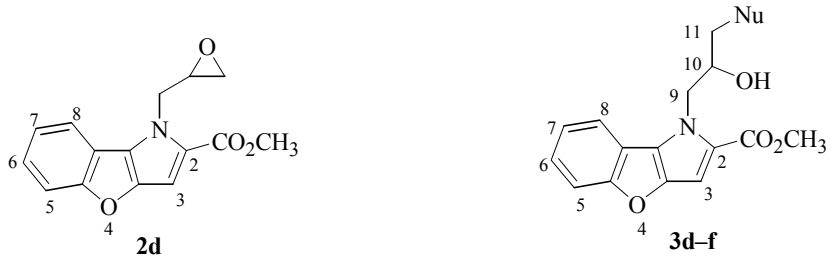
Scheme 1



1, **2 a** R = R^1 = H; **b** R = R^1 = Me; **c** R = Ph, R^1 = H; **d** R+R^1 = –CH=CH–CH=CH–.
3 a R = R^1 = H, Nu = morpholin-1-yl; **b** R = R^1 = Me, Nu = morpholin-1-yl;
c R = Ph, R^1 = H, Nu = piperidin-1-yl; **d** R = R^1 = H, Nu = piperidin-1-yl; **e** R = R^1 = H, Nu = pyrrolidin-1-yl;
f R = R^1 = H, Nu = 4-methylpiperazin-1-yl. **4 a** R = R^1 = H, Nu = pyrrolidin-1-yl; **b** R = R^1 = H, Nu = 4-methylpiperazin-1-yl;
c R = Ph, R^1 = H, Nu = morpholin-1-yl; **d** R = R^1 = H, Nu = pyrrolidin-1-yl; **e** R = Ph, R^1 = H, Nu = 4-methylpiperazin-1-yl

The formation of the compounds **4** is a result of intramolecular reaction of the OH group formed with the CO_2CH_3 group present at C(5) of furo[3,2-*b*]pyrrolo unit under MeOH elimination. It is interesting that the structure of the starting compound influences the product formation. The compound **2a**, which possess free C(2), gave both types of structures **3a** or **4a** and **4b** depending on the amine. The compound **2c** behaves exceptionally with phenyl substituent at C(2). In this case mainly the compounds **4c-e** with the oxazine ring fused to furo[3,2-*b*]pyrrolo moiety were obtained. Finally if the positions C(2) and C(3) were occupied, e.g. in compounds **2b** or **2d,** only the acyclic products **3b, 3d-f** were formed.



All the synthesized compounds are stable solids. Their structure has been confirmed by FT IR, UV, and ^{1}H and ^{13}C NMR (using APT and spectroscopic data of ^{13}C, ^{1}H-COSY techniques).

The formation of cyclic products **4a-e** was confirmed by the absence of signals of CO_2CH_3 groups in their ^{1}H and ^{13}C NMR spectra, which on the other hand were identified in all acyclic compounds **3a-f**. In the IR spectra of acyclic compounds the OH group exhibited characteristic broad bands at 3130-3425 cm^{-1}.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. Samples for analysis were dried over P_4O_{10} at 60°C and 30 Pa for 8-10 h. UV spectra of dioxane solutions (λ_{max} (log ε); λ_{max} in nm, ε in $m^2 \cdot mol^{-1}$) were taken on a Specord UV-vis M-40 (Zeiss, Jena) instrument. Infrared spectra were recorded on a Philips FTIR PU 9802/25 spectrophotometer with only major absorbances being quoted. Unless otherwise stated, IR spectra were measured using KBr pellets (0.5 mg/300 mg KBr). NMR ^{1}H (300 MHz) and ^{13}C (75.43 MHz) spectra were recorded at ambient temperatures using a Varian VXR-300 spectrometer with TMS as an internal reference in $CDCl_3$. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The reported data [3, 14-6] were used for the signal assignment. Elemental analyses were determined using a Carlo Erba CHNS-OEA 1108-Elemental Analyser. The reaction progress and purity of all prepared compounds was followed by TLC (Silufol UV_{254}, Kavalier, Votice, Czech Republic) in the system chloroform–methanol 9:1 and spots were visualized using UV lamp or iodine vapor. Solvents were purified according to published methods. The starting compounds methyl 4H-furo[3,2-*b*]pyrrole-5-carboxylate (**1a**) and 2-phenyl-4H-furo-[3,2-*b*]pyrrole-5-carboxylate (**1c**) were prepared according to ref. [3], and methyl 2,3-dimethyl-4H-furo[3,2-*b*]-pyrrole-5-carboxylate (**1b)** and methyl 1H-benzo[4,5]furo[3,2-*b*]pyrrole-2-carboxylate (**1d)** according to ref. [2].

