Synthesis of New 3-Substituted Indole Derivatives

Huwaida M. E. Hassaneen[a] and Richard M. Pagni[b]

[a] Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
[b] Department of Chemistry, Faculty of Tennessee, Knoxville, TN, USA

Reprint requests to Dr. Huwaida M. E. Hassaneen. E-mail: huwaidahassaneen@hotmail.com

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Treatment of 3-cyanoacetyl-2-methylindole (**1**) with phenyl isothiocyanate gave the corresponding thioacetanilide derivative **3**. The thioacetanilide **3** was utilized as the key intermediate for the synthesis of some new 1,3,4-thiadiazole (**6a**, **b** and **9a – e**), thiophene (**11a**, **b**), thiazolidin-4-one (**4**), thiazole (**12** and **13**), and benzothiazole (**15**) derivatives. The structures of the new compounds were elucidated on the basis of elemental analyses and spectral data.

Key words: 3-Cyanoacetyl-2-methylindole, Thioacetanilide, Hydrazonoyl Halides, Thiadiazole, Thiazole

Introduction

The indole moiety is found in various pharmacologically and biologically active compounds [1]. Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties [2]. For example, five novel indole alkaloids [3], tunicate aplidium meridianum A–E, have been isolated from tunical splidium meridianum. They show cytotoxicity toward murine tumor cell lines and have potent inhibition against several protein kinases [4]. Along with these, the substitution at the 3-position of the indole ring can take place by connecting an additional heterocyclic ring, such as imidazole (topsentins [5], nortopsentins [6]), dihydroimidazole (discodermindole [7]), oxazole (martefragin [8], amazole [9]), oxadiazine (alboinon [10]), maleimide (didemidines [11]), and piperazine (dragmacidone [12]). Therefore, 3-substituted indoles still represent a significant synthetic challenge.

Results and Discussion

The synthetic procedures adopted to obtain the target compounds are depicted in Schemes 1 – 3. Previously, 2-methylindole was reacted with cyanoacetic acid to give 3-oxo-propionitrile **1** [13]. It is known that a great variety of reactants bearing the N=C=S fragment undergo cyclization on reaction with hydrazonoyl halides and α-halocarbonyl compounds to afford thiadiazoles, thiazoles, thiophenes, 2,3-dihydrothiazoles, and thiazolidines [14], which have been shown to exhibit antiprotozoal [15] and fungicidal properties [16]. Thus, the base-catalyzed reaction of the acidic methylene compound **1** with phenyl isothiocyanate in dry DMF at r. t. yielded the non-isolable potassium salt **2**. Treatment of **2** with dilute hydrochloric acid gave the thioacetanilide derivative **3**. The structure of **3** was confirmed based on analytical and spectral data. Cyclization of the potassium salt of the thioacetanilide derivative **2** with chloroacetyl chloride afforded the thiazolidin-4-one derivative **4**. The IR spectrum of compound **4** had a strong absorption band at 1733 cm^{-1} due to the CO group, confirming the presence of the thiazolidinone ring; another piece of evidence for the cyclization was the appearance of a singlet due to two equivalent protons in the ^1H NMR spectrum, at δ = 4.05 ppm, which represents the C5 protons of the thiazolidinone ring. In addition, the ^{13}C NMR spectrum displayed characteristic signals at δ = 173.2, 112.7 and 30.6 ppm due to C4 (thiazolidin-5-one), CN and CH_2 carbons, respectively, beside all the other carbons at the expected chemical shifts.

The thioacetanilide **3**, when treated with hydrazonoyl halides of type **5a**, **b** in refluxing ethanol and in the presence of triethylamine, afforded, in each case, only the 1,3,4-thiadizoles **6a**, **b** (Scheme 2). Elemental analyses and spectral data of the reaction products were in complete agreement with the proposed structures. For example, **6a** had characteristic absorption peaks in its IR spectrum at 3280, 2197 and 1666 cm^{-1} due to NH, CN and C=O groups, respectively. In addi-

