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Reactivity of 3-Cyanoacetylindole Derivatives: Synthesis of 3-Hydrazonopyrazolyl and 3-Thiadiazolyl Indole Derivatives

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Abstract

The coupling reaction of 3-cyanoacetyl-2-methylindole 1a with the aromatic diazonium salts gave the corresponding arylhydrazones **2a-e**. Compounds **2** were used for synthesis of 4-aminopyrazole-5-carbonitrile **4a-e** and 5-amino-4-arylazo-3-pyrazoles **5a-e** derivatives. Also, treatment of 3-cyanoacetyl-2-phenylindole **1b** with phenyl isothiocyanate gave the corresponding thioacetanilide **7**. The later compound **7** was utilized as the key intermediate for the synthesis of some new thiadiazole derivatives **9a-r**. The structures of all new compounds were elucidated on the basis of elemental analysis and spectral data.

Keywords: 3-Methyl Indole, 3-Phenyl Indole, Phenyl Isothiocyanate, Cyanoacetic Acid

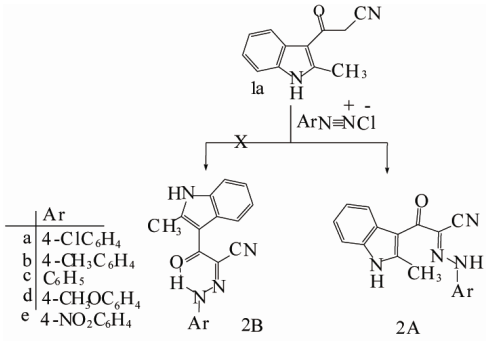
1. Introduction

The indole moiety is found in various pharmacologically and biologically active compounds [1,2]. Many indole alkaloids are recognized as one of the rapidly growing groups of marine invertebrate metabolites for their broad spectrum of biological properties [3-6]. For example, five novel indole alkaloids [7,8], 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 [9,10]. 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 [11,12], nortopsentins [13]), dihydroimidazole (disc odermindole [14]), oxazole (martefragin [15], amazole [16]), oxadiazine (alboinon [17]), maleimide (didemidines [18]), and piperazine (dragmacidone [19]). Therefore, 3-substituted indoles still represent a significant synthetic challenge.

2. Results and Discussion

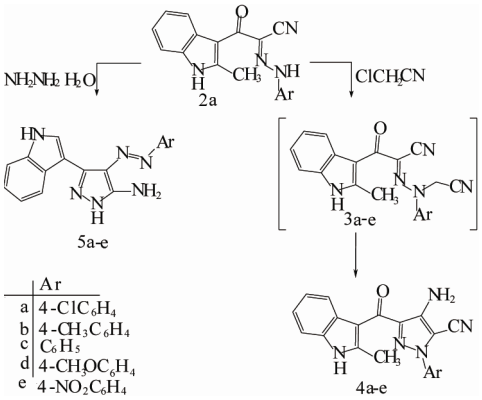
As a part of our program aimed at developing a synthesis for pyrazole [20] and thiadiazole derivatives [21-23], we report here an efficient synthesis for aminopyrazoles, which are used as precursors for biologically active fused pyrazoles. Thus, reacting 2-methylindole with cyanoacetic acid in acetic anhydride, utilizing a literature procedure [24], led to formation of 3-cyanoacetyl-2-methylindole **1a**. The latter compound **1** reacted with aromatic diazonium salts to yield the corresponding arylhydrazones **2a-e** in excellent yields (**Scheme 1**). The *E*-structure for hydrazones **2A** was preferred over possible hydrogen-bonded *Z*-structure **2B** based on analog of the recently-reported structure of 3-substituted-2-aryl-hydrazono-3-oxoalkanenitriles, whose E-structure has confirmed by X-ray crystal structure determination [25] and supported by theoretical calculation [26].

Compound **2** reacted readily with chloroacetonitrile in presence of triethylamine to give products of molecular



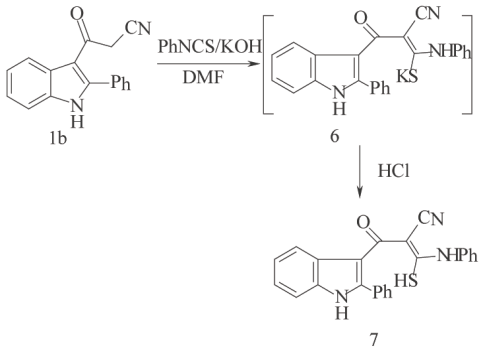
Scheme 1. MCR of *α*-cyanoketenes S, S-acetals, amine and guanidine carbonate.

formula corresponding to structure **4** or its isomeric structure **3** in excellent yield. Structure **4** was readily established based on ^{1}H NMR data which revealed the absence of a signal for the methylene group and appearance of two deuterium oxide exchangeable protons at δ 6.40 ppm for amino group. it is believed that **4a-e** has resulted from in stiu cyclization of the initially formed **3a-e** (Scheme 2). Also, treatment of **2a-e** with hydrazine hydrate in refluxing ethanol gave 5-amino-4-arylazo-3- -(indole-3`-yl)pyrazoles **5a-e** in excellent yield (**Scheme 2**). The structures of the products 5a-e were established on the basis of elemental analysis and spectral data (see exeperimental).



