Reactions of 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile and 6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole-5-carbonitrile with substituted benzylidenemalononitriles, α,β-acetylenic esters and ketones

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Reactions of 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**1a**) with substituted benzylidenemalononitriles gave 4-amino-2-(1-cyano-2-arylvinyl)benzothieno[2,3-*d*]pyrimidine derivatives (**3**) as (*E*,*Z*)-mixtures and in one case (**2c**) as separated (*Z*)- and (*E*)-isomers. Similar treatment of 6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole-5-carbonitrile (**4**) yielded similarly-formed pyrazolopyranopyrimidine derivatives (**5a**,**b**) as (*Z*)- and (*E*)-stereoisomers. Attempted acetylation of the aminobenzothienopyrimidines resulted in degradation of the pyrimidine ring and the formation of *N*-(3-cyano-4,5,6,7-tetrahydro[1]benzothien-2-yl)acetamide (**1b**). Treatment of **4** with acetylenic esters and ketones (**6a**–**d**) afforded the (*Z*)-substituted enaminopyrano[2,3-*c*]pyrazole derivatives. Reacting **1a** with aroyl phenyl acetylenes gave by Michael addition the enamino-ketones (**8a**–**c**).

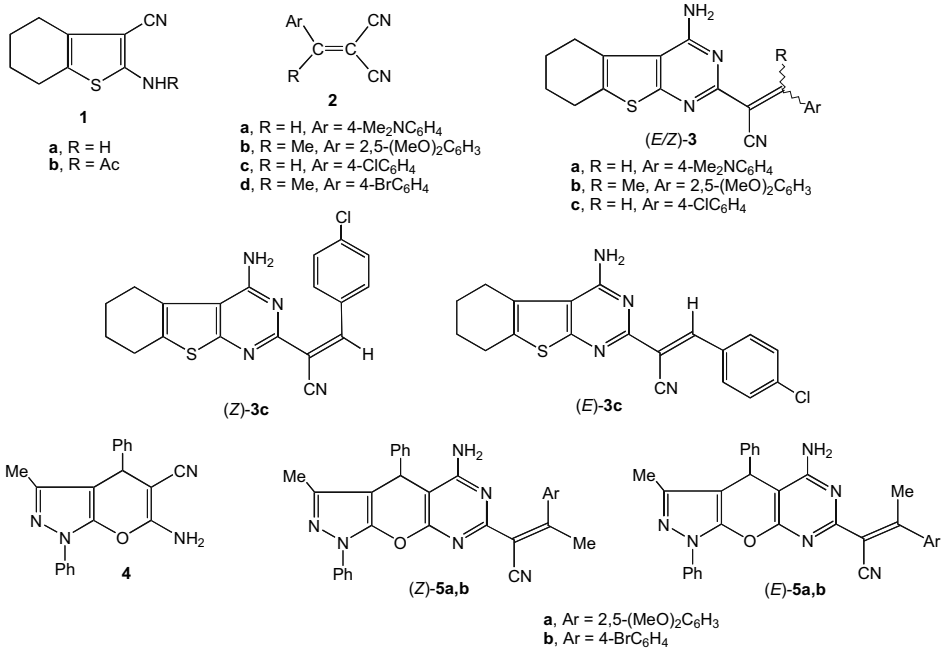
Keywords: fused [1]benzothiophenes, pyrazoles, pyrans, pyrimidines, *o*-aminonitriles, malononitriles, Michael additions, acetylenic esters and ketones

It is reported[1] that the reaction of 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile with methyl β-methoxyacrylate gives a benzothienopyridine derivative. In continuation of our own studies[2] on this aminonitrile and on 6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole-3-carbonitrile, the present work deals with their reactions with substituted benzylidenemalononitriles and with α,β-acetylenic esters and ketones. The reported biological activities[3-6] of the thienopyrimidines and pyranopyrimidines prompted the author to study these reactions on the hope of finding new biologically active compounds.

Results and discussion

Treatment of 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile(**1a**) with the substituted benzylidenemalononitrile derivatives **2a–c** in refluxing n-butanol afforded the benzothieno[2,3-*d*]pyrimidine derivatives **3a**–**c** as (*E*,*Z*) mixtures: (*E*/*Z*)-**3c** isomers in the case of **2c**. Similar treatment of 6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*] pyrazole-5-carbonitrile (**4**) with **2b** and **2d** gave the pyrazolopyranopyrimidine derivatives **5a**,**b** in (*Z*)-and (*E*)-forms as the minor and major stereoisomers, respectively.