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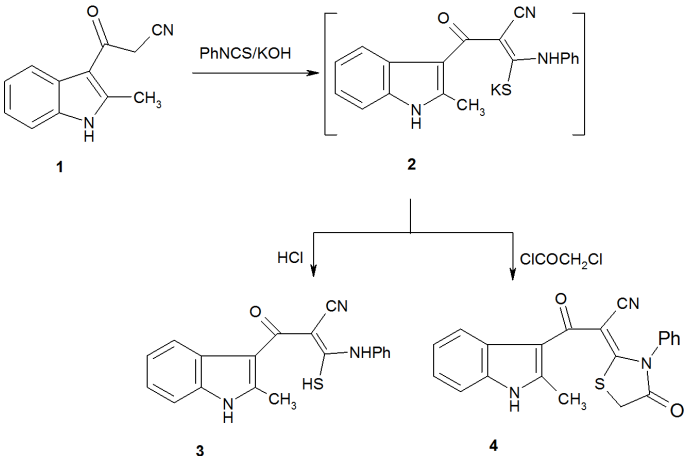
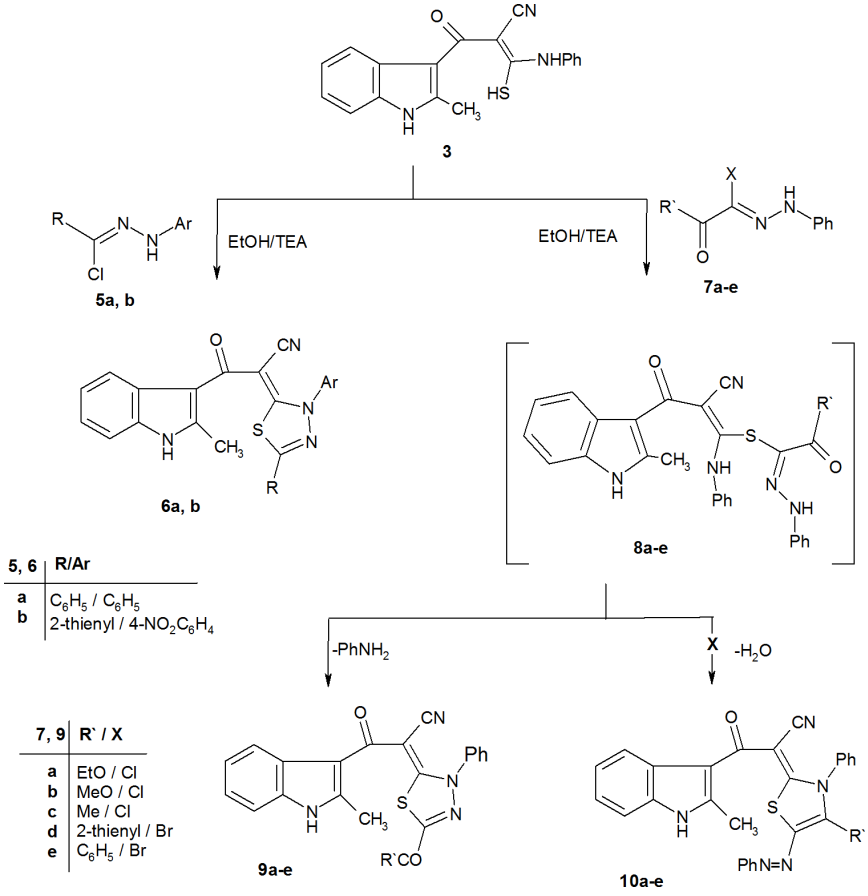


Scheme 1.



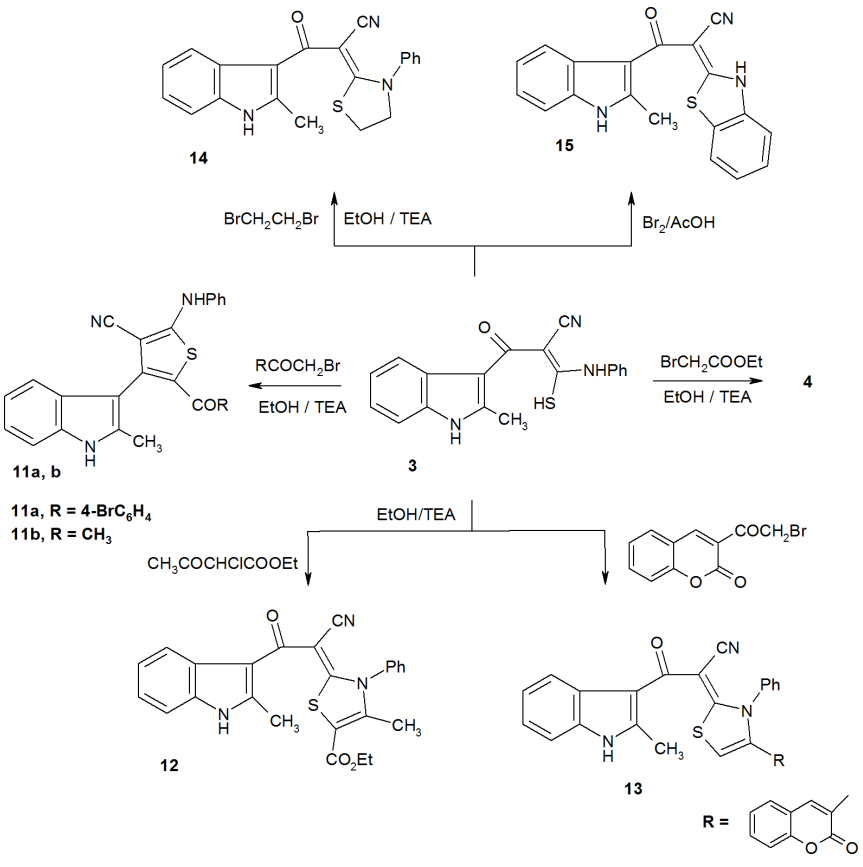
5, 6	R/Ar
a	C_6H_5 / C_6H_5
b	2-thienyl / 4-$NO_2C_6H_4$

