Synthesis and anticancer evaluation of new derivatives of 3-phenyl-1,5-dimethyl-1*H*-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine

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The synthesis of new derivatives of 3-phenyl-1,5-dimethyl-1*H*-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-*e*][1,3,4]oxadiazines **5a–e** and **7a–e** is described through heterocyclisation of hydrazino derivative **(3)** with aromatic aldehydes or carbon disulfide and alkyl halides. [(1,5-Dimethyl-3-phenyl-1*H*-[1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-*e*][1,3,4]oxadiazin-7-yl) sulfanyl]methyl cyanide was singled out to be 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 quantified by MTT assay.

Keywords: triazolopyrimidooxadiazine, heterocyclisation, anti-cancer, HeLa, MCF-7, HepG2

Over the past decade, fused pyrimidines and heterocyclic annulated pyrimidines have been the centre of attention due to their applications as anticancer,[1] antiviral,[2] antitumor,[3] and anti-inflammatory agents.[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] or antidepressant[11] activities. It therefore seemed promising to synthesise fused triazolopyrimidooxadiazine derivatives as potential pharmacologically active compounds.

Many methods for the synthesis of 1,2,4-triazoles have been reported which include utilising toxic reagents such as phosphorus oxychloride,[12] lead tetraacetate[13] or bromine.[14] Other oxidative reagents like chloramines T,[15] iodobenzene diacetate,[16,17] iron(III) chloride[18] and $CuCl_2$[19] as well as electrochemical methods[20] have been used to synthesise these heterocyclic compounds. The synthesis of various triazoles derivatives was also accomplished by conversion of iminophosphoranes into triazolopyrimidines through the initial aza-Wittig reaction between the iminophosphoranes and the isocyanate giving a carbodimide as intermediate which easily undergoes ring closure.[21] Various substituted hydrazonoyl chlorides on heating under reflux in the presence of Et_3N for a long time[22] or the treatment of 2-thioxo-1,3,6-trihydropyrimidine-5-carboxylate with the appropriate hydrazonoyl halides in boiling $CHCl_3$[23] afforded the corresponding 1,2,4-triazoles.

As part of our ongoing studies dealing with the synthesis of various derivatives of fused pyrimidines[24–26] and oxadiazines,[27,28] we describe here the synthesis of new derivatives of [1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine **5a–e** and **7a–e** and the outcome of our preliminary evaluations of their anti-proliferative activity.

Results and discussion

Chemistry

5-Bromo-2-chloro-6-methyl-4-(1-methylhydrazino)pyrimidine **(1)** was prepared from the reaction of 5-bromo-2,4-dichloro-6-methyl pyrimidine with methyl hydrazine according to our previous published method.[29] Treatment of compound **(1)** with benzoyl chloride in the presence of K_2CO_3 in boiling dry CH_3CN afforded 7-chloro-1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]oxadiazine **(2)**.[27] Subsequent reaction of this compound with hydrazine hydrate led to the replacement of the chorine atom with hydrazine and gave quantitatively the hydrazino derivative **(3)** which was utilised as the precursor for the synthesis of new tricyclic compounds **5a–e** and **7a–e**. Thus, heating under stirring of the compound **(3)** with various aromatic aldehydes in the presence of a few drops of acetic acid in ethanol resulted in the formation of corresponding hydrazones **4a–e**. The latter compounds were cyclised by refluxing in nitrobenzene as solvent and oxidatizing agent to obtain the new derivatives of tricyclic compounds **5a–e**. The structure elucidation of these compounds was achieved by their physical, chemical and spectral data. For example, the IR spectrum of compound **(4d)** showed the presence of the characteristic absorption N–H stretching band around 3320 cm^{-1}. The ^1H NMR spectrum of compound **(4d)** also showed a singlet D_2O exchangeable peak at δ 7.98 ppm for N–H proton while the IR and ^1H NMR spectra of compound **(5d)** revealed the absence of NH moiety and also showed a molecular ion peak at *m/z* 390 (M^+) and 392 ($M^+ + 2$) in the mass spectrum confirming the desired structure. (Scheme 1)