The structures of compounds **3** and **5** are substantiated by their microanalytical and spectral data. Their IR spectra show absorptions characteristic of NH and C≡N groups. Analysis of the ^{1}H NMR spectra allowed the inference that each compound of (*E*/*Z*)-**3a-c** exists as a mixture of (*E*) and (*Z*)-stereoisomers in ratio of 2 : 3. The presence of the two stereoisomers was evidenced by the observation of two signals consistent with the olefinic proton for compounds **3a**



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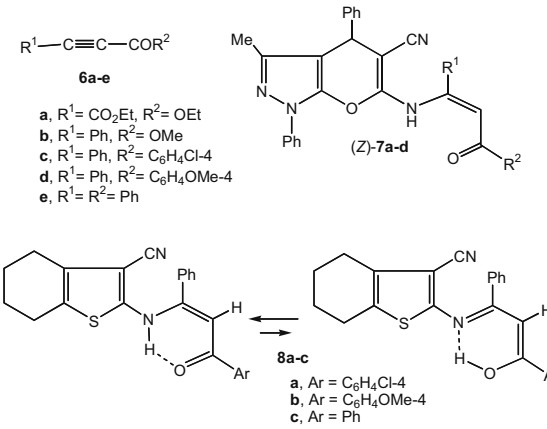
and **3c**, and the methyl protons for compound **3b**. The higher ratio of (*Z*)-isomers as compared with the (*E*) counterparts can be attributed to the existence of the aryl moiety on the less hindered side. Configurational assignments to (*Z*)-**3**, (*E*)-**3**, (*Z*)-**5** and (*E*)-**5** are based on the assumption that the olefinic or methyl protons of the (*E*)-isomers are more deshielded by the aryl group as well as the hetero ring, compared with the (*Z*)-counterparts. The EI MS spectra of compounds **3** and **5** did not show the molecular ion peaks, probably due to their ready decomposition in the ionisation chamber, but they showed some abundant peaks (see Experimental).

The formation of compounds **3** and **5** can be explained as shown in Scheme 1. Nucleophilic attack by the amino group of compound **1a** or **4** at one of the cyano groups[7] of compounds **2** gives intermediate **A**, and cyclisation to the ring cyano group follows to give **3** and **5**.

Treatment of compounds **3a**–**c** with refluxing acetic anhydride in the hope of obtaining their *N*-acetyl derivatives was unsuccessful: 2-acetylamino[1]benzothiophene-3-carbonitrile (**1b**) was the only isolated product in each case. The structure of **1b** was substantiated by the infrared and ^{1}H NMR spectra, the latter of which were devoid of any absorption attributable to aryl groups. The structure was confirmed by comparison with an authentic sample[8] prepared by refluxing **1a** with acetic anhydride.

A rationalisation for the conversion of compounds **3a**–**c** into **1b** is presented in Scheme 2. Protonation at N_1 ring nitrogen by a trace of acetic acid present in acetic anhydride, followed by ring cleavage, gives the substituted benzylidenemalononitrile derivatives **2a**–**c**, and **1a**. Acetylation of **1a** with acetic anhydride gives **1b**. The detection by TLC of the substituted benzylidenemalononitriles **2a**–**c** in the reaction mixtures lends support to this proposal.

Reactions of 6-amino-1,4-dihydro-3-methyl-1,4-diphenyl pyrano[2,3-*c*]pyrazole-5-carbonitrile (**4**) with the acetylenic esters and ketones **6a**-**d** in refluxing ethanol in the presence of a catalytic amount of triethylamine gave the ethenylamino-pyrano[2,3-*c*]pyrazole derivatives (*Z*)-**7a**–**d**. However, the treatment of 2–amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**1a**) with acetylenic ketones **6c**–**e** in refluxing n-butanol in presence of piperidine yielded the enaminoketones (*Z*)-**8a**–**c** as amino-imino tautomeric mixtures in 3 : 2 ratios.

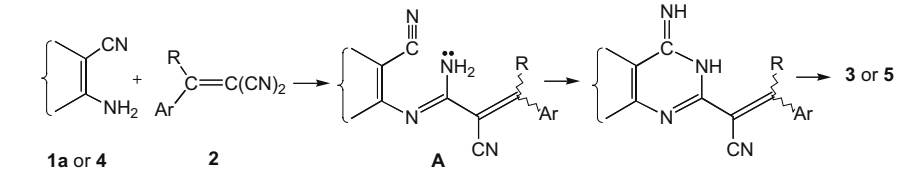


The infrared spectra of compounds **7** and **8** show NH, CN and C=O group absorptions. The (*Z*)-configuration is assigned to **7** and **8** is based on the higher δ value observed for the olefinic proton, as it is more deshielded by the oxo group in case of **7a** as well as the aryl groups in case of compounds **7b**–**d** and **8**, as compared with the (*E*)-counterpart. The low frequency of the absorption of the CO groups is evidence for the existence of **7** and **8** in their chelated forms shown. In chloroform solution, the ^{1}H NMR spectra of compounds **8** show two broad singlet signals for NH and OH protons. This is consistent with their existence as an amino-imino dynamic equilibrium in ratios of 3 : 2. The down field shifts of the NH and OH protons are in harmony with their existence as chelated forms as shown. The higher proportion of the amino tautomers compared with the imines is due to their relative thermodynamic stabilities.