Methyl 4-Oxiranylmethyl-4H-furo[3,2-*b*]pyrrole-5-carboxylate (2a). A suspension of **1a** (4 g, 24 mmol) in freshly distilled 2-chloromethyloxirane (100 ml) and trimethylbenzylammonium hydroxide (0.15 ml, 40% ethanolic solution) was mixed and refluxed (6 h), cooled, filtered, and evaporated in vacuo, and the dark residue was crystallized from methanol. Yield 5.2 g (52%); mp 76-77°C (methanol). Found, %: C 59.62; H 5.21; N 6.28. $C_{11}H_{11}NO_4$ (221.21). Calculated, %: C 59.73; H 5.01; N 6.33. UV (dioxane), λ_{max}, nm (log ε): 297 (3.48), 356 (2.39). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.50 (1H, d, $J_{2,3}$ = 2.2, H-2); 6.51 (1H, dd, $J_{2,3}$ = 2.2, $J_{3,6}$ = 0.7, H-3); 6.48 (1H, d, $J_{3,6}$ = 0.7, H-6); 5.00 (1H, dd, $J_{7d,7e}$ = 14.7, $J_{7d,8c}$ = 2.9, H-7d); 4.29 (1H, dd, $J_{7d,7e}$ = 14.7, $J_{7e,8c}$ = 5.6, H-7e); 3.83 (3H, s, COO$\underline{CH_3}$); 3.35 (1H, m, H-8c); 2.80 (1H, t, $J_{9a,9b}$ = 4.7, $J_{9b,8c}$ = 4.7, H-9b); 2.51 (1H, dd, $J_{9a,9b}$ = 4.7, $J_{9a,8c}$ = 2.5, H-9a). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.45 ($\underline{CO}OCH_3$); 148.66 ($C_{(2)}$); 145.76 ($C_{(6a)}$); 133.72 ($C_{(3a)}$); 122.96 ($C_{(5)}$); 98.99 ($C_{(3)}$); 98.87 ($C_{(6)}$); 51.34 (COO$\underline{CH_3}$); 51.12 ($C_{(8)}$); 48.99 ($C_{(7)}$); 45.14 ($C_{(9)}$).

The compounds **2b-d** were prepared similarly starting from **1b-d.**

Methyl 2,3-Dimethyl-4-oxiranylmethyl-4H-furo[3,2-*b*]pyrrole-5-carboxylate (2b). Yield 69%; mp 95°C (methanol). Found, %: C 62.75, H 6.23, N 5.58. $C_{13}H_{15}NO_4$ (249.26). Calculated, %: C 62.64, H 6.07, N 5.62. UV (dioxane), λ_{max}, nm (log ε): 312 (3.54), 356 (2.35). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 6.73 (1H, s, H-6); 4.90 (1H, dd, $J_{7d,7e}$ = 14.8, $J_{7e,8c}$ = 2.7, H-7d); 4.43 (1H, dd, $J_{7d,7e}$ = 14.8, $J_{7e,8c}$ = 5.2, H-7e); 3.80 (3H, s, COO$\underline{CH_3}$); 3.33 (1H, m, H-8c); 2.77 (1H, t, $J_{9a,9b}$ = 4.7, $J_{9b,8c}$ = 4.5, H-9b); 2.42 (1H, dd, $J_{9a,9b}$ = 4.7, $J_{9a,8c}$ = 2.6, H-9a); 2.30 (3H, s, $C_{(2)}$–CH_3); 2.14 (3H, s, $C_{(3)}$–CH_3). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.51 ($\underline{CO}OCH_3$); 155.26 ($C_{(2)}$); 143.58 ($C_{(6a)}$); 135.32 ($C_{(3a)}$); 120.85 ($C_{(5)}$); 103.89 ($C_{(3)}$); 98.66 ($C_{(6)}$); 51.69 (COO$\underline{CH_3}$); 50.87 ($C_{(8)}$); 47.47 ($C_{(7)}$); 45.10 ($C_{(9)}$); 12.45 ($C_{(2)}$–$\underline{CH_3}$); 8.33 ($C_{(3)}$–$\underline{CH_3}$).

