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SYNTHESIS OF NOVEL THIAZOLE AND 1,3,4-THIADIAZOLE DERIVATIVES INCORPORATING PHENYLSULFONYL MOIETY

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Abstract – Reaction of 1-(benzothiazol-2-yl)-2-phenylsulfonyl-1-ethanone (**1**) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)-1-ethanone (**2**) with phenyl isothiocyanate afforded the corresponding potassium salts **3** and **4**, respectively. The potassium salts **3** and **4** were converted into the corresponding (*Z*)-1-(benzothiazol-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl) propenone (**5**) and (*Z*)-1-(1-methylbenzimidazole-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl)propenone (**6**), respectively upon acidification with HCl. The latter products were used as versatile building blocks for novel 1,3,4-thiadiazole derivatives *via* their reactions with the appropriate hydrazonyl halides. They have been also utilized for the synthesis of thiazole ring systems incorporating phenylsulfonyl moiety.

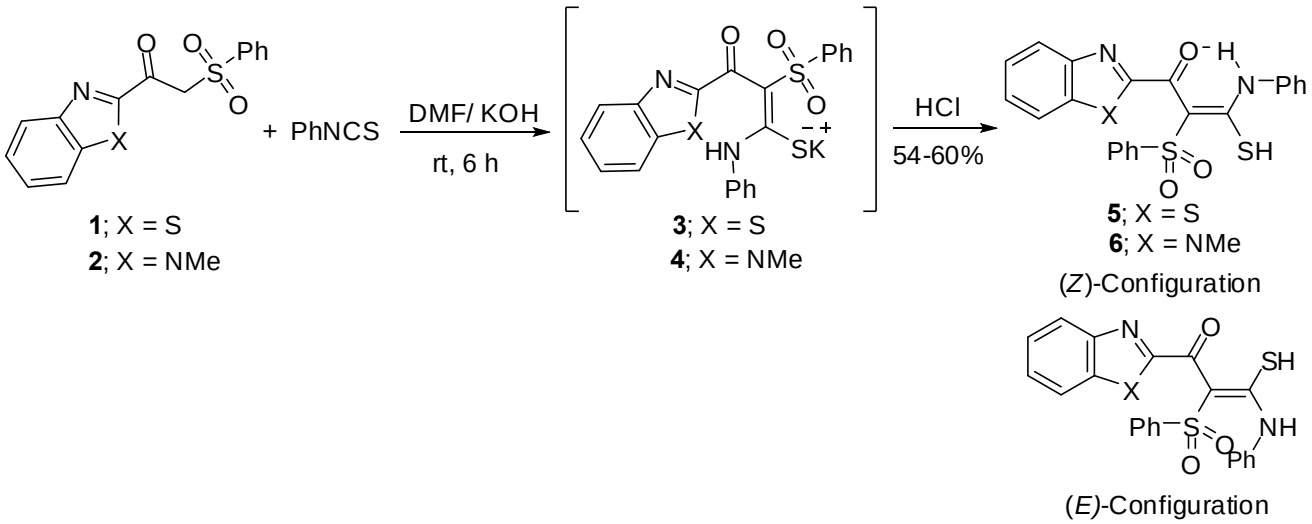
INTRODUCTION

Benzothiazole and benzimidazole derivatives are recognized as important heterocycles due to their diverse pharmacological properties.[1] Their derivatives have attracted continuing interest because of their varied biological activities such as antiviral,[2-5] antibacterial,[6,7] antifungal,[8-11] antitumour,[12-15] anticancer,[16,17] antitubercular,[18,19] antimalarial,[20] anticonvulsant,[21] antihelminthic agentsin veterinary medicine,[22-24] analgesic,[25,26] anti-inflammtory,[27,28] antidiabetic agents,[29] anti-HIV,[30,31] anticoagulative agents,[32,33] antihypertensive,[34,35] antineoplastic,[36,37] anxiolytic agents.[38,39] Many of their derivatives are now included in many of commercialized drugs.[40-42] On the other hand, β-ketosulfone moiety displays a

broad range of synthetic potentiality.[43,44] In continuation of our research work aiming at the synthesis of a variety of heterocycles for biological screening,[45-60] we report here on the utility of (*Z*)-1-(benzothiazol-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl)propenone (**5**) and (*Z*)-1-(1-methylbenzimidazole-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl)propenone (**6**) as reactive intermediates, for the synthesis of the 1,3,4-thiadiazole and 1,3-thiazole heterocycles incorporating phenylsulfonyl moiety of potential biological activity.

RESULTS AND DISCUSSION

Treatment of 1-(benzothiazol-2-yl)-2-(phenylsulfonyl)ethanone (**1**)[46] and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (**2**)[46] with phenyl isothiocyanate, in DMF in the presence of potassium hydroxide, at rt afforded the corresponding potassium salts **3** and **4,** respectively. Treatment of these intermediate salts with HCl afforded, in each case, a single product (as examined by TLC). The reaction products were identified as (*Z*)-1-(benzothiazol-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl)prop-2-en-1-one (**5**) and (*Z*)-1-(1-methylbenzimidazole-2-yl)-3-mercapto-3-(phenylamino)-2-(phenylsulfonyl)prop-2-en-1-one (**6**), respectively (Scheme 1). The IR spectra of compounds **5** and **6** showed, in each case, a band near 3345 cm^{-1} due to NH group and strong absorption bands at 1685 and 1680 cm^{-1} due to carbonyl functions.

