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Novel synthesis of Pyrimido[4,5- *e*] [1,3,4] thiadiazines

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Abstract – Treatment of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine with dimethylthiocarbamoylchloride gave 7-chloro-*N*,*N*,1,5-tetramethyl-1H-pyrimido[4,5-e][1,3,4]thiadiazin-3-amine in basic acetonitrile. The latter compounds were reacted with secondary amines in boiling ethanol to afford the related 7-amino derivatives.

Keywords: 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine, dimethylthiocarbamoylchloride, pyrimidothiadiazine, 15- lipoxygenase.

Introduction

Despite significant advances in medical sciences, cancer is still an intractable disease in human and is a major cause of death around the world **.** The treatment of cancer is still required. Tnus, there has been increscent interest in the field of cancer chemotherapy by discovery and development of novel drugs with high efficacy, low toxicity, and minimum side effects **.** During recent years, several research developed different noel small molecule poly cyclic aromatic hydrocarbon (PAHs) heterocycles with potential antineoplastic activity . In this view, privileged heterocyclic structures have been constructed around the acenaphthene core. Some of the acenaphthene derivatives containing thiazole backbone have been reported as antitumor agents **.**

We are currently witnessing a decline in the development of efficient new anti cancer drugs, despite the salient effort made on all fronts of cancer drug discovery. This trend presumably relates to the substantial heterogeneity and the inherent biological complexity of cancer, which hinder drug development success. Protein-protein intractions (PPIs) are key player in numerous cellular processes and abberant interruption of this complex network provides a basis for various disease states, including cancer. We attempt to access diversity space for the discovery of small molecules that disrupt oncogenic PPIs, namely Bcl-2 intractions**.**

Our motives in pyrimido[4,5- *e*] [1,3,4] thiadiazine synthesis emerges from few reports on their variety biological applications. These compounds have been described as being nucleoside analogues [1,2], antiinflammatory, hypotensive, diuretic [3,4], and phosphodiesterase inhibitor [4] agents. Despite their importance from pharmacological and synthetic point of views, comparatively few methods for their preparation have been reported. This report and pursuing of our research on biologically active compounds [5-8], convinced us to prepare a novel group of this class of heterocycles.

Exprimental

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu Spectrometer. The ^{1}HNMR (100 MHz) spectra were recorded on a Bruker AC 100 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV. Elemental

analysis was obtained on a Thermo Finnigan Flash EA microanalyzer. 1-(5-Bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** and its precursor were prepared according to published method [9,10].

7-Chloro-*N*,*N*,1,5-tetramethyl-1*H*-pyrimido[4,5-*e*][1,3,4] thiadiazin-3-amine (3)

1-(5-Bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** (2.5 gr, 10 mmol), dimethythiocarbamoylchloride (1.23 gr, 10mmol) and triethyamine (3ml) were dissolved in acetonitrile (20ml) and boiled under reflux condition for 3 hr. The solvent was removed under *vacuu* and the residue was recrystallized from hexane to obtaine yellow powder in 70% yield. mp 47-49 ^{o}C; IR: 800, 2900, 2950 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 2.25 (s, 3H, 5-CH_3), 3.11 & 3.17 (s, 6h, N(Me)$_2$), 3.4 (s, 3H, 1-CH_3); ms: m/z , 257 (60), 259 (20). *Anal*. Calcd. for $C_9H_{12}ClN_5S$: C, 41.94; H, 4.69; N, 27.17; S, 12.44 Found : C, 42.16; H, 4.78; N, 26.96; S, 12.21.

General procedure for the reaction of 7-Chloro-*N*,*N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (3) with amines

7-Chloro-*N*,*N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*] [1,3,4]thiadiazin-3-amine **3** (2 mmol) in ethanol (10ml) was heated under reflux with 1ml of either morpholine, pyrrolidine, piperidine, 1-methylpiperazine or 1-phenylpiperazine for 4 hr. The solvent was removed under *vacuu* and the residue was recrystallized from ethanole to obtaine compounds **4a-e**.

