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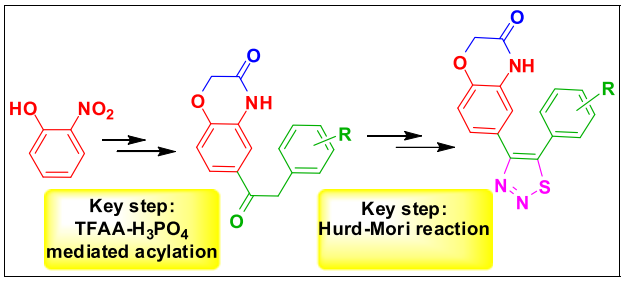

The synthesis of novel 1,2,3-thiadiazol derivatives containing 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one moiety as one of the substituents has been reported. A combined application of $H_3PO_4/(CF_3CO)_2O$ mediated acylation followed by Hurd–Mori reaction has been explored to synthesize these compounds. The scope and limitation of this strategy along with the reaction mechanism of the key step is discussed.

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INTRODUCTION

1,2,3-Thiadiazoles (**A**, Figure 1), an important class of heterocyclic compounds, have found diverse applications in medicine and agriculture including bactericides, fungicides, and antiviral agents [1,2]. For example, 4,5-bis-(4′-methoxy-pheny1)-l,2,3-thiadiazole (**B**) was found to be an active inhibitor of collagen-induced platelet aggregation in vitro [3]. 4,5-Diphenyl-1,2,3-thiadiazole (**C**) was identified as a mechanism-based inhibitor of some CYP450 enzymes (CYP2B4, CYP1A2), but not others (CYP2E1) [4]. 1,2,3-Thiadiazoles are also useful intermediates in various organic synthesis [5]. In our continuing effort to identify triaryl substituted heterocyclic compounds of potential pharmacological interest [6–15] we became interested to build a library of small molecules incorporating the 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one moiety (e.g., compound **D**, Figure 2) for assessing their anti-cancer properties in vitro. Accordingly, a number of compounds containing the benzoxazinone moiety attached to a five-membered central heterocyclic ring was synthesized and tested for their anticancer properties in vitro [16]. An imidazole derivative **E** (Figure 2) was identified as a potent antileukemic agent. In further continuation of this research, we planned to synthesize 4,5-disubstituted 1,2,3-thiadiazole based library of compounds represented by **F** (Figure 2) containing 2*H*-benzo [*b*][1,4]oxazin-3(4*H*)-one moiety as one of the key substituents. Herein, we report a concise synthesis of compound **F**.

Because of their importance and applications in medicinal and synthetic chemistry, many methods have been developed for the synthesis of 1,2,3-thiadiazole [1,2]. One of the widely used methods for this purpose include Hurd–Mori reaction, which involves cyclization of α-methylene ketones employing (*p*-tolylsulfonyl) hydrazone intermediates [17–19]. A series of 4,5-diaryl- and 4-aryl-substituted 1,2,3-thiadiazoles were prepared by using this strategy. Thus, aldehydes and ketones were treated with (*p*-tolylsulfonyl) hydrazide or ethylcarbazate to form hydrazones that, in most experiments, were treated with neat thionyl chloride to produce the corresponding 1,2,3-thiadiazoles [3]. The supply of ketones in turn is generally maintained by the reaction of Grignard reagents with Weinreb amide followed by quenching of the resulting tetrahedral intermediate generated in situ. Although the methodology is handy for the preparation of various aryl ketones, the process however requires the use of low temperature, anhydrous reaction conditions, and more importantly moisture sensitive Grignard reagents preparation of which often involve cumbersome procedures. An alternative and simplest method involves the Friedel–Crafts acylation [20] of arenes using arylacetyl chloride or acid in the presence of stoichiometric amount of $AlCl_3$ or $ZnCl_2$–$POCl_3$ mixture. Because this process leads to the formation of environmentally harmful gaseous HCl, thus, a more convenient method was developed by reacting arylacetic acids with appropriate arenes in the presence of trifluoroacetic anhydride/ phosphoric acid [21]. This prompted us to apply this C–C bond forming reaction followed by Hurd–Mori reaction to synthesize our target compounds. To the best of our knowledge, this strategy has not been explored earlier for the preparation of compounds represented by **F**.

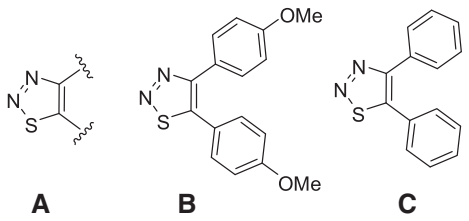


Figure 1. 1,2,3-Thiadiazole and derivatives.