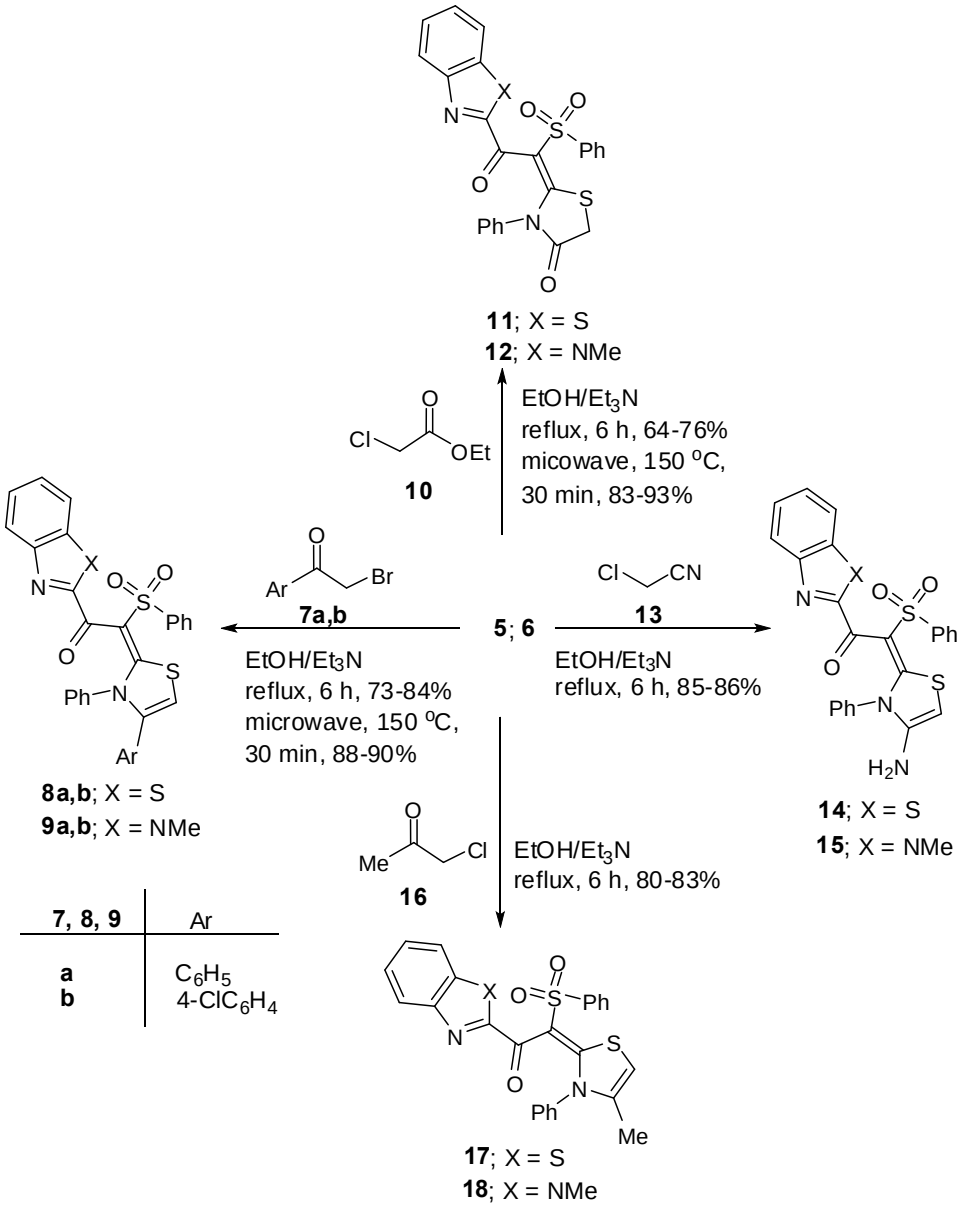


Scheme 1

Compounds **5** and **6** were assigned the (*Z*) configuration which is stabilized by hydrogen bonding rather than the (*E*) configuration which could suffer from steric hindrance. Compounds **5** and **6** react with 2-bromoacetophenone (**7a**) and **2**-bromo-4′-chloroacetophenone (**7b**), in EtOH under conventional heating and under microwave conditions in the presence of an equivalent amount of triethylamine, to afford the corresponding polysubstituted thiazole derivatives **8a,b** and **9a,b**, respectively (Scheme 2). The IR spectra of the isolated products **8a** and **9a** showed strong absorption bands at 1685 and 1678 cm^{-1}, respectively

due to carbonyl functions. The ^{1}H NMR spectra of **8a** and **9a** revealed in each case a characteristic singlet signal near δ 6.65 due to thiazole proton. Their mass spectra showed, in each case, a peak corresponding to the molecular ion (see Experimental Section).

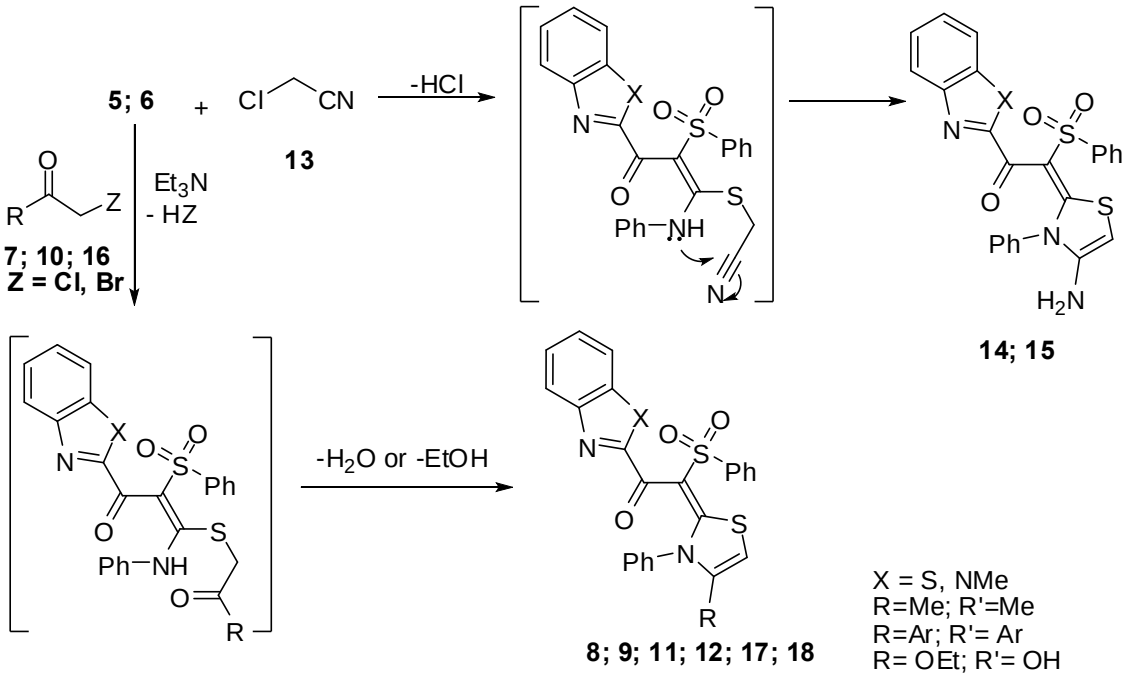
Similarly, compounds **5** and **6** reacted with ethyl chloroacetate to afford, in each case, a single product identified as (*Z*)-2-(2-(benzothiazol-2-yl)-2-oxo-1-(phenylsulphonyl)ethylidene)-3-phenylthiazolidin-4-one (**11**) and (*Z*)-2-(2-(1-methylbenzimiazol-2-yl)-2-oxo-1-(phenylsulphonyl)ethylidene)-3-phenyl-thiazolidin-4-one (**12**), respectively (Scheme 2). The ^{1}H NMR spectra of isolated products revealed multiplet signals in the range δ 7.21-8.14 and 7.20-7.94, respectively characteristic for aromatic protons. Their IR spectra showed bands at 1695, 1655 cm^{-1} for compound **11** and at 1678, and 1635 cm^{-1} for compound **12**, due to two carbonyl functions. The mass spectra of the reaction products revealed, in each case, a peak corresponding to the molecular ion.