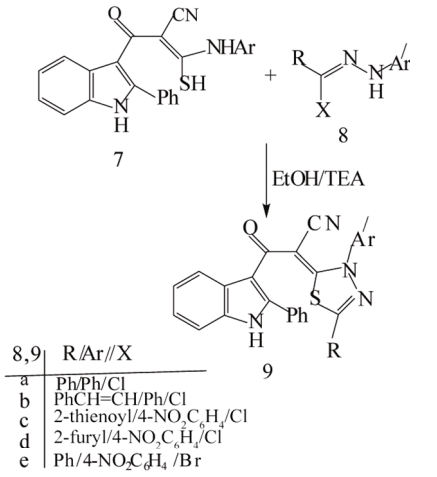
Scheme 2. Synthesis of amino-pyrazole derivatives 4 and 5.

It is known that a great variety of reactants bearing the N=C=S fragment undergo cyclization on reaction of hydrazonoyl halide compounds to afford thiadiazole derivatives [21-23], which have been shown to exhibit antiprotozoal [27] and fungicidal properties [28]. Thus, the base-catalyzed reaction of the 3-cyanoacetyl-2-phenylindole **1b** with phenyl isothiocyanate in dry DMF at room temperature yielded the non-isolable potassium salt which by treatment with dilute hydrochloric acid gave the corresponding thioacetanilide **7** (**Scheme 3**). The structure of **7** was confirmed based on analytical and spectral data (see experimental section). For example **7** had characteristic absorption peaks in its IR spectrum at 3343, 2202, 1675 cm^{-1} due to NH, CN, CO groups respectively. In addition, the mass spectrum revealed a peak at m/z = 395 corresponding to the molecular ion.



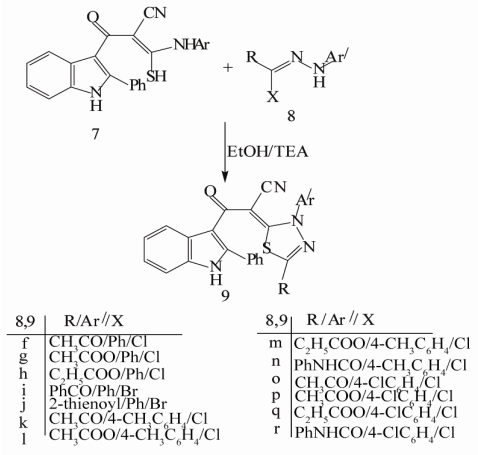
Scheme 3. Synthesis of thioacetanilide 7.

Treatment of thioacetanilide **7** with hydrazonoyl halides **8a-e** in refluxing ethanol and in presence of triethylamine, afforded, in each case, only the 1,3,4-thiadiazoles **9a-e** (**Scheme 4**). Elemental analyses and spectral data of the reaction products were in complete agreement with the proposed structures. For example **9b** had characteristic absorption peaks in its IR spectrum at 3327, 2195 cm^{-1} due to NH, CN groups respectively. In addition, the mass spectrum revealed a peak at m/z = 522 corresponding to its molecular ion (see experimental section).



Scheme 4. 1,3,4-thiadiazoles 9.

To study the effect of carbonyl group of hydrazonoyl halide in the cyclization reaction, the thioacetanilide **7** was treated with hydrazonoyl halides **8f-r** in refluxing ethanol and in presence of triethylamine, afforded, in each case, only one isomer 1,3,4-thiadiazole derivatives **9f-r** (**Scheme 5**), which indicate that, there is no effect of the presence of carbonyl group in the cyclization reaction. Elemental analyses and spectral data of the reaction products were in complete agreement with the proposed structures. For example, **9k** had characteristic absorption peaks in its IR spectrum at 3304, 2195, 1693 cm^{-1} due to NH, CN, CO groups respectively. In addition, the mass spectrum revealed a peak at m/z = 476 corresponding to the molecular ion. Its ^{1}H NMR showed two singlet signals at δ = 2.35 and 2.61 ppm due to two methyl groups, in addition to one singlet signal due to proton at δ 11.9 ppm represents NH group. Also, the ^{13}C NMR spectrum displayed characteristic signals at δ = 190.40, 184.27, 114.7, 25.91, 20.79 ppm due to 2CO, CN, 2CH_3 carbons respectively, in addition to all the other carbons at the expected chemical shifts (**Scheme 5**).