RESULTS AND DISCUSSION

The key starting material **4** was conveniently prepared [16] from 2-nitrophenol (**1**) via a three-step process (Scheme 1). Thus, reaction of 2-nitrophenol (**1**) with ethyl bromoacetate followed by reduction and in situ cyclization of the resulting ether derivative **2** provided the desired benzoxazinone **3**. Subsequent reaction of compound **3** with phenyl acetic acid in the presence of $H_3PO_4/(CF_3CO)_2O$ provided the ketone **4** in good yield. It is worthy to mention that $H_3PO_4/(CF_3CO)_2O$ mediated C–C bond formation represents a rapid, efficient, and environmental friendly acylation process that does not require the use of moisture sensitive acyl halides and $AlCl_3$.

Having prepared the ketone **4**, we then treated these compounds with ethyl carbazate in the presence of *p*-toluene sulphonic acid (*p*-TSA) in toluene and the results are summarized in Table 1. A variety of hydrazones (**5**) were prepared smoothly by using this method. The presence of two NH in compound **5**, that is, one belongs to 2*H*-benzo [*b*][1,4]oxazin-3(4*H*)-one ring and another to hydrazone moiety was evident from the appearance of signals in the region 10.8–10.7 and 10.5–10.4 δ in ^{1}H NMR spectra. Additionally, the signal appeared at δ 4.69 was accounted for the –OCH_2CO– moiety of benzoxazinone ring. All these compounds were used for the next step.

The hydrazone **5** undergoes a facile cyclization in the presence of excess thionyl chloride providing a range of desired 1,2,3-thiadiazol derivatives (Table 2). The 2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one moiety present in **5** was well-tolerated under the conditions employed. However, yields of product **6** were found to be not particularly high perhaps due to a number of possible side reactions such as chlorination, aromatization, or sulfonylation that are usually known to be associated with the Hurd–Mori reaction [22]. Nevertheless, all the compounds prepared were well-characterized by spectral data (^{1}H NMR, IR, and MS) and the purity was determined by HPLC methods.

The mechanism of the Hurd–Mori reaction has been investigated earlier [23,24]. On the basis of these reports, a plausible mechanism can be proposed for the present synthesis of 1,2,3-thiadiazol derivatives (Scheme 2). The reaction can be viewed as a [4 + 1] approach involving four atoms from compound **5** and one (the sulfur atom) from $SOCl_2$. The reaction seems to proceed via initial generation of an intermediate, that is, thiadiazoline-1-one **X**, which undergoes subsequent aromatization to form the expected 1,2,3-thiadiazoles **6**. The latter process probably involves a Pummerer-type rearrangement of the sulfoxide **X** with the participation of the excess of thionyl chloride. Thus, elimination of SO_2 and HCl followed by the cleavage of the ethoxycarbonyl group (aided by the chloride ion) from the resulting salt provides compound **6**.

CONCLUSIONS

In conclusion, we have reported a two-step strategy to synthesize novel 1,2,3-thiadiazol derivatives. A combined application of $H_3PO_4/(CF_3CO)_2O$ mediated acylation followed by Hurd–Mori reaction has been explored to

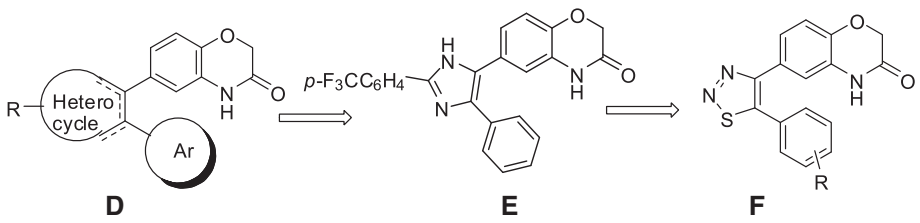


Figure 2. Triaryl substituted heterocyclic class of compounds as potential anti-cancer agents.

Scheme 1. Preparation of ketone **4**; reagents and condition: (a) K_2CO_3, $BrCH_2CO_2Et$, acetone, 50°C, 1 h (92%); (b) Fe powder, CH_3CO_2H, 0°C for 3 h, room temp for 2 h, reflux for 2 h (91%); (c) $C_6H_5CH_2CO_2H$, $H_3PO_4/(CF_3CO)_2O$, room temp, 1 h (80–86%).