Scheme 2

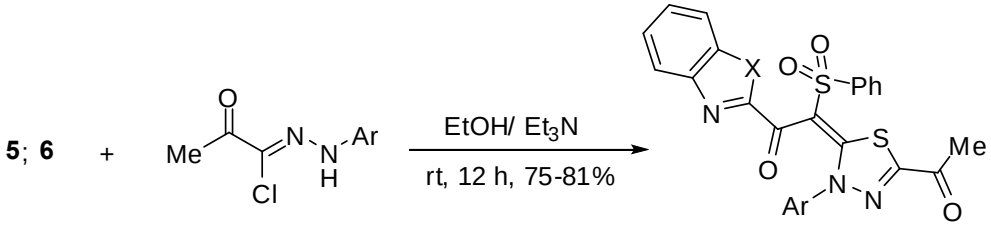
In a similar manner, compounds **5** and **6** reacted with chloroacetonitrile and with chloroacetone to afford the products identified as (*Z*)-2-(4-amino-3-phenylthiazol2-(3*H*)-ylidene-1-(benzothiazol-2-yl)-2-(phenylsulfonyl)ethanone (**14**), (*Z*)-2-(4-amino-3-phenylthiazol-2-(3*H*)-ylidene-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (**15**), (*Z*)-1-(benzothiazol-2-yl)-2-(4-methyl-3-phenylthiazol-2-(3*H*)-ylidene)-2-phenylsulphonyl)ethanone (**17**) and (*Z*)-1-(benzimidazol-2-yl)-2-(4-methyl-3-phenylthiazol-2-(3*H*)ylidene)-2-(phenylsulphonyl)ethanone (**18**), respectively (Scheme 2). The IR spectra of the isolated products **14** and **15**, revealed, in each case, bands near 3331 and 3325 cm^{-1} due to NH_2 group. The ^1H NMR spectrum of compound **17**, taken as an example, revealed singlet signals at δ 1.73 and 5.79 due to CH_3 and CH-thiazole ring protons, respectively and a multiplet signal in region δ 6.91-8.14 due to aromatic protons.

A plausible mechanism illustrating the formation of compounds **8**, **9**, **11**, **12**, **14**, **15**, **17** and **18** is depicted in Scheme 3.



Scheme 3

Treatment of compounds **5** and **6** with 2-oxo-*N*-arylpropanehydrazonyl chlorides **19a-d**, afforded in each case, only one isolable product (as examined by TLC) (Scheme 4). The elemental analyses and spectral data of the reaction products were in complete agreement with the 1,3,4-thiadiazole structures **20a-d** and **21a-d**. For example, the IR spectra of the isolated products revealed, in each case, the appearance of the carbonyl absorption bands near 1675, 1645 cm^{-1} for compounds **20a-d** and 1665, 1625 cm^{-1} in case of compounds **21a-d**. Their mass spectra revealed, in each case, a peak corresponding to the molecular ion.



19a-d

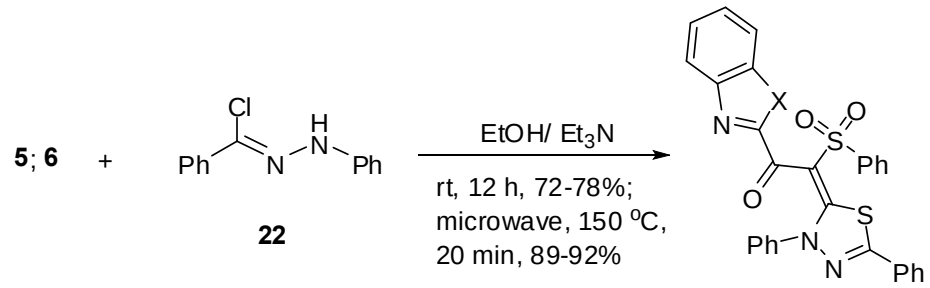
20a-d; X = S

21a-d; X = NMe

19, 20, 21	Ar
a	C_6H_5
b	4-MeC_6H_4
c	4-ClC_6H_4
d	4-$OMeC_6H_4$

Scheme 4

When compounds **5** and **6** were treated with *N*-phenylbenzohydrazonyl chloride (**22**) they afforded the corresponding (*Z*)-1-(benzothiazol-2-yl)-2-(3,5-diphenyl-1,3,4-thiadiazole-2-(3*H*)ylidene)-2-(phenylsulfonyl)ethanone (**23**) and (*Z*)-2-(3,5-diphenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (**24**), respectively (Scheme 5).



