Heterocycles of biological importance: Part 7¹.

Synthesis of biologically active pyrimido[2,1-*b*]benzothiazoles from acetylenic acids and 2-aminobenzothiazoles

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Abstract

Conjugate addition of the imino nitrogen of 2-aminobenzothiazoles **1** to the alkyne β -carbon atom of acetylenic acids **2** followed by ring closure gives rise to novel 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones in good yield.

Keywords: Michael addition, amidines, fused nitrogen heterocycles, cyclocondensation

Introduction

Condensed pyrimidine compounds have been shown to exhibit interesting pharmacological properties² and a number of synthetic methods³⁻¹¹ has been reported for their preparation. As a part of an ongoing study of the syntheses of heterocyclic compounds of potential biological activity from allenic and acetylenic compounds,¹²⁻¹³ we have shown recently¹⁴ that substituted and unsubstituted 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones are a new group of GABA_A/benzodiazepine receptor ligands. In this paper we wish to present the preparation of these compounds.

Results and Discussion

The conjugate addition of 2-aminobenzothiazole **1** to the acetylenic acids **2** in butanol, followed by cyclocondensation, gave the corresponding 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones **6-8** in 68–86% yield (Scheme 1).

Scheme 1

The structures of these compounds were established beyond any doubt by their ¹H-NMR and ¹³C-NMR spectra and by additional COSY, HMQC (Heteronuclear Multiple-Quantum Correlation) and HMBC (Heteronuclear Multiple-Bond Correlation) experiments.

When 2-aminobenzothiazoles **1a-1d** were allowed to react with phenyl propiolic acid (**2c**), 4-phenyl-2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones **8a-8d** were obtained. The NMR spectra of the 8-methoxy compound **8c** and the 8-ethoxy compound **8d** showed singlets at δ 6.20 ppm and δ 6.15 ppm, respectively, attributed to 3-H, and doublets at δ 6.01 ppm and δ 5.96 ppm, respectively, for 6-H. The shielding effects observed for the 6-H in the compounds **8a-8d** is due to the diamagnetic effect of the phenyl group attached to C-4.

The above data exclude the formation of the isomeric 2-phenyl-4*H*-pyrimido[2,1-*b*]benzothiazole-4-ones **9** which should exhibit a deshielded proton (6-H) near δ 9 ppm resulting from the anisotropic effect of the carbonyl group⁵. Further evidence for the formation of the 2-one derivatives was obtained from the fact that no shielding effect was noticed in compounds **6a-d** and **7a-d** where the phenyl group was replaced by H or 1-pentyl, respectively.

The reaction of 2-aminobenzothiazoles **1** with acetylenic acids **2** is rationalized as shown (Scheme 1), whereby the alkynoic acid is first attacked at the β -carbon atom by the ring nitrogen atom of the benzothiazole. An attack of the 2-amino group of **1** on the β -carbon of **2** which eventually would generate the isomeric product **9** definitely does not occur^{15, 16} (Scheme 2).

Scheme 2

Experimental Section

General Procedures. All the melting points were determined with a Reichert Thermovar microscope and are uncorrected. Electron impact mass spectra (direct inlet, 70 eV) were recorded with a Jeol JMS-SX102 spectrometer. The Ultraviolet (UV) spectra were determined in an ethanol-chloroform mixture (1:1) on a Perkin – Elmer 554 instrument and the Infrared (IR) spectra were recorded with a Varian Cary 2290 and Perkin Elmer 298 spectrometers. ¹H-NMR (500 MHz) and ¹³C-NMR spectra (125 MHz) were recorded at room temperature with a Bruker instrument using an inverse 5 mm probe equipped with a shielded gradient coil. Chemical shifts (δ) are given in ppm and coupling constants (in brackets) are reported in Hz. COSY, HMQC and HMBC experiments were performed with gradient enhancements using sine shaped gradient pulses, and for the 2D heteronuclear correlation spectroscopy, the refocusing delays were optimised for ¹J_{CH} = 145 Hz and ²J_{CH} = 10 Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker UXNMR software (rev. 941001). Combustion analyses were performed with CHN + O/S elemental analyser “CARLO ERBA” model 1106. The purity of the samples was checked routinely by TLC.