8,9	R/Ar // X
f	$CH_3CO/Ph/Cl$
g	$CH_3COO/Ph/Cl$
h	$C_2H_5COO/Ph/Cl$
i	$PhCO/Ph/Br$
j	2-thienoyl/Ph/Br
k	$CH_3CO/4\text{-}CH_3C_6H_4/Cl$
l	$CH_3COO/4\text{-}CH_3C_6H_4/Cl$

8,9	R / Ar // X
m	$C_2H_5COO/4\text{-}CH_3C_6H_4/Cl$
n	$PhNHCO/4\text{-}CH_3C_6H_4/Cl$
o	$CH_3CO/4\text{-}ClC_6H_4/Cl$
p	$CH_3COO/4\text{-}ClC_6H_4/Cl$
q	$C_2H_5COO/4\text{-}ClC_6H_4/Cl$
r	$PhNHCO/4\text{-}ClC_6H_4/Cl$

Scheme 5. Synthesis of 1,3,4-thiadiazoles 9.

3. Experimental Section

3.1. General

All melting points were determined on an electrothermal GallenKamp melting point apparatus and are uncorrected. The IR spectra were recorded as KBr Pellets on a Jasco FTIR-460 plus Fourier transform infrared spectrophotometer.^{1}H and ^{13}C NMR spectra were recorded at (300 MHz) and (75 MHz) respectively on Varian EM-300 MHz spectrometer. Chemical shifts (δ) are given from TMS (ppm) as internal standard for ^{1}H NMR and ^{13}C NMR. Mass spectra were recorded on AEI MS 30 mass spectrometer operating at 70 eV. The elemental analyses were performed at the Microanalytical Center of Cairo University.

3.2. General Method for Preparation of (E)-N'-aryl-2-(2-methyl-1H-indol-3-yl) -2-oxo-acetohydrazonoyl cyanide 2a-e

A cold solution of aryldiazonium salt (10 mmol) was prepared by adding a solution of sodium nitrite (10 mmol in water) to a cold solution of the aromatic amine hydrochloride (10 mmol) with stirring. The resulting solution of the diazonium salt was added to a cold solution of compound **1a** (10 mmol) in pyridine (100 mL). The reaction mixture was stirred at room temperature for 30 min. the solid product so formed was collected, washed with water, and crystallized from suitable solvent to afford **2a-e.**

(*E*)-*N'*-(4-*Chlorophenyl*)-2-(2-*methyl*-*1H*-*indol*-3-*yl*)-2-*oxoacetohydrazonoyl cyanide* 2*a*:

Orange crystals; m.p: 244˚C (acetonitrile); yield (85%); IR (KBr): υ = 3299 (NH), 2204 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 7.01-7.72 (m, 8H, ArH), 11.91 (s, 1H, NH), 12.02 (s, 1H, NH). MS: m/z (%) = 336 [M$^+$], 307, 210, 158, 130. Anal. for $C_{18}H_{13}ClN_4O$: calcd. C, 64.19; H, 3.89; Cl, 10.53; N, 16.64. found C, 63.88; H, 3.56; Cl, 10.20; N, 16.31.

(*E*)-2-(2-*Methyl*-1*H*-*indol*-3-*yl*)-2-*oxo*-*N'*-*p*-*tolylaceto*-*hydrazonoyl cyanide* 2*b*:

Yellow crystals; m.p: 207˚C (methanol); yield (87%); IR(KBr): υ = 3348 (NH), 2216 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 2.50 (s, 3H, indole-CH_3), 7.04 - 7.75 (m, 8H, Ar H), 11.85 (s, 1H, NH), 11.98 (s, 1H, NH).^{13}C NMR (DMSO-d_6): δ = 23.92, 29.81, 120.05, 120.12, 123.0, 194.94, 125.01, 130.01, 130.42, 131.01, 136.97, 139.15, 143.0, 144.32, 149.22, 153.32, 192.56. MS: m/z (%) = 316 [M$^+$], 287, 210, 158, 130, 91. Anal. for $C_{19}H_{16}N_4O$: Calcd. C, 72.13; H, 5.1; N, 17.71. found C, 71.81; H, 4.7; N, 17.39.

(*E*)-2-(2-*Methyl*-1*H*-*indol*-3-*yl*)-2-*oxo*-*N'*-*phenyl*-*Acet*-*ohydrazonoyl cyanide* 2*c*:

Yellow crystals ; m.p: 235˚C (ethanol); yield (83%); IR (KBr): υ = 3366 (NH), 2200 (CN) cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 2.50 (s, 3H, indole-CH_3), 7.03 - 7.71 (m, 9H, ArH), 11.94 (s, 1H, NH),11.98 (s, 1H, NH).MS: m/z (%) = 302 [M$^+$], 273, 210, 158, 130, 77. Anal. for $C_{18}H_{14}N_4O$: calcd. C, 71.51; H, 4.67; N, 18.53. found C, 71.12; H, 4.41; N, 18.28.

(*E*)-*N'*-(4-*Methoxyphenyl*)-2-(2-*methyl*-*1H*-*indol*-3-*yl*)-2-*oxoacetohydrazonoyl cyanide* 2*d*:

Yellow crystals; m.p: 194˚C (ethanol); yield (77%); IR (KBr): υ = 3265 (NH), 2201 (CN) cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ = 2.50 (s, 3H, indole-CH_3), 3.69 (s, 3H, OCH_3), 6.82 - 7.69 (m, 8H, Ar H), 11.89 (s, 1H, NH), 11.98 (s, 1H, NH). MS: m/z (%) = 332 [M$^+$], 158, 130. Anal. for $C_{19}H_{16}N_4O_2$: calcd. C, 68.66; H, 4.85; N, 16.86. found C, 68.29; H, 4.46; N, 16.38.