22

23; X = S

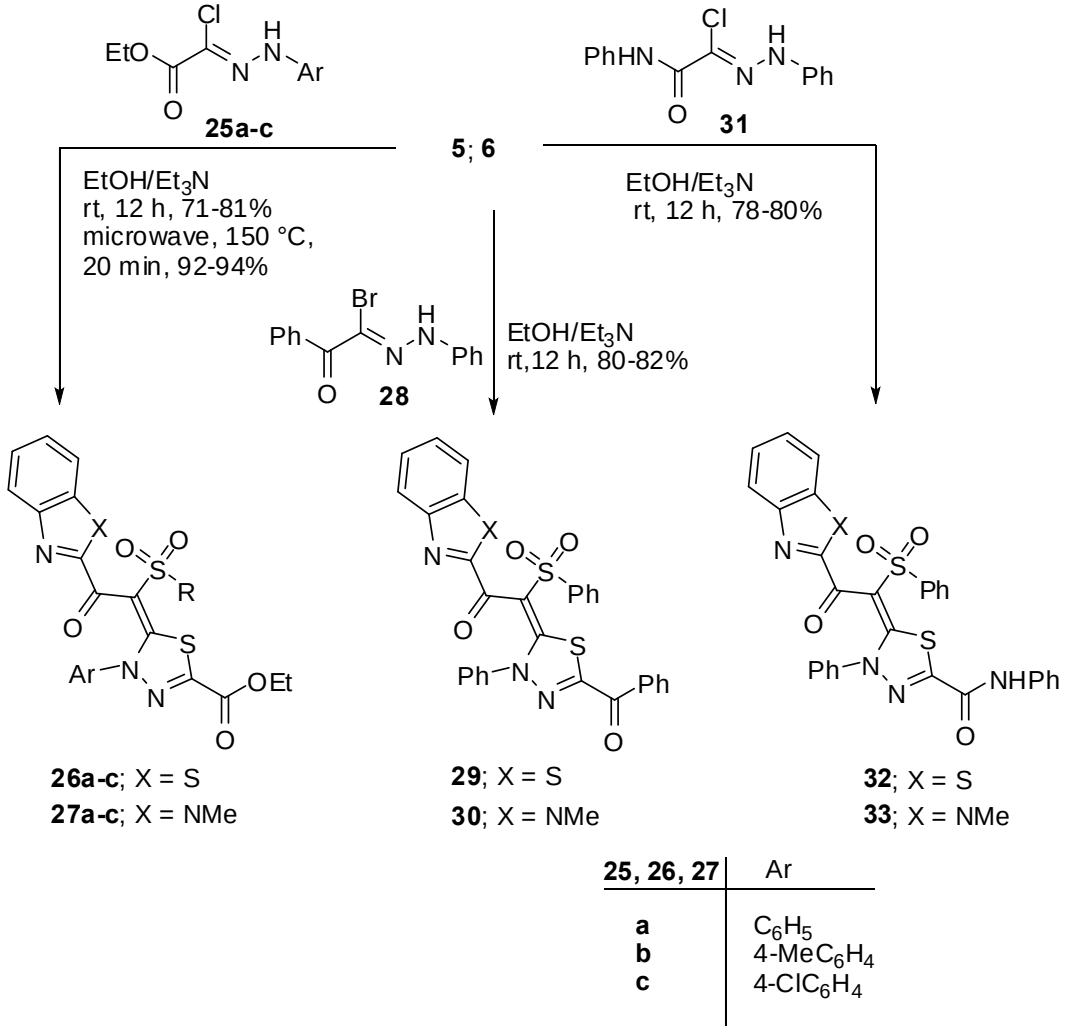
24; X = NMe

Scheme 5

In a similar manner, compounds **5** and **6** react with the hydrazonyl halides **25a-c**, under the same reaction conditions, to afford, in each case, a single product. The isolated products were identified as (*Z*)-ethyl 4-aryl-5-(2-(benzothiazol-2-yl)-2-oxo-1-((phenylsulfonyl)ethylidene)-4,5-dihyro-1,3,4-thiadiazole-2-carboxylate derivatives **26a-c**, and (*Z*)-ethyl 4-aryl-5-(2-(1-methylbenzimidazol-2-yl)-2-oxo-1-((phenylsulfonyl)ethylidene)-4,5-dihyro-1,3,4-thiadiazole-2-carboxylate derivatives **27a-c**, respectively (Scheme 6). The structures of the reaction products were confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectra of the isolated products revealed, in each case, the appearance of two strong carbonyl absorption bands near 1680 and 1654 cm^{-1}. Their mass spectra revealed, in each case, a peak corresponding to the molecular ion (see Experimental Section).

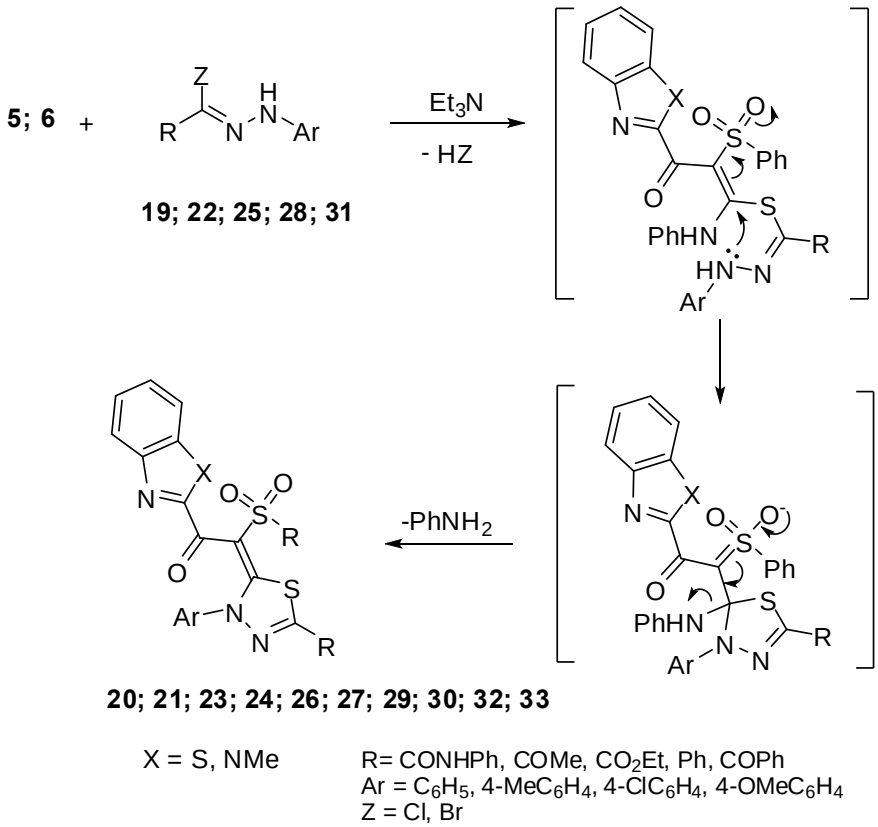
Compounds **5** and **6** reacted also with the hydrazonyl halides **28** and **31** and afforded the corresponding (*Z*)-1-(benzothiazol-2-yl)-2-(5-benzoyl-3-phenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-2-(phenylsulfonyl)-

ethanone (**29**), (*Z*)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(5-benzoyl-3-phenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-2-(phenylsulfonyl)ethanone (**30**), (*Z*)-5-(2-(benzothiazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*N*-4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (**32**) and (*Z*)-5-(2-(1-methyl-1*H*-benzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*N*-4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (**33**), respectively (Scheme 6). The IR spectra of the isolated products **32** and **33** revealed, in each case, an absorption band near 3395 cm^{-1} due to NH function. The ^1H NMR spectrum of compound **32** showed, in addition to aromatic proton multiplet in the region 6.80-8.15 ppm, a D_2O- exchangeable signal at 10.60 ppm due to NH proton



Scheme 6

A general reasonable mechanism for the reaction of compounds **5** and **6** with the hydrazonyl halides **19a-d**, **22**, **25a-c**, **28** and **31** leading to the formation of the products **20**, **21**, **23**, **24**, **26**, **27**, **29**, **30**, **32** and **33** is shown in Scheme 7.



Scheme 7

EXPERIMENTAL

Melting points were determined in open glass capillaries with a Gallenkamp apparatus. The IR spectra were recorded using KBr disks on a Pye Unicam SP 3-300 or a Shimadzu FTIR 8101 PC IR spectrophotometer. The NMR spectra were recorded with a Varian Mercury VXR-300 NMR spectrometer at 300 and 75 MHz for ^{1}H and ^{13}C NMR spectra, respectively, using $CDCl_3$ and DMSO-*d6* as solvents. Chemical shifts were related to that of the solvent. Mass spectra (EI) were obtained at 70 eV with a Shimadzu GCMQP 1000 EX spectrometer. TLC analyses were performed using pre-coated silica gel 60778 plates (Fluka), and the spots were visualized with UV light at 254 nm. Fluka silica gel 60741 (70–230 mesh) was used for flash column chromatography. Microwave experiments were carried out using a CEM Discover LabMate microwave apparatus (300 W with ChemDriver Software).

1-(Benzothiazol-2-yl)-2-(phenylsulfonyl)ethanone (**1**) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (**2**) were prepared according to our reported procedure.[46]

Reaction of 1-(benzothiazol-2-yl)-2-(phenylsulfonyl)ethanone (1) and 1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (2) with phenyl isothiocyanate.

General procedure:

To a stirred solution of KOH (0.56 g, 10 mmol) in DMF (20 mL), the appropriate ketosulfone **1** or **2** (l0

mmol) was added. After stirring for 30 min, phenyl isothiocyanate (1.35 g, 10 mmol) was added to the resulting mixture. Stirring was continued for 6 h, then poured over crushed ice containing HCl. The formed solid product was filtered off, washed with water, dried and finally recrystallized from EtOH/DMF to afford 1-(benzothiazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulphonylprop-2-en-1-one **(5)** and 1-(1-methylbenzimidazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulphonylprop-2-en-1-one (**6)**, respectively.

(*Z*)-1-(Benzothiazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulfonylprop-2-en-1-one (5): Yield (60%), mp 113-115 °C; IR (KBr) ν_{max}/cm^{-1}: 3345 (NH), 2580 (SH), 1685 (CO); ^{1}H NMR (DMSO-d_6) δ 4.21 (s, 1H, D_2O-exchangable, NH), 6.57-8.14 (m, 14H, ArH), 11.3 (s, 1H, D_2O-exchangable, SH); MS (*m/z*, %): 452 (M^+, 100%); Anal. Calcd for $C_{22}H_{16}N_2O_3S_3$ (452.57): C, 58.39; H, 3.56; N, 6.19; S, 21.26%. Found: C, 58.43; H, 3.49; N, 6.12; S, 21.19%.