Synthesis of 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones **6a-d**, **7a-d** and **8a-d**

The alkynoic acid **2a-c** (20 mmol) and the appropriate 2-aminobenzothiazole (**1a-d**, 10 mmol) were heated to reflux in 1-butanol (50 mL) for 48 hours. Evaporation of solvent under reduced pressure gave the crude product which was crystallized from hexane/ethyl acetate to give the 2*H*-pyrimido[2,1-*b*]benzothiazol-2-ones.

2H-Pyrimido[2,1-*b*]benzothiazol-2-one (6a). From **1a** and **2a**, Yield: 68 %; colourless crystals mp 272 – 275 °C [Lit⁴: mp 272 – 275 °C]; IR: ν/cm^{-1} 1630 (C=O), 1583 (C=N), 1533 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 260 (4.03), 300 (4.11). NMR data: δ_{H} (CDCl₃) 6.32 (1H, d, $J_{3,4}$ 7.7 Hz, 3-H), 7.46 (1H, dd, $J_{7,6} = J_{7,8}$ 8.0 Hz, 7-H), 7.58 (1H, dd, $J_{8,7} = J_{8,9}$ 8.0 Hz, 8-H), 7.98 (1H, d, $J_{9,8}$ 7.9 Hz, 9-H), 8.03 (1H, d, $J_{6,7}$ 8.2 Hz, 6-H), 8.86 (1H, d, $J_{4,3}$ 7.7 Hz, 4-H). δ_{C} (CDCl₃) 110.8 (C-3), 122.9 (C-9a), 123.7 (C-6), 126.1 (C-9), 127.2 (C-7), 128.8 (C-8), 134.8 (C-4), 135.0 (C-5a), 163.6 (C-10a), 166.9 (C-2). MS (EI): m/z 202.0213 (M^+ , 100 %, C₁₀H₆N₂OS requires 202.0201) 176 (32), 174 (64), 150 (15), 148 (13); Anal. Calcd. for C₁₀H₆N₂OS: C, 59.41; H, 2.97; N, 13.86; O, 7.92; S, 15.84. Found: C, 59.49; H, 3.03; N, 13.78; S, 15.70.

7,8-Dimethyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (6b). From **1b** and **2a**, Yield: 75%; colourless crystals, no melt below 300°C. IR: ν/cm^{-1} 1640 (C=O), 1617 (C=N), 1570 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 265 (4.16), 276 (4.12), 307 (4.26). NMR data: δ_{H} (CDCl₃) 2.30 (3H, s, 8-CH₃), 2.35 (3H, s, 7-CH₃), 6.41 (1H, d, $J_{3,4}$ 7.7 Hz, 3-H), 7.35 (1H, s, 9-H), 7.37 (1H, s, 6-H), 8.24 (1H, d, $J_{4,3}$ 7.7 Hz, 4-H); δ_{C} (CDCl₃) 19.7 (7-CH₃), 20.1 (8-CH₃), 111.5 (C-3), 112.1 (C-6), 120.6 (C-9a), 123.5 (C-9), 132.2 (C-5a), 133.1 (C-4), 136.3 (C-8), 137.0 (C-7), 164.3 (C-10a), 168.5 (C-2). MS (EI): m/z 230.0513 (M^+ , 100 %, C₁₂H₁₀N₂OS requires 230.0514) 204 (20), 202 (52), 189 (18), 187 (15). Anal. Calcd. for C₁₂H₁₀N₂OS: C, 62.61; H, 4.35; N, 12.17; O, 6.96; S, 13.91. Found: C, 62.72; H, 4.39; N, 12.11; S, 13.83.

8-Methoxy-2H-pyrimido[2,1-*b*]benzothiazol-2-one (6c). From **1c** and **2a**, Yield: 80%; colourless crystals; no melt below 300°C (Lit⁴: > 300 °C). IR: ν/cm^{-1} 1636 (C=O), 1492 (C=N), 1472 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 242 (4.27), 277 (4.12), 311 (4.21). NMR data: δ_{H} (CDCl₃) 3.82 (3H, s, 8-OCH₃), 6.29 (1H, d, $J_{3,4}$ 7.7 Hz, 3-H), 7.16 (1H, dd, $J_{7,6}$ 9.1 Hz and $J_{7,9}$ 2.6 Hz, 7-H), 7.64 (1H, d, $J_{9,7}$ 2.6 Hz, 9-H), 7.95 (1H, d, $J_{6,7}$ 9.1 Hz, 6-H), 8.81 (1H, d, $J_{4,3}$ 7.7 Hz, 4-H); δ_{C} (CDCl₃) 55.9 (8-OCH₃), 108.0 (C-9), 110.6 (C-3), 113.5 (C-7), 114.4 (C-6), 124.3 (C-9a), 128.6 (C-5a), 135.0 (C-4), 157.6 (C-8), 163.2 (C-10a), 166.7 (C-2). MS (EI): m/z 232.0319 (M^+ , 100 %, C₁₁H₈N₂O₂S requires 232.0306) 206 (18), 204 (33), 191 (20), 189 (27). Anal. Calcd. for C₁₁H₈N₂O₂S: C, 56.90; H, 3.45; N, 12.07; O, 13.79; S, 13.79. Found: C, 56.85; H, 3.51; N, 12.07; S, 13.88.

