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## SYNTHESIS OF SOME NOVEL THIADIAZOLES AND THIAZOLES LINKED TO PYRAZOLE RING

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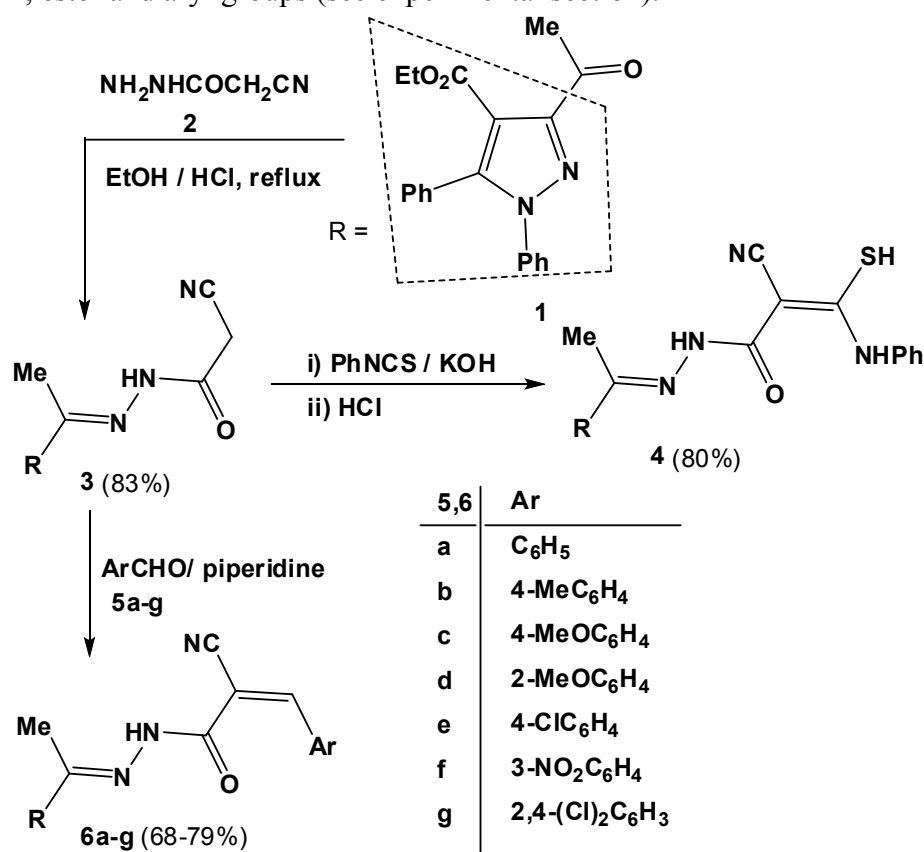
**Abstract** – The novel compound namely ethyl 3-(1-(2-(2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate **3** was used as key intermediate for synthesizing the thioanilide derivative **4** and the arylidene derivatives **6**. The reaction of **4** with a number of haloketones and haloesters furnished the respective thiazole derivatives **8**, **10** and **11a,b**. Moreover, the reaction of **4** with *N*-aryl-2-oxopropane hydrazonoyl chloride **13** and ethyl (*N*-arylhrazono)chloroacetate **17** in absolute ethanol in the presence of triethylamine at reflux afforded a new series of thiadiazoles **15** and **19**, respectively. The mechanisms that account for formation of products **15** and **19** were discussed. Also, the structures of all the newly synthesized products were confirmed based on elemental analysis, spectral data and by alternative methods.

1,3,4-Thiadiazole derivatives have attracted considerable interest owing to their wide spectra of biological activities such as antibacterial, antifungal, antihepatitis B viral, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic, analgesic, antitubercular, and anticonvulsant activities.<sup>1-11</sup> In addition, many pyrazole derivatives have attracted considerable attention in the recent years due to their diverse biological activities.<sup>12-20</sup>

In continuation to our interest in the chemical and pharmacological properties of pyrazole and thiadiazole derivatives, we report herein a facile synthetic strategy for preparation of some new 1,3,4-thiadiazole and thiazole derivatives linked to pyrazole moiety. The biological activities of the synthesized products will be reported in extended work.

The required starting compound **3** was prepared by reaction of ethyl 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate **1** with cyanoacetic acid hydrazide **2** in EtOH containing drops of concentrated HCl under reflux for 6 h (Scheme 1). The structural assignment of the compound **3** was based on both elemental analysis and spectral data (IR, <sup>1</sup>H NMR, Mass). For example, the IR spectrum of compound **3** revealed four characteristic absorption bands at  $\nu$  1692, 1729, 3263 and 2228  $\text{cm}^{-1}$  assignable to the ester, amide carbonyl groups, -NH and nitrile groups. The <sup>1</sup>H NMR spectrum of **3** exhibited two singlet signals at  $\delta$  2.94, 11.19 ppm assigned for the -CH<sub>2</sub>- and the -NH protons, in addition to the expected signals assigned for the aromatic and ester protons. The mass spectrum of **3** showed a molecular ion peak at its expected value.