Methyl 4-Oxiranylmethyl-2-phenyl-4H-furo[3,2-*b*]pyrrole-5-carboxylate (2c). Yield 79%; mp 103-104°C (methanol). Found, %: C 68.78, H 5.22, N 4.81. $C_{17}H_{15}NO_4$ (297.31). Calculated, %: C 68.68; H 5.09; N 4.71. UV (dioxane), λ_{max}, nm (log ε): 336 (3.69). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.70 (2H, m, *o*-Ph); 7.37 (2H, m, *m*-Ph); 7.26 (1H, m, *p*-Ph); 6.85 (1H, d, $J_{3,6}$ = 0.9, H-6); 6.77 (1H, d, $J_{3,6}$ = 0.9, H-3); 4.97 (1H, dd, $J_{7d,7e}$ = 14.7, $J_{7d,8c}$ = 2.7, H-7d); 4.26 (1H, dd, $J_{7d,7e}$ = 14.7, $J_{7e,8c}$ = 5.8, H-7e); 3.82 (3H, s, COO$\underline{CH_3}$); 3.35 (1H, m, H-8c); 2.81 (1H, t, $J_{9a,9b}$ = 4.7, $J_{9b,8c}$ = 4.7, H-9b); 2.53 (1H, dd, $J_{9a,9b}$ = 4.7, $J_{9a,8c}$ = 2.6, H-9a); NMR ^{13}C ($CDCl_3$), δ, ppm: 162.26 ($\underline{CO}OCH_3$); 159.94 ($C_{(2)}$); 145.51 ($C_{(6a)}$); 135.31 ($C_{(3a)}$); 130.94 (*i*-Ph); 128.63 (*o*-Ph); 127.97 (*p*-Ph); 124.00 (*m*-Ph); 122.69 ($C_{(5)}$); 98.88 ($C_{(6)}$); 93.56 ($C_{(3)}$); 51.35 (COO$\underline{CH_3}$); 51.08 ($C_{(8)}$); 48.97 ($C_{(7)}$); 45.11 ($C_{(9)}$).

Methyl 1-Oxiranylmethyl-1H-benzo[4,5]furo[3,2-*b*]pyrrole-2-carboxylate (2d). Yield 50%; mp 119-121°C. Found, %: C 66.38, H 4.88, N 5.19. $C_{15}H_{13}NO_4$ (271.27). Calculated, %: C 66.41, H 4.83, N 5.16. UV (dioxane), λ_{max}, nm (log ε): 326 (3.54), 361 (2.32). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.71-7.27

(4H, m, H-5, H-6, H-7, H-8); 6.89 (1H, s, H-3); 5.09 (1H, dd, $J_{9d,9e}$ = 14.7, $J_{9d,10c}$ = 3.1, H-9d); 4.63 (1H, dd, $J_{9d,9e}$ = 14.7, $J_{9e,10c}$ = 5.4, H-9e); 3.86 (3H, s, COO$\underline{CH_3}$); 3.45 (1H, m, H-10c); 2.81 (1H, t, $J_{11a,11b}$ = 4.6, $J_{11b,10c}$ = 4.6, H-11b); 2.57 (1H, dd, $J_{11a,11b}$ = 4.6, $J_{11a,10c}$ = 2.6, H-11a). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.07 ($\underline{CO}OCH_3$); 160.61 ($C_{(4a)}$); 147.18 ($C_{(3a)}$); 128.74 ($C_{(2)}$); 125.00 ($C_{(6)}$); 123.48 ($C_{(8b)}$); 122.76 ($C_{(7)}$); 118.37 ($C_{(8)}$); 118.14 ($C_{(8a)}$); 112.58 ($C_{(5)}$); 99.06 ($C_{(3)}$); 51.57 (COO$\underline{CH_3}$); 51.34 ($C_{(10)}$); 49.17 ($C_{(9)}$); 45.16 ($C_{(11)}$).

Reactions of Compounds 2a-d with Heterocyclic Amines (General Procedure). A solution of the selected amine (morpholine, piperidine, pyrrolidine or 4-methylpiperazine) (30 mmol) and one of the compounds **2a-d** (5 mmol) in methanol (7 ml) was refluxed until the reaction was ceased (TLC-checked). After evaporation of the amine excess and methanol in vacuum the crude product was purified by column chromatography (silica gel and $CHCl_3$ as eluent) and crystallized.