8-Ethoxy-2H-pyrimido[2,1-*b*]benzothiazol-2-one (6d). From **1d** and **2a**, Yield: 83%; colourless crystals (83 %); no melt below 300°C. IR: ν/cm^{-1} 1640 (C=O), 1585 (C=N), 1500 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 240 (4.30), 278 (4.12), 313 (4.23). NMR data: δ_{H} (CDCl₃) 1.35 (3H, t, J 6.9 Hz, 8-OCH₂CH₃), 4.09 (2H, q, J 6.9 Hz, 8-OCH₂CH₃), 6.29 (1H, d, $J_{3,4}$ 7.7 Hz, 3-H), 7.15 (1H, dd, $J_{7,6}$ 9.0 Hz and $J_{7,9}$ 2.4 Hz, 7-H), 7.61 (1H, d, $J_{9,7}$ 2.4 Hz, 9-H), 7.92 (1H, d, $J_{6,7}$ 9.0 Hz, 6-H), 8.80 (1H, d, $J_{4,3}$ 7.7 Hz, 4-H). δ_{C} (CDCl₃) 14.5 (8-OCH₂CH₃), 64.0 (8-OCH₂CH₃), 108.4 (C-9), 110.6 (C-3), 113.5 (C-7), 114.8 (C-6), 124.3 (C-9a), 128.5 (C-5a), 135.0 (C-4), 156.8 (C-8), 163.2 (C-10a), 166.7 (C-2). MS (EI): m/z 246.0461 (M^+ , 100 %, C₁₂H₁₀N₂O₂S requires 246.0463) 218 (32), 192 (21), 190 (55), 165 (10). Anal. Calcd. for C₁₂H₁₀N₂O₂S: C, 58.54; H, 4.06; N, 11.38; O, 13.01; S, 13.01. Found: C, 58.65; H, 4.04; N, 11.28; S, 13.01.

4-Pentyl- 2H-pyrimido[2,1-*b*]benzothiazol-2-one (7a). From **1a** and **2b**, Yield 75%; colourless crystals, mp 138-140°C. IR: ν/cm^{-1} 1634 (C=O), 1576 (C=N), 1500 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 225 (4.47), 262 (4.13), 293 (4.06), 301 (4.08). NMR data: δ_{H} (CDCl₃) 0.86 (3H, t, $J_{5',4'}$ 7.2 Hz, 5'-H), 1.33 (2H, m, 4'-H), 1.43 (2H, m, 3'-H), 1.70 (2H, tt, $J_{2',1'}$ 8 Hz and $J_{2',3'}$ 8 Hz, 2'-H), 3.02 (2H, t, $J_{1',2'}$ 7.5 Hz, 1'-H), 6.13 (1H, s, 3-H), 7.36 (1H, dd, $J_{8,7}$ 9 Hz and $J_{8,9}$ 8 Hz, 8-H), 7.42 (1H, dd, $J_{7,6}$ 9.0 Hz and $J_{7,8}$ 8 Hz 7-H), 7.61 (1H, d, $J_{9,8}$ 7.8 Hz, 9-H), 7.74 (1H, d, $J_{6,7}$ 8.6 Hz, 6-H). δ_{C} (CDCl₃) 13.7 (C-5'), 22.1 (C-4'), 26.5 (C-2'), 30.7 (C-3'), 33.5 (C-1'), 110.7 (C-3), 116.0 (C-6), 123.1 (C-9), 124.1 (C-9a), 126 (C-7), 126.9 (C-8), 135.6 (C-5a), 151.5 (C-4), 164.8 (C-10a), 167.1 (C-2). MS (EI): m/z 272.0986 (M^+ , 97 %, C₁₅H₁₆N₂OS requires 272.0983) 230 (39), 216 (54), 188 (43), 187 (42), 176 (100), 146 (16). Anal. Calcd. for C₁₅H₁₆N₂OS: C, 66.18; H, 5.88; N, 10.29; O, 5.88; S, 11.76. Found: C, 66.01; H, 5.83; N, 10.25; S, 11.76.

