Synthesis of Novel 2-Alkoxy-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitriles

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Reaction of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclo-hepten-5-ones (**1**) with malononitrile in the appropriate alcohol in the presence of sodium afforded the corresponding 2-alkoxy-4-aryl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitriles (**2**) and not their isomeric forms 2-alkoxy-4-aryl-6,7-dihydro-5*H*-benzo[3,4]-cyclohepta[1,2-*c*]pyridine-1-carbonitriles (**3**). The proposed structure was confirmed *via* independent synthesis of (**2**) through the reaction of 6,7,8,9-tetrahydro-5-benzocycloheptenone (**4**) with the appropriate ylidenemalononitriles **5** under the same reaction conditions. Single crystal X-ray diffraction proves the structures of **2a,b**.

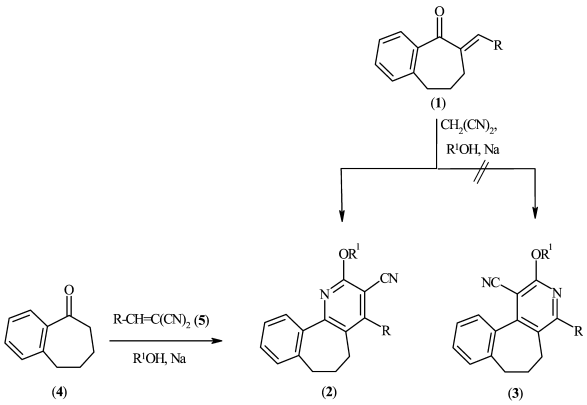
Key words: 5*H*-Benzocyclohepten-5-ones, 5*H*-Benzo[6,7]cyclohepta-[1,2-*b*]pyridine-3-carbonitriles, Ylidenemalononitriles, Michael Reaction

Introduction

Many publications deal with the biological properties of benzocyclohepta[1,2-*b*]pyridine derivatives with regard to anti-inflammatory [1 – 5], antihistaminic [6 – 16], antitumor [17 – 26], and anti HIV activities [17] as well as to treating hepatitis delta virus infection [27]. It is intended in the present work not only to investigate the synthesis of novel benzocyclohepta[1,2-*b*]pyridinecarbonitrile derivatives *via* a facile synthetic approach utilizing easily accessible chemical materials but also to study the mechanistic route obeyed by the reaction sequence.

Results and Discussion

Reaction of 6-arylmethylene-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-ones (**1a – f**) with malononitrile in the appropriate alcohol in the presence of sodium afforded colourless products. The structures were established to be either 2-alkoxy-4-aryl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitriles (**2a – l**) or their isomeric forms 2-alkoxy-4-aryl-6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*c*]pyridine-1-carbonitriles (**3a – l**) based on spectroscopic (IR, ^{1}H NMR and mass spectra) as well as elemental analyses data. The IR spectra reveal the absence of any carbonyl group and exhibit a strong stretching vibration nitrile absorption band at



1a, 5a; R = Ph
1b, 5b; R = 4-ClC_6H_4
1c, 5c; R = 4-FC_6H_4
1d, 5d; R = 4-$H_3CC_6H_4$
1e, 5e; R = 4-$H_3COC_6H_4$
1f, 5f; R = 2-thienyl

2a; R = Ph, $R^1 = CH_3$
2b; R = Ph, $R^1 = C_2H_5$
2c; R = 4-ClC_6H_4, $R^1 = CH_3$
2d; R = 4-ClC_6H_4, $R^1 = C_2H_5$
2e; R = 4-FC_6H_4, $R^1 = CH_3$
2f; R = 4-FC_6H_4, $R^1 = C_2H_5$

2g; R = 4-$H_3CC_6H_4$, $R^1 = CH_3$
2h; R = 4-$H_3CC_6H_4$, $R^1 = C_2H_5$
2i; R = 4-$H_3COC_6H_4$, $R^1 = CH_3$
2j; R = 4-$H_3COC_6H_4$, $R^1 = C_2H_5$
2k; R = 2-thienyl, $R^1 = CH_3$
2l; R = 2-thienyl, $R^1 = C_2H_5$

Scheme 1.

$\nu = 2223 - 2218$ cm^{-1}. ^{1}H NMR spectra show the alkoxide residue confirming the involvement of either methoxide (singlet at $\delta = 4.01 - 4.15$) or ethoxide (triplet at $\delta = 1.38 - 1.49$, quartet at $\delta = 4.49 - 4.61$) functions derived from the corresponding alcohol used in the reaction.