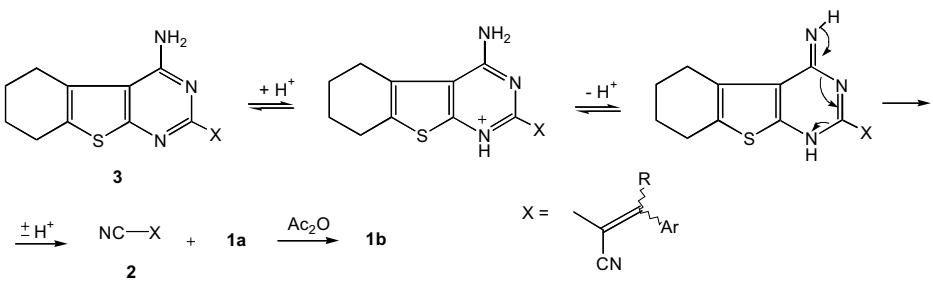
Further support for the assigned structures of compounds **7** and **8** is found in their mass spectra. Compounds **7a, c** and **8a**–**c** reveal the molecular ions, and other abundant peaks. However, the molecular ion peaks are missing in the cases of compounds **7b**, **d** but they show some important peaks.

Conclusion

It is concluded that reactions of the aminobenzothiophene and aminopyranopyrazole carbonitrile derivatives with substituted benzylidenemalononitriles proceed by attack of



Scheme 1



Scheme 2

the amino group at one of the two cyano groups and not at the β-carbon of the unsaturated system.[7,13] On the other hand, in their reactions with acetylenic esters and ketones, attack of the amino group at the β-carbon of the acetylenic system[14-16] takes place, rather than at the carbonyl function.

Experimental

Melting points were measured on an electrothermal melting point apparatus. Elemental analyses were carried out at the Microanalytical Unit of Cairo University. IRspectra were measured on a Unicam SP1200 spectrometer using the KBr wafer technique. ^{1}H NMR spectra were measured on a Varian Gemini 200 MHz instrument with chemical shifts (δ) expressed in ppm downfield from Me_4Si. Mass spectra were recorded on a Shimadzu GC-MS QP 1000 EX instrument operating at 70 eV. Column chromatography and TLC were run on silica Gel Voeim, activity III/30 mm according to Brockmann & Schodder, and TLC aluminium sheets silica gel 60 F_{254} (Merck). 'Light petroleum' refers to the fraction b.p. 60–80 °C, unless otherwise specified.

2-Amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile(**1a**),[8] 6-amino-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-*c*]pyrazole-5-carbonitrile (**4**),[9] substituted benzylidenemalononitriles (**2**),[10] and acetylenic esters[11] and ketones[12] (**6**) were prepared according to literature methods.

Reaction of aminonitrile **1a** *with substituted benzylidenemalononitriles* **2a–c**

A mixture of **1a** (3 mmol) and a substituted benzylidenemalononitrile (**2a–c**) (3 mmol) in n-butanol (20 mL) was heated to reflux for 20 h. The reaction mixture was then concentrated and left to stand at room temperature overnight to give a solid. Crystallisation from the indicated solvent gave the fused aminopyrimidinecarbonitrile (*E*/*Z*)-(**3a–c**). The n-butanol mother liquor in the case of the reaction of **1a** with **2c** was evaporated and chromatographed over silica gel. Successive elution with light petroleum/diethyl ether (9 : 1 v/v) afforded (*E*)-**3c**, and then with light petroleum/diethyl ether) (1 : 1 v/v) gave (*Z*)-**3c**.

(*E*/*Z*)-*2-(4-Amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-2-yl)-3-(4-N,N-dimethylaminophenyl)propenonitrile* (**3a**): 80% Yield, m.p. 120–122 °C (light petroleum b.p. 40–60 °C). IR: ν_{max} 3447, 3329, 3207 (NH), 3060 (aryl-H), 2933, 2911, 2838 (alkyl-H), 2196 (C≡N), 1620(C=N), 1588, 1522 (C=C), 854, 765 cm^{-1}. NMR ($CDCl_3$): δ_H 1.77 (m, 4, $2CH_2$), 2.49 (m, 4, $2CH_2$),3.08 (s, 6, NMe_2 for *E*-isomer), 3.14 (s, 6, NMe_2 for *Z*-isomer), 4.59 (br.s, NH_2 exchangeable), 6.77 (dd, 2, ArH, J_o = 7.88 Hz, J_m = 2.54 Hz), 7.48 (s, 1, CH= for *Z*-isomer), 7.81 (dd, 2, ArH, J_o = 7.26 Hz, J_m = 2.64 Hz),8.26 (s, 1, CH= for *E*-isomer). EI MS: *m/z* (%) 197 (M^+ of **2a**, 3), 180 (M^+ + 2 of **1a**, 3), 178 (M^+ of **1a**, 41), 177 (15), 150 (100). Anal. Calcd for $C_{21}H_{21}N_5S$: C, 67.17; H, 5.64; N, 18.65. Found: C, 66.95; H, 5.89; N, 18.86%.

(*E*/*Z*)-*2-(4-Amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-2-yl)-3-(2,5-dimethoxyphenyl)-but-2-enonitrile* (**3b**): 83% Yield, m.p. 158–160 °C (light petroleum b.p. 80–100 °C). IR: ν_{max} 3446, 3329, 3207 (NH), 3030 (aryl-H), 2933, 2911, 2837 (alkyl-H), 2196 (C≡N), 1620 (C=N), 1521 cm^{-1} (C=C). NMR ($CDCl_3$): δ_H 1.74 (m, 4, 2 CH_2), 2.42 (m, 4, 2 CH_2), 2.56 (s, 3, CH_3, for *Z*-isomer), 2.58 (s, 3, CH_3, for *E*- isomer), 3.77, 3.82 (two singlets, 6, 2 OCH_3), 4.65 (br.s, NH_2 exchageable), 6.73–7.72 (m, 3, ArH). Anal. Calcd for $C_{22}H_{22}N_4O_2S$: C, 65.00; H, 5.46; N, 13.78. Found: C, 64.79; H, 5.53; N, 13.85%.