7,8-Dimethyl-4-pentyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (7b). From **1b** and **2b**, Yield: 77%, Colourless needles; mp 178-181°C. IR: ν/cm^{-1} 1640 (C=O), 1570 (C=N), 1500 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 232 (4.43), 274 (4.06), 307 (4.14); NMR data: δ_{H} (CDCl₃) 0.87 (3H, t, $J_{5',4'}$ 7.3 Hz, 5'-H), 1.35 (2H, tq, $J_{4',3'}$ 8.0 Hz and $J_{4',5'}$ 7.0 Hz, 4'-H), 1.44 (2H, m, 3'-H), 1.70 (2H, tt, $J_{2',1'}$ 8.0 Hz and $J_{2',3'}$ 8.0 Hz, 2'-H), 2.28 (3H, s, 7-CH₃), 2.32 (3H, s, 8-CH₃), 2.98 (2H, t, $J_{1',2'}$ 7.6 Hz, 1'-H), 6.10 (1H, s, 3-H), 7.32 (1H, s, 9-H), 7.46 (1H, s, 6-H). δ_{C} (CDCl₃) 13.7 (C-5'), 19.4 (8-CH₃), 20.6 (7-CH₃), 22.1 (C-4'), 26.7 (C-2'), 30.8 (C-3'), 33.5 (C-1'), 110.6 (C-3), 116.8 (C-6), 121.1 (C-9a), 123.2 (C-9), 133.9 (C-5a), 135.5 (C-7), 136.0 (C-8), 151.3 (C-4), 165.0 (C-10a), 167.3 (C-2). MS (EI): m/z 300.1279 (M^+ , 100 %, C₁₇H₂₀N₂OS requires 300.1296) 258 (36), 244 (39), 216 (36), 204 (85), 189 (13), 174 (11). Anal. Calcd. for C₁₇H₂₀N₂OS: C, 68.00; H, 6.67; N, 9.33; O, 5.33; S, 10.67. Found: C, 68.00; H, 6.70; N, 9.26; S, 10.55.

8-Methoxy-4-pentyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (7c). From **1b** and **2c**, yield: 80%; colourless crystals; mp 174-175 °C. IR: ν/cm^{-1} 1630 (C=O), 1574 (C=N), 1507 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 231 (4.42), 285 (4.10), 308 (4.23). NMR data: δ_{H} (CDCl₃) 0.90 (3H, t, $J_{5',4'}$ 7.3 Hz, 5'-H), 1.37 (2H, tq, $J_{4',3'}$ 8.0 Hz and $J_{4',5'}$ 7.0 Hz, 4'-H), 1.45 (2H, m, 3'-H), 1.73 (2H, tt, $J_{2',1'}$ 8.0 Hz and $J_{2',3'}$ 8.0 Hz, 2'-H), 3.01 (2H, t, $J_{1',2'}$ 7.6 Hz, 1'-H), 3.85 (3H, s, 8-OCH₃), 6.15 (1H, s, 3-H), 6.97 (1H, dd, $J_{7,6}$ 9.4 Hz and $J_{7,9}$ 2.7 Hz, 7-H), 7.12 (1H, d, $J_{9,7}$ 2.7 Hz, 9-H), 7.65 (1H, d, $J_{6,7}$ 9.4 Hz, 6-H). δ_{C} (CDCl₃) 13.8 (C-5') 22.2 (C-4'), 26.5 (C-2'), 30.9 (C-3'), 33.5 (C-1'), 55.8 (8-OCH₃), 107.2 (C-9), 110.6 (C-3), 114.0 (C-7), 117.0 (C-6), 125.9 (C-9a), 129.6 (C-5a), 151.2 (C-4), 157.5 (C-8), 164.5 (C-10a), 167.3 (C-2). MS (EI): m/z 302.1071 (M^+ , 100 %, C₁₆H₁₈N₂O₂S requires 302.1089) 274 (6), 260 (21), 246 (32), 218 (20), 206 (81), 191 (12). Anal. Calcd. for C₁₆H₁₈N₂O₂S: C, 63.57; H, 5.96; N, 9.27; O, 10.60; S, 10.60. Found: C, 63.55; H, 5.95; N, 9.27; S, 10.60.