The reaction was assumed to take place *via* active methylene malononitrile Michael addition to the

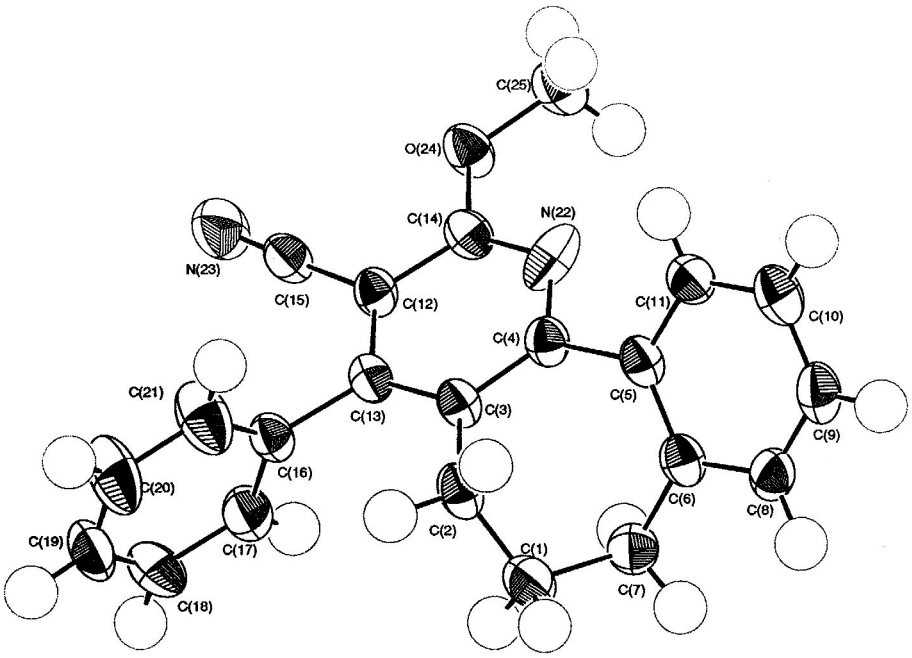


Fig. 1: Single crystal X-ray diffraction of **2a**. Selected intramolecular bond lengths (A°) and bond angles (°) of **2a**: C(1)-C(2) = 1.5319(11); C(2)-C(3) = 1.5215(10); C(3)-C(4) = 1.3981(10); C(4)-C(5) = 1.4881(10); C(5)-C(6) = 1.3957(10); C(6)-C(7) = 1.5108(11); C(7)-C(1) = 1.5302(11); C(3)-C(13) = 1.3978(10); C(13)-C(12) = 1.3977(10); C(12)-C(14) = 1.4102(10); C(12)-C(15) = 1.4506(11); C(14)-N(22) = 1.3152(9); C(15)-N(23) = 1.1390(9); N(22)-C(4) = 1.3629(9); C(14)-O(24) = 1.3501(9); C(1)-C(2)-C(3) = 114.02(7); C(2)-C(3)-C(4) = 118.84(7); C(3)-C(4)-C(5) = 121.95(8); C(4)-C(5)-C(6) = 120.75(7); C(5)-C(6)-C(7) = 120.43(7); C(6)-C(7)-C(1) = 113.68(7); C(7)-C(1)-C(2) = 113.93(7); C(4)-C(3)-C(13) = 118.61(8); C(3)-C(13)-C(12) = 118.00(7); C(13)-C(12)-C(14) = 119.19(7); C(12)-C(14)-N(22) = 123.19(8); C(14)-N(22)-C(4) = 117.82(7); N(22)-C(4)-C(3) = 123.17(7); O(24)-C(14)-N(22) = 120.05(7); O(24)-C(14)-C(12) = 116.75(7); C(14)-C(12)-C(15) = 118.24(8); C(13)-C(12)-C(15) = 122.23(7); C(12)-C(15)-N(23) = 178.33(10).

β-carbon of unsaturated system of **1** affording the Michael adduct intermediate. Alkoxide nucleophilic attacks at one of the Michael adduct intermediate nitrile groups, followed by dehydration and subsequent dehydrogenation finally gave the corresponding 5*H*-benzo[6,7]cyclohepta[1,2-*b*]pyridine-3-carbonitrile **2**. On the other hand, Knoevenagel condensation may take place due to active methylene malononitrile interaction with the ketonic residue of **1** followed by alkoxide nucleophilic attacks at one of the nitrile groups with subsequent cyclization and dehydrogenation affording eventually 5*H*-benzo[3,4]cyclohepta[1,2-*c*]pyridine-1-carbonitrile **3** (Scheme 1).

The isolated products were established to be **2** rather than **3** based on their independent synthesis through the reaction of 6,7,8,9-tetrahydro-5-benzocycloheptenone (**4**) with the appropriate ylidenemalononitriles **5** under the same reaction conditions. In other words, the reaction occurs *via* Michael addition rather than Knoevenagel condensation in a regioselective reaction manner.