On the other hand, heating the hydrazino substituted compound **(3)** with CS_2 in dry pyridine gave the title compound **(6)** which was converted to its alkyl derivatives on treatment with alkyl halides in a mixture of boiling DMF and CH_3CN (1:5). (Scheme 1) The spectral data of compounds **7(a–e)** together with their microanalytical data are in accord with the assigned structures. For instance, the IR spectrum of compound **(6)** displayed an absorption band at 1365 cm^{-1} due to C=S group which was disappeared after alkylation. Also, the ^1H NMR spectrum of product **(7d)** showed a singlet at 4.48 ppm for the methylene protons, two singlets at 2.52 and 3.45 ppm corresponding to the two methyl groups and two multiplets around 7.34–7.78 ppm due to the phenyl groups of the product. The mass spectrum of **(7d)** showed a molecular ion peak at *m/z* 402 (M^+) corresponding to the molecular formula $C_{21}H_{18}N_6OS$.

Pharmacological activities

Human breast cancer (MCF-7) and human hepatocellular carcinoma (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 Roswell Park Memorial Institute medium (RPMI) with 5% (v/v) Fetal Calf Serum (FCS), 100 units/mL penicillin, and 100 μM streptomycin. Cells were seeded overnight, and then incubated with various concentrations of different compounds for 24 h. For MTT assay, cells were seeded at 5,000 cell/well onto 96-well culture plates. For each concentration and time course study,

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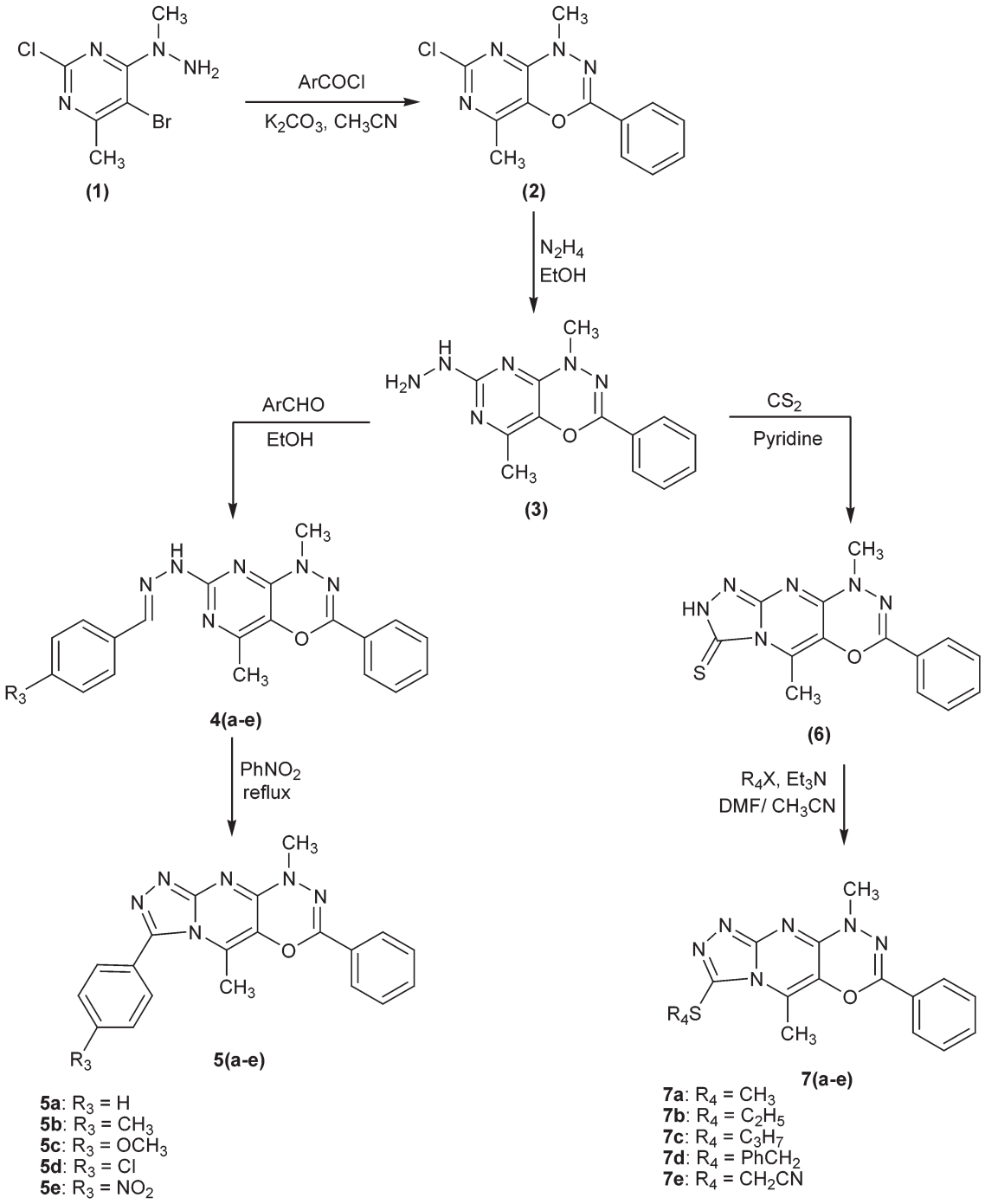

