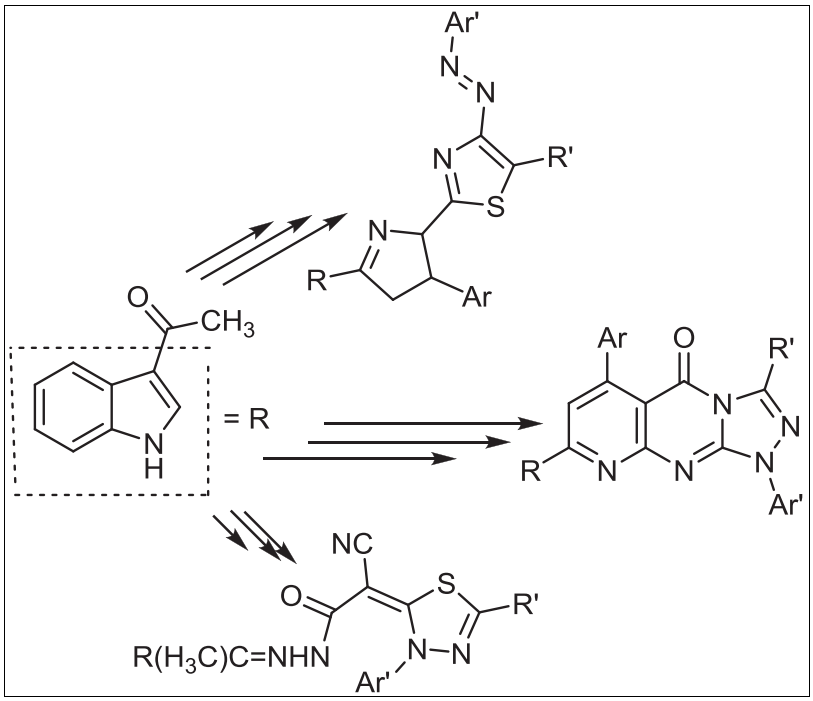
Synthesis of Certain New Thiazole and 1,3,4-Thiadiazole Derivatives via the Utility of 3-Acetylindole

Abdou O. Abdelhamid,[a]* Sobhi M. Gomha,[a] and Saher M. Kandeel[b]

[a]Department of Chemistry, Faculty of Science, Cairo University, Giza 12613, Egypt
[b]Chemistry of Natural Compounds, Department National Research Center, Dokki, Cairo, Egypt
*E-mail: Abdelhamid45@gmail.com

Received July 9, 2015
DOI 10.1002/jhet.2740
Published online 00 Month 2016 in Wiley Online Library (wileyonlinelibrary.com).



2-(2-(1-(1*H*-Indol-3-yl)ethylidene)-hydrazinyl)-4-substituted 5-(aryldiazenyl)thiazoles and 5-((1-(1*H*-indol-3-yl)ethylidene)hydrazono)-2-substituted-4-phenyl-4,5-dihydro-1,3,4-thiadiazoles were synthesized via reaction of hydrazonoyl halides and 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbothioamide and alkyl 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbodithioate in ethanolic triethylamine. Structures of the newly synthesis were elucidated on the basis of elemental analysis, spectral data, and alternative synthetic route whenever possible.

INTRODUCTION

Indole derivatives are present in both animals and plants. The most important compound of this group is tryptophan, an essential amino acid in the human diet that is a 3-substituted indole. Important alkaloids, like serotonin and tryptamin, are also indols substituted in position 3. Indole derivatives can be found in some vegetables (like cabbage), and its anticarcinogenic and antioxidant effects are subjects of research [1]. Also, it has been reported to possess a wide variety of biological properties such as antiviral agents that inhibit herpes simplex virus replication [2–4] and are fungicidal [5], anti-inflammatory [6], anticonvulsant [7], and antibacterial [8]. Other compounds derived from 3-acetylindole are used in the treatment of gastrointestinal disorder [9], are useful as antiproliferative [10,11] and potential antiviral agents [12], are used in the treatment of cardiovascular and central nervous system disorders [13], and are also used as herpes simplex type 1 integrase inhibitors [14]. Encouraged by these observations and in continuation of our previous work in the synthesis of biologically active heterocycles [15–18], we synthesized newer heterocyclic indole derivatives with the hope to obtain better antiviral agents.

RESULTS AND DISCUSSION

Treatment of 1-(1*H*-indol-3-yl)ethan-1-one (**1**) with each of thiosemicarbazide (**2a**) and alkyl hydrazinecarbodithioate **2b–d** in refluxing ethanol afforded 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbothioamide (**3a**)

and methyl 2-(1-(1*H*-indol-3-yl)ethylidene)-hydrazine-1-carbodithioate **3b–d**, respectively (Scheme 1). Structures of **3a–d** were elucidated by elemental analysis, spectral data, and chemical transformation. Thus, **3a** was reacted with the appropriate hydrazonoyl halide **4a–h**, which afforded one isolable product formulated as 2-(2-(1-(1*H*-indol-3-yl)ethylidene)-hydrazinyl)-4-substituted 5-(aryldiazenyl)thiazole **6a–h**, respectively. Structures **6a–h** were elucidated by elemental analysis, spectral data, and alternative synthetic route. Thus, treatment of benzenediazonium chloride with 2-(2-(1-(1*H*-indol-3-yl)ethylidene)hydrazinyl)-4-phenylthiazole (**8**), which was prepared via reaction of **3a** with ω-bromoacetophenone, in ethanolic sodium acetate gave a product identical in all aspect (mp, mixed mp, and spectra) with compound **6f**.