(*E*/*Z*)-*2-(4-Amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-2-yl)-3-(4-chlorophenyl)propenonitrile* (**3c**): Yellow crystals; 50% yield, m.p. 123–125 °C (dilute ethanol). IR: ν_{max} 3440, 3332, 3208 (NH), 3035 (aryl-H), 2929, 2863 (alkyl-H), 2220 (C≡N), 1656 (C=N), 1595, 1560 (C=C), 824 cm^{-1} (δ_{2H}). NMR ($CDCl_3$): δ_H 1.87 (m, 4, 2 CH_2), 2.71 (m, 4, 2 CH_2), 4.73 (br.s, NH_2 exchangeable). For *Z*-isomer: δ_H 7.44 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.6 Hz), 7.73 (s, 1, CH=), 7.86 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.86 Hz). For *E*-isomer: δ_H 7.52 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.8 Hz), 7.88 (dd, 2, ArH, J_o = 8.4 Hz, J_m = 1.9 Hz), 8.38 (s, 1, CH=). EI MS: *m/z* (%) 302 (28), 300 (100), 272 (77), 190 (M^+ + 2 of **2c**, 25), 188 (M^+ of **2c**, 75), 153 (M + · of **2c** -Cl, 100), 134 (15), 126 (25), 102 (12), 101 (10), 100 (17), 89 (40), 80 (30), 77 (13), 63 (26), 62 (27), 51 (24), 50 (55). Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.20; H, 4.12; N, 15.27. Found: C, 62,32; H, 4.27; N, 14.99%.

(*Z*)-*2-(4-Amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d] pyrimidin-2-yl)-3-(4-chlorophenyl)-propenonitrile* (*Z*-**3c**): 23% Yield, m.p. 108–110 °C (light petroleum b.p. 40–60 °C). IR: ν_{max} 3446, 3329, 3207 (NH), 3033 (aryl-H), 2934, 2911, 2837 (alkyl-H), 2196 (C≡N), 1621 (C=N), 1558, 1521 (C=C), 826 cm^{-1} (δ_{2-H}). NMR ($CDCl_3$): δ_H 1.79 (m, 4, 2 CH_2), 2.49 (m, 4, 2 CH_2), 4.62 (br.s, NH_2 exchangeable), 7.52 (dd, 2, ArH, J_o = 8.64 Hz, J_m = 1.96 Hz), 7.74 (s, 1, CH=), 7.86 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.9 Hz). EI MS: *m/z* (%) 190 ($M^{+\cdot}$ + 2 of **2c**, 28), 188 ($M^{+\cdot}$ of **2c**, 76), 180 ($M^{+\cdot}$ + 2 of **1a**, 2), 178 ($M^{+\cdot}$ of **1a**, 38) 177 (14), 163 (11), 161 (32) 154 (12), 152 (base), 151 (11), 150 (97), 137 (25), 126 (21), 100 (12), 99 (14), 76 (23), 75 (24), 74 (13), 63 (18), 62 (16), 51 (24), 50 (32). Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.20; H, 4.12; N, 15.27. Found: C, 61.88; H, 3.92; N, 15.48%.

(*E*)-*2-(4-Amino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)-3-(4-chlorophenyl)-propenonitrile* (*E*-**3c**): Yellow needles; 16% yield, m.p. 140–142 °C (dilute ethanol). IR: ν_{max} 3439, 3342, 3215 (NH), 3093 (aryl-H), 2939, 2921, 2863 (alkyl-H), 2220 (C≡N), 1641 (C=N), 1595, 1560 (C=C), 819 cm^{-1} (δ_{2-H}). NMR ($CDCl_3$): δ_H 1.87 (m, 4, 2 CH_2), 2.69 (m, 4, 2 CH_2), 4.75 (br.s, NH_2 exchangeable), 7.44 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.85 Hz), 7.88 (dd, 2, ArH, J_o = 8.6 Hz, J_m = 1.92 Hz), 8.38 (s, 1, CH=). EI MS: *m/z* (%) 302 (31), 301 (24), 300 (base), 299 (21), 274 (25), 273 (16), 272 (78), 271 (11), 178 ($M^{+\cdot}$ of **1a**, 2.8), 89 (38), 77 (15), 76 (10), 75 (13), 63 (25), 58 (11), 51 (15). Anal. Calcd for $C_{19}H_{15}ClN_4S$: C, 62.20; H, 4.12; N, 15.27. Found: C, 62.48; H, 4.31; N, 15.42%.

