# Synthesis of New Derivatives of 3-Aryl-1,5-dimethyl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines as Potential Antiproliferative Agents



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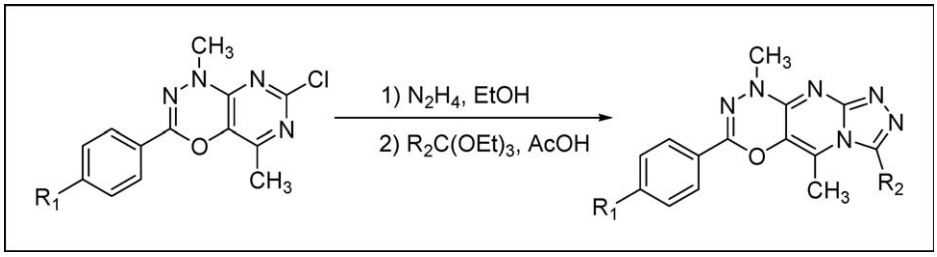


Starting from pyrimido[4,5-e][1,3,4]oxadiazines **(3a-c)**, a synthetic pathway to [1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines **(5a-i)** is described. The reaction of pyrimido[4,5-e][1,3,4]oxadiazines **(3a-c)** with hydrazine hydrate afforded the corresponding hydrazino derivatives **(4a-c)**. Further treatment of these compounds with different orthoesters in acetic acid gave the corresponding [1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines **(5a-i)**. Compound **(3a)** and **(5b)**, as examples, were tested on different cancer cell lines including HeLa, MCF-7, and HepG2. Malignant cells were cultured in DMEM medium and incubated with different concentrations of the titled compounds. Cell viability was quantitated by MTT assay.

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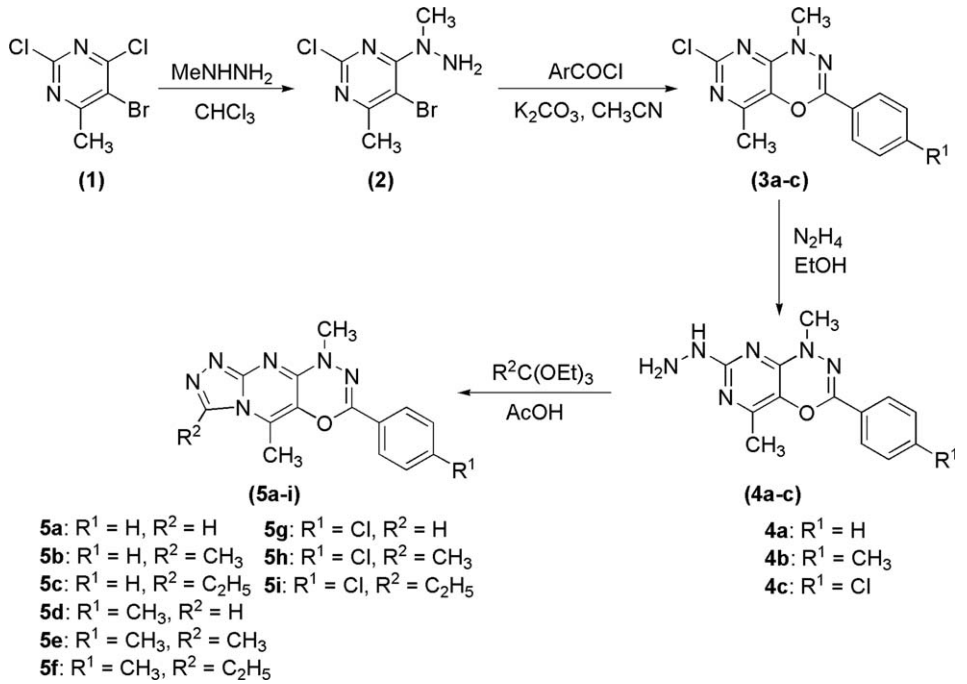
## INTRODUCTION

Pyrimidine derivatives and heterocyclic annulated pyrimidines continue to attract great interest because of the wide variety of interesting biological activities observed for these compounds, such as anticancer [1], antiviral [2], antitumor [3], and anti-inflammatory activities [4]. Moreover, triazoles and especially fused triazoles are an important class of heterocyclic compounds with antifungal [5], bactericidal [5,6], anxiolytic [7,8], anticonvulsant [9], herbicidal [10], and antidepressants activities [11]. Keeping this in view, it was thought worthwhile to synthesize the title compounds wherein the biologically active 1,2,4-triazole moieties are fused to potent, pyrimido[4,5-e][1,3,4]oxadiazine ring at 6,7 positions.