^{13}C NMR spectra of **2a** (decoupled & APT) add good support for the proposed structure which reveal the methoxy carbon at $\delta = 54.66$. The nitrile and aromatic C-3 carbons appear at $\delta = 115.72, 95.04$, respectively. The ^{13}C NMR spectrum of **2b** (APT) exhibits the methyl and methylene carbons of the ethoxy group at $\delta = 14.92, 63.33$ respectively, in addition to the nitrile and aromatic C-3 carbons at $\delta = 115.75, 95.09$. Single crystal X-ray diffraction of **2a** (Fig. 1) and **2b** (Fig. 2), as representative examples, confirm the established structures [28].

Experimental Section

Melting points are uncorrected and were recorded on an Electrothermal 9100 melting point apparatus. IR spectra (KBr) were recorded on a Bruker Vector 22 spectrophotometer. ^{1}H NMR spectra were recorded on Varian GEMINI

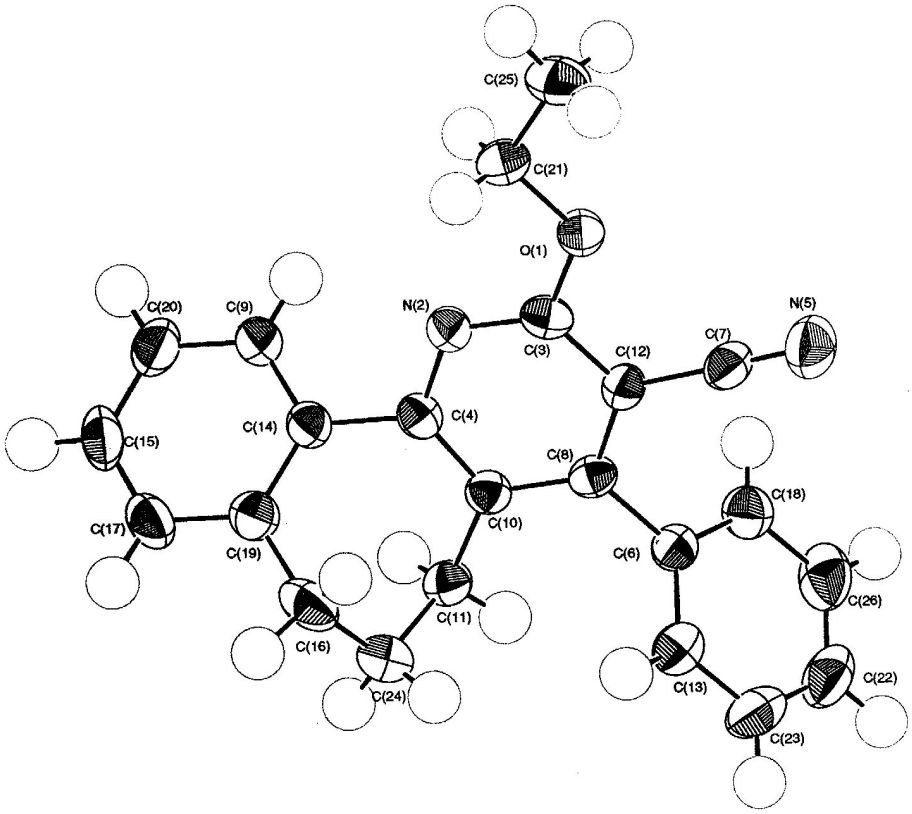


Fig. 2: Single crystal X-ray diffraction of **2b**. Selected intramolecular bond lengths (A°) and bond angles (°) of **2b**: O(1)-C(3) = 1.3560(8); N(2)-C(3) = 1.3141(8); N(2)-C(4) = 1.3569(8); C(3)-C(12) = 1.4080(9); C(4)-C(10) = 1.4039(9); C(4)-C(14) = 1.4790(9); N(5)-C(7) = 1.1376(9); C(7)-C(12) = 1.4376(9); C(8)-C(10) = 1.3973(9); C(8)-C(12) = 1.4095(9); C(10)-C(11) = 1.5137(9); C(11)-C(24) = 1.5330(10); C(14)-C(19) = 1.3998(9); C(16)-C(19) = 1.5091(10); C(16)-C(24) = 1.5326(10); C(3)-N(2)-C(4) = 117.05(6); O(1)-C(3)-N(2) = 120.01(6); O(1)-C(3)-C(12) = 115.54(6); N(2)-C(3)-C(12) = 124.44(6); N(2)-C(4)-C(10) = 123.94(6); C(10)-C(4)-C(14) = 120.67(6); N(5)-C(7)-C(12) = 178.74(12); C(10)-C(8)-C(12) = 118.47(6); C(4)-C(10)-C(8) = 117.97(6); C(4)-C(10)-C(11) = 118.88(6); C(10)-C(11)-C(24) = 113.89(6); C(3)-C(12)-C(7) = 119.23(6); C(3)-C(12)-C(8) = 118.08(6); C(7)-C(12)-C(8) = 122.68(6); C(4)-C(14)-C(19) = 121.79(7); C(19)-C(16)-C(24) = 113.19(6); C(14)-C(19)-C(16) = 118.87(7); C(11)-C(24)-C(16) = 112.63(6).