Reaction of aminonitrile **4** *with substituted benzylidenemalononitriles* **2b,d**

A mixture of **4** (3 mmol) and a substituted benzylidene malononitrile (**2b**,**d**) (3 mmol) in n-butanol (20 mL) was refluxed for 20 h. The reaction mixture was concentrated and chromatographed over silica gel. In the case of the reaction **4** with **2b**, successive elution with light petroleum/ether (4 : 1 v/v) gave (*E*)-**5a**, then with light petroleum/ether (2 : 3 v/v) afforded (*Z*)-**5a**. However, in the case of the reaction with **2d**; elution with petroleum ether/ether (9 : 1 v/v) yielded (*E*)-**5b**, then with petroleum ether/ether (1 : 1 v/v) gave (*Z*)-**5b**.

(E)-2-(5-Amino-1,4-dihydro-3-methyl-1,4-diphenylpyrazolo[4',3':5, 6]pyrano[2,3-d]pyrimidin-7-yl)-3-(2,5-dimethoxyphenyl)-but-2-enonitrile (*E*-**5a**): Yellow crystals; 36% yield, m.p. 125–126 °C (light petroleum b.p. 40–60 °C). IR: ν_{max} 3422, 3326, 3234 (NH), 3062 (aryl-H), 2925, 2847 (alkyl-H), 2212 (C≡N), 1661 (C=N), 1601, 1593 (C=C), 756, 693 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.82 (s, 3, CH_3 pyrazole), 2.29 (s, 3, CH_3), 3.78, 3.82 (two singlets, 6, 2 OCH_3), 4.85 (s, 1, CH), 5.82 (br.s, NH_2 exchangeable), 6.97–7.69 (m, 13, ArH). EI MS: *m/z* (%) 382 (11), 351 (12), 266 (14), 263 (18), 262 (70), 261 (36), 186 (16), 185 (87), 174 (32), 129 (17), 128 (36), 127 (12), 105 (18), 91 (61), 78 (10), 77 (base), 65 (12), 64 (18), 63 (15), 51 (58), 50 (14). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.09. Found: C, 70.98; H, 5.26; N, 14.88%.

(Z)-2-(5-Amino-1,4-dihydro-3-methyl-1,4-diphenylpyrazolo [4',3':5,6]pyrano[2,3-d]pyrimidin-7-yl)-3-(2,5-dimethoxyphenyl)-but-2-enonitrile (*Z*-**5a**): Yellow crystals; 30% yield, m.p. 137–139 °C (ethanol). IR: ν_{max} 3404, 3330, 3208 (NH), 3045 (aryl-H), 2931, 2839 (alkyl-H), 2216 (C≡N), 1642 (C=N), 1540 (C=C), 744, 673 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.61 (s, 3, CH_3 pyrazole), 2.17 (s, 3, CH_3), 3.77, 3.82 (two singlets, 6, 2 OCH_3), 4.77 (s, 1, CH), 5.85 (br. s, NH_2 exchangeable), 6.44–7.37 (m, 13, ArH). EI MS: *m/z* (%) 448 ($M^{+\cdot}$-[Ph + OCH_3], 78), 418 (29), 417 (40), 351 (44), 333 (57), 332 (93), 167 (14), 166 (21), 165 (41), 154 (23), 139 (45), 124 (33), 104 (24), 92 (31), 91 (100), 77 (52), 76 (14), 67 (20), 66 (26), 65 (31), 64 (17), 63 (13), 55 (49), 51 (71), 50 (18). Anal. Calcd for $C_{33}H_{28}N_6O_3$: C, 71.21; H, 5.07; N, 15.09. Found: C, 71.35; H, 4.98; N, 15.29%.

(*E*)-*2-(5-Amino-1,4-dihydro-3-methyl-1,4-diphenylpyrazolo [4',3':5,6]pyrano[2,3-d]pyrimidin-7-yl)-3-(4-bromophenyl)-but-2-enonitrile* (*E*-**5b**): Yellow crystals; 38% yield, m.p. 218–220 °C (petroleum ether b.p. 80–100 °C). IR: ν_{max} 3494, 3389 (NH), 3050 (aryl-H), 2920, 2852 (alkyl-H), 2207 (C≡N), 1608 (C=N), 1578, 1547 (C=C), 827 (δ_{2H}) 762, 693 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.79 (s, 3, CH_3 pyrazolo), 2.30 (s, 3, CH_3), 4.79 (s, 1, CH), 5.75 (br.s, NH_2 exchangeable), 6.59–7.69 (m, 14, ArH). EI MS: *m/z* (%) 354 (M^+-NCC=C(CH_3)C_6H_4Br-*p*, 1), 352 (21), 351 (91), 350 (41), 349 (100), 348 (25), 168 (18), 140 (21), 77 (14), 76 (13), 75 (15), 51 (20). Anal. Calcd for $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60. Found: C, 64.85; H, 4.19; N, 14.49%.