8-Ethoxy-4-pentyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (7d). From **1b** and **2b**, yield 84%; colourless crystals; mp 153-154°C. IR: ν/cm^{-1} 1640 (C=O), 1605 (C=N), 1580 (C=C); UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ) : 219 (4.52), 231 (4.53), 287 (4.19), 310 (4.31). NMR data: δ_{H} (CDCl₃) 0.90 (3H, t, $J_{5',4'}$ 7.3 Hz, 5'-H), 1.36 (2H, tq, $J_{4',3'}$ 8.0 Hz and $J_{4',5'}$ 7.0 Hz, 4'-H), 1.42

(3H, t, J 7.0 Hz, 8-OCH₂CH₃), 1.45 (2H, m, 3'-H), 1.73 (2H, tt, $J_{2',1'}$ 8.0 Hz and $J_{2',3'}$ 8.0 Hz 2'-H), 3.00 (2H, t, $J_{1',2'}$ 7.6 Hz, 1'-H), 4.05 (2H, q, J 7.0 Hz, 8-OCH₂CH₃), 6.15 (1H, s, 3-H), 6.95 (1H, dd, $J_{7,6}$ 9.4 Hz and $J_{7,9}$ 2.6 Hz, 7-H), 7.09 (1H, d, $J_{9,7}$ 2.6 Hz, 9-H), 7.63 (1H, d, $J_{6,7}$ 9.4 Hz, 6-H). δ_C (CDCl₃) 13.8 (C-5'), 14.6 (8-OCH₂CH₃), 22.2 (C-4'), 26.5 (C-2'), 30.9 (C-3'), 33.5 (C-1'), 64.2 (8-OCH₂CH₃), 107.6 (C-9), 110.5 (C-3), 114.0 (C-7), 117.0 (C-6), 125.9 (C-9a), 129.4 (C-5a), 151.2 (C-4), 156.9 (C-8), 164.5 (C-10a), 167.3 (C-2). MS (EI): m/z 316.1256 (M^+ , 100%, C₁₇H₂₀N₂O₂S requires 316.1245) 287 (9), 274 (23), 260 (28), 232 (20), 220 (55), 192 (18). Anal. Calcd. for C₁₇H₂₀N₂O₂S: C, 64.56; H, 6.32; N, 8.86; O, 10.13; S, 10.13. Found: C, 64.29; H, 6.39; N, 8.75; S, 10.05.

4-Phenyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (8a). From **1a** and **2c**, yield: 76%, colourless needles; mp 236-238°C (Lit⁴: 237 - 238 °C). IR: ν/cm^{-1} 1640 (C=O), 1600 (C=N), 1585 (C=C); UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 220 (4.52), 243 (4.39), 300 (4.12). NMR data: δ_H (CDCl₃) 6.10 (1H, d, $J_{6,7}$ 8.6 Hz, 6-H), 6.16 (1H, s, 3-H), 6.95 (1H, dd, $J_{7,6}$ 8.0 Hz and $J_{7,8}$ 8.0 Hz 7-H), 7.21 (1H, dd, $J_{8,7}$ 8.0 Hz and $J_{8,9}$ 8.0 Hz, 8-H), 7.38 (2H, d, $J_{2',3'}$ 7.4 Hz, 2'-H, 6'-H), 7.51 (2H, dd, $J_{3',2'}$ 7.0 Hz and $J_{3',4'}$ 8.0 Hz 3'-H, 5'-H), 7.56 (1H, d, $J_{9,8}$ 8.0 Hz, 9-H), 7.58 (1H, t, $J_{4',3'}$ 8.0 Hz, 4'-H). δ_C (CDCl₃) 112.9 (C-3), 116.2 (C-6), 122.8 (C-9), 123.9 (C-9a), 125.9 (C-7), 126.0 (C-8), 128.0 (C-2', C-6'), 129.2 (C-3', C-5'), 130.7 (C-4'), 131.8 (C-1'), 135.0 (C-5a), 148.9 (C-4), 164.6 (C-10a), 166.8 (C-2). MS (EI): m/z 278.0529 (M^+ , 100 %, C₁₆H₁₀N₂OS requires 278.0514) 250 (67), 237 (7), 176 (64), 150 (12), 148 (8), 102 (13). Anal. Calcd. for C₁₆H₁₀N₂OS: C, 69.06; H, 3.60; N, 10.07; O, 5.76; S, 11.51. Found: C, 69; H, 3.60; N, 10.02; S, 11.56.