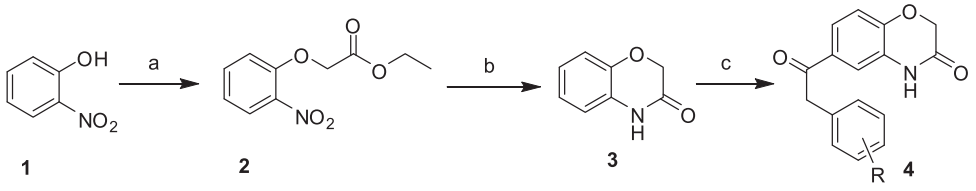
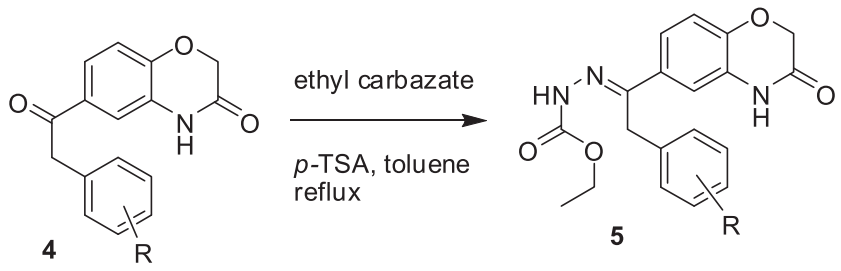


Table 1

Preparation of 2-aryl substituted (*E*)-ethyl-2-(1-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl)ethylidene)hydrazinecarboxylate (**5**).[a]



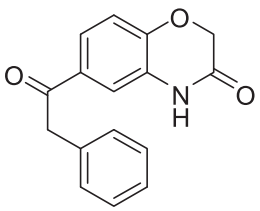
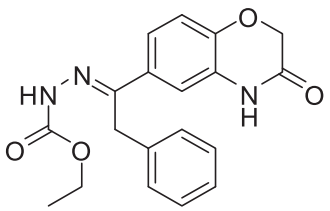
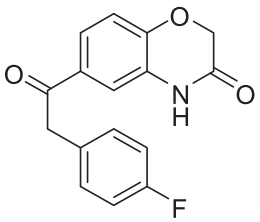
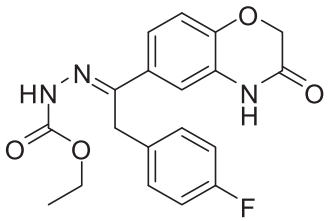
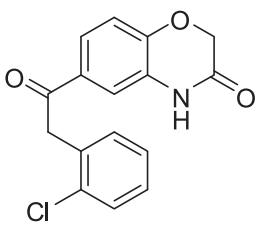
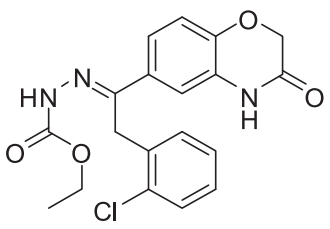
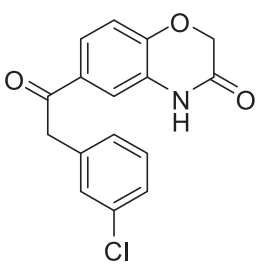
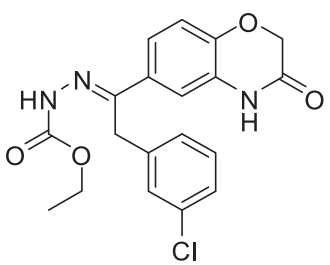
Entry	Ketones **4**	Time (h)	Products **5**	% Yield[b]
1.	 **4a**	24	 **5a**	60
2.	 **4b**	26	 **5b**	72
3.	 **4c**	24	 **5c**	66
4.		20		68

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Table 1
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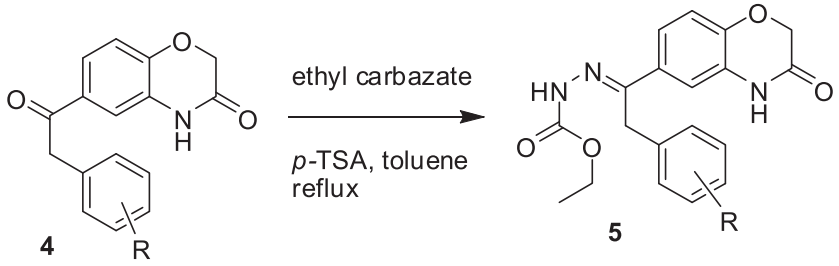
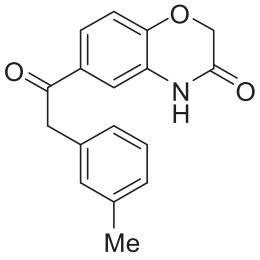
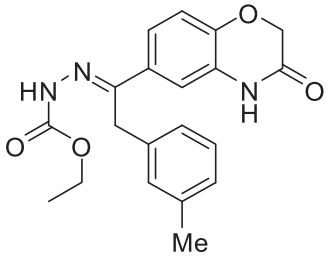
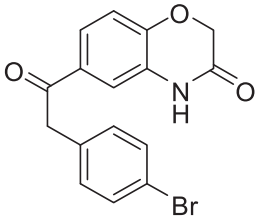
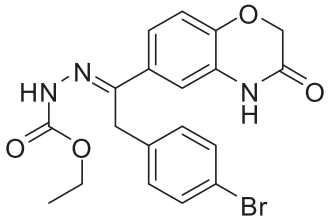