Scheme 1

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.[30,31] Briefly, cells were seeded (5,000 cell/well) onto flat-bottomed 96-well culture plates and allowed to grow 24 h followed by treatment with a typical heterocyclic derivative **(7e)**. 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.

In this study, we attempted to show the possible cytotoxic effects of triazolopyrimidooxadiazine moiety like compound **(7e)** on different malignant cancer cell lines including human breast cancer cell line (MCF-7) and hepatocellular carcinoma cell line (Hep G2). At first, malignant cells were incubated with various concentrations of **(7e)** (50–500 µM). The result showed compound **(7e)** decreased cell viability of cells as a concentration-dependent manner. The IC_{50} values against MCF-7 after 24 h and against HepG2 after 48 h were determined 439.6 and 280.5 µM, respectively (Figs 1 and 2).

Conclusion

We have described the synthesis of new 3-phenyl-1*H*-[1,2,4] triazolo[4',3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazines **5a–e** and **7a–e** through heterocyclisation of hydrazino derivative **(3)** with aromatic aldehydes and also CS_2 and alkylhalides, respectively. Moreover, we have found that these heterocyclic compounds containing the triazolopyrimidooxadiazine moiety can be considered as a novel class of antiproliferative agents

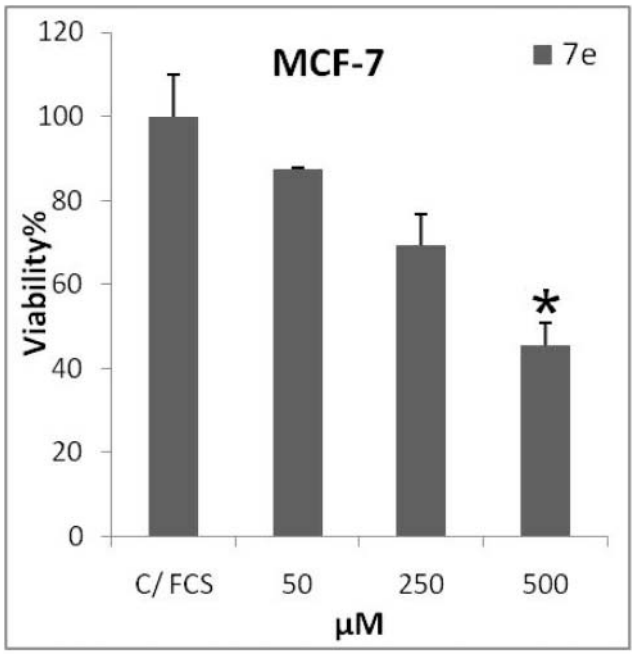

Fig. 1 Dose-dependent growth inhibition of MCF-7 cells by compound **(7e)** (50–500 μM) after 24 h. Viability was quantified by MTT assay. The dose inducing 50% cell growth inhibition (IC_{50}) against MCF-7 was calculated 439.6. Results are Mean ± SEM ($n = 3$). *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ compared to control (C).