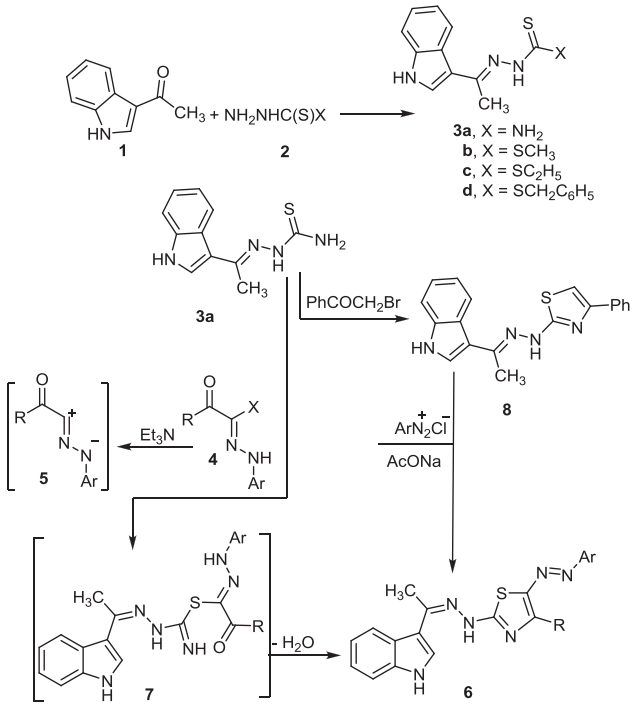
To account for the formation **6**, it is suggested as shown in Scheme 1 that the reaction starts with 1,3-addition of the thiol tautomer of **3a** to the nitrilimine **5**, generated *in situ* via dehydrohalogenation of hydrazonoyl halide **4**, to give the thiohydrazonate **7**, which undergoes *in situ* dehydration to give the thiazole **6** as end product.

Also, treatment of methyl 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazinecarbodithioate (**3b**) with ethyl 2-chloro-2-(2-phenylhydrazono)acetate (**4d**) gave one isolable product, according to thin-layer chromatography (TLC), formulated as ethyl 5-((1-(1*H*-indol-3-yl)ethylidene) hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (**11d**) (Scheme 2).

Structure **11d** was confirmed by elemental analysis, spectral data, and alternative synthesis route. Thus, 2,3 dihydro-1,3,4-thiadiazole [19] **12** was reacted with 3-acetylindole (**1**) in 2-propanol to afford a product identical in all aspects (mp, mixed mp, and spectra) with **11d**. On the other hand, again, each compound **4d** reacted with each of ethyl 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazinecarbodithioate (**3c**) or benzyl 2-(1-(1*H*-indol-3-yl)ethylidene) hydrazinecarbodithioate (**3d**) in ethanolic triethylamine gave a product identical in all aspects (mp, mixed mp, and spectra) with **11d**.

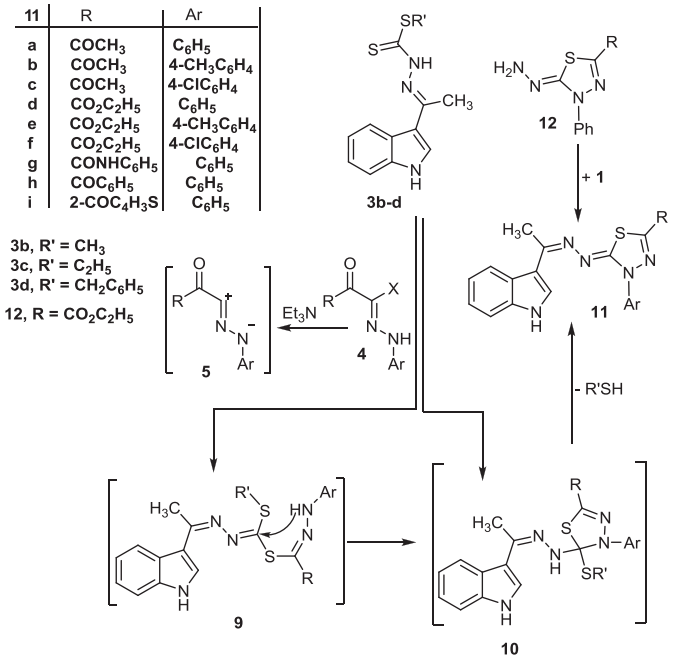
In light of these results, the mechanism outlined in Scheme 2 seems to be the most plausible pathway for the formation of **11** from the reaction of the **3b–d** with **4** [or nitrilimide (**5**)]. The reaction involves the initial formation of thiohydrazonate **9**, which undergoes intramolecular cyclization as soon as it is formed to yield the intermediate **10** or via 1,3-dipolar cycloaddition of **5** to CS double bond

Scheme 1. Synthesis of thiazole derivatives **6a–h.**



4, 6	R	Ar	4, 6	R	Ar
a	CH_3	C_6H_5	e	CH_3	4-ClC_6H_4
b	CH_3	4-$CH_3C_6H_4$	f	C_6H_5	C_6H_5
c	CH_3	4-$CH_3OC_6H_4$	g	2-C_4H_3S	C_6H_5
d	CH_3	4-BrC_6H_4	h	2-$C_{10}H_7$	C_6H_5

