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DABCO-CATALYZED GREEN SYNTHESIS OF THIAZOLE AND 1,3-THIAZINE DERIVATIVES LINKED TO BENZOFURAN

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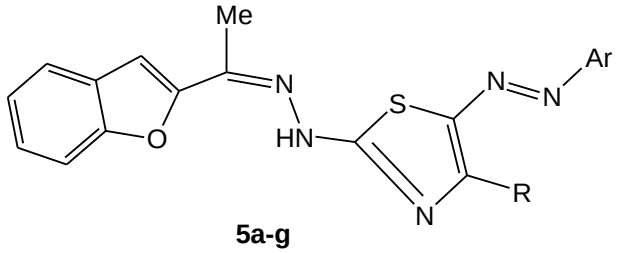
Abstract – An eco-friendly and simple procedure for the reaction of 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide with arylidenemalononitriles and hydrazonoyl halides catalyzed by using sterically hindered organic base, 1,4-diazabicyclo[2.2.2]octane (DABCO) was described. This new protocol has the advantage of good yields and short reaction times. The structure of the newly synthesized compounds was elucidated via elemental analyses and spectral data.

1,4-Diazabicyclo[2.2.2]octane (DABCO), a cage-like compound, is a small diazabicyclic molecule with weak alkalescence, medium-hindrance. It has been widely used in organic reactions and can serve as a weak base and ligand. DABCO is also used to adjust pH of the oxygen-sensitive resin to regulate the reaction rate in Flexplay time-limited DVDs. Antioxidants, such as DABCO are used to improve the lifetime of dyes. This makes DABCO useful in dye lasers and in mounting samples for fluorescence microscopy. DABCO is quite known to be an inexpensive, eco-friendly, high reactive, easy to handle and non-toxic base catalyst for various synthetic organic protocols, affording the corresponding products in excellent yields with high selectivity. The reactions catalyzed by DABCO suffer no environmental problems and in some cases the catalyst could be recovered.[1-18] On the other hand, benzofuran derivatives are a class of fused ring heterocycles that are widely distributed in a large number of natural products and indeed occupy a characteristic site in the field of in medicinal chemistry.[19,20] Therefore, a number of naturally occurring compounds containing benzofuran moiety exhibit a considerable interesting biological and pharmacological activities.[21-24] Thiazole derivatives have been much more studied and synthesized, this is no doubt due to their wide spectra of biological behavior such as antimicrobial, antioxidant,

antitubercular, anticonvulsant, anticancer, and anti-inflammatory activities.[25–34] In addition, 1,3-thiazine derivatives play a vital and important role as medicinal active agents exhibiting a variety of biological potencies such as antimicrobial, anti-inflammatory, and anticancer agents.[35-38] The work done in this article is mostly concentrated on the use of highly reactive hydrazonoyl halides regents which have been strongly combined with different organic substrates affording a versatile number of interesting heterocycles; these reactions were actually base-catalyzed using bases as triethylamine, piperidine or chitosan.[39-44] At the meantime, the use of DABCO as a basic catalyst in such synthetic reactions never been approached. In view of these facts, we report herein the synthesis of a new series of substituted thiazoles and 1,3-thiazines bearing benzofuran moiety using sterically hindered base DABCO as an organic catalyst in short reaction times, easy workup and in good yields.

The new key precursor designed for the planned synthesis namely, 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide **2** was prepared by refluxing a mixture of 2-acetylbenzofuran **1**[45] and thiosemicarbazide in ethanol in the presence of a catalytic amount of hydrochloric acid for 6 h (Scheme 1). The structure **2** was easily established from spectral data (IR, ^{1}H NMR, and MS). For example, the IR spectrum of compound **2** revealed the stretching vibration bands at υ 3432, 3212 cm^{-1} which are assigned to the NH and NH_2 groups. Also, it lacks the carbonyl absorption band.