7, 9	R` / X
a	EtO / Cl
b	MeO / Cl
c	Me / Cl
d	2-thienyl / Br
e	C_6H_5 / Br

Scheme 2.

tion, the mass spectrum revealed a peak at $m/z = 434$ corresponding to the molecular ion (see Experimental Section).

Also, the reaction of α-ketohydrazonoyl halides of type **7** with the thioacetanilide derivative **3** was investigated to see the effect of the presence of the carbonyl group on the course of the reaction. Compound **3** reacted with α-ketohydrazonoyl halides **7a – e** to afford the corresponding thiadiazole derivatives **9a – e** *via* elimination of aniline. Structure **10** was discarded



Scheme 3.

on the basis of elemental analysis and spectral data. For example, the IR spectra of the product **10** would only have one carbonyl absorption band (Scheme 2). The structure of **9** was confirmed on the basis of elemental analyses and spectral data. For example, the ^{1}H NMR spectrum of compound **9a** revealed a triplet and a quartet signal at δ = 1.36 and 4.45 ppm due to the methyl and methylene protons of the ethoxycarbonyl group, respectively. Also the ^{13}C NMR spectra showed corresponding signals at δ = 13.75 and 63.02 ppm, in addition to two signals at 164.88 and 183.16 ppm corresponding to the two carbonyl carbons.

In the second part of this study, compound **3**, when treated with phenacyl bromide or bromoacetone in refluxing ethanol and in the presence of a catalytic amount of triethylamine, gave the corresponding 3-(2-methyl-1*H*-indol-3-yl)thiophene derivatives **11a**, **b**, respectively, which are analogs of tenidap, as depicted in Scheme 3. The IR spectra of compounds **11a**, **b** showed characteristic bands at 3181, 2182 and 1706 cm^{-1} due to NH, CN and C=O groups, respectively, and the ^{1}H NMR spectra revealed a singlet at $\delta \approx$ 7.34 ppm characteristic of the NHPh group. Also, the mass spectra gave the correct molecular ion peaks. Treatment of the thioacetanilide **3** with ethyl bromoacetate, ethyl 2-chloroacetoacetate or 2-(ω-bromoacetyl) coumarine under the same reaction conditions yielded the corresponding thiazolidin-4-one derivative **4** and thiazole derivatives **12** and **13**, respectively, in high yield (Scheme 3). The structures of compounds **4**, **12** and **13** were established on the basis of elemental analyses and spectral data (see Experimental Section).

The reaction of thioacetanilide derivative **3** with 1,2-dibromoethane in ethanol and in the presence of triethylamine gave the corresponding cyclic ketene *S*,*N*-acetal **14**. A similar reaction has been reported in the literature [17]. The structure of **14** was proven based on its analytical and spectral data. The ^{1}H NMR spectrum of **14** displayed characteristic signals at δ = 3.2 (t, 2H, CH_2-S) and 4.1 ppm (t, 2H, N-CH_2) beside the expected signals for its other protons.

Thioacetanilide **3** underwent oxidative cyclization on treatment with bromine in acetic acid to give the benzothiazole derivative **15** (Scheme 3). Similar chemistry has been reported in the literature [18]. The structure of compound **15** was established on the basis of elemental analysis and spectral data (see Experimental Section).