Methyl 4-(2-Hydroxy-3-morpholin-4-yl-propyl)-4*H*-furo[3,2-*b*]pyrrole-5-carboxylate (3a). Yield 79%; mp 132-134°C (methanol). Found, %: C 58.63; H 6.68; N 9.01. $C_{15}H_{20}N_2O_5$ (308.33). Calculated, %: C 58.43%; H 6.54; N 9.09. UV (dioxane), λ_{max}, nm (log ε): 298 (3.44); 269 (3.03). IR (KBr), ν, cm^{-1}: 1686 (CO); 3130 (OH). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.50 (1H, d, $J_{2,3}$ = 2.3, H-2); 6.83 (1H, d, $J_{3,6}$ = 0.9, H-6); 6.53 (1H, dd, $J_{2,3}$ = 2.2, $J_{3,6}$ = 0.9, H-3); 4.63 (1H, dd, $J_{7d,7e}$ = 14.1, $J_{7d,8c}$ = 3.4, H-7d); 4.34 (1H, dd, $J_{7d,7e}$ = 14.1, $J_{7e,8c}$ = 6.6, H-7e); 4.10 (1H, m, H-8c); 3.82 (3H, s, COO$\underline{CH_3}$); 2.48 (1H, dd, $J_{9a,9b}$ = 12.4, $J_{9a,8c}$ = 3.9, H-9a); 2.32 (1H, dd, $J_{9a,9b}$ = 12.4, $J_{9b,8c}$ = 9.9, H-9b); morpholin-4-yl: 3.62 (4H, m, $O(CH_2)_2$); 2.50 (4H, m, $N(CH_2)_2$). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.81 ($\underline{CO}OCH_3$); 148.55 ($C_{(2)}$); 145.65 ($C_{(6a)}$); 134.37 ($C_{(3a)}$); 122.99 ($C_{(5)}$); 99.34 ($C_{(3)}$); 98.96 ($C_{(6)}$); 67.21 ($C_{(8)}$); 53.65 ($C_{(7)}$); 51.18 (COO$\underline{CH_3}$); 50.93 ($C_{(9)}$); morpholin-4-yl: 66.93 ($O(CH_2)_2$); 61.39 ($N(CH_2)_2$).

Methyl 4-(2-Hydroxy-3-morpholin-4-yl-propyl)-2,3-dimethyl-4H-furo[3,2-*b*]pyrrole-5-carboxylate (3b). Yield 60%; mp 94-95°C (methanol). Found, %: C 60.92; H 7.09; N 8.45. $C_{17}H_{24}N_2O_5$ (336.38). Calculated, %: C 60.70; H 7.19; N 8.33. UV (dioxane), λ_{max}, nm (log ε): 312 (3.48); 307 (3.46); 270 (2.87). IR (KBr), ν, cm^{-1}: 1688 (CO); 3425 (OH). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 6.70 (1H, s, H-6); 4.61 (1H, dd, $J_{7d,7e}$ = 14.0, $J_{7d,8c}$ = 3.2, H-7d); 4.24 (1H, dd, $J_{7d,7e}$ = 14.0, $J_{7e,8c}$ = 7.5, H-7e); 4.03 (1H, m, H-8c); 3.76 (3H, s, COO$\underline{CH_3}$); 2.46 (1H, dd, $J_{9a,9b}$ = 12.4, $J_{9a,8c}$ = 4.2, H-9a); morpholin-4-yl: 3.63 (4H, m, $O(CH_2)_2$); 2.59-2.40 (5H, m, $N(CH_2)_2$, H-9b); 2.28 (3H, s, $C_{(2)}$–CH_3); 2.17 (3H, s, $C_{(3)}$–CH_3). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.73 ($\underline{CO}OCH_3$); 155.08 ($C_{(2)}$); 143.46 ($C_{(6a)}$); 135.43 ($C_{(3a)}$); 120.62 ($C_{(5)}$); 103.98 ($C_{(3)}$); 98.55 (C(6)); 67.46 ($C_{(8)}$); 53.61 ($C_{(7)}$); 50.81 (COO$\underline{CH_3}$); 50.32 ($C_{(9)}$); 12.41 ($C_{(2)}$–$\underline{CH_3}$); 8.55 ($C_{(3)}$–$\underline{CH_3}$); morpholin-4-yl: 66.80 ($O(CH_2)_2$); 61.67 ($N(CH_2)_2$).

Methyl 4-(2-Hydroxy-3-piperidin-1-yl-propyl)-2-phenyl-4H-furo[3,2-*b*]pyrrole-5-carboxylate (3c). Yield 58%; mp 117°C (methanol). Found, %: C 69.39; H 6.77; N 7.43. $C_{22}H_{26}N_2O_4$ (382.45). Calculated, %: C 69.09; H 6.85; N 7.32. UV (dioxane), λ_{max}, nm (log ε): 354 (3.37); 338 (3.42); 282 (2.51). IR (KBr), ν, cm^{-1}: 1697 (CO); 3208 (OH). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.71 (2H, m, *o*-Ph); 7.37 (2H, m, *m*-Ph); 7.25 (1H, m, *p*-Ph); 6.82 (1H, s, H-6); 6.80 (1H, s, H-3); 4.62 (1H, dd, $J_{7d,7e}$ = 14.1, $J_{7d,8c}$ = 3.3, H-7d); 4.30 (1H, dd, $J_{7d,7e}$ = 14.1, $J_{7e,8c}$ = 6.6, H-7e); 4.08 (1H, m, H-8c); 3.81 (3H, s, COO$\underline{CH_3}$); 2.41 (1H, dd, $J_{9a,9b}$ = 12.4, $J_{9a,8c}$ = 3.9, H-9a); 2.25 (1H, dd, $J_{9a,9b}$ = 12.4, $J_{9b,8c}$ = 10.1, H-9b); piperidin-1-yl: 2.53-2.30 (4H, m, $N(CH_2)_2$); 1.51-1.40 (6H, m, 3 × CH_2). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.55 ($\underline{CO}OCH_3$); 159.71 ($C_{(2)}$); 145.42 ($C_{(6a)}$); 136.02 ($C_{(3a)}$); 131.16 (*i*-Ph); 128.63 (*o*-Ph); 127.85 (*p*-Ph); 124.00 (*m*-Ph); 122.70 ($C_{(5)}$); 98.69 ($C_{(6)}$); 94.27 ($C_{(3)}$); 67.19 ($C_{(8)}$); 54.59 ($C_{(7)}$); 51.10 ($C_{(9)}$); 51.07 (COO$\underline{CH_3}$); piperidin-1-yl: 61.52 ($N(CH_2)_2$); 26.03 (2 × CH_2); 24.17 (CH_2).