Table 1. Effect of different catalysts on the reaction time and yields of derivatives **5a-g**

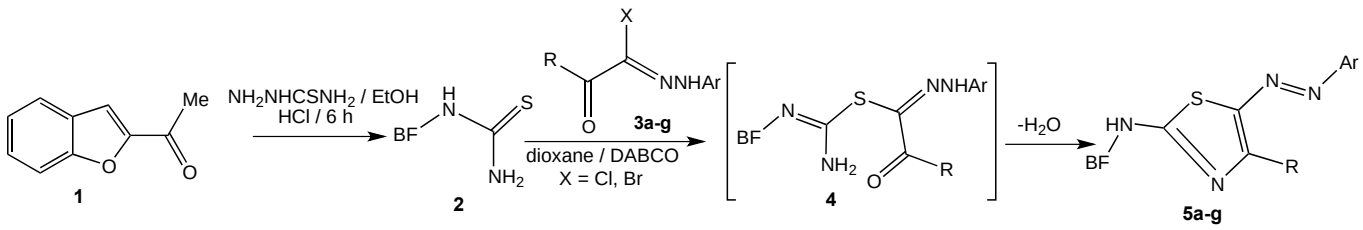


5a-g

No.	R	Ar	TEA		DABCO	
			Yield (%)	Time (h)	Yield (%)	Time (h)
5a	Me	C_6H_5	67	4	75	1.5
5b	Me	4-MeC_6H_4	69	3	79	1
5c	Me	4-MeOC_6H_4	66	4	74	1.5
5d	Me	4-ClC_6H_4	70	2.5	78	1
5e	Me	4-BrC_6H_4	71	2.5	78	1
5f	2-naphthyl	C_6H_5	69	3	76	1.5
5g	2-thienyl	C_6H_5	70	3	80	1

^{1}H NMR spectrum of compound **2** displayed two signals at δ 8.40 and 10.48 ppm most probably assigned to the NH_2 and NH protons, respectively in addition to the expected signals of the methyl and aromatic protons. The mass spectrum gave a molecular ion peak at *m/z* 233 which is consistent with the molecular formula of compound **2**. Thereafter, our study was extended to investigate the reactivity of compound **2** towards hydrazonoyl halides for the construction of novel heterocyclic compounds containing 1,3-thiazole ring. In this set of experiments, two basic catalysts namely triethylamine and DABCO were tested with the target to determine the optimum reaction conditions. The results are summarized in Table1.

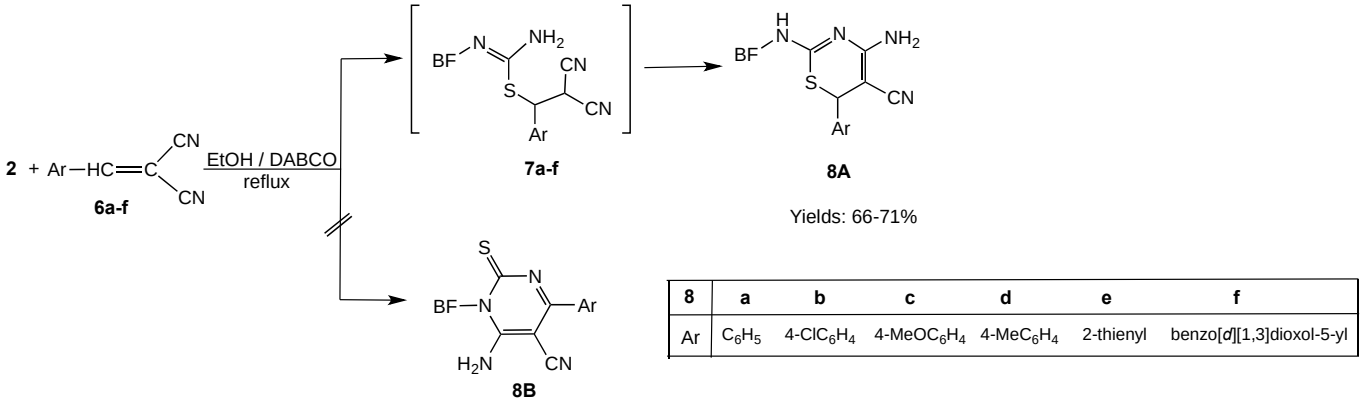
This study obviously showed that the required compounds **5a-g** (Scheme 1) were obtained in much longer reaction time (2.5-4 h) and comparatively lower yields (66-71%) by using TEA, however, the use of DABCO to catalyze the reaction has improved the yields of the products to 74-80% within time intervals of 1-1.5 h (Table 1). Thus, comparing DABCO and TEA as catalysts for the synthesis of 1,3-thiazole derivatives **5a-g** from hydrazonoyl halides, it was found that as shown from Table 1, DABCO was the best choice as a basic catalyst. The reaction proceeds smoothly with electron-rich, as well as electron-deficient substituent on aromatic benzene ring of hydrazonoyl halides **3a-g**. The structure proof of products **5** was totally dependent on elemental and spectral (IR, ^{1}H NMR, and MS) data. In the ^{1}H NMR spectra of these compounds, the most newly characteristic signals appeared due to R group which might be methyl, naphthyl or thienyl, in addition, the aromatic region showed an increment in the integration area. Also, a singlet signal around δ 10.75 ppm assigned to the -NH proton was observed. The mass spectra of all products **5** exhibited in each case, a molecular ion peak at the correct molecular weight for the respective compound (see Experimental section). A plausible explanation for the formation of products **5** could be suggested, that intermediate **4** is initially formed *via* nucleophilic attack of the thiol group of compound **2** to the electron-deficient carbon of the hydrazone group of compounds **3** which undergoes dehydrative cyclization to give the final products **5a-g.**