Entry	Ketones **4**	Time (h)	Products **5**	% Yield[b]
	4d		**5d**	
5.	 **4e**	24	 **5e**	65
6.	 **4f**	26	 **5f**	62

[a]All the reactions were carried out using ketone **4** (1.0 equiv, 0.74 mmol), ethyl carbazate (1.1 equiv, 0.84 mmol), and *p*-toluene sulfonic acid (10 mg, 0.058 mmol) in toluene (20 mL) under refluxing condition.
[b]Isolated yield.

synthesize these compounds. All the compounds synthesized contain a benzoxazinone moiety attached to a five-membered central heterocyclic ring and represent a new class of small molecules based on 1,2,3-thiadiazol framework. The present strategy therefore has potential to generate diversity-based 1,2,3-thiadiazols of potential pharmacological interest.

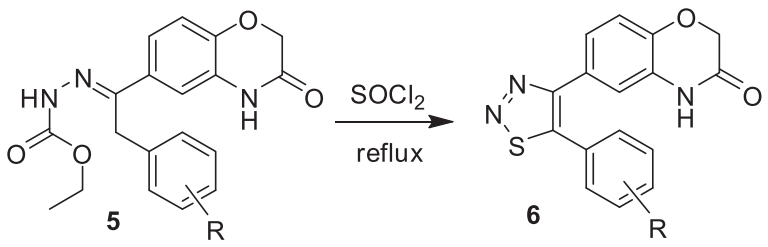
EXPERIMENTAL

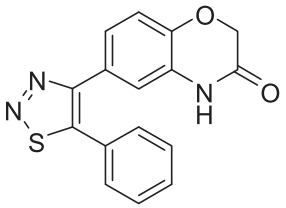
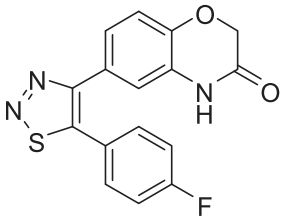
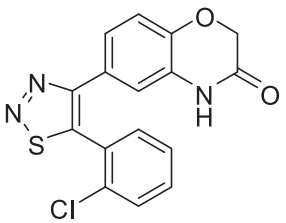
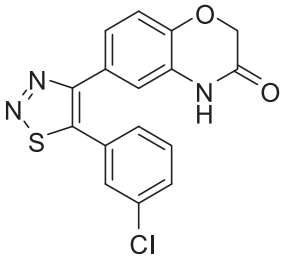
Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography on silica gel plates (60 F254), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (100–200 mesh) using distilled hexane, ethyl acetate, and dichloromethane. ^{1}H NMR spectra were determined in $CDCl_3$ or DMSO-d_6 solution by using Varian 400 MHz spectrometer (Varian Inc., Palo Alto, CA). Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ = 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on an FT-IR spectrometer (Perkin Elmer, Jasco Corporation, Tokyo, Japan). Melting points were determined using melting point apparatus (BÜCHI Labortechnik, Switzerland) and are uncorrected. MS spectra were obtained on a mass spectrometer (Agilent Technologies Inc., Wilmington, DE).

Synthesis of (2-nitrophenoxy) ethyl acetate (2). To a stirred solution of 2-nitro phenol (10 g, 0.071 mol) in acetone (25 mL), K_2CO_3 (21.5 g 0.156 mol) was added at room temperature and stirred for 15 min. Then ethyl bromoacetate (13.2 g, 0.079 mol) was added dropwise. After completion of addition, temperature was raised to 50°C and stirred for 1 h. The reaction mixture was cooled and the solid separated out was filtered and washed with acetone. Filtrate was concentrated in reduced pressure. The crude was partitioned between methyl tertiary butyl ether and water. The

Table 2

Preparation of 1,2,3-thiadiazol derivatives (**6**).[a]



Entry	Hydrazones **5**	Time (h)	Products **6**	% Yield[b]
1.	**5a**	3	 **6a**	60
2.	**5b**	2.5	 **6b**	62
3.	**5c**	4	 **6c**	63
4.	**5d**	3	 **6d**	62

(*Continued*)

Table 2
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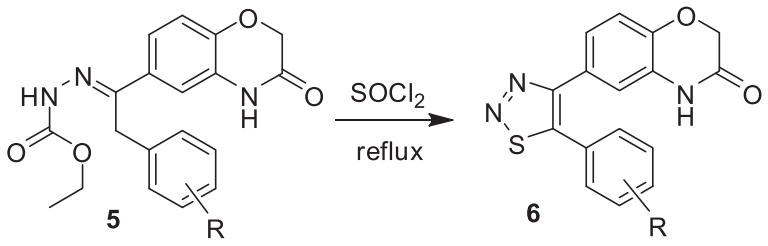
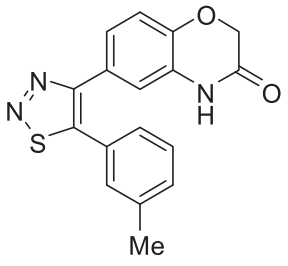
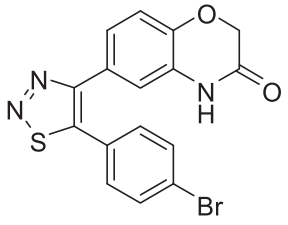