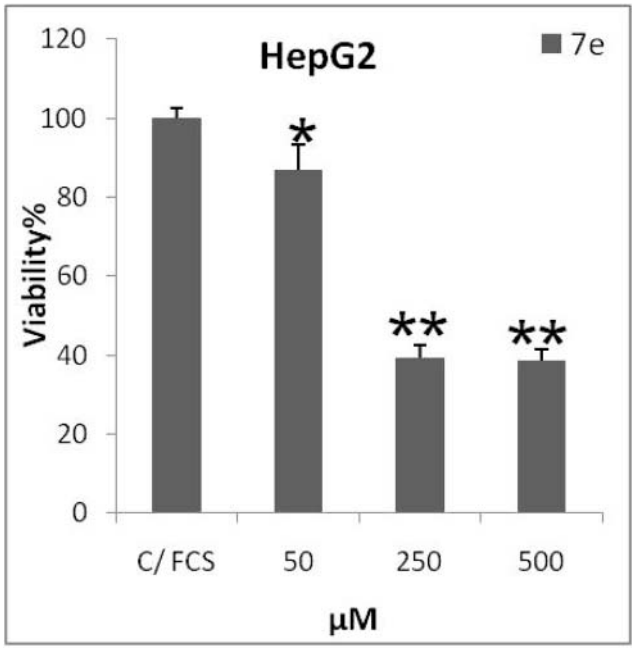

Fig. 2 Dose-dependent growth inhibition of malignant cell lines by compounds **(7e)** (50 to 500 μM) after 48 h. Viability was quantified by MTT assay. The dose inducing 50% cell growth inhibition (IC_{50}) against HepG2 was calculated 280.5. Results are Mean ± SEM ($n = 3$). *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$ compared to control (C).

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.

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. RPMI and FCS were purchased from Gibco.

*1,5-Dimethyl-7-hydrazino-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4] oxadiazine* **(3):** To a solution of 7-chloro-1,5-dimethyl-3-phenyl-1H-pyrimido[4,5-e][1,3,4]oxadiazine **(2)**[27] (3.7 mmol, 1.1 g) 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 recrystallised from ethanol. Yield = 77%, m.p. = 200–201 °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 3300, 3295, 1110 cm^{-1}; *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%.

Synthesis of hydrazones **4a–e***; general procedure*

To a solution of 3-phenyl-1,5-dimethyl-7-hydrazino-1*H*-pyrimido[4,5-*e*][1,3,4]oxadiazine **(3)** (0.37 mmol, 0.1 g) and an appropriate aromatic aldehydes (0.4 mmol) in ethanol (10 mL), a few drops of glacial acetic acid was added and the reaction mixture was heated under reflux condition for 2 h. The resulting solid was consecutively filtered off, washed with water and recrystallised from ethanol.

*Benzaldehyde-1-(1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]oxadiazin-7-yl) hydrazone* **(4a):** Yield = 85%, m.p. = 210–213 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.18 (s, 3H, CH_3–pyrimidine), 3.29 (s, 3H, CH_3–N), 7.08–7.92 (m, 11H, Ar and CH=N–), 8.13 (br s, 1H, NH, D_2O exchangable); IR (KBr disc) ν 3200, 1590, 1040 cm^{-1}. *m/z* 358 (M^+); Anal. Calcd for $C_{20}H_{18}N_6O$:C, 67.02; H, 5.06; N, 23.45. Found: C, 66.89; H, 5.05; N, 23.37%.

*4-Methylbenzaldehyde-1-(1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]oxadiazin-7-yl) hydrazone* **(4b):** Yield = 82%, m.p. = 220–224 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.29 (s, 3H, CH_3–pyrimidine), 2.37 (s, 3H, CH_3-phenyl), 3.29 (s, 3H, CH_3–N), 7.07–7.91 (m, 10H, Ar and CH=N–), 8.10 (br s, 1H, NH, D_2O exchangable); IR (KBr disc) ν 3279, 1588, 1025 cm^{-1}. *m/z* 372 (M^+); Anal. Calcd for $C_{21}H_{20}N_6O$: C, 67.73; H, 5.41; N, 22.57. Found: C, 67.70; H, 5.46; N, 22.53%.