200 MHz and Varian MERCURY 300 MHz spectrometers. ^{13}C NMR spectra were recorded on a Varian MERCURY 300 (75 MHz) spectrometer. Mass spectra were recorded on a Finnigan SSQ 7000 (EI 70 ev) spectrometer. The starting compounds **1a – f** [29] and **5a – f** [30] were prepared according to the reported procedures.

2-Alkoxy-4-aryl-6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2- *b*]pyridine-3-carbonitriles 2a – l

Method "A": A mixture of equimolar amounts of the appropriate **1** and malononitrile (5 mmol) in the proper alcohol (25 ml) containing sodium (0.5 g) was stirred at room temperature (20 – 25 °C) for the appropriate time. The separated solid was collected, washed with water and crystallized from a suitable solvent affording the corresponding **2**.

Method "B": A mixture of equimolar amounts of the appropriate **5** and 6,7,8,9-tetrahydro-5-benzocycloheptenone (**4**) (5 mmol) in the proper alcohol (25 ml) containing sodium (0.5 g) was stirred at room temperature (20 – 25 °C) for the appropriate time. The separated solid was collected, washed with water and crystallized from a suitable solvent affording the corresponding **2**.

*6,7-Dihydro-2-methoxy-4-phenyl-5H-benzo[6,7]cyclohepta-[1,2-b]pyridine-3-carbonitrile (***2a***)*

Reaction time 48, 24 h (method A & B respectively), colourless crystals from methanol, M.p. 189 – 191 °C, yield 55, 49 % (method A & B respectively). – IR: $\tilde{\nu}$ = 2223 (C≡N), 1601, 1554 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): δ = 2.12 – 2.23 (m, 4H, 2 CH_2), 2.64 (t, J = 7 Hz, 2H,

Table 1. Single crystal X-ray experimental data of compounds **2a** and **2b**.

	Compd. **2a**	Compd. **2b**
Chemical formula	$C_{22}H_{18}N_2O$	$C_{23}H_{20}N_2O$
Chemical formula weight	326.399	340.426
Exptl. crystal description	needles	prismatic
Exptl. crystal colour	colourless	colourless
Cell measurement temperature	298 K	298 K
Diffraction measurement device	Kappa CCD	Kappa CCD
Computing data collection	Kappa CCD	Kappa CCD
Computing data reduction	Denzo and Scalepak (Otwinowski & Minor, 1997)	
Diffraction reflections limit *h* min.	−10	−17
Diffraction reflections limit *h* max.	10	17
Diffraction reflections limit *k* min.	−13	−15
Diffraction reflections limit *k* max.	13	13
Diffraction reflections limit *l* min.	−13	−25
Diffraction reflections limit *l* max.	13	25
Cell formula units z	2	4
Exptl. crystal density diffraction	1.266 g/cm^3	1.228 g/cm^3
Space group	triclinic P-1	monoclinic P21/c
Unit-cell dimensions		
a/Å	8.5304 (9)	13.3696 (9)
b/Å	10.6606 (12)	11.5674 (8)
c/Å	11.1034 (14)	19.5101 (11)
Cell volume, V/Å^3	856.6 (2)	1841.0 (2)

	Compd. **2a**	Compd. **2b**
Diffraction reflections number	5491	7217
Diffraction reflection theta max.	26.28	27.52
Diffraction reflections average R equivalents	0.049	0.055
Cell measurement reflections used	6365	4550
Cell measurement theta min.	2.910	2.910
Cell measurement theta max.	26.373	27.485
Computing cell refinement	HKL Scalepack (Otwinowski & Minor 1997)	
Computing structure solution	SHELXS-97 (Sheldrick, 1997)	SIR92 (Altomare *et al.*, 1994)
Exptl. crystal F 000	344	720
Reflections d resolution low	1.86	1.83
Reflections d resolution high	0.64	0.62
Refine 1s matrix type	full	full
Refine-1s-shift/su-max.	0.033	0.046
Refine-1s-shift/su-mean	0.007	0.010
Reflections number total	3386	4195
Refine-1s-R-factor-all	0.124	0.188
Refine-1s-wR-factor-all	0.057	0.055
Refine-1s-goodness-of-fit-all	1.152	1.786
Computing structure refinement	"Maxus (Mackay *et al.*, 1999)"	
Computing molecular graphics	"Ortep (Johnson, 1976)"	

CH_2), 4.15 (s, 3H, OCH_3), 7.26 – 7.84 (m, 9H, arom. H). – ^{13}C NMR (decoupled & APT) ($CDCl_3$): $\delta = 26.26$, 31.62, 34.09 (3CH_2), 54.66 (OCH_3), 95.04 (arom. C-3), 115.72 (C≡N), 127.05, 128.73, 128.94, 129.40, 129.51, 130.08 (arom. CH), 126.65, 136.15, l39.49, 140.23, 156.43, 160.60, 162.97 (arom. quaternary C). – MS: *m/z* (%) = 326 (100) [M$^+$], 325 (88), 311 (5), 295 (8). – $C_{22}H_{18}N_2O$ (326.38): calcd. C 80.95, H 5.56, N 8.59; found C 80.86, H 5.51, N 8.60.