Entry	Hydrazones **5**	Time (h)	Products **6**	% Yield[b]
5.	**5e**	4	 **6e**	60
6.	**5f**	4	 **6f**	65

[a]All the reactions were carried out using compound **5** (0.28 mmol) and $SOCl_2$ (4 mL) under refluxing conditions.
[b]Isolated yield.

organic layer was extracted with ethyl acetate (2 × 20 mL), washed with water (20 mL), dried over anhydrous sodium sulfate, and concentrated to give the title compound (15.4 g, yield 92%); mp 39–40°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85 (1H, d, J = 8.2 Hz, ArH), 7.50 (1H, t, J = 7.8 Hz, ArH), 7.10 (2H, d, J = 7.7 Hz, ArH), 4.75 (2H, s, OCH_2), 4.30–4.20 (2H, m, OCH_2), 1.30 (3H, t, J = 7.3 Hz, CH_3); *m/z* (CI) 224 (M + 1, 100%).

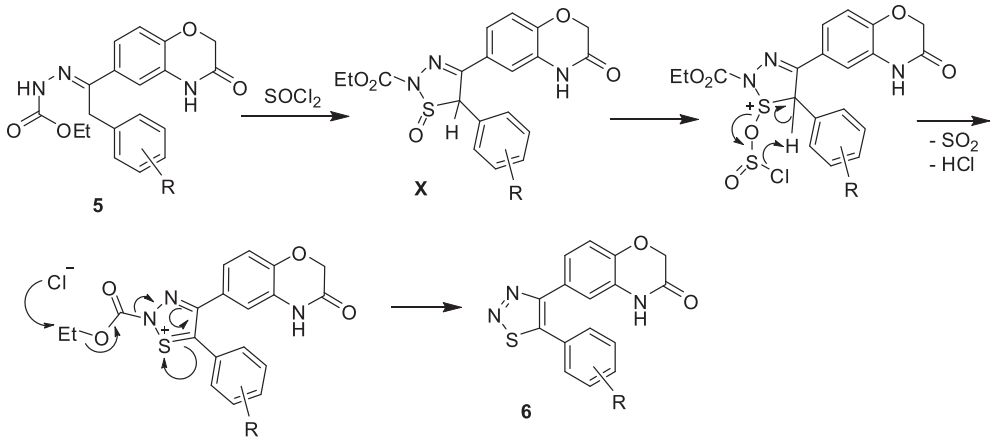
Synthesis of 4*H*-benzo[1, 4]oxazin-3-one (3). To a solution of **2** (15.4 g 0.068 mol) in acetic acid (75 mL) , Fe powder (38.4 g, 0.68 mol) was added portion wise for 3 h at 0°C. The reaction was exothermic. The reaction mixture was allowed to stir at room temperature for 2 h and heated to reflux for 2 h. After completion of the reaction, the reaction mixture was cooled to room temperature, filtered on celite, and the cake was washed with acetic acid. Acetic acid was concentrated to ¼ of its volume and diluted with water (75 mL). The solid separated was filtered, washed with water (20 mL), and dried to give the title compound (7.5 g, yield 91%); mp 173–174°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.95 (1H, s, NH), 7.00–6.80 (4H, m, ArH), 4.60 (2H, s, OCH_2); *m/z* (CI) 150 (M + 1, 100%).

General procedure for the synthesis 6-arylacetyl-4*H*-benzo [1,4]-oxazin-3-one (4). Phosphoric acid (3.15 g, 0.032 mol) and TFAA (21.8 ml, 0.104 mol) were added to the mixture of 4*H*-Benzo [1,4]oxazin-3-one (4 g, 0.026 mol) and substituted phenylacetic acid (1.1 eq) at 0°C. After completion of addition, the mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was cooled to 0°C and adjusted the pH to 7 by adding the saturated $NaHCO_3$ solution. The precipitated solid was filtered, washed with water, and dried to give the desired product.

6-Phenylacetyl-4*H*-benzo[1,4]-oxazin-3-one (4a). Yield 85%; mp 188–189°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.85 (1H, bs, NH), 7.70 (1H, d, J = 7.8 Hz, ArH), 7.50 (1H, s, ArH),7.40–7.20 (5H, m, ArH), 6.95 (1H, d, J = 7.8 Hz, ArH), 4.65 (2H, s, CH_2), 4.20 (2H, s, CH_2); *m/z* (CI) 266 (M-1, 100%).