(*Z*)-*2-(5-Amino-1,4-dihydro-3-methyl-1,4-diphenylpyrazolo [4',3':5,6]pyrano[2,3-d]pyrimidin-7-yl)-3-(4-bromophenyl)-but-2-enonitrile* (*Z*-**5b**): Yellow crystals; 23% yield, m.p. 205–207 °C (ethanol). IR: ν_{max} 3395, 3307, 3207 (NH), 3076 (aryl-H), 2954, 2878, 2818 (alkyl-H), 2215 (C≡N), 1650, 1641 (C=N), 1606, 1542 (C=C), 832 cm^{-1} (δ_{5-H}). NMR ($CDCl_3$): δ_H 1.74 (s, 3, CH_3 pyrazole), 2.17 (s, 3, CH_3), 4.72 (s, 1, CH), 5.81 (br.s, NH_2 exchangeable),

6.24–7.70 (m, 14, ArH). EI MS: *m/z* (%) 497 (M^+-Ph, 1.4), 479 ($M^{+\cdot}$-[Ph + 18], 2.7), 400 (M^+-[Ph + 18 + Br], 7.2), 374 (M^+-[Ph + 18 + Br + CN], 2), 291 (1.5), 289 (1.5), 287 (15), 286 (100), 285 (19), 284 (96), 116 (13), 102 (11), 91 (18), 77 (22), 76 (13), 75 (12), 51 (26), 50 (12). Anal. Calcd for $C_{31}H_{23}BrN_6O$: C, 64.70; H, 4.03; N, 14.60. Found: C, 64.52; H, 3.98; N, 14.75%.

Reaction of acetic anhydride with the aminonitriles **3a–c**

The benzothienopyrimidine derivatives **3a**–**c** (0.4 g) were each refluxed in acetic anhydride (15 mL) for 4 h. The reaction mixture was cooled and poured into ice-cold water to give the same product, 2-acetylamino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**1b**), m.p. 208–210 °C (light petroleum/benzene) (lit.[8] m.p. 215–216 °C) in 65–87% yields. IR: ν_{max} 3266, 3219 (NH), 2992, 2926, 2840 (alkyl-H), 2209 (C≡N), 1688 (C=O), 1637, 1551 (C=C). NMR (DMSO-d_6): δ_H 1.76 (m, 4, $2CH_2$), 2.18 (s, 3, CH_3), 2.58 (m, 4, $2CH_2$), 11.52 (br.s, NH exchangeable). This substance was identical in all respects (m.p., mixed m.p. and TLC) with an authentic sample prepared from the reaction of **1a** with acetic anhydride.

Reactions of the aminonitrile ***4*** *with acetylenic esters and ketones* **6a–d**

An acetylenic ester (**6a**,**b**) or ketone (**6c**,**d**) (2 mmol) was added to a solution of **4** (2 mmol) in ethanol (20 mL) containing triethylamine (three drops) and the mixture was refluxed for 20 h. The reaction mixture was then concentrated and left to stand at room temperature overnight to provide a solid. Recrystallisation from the indicated solvent gave the relevant adduct (**7a**–**d**).

(*Z*)-*1,4-Dihydro-3-methyl-1,4-diphenyl-6-[(1,2-diethoxycarbonylethenyl)amino]pyrano[2,3-c]pyrazole-5-carbonitrile* (*Z*-**7a**): 40% Yield, m.p. 100–102 °C (light petroleum/benzene). IR: ν_{max} 3434 br. (NH), 2980, 2924, 2871 (alkyl-H), 2214 (C≡N), 1727 (C=O), 1631 (C=N), 1600, 1542 (C=C), 753, 692 (δ_{5H}). NMR (DMSO-d_6): δ_H 1.20 (m, 6, $2CH_2\underline{CH_3}$), 2.08 (S, 3, CH_3), 4.22 (m, 4, $2\underline{CH_2}CH_3$), 5.20 (s, 1, CH), 6.57 (s, 1, CH=), 7.26–7.43 (m, 10, ArH), 8.60 (br.s, NH exchangeable). EI MS: *m/z* (%) 498 (M^+, 1), 453 (M^+-OEt, 8), 425 (M^+-CO_2Et,12) 408 (M^+-2OEt, 15), 352 (M^+-$2CO_2$Et, 20), 328 (30), 262 (91), 185 (77), 174 (43), 128 (40), 119 (32), 93 (100), 91 (36), 77 (35). Anal. Calcd for $C_{28}H_{26}N_4O_5$: C, 67.46; H, 5.26; N, 11.24. Found: C, 67.29; H, 5.32; N, 11.35%.

(Z)-Methyl 3-[(5-cyano-1,4-dihydro-1,4-diphenyl-3-methylpyrano[2,3-c]pyrazol-6-yl)amino]-3-phenylprop-2-enoate (*Z*-**7b**): Yellow crystals; 39% yield, m.p. 145–148 °C (light petroleum b.p. 80–100 °C). IR: ν_{max} 3340, 3280, 3180 (NH), 3050 (aryl-H), 2960, 2900, 2840 (alkyl-H), 2160 (C≡N), 1720 (C=O), 1650 (C=N), 1590, 1550 (C=C), 760, 690 cm^{-1} (δ_{5H}). NMR (DMSO-d_6): δ_H 1.91 (s, 3, CH_3), 3.93 (s, 3, OCH_3), 4.59 (br.s, NH, exchangeable), 5.10 (s, 1, CH), 6.48 (s, 1 CH=), 7.05–7.81 (m, 15, ArH). EI MS: *m/z* (%) 460 (25), 459 (22), 458 (52), 457 (M^+-OCH_3, 85), 265 (18), 264 (56), 263 (78), 261 (15), 197 (16), 195 (34), 185 (20), 138 (13), 137 (12), 136 (20), 131 (20), 129 (26), 128 (32), 127 (10), 116 (30), 115 (36), 105 (16), 103 (16), 102 (12), 101 (14), 89 (12), 77 (54), 75 (16), 64 (12), 59 (100), 51 (26). Anal. Calcd for $C_{30}H_{24}N_4O_3$: C, 73.76; H, 4.95; N, 11.47. Found: C, 73.51; H, 5.08; N, 11.69%.