Scheme 2. Synthesis of thiadiazoles **11a–i.**

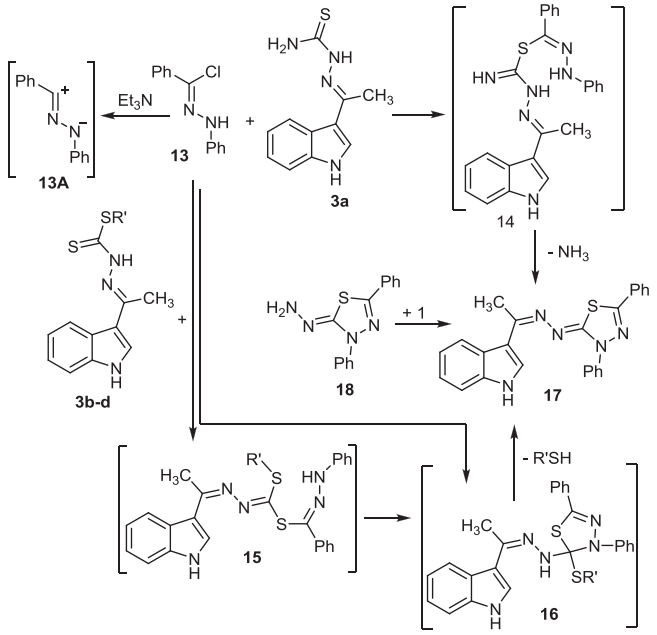


of **3a–d**, which afforded intermediate **10**, which gave a final product **11** via elimination of alkyl mercaptan.

Analogously, treatment of the appropriate **3b–d** with the appropriate **4a**, **b**, **c**, and **e–h** afforded 2,3-dihydro-1,3,4-thiadiazoles **11a**, **b**, **c**, **and e–h**, respectively, in a good yield (Scheme 2).

In contrast, 1-(chloro(phenyl)methylene)-2-phenylhydrazine (**13**) was reacted with **3a** in ethanolic triethylamine under reflux gave one isolable product, according to TLC, 2-(1-(1*H*-indol-3-yl)ethylidene)-1-(3,5-diphenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-hydrazine (**17**) (Scheme 3). Structure **17** was elucidated by elemental analysis, spectral data, and alternative synthetic routes. Thus, compound **13** was reacted with each of **3b–d**, which afforded a product identical in all aspects (mp, mixed mp, and spectra) with **17**. Also, compound **17** was obtained via reaction of 2-hydrazono-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole [20] (**18**) with 3-acetylindole (**1**) in boiling propan-2-ol.

Scheme 3. Synthesis of 2-((1-(1*H*-indol-3-yl)ethylidene)hydrazono)-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (**17**).

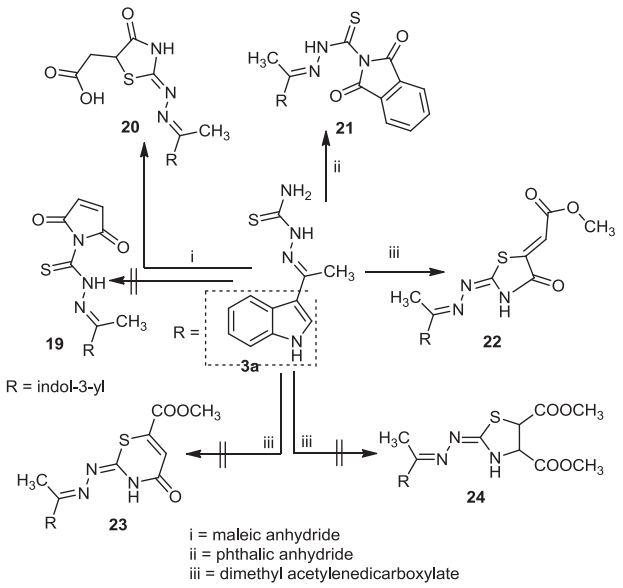


The mechanism outlined in Scheme 3 seems to be the most plausible pathway for the formation of **17** from the reaction of the **3a** with **13**. The reaction involves the initial formation of thiohydrazonate **14**, which undergoes cyclization as soon as it is formed to yield the final product **17** via loss of one molecule of ammonia. Also, the mechanism of synthesis **17** via reaction **13** with the appropriate **3b–d** may be taken through two ways: (1) the reaction involves the initial formation of thiohydrazonate **15**, which undergoes intramolecular cyclization as soon as it is formed to yield the intermediate **16**, and (2) via 1,3-dipolar cycloaddition of **13A** to CS double bond of **3a–d** afforded intermediate **16**, which undergoes *in situ* to a final product **17** via elimination of alkyl mercaptan.

Treatment of **3a** with maleic anhydride in ethanol under reflux gave one isolable product according to TLC. The product was formulated as follows: *N′*-(1-(1*H*-indol-3-yl) ethylidene)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-carbothiohydrazide (**19**) or 2-(2-((1-(1*H*-indol-3-yl)ethylidene) hydrazono)-4-oxothiazolidin-5-yl)acetic acid (**20**) (Scheme 3). Compound **19** was ruled out on the basis of spectral data [^{1}H NMR spectrum showed $\delta = 2.35$ (s, 3H, CH_3), 2.85–2.91 (dd, 2H, CH_2), 4.32–4.36 (q, 1H, CH thiazolidone H-5), 7.1–8.3 (m, 5H, ArH's), 8.45 (s, br, 2H, NH and OH), 11.51 (s, br, 1H, NH)].