*6,7-Dihydro-2-ethoxy-4-phenyl-5H-benzo[6,7]cyclohepta-[1,2-b]pyridine-3-carbonitrile (***2b***)*

Reaction time 48 h (method A), colourless crystals from methanol, M. p. 151 – 153 °C, yield 53 % (method A). – IR: $\tilde{\nu} = 2222$ (C≡N), 1600, 1549 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 1.38$ (t, $J = 6.9$ Hz, 3H, CH_3), 2.00 – 2.10 (m, 4H, 2 CH_2), 2.53 (t, $J = 6.9$ Hz, 2H, CH_2), 4.49 (q, $J = 6.9$ Hz, 2H, OCH_2), 7.14 – 7.65 (m, 9H, arom. H). – ^{13}C NMR (APT) ($CDCl_3$): $\delta = 14.92$ (CH_3), 26.25, 31.64, 34.07 (CH_2), 63.33 (OCH_2), 95.09 (arom. C-3), 115.75 (C≡N), 127.02, 128.72, 128.92, 129.35, 129.49, 130.00 (arom. CH). 126.37, 136.26, 139.58, 140.22, 156.40, 160.56, 162.74 (arom. quaternary C). – MS: *m/z* (%) = 340 (100) [M$^+$], 339 (68), 311 (28), 295 (6). – $C_{23}H_{20}N_2O$ (340.41): calcd. C 81.15, H 5.92, N 8.23; found C 81.11, H 5.89, N 8.16.

*4-(4-Chlorophenyl)-6,7-dihydro-2-methoxy-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2c***)*

Reaction time 24 h (method A & B), colourless crystals from methanol, M.p. 174 – 176 °C, yield 44, 56 % (method A & B respectively). – IR: $\tilde{\nu} = 2221$ (C≡N), 1597, 1548 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 2.06$-2.24 (m, 4H, 2 CH_2), 2.63 (t, $J = 6.6$ Hz, 2H, CH_2), 4.14 (s, 3H, OCH_3), 7.25 – 7.81 (m, 8H, arom. H). – MS: *m/z* (%) = 360 (100) [M$^+$], 359 (70), 345 (8), 329 (2). – $C_{22}H_{17}ClN_2O$ (360.83): calcd. C 73.23, H 4.75, N 7.77; found C 73.36, H 4.80, N 7.81.

*4-(4-Chlorophenyl)-6,7-dihydro-2-ethoxy-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2d***)*

Reaction time 48 h (method A), colourless crystals from ethanol, M. p. 193 – 195 °C, yield 53 % (method A). – IR: $\tilde{\nu} = 2220$ (C≡N), 1596, 1550 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 1.49$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.07 – 2.21 (m, 4H, 2 CH_2), 2.64 (t, $J = 6.8$ Hz, 2H, CH_2), 4.61 (q, $J = 7.2$ Hz, 2H, OCH_2), 7.30 – 7.80 (m, 8H, arom. H). – MS: *m/z* (%) = 374 (100) [M$^+$], 373 (64), 345 (27), 329 (5). – $C_{23}H_{19}ClN_2O$ (374.85): calcd. C 73.69, H 5.11, N 7.47; found C 73.54, H 5.04, N 7.50.

*6,7-Dihydro-4-(4-fluorophenyl)-2-methoxy-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2e***)*

Reaction time 24 h (method B), colourless crystals from methanol, M. p. 185 – 187 °C, yield 70 % (method B). – IR: $\tilde{\nu} = 2219$ (C≡N), 1602, 1553 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 2.00 - 2.10$ (m, 4H, 2 CH_2), 2.52 (t, $J = 6.9$ Hz, 2H, CH_2), 4.02 (s, 3H, OCH_3), 7.06 – 7.67 (m, 8H, arom. H). – MS: *m/z* (%) = 344 (100) [M$^+$], 343 (38), 329 (43), 313 (35). – $C_{22}H_{17}FN_2O$ (344.38): calcd. C 76.72, H 4.98, N 8.14; found C 76.79, H 5.04, N 8.19.