Numerous methods for the synthesis of 1,2,4-triazoles have been reported in the literature, which includes utilizing toxic reagents such as phosphorus oxychloride [12], lead tetraacetate [12,13], and bromine [13,14] as well as other oxidative reagents like chloramines T [15], iodobenzene diacetate [16,17], iron(III) chloride [18], and $CuCl_2$ [19]. The synthesis of 1,2,4-triazoles through electrochemical method [20] have also been reported. Various triazole derivatives have also been prepared through conversion of iminophosphoranes into triazolopyrimidines by initial aza-Wittig reaction between the iminophosphoranes and isocyanate giving a carbodimide as intermediate, which easily undergoes ring closure [21]. Likewise triazoles have been synthesized by refluxing various substituted hydrazonoyl chlorides in the presence of $Et_3N$ for a long time [22] or by treatment of 2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate with appropriate hydrazonoyl halides in boiling $CHCl_3$ [23].

In continuation of our studies towards the synthesis of fused heterocycles of biological importance containing pyrimidine [24] and oxadiazine [25] moieties, we describe here the synthesis of some new derivatives of 3-aryl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazine **(5a-i)**.

**Scheme 1**




## RESULTS AND DISCUSSION

**Chemistry.** 5-Bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine **(2)** was prepared from the reaction of 5-bromo-2,4-dichloro-6-methyl pyrimidine **(1)** with methyl hydrazine according to our previous published method [26]. Treatment of the latter compound with aromatic acyl halides in the presence of $K_2CO_3$ in boiling acetonirile afforded the pyrimido[4,5-e][1,3,4]oxadiazines **(3a-c)**. Subsequent reaction of these compounds with hydrazine led to the replacement of the chorine atom to give the hydrazino derivatives quantitatively **(4a-c)**. The latter products subsequently underwent cyclocondensation with triethylorthoesters in boiling acetic acid to give the desired tricyclic [1,2,4]triazolo [4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines **(5a-i)**. (Scheme 1) The structural assignment of compounds **(5a-i)** is based upon spectroscopic and microanalytical data. For example, the $^1$H-NMR spectrum of **(5b)** did not show the $NH_2$ and NH signals of the precursor **(4a)** at δ 3.8 and 5.8 ppm, but instead showed a sharp $^1$H signal at δ 8.3 ppm belonging to the triazole ring indicating the formation of the tricyclic compound **(5b)**. The IR spectrum was devoid of the $NH_2$ and NH absorption bands at ν = 3360, 3335, and 3260 $cm^{-1}$ of the precursor. The mass spectrum of **(5a)** showed a molecular ion peak at $m/z = 294$ ($M^+$) corresponding to the molecular formula $C_{15}H_{14}N_6O$.

**Pharmacology.** HeLa, MCF-7 and HepG2 were obtained from Pasteur Institute (Tehran, Iran) and maintained at 37°C in a humidified atmosphere (90%) containing 5% $CO_2$. Cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM) with 5% (v/v) fetal bovine serum, 100 units/mL penicillin, and 100 μg/mL streptomycin. Cells were seeded overnight, and then incubated with various concentrations of different extracts for 24 h and 48 h.

For MTT assay, cells were seeded at 5000 cell/well onto 96-well culture plates. For assay of apoptosis, cells were seeded at 100,000 cell/well onto a 24-well plate. For each concentration and time course study, there was a control sample which remained untreated and received the equal volume of medium.

The cell viability was determined using a modified 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT) assay [27,28]. Briefly, cells were seeded (5000 cell/well) onto flat-bottomed 96-well culture plates and allowed to grow 24 h followed by treatment with a typical heterocyclic derivative **(5b)**. After removing the medium, cells were labeled with MTT solution (5 mg/mL in PBS) for 4 h and resulting formazan was dissolved in DMSO (100 μL). The absorption was measured at 570 nm (620 nm as a reference) in an ELISA reader.

To investigate the potential antitumor activities of fused heterocyclic compounds with pyrimidooxadiazine moiety, compound **(3a)** and **(5b)**, as example, were selected and tested for their antiproliferative activities in HeLa cell line. Structural changes at the C-7 and the addition of a triazole ring on pyrimido [4,5-e][1,3,4] oxadiazines appear to have a considerable effect on the biological activity. This may indicate that triazole ring is a crucial component of the antiproliferation pharmacophore.