Analogously, **3** reacted with phthalic anhydride in boiling ethanol afforded *N′*-(1-(benzofuran-3-yl)ethylidene)-1,3-dioxoisoindoline-2-carbothiohydrazide (**21**) in a good yield. Structure of **21** was elucidated on basis of elemental analysis and spectral data. ^{1}H NMR spectrum showed signals at $\delta = 2.46$ (s, 3H, CH_3), 7.16–8.29 (m, 9H, ArH's, and indole H-2), 11.89 (s, br, 1H, NH).

Scheme 4. Synthesis of thiazolide derivates **20** and **22** and 1,3-dioxoisoindoline-2-carbothiohydrazide (**21**).



Finally, **3** was reacted with dimethyl acetylenedicarboxylate in ethanol under reflux gave one isolable product, according TLC, formulated as follows: methyl 2-(-2-((-1-(benzofuran-3-yl)ethylidene) hydrazono)-4-oxothiazolidin-5-ylidene)acetate (**22**) or methyl 2-((-1-(1*H*-indol-3-yl)ethylidene)hydrazono)-4-oxo-3,4-dihydro-2*H*-1,3-thiazine-6-carboxylate (**23**) or dimethyl 2-((1-(1*H*-indol-3-yl)ethylidene)hydrazono) thiazolidine-4,5-dicarboxylate (**24**) (Scheme 4). Structures **23** and **24** were excluded on the basis of ^{1}H NMR spectrum, which showed signals at $\delta = 2.43$ (s, 3H, CH_3), 3.79 (s, 3H, $COOCH_3$), 6.69 (s, 1H, C=CH), 6.91–8.29 (m, 5H, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH), 12.62 (s, 1H, D_2O-exchangeable NH).

CONCLUSION

In conclusion, reaction of 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbothioamide and alkyl 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbodithioate with hydrazonoyl halides yielded the condensation products 5-arylazothiazoles **6** and 1,3,4-thiadiazoles **11** and **17**, respectively. Also, 2-(1-(1*H*-indol-3-yl)ethylidene)hydrazine-1-carbothioamide was reacted each with maleic anhydride, phthalic anhydride, and dimethyl acetylenes, which afforded **20–22**, respectively. The structures of the newly synthesized compounds were confirmed by spectral data, elemental analyses, and alternate syntheses whenever possible.

EXPERIMENTAL

Melting points were measured on an Electrothermal IA 9000 (Bibby Sci. Lim. Stone, Staffordshire, UK) series digital melting point apparatus. IR spectra were recorded in potassium bromide discs on PyeUnicam SP 3300 and Shimadzu FTIR 8101 PC infrared spectrophotometers. NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer operating at 300 MHz (^{1}H NMR) and run in deuterated dimethylsulfoxide (DMSO-d_6). Chemical shifts were related to those of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were measured by using a German made Elementarvario LIII CHNS analyzer. Compound **3a** [21] and hydrazonoyl halides [22–27] **4**, **13**, and **2b–d** [28] were prepared as reported in the literature.

Synthesis of alkyl 2-(1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethylidene) hydrazine carbodithioate (3b–d). To a solution of 3-acetyl-1*H*-indole **1** (1.59 g, l0 mmol) in 2-propanol (20 mL), alkyl hydrazinecarbodithioate **2b–d** (10 mmol) was added. The mixture was stirred at room

temperature for 2 h. The solid product was filtered off and recrystallized from ethanol to afford **3b–d**.

Methyl 2-(1-(1H-indol-3-yl)ethylidene)hydrazinecarbodithioate (3b). Yellow solid; 69%; mp 203–205°C; IR (KBr): $\nu = 3444$, 3157 (2NH), 2943 (CH), 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.43$ (3H, s, CH_3), 2.51 (3H, s, CH_3), 7.13–8.28 (6H, m, Ar–H and NH), 11.88 (1H, s, NH); mass spectrometry (MS) *m/z* (%): 263 (M^+, 30), 220 (50), 176 (63), 100 (72), 86 (100), 56 (93). *Anal.* Calcd for $C_{12}H_{13}N_3S_2$ (263.38): C, 54.72; H, 4.97; N, 15.95. Found: C, 54.64; H, 4.86; N, 15.79%.

Ethyl 2-(1-(1H-indol-3-yl)ethylidene)hydrazinecarbodithioate (3c). Yellow solid; 64%; mp 181–183°C; IR (KBr): $\nu = 3417$, 3126 (2NH), 2912 (CH), 1591 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 1.41$ (3H, t, $\underline{CH_3}CH_2S$), 2.51 (3H, s, CH_3), 3.40 (2H, q, $S\underline{CH_2}CH_3$), 7.11–8.22 (6H, m, Ar–H and NH), 11.82 (1H, s, NH); MS *m/z* (%): 277 (M^+, 73), 262 (50), 248 (100), 206 (51), 192 (74), 176 (50), 107 (21). *Anal.* Calcd for $C_{13}H_{15}N_3S_2$ (277.41): C, 56.28; H, 5.45; N, 15.15. Found: C, 56.21; H, 5.36; N, 15.04%.