(*Z*)-1-(1-Methylbenzimidazol-2-yl)-3-mercapto-3-phenylamino-3-phenylsulphonylprop-2-en-1-one (6): Yield (54%), mp 117-119 °C; IR (KBr) ν_{max}/cm^{-1}: 3346 (NH), 2570 (SH), 1680 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 4.21 (s, 1H, D_2O-exchangable, NH), 6.39-7.93 (m, 14H, ArH), 11.3 (s, 1H, D_2O-exchangable, SH); MS (*m/z*, %): 449 (M^+, 100%); Anal. Calcd for $C_{23}H_{19}N_3O_3S_2$ (449.55): C, 61.45; H, 4.26; N, 9.35; S, 14.27%. Found: C, 61.43; H, 4.29; N, 9.31; S, 14.30%.

Reaction of compounds 5 and 6 with α-haloketones 7a,**b**, **ethyl bromoacetate, chloroacetonitrile and chloroacetone.**

(A) Thermal method

General procedure:

To a solution of compounds **5** and **6** (1 mmol) and the appropriate α-haloketones **7**, ethyl chloroacetate, chloroacetonitrile or chloroacetone (1 mmol), in EtOH (20 mL), was added triethylamine (0.5 mL). The reaction mixture was refluxed for 6 h, and then allowed to cool. The formed solid product was filtered off, washed with EtOH, dried and finally recrystallized from DMF/H_2O to afford the corresponding thiazole derivatives **8a**,**b**, **9a**,**b**, **11**, **12**, **14**, **15**, **17** and **18**, respectively.

(B) Microwave method (MW)

General procedure:

An ethanolic mixture of compounds **5** or **6** (1 mmol) and the appropriate α-haloketones **7**, ethyl chloroacetate, chloroacetonitrile or chloroacetone (1 mmol) and few drops of triethylamine were added in a process vial. The vial was capped properly and irradiated with microwave under pressurized conditions (17.2 bars, 150 °C) for 30 min. The reaction mixture was evaporated under reduced pressure and residual solid was taken in ethanol then collected by filtration, washed with ethanol, dried and finally recrystallized from the proper solvent to afford the products **8a**, **9a**, **11** and **12**, respectively.

(*Z*)-1-(Benzothiazol-2-yl)-2-(3,4-diphenylthiazol-2-(3*H*)-ylidene)-2(phenylsulfonyl)ethanone (8a):

Yield: 88% (microwave); 73% (thermal), mp 170-172 °C; IR (KBr) ν_{max}/cm^{-1}: 1685 (CO); ^{1}H NMR (DMSO-d_6) δ 6.65 (s, 1H, thiazol-5-CH), 6.86-8.14 (m, 19H, ArH); ^{13}C NMR (DMSO-d_6) δ 107.11, 118.80, 120.95, 121.60, 124.15, 124.28, 125.27, 128.09, 128.45, 128.51, 128.76, 129.33, 129.80, 129.84, 131.16, 133.43, 137.23, 137.49, 142.19, 144.20, 155.10, 156.54, 162.69, 182.37; MS (*m/z*, %): 552 (M$^+$, 100%); Anal. Calcd for $C_{30}H_{20}N_2O_3S_3$ (552.69): C, 65.19; H, 3.65; N, 5.07; S, 17.40%. Found: C, 65.23; H, 3.59; N, 5.01; S, 17.31%.

(*Z*)-1-(Benzothiazol-2-yl)-2-(4-(4-chlorophenyl)(3-phenyl)thiazol-2-(3H)-ylidene)-2-(phenylsulfonyl)-ethanone (8b): Yield (84%), mp 179-181 °C; IR (KBr) ν_{max}/cm^{-1}: 1695 (CO); ^{1}H NMR (DMSO-d_6) δ 6.65 (s, 1H, thiazole-5-H), 6.83-8.14 (m, 18H, ArH); MS (*m/z*, %): 586 (M$^+$); Anal. Calcd for $C_{30}H_{19}ClN_2O_3S_3$ (587.13): C, 61.37; H, 3.26; N, 4.77; S, 16.38%. Found: C, 61.33; H, 3.23; N, 4.69; S, 16.34%.

(*Z*)-1-(1-Methylbenzimidazol-2-yl)-2-(3,4-diphenylthiazol-2-(3*H*)-ylidene)-2-(phenylsulfonyl)-ethanone (9a): Yield: 90% (microwave); 75% (thermal), mp 190-192 °C; IR (KBr) ν_{max}/cm^{-1}: 1678 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH3), 6.65 (s, 1H, thiazole-5- CH), 7.20-7.97 (m, 19H, ArH); ^{13}C NMR (DMSO-d_6) δ 32.11, 107.16, 113.29, 114.87, 118.80, 120.95, 121.60, 122.71, 124.15, 124.28, 125.27, 128.09, 128.45, 128.51, 128.76, 129.33, 129.80,129.84, 131.16, 133.43, 134.53, 137.49, 139.11, 142.19, 144.20, 156.57, 182.30; MS (*m/z*, %): 549 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{23}N_3O_3S_2$ (549.66): C, 67.74; H, 4.22; N, 7.64; S, 11.67%. Found: C, 67.71; H, 4.19; N, 7.69; S, 11.73%.

(*Z*)-2-(4-(4-Chlorophenyl)-3-phenylthiazol-2-(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (9b): Yield (84%), mp 188-190 °C; IR (KBr) ν_{max}/cm^{-1}: 1681 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.65 (s, 1H, thiazole-5-H), 6.93-7.94 (m, 18H, ArH); MS (*m/z*, %): 584 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{22}ClN_3O_3S_2$ (584.11): C, 63.74; H, 3.80; N, 7.19; S, 10.98%. Found: C, 63.69; H, 3.76; N, 7.13; S, 10.91%.

(*Z*)-2-(2-(Benzothiazol-2-yl)-2-oxo-1-(phenylsulphonyl)ethylidene)-3-phenylthiazolidin-4-one (11): Yield: 93% (microwave); 76% (thermal), mp 236-238 °C; IR (KBr) ν_{max}/cm^{-1}: 1695 and 1655 (CO); ^{1}H NMR (DMSO-d_6) δ 4.11 (s, 2H, thiazole-5-H), 7.21-8.14 (m, 14H, ArH); MS (*m/z*, %): 492 (M$^+$, 100%); Anal. Calcd for $C_{24}H_{16}N_2O_4S_3$ (492.59): C, 58.52; H, 3.27; N, 5.69; S, 19.53%. Found: C, 58.50; H, 3.23; N, 5.75; S, 19.54%.

(*Z*)-2-(2-(1-Methylbenzimiazol-2-yl)-2-oxo-1-(phenylsulphonyl)ethylidene)-3-phenylthiazolidin-4-one (12): Yield: 83% (microwave); 64% (thermal), mp 200-202 °C; IR (KBr) ν_{max}/cm^{-1}: 1678 and 1635 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3) 4.11 (s, 2H, thiazole-5-CH), 7.20-7.94 (m, 14H, ArH); MS (*m/z*, %): 489 (M$^+$, 100%); Anal. Calcd for $C_{25}H_{19}N_3O_4S_2$ (489.57): C, 61.33; H, 3.91; N, 8.58; S, 13.10%. Found: C, 61.24; H, 3.95; N, 8.60; S, 13.11%.