*4-Methoxybenzaldehyde-1-(1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4] oxadiazin-7-yl) hydrazone* **(4c):** Yield = 76%, m.p. = 208–210 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.37 (s, 3H, CH_3–pyrimidine), 3.37 (s, 3H, CH_3-N), 3.79 (s, 3H, OCH_3), 6.88–7.93 (m, 10H, Ar and CH=N–), 8.03 (br s, 1H, NH, D_2O exchangable); IR (KBr disc) ν 3100, 1620, 1045 cm^{-1}. *m/z* 388 (M^+); Anal. Calcd for $C_{21}H_{20}N_6O_2$: C, 64.94; H, 5.19; N, 21.64. Found: C, 64.89; H, 5.15; N, 21.61%.

*4-Chlorobenzaldehyde-1-(1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*] [1,3,4]oxadiazin-7-yl) hydrazone* **(4d):** Yield = 80%, m.p. = 249–251 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.32 (s, 3H, CH_3–pyrimidine), 3.31 (s, 3H, CH_3-N), 7.25–7.91 (m, 10H, Ar and CH=N–), 7.98 (br s, 1H, NH, D_2O exchangable); IR (KBr disc) ν 3320, 1610, 1030 cm^{-1}; *m/z* 392 (M^+), 394 ($M^+ + 2$); Anal. Calcd for $C_{20}H_{17}ClN_6O$: C, 61.15; H, 4.36; N, 21.39; Found: C, 61.11; H, 4.32; N, 21.20%.

*4-Nitrobenzaldehyde-1-(1,5-dimethyl-3-phenyl-1*H*-pyrimido[4,5-*e*][1,3,4]oxadiazin-7-yl) hydrazone* **(4e):** Yield = 75%, m.p. = 281–283 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.28 (s, 3H, CH_3–pyrimidine), 3.28 (s, 3H, CH_3-N), 7.32–8.33 (m, 10H, Ar and CH=N–), 8.42 (br s, 1H, NH, D_2O exchangable); IR (KBr disc) ν 3100, 1590, 1025 cm^{-1}. *m/z* 403 (M^+); Anal. Calcd for $C_{20}H_{17}N_7O_3$: C, 59.55; H, 4.25; N, 24.31. Found: C, 59.46; H, 4.20; N, 24.25%.

Synthesis of 7-aryl-1,5-dimethyl-3-phenyl-1H-[1,2,4]triazolo[4',3':1,2] pyrimido[4,5-e][1,3,4]oxadiazines **5a–e;** *general procedure*

A mixture of appropriate hydrazone **4a–e** (2 mmol) in nitrobenzene (2 mL) was heated under reflux for 6 h. After the completion of the reaction which was monitored by TLC using $CHCl_3$: MeOH (9:1), the solvent was removed under reduced pressure and the resulting solid was recrystallised from benzene.

*1,5-Dimethyl-3,7-diphenyl-1*H*-[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-*e*][1,3,4] oxadiazine* **(5a):** Yield = 52%, m.p. = 219–221 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.03 (s, 3H, CH_3–pyrimidine), 3.49 (s, 3H, CH_3–N), 7.32–7.92 (m, 10H, Ar); IR (KBr disc) ν 1675, 1042 cm^{-1}. *m/z* 356 (M^+); Anal. Calcd for $C_{20}H_{16}N_6O$: C, 67.40; H, 4.53; N, 23.58. Found: C, 67.36; H, 4.48; N, 23.52%.

*1,5-Dimethyl-7-(4-methylphenyl)-3-phenyl-1*H-*[1,2,4]triazolo [4',3':1,2] pyrimido[4,5-*e*][1,3,4]oxadiazine* **(5b):** Yield = 45%, m.p. = 217–221 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.05 (s, 3H, CH_3–pyrimidine), 3.50 (s, 3H, CH_3-phenyl), 3.88 (s, 3H, CH_3-N), 7.18–7.84 (m, 9H, Ar); IR (KBr disc) ν 1664, 1019 cm^{-1}. *m/z* 370 (M^+); Anal. Calcd for $C_{21}H_{18}N_6O$:C, 68.09; H, 4.90; N, 22.69. Found: C, 67.95; H, 4.84; N, 22.59%.