Benzyl 2-(1-(1H-indol-3-yl)ethylidene)hydrazinecarbodithioate (3d). Yellow solid; 65%; mp 170–172°C; IR (KBr): $\nu = 3419$, 3234 (2NH), 2968 (CH), 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): $\delta = 2.42$ (3H, s, CH_3), 4.58 (2H, s, CH_2), 7.02–8.48 (10H, m, Ar–H), 11.62 (1H, s, NH), 12.22 (1H, s, NH); MS *m/z* (%): 339 (M^+, 100), 265 (30), 164 (62), 106 (40), 79 (39). *Anal.* Calcd for $C_{18}H_{17}N_3S_2$ (339.48): C, 63.68; H, 5.05; N, 12.38. Found: C, 63.47; H, 5.01; N, 12.24%.

Synthesis of 4-methyl-2-(2-(1-(5-methyl-1-phenyl-1H-1,2,3-triazol-4-yl)ethylidene) hydrazinyl)-5-(aryldiazenyl)thiazole (6a–h). A mixture of thiosemicarbazone **3a** (0.232 g, 1 mmol) and the appropriate hydrazonoyl halides **4** (1 mmol) in dioxane (20 mL) containing triethylamine (0.07 mL) was refluxed for 6 h and allowed to cool, and the solid that formed was filtered off, washed with EtOH, dried, and recrystallized from dimethylformamide (DMF) to give the corresponding 1,3,4-thiadiazolines **6a–h**. The products **6a–h** together with their physical constants are listed subsequently.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-4-methyl-5-(phenyldiazenyl)thiazole (6a). Red solid (70% yield); mp 242–244°C (lit mp (*21*)). ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 14.7$, 16.7, 112.4, 116.6, 120.2, 121.7, 122.5, 122.6, 125.1, 126.0, 129.3, 129.9, 130.4, 135.7, 135.6, 152.8, 154.0, 166.0.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-4-methyl-5-(p-tolyldiazenyl)thiazole (6b). Red solid (73% yield); mp 258–260°C; IR (KBr) $\nu = 3437$, 3234 (2NH), 1577 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.26$ (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.12–8.53 (m, 9H, Ar–H), 10.42 (s, 1H, D_2O-exchangeable NH), 11.77 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 14.7$, 16.7, 112.4, 116.6, 120.5, 121.2, 122.6, 122.5, 125.0, 126.1, 129.1, 129.8, 130.4, 135.6, 135.9, 152.4, 154.0, 166.0; MS, *m/z* (%): 388 (M^+, 23), 373 (29), 277 (41), 105 (100), 77 (50). *Anal.* Calcd for $C_{21}H_{20}N_6S$ (388.49): C, 64.92; H, 5.19; N, 21.63. Found: C, 64.74; H, 5.16; N, 21.48%.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-5-((4-methoxyphenyl)diazenyl)-4-methylthiazole (6c). Red solid (67% yield); mp 212–214°C; IR (KBr) $\nu = 3431$, 3248 (2NH), 1578 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.56$ (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 6.92–8.55 (m, 9H, Ar–H), 10.37 (s, 1H, D_2O-exchangeable NH), 11.73 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 14.37$, 16.37, 55.34 (OCH_3), 112.45, 114.40, 116.67, 120.50, 121.52, 122.44, 124.62, 125.25, 126.09, 129.73, 135.45, 135.87, 148.03, 154.01, 154.01, 161.32, 166.06; MS, *m/z* (%): 404 (M^+, 32), 359 (44), 225 (59), 105 (100), 77 (71). *Anal.* Calcd for $C_{21}H_{20}N_6OS$ (404.49): C, 62.36; H, 4.98; N, 20.78. Found: C, 62.32; H, 4.90; N, 20.59%.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-5-((4-bromophenyl)diazenyl)-4-methylthiazole (6d). Orange solid (67% yield); mp 264–265°C (lit mp (*21*)).

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-5-((4-chlorophenyl)diazenyl)-4-methylthiazole (6e). Orange solid (72% yield); mp 256–258°C (lit mp (*21*)).

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-4-phenyl-5-(phenyldiazenyl)thiazole (6f). Orange solid (68% yield); mp 243–245°C; IR (KBr) $\nu = 3412$, 3278 (2NH), 1602 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.59$ (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.00–8.29 (m, 15H, Ar–H), 10.60 (s, 1H, D_2O-exchangeable NH), 11.79 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 17.3$, 107.4, 110.8, 117.2, 119.7, 121.0, 121.3, 126.7, 129.0, 130.3, 131.1, 133.3, 135.8, 136.6, 155.0, 155.3, 171.6; MS, *m/z* (%): 436 (M^+, 53), 380 (75), 202 (100), 178 (57). *Anal.* Calcd for $C_{25}H_{20}N_6S$ (436.53): C, 68.78; H, 4.62; N, 19.25. Found: C, 68.65; H, 4.64; N, 19.13%.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-5-(phenyldiazenyl)-4-(thiophen-2-yl)thiazole (6g). Orange solid (67% yield); mp 243–245°C; IR (KBr) $\nu = 3409$, 3257 (2NH), 1635 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.63$ (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.01–8.57 (m, 13H, Ar–H), 10.62 (s, 1H, D_2O-exchangeable NH), 11.81 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 442 (M^+, 100), 354 (61), 264 (45), 228 (79), 131(48). *Anal.* Calcd for $C_{23}H_{18}N_6S_2$ (442.56): C, 62.42; H, 4.10; N, 18.99. Found: C, 62.36; H, 4.06; N, 18.69%.