Experimental Section

General

Melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were recorded in KBr using a Pye Unicam SP-1000 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian EM-300 MHz spectrometer (^{1}H NMR 300 MHz) using $CDCl_3$ and [D_6]DMSO as the solvent with TMS as internal standard. ^{13}C NMR spectra were measured on a Varian EM-300 MHz spectrometer (75 MHz). Mass spectra were recorded on an AEI MS 30 mass spectrometer operating at 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt.

*Synthesis of 3-(2-methyl-1H-indol-3-yl)-2-(mercapto(phenylamino)methylene)-3-oxo-propionitrile (**3**)*

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (50 mL), 3-cyanoacetyl-2-methylindole (**1**) (1.98 g, 10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.40 g, 10 mmol) was added, and stirring was continued for further 6 h. The mixture was then poured over crushed ice containing hydrochloric acid. The solid product was filtered off, washed with water, dried and finally recrystallized from ethanol. Yellow crystals; m. p. 135 °C; 73 % yield. – IR (KBr): ν = 1656 (C=O), 2186 (CN), 3254, 3346 (2NH) cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 2.62 (s, 3H, indole-CH_3), 7.20 – 8.02 (m, 10H, Ar H), 11.88 (s, 1H, NH), 14.25 (s, 1H, SH). – ^{13}C NMR ($CDCl_3$): δ = 14.6, 86.8, 109.2, 110.9, 118.4, 120.3, 121.3, 122.7, 125.9, 126.1, 127.7, 129.0, 135.1, 136.8, 140.9, 179.8, 188.7. – Anal. for $C_{19}H_{15}N_3OS$: calcd. C 68.45, H 4.53, N 12.60, S 9.62; found C 68.32, H 4.43, N 12.54, S 9.60.

*Synthesis of 3-(2-methyl-1H-indol-3-yl)-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-3-oxo-propionitrile (**4**)*

Method A: To a cold suspension of finely divided KOH (0.28 g, 5 mmol) in dry dimethylformamide (25 mL) was added the 3-cyanoacetyl-2-methylindole (**1**) (1.0 g, 5 mmol) followed by phenyl isothiocyanate. The mixture was stirred at r. t. for 12 h, and cooled to 0 °C. To the resulting mixture was added a chloroacetyl chloride (0.56 g, 5 mmol) solution, and the mixture was left to stand at r. t. for 24 h before it was poured into ice-cold water. The resulting precipitate was filtered off, and recrystallized from DMF-ethanol.

Method B: To a solution of the thioacetanilide **3** (0.67 g, 2 mmol) in ethanol (20 mL), ethyl bromoacetate (0.334 g, 2 mmol) was added. Triethylamine (0.2 mL) was added dropwise, and the reaction mixture was refluxed for 1 h, then allowed to cool. The solid product was filtered off, washed with ethanol and recrystallized from DMF-ethanol. Yellow crystals; m. p. 290 °C; 83 % yield. – IR (KBr): ν = 1650 (C=O), 1733 (C=O), 2203 (CN), 3194 (NH) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 2.51 (s, 3H, indole-CH_3), 4.05 (s, 2H, thiazolidinone-CH_2), 7.06 – 7.56 (m, 9H, Ar H), 11.74 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO): δ = 13.66, 30.66, 86.71, 110.92, 112.72, 113.36, 114.34, 119.83, 120.43, 121.52, 126.30, 129.15, 130.11, 134.66, 135.21, 141.69, 170.13, 173.26, 185.04. – MS: *m/z* (%) = 373 (6) [M]$^+$. – Anal. for $C_{21}H_{15}N_3O_2S$: calcd. C 67.54, H 4.05, N 11.25, S 8.59; found C 67.34, H 3.95, N 11.22, S 8.55.

*General procedure for the preparation of 2-(3,5-diaryl-1,3,4-thiadiazol-2-ylidene)-3-(2-methyl-1H-indol-3-yl)-3-oxo-propionitriles **6** and **9***

To a solution of the thioacetanilide **3** (0.67 g, 2 mmol) in absolute ethanol (20 mL), one of the appropriate hydrazonoyl halides **5a**, **b** or **7a** – **e** (2 mmol) was added. To the resulting mixture triethylamine (0.3 mL) was added, and the reaction mixture was refluxed for 1 h and then cooled. The solid product was filtered off, washed with ethanol and crystallized from ethanol-DMF to afford the corresponding thiadiazole derivatives **6a**, **b** and **9a** – **e**.