Methyl 1-(2-Hydroxy-3-piperidin-1-yl-propyl)-1H-benzo[4,5]furo[3,2-*b*]pyrrole-2-carboxylate (3d). Yield 50%; mp 126-128°C (methanol). Found, %: C 67.55; H 6.64; N 7.88. $C_{20}H_{24}N_2O_4$ (356.42). Calculated, %: C 67.40; H 6.79; N 7.86. UV (dioxane), λ_{max}, nm (log ε): 324 (3.53); 318 (3.51); 263 (3.04); 253 (2.78). IR (KBr), ν, cm^{-1}: 1695 (CO); 3230 (OH). NMR ^{1}H ($CDCl_3$), δ, ppm, *J* (Hz): 7.85; 7.46; 7.25 (1H, 1H, 2H, m, H-5, H-6, H-7, H-8); 6.87 (1H, s, H-3); 4.80 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9d,10c}$ = 3.5, H-9d); 4.54 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9e,10c}$ = 7.0, H-9e); 4.13 (1H, m, H-10c); 3.82 (3H, s, COO$\underline{CH_3}$); 2.47 (1H, dd, $J_{11a,11b}$ = 12.0, $J_{11a,10c}$ = 4.2, H-11a); 2.34 (1H, dd, $J_{11a,11b}$ = 12.0, $J_{11b,10c}$ = 9.3, H-11b); piperidin-1-yl: 2.60-2.23 (4H, m,

$N(CH_2)_2$); 1.37 (6H, m, 3 × CH_2). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.34 (<u>CO</u>OCH_3); 160.64 ($C_{(4a)}$); 147.04 ($C_{(3a)}$); 129.13 ($C_{(8b)}$); 124.76 ($C_{(6)}$); 123.38 ($C_{(2)}$); 122.49 ($C_{(7)}$); 119.11 ($C_{(8)}$); 118.58 ($C_{(8a)}$); 112.38 ($C_{(5)}$); 98.76 ($C_{(3)}$); 67.67 ($C_{(10)}$); 54.67 ($C_{(11)}$); 51.79 ($C_{(9)}$); 51.26 (COO<u>CH_3</u>); piperidin-1-yl: 61.80 ($N(CH_2)_2$); 26.04 (2 × CH_2); 24.18 (CH_2).

Methyl 1-(2-Hydroxy-3-pyrrolidin-1-yl-propyl)-1H-benzo[4,5]furo[3,2-*b*]pyrrole-2-carboxylate (3e). Yield 34%; mp 99-104°C (methanol). Found, %: C 66.74; H 6.33; N 8.24. $C_{19}H_{22}N_2O_4$ (342.39). Calculated, %: C 66.65; H 6.48; N 8.18. UV (dioxane), λ_{max}, nm (log ε): 325 (3.56); 318 (3.55); 263 (3.07); 253 (3.05). IR (KBr), ν, cm^{-1}: 1697 (CO); 3220 (OH). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.84; 7.46; 7.25 (1H, 1H, 2H, m, H-5, H-6, H-7, H-8); 6.87 (1H, s, H-3); 4.82 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9d,10c}$ = 3.5, H-9d); 4.56 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9e,10c}$ = 7.0, H-9e); 4.12 (1H, m, H-10c); 3.83 (3H, s, COO<u>CH_3</u>); 2.67 (1H, dd, $J_{11a,11b}$ = 12.3, $J_{11a,10c}$ = 4.1, H-11a); 2.50 (1H, dd, $J_{11a,11b}$ = 12.3, $J_{11b,10c}$ = 9.8, H-11b); pyrrolidin-1-yl: 2.43-2.65 (4H, m, $N(CH_2)_2$); 1.70 (4H, m, 2 × CH_2). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.44 (<u>CO</u>OCH_3); 160.65 ($C_{(4a)}$); 147.04 ($C_{(3a)}$); 129.15 ($C_{(8b)}$); 124.79 ($C_{(6)}$); 123.44 ($C_{(2)}$); 122.50 ($C_{(7)}$); 119.13 ($C_{(8)}$); 118.56 ($C_{(8a)}$); 112.39 ($C_{(5)}$); 98.80 ($C_{(3)}$); 69.68 ($C_{(10)}$); 59.22 ($C_{(11)}$); 51.89 ($C_{(9)}$); 51.33 (COO<u>CH_3</u>); pyrrolidin-1-yl: 54.12 ($N(CH_2)_2$); 23.60 (–CH_2–CH_2–).