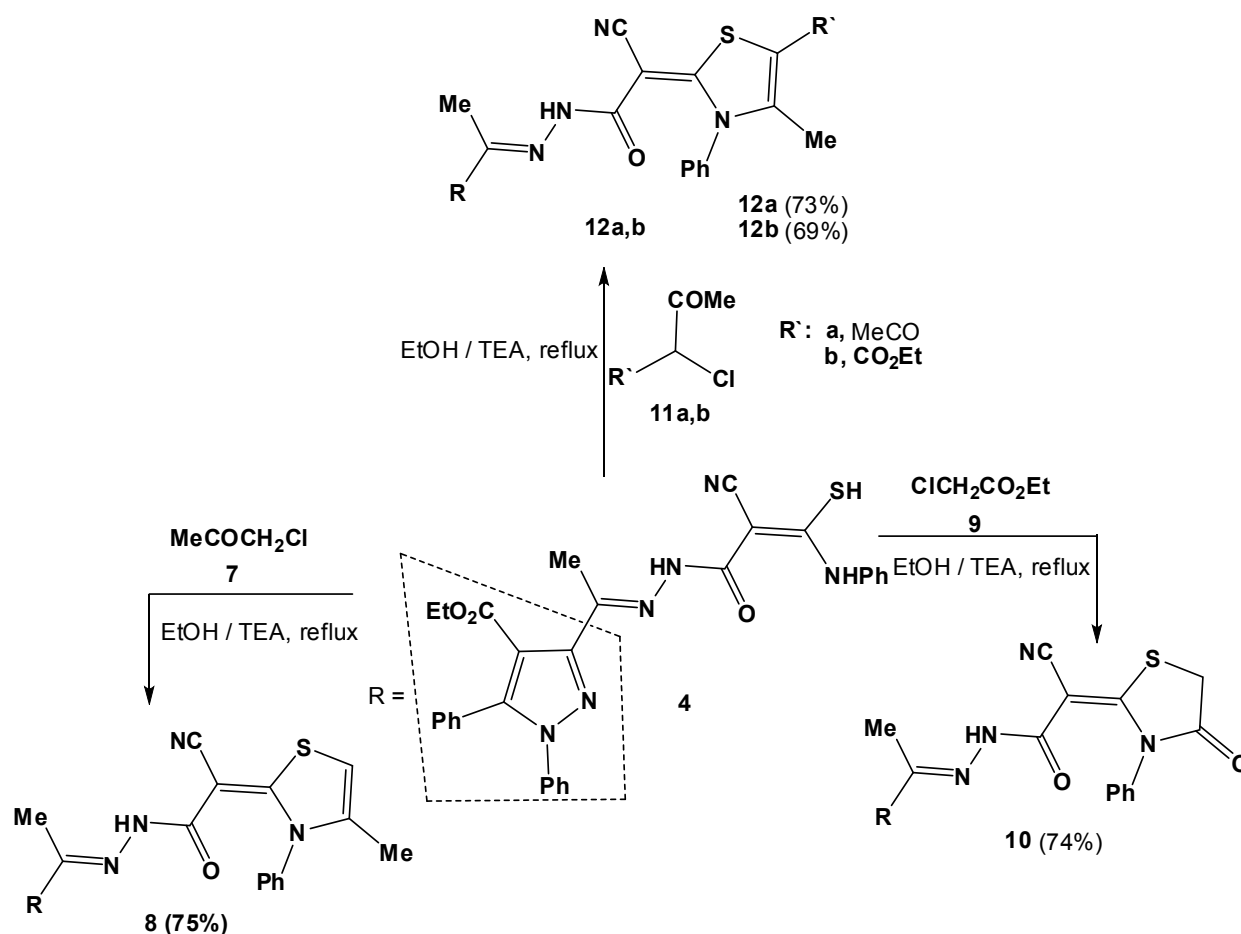
Compound **3** was then used as precursor for synthesis of the thioanilide derivative **4**. Thus, reaction of compound **3** with phenyl isothiocyanate in dimethylformamide in the presence of potassium hydroxide followed by acidification of the produced potassium salt with hydrochloric acid afforded product **4** (Scheme 1). The structure of product **4** was established *via* microanalysis and spectral data (IR, <sup>1</sup>H NMR, Mass). For example, the IR spectrum of thioanilide **4** revealed two absorption bands at  $\nu$  1721, 1693  $\text{cm}^{-1}$  for the two carbonyl groups, in addition to the presence of three absorption bands at  $\nu$  3431, 3185 and 2219  $\text{cm}^{-1}$  assigned for the two NH and nitrile groups. Moreover, the <sup>1</sup>H NMR spectrum of product **4** revealed the absence of signal at  $\delta$  2.94 ppm for the CH<sub>2</sub> group and instead appeared two singlet signals for the protons of NH and the -SH groups, in addition to the expected signals attributed to the protons of methyl, amide NH, ester and aryl groups (see experimental section).



Scheme 1. Synthesis of compounds **3**, **4** and **6a-g**

The mass spectrum of product **4** exhibited a molecular ion peak at  $m/z = 550$  which is consistent with the assigned structure.

In addition to the utility of compound **3** in preparation of the thioanilide **4**, we also used it in synthesis of some novel arylidene derivatives. Thus, reaction of compound **3** with a number of benzaldehyde derivatives **5a-g** in EtOH in the presence of piperidine under reflux for 6 h (monitored by TLC) furnished the respective arylidene derivative **6** (Scheme 1). The structure of products **6a-g** was established via elemental analysis and spectral (IR,  $^1\text{H}$  NMR, Mass) data. For example, the IR spectra of products **6** revealed in each case the characteristic absorption bands as in compound **3**, except  $\nu$  value of the nitrile group decreases as it is conjugated with the arylmethylene double bond ( $\text{ArCH=}$ ). Also, the  $^1\text{H}$  NMR spectra showed the absence of the singlet signal of the protons of  $\text{CH}_2$  group, and instead revealed the characteristic signal assigned for the olefinic proton ( $\text{ArCH=}$ ) near  $\delta$  8.3 ppm, in addition to the other expected signals for the aromatic, NH, Me and  $\text{EtOCO-}$  protons.



**Scheme 2.** Synthesis of thiazole derivatives **8**, **10** and **11a,b**

The utility of thioanilide compound **4** as building block for constructing thiazole ring was explored *via* its reaction with active haloketones and haloesters. Thus, reaction of compound **4** with chloroacetone (**7**),