(*E*)-2-(2-*Methyl*-1*H*-*indol*-3-*yl*)-*N'*-(4-*nitrophenyl*)-2-*oxoacetohydrazonoyl cyanide* 2*e*:

Orange crystals; m.p: 274˚C (acetonitrile); yield (88%); IR (KBr): υ = 3266 (NH), 2218 (CN) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ = 2.52 (s, 3H, indole-CH_3), 7.02 - 8.16 (m, 8H, ArH), 12.06 (s, 1H, NH), 12.39 (s, 1H, NH).MS: m/z (%) = 347 [M$^+$], 318, 158, 130. Anal. for $C_{18}H_{13}N_5O_3$: calcd. C, 62.24; H, 3.77; N, 20.16. found C, 61.90; H, 3.46; N, 19.89.

3.3. General Method for Preparation of 4-amino-1-aryl-3-(2-methyl-1H-indole-3-carbonyl)-1H-pyrazole-5-carbonitrile Derivatives 4a-e

To a solution of **2** (5 mmol) in triethylamine (10 mmol), chloroacetonitrile (16 mmol) was added. The reaction mixture was refluxed for 2 h, and then poured onto cold dilute HCl. The solid product formed was filtered off and crystallized from suitable solvent to afford **4a-e**.

4-*Amino*-1-(4-*chlorophenyl*)-3-(2-*methyl*-1*H*-*indole*-3-

carbonyl)-1*H-pyrazole*-5-*carbonitrile* 4*a*:

Yellow crystals; m.p: 252˚C (acetic acid); yield (88%); IR (KBr): υ = 3471 & 3353 (NH_2), 3313 (NH), 2212 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 6.40 (s, 2H, NH_2), 7.04 - 7.81 (m, 8H, ArH), 12.02 (s, 1H, NH). MS: m/z (%) = 375 [M^+], 360, 158, 130. Anal. for $C_{20}H_{14}ClN_5O$: calcd. C, 63.92; H, 3.75; Cl, 9.43; N, 18.64. found C, 63.51; H, 3.50; Cl, 9.03; N,18.22.

4-*Amino*-3-(2-*methyl*-1*H-indole*-3-*carbonyl*)-1-*p-tolyl*-1*H-pyrazole*-5-*carbonitrile* 4*b*:

Brown crystals; m.p: 188˚C (methanol); yield (91%); IR (KBr): υ = 3473 & 3356 (NH_2), 3312 (NH), 2212 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.21 (s, 3H, CH_3), 2.50 (s, 3H, indole-CH_3), 6.41 (s, 2H, NH_2), 7.05 - 7.79 (m, 8H, ArH), 11.98 (s, 1H, NH). MS: m/z (%) = 355 [M^+], 340, 225, 158, 130, 91. Anal. for $C_{21}H_{17}N_5O$: calcd. C, 70.97; H, 4.82; N, 19.71. found C, 70.55; H, 4.61; N, 19.33.

4-*Amino*-3-(2-*methyl*-1*H-indole*-3-*carbonyl*)-1-*phenyl*-1*H-pyrazole*-5-*carbonitrile* 4*c*:

Brown crystals; m.p: 204˚C (ethanol); yield (87%); IR (KBr): υ = 3470 & 3358 (NH_2), 3311 (NH), 2213 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 6.42 (s, 2H, NH_2), 7.03 - 7.81 (m, 9H, ArH) , 12.0 (s, 1H, NH). MS: m/z (%) = 341 [M^+], 326, 158, 130, 77. Anal. for $C_{20}H_{15}N_5O$: calcd. C, 70.37; H, 4.43; N, 20.52. found C, 69.98; H, 4.11; N, 20.13.

4-*Amino*-1-(4-*methoxyphenyl*)-3-(2-*methyl*-1*H-indole*-3-*carbonyl*)-1*H-pyrazole*-5-*carbonitrile* 4*d*:

Brown crystals; m.p: 214˚C (acetonitrile); yield (89%); IR (KBr): υ = 3471 & 3358 (NH_2), 3313 (NH), 2213 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 3.82 (s, 3H, OCH_3), 6.40 (s, 2H, NH_2), 7.10 - 7.83 (m, 8H, Ar H), 11.95 (s, 1H, NH). MS: m/z (%) = 371 [M^+], 356, 158, 130, 77. Anal. for $C_{21}H_{17}N_5O_2$: calcd. C, 67.91; H, 4.61; N, 18.86. found C, 67.50; H, 4.33; N, 18.43.