(*Z*)-*6-[[2-(4-Chlorobenzoyl)-1-phenylethenyl]amino]-1,4-dihydro-3-methyl-1,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile* (*Z*-**7c**): 43% Yield, m.p. 142–145 °C (light petroleum b.p. 80–100 °C). IR: ν_{max} 3433 br. (NH), 3059 (aryl-H), 2971, 2921, 2857 (alkyl H), 2205 (C≡N), 1658 (C=O), 1588 (C=N and/or C=C), 830 cm^{-1} (δ_{2H}) NMR ($CDCl_3$): δ_H 2.10 (s, 3, CH_3), 5.05 (br.s, NH exchangeable), 5.45 (s, 1, CH), 6.45 (s, 1, CH=), 7.19–7.85 (m, 19, ArH). EI MS: *m/z* (%) 570 ($M^{+\cdot}$ + 2, 0.2), 568 ($M^{+\cdot}$, 0.5), 459 ($M^{+\cdot}$ + 2-C_6H_4Cl, 0.9), 457 (M^+-C_6H_4Cl, 1.5), 263 (22), 246 (13), 219 (52), 139 (COC_6H_4Cl, 32), 119 (19), 91 (100), 77 (30). Anal. Calcd for $C_{35}H_{25}ClN_4O_2$: C, 73.87; H, 4.43; N, 9.84. Found: C, 73.95; H, 4.64; N, 9.72%.

(*Z*)-*1,4-Dihydro-6-[[2-(4-methoxybenzoyl)-1-phenylethenyl]amino]-3-methyl-1,4-diphenylpyrano[2,3-c]pyrazole-5-carbonitrile* (*Z*-**7d**): 26% Yield, m.p. 158–160 °C (light petroleum/benzene). IR: ν_{max} 3446, 3358, 3246 (NH), 3060 (aryl-H), 2934, 2839 (alkyl-H), 2214 (C≡N), 1645 (C=O), 1610 (C=N), 1574, 1515 (C=C), 832 (δ_{2H}), 764, 696 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.56 (s, 3, CH_3), 3.87 (s, 3, OCH_3), 4.76 (br.s, NH exchangeable), 5.37 (s, 1, CH), 6.87 (s, 1, CH=), 7.02 (dd, 2, ArH, J_o = 8.8 Hz, J_m = 2.0 Hz), 7.36–7.61 (m, 15, ArH), 7.55 (dd, 2, ArH, J_o = 8.8 Hz, J_m = 2.4 Hz). EI MS *m/z* (%) 327 (M^+-C_6H_5C=$CHCOC_6H_4OMe$, 3), 326 (21), 325 (100), 324 (14), 310 (12), 255 (19). Anal. Calcd for $C_{36}H_{28}N_4O_3$: C, 76.58; H, 4.99; N, 9.92. Found: C, 76.70; H, 4.66; N, 10.15%.

Reaction of 2-amino-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**1a**) *with acetylenic ketones* **6c–e**

A mixture of **1a** (3 mmol), each of **6c**–**e** (3 mmol) and a few drops of piperidine was refluxed in n-butanol (15 mL) for 20 h. The reaction mixture is concentrated and allowed to stand at room temperature overnight to give a semisolid material. Trituration with methanol gave a solid. Recrystallisation from ethanol afforded 0.1–0.2 g recovered **1a**. Leaving the mother liquor at room temperature overnight afforded a solid product (**8a**–**c**) which was recrystallised from the indicated solvent.

2-[[2-(4-Chlorobenzoyl)-1-phenylethenyl]amino]-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**8a**) *(as amino-imino tautomer)*: Brown crystals; 32% yield, m.p. 181–183 °C (petroleum ether b.p. 80–100 °C). IR: ν_{max} 3445 br. NH, 3059 (aryl-H), 2940, 2837 (alkyl-H), 2205 (C≡N), 1645 (C=O), 1584, 1519 (C=N and/or C=C), 845 (δ_{2H}), 779, 695 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.75 (m, 4, 2 CH_2), 2.48 (m, 4, 2 CH_2), 4.76 (br.s, NH exchangeable for amino-tautomer), 6.11 (s, 1, CH=), 7.36–7.94 (m, 9, ArH), 13.67 (br.s, OH exchangeable for imino-tautomer). EI MS: *m/z* (%) 420 (M^+ + 2, 10), 418 (M^+, 22), 279 (M^+-COC_6H_4Cl, 17), 141 (27), 139 (COC_6H_4Cl, 100), 138 (15), 111 (28), 77 (11). Anal. Calcd for $C_{24}H_{19}ClN_2OS$: C, 68.81; H, 4.57; N, 6.69. Found: C, 68.65; H, 4.71; N, 6.52%.