7,8-Dimethyl-4-phenyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (8b). From **1b** and **2c**, yield 78%, colourless crystals; mp 228-230°C. IR: ν/cm^{-1} 1635 (C=O), 1600 (C=N), 1565 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 221 (4.53), 249 (4.38), 308 (4.22). NMR data: δ_H (CDCl₃) 1.89 (3H, s, 7-CH₃), 2.18 (3H, s, 8-CH₃), 5.79 (1H, s, 6-H), 6.18 (1H, s, 3-H), 7.29 (1H, s, 9-H), 7.38 (2H, d, $J_{2',3'}$ 7.3 Hz, 2'-H, 6'-H), 7.53 (2H, dd, $J_{3',2'}$ 7.0 Hz and $J_{3',4'}$ 8.0 Hz, 3'-H, 5'-H), 7.61 (1H, t, $J_{4',3'}$ 7.5 Hz, 4'-H). δ_C (CDCl₃) 19.4 (8-CH₃), 20.2 (7-CH₃), 112.6 (C-3), 117.3 (C-6), 120.9 (C-9a), 122.9 (C-9), 128.3 (C-2', C-6'), 129.1 (C-3', C-5'), 130.6 (C-4'), 132.0 (C-1'), 133.3 (C-5a), 135.2 (C-7), 135.4 (C-8), 148.9 (C-4), 164.9 (C-10a), 167.0 (C-2). MS (EI): m/z 306.0834 (M^+ , 100 %, C₁₈H₁₄N₂OS requires 306.0827) 278 (53), 265 (7), 204 (50), 189 (12), 129 (6), 102 (7). Anal. Calcd. for C₁₈H₁₄N₂OS: C, 70.59; H, 4.57; N, 9.15; O, 5.23; S, 10.46. Found: C, 70.46; H, 4.56; N, 9.27; S, 10.46.

8-Methoxy-4-phenyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (8c). From **1c** and **2c**, yield 81%, colourless crystals; mp 254-256°C. IR: ν/cm^{-1} 1635 (C=O), 1600 (C=N), 1580 (C=C). UV (EtOH/CHCl₃ 1:1) λ_{max} (nm), (log ϵ): 216 (4.48), 230 (4.48), 247 (4.35), 275 (4.12), 312 (4.19). NMR data: δ_H (CDCl₃) 3.76 (3H, s, 8-OCH₃), 6.01 (1H, d, $J_{6,7}$ 9.4 Hz, 6-H), 6.20 (1H, s, 3-H), 6.52 (1H, dd, $J_{7,6}$ 9.4 Hz and $J_{7,9}$ 2.6 Hz, 7-H), 7.07 (1H, d, $J_{9,7}$ 2.6 Hz, 9-H), 7.41 (2H, d, $J_{2',3'}$ 7.3 Hz, 2'-H, 6'-H), 7.54 (2H, dd, $J_{3',4'}$ 8 Hz and $J_{3',2'}$ 7.0 Hz, 3'-H, 5'-H), 7.61 (1H, t, $J_{4',3'}$ 7.6 Hz, 4'-H). δ_C (CDCl₃) 55.7 (8-OCH₃), 107.0 (C-9), 112.8 (C-3), 113.5 (C-7), 117.2 (C-6), 125.6 (C-9a), 128.2 (C-2', C-6'), 129 (C-5a), 129.3 (C-3', C-5'), 130.8 (C-4'), 131.9 (C-1'), 148.8 (C-

4), 157.5 (C-8), 164.3 (C-10a), 167.0 (C-2). MS (EI): m/z 308.0629 (M^+ , 100 %, $C_{17}H_{12}N_2O_2S$ requires 308.0619) 280 (32), 265 (8), 206 (54), 191 (25), 191 (25), 138 (13), 137 (13). Anal. Calcd. for $C_{17}H_{12}N_2O_2S$: C, 66.23; H, 3.90; N, 9.09; O, 10.39; S, 10.39. Found: C, 66.10; H, 3.97; N, 9.14; S, 10.50.