3,5	a	b	c	d	e	f	g
R	Me	Me	Me	Me	Me	2-naphthyl	2-naphthyl
Ar	C_6H_5	4-MeC_6H_4	4-MeOC_6H_4	4-ClC_6H_4	4-BrC_6H_4	C_6H_5	C_6H_5

Scheme 1. Synthesis of thiosemicarbazone derivative **2** and thiazoles **5a-g**

Consequently, the utility of compound **2** as building block for synthesis of extra series of expected biologically active heterocycles was explored. The nucleophilicity of the heteroatoms of compound **2** was investigated when it allowed to react with arylidenemalononitrile. Thus, reaction of compound **2** with the appropriate arylidenemalononitriles **6a-f** in absolute ethanol under reflux and in the presence of DABCO afforded in each case only one isolable product (as evidenced by TLC analysis of the crude product, 66-71%, Scheme 2). The latter products were identified to be **8A** rather than the pyrimidine derivatives **8B.** The thiazine derivatives **8A** were obtained through the addition of the more nucleophilic sulfur atom while the alternative products **8B** are probably formed when amino nitrogen is attacking nucleophile which is actually weaker than sulfur atom (Scheme 2). Data reported in literature concerning these reactions described the formation of the thiazine moiety over the pyrimidine one.[46-48] Structures of the products **8A** were elucidated on the basis of elemental and spectral data (IR, ^{1}H NMR and MS). The IR spectra showed in each case three bands around υ 3430, 3139 and 2182 cm^{-1} which are assigned to the NH, NH_2 and C≡N groups, respectively. ^{1}H NMR spectrum of product **8a**, taken as a representative example of the products **8**, displayed two signals at δ 8.39 and 10.38 ppm assigned for the NH_2 and NH protons, respectively; the expected signals assigned for the CH_3 and aromatic protons are also shown.