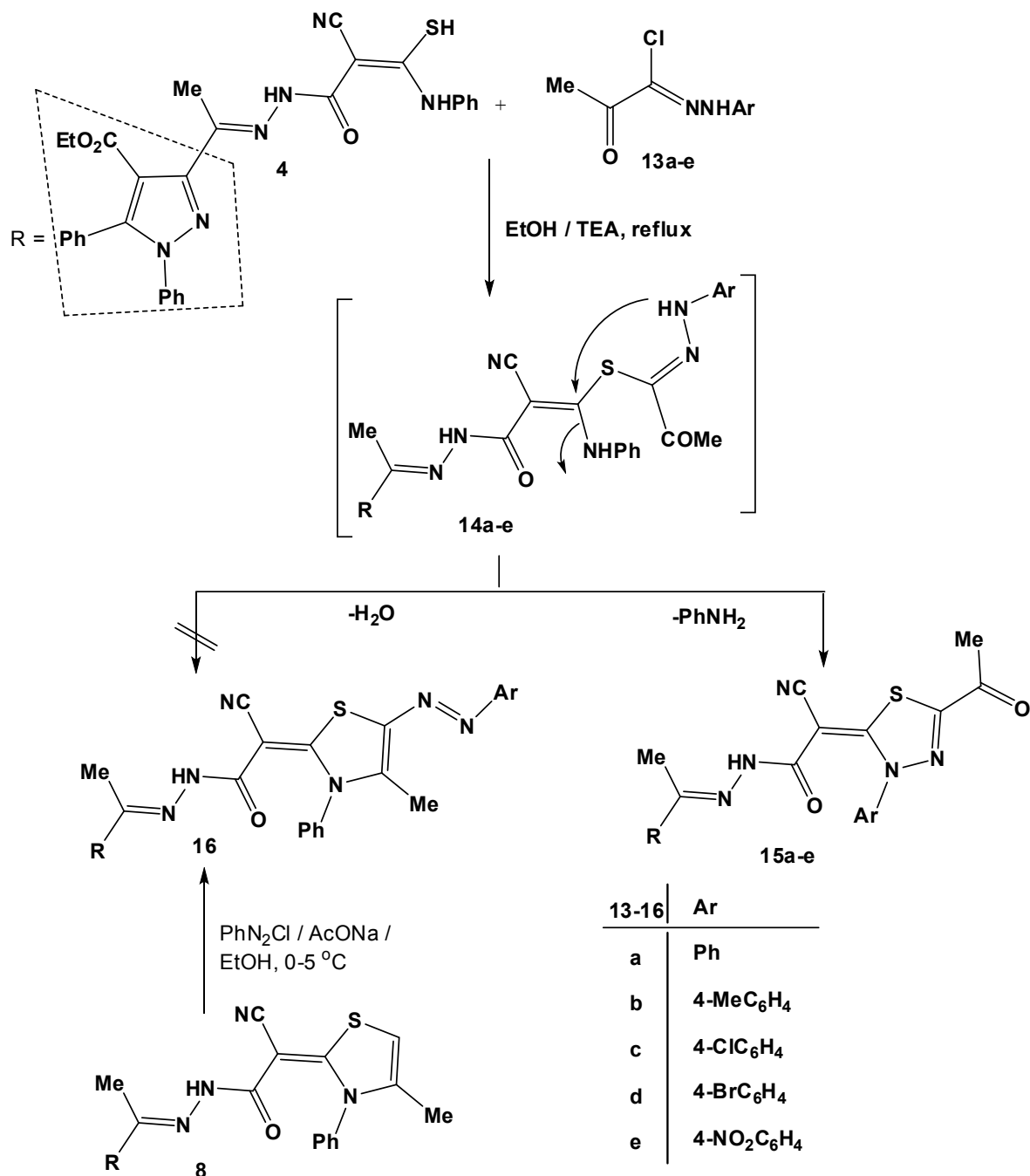
ethyl chloroacetate (**9**), 3-chloro-2,4-pentanedione (**11a**), ethyl 2-chloro-3-oxobutanoate (**11b**) under reflux in ethanol in the presence of triethylamine led to formation of the corresponding thiazole derivatives **8**, **10** and **12a,b**, respectively (Scheme 2).

The structure assigned for the products **8**, **10** and **12a,b** was confirmed by elemental and spectral data (see experimental). It was suggested that the above reactions start with S-alkylation followed by *in situ* intramolecular cyclization of the intermediate by elimination of either ethanol molecule or water to give the final thiazole derivatives **8**, **10** and **12a,b**.<sup>21, 22</sup>

The thioanilide derivative **4** was then used as key intermediate for synthesis of some novel thiadiazole derivatives *via* its reaction with hydrazonoyl halides **13a-e**. Thus, reaction of thioanilide derivative **4** with *N*'-aryl-2-oxo-propanehydrazonoyl chlorides **13a-e** in EtOH in the presence of triethylamine under reflux afforded in each case one isolable product (TLC analysis) which was identified to be **15** and not the other possible structure **16** (Scheme 3). The structure assigned for the products **15** was elucidated on the basis of microanalyses and spectral (IR, <sup>1</sup>H NMR, Mass) data. For example, the IR spectra of products **15** revealed in each case three characteristic absorption bands at  $\nu$  1720, 1690 and 1652 cm<sup>-1</sup> due to the three carbonyl groups, in addition to the presence of two absorption bands at  $\nu$  3423 and 2219 cm<sup>-1</sup> attributed to the amide-NH and the nitrile groups. Moreover, the <sup>1</sup>H NMR spectra of products **15**, exhibited in each case the disappearance of the signals due to the protons of the -NH and -SH groups and instead displayed a signal at  $\delta$  2.72 ppm due to the acetyl group of the thiadiazole moiety. The mass spectra of products **15** showed in each case a molecular ion peak at the correct molecular weight. To account for formation of products **15** it was suggested that reaction of **4** with the nitrilimine, formed *in situ* by treatment of **13** with triethylamine, results in formation of the non-isolable intermediate **14** *via* 1,3-nucleophilic addition, which underwent cyclization by elimination of aniline molecule to give the thiadiazole derivative **15** (Scheme 3).

To provide further evidence that reaction of thioanilide **4** with hydrazonoyl chlorides **13** gave products **15** and not **16**, we synthesized the latter by an equivocal method as outlined in Scheme 3. Thus, treatment of the thiazole derivative **8** with benzenediazonium chloride in ethanol in the presence of basic catalyst (NaOAc) at low temperature (0-5 °C) afforded the coupling product **16a**.<sup>23</sup> Which is completely different from **15a** (mp, mixed mp., IR). The structure of product **16a** was confirmed by both elemental and spectral data (IR, <sup>1</sup>H NMR, Mass) (see experimental section).

Also, reaction of thioanilide derivative **4** with another type of hydrazonoyl chloride, namely ethyl 2-chloro-2-(2-arylhydrazono)ethanoate **17a-f** in refluxing ethanol in the presence of triethylamine, afforded in each case a single isolable product. There are two expected cyclization routes leading to either the 1,3,4-thiadiazole structure **19** or 1,3-thiazolone structure **20** can be suggested for the reaction product *via* loss of either aniline or EtOH molecule from the intermediate **18**, respectively, as outlined in Scheme 4.