2-(2-(1-(1H-Indol-3-yl)ethylidene)hydrazinyl)-4-(naphthalen-2-yl-5-(phenyl diazenyl)thiazole (6h). Orange solid (60% yield); mp 267–269°C; IR (KBr) $\nu = 3415$, 3298 (2NH), 1614 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6)

δ = 2.61 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 7.25–8.36 (m, 13H, Ar–H), 10.67 (s, 1H, D_2O-exchangeable NH), 11.85 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 486 (M^+, 100), 422 (86), 376 (78), 335 (54), 188 (29), 147 (18). *Anal.* Calcd for $C_{29}H_{22}N_6S$ (486.59): C, 71.58; H, 4.56; N, 17.27. Found: C, 71.48; H, 4.43; N, 17.20%.

Synthesis of 2-(2-(1-(1H-indol-3-yl)ethylidene)hydrazinyl)-4-phenylthiazole (8). To a solution of 2-(1-(1H-indol-3-yl) ethylidene)hydrazine-1-carbothioamide (**3a**) (2.3 g, l0 mmol) in ethanol (20 mL), phenacyl bromide (0.197 g, 1 mmol) was added. The mixture was refluxed for 2 h and then cooled to room temperature. The solid product was filtered off, washed with ethanol, and recrystallized from ethanol to afford the thiazole derivative **9** as white solid (75% yield); mp 178–180°C; IR (KBr) ν = 3425, 3161 (2NH), 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.66 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 6.96–8.42 (m, 11H, Ar–H and thiazole H-5), 10.81 (s, 1H, D_2O-exchangeable NH), 12.09 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 332 (M^+, 17), 179 (59), 138 (100), 108 (63), 65 (69). *Anal.* Calcd for $C_{19}H_{16}N_4S$ (332.42): C, 68.65; H, 4.85; N, 16.85. Found: C, 68.69; H, 4.72; N, 16.76%.

Alternate synthesis of 6f. To a solution of **8** (0.332 g, 1 mmol) in ethanol (20 mL) was added sodium acetate trihydrate (0.138 g, 1 mmol), and the mixture was cooled to 0–5°C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride [prepared by diazotizing aniline (1 mmol) dissolved in hydrochloric acid (6*M*, 1 mL) with a solution of sodium nitrite (0.07 g, 1 mmol) in water (2 mL)]. After complete addition of the diazonium salt, the reaction mixture was stirred for a further 30 min in an ice bath. The solid that separated was filtered off, washed with water, and finally recrystallized from DMF to give the corresponding product, **6f**, which was identical in all aspects (mp, mixed mp, and IR spectra) with those obtained from reaction of **3a** with **4f** but in 71% yield.

General procedure for synthesis of 2-((1-(1H-indol-3-yl) ethylidene)hydrazono)-3-phenyl-5-substituted-2,3-dihydro-1,3,4-thiadiazole derivatives (11a–i). To a mixture of alkyl carbodithioate **3b–d** (0.305 g, 1 mmol) and the appropriate hydrazonoyl halides **4** (1 mmol) in ethanol (20 mL), triethylamine (0.5 mL) was added, the mixture was stirred at room temperature for 2 h. The resulting solid was collected and recrystallized from DMF to give the corresponding 1,3,4-thiadiazolines **8a–i**. The products **8a–i** together with their physical constants are listed subsequently.

1-(5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethanone (11a). Yellow solid (79% yield); mp 234–336°C; IR (KBr): ν = 3259 (NH), 1697 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.37 (3H, s, CH_3), 3.89 (3H, s, CH_3), 6.84–8.29 (10H, m, Ar–H), 11.87 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 20.2, 24.9, 112.2, 113.6, 120.2, 121.4, 122.5, 123.0, 127.3, 129.8, 135.6, 138.9, 150.4, 153.7, 157.8, 191.0; MS, *m/z* (%): 375 (M^+, 52), 285 (87), 231 (633), 163 (70), 43 (100). *Anal.* Calcd for $C_{20}H_{17}N_5OS$ (375.45): C, 63.98; H, 4.56; N, 18.65. Found: C, 63.81; H, 4.48; N, 18.59%.

1-(5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethanone (11b). Yellow solid (72% yield); mp 234–336°C; IR (KBr): ν = 3311 (NH), 1699 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.22 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.87 (3H, s, CH_3), 7.05–8.29 (9H, m, Ar–H), 11.89 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 20.24, 21.6, 24.6, 112.45, 113.5, 120.2, 121.6, 122.5, 124.1, 125.7, 125.9, 129.6, 133.9, 135.6, 138.8, 150.4, 153.6, 157.8, 191.0; MS, *m/z* (%): 389 (M^+, 18), 281 (27), 179 (323), 119 (53), 93 (100). *Anal.* Calcd for $C_{21}H_{19}N_5OS$ (389.47): C, 64.76; H, 4.92; N, 17.98. Found: C, 64.71; H, 4.80; N, 17.75%.