4-*Amino*-3-(2-*methyl*-1*H-indole*-3-*carbonyl*)-1-(4-*nitrophenyl*)-1*H-pyrazole*-5-*carbonitrile* 4*e*:

Brown crystals; m.p: 289˚C (acetonitrile); yield (88%); IR (KBr): υ = 3472 & 3355 (NH_2), 3311 (NH), 2217 (CN) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 6.54 (s, 2H, NH_2), 7.08 - 8.46 (m, 8H, ArH), 12.06 (s, 1H, NH). MS: m/z (%) = 386 [M^+], 371, 158, 130, 77. Anal. for $C_{20}H_{14}N_6O_3$: calcd. C, 62.17; H, 3.65; N, 21.75. found C, 61.80; H, 3.41; N, 21.33.

3.4. General Method for Preparation of (Z)-4-(2-Aryl-hydrazono)-5-(2-methyl-1H-indol-3-yl)-4H-pyrazol-3-amine derivatives 5a-e

To an appropriate compounds **2** (10 mmol) hydrazine hydrate (10 mmol) was added in ethanol (20 mL). The reaction mixture was refluxed for 6 h, the solvent was evaporated and the crude product was collected then crystallized from benzene to afford the corresponding compounds **5a-e**.

(*Z*)-4-(2-(4-*Chlorophenyl*)*hydrazono*)-5-(2-*methyl*-1*H-indol*-3-*yl*)-4*H-pyrazol*-3-*amine* 5*a*:

Orange crystals; m.p: 232˚C; yield (87%); IR (KBr): υ = 3473 & 3454 (NH_2), 3356 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.49 (s, 3H, indole-CH_3), 6.19 (s, 2H, NH_2), 7.02 - 7.64 (m, 8H, ArH), 11.48 (s, 1H, NH), 12.30 (s, 1H, NH). MS: m/z (%) = 350 [M^+], 335, 224. Anal.for $C_{18}H_{15}ClN_6$: calcd. C, 61.63; H, 4.31; Cl, 10.11; N, 23.96. found C, 61.29; H, 4.10; Cl, 9.75; N, 23.48.

(*Z*)-5-(2-*Methyl*-1*H-indol*-3-*yl*)-4-(2-*p-tolylhydra-zono*)-4*H-pyrazol*-3-*amine* 5*b*:

Yellow crystals; m.p: 235˚C; yield (89%); IR (KBr): υ = 3468 & 3450 (NH_2), 3355 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 2.49 (s, 3H, indole-CH_3), 6.15 (s, 2H, NH_2), 7.01 - 7.53 (m, 8H, ArH), 11.45 (s, 1H, NH) ,12.28 (s, 1H, NH).MS: m/z (%) = 330 [M^+], 315, 224, 91. Anal. for $C_{19}H_{18}N_6$: Calcd. C, 69.07; H, 5.49; N, 25.44. found C, 68.72; H, 5.30; N, 25.01.

(*Z*)-5-(2-*Methyl*-1*H-indol*-3-*yl*)-4-(2-*phenylhydrazono*)-4*H-pyrazol*-3-*amine* 5*c*:

Yellow crystals; m.p: 202˚C; yield (85%); IR (KBr): υ = 3468 & 3450 (NH_2), 3353 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) : δ = 2.50 (s, 3H, indole-CH_3), 6.21 (s, 2H, NH_2), 7.0 - 7.62 (m, 9H, ArH), 11.43 (s, 1H, NH), 12.28 (s, 1H, NH). M: m/z (%) = 316 [M^+], 301, 224, 77. Anal. for $C_{18}H_{16}N_6$: calcd. C, 68.34; H, 5.10; N, 26.56. found C, 67.98; H, 4.82; N, 26.13.

(*Z*)-4-(2-(4-*Methoxyphenyl*)*hydraono*)-5-(2-*methyl*-1*H-indol*-3-*yl*)-4*H-pyrazol*-3-*amine* 5*d*:

Yellow crystals; m.p: 180˚C; yield (80%);IR (KBr): υ = 3389 & 3187 (NH_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.49 (s, 3H, indole-CH_3), 3.76 (s, 3H, OCH_3), 6.18 (s, 2H, NH_2), 6.93 - 7.60 (m, 8H, ArH), 11.41 (s, 1H, NH), 12.11 (s, 1H, NH). MS: m/z (%) = 346 [M^+], 331, 224, 123. Anal. for $C_{19}H_{18}N_6O$: calcd. C, 65.88; H, 5.24; N, 24.26. found: C, 65.45; H, 5.01; N, 23.86.

(*Z*)-5-(2-*Methyl*-1*H-indol*-3-*yl*)-4-(2-(4-*nitrophenyl*)*hydrazono*)-4*H-pyrazol*-3-*amine* 5*e*:

Red crystals; m.p: 285˚C; yield (81%); IR (KBr): υ = 3467 & 3399 (NH_2), 3349 (NH) cm^{-1}; ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, indole-CH_3), 6.50 (s, 2H, NH_2), 7.0 - 8.26 (m, 8H, ArH), 11.30 (s, 1H, NH), 12.18 (s, 1H, NH). MS: m /z (%) = 361 [M^+], 346, 224. Anal. for $C_{18}H_{15}N_7O_2$: calcd. C, 59.83; H, 4.18; N, 27.13. found C, 59.44; H, 4.01; N, 26.87.