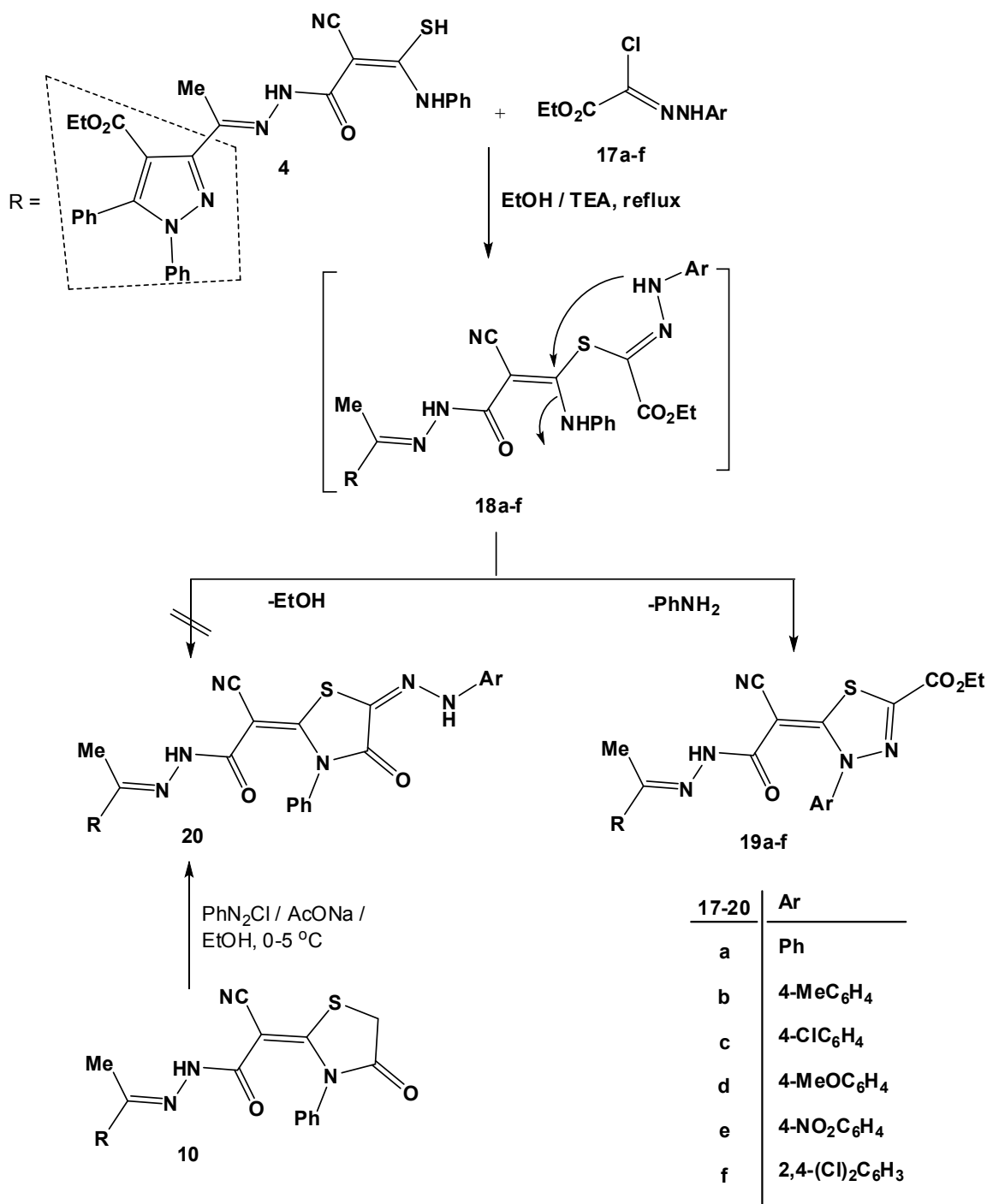


**Scheme 3.** Synthesis of thiadiazole derivatives **15a-e** and thiazole derivative **16a**

However in all cases, the reaction proceeded *via* loss of aniline similar to the mechanism depicted in Scheme 3, and the reaction product was proved, in each case, to be 1,3,4-thiadiazole **19**, based on elemental analysis and spectral data (IR, MS, <sup>1</sup>H NMR and <sup>13</sup>C NMR) which are in support with structure **19** rather than **20**. For example, the IR spectra of products **19a-f** revealed in each case three characteristic absorption bands near  $\nu$  1724, 1712 and 1654 cm<sup>-1</sup> due to the carbonyl group of the two ester and the amide groups, in addition to the presence of two absorption bands at  $\nu$  3427 and 2223 cm<sup>-1</sup> attributed to the amide-NH and the nitrile groups. The <sup>1</sup>H NMR spectra of product **19**, exhibited in each case the

disappearance of the signal due to the protons of PhNH- and thiol groups and instead displayed the signals characteristic for the ester group (EtOCO) of the thiadiazole moiety.

Further evidence for the formation of products **19** from the reaction of thioanilide **4** with hydrazoneyl chlorides **17** was achieved by synthesizing the other possible products **20** by an equivocal procedure. Thus, reaction of the thiazolone derivative **10** with benzenediazonium chloride in ethanol in the presence of sodium acetate as basic catalyst at low temperature (0-5 °C) afforded product **20a**<sup>24</sup> (Scheme 4). The structure of product **20a** was established on the basis of elemental analysis and spectral data (IR, <sup>1</sup>H NMR, Mass) (see Experimental section).



**Scheme 4.** Synthesis of thiadiazole derivatives **19a-e** and thiazolone derivative **20a**

The stereochemistry of Me-C=N-NH in all the synthesized compounds is *anti*-form according to our previous work based on NOE difference experiments and the minimum energy conformations MM2 force field calculations.<sup>25</sup> The stereochemistry of the second double bond in compounds **4**, **6a-g**, **8**, **10**, **12a,b**, **15a-e**, **16**, **19a-f** and **20** is *E*-form to decrease steric hindrance. The stereochemistry of the hydrazo-double bond in compound **20** is *E*-form due to the stability caused with formation of hydrogen bond with carbonyl group of the thiazolone moiety.

In this study, novel thioanilide derivative was synthesized and used as a key intermediate for the synthesis of a new series of thiadiazoles *via* its reaction with N-aryl-2-oxopropane hydrazonoyl chloride and ethyl (N-arylhydrazono) chloroacetate. The mechanisms that account for formation of products were discussed. Also, the structures of all the newly synthesized products were confirmed based on elemental analysis, spectral data and by alternative methods.

## EXPERIMENTAL

Melting points were measured on an Electrothermal IA 9000 series digital melting point apparatus. IR spectra were recorded in potassium bromide discs on Pye Unicam 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 (<sup>1</sup>H NMR) and run in deuterated dimethyl sulfoxide (DMSO-*d*<sub>6</sub>). Chemical shifts were related to that of the solvent. <sup>13</sup>C NMR was recorded on a BRUKER spectrometer at 75 MHz. Mass spectra was recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were measured by using a German made Elementar vario LIII CHNS analyzer. Hydrazonoyl halides **13** and **17**<sup>26-30</sup> were prepared as reported in the respective literature.