(*Z*)-2-(4-Amino-3-phenylthiazol-2-(3*H*)-ylidene-1-(benzothiazo-2-yl)-2-(phenylsulfonyl)ethanone (14): Yield (85%), mp 282-284 °C; IR (KBr) ν_{max}/cm^{-1}: 3331 (NH_2), 1640 (CO); ^{1}H NMR (DMSO-d_6) δ 5.20 (s, 2H, NH_2), 5.76 (s, 1H, thiazole-5-CH), 6.91-8.14 (m, 14H, ArH); MS (*m/z*, %): 491 (M^+, 100%); Anal. Calcd for $C_{24}H_{17}N_3O_3S_3$ (491.61): C, 58.64; H, 3.49; N, 8.55; S, 19.57%. Found: C, 58.68; H, 3.45; N, 8.48; S, 19.50%.

(*Z*)-2-(4-Amino-3-phenylthiazol-2-(3*H*)-ylidene-1-(1-methylbenzimidazo-2-yl)-2-(phenylsulfonyl)-ethanone (15): Yield (85%), mp 246-248 °C; IR (KBr) ν_{max}/cm^{-1}: 3325 (NH_2), 1635 (CO); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 5.20 (s, 2H, D_2O-exchange, NH_2), 5.76 (s, 1H, thiazole-5-CH), 6.91-7.83 (m, 14H, ArH); MS (*m/z*, %): 488 (M^+, 100%); Anal. Calcd for $C_{25}H_{20}N_4O_3S_2$ (488.58): C, 61.46; H, 4.13; N, 11.47; S, 13.13%. Found: C, 61.43; H, 4.16; N, 11.49; S, 13.11%.

(*Z*)-1-(Benzothiazol-2-yl)-2-(4-methyl-3-phenylthiazol-2-(3*H*)ylidene-2-(phenylsulphonyl)ethanone (17): Yield (80%), mp 181-183 °C; IR (KBr) ν_{max}/cm^{-1}: 1638 (CO); ^{1}H NMR (DMSO-d_6) δ 1.73 (s, 3H, CH_3), 5.79 (s, 1H, thiazole-5-CH), 6.91-8.14 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6) δ 20.05, 107.15, 118.76, 121.00, 121.64, 124.23, 124.32, 125.28, 128.81, 129.27, 129.83, 131.11, 133.54, 137.26, 139.03, 142.30, 144.65, 155.29, 156.55, 162.71, 182.28; MS (*m/z*, %): 490 (M^+, 100%); Anal. Calcd for $C_{25}H_{18}N_2O_3S_3$ (490.62): C, 61.20; H, 3.70; N, 5.71; S, 19.61%. Found: C, 61.13; H, 3.64; N, 5.65; S, 19.55%.

(*Z*)-1-Methyl-(benzimidazol-2-yl)-2-(4-methyl-3-phenylthiazol-2-(3*H*)-ylidene)-2-(phenylsulphonyl)-ethanone (18): Yield (83%), mp 170-172 °C; IR (KBr) ν_{max}/cm^{-1}: 1636 (CO); ^{1}H NMR (DMSO-d_6) δ 1.71 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 5.79 (s, 1H, thiazole-5-CH), 6.35-7.83 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6) δ 19.87, 32.12, 107.16, 113.29, 114.87, 118.80, 121.60, 124.15, 124.28, 125.27, 128.51, 129.33, 129.80, 131.16, 133.40, 134.42, 137.53, 139.15, 142.11, 144.20, 156.55, 182.30; MS (*m/z*, %): 487 (M^+, 100%); Anal. Calcd for $C_{26}H_{21}N_3O_3S_2$ (487.59): C, 64.04; H, 4.34; N, 8.62; S, 13.15%. Found: C, 64.09; H, 4.28; N, 8.59; S, 13.09%.

Reaction of compounds 5 and 6 with hydrazonyl halides 19a-d, 22, 25a-c, 28 and 31.

(A) Thermal method

General procedure:

To a mixture of compounds **5** or **6** (1 mmol) in EtOH (20 mL), triethylamine (0.5 mL), the appropriate hydrazonyl halide **19a-d**, **22**, **25a-c**, **28** or **31** (1 mmol) was added portion wise over a period of 30 min. The reaction mixture was stirred at room temperature for 12 h, during which hydrazonyl halide went into solution and a yellowish-red colored product precipitated. The solid product was filtered off, washed with water, dried and finally recrystallized from EtOH/DMF to afford the corresponding 1,3,4-thiadiazole

derivatives **20a-d**, **21a-d**, **23**, **24**, **26a-c**, **27a-c**, **29**, **30**, **32** and **33**, respectively**.**

(B) Microwave method

General procedure:

To a mixture of compounds **5** or **6** (1 mmol) and the appropriate hydrazonyl halide **22** or **25a** (1 mmol) few drops of triethylamine were added in a process vial. The vial was capped properly and irradiated by microwave under pressurized conditions (17.2 bars, 150 ^{o}C) for 20 min. A yellowish-red colored product was formed. The solid product was filtered off, washed with water, dried and recrystallized from EtOH/DMF to afford the corresponding 1,3,4-thiadiazole derivatives **23**, **24**, **26a** and **27a**, respectively.

(*Z*)-2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2-(3*H*)-ylidene)-1-(benzothiazol-2-yl)-2-(phenylsulphonyl)-ethanone (20a): Yield (81%), mp 210-212 °C; IR (KBr) ν_{max}/cm^{-1}: 1675, 1645 (CO), 1598 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 7.23-8.14 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6) δ 24.7, 102.35, 114.33, 118.71, 119.79, 122.53, 123.43, 124.18, 126.93, 127.23, 128.63, 129.52, 132.98, 136.55, 142.54, 143.74, 152.02, 151.32, 155.50, 182.34, 192.87; MS (*m/z*, %): 519 (M^{+}, 100%); Anal. Calcd for $C_{25}H_{17}N_3O_4S_3$ (519.62): C, 57.79; H, 3.30; N, 8.09; S, 18.51%. Found: C, 57.71; H, 3.23; N, 8.00; S, 18.44%.

(*Z*)-2-(5-Acetyl-3-*p*-tolyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1(benzothiazol-2-yl)-2-(phenylsulfonyl)-ethanone (20b): Yield (76%), mp 258-260 °C; IR (KBr) ν_{max}/cm^{-1}: 1675, 1637 (CO), 1606 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.42 (s, 3H, CH_3) 7.23-8.14 (m, 13H, ArH); MS (*m/z*, %): 533 (M^{+}, 100%); Anal. Calcd for $C_{26}H_{19}N_3O_4S_3$ (533.64): C, 58.52; H, 3.59; N, 7.87; S, 18.03%. Found: C, 58.47; H, 3.51; N, 7.80; S, 17.98%.