*2-(3,5-Diphenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(2-methyl-1H-indol-3-yl)-3-oxo-propionitrile (**6a**)*

Colorless crystals; m. p. 273 °C; 79 % yield. – IR (KBr): ν = 1666 (C=O), 2197 (CN), 3280 (NH) cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 2.54 (s, 3H, indole-CH_3), 7.07 – 7.96 (m, 14H, Ar H), 11.48 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO): δ = 13.49, 76.71, 105.23, 109.08, 110.61, 112.18, 115.95, 119.67, 121.02, 126.51, 126.62, 127.22, 128.04, 129.30, 130.26, 131.45, 138.67, 139.25, 149.69, 156.90, 163.40, 182.93. – MS: *m/z* (%) = 434 (28) [M]$^+$. – Anal. for $C_{26}H_{18}N_4OS$: calcd. C 71.87, H 4.18, N 12.89, S 7.38; found C 71.69, H 4.12, N 12.79, S 7.35.

*3-(2-Methyl-1H-indol-3-yl)-2-(3-(4-nitrophenyl)-5-thiophen-2-yl-1,3,4-thiadiazol-2(3H)-ylidene)-3-oxo-propionitrile (**6b**)*

Orange crystals; m. p. 232 °C; 81 % yield. – IR (KBr): ν = 1659 (C=O), 2193 (CN), 3285 (NH) cm^{-1}. – ^{1}H NMR ([D_6]DMSO) δ = 2.50 (s, 3H, indole-CH_3), 7.06 – 7.33 (m, 4H, Ar-H), 7.58 (t, 1H, thiophene-4-H), 7.93 – 7.98

(m, 2H, thiophene 3H, 5H), 8.13 (d, 2H, *p*-nitrophenyl), 8.50 (d, 2H, *p*-nitrophenyl), 11.63 (s, 1H, NH). – Anal. for $C_{24}H_{15}N_5O_3S_2$: calcd. C 59.37, H 3.11, N 14.42, S 13.21; found C 59.22, H 3.06, N 14.38, S 13.13.

*Ethyl 5-(1-cyano-2-(2-methyl-1H-indol-3-yl)-2-oxoethylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**9a**)*

Yellow crystals; m. p. 280 °C; 79 % yield. – IR (KBr): ν = 1666 (C=O), 1718 (C=O), 2210 (CN), 3289 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 1.36 (t, 3H, *J*= 7.2 Hz, CH_2CH_3), 2.50 (s, 3H, indole-CH_3), 4.45 (q, 2H, *J* = 7.2 Hz, CH_2CH_3) 7.06 – 7.76 (m, 9H, Ar H), 11.58 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 13.57, 13.75, 63.02, 77.95, 110.77, 111.86, 115.27, 119.68, 119.94, 121.24, 126.34, 127.37, 129.21, 130.81, 134.71, 138.29, 139.82, 149.08, 157.89, 164.88, 183.16. – Anal. for $C_{23}H_{18}N_4O_3S$: calcd. C 64.17, H 4.21, N 13.01, S 7.45; found C 64.11, H 4.12, N 12.85, S 7.36.

*Methyl 5-(1-cyano-2-(2-methyl-1H-indol-3-yl)-2-oxoethylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**9b**)*

Yellow crystals; m. p. 275 °C; 75 % yield. – IR (KBr): ν = 1672 (C=O), 1725 (C=O), 2208 (CN), 3312 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 2.52 (s, 3H, indole-CH_3), 3.90 (s, 3H, CH_3), 7.05 – 7.77 (m, 9H, Ar H), 11.55 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 13.65, 53.52, 77.95, 110.67, 111.81, 115.14, 119.85, 121.15, 126.31, 127.21, 129.11, 130.68, 134.65, 138.22, 139.73, 148.79, 149.01, 157.79, 164.77, 183.11. – Anal. for $C_{22}H_{16}N_4O_3S$: calcd. C 63.45, H 3.87, N 13.45, S 7.70; found C 63.39, H 3.83, N 13.37, S 7.66.

*2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(2-methyl-1H-indol-3-yl)-3-oxo-propionitrile (**9c**)*

Yellow crystals; m. p. 303 °C; 70 % yield. – IR (KBr): ν = 1652 (C=O), 1693 (C=O), 2198 (CN), 3322 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 2.47 (s, 3H, CH_3CO), 2.52 (s, 3H, indole-CH_3), 7.05 – 7.79 (m, 9H, Ar H), 11.55 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 13.66, 25.97, 78.30, 110.86, 112.19, 115.43, 119.82, 120.05, 121.34, 126.52, 127.46, 129.55, 130.87, 134.83, 138.43, 139.94, 155.73, 165.36, 183.68, 190.47. – Anal. for $C_{22}H_{16}N_4O_2S$: calcd. C 65.99, H 4.03, N 13.99, S 8.01; found C 65.88, H 4.00, N 13.92, S 7.91.