*6,7-Dihydro-2-ethoxy-4-(4-fluorophenyl)-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2f***)*

Reaction time 72 h (method A), colourless crystals from ethanol, M. p. 160 – 162 °C, yield 56 % (method A). – IR: $\tilde{\nu} = 2222$ (C≡N), 1600, 1554 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 1.48$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.07 – 2.23 (m,

4H, 2 CH_2), 2.63 (t, $J = 6.9$ Hz, 2H, CH_2), 4.60 (q, $J = 7.2$ Hz, 2H, OCH_2), 7.17 – 7.77 (m, 8H, arom. H). – MS: *m/z* (%) = 358 (88) [M^+], 357 (100), 329 (86), 313 (31). – $C_{23}H_{19}FN_2O$ (358.40): calcd. C 77.07, H 5.34, N 7.82; found C 77.17, H 5.43, N 7.95.

*6,7-Dihydro-2-methoxy-4-(4-methylphenyl)-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2g***)*

Reaction time 24 h (method A & B), colourless crystals from methanol, M. p. 196 – 198 °C, yield 71, 53 % (method A & B respectively). – IR: $\tilde{\nu} = 2220$ (C≡N), 1606, 1552 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 2.09 - 2.26$ (m, 4H, 2 CH_2), 2.42 (s, 3H, CH_3), 2.63 (t, $J = 6.9$ Hz, 2H, CH_2), 4.13 (s, 3H, OCH_3), 7.23 – 7.81 (m, 8H, arom. H). – MS: *m/z* (%) = 340 (99) [M^+], 339 (100), 325 (36); 309 (13). – $C_{23}H_{20}N_2O$ (340.41): calcd. C 81.15, H 5.92, N 8.23; found C 81.10, H 5.91, N 8.34.

*6,7-Dihydro-2-ethoxy-4-(4-methylphenyl)-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2h***)*

Reaction time 48 h (method A), colourless crystals from ethanol, M. p. 169 – 171 °C, yield 51 % (method A). – IR: $\tilde{\nu} = 2222$ (C≡N), 1604, 1551 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 1.48$ (t, $J = 6.9$ Hz, 3H, CH_2CH_3), 2.09 – 2.25 (m, 4H, 2 CH_2), 2.43 (s, 3H, CH_3), 2.63 (t, $J = 6.9$ Hz, 2H, CH_2), 4.59 (q, $J = 6.9$ Hz, 2H, OCH_2), 7.23 – 7.78 (m, 8H, arom. H). – MS: *m/z* (%) = 354 (100) [M^+], 353 (74), 325 (23), 309 (8). – $C_{24}H_{22}N_2O$ (354.44): calcd. C 81.32, H 6.26, N 7.91; found C 81.41, H 6.24, N 7.99.

*6,7-Dihydro-2-methoxy-4-(4-methoxyphenyl)-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2i***)*

Reaction time 24 h (method A & B), colourless crystals from ethanol, M. p. 173 – 175 °C, yield 67, 56 % (method A & B respectively). – IR: $\tilde{\nu} = 2223$ (C≡N), 1607, 1554 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 2.02 - 2.13$ (m, 4H, 2 CH_2), 2.52 (t, $J = 6.9$ Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 6.89 – 7.69 (m, 8H, arom. H). – MS: *m/z* (%) = 356 (100) [M^+], 355 (71), 341 (17), 325 (4). – $C_{23}H_{20}N_2O_2$ (356.41): calcd. C 77.50, H 5.66, N 7.86; found C 77.62, H 5.71, N 7.74.

*6,7-Dihydro-2-ethoxy-4-(4-methoxyphenyl)-5H-benzo-[6,7]cyclohepta[1,2-b]pyridine-3-carbonitrile (***2j***)*

Reaction time 48 h (method A), colourless crystals from ethanol, M. p. 145 – 147 °C, yield 49 % (method A). – IR: $\tilde{\nu} = 2223$ (C≡N), 1607, 1552 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 1.49$ (t, $J = 7.2$ Hz, 3H, CH_2CH_3), 2.10 – 2.24 (m, 4H, 2 CH_2), 2.64 (t, $J = 6.4$ Hz, 2H, CH_2), 3.88 (s, 3H, OCH_3), 4.60 (q, $J = 7.2$ Hz, 2H, OCH_2), 7.02 – 7.78 (m, 8H, arom. H). – MS: *m/z* (%) = 370 (100) [M^+], 369 (72), 341 (23), 325 (7). – $C_{24}H_{22}N_2O_2$ (370.44): calcd. C 77.81, H 5.99, N 7.56; found C 77.66, H 5.79, N 7.49.

*6,7-Dihydro-2-methoxy-4-(2-thienyl)-5H-benzo[6,7]-cyclohepta[1,2-b]pyridine-3-carbonitrile (***2k***)*

Reaction time 24 h (method A), colourless crystals from methanol, M. p. 169 – 171 °C, yield 66 % (method A). – IR: $\tilde{\nu} = 2223$ (C≡N), 1602, 1554 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 2.15 - 2.37$ (m, 4H, 2 CH_2), 2.62 (t, $J = 7$ Hz, 2H, CH_2), 4.12 (s, 3H, OCH_3), 7.15 – 7.81 (m, 7H, arom. H). – MS: *m/z* (%) = 332 (100) [M^+], 331 (69), 317 (13), 301 (5). – $C_{20}H_{16}N_2OS$ (332.41): calcd. C 72.26, H 4.85, N 8.43; found C 72.22, H 4.82, N 8.39.