8-Ethoxy-4-phenyl-2H-pyrimido[2,1-*b*]benzothiazol-2-one (8d). From **1d** and **2c**, Yield 86%, colourless crystals; mp 211-213°C. IR: ν/cm^{-1} 1640 (C=O), 1600 (C=N), 1580 (C=C). UV (EtOH/ $CHCl_3$ 1:1) λ_{max} (nm), (log ϵ): 214 (4.44), 230 (4.43), 246 (4.31), 274 (4.06), 312 (4.16). NMR data: δ_H ($CDCl_3$) 1.31 (3H, t, J 7 Hz, 8- OCH_2CH_3), 3.93 (2H, q, J 7 Hz, 8- OCH_2CH_3), 5.96 (1H, d, $J_{6,7}$ 9.4 Hz, 6-H), 6.15 (1H, s, 3-H), 6.47 (1H, dd, $J_{7,6}$ 9.4 Hz and $J_{7,9}$ 2.5 Hz, 7-H), 7.02 (1H, d, $J_{9,7}$ 2.5 Hz, 9-H), 7.38 (2H, d, $J_{2',3'}$ 7.4 Hz, 2'-H, 6'-H), 7.51 (2H, dd, $J_{3',4'}$ 8.0 Hz and $J_{3',2'}$ 7.0 Hz, 3'-H, 5'-H), 7.58 (1H, d, $J_{4',3'}$ 7.5 Hz, 4'-H). δ_C ($CDCl_3$) 14.4 (8- OCH_2CH_3), 64.0 (8- OCH_2CH_3), 107.4 (C-9), 112.6 (C-3), 113.5 (C-7), 117.1 (C-6), 125.4 (C-9a), 128.1 (C-2', C-6'), 128.6 (C-5a), 129.2 (C-3', C-5'), 130.8 (C-4'), 131.8 (C-1'), 148.7 (C-4), 156.8 (C-8), 164.3 (C-10a), 166.9 (C-2). MS (EI): m/z 322.0777 (M^+ , 100 %, $C_{18}H_{14}N_2O_2S$ requires 322.0776) 294 (22), 266 (18), 220 (28), 192 (37), 191 (29), 129 (9). Anal. Calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.08; H, 4.35; N, 8.69; O, 9.94; S, 9.94. Found: C, 67.02; H, 4.43; N, 8.61; S, 9.92.

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References

1. Part 6: Wahe, H.; Asobo, P. F.; Cherkasov, R. A.; Nkengfack, A. E.; Folefoc, N. G.; Fomum, Z. T.; Doepp, D.; accepted by *ARKIVOC*.
2. Burger, A. *Medicinal Chemistry* 3rd Edition; Wiley- Interscience: New York, N. Y., 1970, pp 72, 544 and 719.
3. Mosby, W. L. "Fused 6/6 ring systems with one extra heteroatom" In "*Heterocyclic systems with bridgehead nitrogen atoms*", Part 2, Weissberger, A. Ed.; Wiley Interscience: New York, N. Y., 1961, pp 749.
4. Al-Jallo, H. N.; Muniem, M. A. *J. Heterocyclic Chem.* **1978**, *15*, 849.
5. Alamino, R. J. *J. Heterocyclic Chem.* **1973**, *10*, 769.
6. Dunwell, D. W.; Evans, D. *J. Chem. Soc. C* **1971**, 2094.

7. Santagati, A.; Santagati, M.; Russo, F. *J. Heterocyclic Chem.* **1988**, 25, 949.
8. Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, 44, 1811.
9. Doad, G. J. S.; Okor, D.; Schenmann, F. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2993.
10. Acheson, R. M.; Wallis, D. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1905.
11. Landreau, C.; Deniaud, D.; Evain, M.; Reliquet, A.; Meslin, J. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 741.
12. Fomum, Z. T.; Asobo, P. F.; Ifeadike, P. N. *J. Heterocyclic Chem.* **1984**, 21, 1125.
13. Fomum, Z. T.; Ifeadike, P. N. *J. Heterocyclic Chem.* **1985**, 22, 1611.
14. Ai, J.; Wang, X.; Wahe, H.; Fomum, Z. T.; Sterner, O.; Nielsen, M.; Witt, M. R. *Pharmacology* **2000**, 60, 175.
15. Chan, C. K.; Ma, J. C. N.; Mak, T. C. W. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1070.
16. Asobo, P. F.; Wahe, H.; Mbafor, J. T.; Nkengfack, A. E.; Fomum, Z. T.; Sopbue, E. F.; Doepp, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 457.