6-(2-(4-fluorophenyl)acetyl)-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4b). Yield 80%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.74 (1H, d, J = 8.4 Hz, ArH), 7.52 (1H, s, ArH), 7.35–7.20 (2H, m, ArH), 7.18–7.05 (3H, m, ArH), 4.70 (2H, s, OCH_2), 4.30 (2H, m, ═C–CH_2Ph); *m/z* (CI) 284 (M-1, 100%).

Scheme 2. Proposed reaction mechanism for the synthesis of 1,2,3-thiadiazol derivatives (**6**).



6-(2-(2-chlorophenyl)acetyl)-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4c). Yield 82%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.90–7.70 (1H, m, ArH), 7.53 (1H, s, ArH), 7.55–7.25 (4H, m, ArH), 7.05 (1H, d, J = 8.4 Hz, ArH), 4.69 (2H, s, OCH_2), 4.42 (2H, s, =C–CH_2Ph); *m/z* (CI) 300 (M-1, 100%).

6-(2-(3-chlorophenyl)acetyl)-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4d). Yield 82.3%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s, NH), 7.75–7.65 (1H, m, ArH), 7.55 (1H, s, ArH), 7.40–7.25 (3H, m, ArH), 7.20 (1H, d, J = 7.2 Hz, ArH), 7.17 (1H, d, J = 7.2 Hz, ArH), 4.67 (2H, s, OCH_2), 4.32 (2H, s, = C–CH_2–Ph); *m/z* (CI) 300 (M-1, 100%).

6-(2-(3-methylphenyl)acetyl)-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4e). Yield 80.6%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.72 (2H, d, J = 2.2 Hz, ArH), 7.55 (1H, s, ArH), 7.20–7.15 (1H, m, ArH), 7.15–7.00 (4H, m, ArH), 4.69 (2H, s, OCH_2), 4.16 (2H, s, =C–CH_2–Ph), 2.33 (3H, s, CH_3); *m/z* (CI) 280 (M-1, 100%).

6-(2-(4-bromophenyl)acetyl)-2*H*-benzo[b][1,4]oxazin-3(4H)-one (4f). Yield 81.5%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.74 (1H, d, J = 8.4 Hz, ArH), 7.41–7.57 (3H, m, ArH), 7.30–7.10 (2H, m, ArH), 7.05 (1H, d, J = 8.3 Hz, ArH), 4.69 (2H, s, OCH_2), 4.27 (2H, s, =C–CH_2–Ph); *m/z* (CI) 344 (M-2, 100%).

General procedure for the preparation of 2-aryl substituted (*E*)-ethyl-2-(1-(3-oxo-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-6-yl) ethylidene)hydrazinecarboxylate (5). A mixture of 6-aryl acetyl-4*H*-benzo[1,4]-oxazin-3-one (0.74 mmol), ethyl carbazate (0.84 mmol), and *p*-toluene sulfonic acid (10 mg, 0.058 mmol) in toluene (20 mL) was refluxed (with the simultaneous removal of water formed) in a Dean–Stark apparatus for the time indicated in Table 1. The mixture was cooled to room temperature. The solid separated was filtered, washed with toluene (3 × 5 mL) and dried under high vacuum to afford the desired compound.

N′-[1-(3-Oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-2-phenyl-ethylidene]-hydrazinecarboxylic acid ethyl ester (5a). Yield 60%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s, NH), 10.45 (1H, s, NH), 7.40 (1H, s, ArH), 7.30–7.10 (6H, m, ArH),6.95–6.85 (1H, m, ArH), 4.69 (2H, s, OCH_2) 4.22–4.12 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 1.25 (3H, t, J = 7.1 Hz, CH_3); *m/z* (CI) 354 (M + 1, 100%); Elementary analysis found: C, 64.44; H, 5.45; N, 11.98; $C_{19}H_{19}N_3O_4$ requires C, 64.58; H, 5.42; N, 11.89%.

N′-[2-(4-Fluoro-phenyl)-1-(3-oxo-3,4-dihydro-2*H*-benzo[1,4] oxazin-6-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (5b). Yield 72%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.78 (1H, s, NH), 10.45 (1H, s, NH), 7.37 (1H, d, J = 2.0 Hz, ArH), 7.23 (1H, dd, J_1 = 2.0 Hz, J_2 = 4.5 Hz, ArH), 7.14–7.05 (4H, t, J = 4.5 Hz, ArH), 6.85 (1H, d, J = 8.6 Hz, ArH), 4.69 (2H, s, OCH_2), 4.25–4.12 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 1.25 (3H, t, J = 7.5 Hz, CH_3); *m/z* (CI) 372 (M + 1, 100%); Elementary analysis found: C, 61.54; H, 4.62; N, 11.58; $C_{19}H_{18}FN_3O_4$ requires C, 61.45; H, 4.89; N, 11.32%.