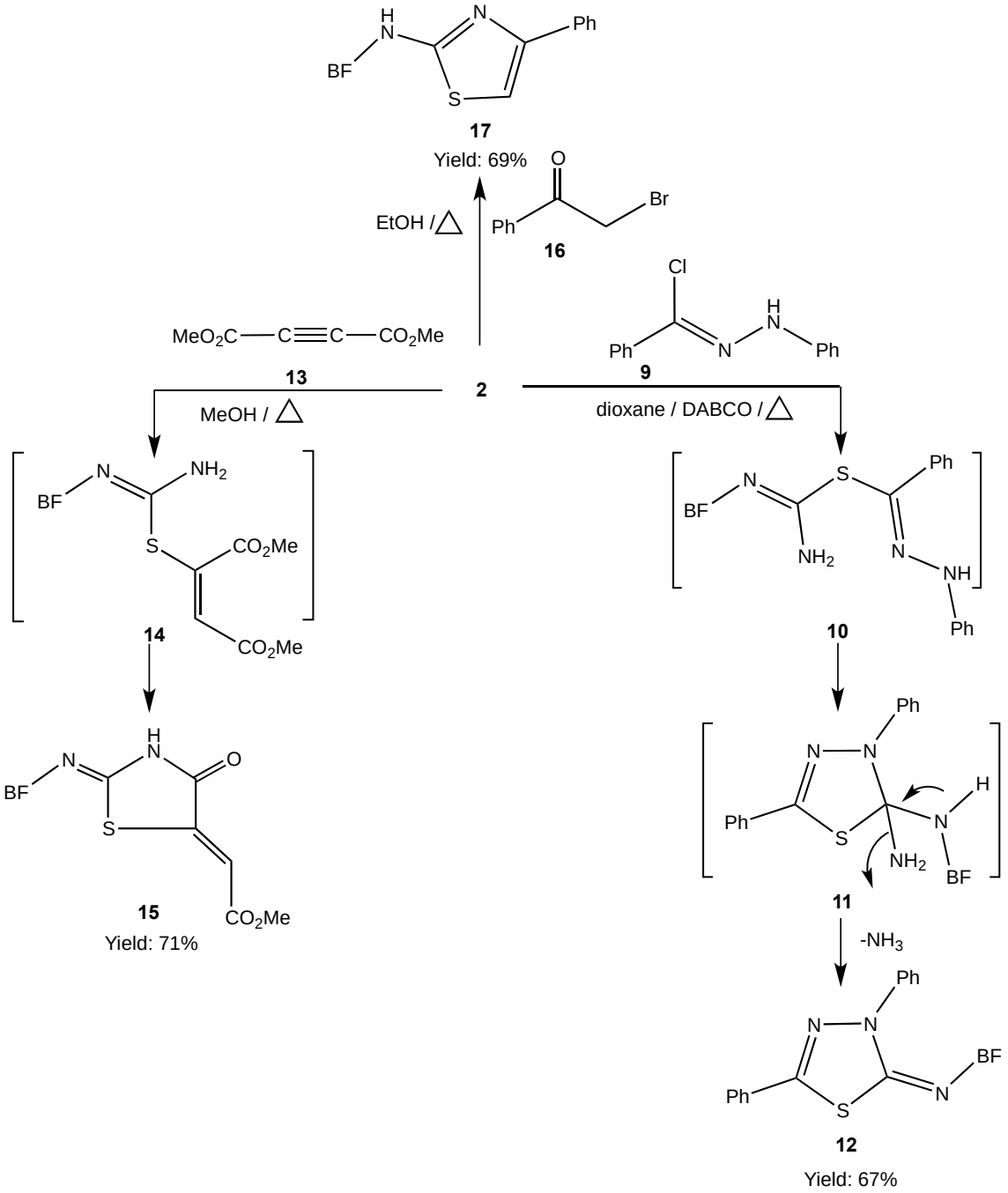


8	a	b	c	d	e	f
Ar	C_6H_5	4-ClC_6H_4	4-$MeOC_6H_4$	4-MeC_6H_4	2-thienyl	benzo[*d*][1,3]dioxol-5-yl

Scheme 2. Synthesis of 1,3-thiazines **8a-f**

In turn, we have evaluated that, the reaction of thiosemicarbazone **2** with *N*-phenylcarbohydrazonoyl chloride **9** gave 1,3,4-thiadiazole derivative **12** (67%) as the final product (Scheme 3). The reaction proceeded *via S*-alkylation, with removal of hydrogen chloride, to give *S*-alkylated intermediate **10**. Intermolecular Michael type addition of **10** under the employed reaction conditions, gave cycloadduct **11**. The final product **12** was obtained from the addition product **11** through elimination of ammonia molecule (Scheme 3). The characterization of the isolated product **12** is based on its spectral data (IR, ^{1}H NMR, and MS) and elemental analyses (see Experimental section). Furthermore, the Michael type addition aptitude of the title compound **2** to activated unsaturated compounds was more investigated; hence, the reaction of compound **2** with dimethyl acetylenedicarboxylate (DMAD) (**13**) was conducted wishing to prepare new bioactive candidates. Thus, reaction of compound **2** with DMAD in methanol

under reflux afforded product **15** (71%) *via* elimination of methanol from the non-isolable intermediate **14** (Scheme 3).