1-(5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-(4-chlorophenyl)-4,5-dihydro-1,3,4-thiadiazol-2-yl)ethanone (11c). Yellow solid (77% yield); mp 267–169°C; IR (KBr): ν = 3228 (NH), 1703 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 2.36 (3H, s, CH_3), 3.89 (3H, s, CH_3), 7.13–8.29 (9H, m, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 409 (M^+, 37), 325 (31), 259 (46), 143 (69), 78 (100). *Anal.* Calcd for $C_{20}H_{16}ClN_5OS$ (409.89): C, 58.60; H, 3.93; N, 17.09. Found: C, 58.57; H, 3.74; N, 16.87%.

Ethyl 5-((1-(1H-indol-3-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (11d). Yellow solid (74% yield); mp 173–175°C; IR (KBr): ν = 3163 (NH), 1714 (C=O), 1604 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.32 (3H, t, J = 7.0, CH_2CH_3), 2.44 (3H, s, CH_3), 4.22 (2H, q, J = 7.0, CH_2CH_3), 6.82–8.28 (10H, m, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.3, 20.0, 62.5, 107.2, 112.1, 119.0, 121.2, 121.5, 127.2, 129.4, 131.2, 133.5, 135.6, 137.3, 149.6, 159.5, 159.4, 161.4; MS, *m/z* (%): 405 (M^+, 12), 284 (27), 147 (64), 122 (43), 105 (100), 77 (34). *Anal.* Calcd for $C_{21}H_{19}N_5O_2S$ (405.47): C, 62.21; H, 4.72; N, 17.27. Found: C, 62.05; H, 4.68; N, 17.13%.

Ethyl 5-((1-(1H-indol-3-yl)ethylidene)hydrazono)-4-(p-tolyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (11e). Yellow solid (72% yield); mp 180–182°C; IR (KBr): ν = 3159 (NH), 1703 (C=O), 1603 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ = 1.31 (3H, t, J = 7.0, CH_2CH_3), 2.20 (3H, s, CH_3), 2.44 (3H, s, CH_3), 4.18 (2H, q, J = 7.0, CH_2CH_3), 7.02–8.29 (9H, m, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 419 (M^+, 13), 360 (96), 222 (60), 151 (100), 130 (28), 83 (37). *Anal.* Calcd for $C_{22}H_{21}N_5O_2S$ (419.50):

C, 62.99; H, 5.05; N, 16.69. Found: C, 62.86; H, 5.02; N, 16.53%.

Ethyl 5-((1-(1H-indol-3-yl)ethylidene)hydrazono)-4-(4-chlorophenyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (11f). Yellow solid (77% yield); mp 212–214°C; IR (KBr): $\nu = 3157$ (NH), 1726 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 1.28$ (3H, t, $J = 7.0$, CH_2CH_3), 2.44 (3H, s, CH_3), 4.19 (2H, q, $J = 7.0$, CH_2CH_3), 7.13–8.28 (9H, m, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 14.3$, 20.0, 21.1, 62.8, 107.2, 114.1, 118.3, 119.0, 121.5, 128.5, 129.4, 132.2, 133.5, 135.6, 137.3, 149.6, 159.5, 159.4, 161.4; MS, *m/z* (%): 439 (M^+, 12), 346 (14), 198 (71), 105 (62), 118 (38), 77 (100). *Anal.* Calcd for $C_{21}H_{18}ClN_5O_2S$ (439.92): C, 57.33; H, 4.12; N, 15.92. Found: C, 57.23; H, 4.11; N, 15.75%.

5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-N,4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (11g). Yellow solid (83% yield); mp 267–279°C; IR (KBr): $\nu = 3288$, 3161 (NH), 1680 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.44$ (3H, s, CH_3), 7.15–8.28 (15H, m, Ar–H), 11.17 (s, 1H, D_2O-exchangeable NH), 11.89 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 452 (M^+, 4), 377 (48), 253 (17), 193 (16), 142 (38), 91(100), 84 (70). *Anal.* Calcd for $C_{25}H_{20}N_6OS$ (452.53): C, 66.35; H, 4.45; N, 18.57. Found: C, 66.29; H, 4.35; N, 18.39%.

(5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(phenyl)methanone (11h). Yellow solid (80% yield); mp 252–254°C; IR (KBr): $\nu = 3248$ (NH), 1697 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.42$ (3H, s, CH_3), 7.19–8.29 (15H, m, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 437 (M^+, 100), 346 (29), 331 (12), 273 (20), 217 (38), 93 (63). *Anal.* Calcd for $C_{25}H_{19}N_5OS$ (437.52): C, 68.63; H, 4.38; N, 16.01. Found: C, 68.59; H, 4.22; N, 15.96%.

(5-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)(thiophen-2-yl)methanone (11i). Yellow solid (78 yield); mp 243–245°C; IR (KBr): $\nu = 3157$(NH), 1690 (C=O), 1595 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.40$ (3H, s, CH_3), 6.87–8.28 (13H, m, Ar–H), 11.89 (s, 1H, D_2O-exchangeable NH); MS, *m/z* (%): 443 (M^+, 38), 330 (17), 261 (11), 139 (48), 125 (100). *Anal.* Calcd for $C_{23}H_{17}N_5OS_2$ (443.54): C, 62.28; H, 3.86; N, 15.79. Found: C, 62.13; H, 3.80; N, 15.49%.