N′-[2-(2-Chloro-phenyl)-1-(3-oxo-3,4-dihydro-2*H*-benzo[1,4] oxazin-6-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (5c). Yield 66%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s, NH), 10.45 (1H, s, NH), 7.48 (1H, d, J = 8.8 Hz, ArH), 7.32 (1H, s, ArH), 7.28–7.15 (2H, m, ArH), 7.10 (1H, d, J = 8.4 Hz, ArH), 6.95–6.80 (2H, d, J = 7.0 Hz, ArH), 4.69 (2H, s, OCH_2), 4.22–4.12 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 1.25 (3H, t, J = 7.0 Hz, CH_3); *m/z* (CI) 388 (M + 1, 100%); Elementary analysis found: C, 58.65; H, 4.62; N, 10.47; $C_{19}H_{18}ClN_3O_4$ requires C, 58.84; H, 4.68; N, 10.84%.

N′-[2-(3-Chloro-phenyl)-1-(3-oxo-3,4-dihydro-2*H*-benzo[1,4] oxazin-6-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (5d). Yield 68%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.75 (1H, s, NH), 10.45 (1H, s, NH), 7.40 (1H, s, ArH), 7.35–7.20 (3H, m, ArH), 7.18 (1H, s, ArH), 7.05 (1, d, J = 7.2 Hz, ArH), 6.90 (1H, d, J = 7.2 Hz, ArH), 4.69 (2H, s, OCH_2), 4.22–4.12 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 1.25 (3H, t, J = 7.05 Hz, CH_3); *m/z* (CI) 386 (M + 1, 100%); Elementary analysis found: C, 58.97; H, 4.64; N, 10.61; $C_{19}H_{18}ClN_3O_4$ requires C, 58.84; H, 4.68; N, 10.84%.

N′-[1-(3-Oxo-3,4-dihydro-2*H*-benzo[1,4]oxazin-6-yl)-2-m-tolyl-ethylidene]-hydrazinecarboxylic acid ethyl ester (5e). Yield 65%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.78 (1H, s, NH), 10.38 (1H, s, NH), 7.38 (1H, d, J = 2.0 Hz, ArH), 7.22 (2H, dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz ArH), 7.13 (1H, t, J = 7.8 Hz, ArH), 6.98 (1H, d, J = 7.5 Hz, ArH), 6.92 (1H, s, ArH), 6.86 (1H, t, J = 7.8 Hz, ArH), 4.69 (2H, s, OCH_2), 4.20–4.15 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 2.81 (3H, t, J = 1.8 Hz, Ar–CH_3), 1.25 (3H, t, J = 7.0 Hz, CH_3); *m/z* (CI) 368 (M + 1, 100%); Elementary analysis found: C, 65.46; H, 5.75; N, 11.38; $C_{20}H_{21}N_3O_4$ requires C, 65.38; H, 5.76; N, 11.44%.

N′-[2-(4-Bromo-phenyl)-1-(3-oxo-3,4-dihydro-2*H*-benzo[1,4] oxazin-6-yl)-ethylidene]-hydrazinecarboxylic acid ethyl ester (5f). Yield 62%; white solid; ^{1}H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 10.45 (1H, s, NH), 7.47 (2H, d, J = 8.5 Hz, ArH), 7.4 (1H, s, ArH), 7.24 (1H, d, J = 8.0 Hz, ArH), 7.1 (2H, d, J = 8.0 Hz, ArH), 6.90 (1H, d, J = 8.5 Hz, ArH), 4.69 (2H, s, OCH_2), 4.25–4.18 (4H, m, =C–CH_2–Ph and $COCH_2CH_3$), 1.25 (3H, t, J = 7.0 Hz, CH_3); *m/z* (CI) 434 (M + 2, 100%); Elementary

analysis found: C, 52.69; H, 4.32; N, 9.88; $C_{19}H_{18}BrN_3O_4$ requires C, 52.79; H, 4.20; N, 9.72%.

General procedure for the synthesis of Preparation of 1,2,3-thiadiazol derivatives (6). A mixture of 2-aryl substituted (E)-ethyl-2-(1-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-yl) ethylidene)hydrazinecarboxylate (**5**, 0.28 mmol) and $SOCl_2$ (4 mL) was heated to reflux for the time indicated in Table 2. After completion of the reaction, the excess $SOCl_2$ was removed under vacuum and the residue was purified by column chromatography (EtOAc-Hexane 2:3) to give the desired product.