*3-(2-Methyl-1H-indol-3-yl)-2-(3-phenyl-5-thiophene-2-carbonyl)-1,3,4-thiadiazol-2(3H)-ylidene)-3-oxo-propionitrile (**9d**)*

Orange crystals; m. p. 310 °C; 73 % yield. – IR (KBr): ν = 1652 (C=O), 1684 (C=O), 2197 (CN), 3258 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 2.51 (s, 3H, indole-CH_3), 7.06 – 8.39 (m, 12H, Ar H), 11.63 (s, 1H, NH). – Anal. for $C_{25}H_{16}N_4O_2S_2$: calcd. C 64.09, H 3.44, N 11.96, S 13.69; found C 64.01, H 3.37, N 11.91, S 13.61.

*2-(5-Benzoyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-3-(2-methyl-1H-indol-3-yl)-3-oxo-propionitrile (**9e**)*

Orange crystals; m. p. 215 °C; 77 % yield. – IR (KBr): ν = 1643 (C=O), 1694 (C=O), 2199 (CN), 3269 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 2.51 (s, 3H, indole-CH_3), 7.06 – 8.39 (m, 14H, Ar H), 11.63 (s, 1H, NH). – Anal. for $C_{27}H_{18}N_4O_2S$: calcd. C 70.11, H 3.92, N 12.11, S 6.93; found C 70.06, H 3.85, N 12.04, S 6.84.

*General procedure for the preparation of **11a, b**, **12**, and **13***

To a solution of the thioacetanilide **3** (0.67 g, 2 mmol) in ethanol (20 mL), the appropriate α-halogenated compound (2 mmol) and triethylamine (0.2 mL) were added. The reaction mixture was refluxed for 1 h, then allowed to cool. The product was filtered off, washed with ethanol and recrystallized from DMF-ethanol to afford the corresponding derivatives **11a**, **b**, **12** and **13**.

*5-(4-Bromobenzoyl)-4-(2-methyl-1H-indol-3-yl)-2-(phenylamino)thiophene-3-carbonitrile (**11a**)*

Pale-yellow crystals; m. p. 290 °C; 85 % yield. – IR (KBr): ν =1706 (C=O), 2184 (CN), 3181 (NH), 3311 (NH) cm^{-1}. – ^1H NMR: ([D$_6$]DMSO): δ = 2.49 (s, 3H, indole-CH_3), 6.98 – 7.52 (m, 13H, Ar H), 7.34 (s, 1H, NH), 11.27 (s, 1H, NH). – ^{13}C NMR ([D$_6$]DMSO): δ = 13.30, 78.22, 110.41, 110.64, 113.01, 116.73, 119.39, 119.55, 120.68, 122.52, 126.67, 128.84, 129.35, 130.80, 131.82, 133.21, 134.57, 136.55, 137.92, 141.03, 147.35, 165.98, 183.64. – MS: m/z (%) = 512 (20) $[M]^+$. – Anal. for $C_{27}H_{18}BrN_3OS$: calcd. C 63.29, H 3.54, N 8.20, S 6.26; found C 63.22, H 3.46, N 8.13, S 6.21.

*5-Acetyl-4-(2-methyl-1H-indole-3-yl)-2-(phenylamino)-thiophene-3-carbonitrile (**11b**)*

Pale-yellow crystals; m. p. 221 °C; 70 % yield. – IR (KBr): ν = 1709 (C=O), 2195 (CN), 3187 (NH), 3283 (NH) cm^{-1}. – ^1H NMR ([D$_6$]DMSO): δ = 1.98 (s, 3H, CH_3CO), 2.52 (s, 3H, indole-CH_3), 7.05 (s, 1H, NH), 7.18 – 7.94 (m, 9H, Ar H), 11.44 (s, 1H, NH). – MS: m/z (%) = 371 (14) $[M]^+$. – Anal. for $C_{22}H_{17}N_3OS$: calcd. C 71.14, H 4.61, N 11.31, S 8.63; found C 71.08, H 4.55, N 11.23, S 8.56.