Charactristic data

N,*N*,1,5-Tetramethyl-7-(morpholin-4-yl)-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4a**)

This compound was obtained as a green powder in 60% yield, mp 77-78 ^{o}C; IR: 2890, 2930 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 2.16 (s, 3H, 5-CH_3), 3.02 & 3.08 (s, 6h, N(Me)$_2$), 3.35 (s, 3H, 1-CH_3), 3.73 (m, 8H, CH_2-(O&N)); ms: m/z , 308. *Anal*. Calcd. for $C_{13}H_{20}N_6OS$: C, 50.63; H, 6.54; N, 27.25; S, 10.40 Found : C, 50.91; H, 6.78; N, 27.07; S, 10.18.

N,*N*,1,5-Tetramethyl-7-(pyrrolidin-1-yl)-1*H*-pyrimido [4,5-*e*][1,3,4]thiadiazin-3-amine (**4b**)

This compound was obtained as a green powder in 70% yield, mp 72-74 ^{o}C; IR: 2900, 2930 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 1.93(t, 4H, 2 ((CH_2)-CH_2N), 2.15 (s, 3H, 5-CH_3), 3.03 & 3.10 (s, 6h, N(Me)$_2$), 3.37 (s, 3H, 1-CH_3), 3.55 (t, 4H, 2(CH_2N)); ms: m/z , 292. *Anal*. Calcd. for $C_{13}H_{20}N_6S$: C, 53.40; H, 6.89; N, 28.74; S, 10.97 Found : C, 53.61; H, 6.97; N, 28.57; S, 10.71.

N,*N*,1,5-Tetramethyl-7-(piperidin-1-yl)-1*H*-pyrimido [4,5-*e*][1,3,4]thiadiazin-3-amine (**4c**)

This compound was obtained as a green powder in 75% yield, mp 83-85 ^{o}C; IR: 2870, 2910 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 1.2-1.7 (m, 6H, 3CH_2), 2.17 (s, 3H, 5-CH_3), 3.04 & 3.11 (s, 6h, N(Me)$_2$), 3.32 (s, 3H, 1-CH_3), 3.52 (t, 4H, 2(CH_2N)); ms: m/z , 306. *Anal*. Calcd. for $C_{14}H_{22}N_6S$: C, 54.87; H, 7.24; N, 27.43; S, 10.46 Found : C, 55.09; H, 7.38; N, 27.25; S, 10.21.

N,*N*,1,5-Tetramethyl-7-(4-methylpiperazin-1-yl)-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4d**)

This compound was obtained as a green powder in 55% yield, mp 65-67 ^{o}C; IR: 2850, 2920 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 2.15 (s, 3H, 5-CH_3), 2.30 (m, 7H, 2(CH_2N)-CH_3), 3.04 & 3.10 (s, 6h, N(Me)$_2$), 3.34 (s, 3H, 1-CH_3), 3.49 (t, 4H, 2(CH_2N)); ms: m/z , 321. *Anal*. Calcd. for $C_{14}H_{22}N_6S$: C, 52.31; H, 7.21; N, 30.50; S, 9.98 Found : C, 52.55; H, 7.39; N, 30.28; S, 9.71.