To further improve the antiproliferative activity, our effort was focused on determining the effect of the

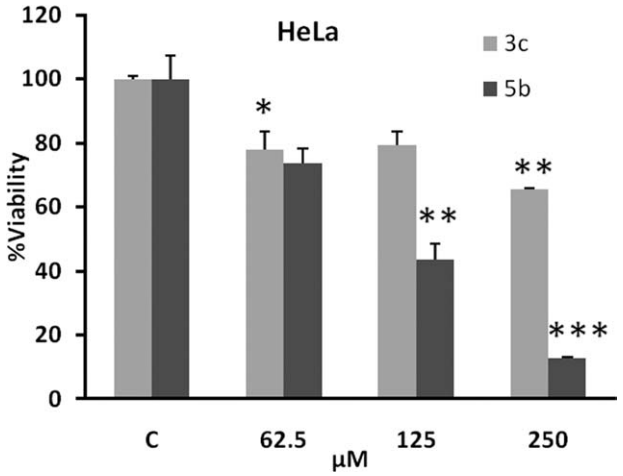



**Figure 1.** Dose-dependent growth inhibition of HeLa cells by compounds **3c** and **5b** (62.5 to 250 μM) for 24 h. Viability was quantitated by MTT assay. The dose inducing 50% cell growth inhibition ($IC_{50}$) against HeLa was calculated 106.3 μM. Results are Mean ± SEM (n = 3). $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with control (*C*).

triazole ring. Therefore, the tricyclic compound **(5b)** was also evaluated for its inhibitory activity on HepG2 and MCF-7 cell lines.

Cytotoxicity of compound **(5b)** was examined on malignant cell lines. At first, malignant cells were incubated with various concentrations of **(5b)** (25–400 μM) for 24 h. The result showed compound **(5b)** decreased cell viability of cells as a concentration-dependent manner. The toxicity started as little as 50 μM and during the 24 h, the dose inducing 50% cell growth inhibition ($IC_{50}$) against HeLa, MCF-7 and HepG2 were calculated 106.3, 555.8, and 294.1 μM, respectively (Figs. 1 and 2).

## CONCLUSION

In summary, we have described the synthesis of new 3-aryl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines **(5a-i)** through heterocyclization of hydrazino derivatives **(4a-c)** with triethylorthoesters in boiling acetic acid. Moreover, we have found that these heterocyclic compounds containing the triazolopyrimidooxadiazine moiety can be considered as a novel class of antiproliferative agents on the basis of a cell-based screening method. Further work is in progress in our laboratory to explain the mechanism of the cell death in cancer cell lines. The results will be reported elsewhere.

## EXPERIMENTAL

Melting points were recorded on an Electrothermal type 9100 melting point apparatus and are not corrected. The $^1$H-NMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. The mass spectra were scanned on a Varian Mat CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium (MTT), were purchased from Sigma (St. Louis, MD). RPMI and FCS were purchased from Gibco (Grand Island, NY). General procedure for the synthesis of 3-aryl-7-chloro-1,5-dimethyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine (3a-c).

To a magnetically stirred solution of 5-bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine**(2)** (1 mmol, 0.25 g) and an appropriate acyl halide (1 mmol) in dry acetonitrile (20 mL), $K_2CO_3$ (2 mmol, 0.28 g) was added and stirred at room temperature for 1 h. Then, the mixture was refluxed for 6–7 h and the progress of the reaction was monitored by TLC using petroleum ether: ethylacetate (7:3). After the completion of the reaction, the mixture was cooled and the solvent was removed under reduced pressure. Water (5 mL) was added to the resulting precipitate, and the mixture was neutralized by 0.1*N* HCl solution. The crude solid was filtered and recrystallized from ethanol: water.

***7-Chloro-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine (3a).*** yield = 70%, mp = 156–157°C, $^1$H-NMR ($CDCl_3$, ppm) δ 2.22 (s, 3H, $CH_3$-pyrimidine), 3.21 (s, 3H, $CH_3$—N), 7.1–7.8 (m, 5H, phenyl); ir (KBr disc) ν 3010, 2950, 1154 $cm^{-1}$ (C—O), ms (*m*/*z*) 274 ($M^+$), 276 ($M^+ + 2$). Anal. Calcd. for $C_{13}H_{11}ClN_4O$: C, 56.84; H, 4.04; N, 20.39; Found: C, 55.48; H, 3.20; N, 21.97.