*Ethyl 2-(1-cyano-2-(2-methyl-1H-indol-3-yl)-2-oxoethylidene)-4-methyl-3-phenyl-2,3-dihydrothiazole-5-carboxylate (**12**)*

Pale-yellow crystals; m. p. 308 °C; 77 % yield. – IR (KBr): ν = 1610 (C=O), 1719 (C=O), 2190 (CN), 3368 (NH)

cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 1.34 (t, 3H, J= 7.2 Hz, ester-CH_3), 2.24 (s, 3H, thiazole-CH_3), 2.43 (s, 3H, indole-CH_3), 4.35 (q, 2H, J = 7.2 Hz, ester-CH_2) 6.99 – 7.65 (m, 9H, Ar H), 11.45 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO): δ = 13.53, 13.67, 14.12, 61.25, 80.02, 110.67, 112.68, 116.03, 119.67, 120.93, 121.02, 126.54, 128.88, 129.73, 131.0, 134.66, 136.22, 138.85, 147.53, 153.98, 161.21. 165.10, 184.05. – Anal. for $C_{25}H_{21}N_3O_3S$: calcd. C 67.70, H 4.77, N 9.47, S 7.23; found C 67.64, H 4.71, N 9.37, S 7.18.

*3-(2-Methyl-1H-indol-3-yl)-2-(4-(2-oxo-chromen-3(2H)-yl)-3-phenyl)-thiazole-2(3H)-ylidene)-3-oxo-propionitrile (**13**)*

Yellow Crystals; m. p. 313 °C; 77 % yield. – IR (KBr): ν = 1650 (C=O), 1686 (C=O), 2191 (CN), 3313 (NH) cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 2.60 (s, 3H, indole-CH_3), 7.09 – 8.0 (m, 14H, Ar H), 8.34 (s, 1H, thiazole-CH), 11.38 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO). – δ = 13.69, 84.99, 109.88, 110.90, 112.45, 113.87, 115.60, 116.0, 118.0, 119.94, 120.11, 120.7, 121.5, 124.99, 125.99, 129.39, 133.01, 134.77, 138.14, 140.68, 144.69, 152.45, 156.71, 181.87, 182.56. – MS: m/z (%) = 501 (11) $[M]^+$. – Anal. for $C_{30}H_{19}N_3O_3S$: calcd. C 71.84, H 3.82, N 8.38, S 6.39; found C 71.77, H 3.76, N 8.29, S 6.33.

*Synthesis of 3-(2-methyl-1H-indol-3-yl)-2-(-3-phenyl-thiazolidin-2-ylidene)-3-oxo-propionitrile (**14**)*

To a suspension of **3** (0.67 g, 2 mmol) in absolute ethanol (10 mL), dibromoethane (0.38 g, 2 mmol) and triethylamine (0.2 mL) were added. The reaction mixture was heated under reflux for 2 h. The product formed was filtered and recrystallized from DMF to give pale-yellow crystals; m. p. 231 °C; 82 % yield. – IR (KBr): ν = 1650 (C=O), 2195 (CN), 3185 (NH) cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 2.51 (s, 3H, indole-CH_3), 3.22 (t, 2H, S-CH_2), 4.11 (t, 2H, CH_2-N), 6.97 – 7.93 (m, 9H, Ar H), 11.03 (s, 1H, NH). – MS: m/z (%) = 359 (11) $[M]^+$. – Anal. for $C_{21}H_{17}N_3OS$: calcd. C 70.17, H 4.77, N 11.69, S 8.92; found C 70.11, H 4.69, N 11.62, S 8.88.

*Synthesis of 2-(benzothiazol-2(3H)-ylidene)-3-(2-methyl-1H-indol-3-yl)-3-oxo-propionitrile (**15**)*

A solution of compound **3** (0.67 g, 2 mmol) in glacial acetic acid (10 mL) was cooled to 0 °C. A solution of bromine (0.32 g, 4 mmol) in glacial acetic acid (5 mL) was added dropwise during 10 min, followed by stirring for 6 h. The product was obtained after adding ice-cold water. It was filtered, and recrystallized from DMF to give yellow crystals; m. p. 333 °C; 62 % yield. – IR (KBr): ν = 1661 (C=O), 2193 (CN), 3076 (NH), 3284 (NH) cm^{-1}. – ^1H NMR ([D_6]DMSO): δ = 2.49 (s, 3H, indole-CH_3), 7.37 – 8.04 (m, 8H, Ar H), 10.11 (s, 1H, NH), 11.32 (s, 1H, NH). – ^{13}C NMR ([D_6]DMSO): δ = 13.49, 79.10, 113.69, 114.28, 115.14, 119.02, 122.34, 124.28, 124.55, 126.54, 126.90, 127.47, 129.01, 134.68, 135.16, 138.69, 167.48, 179.87, 182.66. – Anal. for $C_{19}H_{13}N_3OS$: calcd. C 68.86, H 3.95, N 12.68, S 9.68; found C 68.79, H 3.90, N 12.56, S 9.57.