3.5. General Method for Preparation of (Z)-3mercapto-2-(2-phenyl-1H-indole-3-carbonyl)-3-(phenylamino) Acrylonitrile 7.

To a stirred solution of potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide (50 mL), 3-cyan-oacetyl-2-phenylindole **1b** (2.6 g, 10 mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.4 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 acetonitrile to afford **7**.

(*Z*)-3-*Mercapto*-2-(2-*phenyl*-1*H*-*indole*-3-*carbonyl*)-3-(*phenylamino*)*acrylonitrile* 7:

Yellow crystals; m.p. 186˚C; yield (78%). IR (KBr): υ = 3343 (NH), 2202 (CN), 1676 (CO) cm^{-1}. MS: m/z (%) = 395 [M^+]. Anal. for $C_{24}H_{17}N_3OS$: calcd. C, 72.89; H, 4.33; N, 10.63; S, 8.11.found C, 72.45; H, 4.10; N, 10.47; S, 7.87.

3.6. General Procedure for the Preparation of 2-(3,5-Diaryl-1,3,4-thiadiazol-2-ylidene)-3-(2-phenyl-1H-indole-3-yl)-3-oxo-propionitriles 9a-r .

To a solution of the thioacetanilide **7** (0.79 g, 2 mmol) in absolute ethanol (20 mL), hydrazonoyl halides **8** (2 mmol) was added. To the resulting mixture triethylamine (0.3 mL) was added, and the reaction mixture was refluxed for 3 h and then cooled. The solid product was filtered off, washed with ethanol and crystallized from suitable solvent to afford the corresponding thiadiazole derivatives **9a-r**.

(*Z*)-*2*-(3,5-*diphenyl*-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)*propane-nitrile* 9*a*:

Yellow crystals; m.p. 305˚C (dioxane); yield (79%). IR (KBr): υ = 3277 (NH), 2199 (CN) cm^{-1}. MS: m/z (%) = 496 [M^+]. Anal. for $C_{31}H_{20}N_4OS$: calcd. C, 74.98; H, 4.06; N, 11.28; S, 6.46.found C, 74.49; H, 3.89; N, 10.92; S, 6.17.

(*Z*)-3-*Oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)-2-(3-*phenyl*-5-*styryl*-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)*prop-anenitrile* 9*b*:

Yellow crystals; m.p. 299˚C (acetonitrile); yield (73%). IR (KBr): υ = 3327 (NH), 2195 (CN) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 7.18 - 7.9 (m, 21H, ArH), 8.8 (s, 1H, NH). MS: m/z (%) = 522 [M^+]. Anal. for $C_{33}H_{22}N_4OS$: calcd. C, 75.84; H, 4.24; N, 10.72; S, 6.14.found C, 75.40; H, 4.01; N, 10.43; S, 5.86.

(*Z*)-2-(3-(4-*Nitrophenyl*)-5-(*thiophen*-2-*yl*)-1,3,4-*thiadia-zol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*) *propanenitrile* 9*c*:

Yellow crystals; m.p. 361˚C (dioxane); yield (80%). IR (KBr): υ = 3340 (NH), 2203 (CN) cm^{-1}. MS: m/z (%) = 547 [M^+]. Anal. for $C_{29}H_{17}N_5O_3S_2$: calcd. C, 63.61; H, 3.13; N, 12.79 S, 11.71.found C, 63.19; H, 3.01; N, 12.45; S, 11.35.

(*Z*)-2-(5-(*Furan*-2-*yl*)-3-(4-*nitrophenyl*)-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*) *propanenitrile* 9*d*:

Yellow crystals; m.p. 328˚C (acetonitrile); yield (78%). IR (KBr): υ = 3345 (NH), 2203 (CN) cm^{-1}. MS: m/z (%) = 531 [M^+].Anal. for $C_{29}H_{17}N_5O_4S$: calcd. C, 65.53; H, 3.22; N, 13.18; S, 6.03. found: C, 65.11; H, 3.0; N, 12.84; S, 5.73.

(*Z*)-2-(3-(4-*Nitrophenyl*)-5-*phenyl*-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)*propane-nitrile* 9*e*:

Yellow crystals; m.p.310˚C (dioxane); yield (81%). IR (KBr): υ = 3336 (NH), 2200 (CN) cm^{-1}. MS: m/z (%) = 541 [M^+]. Anal. for $C_{31}H_{19}N_5O_3S$: calcd. C, 68.75; H, 3.54; N, 12.93; S, 5.92. found: C, 68.24; H, 3.31; N, 12.61; S, 5.70.