Synthesis of 2-((1-(1H-indol-3-yl)ethylidene)hydrazono)-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (15).

Method A. To a mixture of alkyl carbodithioate **3b–d** (1 mmol) and *N′*-phenylbenzohydrazonoyl chloride **11** (0.230 g, 1 mmol) in ethanol (10 mL), triethylamine (0.5 mL) was added, and the mixture was stirred at room temperature for 2 h. The resulting solid was collected and recrystallized from DMF to give 1,3,4-thiadiazoline **11** as yellow solid (78% yield); mp 269–271°C; IR (KBr): $\nu = 3159$ (NH), 1612 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) $\delta = 2.44$ (3H, s, CH_3), 7.13–8.28 (15H, m, Ar–H), 11.89 (s, 1H, D_2O-exchangeable NH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 20.6$, 112.4, 113.6, 119.5, 121.0, 122.5, 123.0, 125.3, 125.7, 126.1, 129.2, 130.0, 131.2, 132.8, 135.5, 138.0, 153.7, 156.3, 167.4; MS, *m/z* (%): 409 (M^+, 28), 303 (90), 273 (47), 165 (100), 77 (42). *Anal.* Calcd for $C_{24}H_{19}N_5S$ (409.51): C, 70.39; H, 4.68; N, 17.10. Found: C, 70.24; H, 4.48; N, 17.03%.

Method B. A mixture of thiosemicarbazone **3a** (0.232 g, 1 mmol) and *N′*-phenylbenzohydrazonoyl chloride **13** (0.230 g, 1 mmol) in dioxane (10 mL) containing triethylamine (0.07 mL) was refluxed for 6 h and allowed to cool, and the solid formed was filtered off, washed with EtOH, dried, and recrystallized from DMF to give the corresponding product, **11**, which was identical in all aspects (mp, mixed mp, and IR spectra) with those obtained from method A but in 62% yield.

Synthesis of compounds 20–22. To a solution of thiosemicarbazone **3a** (0.232 g, 1 mmol) in dry methanol (20 mL) was added maleic anhydride or phthalic anhydride or dimethyl acetylene dicarboxylate (1 mmol). The solution was refluxed for 2 h. The precipitate was filtered, washed with methanol, and recrystallized from DMF to give compounds **20–22**, respectively.

2-(2-((1-(1H-Indol-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-yl) acetic acid (20). White solid (69% yield); mp 305–307°C; IR (KBr): $\nu = 3419$, 3406, 3244 (2NH and OH), 1730, 1670 (2C=O), 1606 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.44$ (s, 3H, CH_3), 2.85 (dd, 1H, CH_2), 2.94(dd, 1H, CH_2), 4.33 (dd, 1H, CH), 6.70–8.41 (m, 6H, Ar–H and NH), 11.51 (s, 1H, D_2O-exchangeable NH), 11.94 (s, 1H, D_2O-exchangeable OH); ^{13}C NMR (75 MHz, DMSO-d_6) $\delta = 15.0$, 36.1, 41.2, 107.0, 112.1, 119.3, 121.0, 121.3, 130.2, 133.7, 137.3, 156.6, 159.5, 173.5, 177.0; MS *m/z* (%): 330 (M^+, 21), 312 (81), 210 (25), 150 (100), 104 (29), 76 (17). *Anal.* Calcd for $C_{15}H_{14}N_4O_3S$ (330.36): C, 54.53; H, 4.27; N, 16.96. Found: C, 54.38; H, 4.17; N, 16.82%.

N′-(1-(1H-Indol-3-yl)ethylidene)-1,3-dioxoisoindoline-2-carbothiohydrazide (21). White solid (73% yield); mp 326–328°C; IR (KBr): $\nu = 3406$, 3186 (2NH), 1627 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6): $\delta = 2.44$ (s, 3H, CH_3), 7.16–8.29 (m, 9H, Ar–H), 11.9 (s, 1H, D_2O-exchangeable NH), 11.89 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%): 362 (M^+, 100), 347 (59), 291 (53), 263 (25), 83 (43). *Anal.* Calcd for $C_{19}H_{14}N_4O_2S$ (362.41): C, 62.97; H, 3.89; N, 15.46. Found: C, 62.85; H, 3.77; N, 15.37%.

Methyl 2-(2-((1-(1H-indol-3-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-ylidene) acetate (22). Canary yellow solid (78% yield); mp 288–290°C; IR (KBr): $\nu = 3412$, 3159 (2NH), 1694, 1686 (2C=O), 1602 (C=N) cm^{-1}; ^1H

NMR (DMSO-d_6): $\delta = 2.43$ (s, 3H, CH_3), 3.79 (s, 3H, $COOCH_3$), 6.69 (s, 1H, C=CH), 6.91–8.29 (m, 5H, Ar–H), 11.88 (s, 1H, D_2O-exchangeable NH), 12.62 (s, 1H, D_2O-exchangeable NH); MS *m/z* (%): 342 (M^+, 8), 307 (47), 190 (100), 160 (93), 77 (52). *Anal.* Calcd for $C_{16}H_{14}N_4O_3S$ (342.37): C, 56.13; H, 4.12; N, 16.36. Found: C, 56.04; H, 4.03; N, 16.20%.

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