Methyl 1-[2-Hydroxy-3-(4-methylpiperazin-1-yl)-propyl)-1H-benzo[4,5]furo[3,2-*b*]pyrrole-2-carboxylate (3f). Yield 63%; mp 69-72°C (methanol). Found, %: C 64.49; H 6.71; N 11.17. $C_{20}H_{25}N_3O_4$ (371.43). Calculated, %: C 64.67; H 6.78; N 11.31. UV (dioxane), λ_{max}, nm (log ε): 325 (3.54); 318 (3.53); 263 (3.05); 253 (3.02). IR (KBr), ν, cm^{-1}: 1696 (CO); 3240 (OH). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.85; 7.47; 7.26 (1H, 1H, 2H, m, H-5, H-6, H-7, H-8); 6.89 (1H, s, H-3); 4.82 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9d,10c}$ = 3.4, H-9d); 4.56 (1H, dd, $J_{9d,9e}$ = 14.0, $J_{9e,10c}$ = 7.1, H-9e); 4.14 (1H, m, H-10c); 3.83 (3H, s, COO<u>CH_3</u>); 2.52 (1H, dd, $J_{11a,11b}$ = 12.4, $J_{11a,10c}$ = 4.3, H-11a); 2.43 (1H, dd, $J_{11a,11b}$ = 12.4, $J_{11b,10c}$ = 9.4, H-11b); 4-methylpiperazin-1-yl: 2.60 (4H, m, $N(CH_2)_2$), 2.45 (4H, m, $N(CH_2)_2$); 2.28 (3H, s, N–CH_3). NMR ^{13}C ($CDCl_3$), δ, ppm: 162.38 (<u>CO</u>OCH_3); 160.64 ($C_{(4a)}$); 147.04 ($C_{(3a)}$); 129.13 ($C_{(8b)}$); 124.83 ($C_{(6)}$); 123.40 ($C_{(2)}$); 122.54 ($C_{(7)}$); 119.05 ($C_{(8)}$); 118.54 ($C_{(8a)}$); 112.46 ($C_{(5)}$); 98.87 ($C_{(3)}$); 67.79 ($C_{(10)}$); 53.13 ($C_{(11)}$); 51.74 ($C_{(9)}$); 51.33 (COO<u>CH_3</u>); 4-methylpiperazin-1-yl: 61.09 ($N(CH_2)_2$); 55.07 ($N(CH_2)_2$); 45.90 (N–CH_3).

6-Pyrrolidin-1-ylmethyl-4,5-dihydrofuro[2',3':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-one (4a). Yield 45%; mp 128-130°C (methanol). Found, %: C 64.72; H 6.11; N 10.68. $C_{14}H_{16}N_2O_3$ (260.29). Calculated, %: C 64.60; H 6.20; N 10.76. UV (dioxane), λ_{max}, nm (log ε): 305 (3.44); 298 (3.42); 270 (3.05). IR (KBr), ν, cm^{-1}: 1695 (CO); NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.56 (1H, d, $J_{2,3}$ = 2.2, H-2); 6.92 (1H, d, $J_{3,9}$ = 0.7, H-9); 6.46 (1H, dd, $J_{2,3}$ = 2.2, $J_{3,9}$ = 0.7, H-3); 4.82 (1H, m, H-6c); 4.32 (1H, dd, $J_{5d,5e}$ = 12.8, $J_{5d,6c}$ = 3.4, H-5d); 4.07 (1H, dd, $J_{5d,5e}$ = 12.8, $J_{5e,6c}$ = 10.1, H-5e); 2.97 (1H, dd, $J_{10a,10b}$ = 12.8, $J_{10a,6c}$ = 7.6, H-10a); 2.85 (1H, dd, $J_{10a,10b}$ = 12.8, $J_{10b,6c}$ = 5.1, H-10b); pyrrolidin-1-yl: 2.62 (4H, m, $N(CH_2)_2$); 1.79 (4H, m, 2 × CH_2). NMR ^{13}C ($CDCl_3$), δ, ppm: 159.21 ($C_{(8)}$); 149.59 ($C_{(2)}$); 147.46 ($C_{(9a)}$); 130.49 ($C_{(3a)}$); 120.35 ($C_{(8a)}$); 97.85 ($C_{(3)}$); 97.45 ($C_{(9)}$); 76.17 ($C_{(6)}$); 57.11 ($C_{(5)}$); 45.06 ($C_{(10)}$); pyrrolidin-1-yl: 54.84 ($N(CH_2)_2$); 23.58 (–CH_2–CH_2–).