[1] W. J. Houlihan, W. A. Remers, R. K. Brown, *Indoles*, Wiley: New York, NY, **1992**; R. J. Sundberg, *The Chemistry of Indoles*: Part I, Academic Press: New York, **1996**.

[2] a) A. Casapullo, G. Bifulco, I. Bruno, R. Riccio, *J. Nat. Prod*. **2000**, *63*, 447 – 451; b) B. Bao, Q. Sun, X. Yao, J. Hong, C. O. Lee, C. J. Sim, K. S. Im, J. H. Jung, *J. Nat. Prod*. **2005**, *68*, 711 – 715; c) T. Kouko, K. Matsumura, T. Kawasaki, *Tetrahedron* **2005**, *61*, 2309 – 2318; d) K. Kaniwa, M. A. Arai, X. Li, M. Ishibashi, *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4254 – 4257.

[3] a) L. H. Franco, E. B. K. Joffe, L. Puricelli, M. Tatian, A. M. Seldes, J. A. Palermo, *J. Nat. Prod*. **1998**, *61*, 1130 – 1132; b) A. A. R. Mohamed, El-S. Mahmound, *Bioorg. Med. Chem.* **2007**, *15,* 1206 – 1217.

[4] a) B. Jiang, C. G. Yang, W. N. Xiong, J. Wang, *Bioorg. Med. Chem*. **2001**, *9*, 1149 – 1154; b) M. Gompel, M. Leost, E. B. K. Joffe, L. Puricelli, L. H. Franco, J. Palermo, L. Meijer, *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1703 – 1707.

[5] a) I. Kawasaki, M. Yamashita, S. Ohta, *J. Chem. Soc., Chem. Commun*. **1994**, 2085 – 2086; b) I. Kawasaki, M. Yamashita, S. Ohta, *Chem. Pharm. Bull*. **1996**, *44*, 1831 – 1839.

[6] I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita, S. Ohta, *Heterocycles* **1998**, *48*, 1887 – 1901.

[7] H. H. Sun, J. Sakemi, *J. Org. Chem.* **1991**, *56*, 4307 – 4308.

[8] H. C. Vervoort, S. E. Richards-Gross, W. Fenical, A. Y. Lee, J. Clardy, *J. Org. Chem*. **1997**, *62*, 1486 – 1490.

[9] S. Takahashi, T. Matsunaga, C. Hasegawa, H. Saito, D. Fujita, F. Kiuchi, Y. Tsuda, *Chem. Pharm. Bull.* **1998**, *46*, 1527 – 1529.

[10] a) I. N'Diaye, G. Guella, G. Chiasera, Y. Mancini, F. Pietra, *Tetrahedron Lett*. **1994**, *35*, 4827 – 4830; b) G. Guella, Y. Mancini, I. N'Diaye, F. Pietra, *Helv. Chim. Acta* **1999**, *77*, 1994 – 2006.

[11] T. Bergmann, D. Schories, B. Steffan, *Tetrahedron* **1997**, *53*, 2055 – 2060.

[12] S. Kohmoto, Y. Kashman, O. J. McConnell, K. L. Rinehart, Jr., A. Wright, F. Koehn, *J. Org. Chem*. **1988**, *53*, 3116 – 3118.

[13] J. Slatt, I. Romero, J. Bergman, *Synthesis* **2004**, 2760 – 2765.

[14] a) N. M. Elwan, H. M. E. Hassaneen, H. M. Hassaneen, *Heteroatom Chem*. **2002**, *13*, 585 – 591; b) M. A. A. Radwan, E. A. Ragab, N. M. Sabry, S. M. El-Shenawy, *Bioorg. Med. Chem*. **2007**, *15*, 3832 – 3841.
[15] S. K. Mallick, A. R. Martin, *J. Med. Chem*. **1971**, *14*, 528 – 532.
[16] S. R. Singh, *J. Ind. Chem. Soc*. **1975**, *52*, 734 – 735.
[17] L. Bukowski, *Pharmazie* **2001**, *56*, 23 – 27.
[18] S. I. El-Desoky, H. A. Etman, S. B. Bondock, A. A. Fadda, M. A. Metwally, *Sulfur Lett*. **2002**, *25*, 199 – 205.