**Synthesis of (*E*)-ethyl 3-(1-(2-(2-cyanoacetyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**3**).** To a solution of 2-cyanoacetohydrazide **2** (1.0 g, 10 mmol) and ethyl 3-acetyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**1**) (3.34 g, 10 mmol) in absolute EtOH (30 mL) three drops of conc. HCl were added and the reaction mixture was refluxed for 6 h. then left to cool. The solid product formed was collected by filtration, dried and recrystallized from EtOH to give **3**. Yield 83%; yellow microcrystals; mp 188-190 °C; IR (KBr):  $\nu$  1692, 1729 (2C=O), 2228 (CN), 3263 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.16 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.90 (s, 3H, CH<sub>3</sub>), 2.94 (s, 2H, CH<sub>2</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.29-7.37 (m, 10H, ArH), 11.19 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 415 (M<sup>+</sup>, 42), 361 (73), 214 (100), 116 (58), 59 (74). Anal. Calcd for C<sub>23</sub>H<sub>21</sub>N<sub>5</sub>O<sub>3</sub> (415.44): C, 66.49; H, 5.09; N, 16.86. Found C, 66.30; H, 5.02; N, 16.74%.

**Synthesis of ethyl 3-((*E*)-1-(2-((*E*)-2-cyano-3-(phenylamino)-3-thioxopropanoyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**4**).** To an ice-cold suspension of finely powdered potassium

hydroxide (1.1 g, 0.02 mol) in dry DMF (5 mL), ethyl 3-(1-(2-(2-cyanoacetyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**3**) (4.15 g, 0.01 mol) and then the phenyl isothiocyanate (1.35, 0.01 mol) were added in portions with stirring. After complete addition, stirring was continued at room temperature for an over-night. The reaction mixture was then poured into ice/cold H<sub>2</sub>O and acidified with concentrated HCl. The obtained precipitate was filtered, washed with H<sub>2</sub>O, dried, and crystallized from EtOH to give the product **4** in 80% yield as yellow solid, mp 185-187 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3431, 3185 (2NH), 2219 (CN), 1721, 1693 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.19 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.91 (s, 3H, CH<sub>3</sub>), 4.25 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.16-7.88 (m, 15H, ArH), 10.57, 11.19 (2s, 2H, D<sub>2</sub>O exchangeable, 2NH), 13.52 (s, 1H, SH); MS *m/z* (%): 550 (M<sup>+</sup>, 100), 397 (64), 285 (39), 165 (42), 77 (90), 59 (81). Anal. Calcd. for C<sub>30</sub>H<sub>26</sub>N<sub>6</sub>O<sub>3</sub>S (550.63): C, 65.44; H, 4.76; N, 15.26; Found. C, 65.27; H, 4.59; N, 15.08%.

#### Reaction of **3** with aromatic aldehydes **5a-g**:

**General procedure:** A mixture of **3** (0.415 g, 1 mmol), and the appropriate aromatic benzaldehyde derivative **5** (1 mmol) in 20 mL absolute EtOH in the presence of and 0.5 mL piperidine, was refluxed for 4-6 h (monitored by TLC). The reaction mixture was left to cool and the formed solid was filtered off, washed with water, dried and recrystallized from DMF to give **6a-g**.

**Ethyl 3-((*E*)-1-(2-((*Z*)-2-cyano-3-phenylacryloyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**6a**).** Yield 72%; yellow solid; mp 213-215 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3412, 3182 (2NH), 2218 (CN), 1725, 1673 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.17 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.87 (s, 3H, CH<sub>3</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.98-7.68 (m, 15H, ArH), 8.66 (s, 1H, CH=), 11.26 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 503 (M<sup>+</sup>, 63), 416 (37), 284 (100), 192 (60), 77 (74). Anal. Calcd for C<sub>30</sub>H<sub>25</sub>N<sub>5</sub>O<sub>3</sub> (503.55): C, 71.56; H, 5.00; N, 13.91. Found C, 71.42; H, 4.87; N, 13.79%.

**Ethyl 3-((*E*)-1-(2-((*Z*)-2-cyano-3-(*p*-tolyl)acryloyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**6b**).** Yield 77%; yellow solid; mp 181-183 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3412, 3182 (2NH), 2218 (CN), 1725, 1673 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.07 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.88 (s, 3H, CH<sub>3</sub>), 2.25 (s, 3H, CH<sub>3</sub>), 4.20 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.06-7.82 (m, 14H, ArH), 8.64 (s, 1H, CH=), 11.15 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 517 (M<sup>+</sup>, 61), 442 (47), 318 (100), 230 (63), 63 (79). Anal. Calcd for C<sub>31</sub>H<sub>27</sub>N<sub>5</sub>O<sub>3</sub> (517.58): C, 71.94; H, 5.26; N, 13.53. Found C, 71.86; H, 5.17; N, 13.38%.

**Ethyl 3-((*E*)-1-(2-((*Z*)-2-cyano-3-(4-methoxyphenyl)acryloyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (**6c**).** Yield 77%; yellow solid; mp 230-232 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3424, 3174 (2NH), 2219 (CN), 1718, 1670 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 3.75 (s, 3H, OCH<sub>3</sub>), 4.17 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.96-7.95 (m, 14H, ArH), 8.58 (s, 1H, CH=), 11.25 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 533 (M<sup>+</sup>, 73), 421 (50), 318 (100), 258 (82), 77 (95). Anal. Calcd for C<sub>31</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> (533.58): C, 69.78; H, 5.10; N, 13.13. Found C, 69.66; H, 5.04; N, 13.02%.



**Ethyl 3-((E)-1-(2-((Z)-2-cyano-3-(2-methoxyphenyl)acryloyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (6d).** Yield 68%; yellow solid; mp 186-188 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3408, 3193 (2NH), 2218 (CN), 1720, 1674 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 4.21 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.17-7.38 (m, 14H, ArH), 8.64 (s, 1H, CH=), 11.15 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 533 (M<sup>+</sup>, 73), 421 (50), 318 (100), 258 (82), 77 (95). MS *m/z* (%): 533 (M<sup>+</sup>, 47), 318 (83), 237 (72), 193 (37), 127 (60), 59 (100). Anal. Calcd for C<sub>31</sub>H<sub>27</sub>N<sub>5</sub>O<sub>4</sub> (533.58): C, 69.78; H, 5.10; N, 13.13. Found C, 69.64; H, 5.02; N, 13.10%.

**Ethyl 3-((E)-1-(2-((Z)-2-cyano-3-(4-chlorophenyl)-2-cyanoacryloyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (6e).** Yield 79%; yellow solid; mp 250-252 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3422, 3190 (2NH), 2221 (CN), 1723, 1682 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.91 (s, 3H, CH<sub>3</sub>), 4.24 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.31-7.58 (m, 14H, ArH), 8.65 (s, 1H, CH=), 11.19 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 539 (M<sup>+</sup> + 2, 30), 537 (M<sup>+</sup>, 100), 340 (42), 251 (38), 153 (72), 95 (69). Anal. Calcd for C<sub>30</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>3</sub> (537.16): C, 66.97; H, 4.50; N, 13.02. Found C, 66.75; H, 4.38; N, 12.91%.