*6,7-Dihydro-2-ethoxy-4-(2-thienyl)-5H-benzo[6,7]-cyclohepta[1,2-b]pyridine-3-carbonitrile (***2l***)*

Reaction time 24 h (method A), colourless crystals from light petroleum (60 – 80 °C), M.p. 154 – 156 °C, yield 58 % (method A). – IR: $\tilde{\nu} = 2218$ (C≡N), 1601, 1552 cm^{-1} (C=N, C=C). – ^1H NMR ($CDCl_3$): $\delta = 1.49$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.18 – 2.38 (m, 4H, 2 CH_2), 2.64 (t, $J = 6.9$ *Hz*, 2H, CH_2), 4.61 (q, $J = 6.9$ Hz, 2H, OCH_2), 7.17 – 7.78 (m, 7H, arom. H). – MS: *m/z* (%) = 346 (100) [M^+], 345 (59), 317 (60), 301 (20). – $C_{21}H_{18}N_2OS$ (346.43): calcd. C 72.80, H 5.24, N 8.09; found C 72.91, H 5.28, N 8.12.

[1] D. K. Agrawal, Expert Opin. Invest. Drugs **10**, 547 (2001).

[2] M. B. Affrime, C. R. Banfield, S. K. Gupta, D. Padhi, (Schering Corporation, USA) PCT Int. Appl. WO 01 21, 161 (Cl. A61k31/00) 29 Mar. 2001; Chem. Abstr. **134**, 247244 (2001).

[3] K. A. Heithoff, (Schering Corporation, USA) PCT Int. Appl. WO 01 21,162 (Cl. A61K31/00) 29 Mar. 2001; Chem. Abstr. **134**, 231867 (2001).

[4] R. Scannel, P. Chatelain, A. Toy-Palmer, E. Differding, J. Ellis, M. A. Lassoie, M. Young, X. Cai, S. Hussoin, G. Grewal, T. Lewis, (UCB, S. A. Belg.) PCT Int. Appl. WO 00 58,295 (Cl. CO7D295/00) 5 Oct. 2000; Chem. Abstr. **133**, 281798 (2000).

[5] J. K. Wong, J. J. Piwinski, (Schering Corporation, USA) U. S. US 5,561,117 (Cl. 514 – 291; A61K31/44) 1 Oct. 1996; Chem. Abstr. **125**, 293023 (1996).

[6] J. J. Piwinski, D. P. Schumacher, E. Aronov, A. Khusid, (Schering Corporation, USA) PCT Int. Appl. WO 00 57,880 (Cl. A61K31/445) 5 Oct. 2000; Chem. Abstr. **133**, 266736 (2000).

[7] M. Queralt, P. Brazis, M. Merlos, F. De Mora, A. Puigdemont, Inflammation Res. **49**, 355 (2000).

[8] S. U. Lugo, J. V. Ramos, S. M. Arellano, O. Michel,

(Schering Corp., USA) PCT Int.. Appl. WO 00 51,605 (Cl. A61K31/445) 8 Sep. 2000; Chem. Abstr. **133**, 227792 (2000).

[9] T. Fujimoto, K. Okazaki, H. Kami, K. Kase, E. Yoshizawa, T. Shibahara (Schering- Plough K. K., Japan) PCT Int. Appl. WO 98 48,803 (Cl. A61K31/445) 5 Nov. 1998; Chem. Abstr. **129**, 335795 (1998).

[10] N. Singh, S. K. Puri, Acta Trop. **69**, 255 (1998).

[11] P. E. Koochaki, (Procter & Gamble Company USA) PCT Int. Appl. WO 97 49,243 (Cl. A61K31/57) 11 Dec. 1997; Chem. Abstr. **128**, 80034 (1998).

[12] S. Mitra, USA U.S. US 5,648,358 (Cl. 514 – 264; A61K31/52) 15 Jul. 1997; Chem. Abstr. **127**, 140556 (1997).

[13] E. Carceller, N. Recasens, C. Almansa, J. Bartroli, M. Merlos, M. Giral, (J. Uriach & Cia. S. A., Spain) Spain. ES 2,087,028 (Cl. CO7D401/14) 1 Jul. 1996; Chem. Abstr. **125**, 275911 (1996).

[14] E. Carceller, N. Recasens, C. Almansa, J. Bartroli, M. Merlos, M. Giral, (J. Uriach & Cia. S. A., Spain) Spain. ES 2,087,818 (Cl. CO7D401/14) 16 Jul. 1996; Chem. Abstr. **125**, 275664 (1996).