***7-Chloro-1,5-dimethyl-3-(4-methylphenyl)-1H-pyrimido[4,5-e][1,3,4]oxadiazine (3b).*** yield = 60%, mp = 150–151°C, $^1$H-NMR ($CDCl_3$, ppm) δ 2.23 (s, 3H, $CH_3$-pyrimidine), 2.40 (s, 3H, $CH_3$-phenyl), 3.21 (s, 3H, $CH_3$—N), 7.3 (d, $J = 7$ Hz, 2H, phenyl), 7.8 (d, $J = 7$ Hz, 2H, phenyl); ir (KBr disc) ν 3015, 2930, 1152 $cm^{-1}$ (C—O), ms (*m*/*z*) 288 ($M^+$), 290 ($M^+ + 2$). Anal. Calcd. for $C_{14}H_{13}ClN_4O$: C, 58.24; H, 4.54; N, 19.40; Found: C, 58.32; H, 4.60; N, 19.61.

***7-Chloro-3-(4-chlorophenyl)-1,5-dimethyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine (3c).*** yield = 50%, mp = 175–176°C, $^1$H-NMR ($CDCl_3$, ppm) δ 2.22 (s, 3H, $CH_3$-pyrimidine), 3.21 (s, 3H, $CH_3$—N), 7.3 (d, $J = 8$ Hz, 2H, phenyl), 7.7 (d, $J = 8$ Hz, 2H, phenyl); ir (KBr disc) ν 3060, 2950, 1153 $cm^{-1}$ (C—O), ms (*m*/*z*)

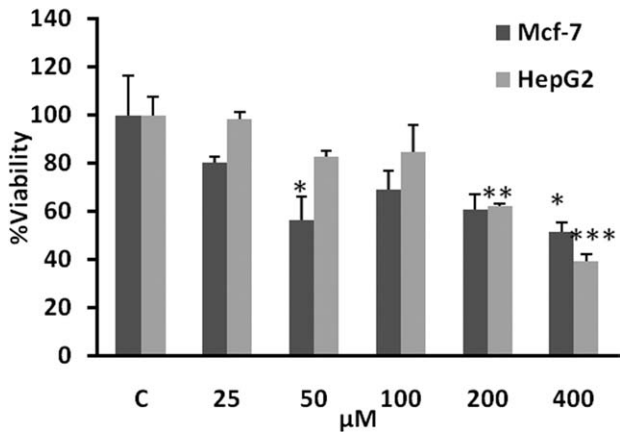



**Figure 2.** Dose-dependent growth inhibition of malignant cell lines by compounds **5b** (25 to 400 μM) for 24 h. Viability was quantitated by MTT assay. The dose inducing 50% cell growth inhibition ($IC_{50}$) against Hep-G2 and MCF-7 was calculated 294.1 and 555.8 μM, respectively. Results are Mean ± SEM (n = 3). $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with control (*C*).

**Table 1**

Physical, spectral, and microanalytical data of 3-aryl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazine (**5a-i**).