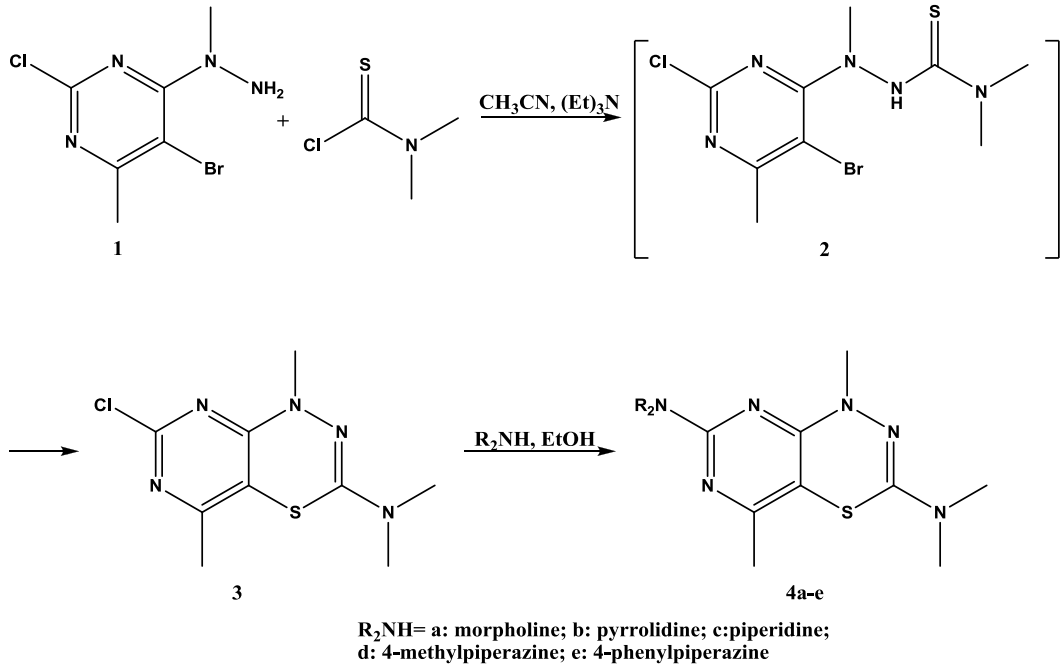
N,*N*,1,5-Tetramethyl-7-(4-phenylpiperazin-1-yl)-1*H*-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine (**4d**)

This compound was obtained as a green powder in 80% yield, mp 92-94 ^{o}C; IR: 2870, 2940 cm-^{1}; ^{1}HNMR: ($CDCl_3$) δ, 2.17 (s, 3H, 5-CH_3), 2.37 (t, 4H, 2(CH_2N)-Ph), 3.03 & 3.09 (s, 6h, N(Me)$_2$), 3.35 (s, 3H, 1-CH_3), 3.52 (t, 4H, 2(CH_2N)), 7.2-7.5 (m, 5H, aromatic); ms: m/z , 383. *Anal*. Calcd. for $C_{19}H_{25}N_7S$: C, 59.50; H, 6.57; N, 25.57; S, 8.36 Found : C, 59.75; H, 6.71; N, 25.32; S, 8.12.

Results

The current synthesis is based upon intramolecular heterocyclization of the key intermediate hydrazinecarbothioamide **2** which was *in situ* prepared from the reaction of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine **1** with dimethylthiocarbamoylchloride as shown in Scheme 1.

In the second stage 7-chloro-*N*,*N*,1,5-tetramethyl-1H-pyrimido[4,5-*e*][1,3,4]thiadiazin-3-amine **3** was reacted with secondary amines in boiling ethanol to afford the new pyrimido[4,5-*e*][1,3,4]thiadiazine derivatives **4a-e**.



Scheme 1: preparation of compounds **3** and **4a-e**.

The structure of new derivatives **3** and **4a-e** were confirmed by their spectral and microanalytical data. The IR spectrum of **3** was devoid of the stretching vibration bands at 3450 & 3300 cm^{-1} due to NH_2 functionality of the precursor **1** or intermediate **2**. The ^1H NMR spectrum of **3** was also devoid of the broad NH_2 signal at δ 4.2 ppm of the precursor but showed two singlets at δ 3.11 & 3.17 ppm assignable to 6 protons for $N(Me)_2$ group which indicates the formation of compound **3**. The molecular ions of **3** (M: M+2) was observed at 257 & 259 (60%:20%) corresponding to the molecular formula $C_9H_{12}ClN_5S$, which was adequately confirmed by its elemental analysis (C, 42.16; H, 4.78; N, 26.96; S, 12.21).

The IR spectra of compounds **4a-e** did not show the stretching vibration band of C-Cl of the precursor **3** and verified the replacement of chlorine atom by amines, which

was amplified by lacking of the expected isotopic pattern of chlorine atom in their mass spectra. The ^{1}H NMR spectra of **4a-e** also sowed the methylen groups due the substituted amines plus a slight shift of methyl groups of their precursor **3** to high field.

Conclusion

In conclusion sequential treatment of 1-(5-bromo-2-chloro-6-methylpyrimidin-4-yl)-1-methylhydrazine with dimethylthiocarbamoylchloride and amines is a general and convenient access to novel pyrimido[4,5- *e*] [1,3,4] thiadiazines.

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