**Ethyl 3-((E)-1-(2-((Z)-2-cyano-3-(3-nitrophenyl)acryloyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (6f).** Yield 71%; yellow solid; mp 203-205 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3417, 3210 (2NH), 2223 (CN), 1724, 1680 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.07 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.69 (s, 3H, CH<sub>3</sub>), 4.24 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.85-7.95 (m, 14H, ArH), 8.69 (s, 1H, CH=), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 548 (M<sup>+</sup>, 57), 412 (72), 318 (100), 250 (49), 77 (86). Anal. Calcd for C<sub>30</sub>H<sub>24</sub>N<sub>6</sub>O<sub>5</sub> (548.55): C, 65.69; H, 4.41; N, 15.32. Found C, 65.49; H, 4.35; N, 15.18%.

**Ethyl 3-((E)-1-(2-((Z)-2-cyano-3-(2,4-dichlorophenyl)acryloyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (6g).** Yield 77%; yellow solid; mp 240-242 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3420, 3216 (2NH), 2226 (CN), 1721, 1682 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.65 (s, 3H, CH<sub>3</sub>), 4.20 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.33-7.86 (m, 13H, ArH), 8.64 (s, 1H, CH=), 11.19 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 571 (M<sup>+</sup>, 100), 418 (59), 318 (88), 235 (73), 125 (42), 77 (82). Anal. Calcd for C<sub>30</sub>H<sub>23</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>3</sub> (571.12): C, 62.94; H, 4.05; N, 12.23. Found C, 62.75; H, 3.83; N, 12.11%.

#### Reaction of thioanilide derivatives 4 with active $\alpha$ -haloketones and $\alpha$ -haloesters

General procedure: To a mixture of thioanilide **4** (0.55 g, 1 mmol) and the appropriate chloroacetone (**7**), ethyl chloroacetate (**9**), 3-chloropentane-2,4-dione (**11a**), and ethyl 2-chloro-3-oxobutanoate (**11b**) (1 mmol) in EtOH (20 mL), was added triethylamine (0.5 mL) at room temperature. The reaction mixture was heated under reflux until all the starting material was consumed (2–6 h, monitored by TLC). The solid that formed, after cooling, was filtered and recrystallized from DMF to give the corresponding thiazole derivatives **8**, **10** and **12a,b**, respectively.

**Ethyl 3-((*E*)-1-(2-((*E*)-2-cyano-2-(4-methyl-3-phenylthiazol-2(3*H*)-ylidene)acetyl)hydrazono)-ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (8).** Yield 75%; yellow solid; mp 213-315 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3429 (NH), 2220 (CN), 1720, 1671 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>), 2.10 (s, 3H, CH<sub>3</sub>), 4.23 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.42 (s, 1H, thiazole-H5), 7.14-7.73 (m, 15H, ArH), 11.14 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 588 (M<sup>+</sup>, 64), 406 (70), 348 (64), 218 (39), 77 (100), 59 (83). Anal. Calcd for C<sub>33</sub>H<sub>28</sub>N<sub>6</sub>O<sub>3</sub>S (588.68): C, 67.33; H, 4.79; N, 14.28; Found C, 67.23; H, 4.71; N, 14.14%.

**Ethyl 3-((*E*)-1-(2-((*E*)-2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)acetyl)hydrazono)ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (10).** Yield 74%; yellow solid; mp 242-244 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3428 (NH), 2220 (CN), 1728, 1671, 1658 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.83 (s, 3H, CH<sub>3</sub>), 4.11 (s, 2H, CH<sub>2</sub>), 4.24 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.14-7.73 (m, 15H, ArH), 11.05 (s, 1H, D<sub>2</sub>O exchangeable, NH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  13.4, 15.3 (CH<sub>3</sub>), 31.5, 62.3 (CH<sub>2</sub>), 82.4, 116.7, 118.3, 120.2, 124.3, 126.2, 127.3, 127.8, 128.0, 128.4, 129.3, 130.1, 135.6, 138.3, 140.8, 143.8, 145.4, 148.1, 157.2, 160.5, 162.5, 164.9, 171.0; MS *m/z* (%): 590 (M<sup>+</sup>, 100), 426 (64), 356 (39), 212 (53), 51 (72). Anal. Calcd for C<sub>32</sub>H<sub>26</sub>N<sub>6</sub>O<sub>4</sub>S (590.65): C, 65.07; H, 4.44; N, 14.23; Found C, 65.02; H, 4.35; N, 14.18%.

**Ethyl 3-((*E*)-1-(2-((*E*)-2-(5-acetyl-4-methyl-3-phenylthiazol-2(3*H*)-ylidene)-2-cyanoacetyl)hydrazono)-ethyl)-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (12a).** Yield 69%; yellow solid; mp 182-184 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3423 (NH), 2221 (CN), 1723, 1697, 1649 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>), 2.22 (s, 3H, CH<sub>3</sub>), 2.42 (s, 3H, CH<sub>3</sub>), 4.23 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.11-7.79 (m, 15H, ArH), 11.07 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 630 (M<sup>+</sup>), 468 (38), 357 (96), 319 (100), 77 (86), 51 (72). Anal. Calcd for C<sub>35</sub>H<sub>30</sub>N<sub>6</sub>O<sub>4</sub>S (630.72): C, 66.65; H, 4.79; N, 13.32; Found C, 66.47; H, 4.66; N, 13.25%.

**(*E*)-Ethyl 2-(1-cyano-2-((*E*)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1*H*-pyrazol-3-yl)ethylidene)-hydrazinyl)-2-oxoethylidene)-4-methyl-3-phenyl-2,3-dihydrothiazole-5-carboxylate (12b).** Yield 73%; yellow solid; mp 320-322 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3426, 3170 (2NH), 2221 (CN), 1720, 1677, 1651 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.06 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.81 (s, 3H, CH<sub>3</sub>), 2.20 (s, 3H, CH<sub>3</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.04-7.89 (m, 20H, ArH), 11.16, 11.47 (2s, 2H, D<sub>2</sub>O exchangeable, 2NH); MS *m/z* (%): 707 (M<sup>+</sup>, 52), 670 (70), 576 (66), 369 (38), 77 (45), 64 (100). Anal. Calcd for C<sub>40</sub>H<sub>33</sub>N<sub>7</sub>O<sub>4</sub>S (707.23): C, 67.88; H, 4.70; N, 13.85; Found C, 67.69; H, 4.63; N, 13.76%.