(*Z*)-2-(5-*Acetyl*-3-*phenyl*-1,3,4-*thiadizol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)*propanenitrile* 9*f*:

Yellow crystals; m.p. 311˚C (acetonitrile); yield (76%). IR (KBr): υ = 3300 (NH), 2194 (CN), 1693 (CO) cm^{-1}.^{1}H NMR ($CDCl_3$): δ = 2.67 (s, 3H, indole-CH_3), 7.19 - 8.21 (m, 14H, Ar H), 8.56 (s, 1H, NH). MS: m/z (%) = 462 [M^+]. Anal. for $C_{27}H_{18}N_4O_2S$: calcd. C, 70.11; H, 3.92; N, 12.11; S, 6.93. found C, 69.51; H, 3.73; N, 11.81; S, 6.70.

(*Z*)-*Methyl*-5-(1-*cyano*-2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*) *ethylidene*)-4-*phenyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylate* 9*g*:

Yellow crystals; m.p.247˚C (acetonitrile); yield (73%). IR (KBr): υ = 3322 (NH), 2200 (CN), 1752 (CO), 1725 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.05 (s, 3H, ester-CH_3), 7.19 - 7.90 (m, 14H, Ar H), 8.57 (s, 1H, NH). MS: m/z (%) = 478 [M^+]. Anal. for $C_{27}H_{18}N_4O_3S$: calcd. C, 67.77; H, 3.79; N, 11.71; S, 6.70.found C, 67.40; H, 3.58; N, 11.43; S, 6.49.

(*Z*)-*Ethyl*-5-(1-*cyano*-2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*) *ethylidene*)-4-*phenyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylate* 9*h*:

Yellow crystals; m.p.272˚C (acetonitrile); yield (74%). IR (KBr): υ = 3309 (NH), 2202 (CN), 1743 (CO), 1712 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 1.36 (t, 3H, ester-CH_3), 4.46 (q, 2H, ester-CH_2), 7.09 - 7.63 (m, 14H, Ar H), 11.94 (s, 1H, NH). MS: m/z (%) = 492 [M^+]. Anal. for $C_{28}H_{20}N_4O_3S$: calcd. C, 68.28; H, 4.09; N, 11.37; S, 6.51.found C, 67.91; H, 3.92; N, 11.02; S, 6.25.

(*Z*)-2-(5-*Benzoyl*-3-*phenyl*-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)-*propanenitrile* 9*i*:

Yellow crystals; m.p. 282˚C (dioxane); yield (78%).

IR (KBr): υ = 3316 (NH), 2202 (CN), 1650 (CO) cm^{-1}. MS: m/z (%) = 524 [M^+]. Anal. for $C_{32}H_{20}N_4O_2S$: calcd. C, 73.27; H, 3.84; N, 10.68; S, 6.11. found C, 72.92; H, 3.61; N, 10.29; S, 5.89.

(*Z*)-3-*Oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)-2-(3-*phenyl*-5-(*thiophene*-2-*carbonyl*)-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*) *propanenitrile* 9*j*:

Yellow crystals; m.p. 303˚C (acetonitrile); yield (72%). IR (KBr): υ = 3264 (NH), 2199 (CN), 1632 (CO) cm^{-1}. MS: m/z (%) = 530 [M^+]. Anal. for $C_{30}H_{18}N_4O_2S_2$: calcd. C, 67.91; H, 3.42; N, 10.56, S, 12.09. found C, 67.48; H, 3.21; N, 10.28; S, 11.81.

(*Z*)-2-(5-*Acetyl*-3-*p*-*tolyl*-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)*propanenitrile* 9*k*:

Yellow crystals; m.p. 327˚C (dioxane); yield (78%). IR (KBr): υ = 3304 (NH), 2195 (CN), 1693 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.35 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.12-7.63 (m, 13H, ArH), 11.9 (s, 1H, NH).^{13}C NMR (DMSO-d_6): δ = 20.79, 25.91, 66.26, 79.28, 111.45, 114.70, 119.68, 120.51, 122.32, 126.58, 127.17, 128.31, 128.51, 129.38, 131.80, 135.55, 139.90, 140.25, 155.68, 164.65, 184.27, 190.40. MS: m/z (%) = 476 [M^+]. Anal. for $C_{28}H_{20}N_4O_2S$: calcd. C, 70.57; H, 4.23; N, 11.76; S, 6.73.found C, 70.09; H, 4.02; N, 11.47; S, 6.49.

(*Z*)-*Methyl*5-(1-*cyano*-2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*) *ethylidene*-4-*p*-*tolyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylate* 9*l*:

Yellow crystals; m.p. 270˚C (dioxane); yield (82%). IR (KBr): υ = 3342 (NH), 2199 (CN), 1752 (CO), 1726 (CO) cm^{-1}. MS: m/z (%) = 492 [M^+]. Anal. for $C_{28}H_{20}N_4O_3S$: calcd. C, 68.28; H, 4.24; N, 11.37; S, 6.51.found C, 67.93; H, 4.01; N, 11.03; S, 6.28.