Scheme 3. Synthesis of compounds **12, 15** and **17**

The structure of compound **15** was established on the basis of its spectral data. For example, the ^{1}H NMR spectrum of product **15** revealed the presence of a singlet signal at δ 6.62 ppm assigned to the olefinic CH proton of =CH-CO_2Me group, in addition to the signals of the aromatic, methyl and ester protons (see Experimental section).Finally, more thiazole derivative could be established from reaction of ethylidenethiosemicarbazide **2** with phenacyl bromide **16** under thermal conditions in ethanol to afford

4-phenylthiazole derivative **17** (69%, Scheme 3) based on analytical and spectroscopic data (see Experimental section).

CONCLUSION

In the present paper, a simple and convenient method was developed for the synthesis of new ethylidenehydrazono-1,3-thiazines and ethylidenehydrazonothiazoles incorporating benzofuran moiety using DABCO as a catalyst which has advantages over other basic catalysts as being an ecofriendly catalyst, deliver good to excellent yields, handled safely, could be recycled and in many cases decreases the reaction times. At the same time as we mentioned before the reactions of hydrazonoyl halides with different substrates were catalyzed by TEA and in some cases chitosan was used, but this is the first time to use DABCO to catalyze these reactions.

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 or 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 that of the solvent. ^{13}C NMR was recorded at 75 MHz. 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 CHN analyzer.

Synthesis of 2-(1-(benzofuran-2-yl)ethylidene)hydrazinecarbothioamide (2). A mixture of 2-acetyl-benzofuran **1** (1.60 g, l0 mmol) and thiosemicarbazide (0.91 g, 10 mmol) in 50 mL EtOH containing catalytic amount of hydrochloric acid was refluxed for 6 h. The desired thiosemicarbazone precipitated from the reaction mixture was filtered, washed with EtOH and recrystallized from dioxane to give pure thiosemicarbazone derivative **2** as white solid (70% yield); mp 206-208 °C; IR (KBr): ν 3432, 3295, 3212 (NH_2, NH), 3035, 2987 (CH), 1599 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.23-7.83 (m, 5H, Ar-H), 8.40 (s, br, 2H, NH_2), 10.48 (s, br, 1H, NH);); ^{13}C NMR (DMSO-d_6): δ 13.4 (CH_3), 106.7, 111.3, 121.6, 123.3, 125,5, 128.1, 139.5, 153.6, 154.5 (Ar-C), 179.0 (C=S) ppm; MS *m/z* (%): 233 (M^+, 16), 202 (100), 146 (42), 105 (73), 77(79). Anal. Calcd for $C_{11}H_{11}N_3OS$ (233.06): C, 56.63; H, 4.75; N, 18.01. Found C, 56.49; H, 4.70; N, 17.92%.

Synthesis of 2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-4-methyl-5-(aryldiazenyl)thiazole (5a-g).

