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## Research Paper

### Synthesis of new acetamides encompassing Thiazolidinedione and Pyrimidines

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**Abstract:** Synthesis of dioxothiazolidin-5-yl)-N-(4,6-diphenylpyrimidin-2-yl) acetamides, (**6a-h**) has been carried. The new amides were obtained by condensing 2, 4-thiazolidinedione acetic acid (**5**) with 4, 6-disubstituted amino pyrimidines, (**4a-h**) in the presence of coupling reagent, DCC. The precursors, 4, 6-disubstituted amino pyrimidines, required for the synthesis have been freshly prepared by carrying one pot multicomponent cyclocondensation of aromatic aldehydes, (**1a-h**) aromatic acetophenones, (**2a-h**) and guanidine hydrochloride (**3**) in aqueous PEG-400 in the presence of KOH.

## Introduction

Pyrimidine scaffold is one of the most wanted pharmacophores.<sup>[1]</sup> Pyrimidines show elegant pharmacological activities viz. analgesics<sup>[2]</sup> and anti-inflammatory.<sup>[3]</sup> Pyrimidines occur in pesticides<sup>[4]</sup> and plant growth regulators.<sup>[5]</sup> Lobeglitazone,<sup>[6]</sup> Sulfadimidine<sup>[7]</sup> and Bacimethrin<sup>[8]</sup> are having pyrimidine moieties and display antidiabetic, antibacterial and antibiotic activities, respectively. Naturally occurring L- lathrine displays wide range of biological activities such as hypoglycemic and antitumor.<sup>[9]</sup> Some pyrimidines are valuable drugs for the treatment of hyperthyroidism, acute leukemia in children and adult granulocytic leukemia.<sup>[10]</sup> The polysubstituted pyrimidines<sup>[11]</sup> are also used

for the treatment of hypoxemia,<sup>[12]</sup> neuronosis<sup>[13]</sup> and neuropathy.<sup>[14]</sup> Pyrimidines also act as potential antitumor agents.<sup>[15]</sup>

Thiazolidinedione derivatives have been displayed wide variety of bioactivities like, antimicrobial,<sup>[16]</sup> protein tyrosine phosphate inhibitor,<sup>[17]</sup> anticancer,<sup>[18]</sup> follicle stimulating hormone (FSH) agonists,<sup>[19]</sup> anticonvulsant,<sup>[20]</sup> antidiabetic,<sup>[21]</sup> Ca<sup>2+</sup> channel blocker<sup>[22]</sup> and anti HIV.<sup>[23]</sup>

Amide linkages are present in various antidiabetic drugs like, KRP-297,<sup>[24]</sup> PF00287586,<sup>[25]</sup> RO0274375<sup>[26]</sup> and Benzaifibrate.<sup>[27]</sup> Chittiboyina *et. al.* have synthesized dithiolane thiazolidinedione having amido bond and PPAR agonist property.<sup>[28]</sup> Amido linkages are found to be present in c-Jun N-terminal kinase-1 (JNK-

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1) inhibitors<sup>[29]</sup> and they are found to be useful in treating type II diabetes mellitus.

There is scanty information on the heteryl molecules having 2,4-thiazolidinedione and pyrimidine ring systems bridged by amido linkers. Considering the pharmacological importance of 2, 4-thiazolidinediones, pyrimidines and amido group here it was thought worthwhile to bridge 2, 4-thiazolidinediones, pyrimidines by amido linker for obtaining the new products, expecting intensified pharmacological activity.

## Results and Discussion

4, 6-Diarylsubstituted amino pyrimidines, (**4a-h**) (**Table 1**) were synthesized by allowing the interaction of multicomponents aromatic aldehydes, (**1a-h**) aromatic acetophenones, (**2a-h**) and guanidine hydrochloride, (**3**) in PEG-400 in presence of KOH at r.t.<sup>[30]</sup> A series of new dioxothiazolidin-5-yl)-N-(4, 6-diphenylpyrimidin-2-yl) acetamides, (**6a-h**) has been prepared by condensing 2, 4-thiazolidinedione acetic acid (**5**) with 4, 6-disubstituted amino pyrimidines, (**4a-h**) in DMF using coupling reagent, N, N-dicyclohexylcarbodiimide (DCC) at room temperature (**Scheme 1**).