(*Z*)-*Ethyl*-5-(1-*cyano*-2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*) *ethylidene*-4-*p*-*tolyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylate* 9*m*:

Yellow crystals; m.p. 280˚C (acetonitrile); yield (73%). IR (KBr): υ = 3317 (NH), 2206 (CN), 1752 (CO), 1720 (CO) cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3H, ester-CH_3), 2.34 (s, 3H, CH_3), 4.45 (q, 2H, ester-CH_2), 7.09 - 7.62 (m, 13H, Ar H), 11.93 (s, 1H, NH). MS: m/z (%) = 506 [M^+]. Anal.for $C_{29}H_{22}N_4O_3S$: calcd. C, 68.76; H, 4.38; N, 11.06; S, 6.33.found C, 68.33; H, 4.15; N, 10.31; S, 6.14.

(*Z*)-5-(1-*Cyano*-2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*)*ethyl idene*)-N-*phenyl*-4-*p*-*tolyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxamide* 9*n*:

Yellow crystals; m.p. 298˚C (dioxane); yield (81%). IR (KBr): υ =3276 (NH), 2207 (CN), 1667 (CO) cm^{-1}.^{1}H NMR (DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 7.24 - 7.82 (m, 18H, Ar H), 10.92 (s, 1H, NH), 11.87 (s, 1H, NH).^{13}C NMR (DMSO-d_6): δ = 20.79, 66.24, 78.92, 111.53, 114.91, 119.72, 120.41, 120.65, 120.93, 122.23, 124.73, 126.99, 127.19, 128.19, 128.49, 128.60, 129.23, 131.82, 135.53, 137.28, 139.63, 140.24, 153.82, 155.96, 164.63, 184.18. MS: m/z (%) = 553 [M^+]. Anal. for $C_{33}H_{23}N_5O_2S$: calcd. C, 71.59; H, 4.19; N, 12.65; S, 5.79.found C, 71.12; H, 3.98; N, 12.30; S, 5.61.

(*Z*)-2-(5-*Acetyl*-3-(4-*chlorophenyl*)-1,3,4-*thiadiazol*-2(3*H*)-*ylidene*)-3-*oxo*-3-(2-*phenyl*-1*H*-*indol*-3-*yl*)*propanenitrile* 9*o*:

Yellow crystals; m.p. 347˚C (dioxane); yield (81%). IR (KBr): υ = 3312 (NH), 2194 (CN), 1692 (CO) cm^{-1}. MS: m/z (%) = 496 [M^+]. Anal. for $C_{27}H_{17}ClN_4O_2S$: calcd. C, 65.25; H, 3.45; Cl, 7.13; N, 11.27; S, 6.45. found C, 64.76; H, 3.22; Cl, 6.85; N, 10.88; S, 6.21.

(*Z*)-*Methyl*-4-(4-*chlorophenyl*)-5-(1-*cyano*-2-(2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*)*ethylidene*)-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylat* 9*p*:

Yellow crystals; m.p.260˚C (dioxane); yield (80%). IR (KBr): υ =3350 (NH), 2197(CN), 1757(CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.98 (s, 3H, ester-CH_3), 7.11 - 7.68 (m, 13H, Ar H), 11.99 (s, 1H, NH).^{13}C NMR (DMSO-d_6): δ = 53.84, 66.32, 79.15, 111.14, 111.70, 114.91, 119.82, 120.72, 122.49, 127.25, 128.43, 128.49, 128.67, 128.87, 129.09, 131.85, 135.14, 135.63, 136.82, 140.37, 149.24, 158.33, 164.59, 183.98. MS: m/z (%) = 512 [M^+]. Anal.for $C_{27}H_{17}ClN_4O_3S$: calcd. C, 63.22; H, 3.34; Cl, 6.91; N, 10.92; S, 6.25.found: C, 62.81; H, 3.20; Cl, 6.65; N, 10.59; S, 6.01.

(*Z*)-*Ethyl*4-(4-*chlorophenyl*)-5-(1-*cyano*-2-(2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*)*ethylidene*)-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxylate* 9*q*:

Yellow crystals; m.p. 266˚C (acetonitrile); yield (79%). IR (KBr): υ = 3302 (NH), 2202 (CN), 1758 (CO), 1720 (CO) cm^{-1}. MS: m/z (%) = 526 [M^+]. Anal. for $C_{28}H_{19}ClN_4O_3S$: calcd. C, 63.81; H, 3.63; Cl, 6.73; N, 10.63; S, 6.08.found C, 63.39; H, 3.37; Cl, 6.45; N, 10.30; S, 5.81.

(*Z*)-4-(4-*Chlorophenyl*)-5-(1-*cyano*-2-(2-*oxo*-2-(2-*phenyl*-1*H*-*indol*-3-*yl*)*ethylidene*)-*N*-*phenyl*-4,5-*dihydro*-1,3,4-*thiadiazole*-2-*carboxamide* 9*r*:

Yellow crystals; m.p. 328˚C (dioxane); yield (83%). IR (KBr): υ = 3289 (NH), 2205 (CN), 1664 (CO) cm^{-1}. MS: m/z (%) = 573 [M^+]. Anal. for $C_{32}H_{20}ClN_5O_2S$: calcd. C, 66.95; H, 3.51; Cl, 6.18; N, 12.20; S, 5.59. found C, 66.47; H, 3.28; Cl, 5.92; N, 11.78; S, 5.24.

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