6-(4-Methylpiperazin-1-yl)methyl-5,6-dihydrofuro[2',3':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-one (4b). Yield 62%; mp 163-164°C (methanol). Found, %: C 62.46; H 6.59; N 14.66. $C_{15}H_{19}N_3O_3$ (289.33). Calculated, %: C 62.27; H 6.62; N 14.52. UV (dioxane), λ_{max}, nm (log ε): 305 (3.46); 298 (3.45); 270 (3.05). IR (KBr), ν, cm^{-1}: 1698 (CO). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.54 (1H, d, $J_{2,3}$ = 2.3, H-2); 6.90 (1H, d, $J_{3,9}$ = 0.7, H-9); 6.45 (1H, dd, $J_{2,3}$ = 2.3, $J_{3,9}$ = 0.7, H-3); 4.81 (1H, m, H-6c); 4.25 (1H, dd, $J_{5d,5e}$ = 12.8, $J_{5d,6c}$ = 3.4, H-5d); 4.04 (1H, dd, $J_{5d,5e}$ = 12.8, $J_{5e,6c}$ = 10.0, H-5e); 2.80 (1H, dd, $J_{10a,10b}$ = 13.2, $J_{10a,6c}$ = 7.1, H-10a); 2.72 (1H, dd, $J_{10a,10b}$ = 13.2, $J_{10b,6c}$ = 5.1, H-10b); 4-methylpiperazin-1-yl: 2.58 (4H, m, $N(CH_2)_2$); 2.42 (4H, m, $N(CH_2)_2$); 2.28 (3H, s, N–CH_3). NMR ^{13}C ($CDCl_3$), δ, ppm:159.30 ($C_{(8)}$); 149.71 ($C_{(2)}$); 147.51 ($C_{(9a)}$); 130.55 ($C_{(3a)}$); 120.36 ($C_{(8a)}$); 97.86 ($C_{(3)}$); 97.60 ($C_{(9)}$); 75.45 ($C_{(6)}$); 59.10 ($C_{(5)}$); 45.04 ($C_{(10)}$); 4-methylpiperazin-1-yl: 55.01 ($N(CH_2)_2$); 54.01 ($N(CH_2)_2$); 45.97 (N–CH_3).

6-Morpholin-4-ylmethyl-2-phenyl-5,6-dihydrofuro[2',3':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-one (4c). Yield 64%; mp 169-170°C (methanol). Found, %: C 68.32; H 5.62; N 7.79. $C_{20}H_{20}N_2O_4$ (352.38). Calculated, %: C 68.17; H 5.72; N 7.95. UV (dioxane), λ_{max}, nm (log ε): 354 (3.36); 338 (3.40); 280 (2.48). IR (KBr), ν, cm^{-1}: 1692 (CO). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.70 (2H, m, *o*-Ph); 7.39 (2H, m, *m*-Ph); 7.30

(1H, m, *p*-Ph); 6.91 (1H, s, H-9); 6.67 (1H, s, H-3); 4.81 (1H, m, H-6c); 4.29 (1H, dd, $J_{5d,5e}$ = 12.9, $J_{5d,6c}$ = 3.4, H-5d); 4.04 (1H, dd, $J_{5d,5e}$ = 12.9, $J_{5e,6c}$ = 10.0, H-5e); 2.80 (1H, dd, $J_{10a,10b}$ = 13.4, $J_{10a,6c}$ = 5.1, H-10a); 2.70 (1H, dd, $J_{10a,10b}$ = 13.4, $J_{10b,6c}$ = 7.0, H-10b); morpholin-4-yl: 3.69 (4H, m, $O(CH_2)_2$); 2.55 (4H, m, $N(CH_2)_2$). NMR ^{13}C ($CDCl_3$), δ, ppm: 161.12 ($C_{(8)}$); 159.06 ($C_{(2)}$); 147.18 ($C_{(9a)}$); 132.19 ($C_{(3a)}$); 130.54 (*i*-Ph); 128.81 (*o*-Ph); 128.53 (*p*-Ph); 124.10 (*m*-Ph); 119.93 ($C_{(8a)}$); 97.58 ($C_{(9)}$); 92.21 ($C_{(3)}$); 75.08 ($C_{(6)}$); 59.58 ($C_{(5)}$); 44.92 ($C_{(10)}$); morpholin-4-yl: 66.83 ($O(CH_2)_2$); 54.41 ($N(CH_2)_2$).