In one of the efforts the condensation of acid chloride derived from the interaction of 2,4-thiazolidineacetic acid and thionyl chloride and 4,6-disubstitued amino pyrimidines has been carried in the presence of pyridine at r. t. for obtaining the titled acetamides (**6a-h**). Here it was noticed that this route gave poor yields of the products and has two steps. The reagents required for this route are pyridine and thionyl chloride other than the condensing reagent, which are toxic and irritant.

Then these condensation was safely carried by allowing the interactions of 2, 4-thiazolidineacetic acid, (**5**) and the amino pyrimidines, (**4**) in DMF using DCC as coupling reagent at r. t. These protocol gave better yields of the desired acetamides, (**6a-h**) and has been found to be relatively convenient and safe (**Table 2**).

## Conclusions

We have developed a convenient route for the synthesis of new thiazoldinediones containing pyrimidines bridged by amido linker using coupling reagent DCC. The starting materials required for the synthesis, amino pyrimidines have been freshly and easily obtained in greener reaction medium, PEG-400, starting from readily available materials..

## Experimental Section

Solvents and reagents were of LR grade, obtained from commercial sources and used without further purification. <sup>1</sup>H-NMR spectra were recorded at 300 MHz on Bruker DRX-300. <sup>13</sup>C-NMR spectra were recorded at 100 MHz on Jeol. The mass spectra were recorded on JEOL – Accu TOF DART-MS- T 100Lc. Melting points are determined following open capillary method and are uncorrected.

### Synthesis of 2-Amino-4, 6 diarylpyrimidines (**4a-h**)

Potassium hydroxide (25 mmol) was dissolved in 90 % aq. PEG-400 (10 mL). To the above solution acetophenone (10 mmol) was added and the reaction content was stirred for 0.5 h. After that aromatic aldehyde (10 mmol) was introduced to the stirred mass and stirring was then continued at room temperature for 5.5 h. The progress of the reaction was monitored by thin layer chromatography. After confirming *in situ*

formation of the intermediate chalcone, then guanidine hydrochloride (12 mmol) was added to the reaction mass in portions. The progress of the reaction was monitored by TLC. The reaction content was further stirred at room temperature for 4 h till the completion of the condensation. It was then poured on ice cold water. The obtained solid was filtered, washed with water and crystallized using proper solvent. PEG-400 was recovered from the filtrate by vacuum distillation of the aqueous filtrate and recycled for the same reaction sequence. The melting points and the yields of the derivatives are recorded in the **Table 1**.

#### Synthesis of dioxothiazolidin-5-yl)-N-(4, 6-diphenylpyrimidin-2-yl) acetamides (6a-h)

A mixture of 2, 4-thiazolidinedione acetic acid **5** (10 mmol) and DCC (11mmol) was stirred in DMF (30 mL) at 0°C for 30 min. To this solution 4, 6-disubstituted amino pyrimidines, (**4a-h**) (10 mmol) was added. The progress of the reaction was monitored by TLC. After stirring the reaction mass for 6.5 h. it was diluted using ethyl acetate (60 mL) and again stirred at r. t. for five minutes. The diluted reaction mass was filtered. The filtrate was washed successively with HCl (2N), aq. solution of sodium carbonate and brine solution. The organic layer was then vacuum distilled and the solid residue was purified using column employing mobile phase, ethyl acetate and petroleum ether (7:3). The melting points

and the yields of the desired products, (**6a-h**) are recorded in the **Table 2**.