(*Z*)-2-(5-Acetyl-3-(4-chlorophenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(benzothiazol-2-yl)-2-(phenyl-sulfonyl)ethanone (20c): Yield (78%), mp 228-230 °C; IR (KBr) ν_{max}/cm^{-1}: 1673, 1642 (CO), 1603 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 7.34-8.14 (m, 13H, ArH); MS (*m/z*, %): 553 (M^{+}, 100%); Anal. Calcd for $C_{25}H_{16}ClN_3O_4S_3$ (554.06): C, 54.19; H, 2.91; N, 7.58; S, 17.36%. Found: C, 54.11; H, 2.87; N, 7.53; S, 17.29%.

(*Z*)-2-(5-Acetyl-3-(4-methoxyphenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(benzothiazol-2-yl)-2-(phenylsulfonyl)ethanone (20d): Yield (73%), mp 186-188 °C; IR (KBr) ν_{max}/cm^{-1}: 1671, 1645 (CO), 1596 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.14-8.13 (m, 13H, ArH); MS (*m/z*, %): 549 (M^{+}, 100%); Anal. Calcd for $C_{26}H_{19}N_3O_5S_3$ (549.64): C, 56.81; H, 3.48; N, 7.65; S, 17.50%. Found: C, 56.78; H, 3.41; N, 7.57; S, 17.48%.

(*Z*)-2-(5-Acetyl-3-phenyl-1,3,4-thiadiazol-2-(3*H*)-ylidene)1-(1-methylbenzimidazol-2-yl-)-2-(phenylsulphonyl)ethanone (21a): Yield (79%), mp 202-204 °C; IR (KBr) ν_{max}/cm^{-1}: 1665, 1625 (CO), 1588 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.67-7.79 (m, 14H, ArH);

MS (*m/z*, %): 516 (M^+, 100%); Anal. Calcd for $C_{26}H_{20}N_4O_4S_2$ (516.59): C, 60.45; H, 3.90; N, 10.85; S, 12.41%. Found: C, 60.36; H, 3.86; N, 10.78; S, 12.37%.

(*Z*)-2-(5-Acetyl-3-*p*-tolyl-1,3,4-thiadiazol2(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (21b): Yield (75%), mp 210-212 °C; IR (KBr) ν_{max}/cm^{-1}: 1667, 1623 (CO), 1597 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 6.98-7.89 (m, 13H, ArH); MS (*m/z*, %): 530 (M^+, 100%); Anal. Calcd for $C_{27}H_{22}N_4O_4S_2$ (530.62): C, 61.12; H, 4.18; N, 10.56; S, 12.09%. Found: C, 61.06; H, 4.08; N, 10.49; S, 12.02%.

(*Z*)-2-(5-Acetyl-3-(4-chlorophenyl)1,3,4thiadiazol-2(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (21c): Yield (80%), mp 296-298 °C; IR (KBr) ν_{max}/cm^{-1}: 1666, 1630 (CO), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 7.11-7.99 (m, 13H, ArH); ^{13}C NMR (DMSO-d_6): δ 24.74, 32.07, 106.62, 111.73, 114.32, 121.43, 123.95, 126.45, 127.94, 129.23, 129.43, 134.02, 137.06, 139.41, 140.82, 142.31, 145.22, 146.31, 153.37, 160.05, 182.34, 190.53; MS (*m/z*, %): 550 (M^+, 100%); Anal. Calcd for $C_{26}H_{19}ClN_4O_4S_2$ (551.04): C, 56.67; H, 3.48; N, 10.17; S, 11.64%. Found: C, 56.70; H, 3.46; N, 10.13; S, 11.71%.

(*Z*)-2-(5-Acetyl-3-(4-methoxyphenyl)1,3,4-thiadiazol-2(3*H*)-ylidene)-1-(1-methylbenzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (21d): Yield (80%), mp 181-183 °C; IR (KBr) ν_{max}/cm^{-1}: 1664, 1627 (CO), 1593 (C=N); ^{1}H NMR (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.02 (s, 3H, NCH_3), 6.84-7.99 (m, 13H, ArH); MS (*m/z*, %): 546 (M^+, 100%); Anal. Calcd for $C_{27}H_{22}N_4O_5S_2$ (546.62): C, 59.33; H, 4.06; N, 10.25; S, 11.73%. Found: C, 59.24; H, 4.00; N, 10.17; S, 11.67%.

(*Z*)-1-(Benzothiazol-2-yl)-2-(3,5-diphenyl-1,3,4-thiadiazole-2-(3*H*)ylidene)-2-(phenylsulfonyl)ethanone (23): Yield: 89% (microwave); 72% (thermal), mp 254-256 °C; IR (KBr) ν_{max}/cm^{-1}: 1665 (CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.80-8.14 (m, 19H, ArH); MS (*m/z*, %): 553 (M^+, 100%); Anal. Calcd for $C_{29}H_{19}N_3O_3S_3$ (553.67): C, 62.91; H, 3.46; N, 7.59; S, 17.37%. Found: C, 62.86; H, 3.39; N, 7.50; S, 17.28%.

(*Z*)-2-(3,5-Diphenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (24): Yield: 92% (microwave); 78% (thermal), mp 188-190 °C; IR (KBr) ν_{max}/cm^{-1}: 1661 (CO), 1595 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.80-7.92 (m, 19H, ArH); MS (*m/z*, %): 550 (M^+, 100%); Anal. Calcd for $C_{30}H_{22}N_4O_3S_2$ (550.65): C, 65.44; H, 4.03; N, 10.17; S, 11.65%. Found: C, 65.45; H, 3.97; N, 10.11; S, 11.57 %.

(*Z*)-Ethyl 5-(2-(benzothiazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-4-phenyl-4,5,di-hydro-1,3,4-thiadiazole-2-carboxylate (26a): Yield: 94% (microwave); 77% (thermal), mp 252-254 °C; IR (KBr) ν_{max}/cm^{-1}: 1680, 1654 (CO), 1598 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3) 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.80-8.14 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6) δ 14.19, 61.30, 113.25, 118.60,

118.98, 119.84, 121.91, 122.90, 124.15, 124.27, 125.32, 128.34, 129.24, 129.51, 133.40, 139.60, 143.03, 147.25, 155.11, 159.70, 162.73, 182.30; MS (*m/z*, %): 549 (M^+, 100%); Anal. Calcd for $C_{26}H_{19}N_3O_5S_3$ (549.64): C, 56.81; H, 3.48; N, 7.65; S, 17.50%. Found: C, 56.76; H, 3.41; N, 7.59 S, 17.44%.

(*Z*)-Ethyl 5-(2-(benzothiazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*p*-tolyl-4,5-di-hydro-1,3,4-thiadiazole-2-carboxylate (26b): Yield (79%), mp 249-251 °C; IR (KBr) ν_{max}/cm^{-1}: 1680, 1653 (CO), 1605 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 2.32 (s, 3H, CH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.82-8.14 (m, 13H, ArH); MS (*m/z*, %): 563 (M^+, 100%); Anal. Calcd for $C_{27}H_{21}N_3O_5S_3$ (563.67): C, 57.53; H, 3.76; N, 7.45; S, 17.07 %. Found: C, 57.45, H, 3.70; N, 7.38 S, 16.99%.