| Entry | Yield (%) | mp (°C) | Spectral data[a] | Molecular formula | C% (Calcd) | H% (Calcd) | N% (Calcd) |
|---|---|---|---|---|---|---|---|
| **5a** | 65 | 270–271 | $^1$H NMR: δ 2.19 (s, 3H, $CH_3$-pyrimidine), 3.45 (s, 3H, $CH_3$—N), 7.42–7.83 (m, 5H, ph), 8.33 (s, 1H, triazol). ir: ν 3005, 2920, 1610, 1550, 1490, 1005 cm$^{-1}$, *m/z* 280 ($M^+$). | $C_{14}H_{12}N_6O$ | 59.89 (59.99) | 4.30 (4.32) | 29.88 (29.98) |
| **5b** | 72 | 324–326 | $^1$H NMR: δ 2.60 (s, 3H, $CH_3$-pyrimidine), 2.75 (s, 3H,$CH_3$-triazol), 3.42(s, 3H, $CH_3$—N), 7.32–7.81 (m, 5H, ph), ir: ν 3000, 2900, 1610, 1550, 1490, 1005 cm$^{-1}$, *m/z* 294 ($M^+$). | $C_{15}H_{14}N_6O$ | 61.10 (61.22) | 4.72 (4.79) | 28.48 (28.55) |
| **5c** | 50 | 330 | $^1$H NMR: δ 1.53 (t, 3H, $CH_3$), 2.64 (s, 3H, $CH_3$-pyrimidine), 3.25 (q, 2H, $CH_2$-triazol), 3.51 (s, 3H, $CH_3$—N), 7.43–7.94 (m, 5H, ph). ir: ν 3015, 2940, 1605, 1555, 1500, 1015 cm$^{-1}$, *m/z* 308 ($M^+$). | $C_{16}H_{16}N_6O$ | 62.21 (62.32) | 5.17 (5.23) | 27.03 (27.26) |
| **5d** | 74 | 290–291 | $^1$H NMR: δ 2.42 (s, 3H, $CH_3$-pyrimidine), 2.50 (s, 3H, $CH_3$-ph), 3.47 (s, 3H, $CH_3$—N), 7.27 (d, $J$ = 7.5 Hz, 2H, ph), 7.70 (d, $J$ = 7.5 Hz, 2H, ph), 8.32 (s, 1H, triazol). ir: ν 3000, 2950, 1605, 1540, 1480, 1000 cm$^{-1}$, *m/z* 294 ($M^+$). | $C_{15}H_{14}N_6O$ | 61.14 (61.21) | 4.68 (4.79) | 28.45 (28.55) |
| **5e** | 68 | 314 | $^1$H NMR: δ 2.42 (s, 3H, $CH_3$-pyrimidine), 2.59 (s, 3H, $CH_3$-ph), 2.75 (s, 3H, $CH_3$- triazol), 3.42 (s, 3H, $CH_3$—N), 7.32 (d, $J$ = 7.5 Hz, 2H, ph), 7.73 (d, $J$ = 7.5 Hz, 2H, ph). ir: ν 3010, 2910, 1630, 1560, 1500, 1020 cm$^{-1}$, *m/z* 308 ($M^+$). | $C_{16}H_{16}N_6O$ | 62.29 (62.32) | 5.17 (5.23) | 27.20 (27.26) |
| **5f** | 46 | 340–343 | $^1$H NMR: δ 1.43 (t, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$-pyrimidine), 2.60 (s, 3H, $CH_3$-ph), 2.75 (s, 3H, $CH_3$- triazol), 3.42 (s, 3H, $CH_3$—N), 7.34 (d, $J$ = 7.5 Hz, 2H, ph), 7.73 (d, $J$ = 7.5 Hz, 2H, ph). ir: ν 3015, 2920, 1620, 1565, 1515, 1025 cm$^{-1}$, *m/z* 322 ($M^+$). | $C_{17}H_{18}N_6O$ | 63.31 (63.34) | 5.57 (5.63) | 25.89 (26.07) |
| **5g** | 62 | 293–295 | $^1$H NMR: δ 2.44 (s, 3H, $CH_3$-pyrimidine), 3.30 (s, 3H, $CH_3$—N), 7.52 (d, $J$ = 7.3 Hz, 2H, ph), 7.91 (d, $J$ = 7.3 Hz, 2H, ph), 8.82 (s, 1H, triazol). ir: ν 3050, 2900, 1625, 1560, 1480, 1010 cm$^{-1}$, *m/z* 314 ($M^+$), 316 ($M^+ + 2$). | $C_{14}H_{11}ClN_6O$ | 53.40 (53.43) | 3.48 (3.52) | 26.65 (26.70) |
| **5h** | 57 | 319–320 | $^1$H NMR: δ 2.44 (s, 3H, $CH_3$-pyrimidine), 2.76 (s, 3H, $CH_3$- triazol), 3.30 (s, 3H, $CH_3$—N), 7.53 (d, $J$ = 7.3 Hz, 2H, ph), 7.94 (d, $J$ = 7.3 Hz, 2H, ph), ir: ν 3090, 2990, 1650, 1600, 1550, 1490, 1080 cm$^{-1}$, *m/z* 328 ( $M^+$), 330 ($M^+ + 2$). | $C_{15}H_{13}ClN_6O$ | 54.76 (54.80) | 3.87 (3.99) | 25.54 (25.56) |
| **5i** | 41 | 331–333 | $^1$H NMR: δ 1.53 (t, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$-pyrimidine), 2.88 (q, 2H, $CH_2$), 3.30 (s, 3H, $CH_3$—N), 7.53 (d, $J$ = 7.3 Hz, 2H, ph), 7.95 (d, $J$ = 7.3 Hz, 2H, ph). ir: ν 3100, 2950, 1660, 1590, 1550, 1470, 1065 cm$^{-1}$, *m/z* 342 ( $M^+$), 344 ($M^+ + 2$). | $C_{16}H_{15}ClN_6O$ | 55.98 (56.06) | 4.39 (4.41) | 24.47 (24.52) |

[a] The solvent for $^1$H NMR is $CDCl_3$ and the chemical shifts are in ppm.