4,5,6,7-Tetrahydro-2-[[2-(4-methoxybenzoyl)-1-phenylethenyl]amino][1]benzothiophene-3-carbonitrile (**8b**) *(as amino-imino tautomer)*: Brown crystals; 24% yield, m.p. 188–190 °C (methanol/benzene). IR: ν_{max} 3432, 3335, 3218 NH, 2937, 2903, 2837 (alkyl-H), 2196 (C≡N), 1620 (C=O), 1590, 1519 cm^{-1} (C=N and/or C=C). NMR ($CDCl_3$): δ_H 1.57 (br.s, 4, $2CH_2$), 2.28 (br.s, 4, $2CH_2$), 3.66 (s, 3, OCH_3), 4.49 (br.s, NH exchangeable for amino-tautomer), 5.93 (s, 1, CH=), 6.70–7.78 (m, 9, ArH), 13.45 (br.s, OH exchangeable for imino-tautomer). EI MS: *m/z* (%) 416 (M^+ + 2, 8), 414 ($M^{+\cdot}$, 30), 415 (20), 135 (COC_6H_4OMe, 100), 77 (15). Anal. Calcd for $C_{25}H_{22}N_2O_2S$: C, 72.44; H, 5.35; N, 6.76. Found: C, 72.61; H, 5.12; N, 6.92%.

2-[(2-Benzoyl-1-phenylethenyl)amino]-4,5,6,7-tetrahydro[1]benzothiophene-3-carbonitrile (**8c**) *(as amino-imino tautomer)*: Yellow needles; 43% Yield, m.p. 201–203 °C (methanol/benzene). IR: ν_{max} 3448 br. NH, 3062 (aryl-H), 2922, 2840 (alkyl-H), 2203 (C≡N), 1654 (C=O), 1611, 1591, 1569 (C=N and/or C=C), 769, 694 cm^{-1} (δ_{5H}). NMR ($CDCl_3$): δ_H 1.61 (m, 4, $2CH_2$), 2.27 (m, 4, $2CH_2$), 4.58 (br.s, NH exchangeable for amino-tautomer), 5.97 (s, 1, CH=), 7.05–7.79 (m, 10, ArH), 13.46 (br.s, OH exchangeable for imino-tautomer). EI MS *m/z* (%) 386 (M^+ + 2, 4), 385 (52), 384 (M^+, 25), 383 (11), 356 (10), 282 (14), 281 (10), 280 (14), 279 (17), 105 (COC_6H_5, 100), 77 (41). Anal. Calcd for $C_{24}H_{20}N_2OS$: C, 74.97; H, 5.24; N, 7.29. found: C, 74.62; H, 4.99; N, 7.46%.

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References

1 M. Tompson, I. Forbes and C.N. Johnson, Eur. Pat. Appl. EP 327 223 (Cl. C07D495/04; 09 Aug. 1989, CB Appl. 88/1, 491, 22 Jan 1988, 18 pp.; *Chem. Abstr*., 1990, **112**, 55831 h.
2 A.S.A. Youssef, K.A. Kandeel, F.A. Fouli and W.S.I. Abou El-Magd, *Heteroatom Chem*., 2005, **6**, 16.
3 S.E. Delaszlo, A.A. Patchett, E.E. Allen and W.J. Greenle, Eur. Pat. 1992, 502 725; *Chem. Abstr.,* 1993, **118**, 22 249.
4 G.E. Robinson and C.J. Quire, Eur. Pat., 1988, **253**, 507; *Chem. Abstr*., 1988, **109**, 6318.
5 K.C. Joshi, R. Jain, A. Damdi and K. Sharma, *J. Heterocyclic Chem*., 1988, **25**, 1641.
6 R. Boehm, G. Hanbold, R. Pech and G. Laban, Ger. Pat., 1985, **226**, 893; *Chem. Abstr*., 1986, **104**, 186437.
7 A.S.A. Youssef, *Chem. Pap*., 2002, **56**, 132.
8 J.D. Ramanathan, D.G. Namboothiri, G.F. Shah, A.V. Radhakrishnan, H.J. Mehta and A.C. Padhya, *J. Indian Chem. Soc*., 1978, **55**, 822.
9 G. Tacconi, G. Gatti and G. Desimoni, *J. Prakt. Chem*., 1980, **322** (5), 831; *Chem. Abstr*., 1981, **94**, 174962 w.
10 D.T. Mowry, *J. Am. Chem. Soc*., 1943, **65**, 991.
11 I. Benghiate and E.I. Becker, *J. Org. Chem*., 1958, **33**, 885.
12 W. Parker, R.A. Raphael and O.I. Wilkinson, *J. Chem. Soc*., 1958, 3871.
13 M. Suesse and S. Johne, DD 155 167 (Cl. C07D 495/14), 19 May 1982, Appl. 225 874, 09 Dec. 1980; *Chem. Abstr*., 1982, **97**, 216211v.
14 M.N. Basyouni, M.T. Omar, A.A. El-Khamry and E.A. Ghali, *Egypt J. Chem*., 1980, **23**, 237.
15 F.G. Baddar, F.A. Al-Hajjar and N.R. El-Rayyes, *J. Heterocyclic Chem*., 1978, **15**, 105.
16 F.A. Fouli, M.E. Shaban, E.I. El-Nagdy and A.S.A. Youssef, *Indian J. Chem*., 1988, **27B**, 86.