(*Z*)-Ethyl 5-(2-(benzothiazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-4-chlorophenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate (26c): Yield (81%), mp 264-266 °C; IR (KBr) ν_{max}/cm^{-1}: 1680, 1654 (CO), 1604 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.88-8.14 (m, 13H, ArH); MS (*m/z*, %): 583 (M^+, 100%); Anal. Calcd for $C_{26}H_{18}ClN_3O_5S_3$ (584.09): C, 53.46; H, 3.11; N, 7.19; S, 16.47%. Found: C, 53.37; H, 3.02; N, 7.11; S, 16.40%.

(*Z*)-Ethyl 5-(2-(1-methylbenzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*p*-phenyl-4,5,-dihydro-1,3,4-thiadiazole-2-carboxylate (27a): Yield 92% (microwave); 71% (Thermal), mp 245-247 °C; IR (KBr) ν_{max}/cm^{-1}: 1678, 1652 (CO), 1601 (C=N); ^{1}H NMR (DMSO-d_6): δ 1.25 (t, 3H, J = 7.2 Hz, CH_3), 4.02 (s, 3H, NCH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.80-7.83 (m, 14H, ArH); ^{13}C NMR (DMSO-d_6): δ 14.16, 32.19, 61.31, 113.40, 118.66, 119.07, 122.75, 122.93, 124.11, 124.30, 128.44, 128.54, 129.11, 133.60, 134.19, 138.30, 141.23, 142.12, 147.01, 155.83, 159.75, 164.11, 182.32; MS (*m/z*, %): 546 (M^+, 100%); Anal. Calcd for $C_{27}H_{22}N_4O_5S_2$ (546.62): C, 59.33; H, 4.06; N, 10.25; S, 11.73%. Found: C, 59.27; H, 4.01; N, 10.19 S, 11.68%.

(*Z*)-Ethyl 5-(2-(1-methylbenzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*p*-tolyl-4,5-dihyro-1,3,4-thiadiazole-2-carboxylate (27b): Yield (77%), mp 235-237 °C; IR (KBr) ν_{max}/cm^{-1}: 1682, 1651 (CO), 1607 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.29 (t, 3H, J = 7.2 Hz, CH_3), 2.33 (s, 3H, CH_3), 4.02 (s, 3H, NCH_3), 4.25 (q, 2H, J = 7.2 Hz, CH_2), 6.72-8.14 (m, 13H, ArH); MS (*m/z*, %): 560 (M^+, 100%); Anal. Calcd for $C_{28}H_{24}N_4O_5S_2$ (560.64): C, 59.98; H, 4.31; N, 9.99; S, 11.44%. Found: C, 59.89; H, 4.27; N, 9.90; S, 11.37%.

(*Z*)-Ethyl 4-(4-chlorophenyl)-5-(2-(1-methylbenzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)-ethylidene)-4,5-dihydro-1,3,4,thiadiazole-2-carboxylate (27c): Yield (80%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 1678, 1652 (CO), 1601 (C=N); ^{1}H NMR (DMSO-d_6) δ 1.29 (t, 3H, J = 7.2 Hz, CH_3), 4.02 (s, 3H, NCH_3), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 6.85-7.98 (m, 13H, ArH); MS (*m/z*, %): 580 (M^+, 100%); Anal. Calcd for

$C_{27}H_{21}ClN_4O_5S_2$ (581.06): C, 55.81; H, 3.64; N, 9.64; S, 11.04%. Found: C, 55.75; H, 3.56; N, 9.58; S, 10.97%.

(*Z*)-1-(Benzothiazol-2-yl)-2-(5-benzoyl-3-phenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-2-(phenylsulfonyl)ethanone (29): Yield (78%), mp 202-204 °C; IR (KBr) ν_{max}/cm^{-1}: 1670, 1652 (CO), 1609 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.89-8.14 (m, 19H, ArH); ^{13}C NMR (DMSO-d_6) δ 110.05, 118.67, 118.98, 119.84, 120.77, 121.91, 122.90, 124.15, 124.27, 125.32, 128.34, 128.63, 129.02, 129.24, 129.51, 133.40, 137.81, 139.60, 143.03, 147.25, 155.11, 162.73, 182.30, 185.19; MS (*m/z*, %): 581 (M$^+$, 100%); Anal. Calcd for $C_{30}H_{19}N_3O_4S_3$ (581.68): C, 61.94; H, 3.29; N, 7.22; S, 16.54%. Found: C, 61.88; H, 3.21; N, 7.15; S, 16.48%.

(*Z*)-2-(5-Benzoyl-3-phenyl-1,3,4-thiadiazole-2-(3*H*)-ylidene)-1-(1-methyl-1*H*-benzimidazol-2-yl)-2-(phenylsulfonyl)ethanone (30): Yield (82%), mp 212-214 °C; IR (KBr) ν_{max}/cm^{-1}: 1673, 1648 (CO), 1590 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.80-7.90 (m, 19H, ArH); MS (*m/z*, %): 578 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{22}N_4O_4S_2$ (578.66): C, 64.34; H, 3.83; N, 9.68; S, 11.08%. Found: C, 64.28; H, 3.76; N, 9.59; S, 11.00%.

(*Z*)-5-(2-(Benzothiazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*N*-4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (32): Yield (77%), mp 210-212 °C; IR (KBr) ν_{max}/cm^{-1}: 3395 (NH), 1680, 1669 (CO), 1601 (C=N); ^{1}H NMR (DMSO-d_6) δ 6.80-8.15 (m, 19H, ArH), 10.60 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-*d6*) δ 104.21, 118.89, 119.91, 120.50, 120.94, 122.72, 122.94, 124.12, 124.23, 125.29, 128.36, 128.45, 128.62, 129.29, 129.20, 133.33, 138.27, 139.41, 142.16, 147.21, 155.05, 156.32, 162.67, 182.32; MS (*m/z*, %): 596 (M$^+$, 100%); Anal. Calcd for $C_{30}H_{20}N_4O_4S_3$ (596.70): C, 60.39; H, 3.38; N, 9.39; S, 16.12%. Found: C, 60.32; H, 3.30; N, 9.29; S, 16.04%.

(*Z*)-5-(2-(1-Methyl-1*H*-benzimidazol-2-yl)-2-oxo-1-(phenylsulfonyl)ethylidene)-*N*-4-diphenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide (33): Yield (78%), mp 221-223 °C; IR (KBr) ν_{max}/cm^{-1}: 3393 (NH), 1677 (CO), 1665 **(**CO), 1600 (C=N); ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 3H, NCH_3), 6.80-7.89 (m, 19H, ArH), 10.60 (s, 1H, D_2O-exchangeable, NH); ^{13}C NMR (DMSO-*d6*) δ 32.23, 104.31, 114.68, 115.32, 120.96, 122.75, 122.93, 124.11, 124.30, 128.42, 128.61, 128.73, 129.29, 129.62, 133.68, 134.32, 137.69, 138.28, 141.18, 142.17, 147.09, 155.93, 162.71, 164.17, 182.35; MS (*m/z*, %): 593 (M$^+$, 100%); Anal. Calcd for $C_{31}H_{23}N_5O_4S_2$ (593.68): C, 62.72; H, 3.90; N, 11.80; S, 10.80%. Found: C, 62.65; H, 3.83; N, 11.70; S, 10.72%.

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