[15] E. Carceller, N. Recasens, C. Almansa, J. Almansa, M. Merlos, M. Giral, J. Garcia-Rafanell, J. Forn (J. Uriach y Cia. S. A.) Spain. ES 2,042,421 (Cl. CO7D401/14) 1 Dec. 1993; Chem. Abstr. **121**, 280552 (1994).

[16] E. Carceller, M. Merlos, M. Giral, D. Balsa, C. Almansa, J. Bartroli, J. Garcia- Rafanell, J. Forn, J. Med. Chem. **37**, 2697 (1994).

[17] A. G. Hammam, N. A. A. El-Hafez, W. H. Midura, M. Mikolajczyk, Z. Naturforsch., B: Chem. Sci. **55b**, 417 (2000).

[18] F. G. Njoroge, R. J. Doll, S. W. Remiszewski, (Schering Corporation, USA) U.S. US 5,994,364 (Cl. 514 – 290; A61K31/435) 30 Nov. 1999; Chem. Abstr. **132**, 12331 (2000).

[19] F. G. Njoroge, A. G. Taveras, R. J. Doll, T. Lalwani, C. Alvarez, S. W. Remiszewski, (Schering Corporation, USA) U.S. US 6,030, 982 (Cl. 514 – 290; A61K31/445) 29 Feb. 2000; Chem. Abstr. **132**, 180486 (2000).

[20] A. K. Mallams, (Schering Corporation, USA)U.S. US 5,925,757 (Cl. 544 – 361; CO7D401/14) 20 Jul. 1999; Chem. Abstr. **131**, 87821 (1999).

[21] R.J̇. Doll, J. M. Kelly, A. K. Mallams, F. G. Njoroge, S. W. Remiszewski, A. G. Taveras, (Schering Corporation USA) PCT Int. Appl. WO 98 57,959 (Cl. CO7D401/12) 23 Dec. 1998; Chem. Abstr. **130**, 81411 (1999).

[22] A. B. Cooper, R. J. Doll, V. M. Girijavallabhan, A. Ganguly, J. C. Reader, J. J. Baldwin, C. Y. Huang, (Schering Corporation; Pharmacopeia, Inc., USA) PCT Int. Appl. WO 98 57,960 (Cl. CO7D401/14) 23 Dec. 1998; Chem. Abstr. **130**, 81426 (1999).

[23] R. J. Doll, T. Lalwani, (Schering Corporation, USA) PCT Int. Appl. WO 98 57,965 (Cl. CO7D401/14) 23 Dec. 1998; Chem. Abstr. **130**, 81427 (1999).

[24] R. J. Doll, C. Alvarez, T. Lalwani, Y. T. Liu, (Schering Corporation, USA) PCT Int. Appl. WO 98 57,968 (Cl. CO7D405/14) 23 Dec. 1998; Chem. Abstr. **130**, 81428 (1999).

[25] F. G. Njoroge, B. Vibulbhan, P. Pinto, W. R. Bishop, M S. Bryant, A. A. Nomeir, C. C. Lin, M. Liu, R. J. Doll, V. Girijavallabhan, A. K. Ganguly, J. Med. Chem. **41**, 1561 (1998).

[26] P. C. Ting, D. M. Solomon, W. C. Tom, S. K. White, J. J. Kaminski, S. C. C. Wong, N. I. Carruthers, (Schering Corp.) PCT Int. Appl. WO 95 15,949 (Cl. CO7D211/70) 15 Jun. 1995; Chem. Abstr. **123**, 339752 (1995).

[27] P. J. Casey, J. C. Otto, (Duke University, Casey, P. J.; Otto, J. C.; USA) PCT Int. Appl. WO 97 31,641 (Cl. A61 K31/66) 4 Sep. 1997; Chem. Abstr. **127**, 257608 (1997).

[28] Full crystallographic details, excluding structure factors, have been deposited at Cambridge Crystallographic Data Centre (CCDC) as supplementary publication numbers CCDC 187620 and CCDC 187619 for compounds **2a** and **2b** respectively.

[29] a. N. R. El-Rayyes, H. M. Ramadan, J. Heterocycl. Chem. **24**, 589 (1987). b. Ng. Ph. Buu-Hoi, N. D. Xuong, R. Rips, J. Org. Chem. **22**, 193 (1957). c. V. D. Orlov, Yu. N. Surov, E. I. Mikhedkina, O. A. Nodel'man, A. D. Bazavluk, V. F. Lavrushin, Org. React. (Tartu) **21**, 363 (1984).

[30] a. B. B. Corson, R. W. Stoughton, J. Am. Chem. Soc. **50**, 2825 (1928). b. H. G. Sturz, C. R. Noller, J. Am. Chem. Soc. **71**, 2949 (1949). c. M. A. Weinberger, R. M. Heggie, Can. J. Chem. **43**, 2585 (1965). d. L. Horner, K. Klüpfel, Ann. **591**, 69 (1955).