6-(5-Phenyl-[1,2,3]thiadiazol-4-yl)-4*H*-benzo[1,4]oxazin-3-one (6a). Yield 60%; white solid; mp 179–180°C; IR (KBr, cm^{-1}): 3435, 2924, 1697, 1602, 1500, 1401, 1039; ^1H NMR (DMSO-d_6): δ 10.80 (1H, s, NH), 7.55–7.40 (5H, m, ArH), 7.25 (1H, s, ArH), 6.95 (2H, s, ArH), 4.60 (2H, s, OCH_2); *m/z* (CI) 310 (M + 1, 100%); HPLC 98.5%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA, mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 230 nm, retention time 11.0 min; Elementary analysis found: C, 62.26; H, 3.52; N, 13.47; $C_{16}H_{11}N_3O_2S$ requires C, 62.12; H, 3.58; N, 13.58%.

6-[5-(4-Fluoro-phenyl)-[1,2,3]thiadiazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one (6b). Yield 62%; white solid; mp 197–198°C; IR (KBr, cm^{-1}): 3440, 1702, 1502, 1403, 1237, 1038, 832; ^1H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.55–7.45 (2H, m, ArH), 7.40–7.30 (2H, m, ArH), 7.25 (1H, s, ArH), 7.05–6.95 (2H, m, ArH), 4.60 (2H, s, OCH_2); *m/z* (CI) 329 (M + 2, 100%); HPLC 97.8%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 230 nm, retention time 11.1 min; Elementary analysis found: C, 58.55; H, 3.04; N, 12.98; $C_{16}H_{10}FN_3O_2S$ requires C, 58.71; H, 3.08; N, 12.84%.

6-[5-(2-Chloro-phenyl)-[1,2,3]thiadiazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one (6c). Yield 63%; white solid; mp 195–196°C; IR (KBr, cm^{-1}): 3252, 2923, 1690, 1660, 1497, 1391, 755; ^1H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.67 (1H, d, J = 8.0 Hz, ArH), 7.65–7.45 (3H, m, ArH), 7.30 (1H, s, ArH), 6.98–6.85 (2H, m, ArH), 4.60 (2H, s, OCH_2); *m/z* (CI) 344 (M + 1, 100%). HPLC 98.7%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 215 nm, retention time 11.6 min; Elementary analysis found: C, 55.98; H, 2.90; N, 12.05; $C_{16}H_{10}ClN_3O_2S$ requires C, 55.90; H, 2.93; N, 12.22%.

6-[5-(3-Chloro-phenyl)-[1,2,3]thiadiazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one (6d). Yield 62%; white solid; mp 178–180°C; IR (KBr, cm^{-1}): 3440, 2923, 1709, 1498, 1404, 1039; ^1H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.60–7.45 (3H, m, ArH), 7.40–7.30 (1H, m, ArH), 7.25 (1H, s, ArH), 7.00 (2H, s, ArH), 4.60 (2H, s, OCH_2); *m/z* (CI) 344 (M + 1, 100%); HPLC 97.1%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA, mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 215 nm, retention time 11.8 min; Elementary analysis found: C, 55.75; H, 2.82; N, 12.57; $C_{16}H_{10}ClN_3O_2S$ requires C, 55.90; H, 2.93; N, 12.22%.

6-(5-m-Tolyl-[1,2,3]thiadiazol-4-yl)-4*H*-benzo[1,4]oxazin-3-one (6e). Yield 60%; white solid; mp 171–173°C; IR (KBr, cm^{-1}): 3440, 2923, 1711,1039; ^1H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.40–7.30 (4H, m, ArH), 7.25–7.15 (1H, m, ArH), 7.00 (H, s, ArH), 4.60 (2H, s, OCH_2), 2.30 (3H, s, CH_3); *m/z* (CI) 324 (M + 1, 100%); HPLC 97.6%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 230 nm, retention time 11.8 min; Elementary analysis found: C, 63.34; H, 4.02; N, 12.69; $C_{17}H_{13}N_3O_2S$ requires C, 63.14; H, 4.05; N, 12.99%.

6-[5-(4-Bromo-phenyl)-[1,2,3]thiadiazol-4-yl]-4*H*-benzo[1,4]oxazin-3-one (6f). Yield 65%; white solid; mp 168–170°C; IR (KBr, cm^{-1}): 3442, 2924, 1700,1496,1390,832; ^1H NMR (DMSO-d_6): δ 10.85 (1H, s, NH), 7.77 (2H, d, J = 8.7 Hz, ArH), 7.40 (2H, d, J = 8.4 Hz, ArH), 7.20 (1H, s, ArH), 7.05 (2H, m, OCH_2), 4.60 (2H, s, OCH_2); *m/z* (CI) 386 (M-2, 100%); HPLC 98.2%, column: Intersil C-18 (150 × 4.6 mm), mobile phase A: water, 0.05%TFA, mobile phase B: acetonitrile, gradient (A/%B): 90/10, 10/90, 10/90, 90/10, flow rate: 1.0 mL/min, UV 230 nm, retention time 11.8 min; Elementary analysis found: C, 49.31; H, 2.52; N, 10.98; $C_{16}H_{10}BrN_3O_2S$ requires C, 49.50; H, 2.60; N, 10.82%.

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