*7-(4-Methoxyphenyl)-1,5-dimethyl-3-phenyl-1*H-*[1,2,4]triazolo [4',3':1,2] pyrimido[4, 5-*e*][1,3,4]oxadiazine* **(5c):** Yield = 40%, m.p. = 180–183 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.04 (s, 3H, CH_3–pyrimidine), 3.48 (s, 3H, CH_3-N), 3.88 (s, 3H, OCH_3), 6.89–7.89 (m, 9H, Ar); IR (KBr disc) ν 1667, 1035 cm^{-1}. *m/z* 386 (M^+); Anal. Calcd for $C_{21}H_{18}N_6O_2$ (%): C, 65.27; H, 4.70; N, 21.75. Found: C, 65.17; H, 4.68; N, 21.67%.

*7-(4-Chlorophenyl)-1,5-dimethyl-3-phenyl-1*H-*[1,2,4]triazolo[4', 3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(5d):** Yield = 55%, m.p. = 266–267 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.05 (s, 3H, CH_3–pyrimidine), 3.48 (s, 3H, CH_3–N), 7.38–7.89 (m, 9H, Ar); IR (KBr disc) ν 1667, 1017 cm^{-1}. *m/z* 390 (M^+), 392 ($M^+ + 2$); Anal. Calcd for $C_{20}H_{15}ClN_6O$: C, 61.46; H, 3.87; N, 21.50. Found: C, 61.39; H, 3.86; N, 21.49%.

*1,5-Dimethyl-7-(4-nitrophenyl)-3-phenyl-1*H-*[1,2,4]triazolo[4',3': 1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(5e):** Yield = 61%, m.p. = 280–282 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.09 (s, 3H, CH_3–pyrimidine), 3.47 (s, 3H, CH_3–N), 7.31–8.50 (m, 9H, Ar); IR (KBr disc) ν 1664, 1019 cm^{-1}. *m/z* 401 (M^+); Anal. Calcd for $C_{20}H_{15}N_7O_3$: C, 59.85; H, 3.77; N, 24.43. Found: C, 59.79; H, 3.73; N, 24.40%.

*Synthesis of 1,5-dimethyl-3-phenyl-7,8-dihydro-1*H-*[1,2,4]triazolo [4',3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine-7-thione* **(6):** A solution of3-phenyl-1,5-dimethyl-7-hydrazino-1H-pyrimido[4,5-e][1,3,4]oxadiazine **(3)** (1 mmol, 0.27 g) and CS_2 (1 mL) in dry pyridine (7 mL) was refluxed for 6 h. Then, the mixture was cooled to room temperature and the resulting solid was filtered off and recrystallised from ethanol. Yield = 82%, m.p. = 297–299 °C ^{1}H NMR ($CDCl_3$, ppm) δ 2.60 (s, 3H, CH_3–pyrimidine), 3.42 (s, 3H, CH_3–N), 7.3–7.8 (m, 5H, ph), IR: ν 3320, 3010, 2950, 1460, 1365 cm^{-1}, *m/z* 312 (M^+), Anal. Calcd for $C_{14}H_{12}N_6OS$: C, 53.83; H, 3.87; N, 26.91; S, 10.27. Found: C, 53.64; H, 3.64; N, 26.88; S, 10.02%.

Preparation of 7-alkylsulfinyl-1,5-dimethyl-3-phenyl-1H-[1,2,4] triazolo [4',3':1,2]pyrimido[4,5-e][1,3,4]oxadiazines **7a–e***; general procedure*

To a solution of compound **(6)** (0.3 mmol, 0.7 g) and an appropriate alkyl halide (0.9 mmol) in a mixture of DMF:MeCN (1:5) (12 mL) as solvent, Et_3N (0.9 mmol) was added and the solution was refluxed for 4 h. After the completion of the reaction which was monitored by TLC using chloroform: methanol (9:1), the solvent was removed under reduced pressure. The crude solid was recrystallised from ethanol.