To a solution of the appropriate hydrazonoyl halides **3a-g** (1 mmol) in dioxane (20 mL) was added the basic catalyst DABCO (0.113 g, 1 mmol) or TEA (0.121 g, 1.2 mmol), the mixture was stirred at room temperature for 5 min, then the thiosemicarbazone **2** (0.233 g, 1 mmol) was added, the reaction was heated under reflux till the completion of the reaction as inferred from TLC (Table 1). The excess solvent was removed under reduced pressure, allowed to cool and the solid formed was filtered off, washed with water, dried and recrystallized from DMF to give the corresponding thiazoles **5a-g**.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-4-methyl-5-(phenyldiazenyl)thiazole (5a). Red solid, (75% yield); mp 143-145 °C; IR (KBr) ν 3442 (NH), 2922 (CH), 1597 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.00-7.77 (m, 10H, Ar-H), 10.75 (s, br, 1H, NH); MS, *m/z* (%) 375 (M^+, 17), 238 (43), 222 (37), 180 (50), 77 (100). Anal. Calcd for $C_{20}H_{17}N_5OS$ (375.12): C, 63.98; H, 4.56; N, 18.65. Found: C, 63.92; H, 4.45; N, 18.57%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-4-methyl-5-(*p*-tolyldiazenyl)thiazole (5b). Red solid, (79% yield); mp 137-139 °C; IR (KBr) ν 3444 (NH), 2923 (CH), 1604 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.26 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.13-7.77 (m, 9H, Ar-H), 10.69 (s, br, 1H, NH); MS, *m/z* (%) 389 (M^+, 12), 236 (46), 180 (51), 125 (49), 77 (100). Anal. Calcd for $C_{21}H_{19}N_5OS$ (389.13): C, 64.76; H, 4.92; N, 17.98. Found: C, 64.70; H, 4.84; N, 17.83%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-5-((4-methoxyphenyl)diazenyl)-4-methylthiazole (5c). Red solid, (74% yield); mp 133-135 °C; IR (KBr) ν 3432 (NH), 2916 (CH), 1595 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.49 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.92-7.62 (m, 9H, Ar-H),10.69 (s, br, 1H, NH); MS, *m/z* (%) 405 (M^+, 9), 301 (56), 225 (37), 180 (44), 77 (100). Anal. Calcd for $C_{21}H_{19}N_5O_2S$ (405.13): C, 62.21; H, 4.72; N, 17.27. Found: C, 62.15; H, 4.66; N, 17.08%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-5-((4-chlorophenyl)diazenyl)-4-methylthiazole (5d). Dark red solid, (78% yield); mp 160-162 °C; IR (KBr) ν 3439 (NH), 2923 (CH), 1597 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 7.02-7.89 (m, 9H, Ar-H), 10.82 (s, br, 1H, NH); MS, *m/z* (%) 411 (M^++2, 6), 409 (M^+, 20), 317 (37), 229 (42), 180 (100), 77 (94). Anal. Calcd for $C_{20}H_{16}ClN_5OS$ (409.08): C, 58.60; H, 3.93; N, 17.09. Found: C, 58.48; H, 3.69; N, 17.02%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-5-((4-bromophenyl)diazenyl)-4-methylthiazole (5e). Orange solid, (78% yield); mp 153-155 °C; IR (KBr) ν 3431 (NH), 2918 (CH), 1597 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.48 (s, 3H, CH_3), 2.62 (s, 3H, CH_3), 7.29-7.77 (m, 9H, Ar-H), 10.80 (s, br,

1H, NH); MS, *m/z* (%) 455 (M^+ +2, 9), 453 (M^+, 10), 372 (63), 260 (100), 180 (53), 77 (90). Anal. Calcd for $C_{20}H_{16}BrN_5OS$ (453.03): C, 52.87; H, 3.55; N, 15.41. Found: C, 52.87; H, 3.55; N, 15.41%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-4-(naphthalen-2-yl)-5-(phenyldiazenyl)thiazole (5f). Orange solid, (76% yield); mp 177-179 °C; IR (KBr) ν 3433 (NH), 2923 (CH), 1598 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 7.12-8.45 (m, 16H, Ar-H), 9.01 (s, 1H, naphthalene-H1), 10.93 (s, br, 1H, NH); MS, *m/z* (%) 455 (M^+ +2, 9), 453 (M^+, 10), 372 (63), 260 (100), 180 (53), 77 (90). Anal. Calcd for: $C_{29}H_{21}N_5OS$ (487.15): C, 71.44; H, 4.34; N, 14.36. Found: C, 71.33; H, 4.19; N, 14.18%.

2-(2-(1-(Benzofuran-2-yl)ethylidene)hydrazinyl)-5-(phenyldiazenyl)-4-(thiophen-2-yl)thiazole (5g). Red solid, (80% yield); mp 164-166 °C; IR (KBr) ν 3430 (NH), 2927 (CH), 1598 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 7.24-7.82 (m, 13H, Ar-H), 10.46 (s, br, 1H, NH); MS, *m/z* (%) 443 (M^+ , 27), 342 (68), 225 (100), 180 (57), 77 (81). Anal. Calcd for $C_{23}H_{17}N_5OS_2$ (443.09): C, 62.28; H, 3.86; N, 15.79. Found: C, 62.21; H, 3.68; N, 15.66%.

Synthesis of 1,3-thiazine derivatives 8a-f

A mixture of thiosemicarbazone **2** (0.233 g, 1 mmol) and the appropriate arylidenemalononitrile **6a-f** (1 mmol of each) in EtOH (20 mL) containing DABCO (0.113g, 1 mmol) was refluxed until all the starting material was consumed (1-2 h). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and the precipitate was filtered, washed with water, and recrystallized from dioxane to give the products **8a-f**.