#### **Reaction of the thioanilide derivative 4 with hydrazonoyl chlorides 13a-e and 17a-f**

**General procedure:** To a solution of the thioanilide derivative 4 (0.550 g, 1 mmol) in absolute EtOH (20 mL), the appropriate hydrazonoyl chlorides 13a-e or 17-f (1 mmol) was added, in the presence of triethylamine (0.3 mL). The reaction mixture were refluxed for 4 h (monitored by TLC), allowed to cool

and the solid formed was filtered off, washed with ethanol, dried and recrystallized from EtOH to give the corresponding thiadiazole derivatives **15a–e** and **19a–f**, respectively.

**Ethyl 3-((E)-1-(2-((E)-2-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (15a)**. Yield 70%; brown solid; mp 210–212 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3423 (NH), 2219 (CN), 1720, 1690, 1652 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.19 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.86 (s, 3H, CH<sub>3</sub>), 2.72 (s, 3H, CH<sub>3</sub>), 4.27 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.02–7.95 (m, 15H, ArH), 11.14 (s, 1H, D<sub>2</sub>O exchangeable, NH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  13.2, 14.9, 23.2 (CH<sub>3</sub>), 61.8 (CH<sub>2</sub>), 92.4, 116.1, 119.1, 120.4, 121.5, 125.7, 125.9, 127.3, 128.1, 129.2, 129.7, 131.3, 131.9, 133.6, 137.5, 140.2, 143.6, 147.4, 155.2, 167.3, 169.8, 193.6; MS *m/z* (%): 617 (M<sup>+</sup>, 9), 571 (13), 482 (12), 295 (30), 118 (28), 80 (100), 64 (55). Anal. Calcd for C<sub>33</sub>H<sub>27</sub>N<sub>7</sub>O<sub>4</sub>S (617.68): C, 64.17; H, 4.41; N, 15.87. Found C, 64.13; H, 4.28; N, 15.81%.

**Ethyl 3-((E)-1-(2-((E)-2-(5-acetyl-3-(p-tolyl)-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (15b)**. Yield 73%; brown solid; mp 193–195 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3414 (NH), 2219 (CN), 1723, 1688, 1656 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.04 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 2.27 (s, 3H, CH<sub>3</sub>), 2.72 (s, 3H, CH<sub>3</sub>), 4.27 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.96–7.45 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 631 (M<sup>+</sup>, 24), 590 (32), 489 (28), 318 (61), 135 (100), 86 (87), 64 (88). Anal. Calcd for C<sub>34</sub>H<sub>29</sub>N<sub>7</sub>O<sub>4</sub>S (631.70): C, 64.64; H, 4.63; N, 15.52. Found C, 64.48; H, 4.90; N, 15.40%.

**Ethyl 3-((E)-1-(2-((E)-2-(5-acetyl-3-(4-chlorophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (15c)**. Yield 73%; brown solid; mp 220–222 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3421 (NH), 2219 (CN), 1726, 1680, 1656 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 2.72 (s, 3H, CH<sub>3</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.11–7.55 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 653 (M<sup>+</sup>+2, 15), 651 (M<sup>+</sup>, 39), 572 (33), 495 (38), 369 (25), 77 (41), 64 (100). Anal. Calcd for C<sub>33</sub>H<sub>26</sub>ClN<sub>7</sub>O<sub>4</sub>S (651.15): C, 60.78; H, 4.02; N, 15.04. Found C, 60.57; H, 3.82; N, 15.01%.

**Ethyl 3-((E)-1-(2-((E)-2-(5-acetyl-3-(4-bromophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (15d)**. Yield 74%; brown solid; mp 206–208 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3380 (NH), 2220 (CN), 1724, 1667, 1651 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.04 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 2.71 (s, 3H, CH<sub>3</sub>), 4.20 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 6.99–7.45 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 697 (M<sup>+</sup>+2, 19), 695 (M<sup>+</sup>, 21), 572 (63), 458 (65), 160 (73), 80 (24), 64 (100). Anal. Calcd for C<sub>33</sub>H<sub>26</sub>BrN<sub>7</sub>O<sub>4</sub>S (695.10): C, 56.90; H, 3.76; N, 14.08. Found C, 56.75; H, 3.59; N, 14.02%.

**Ethyl 3-((E)-1-(2-((E)-2-(5-acetyl-3-(4-nitrophenyl)-1,3,4-thiadiazol-2(3H)-ylidene)-2-cyanoacetyl)-hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (15e)**. Yield 70%; brown solid; mp 237–

239 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3426 (NH), 2223 (CN), 1724, 1660, 1656 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.04 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.87 (s, 3H, CH<sub>3</sub>), 2.72 (s, 3H, CH<sub>3</sub>), 4.23 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.10-7.69 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 662 (M<sup>+</sup>, 17), 369 (75), 318 (47), 158 (68), 64 (100). Anal. Calcd for C<sub>33</sub>H<sub>26</sub>N<sub>8</sub>O<sub>6</sub>S (662.67): C, 59.81; H, 3.95; N, 16.91. Found C, 59.73; H, 3.91; N, 16.78%.

**(E)-Ethyl 5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19a).** Yield 70%; brown solid; mp 232-234 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3427 (NH), 2223 (CN), 1724, 1712, 1654 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.32 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.36 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 6.96-7.88 (m, 15H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  12.2, 13.5, 14.9 (CH<sub>3</sub>), 61.8, 62.1 (CH<sub>2</sub>), 91.3, 114.9, 119.3, 120.2, 121.7, 123.1, 123.7, 125.6, 127.5, 128.6, 129.2, 130.4, 131.4, 132.6, 138.3, 140.6, 142.1, 147.9, 151.4, 165.2, 168.5, 172.3; MS *m/z* (%): 647 (M<sup>+</sup>, 20), 573 (32), 119 (20), 91 (29), 64 (100). Anal. Calcd for C<sub>34</sub>H<sub>29</sub>N<sub>7</sub>O<sub>5</sub>S (647.70): C, 63.05; H, 4.51; N, 15.14. Found C, 63.01; H, 4.38; N, 15.05%.