308 ($M^+$), 310 ($M^+ + 2$), 312 ($M^+ + 4$). Anal. Calcd. for $C_{13}H_{10}Cl_2N_4O$: C, 50.51; H, 3.26; N, 18.12; Found: C, 50.60; H, 3.23; N, 18.15.

**General procedure for the preparation of 3-aryl-1,5-dimethyl-7-hydrazino-1H-pyrimido[4,5-e][1,3,4]oxadiazine (4a-c).** To a solution of 3-aryl-1,5-dimethyl-7-chloro-1H-pyrimido[4,5-e][1,3,4]oxadiazine (**3a-c**) (3.7 mmol) in ethanol (20 mL), hydrazine hydrate (2 mL) was added, and the solution was refluxed for 5 h. The resulting precipitate was filtered off and recrystallized from ethanol.

***1,5-Dimethyl-7-hydrazino-3-phenyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine (4a).*** yield = 77%, mp = 200–202°C, $^1$H-NMR (DMSO-$d_6$, ppm): δ 2.21 (s, 3H, $CH_3$), 3.22 (s, 3H, $CH_3$—N), 3.95 (br s, 2H, $NH_2$, $D_2O$ exchangeable), 5.93 (br s, 1H, NH, $D_2O$ exchangeable), 7.31–7.50 (m, 3H, Ph), 7.74–7.89 (m, 2H, Ph); ir (KBr disc) ν 3360, 3335, 3260, 1115 cm$^{-1}$; ms (*m/z*) 270 ($M^+$); Anal. Calcd. for $C_{13}H_{14}N_6O$ (%): C, 57.77; H, 5.22; N, 31.09. Found: C, 57.73; H, 5.05; N, 30.89.

***1,5-Dimethyl-7-hydrazino-3-(4-methylphenyl)-1H-pyrimido[4,5-e][1,3,4]oxadiazine (4b).*** yield = 68%, mp = 196–198°C, $^1$H-NMR (DMSO-$d_6$, ppm): δ 2.19 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 3.21 (s, 3H, $CH_3$), 3.85 (br s, 2H, $NH_2$, $D_2O$ exchangeable), 5.89 (br s, 1H, NH, $D_2O$ exchangeable), 7.21 (d, $J$ = 7.7 Hz, 2H, Ph), 7.69 (d, $J$ = 7.7 Hz, 2H, Ph); ir (KBr disc) ν 3345, 3270, 3260, 1110 cm$^{-1}$; ms (*m/z*) 284 ($M^+$); Anal. Calcd. for $C_{14}H_{16}N_6O$ (%): C, 59.14; H, 5.67; N, 29.56. Found: C, 59.06; H, 5.64; N, 29.45.

***3-(4-Chlorophenyl)-1,5-dimethyl-7-hydrazino-1H-pyrimido[4,5-e][1,3,4]oxadiazine (4c).*** yield = 72 %, mp = 241–243°C, $^1$H-NMR (DMSO-$d_6$, ppm): δ 2.19 (s, 3H, $CH_3$), 3.20 (s, 3H, $CH_3$), 3.89 (br s, 2H, $NH_2$, $D_2O$ exchangeable), 5.92 (br s, 1H, NH, $D_2O$ exchangeable), 7.35 (d, $J$ = 7.9 Hz, 2H, Ph), 7.73 (d, $J$ = 7.9 Hz, 2H, Ph); ir (KBr disc) ν 3320, 3305, 3280, 1105 cm$^{-1}$; ms (*m/z*) 304 ($M^+$), 306 ($M^+ + 2$); Anal. Calcd. for $C_{13}H_{13}ClN_6O$ (%):C, 51.24; H, 4.30; N, 27.58. Found: C, 51.14; H, 4.22; N, 27.51.

**General procedure for the synthesis of 3-aryl-1,5-dimethyl-1H-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-e][1,3,4]oxadiazines (5a-i).** To a solution of 3-aryl-1,5-dimethyl-7-hydrazino-1H-pyrimido[4,5-e][1,3,4]oxadiazine (**4a-c**) (1 mmol) in HOAc (2 mL), the respective triethylorthoester (2 mmol) was added. The reaction solution was heated under reflux for 4 h.

After the completion of the reaction which was monitored by TLC using chloroform: methanol (9:1), the mixture was cooled to room temperature. Water (5 mL) was added and the mixture was neutralized by saturated $NaHCO_3$ solution. The collected solid was recrystallized from ethanol (Table 1).

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