4-Amino-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6-phenyl-6*H*-1,3-thiazine-5-carbonitrile (8a). Yellow solid; (67% yield); mp 224-226 °C; IR (KBr) ν 3430, 3306, 3139 (NH_2 and NH), 2180 (C≡N), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.90 (s, 1H, thiazine-H), 7.24-7.82 (m, 10H, Ar-H), 8.39 (s, br, 2H, NH_2),10.38 (s, br, 1H, NH); MS *m/z* (%): 387 (M^+, 16), 306 (52), 257 (73), 128 (100), 77 (84). Anal. Calcd for $C_{21}H_{17}N_5OS$ (387.12): C, 65.10; H, 4.42; N, 18.08. Found C, 65.03; H, 4.37; N, 17.88%.

4-Amino-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6-(4-chlorophenyl)-6*H*-1,3-thiazine-5-carbonitrile (8b). Yellow solid; (67% yield); mp 224-226 °C; IR (KBr) ν 3430, 3306, 3139 (NH_2 and NH), 2180 (C≡N), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.90 (s, 1H, thiazine-H), 7.24-7.82 (m, 9H, Ar-H), 8.39 (s, br, 2H, NH_2), 10.38 (s, br, 1H, NH); MS *m/z* (%): 387 (M^+,

16), 306 (52), 257 (73), 128 (100), 77 (84). Anal. Calcd for $C_{21}H_{16}ClN_5OS$ (421.08): C, 59.78; H, 3.82; N, 16.60. Found C, 59.71; H, 3.69; N, 16.47%.

4-Amino-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6-(4-methoxyphenyl)-6*H*-1,3-thiazine-5-carbonitrile (8c). Yellow solid; (66% yield); mp 186-188 °C; IR (KBr) ν 3424, 3305, 3142 (NH_2 and NH), 2182 (C≡N), 1591 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 1H, thiazine-H), 7.22-7.82 (m, 9H, Ar-H), 8.37 (s, br, 2H, NH_2), 10.27 (s, br, 1H, NH); MS *m/z* (%): 417 (M^+, 38), 352 (71), 225 (46), 105 (100), 77 (63). Anal. Calcd for $C_{22}H_{19}N_5O_2S$ (417.13591.68): C, 63.29; H, 4.59; N, 16.78. Found C, 63.20; H, 4.44; N, 16.68%.

4-Amino-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6-(*p*-tolyl)-6*H*-1,3-thiazine-5-carbonitrile (8d). Yellow solid; (70% yield); mp 217-219 °C; IR (KBr) ν 3430, 3305, 3138 (NH_2 and NH), 2219 (C≡N), 1589 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.90 (s, 1H, thiazine-H), 7.17-7.80 (m, 9H, Ar-H), 8.34 (s, br, 2H, NH_2), 10.38 (s, br, 1H, NH); MS *m/z* (%): 401 (M^+, 17), 364 (43), 228 (52), 105 (73), 59 (100). Anal. Calcd for $C_{22}H_{19}N_5OS$ (401.13): C, 65.81; H, 4.77; N, 17.44. Found C, 65.74; H, 4.65; N, 17.39%.

4-Amino-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6-(thiophen-2-yl)-6*H*-1,3-thiazine-5-carbonitrile (8e). Brown solid; (67% yield); mp 217-219 °C; IR (KBr) ν 3438, 3306, 3142 (NH_2 and NH), 2218 (C≡N), 1593 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.90 (s, 1H, thiazine-H), 7.24-7.82 (m, 8H, Ar-H), 8.39 (s, br, 2H, NH_2), 10.48 (s, br, 1H, NH); MS *m/z* (%): 393 (M^+, 100), 309 (65), 105 (49), 64 (61). Anal. Calcd for $C_{19}H_{15}N_5OS_2$ (393.07): C, 58.00; H, 3.84; N, 17.80. Found C, 57.93; H, 3.74; N, 17.66%.