*1,5-Dimethyl-7-(methylsulfanyl)-3-phenyl-1*H-*[1,2,4]triazolo[4', 3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(7a):** Yield = 75%, m.p. = 238–240 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.70 (s, 3H, CH_3–pyrimidine), 2.77 (s, 3H, CH_3–S), 3.45 (s, 3H, CH_3–N), 7.35–7.56 (m, 3H, ph), 7.70–7.89 (m, 2H, ph), IR: ν 3020, 2990, 1592 cm^{-1}, *m/z* 326 (M^+), Anal. Calcd for $C_{15}H_{14}N_6OS$: C, 55.20; H, 4.32; N, 25.75; S, 9.82. Found: C, 55.17; H, 4.22; N, 25.66; S, 9.79%.

*7-(Ethylsulfanyl)-1,5-dimethyl-3-phenyl-1*H-*[1,2,4]triazolo[4',3': 1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(7b):** Yield = 67%, m.p. = 221–223 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 1.43 (t, 3H, CH_3), 2.73 (s, 3H, CH_3–pyrimidine), 3.28 (q, 2H, CH_2), 3.45 (s, 3H, CH_3-N), 7.36–7.53 (m, 3H, ph), 7.74–7.88 (m, 2H, ph), IR: ν 3010, 2980, 1590 cm^{-1}, *m/z* 340 (M^+), Anal. Calcd for $C_{16}H_{16}N_6OS$: C, 56.45; H, 4.74; N, 24.69; S, 9.42. Found: C, 56.40; H, 4.62; N, 24.51; S, 9.33%.

*1,5-Dimethyl-3-phenyl-7-(n-propylsulfanyl)-1*H-*[1,2,4]triazolo[4', 3':1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(7c):** Yield = 70%, m.p. = 201–202 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 1.05 (t, 3H, CH_3), 1.85 (sextet, 2H, CH_2), 2.74 (s, 3H, CH_3–pyrimidine), 3.31 (t, 2H, CH_2), 3.46 (s, 3H, CH_3–N), 7.40–7.61 (m, 3H, ph), 7.75–7.89 (m, 2H, ph), IR: ν 3015, 2985, 1580 cm^{-1}, *m/z* 354 (M^+), Anal. Calcd for $C_{17}H_{18}N_6OS$: C, 57.61; H, 5.12; N, 23.71; S, 9.05. Found: C, 57.56; H, 5.01; N, 23.66; S, 8.90%.

*7-(Benzylsulfanyl)-1,5-dimethyl-3-phenyl-1*H-*[1,2,4]triazolo[4',3': 1,2]pyrimido[4,5-*e*][1,3,4]oxadiazine* **(7d):** Yield = 79%, m.p. = 210–211 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.52 (s, 3H, CH_3–pyrimidine), 3.45 (s, 3H, CH_3-N), 4.48 (s, 2H, CH_2), 7.34–7.53 (m, 3H, ph), 7.71–7.78 (m, 2H, ph), IR: ν 3030, 2990, 1590 cm^{-1}, *m/z* 402 (M^+), Anal. Calcd for $C_{21}H_{18}N_6OS$: C, 62.67; H, 4.51; N, 20.88; S, 7.97. Found: C, 62.57; H, 4.49; N, 20.84; S, 7.91%.

[(1,5-Dimethyl-3-phenyl-1H-[1,2,4]triazolo[4',3':1,2]pyrimido[4,5-e][1,3,4]oxadiazin-7-yl)sulfanyl]methyl cyanide **(7e):** Yield = 63%, m.p. = 238–240 °C, ^{1}H NMR ($CDCl_3$, ppm) δ 2.77 (s, 3H, CH_3–pyrimidine), 3.47 (s, 3H, CH_3-N), 4.03 (s, 2H, CH_2CN), 7.40–7.85 (m, 5H, ph), IR: ν 3020, 2980, 2220, 1570 cm^{-1}, *m/z* 351 (M^+), Anal. Calcd for $C_{16}H_{13}N_7OS$: C, 54.69; H, 3.73; N, 27.90; S, 9.13. Found: C, 54.60; H, 3.70; N, 27.87; S, 9.02%.

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