**(E)-Ethyl 5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4-(*p*-tolyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19b).** Yield 74%; brown solid; mp 312-314 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3421 (NH), 2223 (CN), 1729, 1715, 1652 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.05 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.31 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>), 1.87 (s, 3H, CH<sub>3</sub>), 2.29 (s, 3H, CH<sub>3</sub>), 4.20 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.37 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 7.30-7.44 (m, 14H, ArH), 11.15 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 661 (M<sup>+</sup>, 16), 555 (24), 476 (32), 135 (14), 80 (65), 64 (100). Anal. Calcd for C<sub>35</sub>H<sub>31</sub>N<sub>7</sub>O<sub>5</sub>S (661.73): C, 63.53; H, 4.72; N, 14.82. Found C, 63.44; H, 4.59; N, 14.75%.

**(E)-Ethyl 4-(4-chlorophenyl)-5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19c).** Yield 77%; brown solid; mp 220-222 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3427 (NH), 2223 (CN), 1723, 1710, 1652 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.05 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.21 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 4.22 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 4.36 (q, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 6.99-7.73 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS *m/z* (%): 683 (M<sup>+</sup>+2, 12), 681 (M<sup>+</sup>, 30), 572 (48), 473 (52), 369 (44), 125 (55), 77 (72), 64 (100). Anal. Calcd for C<sub>34</sub>H<sub>28</sub>ClN<sub>7</sub>O<sub>5</sub>S (681.16): C, 59.86; H, 4.14; N, 14.37. Found C, 59.63; H, 4.07; N, 14.24%.

**(E)-Ethyl 5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4-(4-methoxyphenyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19d).** Yield 74%; brown solid; mp 213-215 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3425 (NH), 2220 (CN), 1722, 1712, 1648 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.05 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.23 (t, *J* = 7.4 Hz, 3H, CH<sub>3</sub>), 1.89 (s,

3H, CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.26 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub>), 4.36 (q,  $J = 7.4$  Hz, 2H, CH<sub>2</sub>), 6.92-7.68 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS  $m/z$  (%): 677 (M<sup>+</sup>, 21), 480 (35), 318 (100), 261 (74), 106 (54), 77 (86). Anal. Calcd for C<sub>35</sub>H<sub>31</sub>N<sub>7</sub>O<sub>6</sub>S (677.73): C, 62.03; H, 4.61; N, 14.47. Found C, 61.91; H, 4.52; N, 14.30%.

**(E)-Ethyl 5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4-(4-nitrophenyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19e).**

Yield 77%; brown solid; mp 248-250 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3429 (NH), 2225 (CN), 1729, 1715, 1648 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.08 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>), 1.23 (t,  $J = 7.4$  Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 4.26 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub>), 4.38 (q,  $J = 7.4$  Hz, 2H, CH<sub>2</sub>), 7.14-7.89 (m, 14H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS  $m/z$  (%): 692 (M<sup>+</sup>, 8), 369 (16), 444 (100), 371 (17), 80 (33), 64 (100). Anal. Calcd for C<sub>34</sub>H<sub>28</sub>N<sub>8</sub>O<sub>7</sub>S (692.18): C, 58.95; H, 4.07; N, 16.18. Found C, 58.86; H, 4.03; N, 16.12%.

**(E)-Ethyl 5-(1-cyano-2-((E)-2-(1-(4-(ethoxycarbonyl)-1,5-diphenyl-1H-pyrazol-3-yl)ethylidene)hydrazinyl)-2-oxoethylidene)-4-(2,4-dichlorophenyl)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (19f).**

Yield 71%; brown solid; mp 260-262 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3428 (NH), 2220 (CN), 1723, 1710, 1653 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.06 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>), 1.32 (t,  $J = 7.4$  Hz, 3H, CH<sub>3</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 4.27 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub>), 4.39 (q,  $J = 7.4$  Hz, 2H, CH<sub>2</sub>), 6.90-7.43 (m, 13H, ArH), 11.16 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS  $m/z$  (%): 715 (M<sup>+</sup>, 41), 658 (45), 484 (43), 369 (30), 80 (29), 64 (100). Anal. Calcd for C<sub>34</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>7</sub>O<sub>5</sub>S (715.12): C, 56.99; H, 3.80; N, 13.68. Found C, 56.76; H, 3.69; N, 13.58%.

### Synthesis of compounds 16a and 20a

To a solution of thiazole derivative **8** or thiazolone **10** (1 mmol) in EtOH (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 (0.091 mL, 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 products **16a** and **20a**, respectively.

**Ethyl 3-((E)-1-(2-((E)-2-cyano-2-(4-methyl-3-phenyl-5-((E)-phenyldiazenyl)thiazol-2(3H)-ylidene)-acetyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (16a).** Yield 67%; yellow solid; mp 284-286 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3391 (NH), 2218 (CN), 1724, 1655 (2CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t,  $J = 7.2$  Hz, 3H, CH<sub>3</sub>), 1.82 (s, 3H, CH<sub>3</sub>), 2.16 (s, 3H, CH<sub>3</sub>), 4.27 (q,  $J = 7.2$  Hz, 2H, CH<sub>2</sub>), 7.10-7.88 (m, 20H, ArH), 11.15 (s, 1H, D<sub>2</sub>O exchangeable, NH); MS  $m/z$  (%): 692 (M<sup>+</sup>, 31), 482 (50), 214 (100),

77 (86). Anal. Calcd for C<sub>39</sub>H<sub>32</sub>N<sub>8</sub>O<sub>3</sub>S (692.23): C, 67.61; H, 4.66; N, 16.17. Found C, 67.53; H, 4.47; N, 16.05%.

**Ethyl 3-((E)-1-(2-((E)-2-cyano-2-((E)-4-oxo-3-phenyl-5-(2-phenylhydrazono)thiazolidin-2-ylidene)-acetyl)hydrazono)ethyl)-1,5-diphenyl-1H-pyrazole-4-carboxylate (20a).** Yield 69%; yellow solid; mp 262-264 °C; IR(KBr)  $\nu$  (cm<sup>-1</sup>) 3431, 3233 (2NH), 2221 (CN), 1744, 1668, 1649 (3CO); <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  1.09 (t, *J* = 7.2 Hz, 3H, CH<sub>3</sub>), 1.87 (s, 3H, CH<sub>3</sub>), 4.23 (q, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 7.37-7.82 (m, 20H, ArH), 10.47, 11.13 (2s, 2H, D<sub>2</sub>O exchangeable, 2NH); MS *m/z* (%): 694 (M<sup>+</sup>, 32), 418 (36), 390 (61), 276 (49), 77 (100), 51 (51). Anal. Calcd for C<sub>38</sub>H<sub>30</sub>N<sub>8</sub>O<sub>4</sub>S (694.21): C, 65.69; H, 4.35; N, 16.13. Found C, 65.58; H, 4.39; N, 16.04%.

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