4-Amino-6-(benzo[*d*][1,3]dioxol-5-yl)-2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-6*H*-1,3-thiazine-5-carbonitrile (8f). Yellow solid; (71% yield); mp 197-199 °C; IR (KBr) ν 3438, 3305, 3140 (NH_2 and NH), 2178 (C≡N), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.95 (s, 1H, thiazine-H), 6.18 (s, 2H, OCH_2O), 6.89-7.83 (m, 8H, Ar-H), 8.40 (s, br, 2H, NH_2), 9.90 (s, br, 1H, NH); MS *m/z* (%): 431 (M^+, 37), 372 (58), 105 (100), 59 (70). Anal. Calcd for $C_{22}H_{17}N_5O_3S$ (431.11): C, 61.24; H, 3.97; N, 16.23. Found C, 61.17; H, 3.82; N, 16.16%.

Synthesis of 2-((1-(benzofuran-2-yl)ethylidene)hydrazono)-3,5-diphenyl-2,3-dihydro-1,3,4-thiadiazole (12).

A mixture *N*-phenylbenzohydrazonoyl chloride **9** (0.230 g, 1 mmol) and DABCO (0.113g, 1 mmol) in dioxane (20 mL) was stirred at room temperature for 5 min, then thiosemicarbazone **2** (0.233 g, 1 mmol) was added and the whole mixture was refluxed for 1 h. The reaction mixture was then evaporated under reduced pressure to remove excess solvent, allowed to cool and the solid formed was filtered off, washed with water, dried and recrystallized from EtOH to give thiadiazole **12** as yellow solid; (67% yield); mp 188-190 °C; IR (KBr) ν 3056, 2919 (CH), 1598 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.43 (s, 3H, CH_3), 7.26-8.17 (m, 15H, Ar-H); MS *m/z* (%): 410 (M^+, 31), 325 (47), 272 (45), 208 (100), 77 (92). Anal. Calcd for $C_{24}H_{18}N_4OS$ (410.12): C, 70.22; H, 4.42; N, 13.65. Found C, 70.16; H, 4.37; N, 13.53%.

Synthesis of methyl 2-(2-((1-(benzofuran-2-yl)ethylidene)hydrazono)-4-oxothiazolidin-5-ylidene)-acetate (15).

A mixture of thiosemicarbazone **2** (0.233g, 1 mmol) and dimethyl acetylenedicarboxylate **13** (0.142 g, 1 mmol) in MeOH (15 mL) was refluxed for 2 h. The precipitate formed on hot was filtered, washed with MeOH, and recrystallized from DMF to give product **15** as canary yellow solid (71% yield); mp 261-263 °C; IR (KBr) ν 3435 (NH), 1697, 1616 (2C=O), 1590 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.63 (s, 3H, CH_3), 3.72 (s, 3H, $COOCH_3$), 6.62 (s, 1H, C=CH), 7.22-7.71 (m, 5H, Ar-H), 12.89 (s, br, 1H, NH); MS *m/z* (%): 343 (M^+, 30), 281 (39), 202 (42), 225 (100), 77 (63). Anal. Calcd for $C_{16}H_{13}N_3O_4S$ (343.06): C, 55.97; H, 3.82; N, 12.24. Found C, 55.79; H, 3.68; N, 12.14%.

Synthesis of 2-(2-(1-(benzofuran-2-yl)ethylidene)hydrazinyl)-4-phenylthiazole (17). To a solution of thiosemicarbazone **2** (0.233 g, 1 mmol) in EtOH (10 mL), phenacyl bromide **16** (0.197 g, 1 mmol) was added. The mixture was refluxed for 2 h then cooled to room temperature. The solid product was filtered off, washed with EtOH and recrystallized from EtOH to afford the thiazole derivative **17** as yellow solid, (69% yield); mp 180-182 °C; IR (KBr) ν 3441 (NH), 3046, 2926 (CH), 1596 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.61 (s, 3H, CH_3), 6.93-8.34 (m, 11H, Ar-H and thiazole-H5), 10.39 (s, br, 1H, NH); MS, *m/z* (%) 333 (M^+, 14), 285 (71), 180 (48), 113 (48), 77 (100). Anal. Calcd for $C_{19}H_{15}N_3OS$ (333.09): C, 68.45; H, 4.53; N, 12.60. Found: C, 68.38; H, 4.51; N, 12.49%.

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