2-Phenyl-6-pyrrolidin-1-ylmethyl-5,6-dihydrofuro[2',3':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-one (4d). Yield 54%; mp 156-157°C (methanol). Found, %: C 71.55; H 5.83; N 8.39. $C_{20}H_{20}N_2O_3$ (336.38). Calculated, %: C 71.41; H 5.99; N 8.33. UV (dioxane), λ_{max}, nm (log ε): 354 (3.37); 338 (3.42); 280 (2.48). IR (KBr), ν, cm^{-1}: 1705 (CO). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.72 (2H, m, *o*-Ph); 7.40 (2H, m, *m*-Ph); 7.31 (1H, m, *p*-Ph); 6.94 (1H, s, H-9); 6.69 (1H, s, H-3); 4.82 (1H, m, H-6c); 4.33 (1H, dd, $J_{5d,5e}$ = 13.0, $J_{5d,6c}$ = 3.3, H-5d); 4.07 (1H, dd, $J_{5d,5e}$ = 13.0, $J_{5e,6c}$ = 10.3, H-5e); 2.98 (1H, dd, $J_{10a,10b}$ = 12.8, $J_{10a,6c}$ = 5.0, H-10a); 2.86 (1H, dd, $J_{10a,10b}$ = 12.8, $J_{10b,6c}$ = 7.7, H-10b); pyrrolidin-1-yl: 2.63 (4H, m, $N(CH_2)_2$); 1.80 (4H, m, 2 × CH_2). NMR ^{13}C ($CDCl_3$), δ, ppm: 160.95 ($C_{(8)}$); 159.14 ($C_{(2)}$); 147.15 ($C_{(9a)}$); 132.08 ($C_{(3a)}$); 130.55 (*i*-Ph); 128.72 (*o*-Ph); 128.40 (*p*-Ph); 124.12 (*m*-Ph); 120.00 ($C_{(8a)}$); 97.42 ($C_{(9)}$); 92.21 ($C_{(3)}$); 76.04 ($C_{(6)}$); 57.09 ($C_{(5)}$); 45.00 ($C_{(10)}$); pyrrolidin-1-yl: 54.84 ($N(CH_2)_2$); 23.58 (–CH_2–CH_2–).

6-(4-Methylpiperazin-1-yl)methyl-2-phenyl-5,6-dihydrofuro[2',3':4,5]pyrrolo[2,1-*c*][1,4]oxazin-8-one (4e). Yield 42%; mp 189-190°C (methanol). Found, %: C 69.18; H 6.31; N 11.57. $C_{21}H_{23}N_3O_3$ (365.43). Calculated, %: C 69.02; H 6.34; N 11.50. UV (dioxane), λ_{max}, nm (log ε): 354 (3.36); 338 (3.40); 280 (2.45). IR (KBr), ν, cm^{-1}: 1705 (CO). NMR ^1H ($CDCl_3$), δ, ppm, *J* (Hz): 7.71 (2H, m, *o*-Ph); 7.40 (2H, m, *m*-Ph); 7.30 (1H, m, *p*-Ph); 6.92 (1H, s, H-9); 6.67 (1H, s, H-3); 4.81 (1H, m, H-6c); 4.27 (1H, dd, $J_{5d,5e}$ = 12.9, $J_{5d,6c}$ = 3.4, H-5d); 4.02 (1H, dd, $J_{5d,5e}$ = 12.9, $J_{5e,6c}$ = 10.1, H-5e); 2.82 (1H, dd, $J_{10a,10b}$ = 13.3, $J_{10a,6c}$ = 5.0, H-10a); 2.72 (1H, dd, $J_{10a,10b}$ = 13.3, $J_{10b,6c}$ = 7.1, H-10b); 4-methylpiperazin-1-yl: 2.60 (4H, m, $N(CH_2)_2$), 2.45 (4H, m, $N(CH_2)_2$), 2.28 (3H, s, N–CH_3). NMR ^{13}C ($CDCl_3$), δ, ppm: 160.97 ($C_{(8)}$); 159.11 ($C_{(2)}$); 147.11 ($C_{(9a)}$); 132.10 ($C_{(3a)}$); 130.50 (*i*-Ph); 128.75 (*o*-Ph); 128.44 (*p*-Ph); 124.11 (*m*-Ph); 119.93 ($C_{(8)}$); 97.40 ($C_{(9)}$); 92.22 ($C_{(3)}$); 75.27 ($C_{(6)}$); 59.03 ($C_{(5)}$); 44.91 ($C_{(10)}$); 4-methylpiperazin-1-syl: 55.02 ($N(CH_2)_2$); 54.01 ($N(CH_2)_2$); 45.97 (N–CH_3).

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