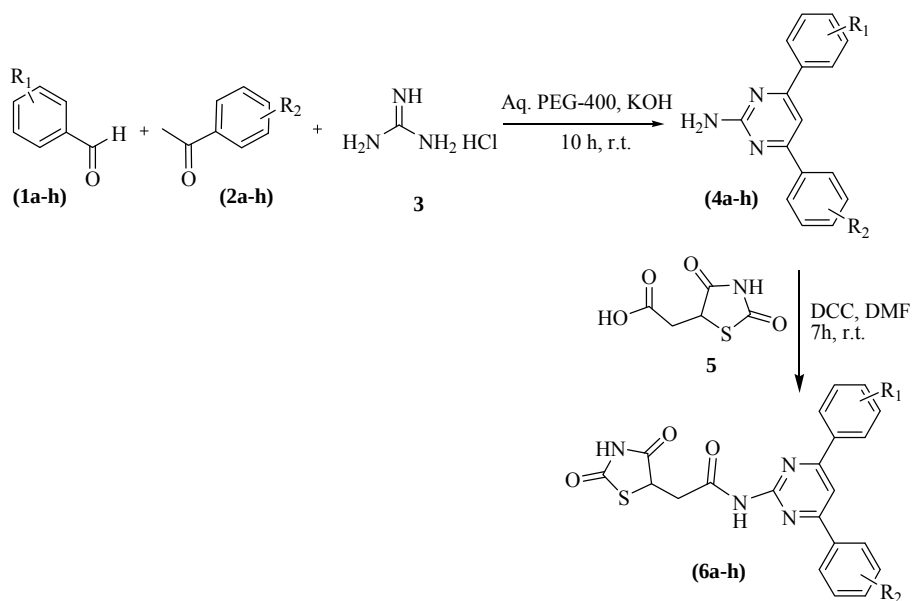
#### Sepctral data of a representative:

##### N-(4-(4-hydroxyphenyl)-6-(4-methoxyphenyl) pyrimidin-2-yl)-2-(2,4-dioxothiazolidin-5-yl) acetamide (6h).

<sup>1</sup>H-NMR (300 MHz, DMSO-*d*<sub>6</sub>, δ ppm): 3.14 (d, 2H, methylene proton, 2,4-TZD AcOH, overlap), 3.45 (s, 3H, -OCH<sub>3</sub>), 3.83 (t, 1H, methyne proton, 2,4-TZD, overlap), 5.57 (s, 1H, OH exchangeable with D<sub>2</sub>O), 6.87 (d, 2H, *J* = 8.0Hz, ArH), 7.06 (d, 2H, *J*=8.0Hz, ArH), 7.53 (s, 1H, pyrimidine ArH), 8.08 (d, 2H, *J* = 8 Hz, ArH), 8.17 (d, 2H, *J* = 8 Hz, ArH), 9.88 (s, 1H, NH, CONH, exchangeable with D<sub>2</sub>O) and 11.94 (s, 1H, NH, exchangeable with D<sub>2</sub>O). Maldi Toff (Scanning mode ESI<sup>+</sup>): *m/z* (% intensity): 451 (M<sup>+</sup>). <sup>13</sup>C-NMR (100 MHz, DMSO-*d*<sub>6</sub>, δ ppm); 33.80, 48.03, 55.82, 100.49, 114.39 (2C), 115.78 (2C), 128.94(2C), 129.09(2C), 132.00, 133.02, 150.10 (2C), 160.01 (2C), 160.17(2C), 160.20(2C), 164.30 (2C) and 165.01(2C).

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**Scheme 1** Synthesis of dioxothiazolidin-5-yl)-N-(4, 6-diphenylpyrimidin-2-yl) acetamides.

**Table 1** One pot synthesis of amino pyrimidines in aq.PEG-400 (**4a-h**)

| Entry | R <sub>1</sub>     | R <sub>2</sub>     | Products <sup>b</sup> | M. P. (°C) | Yields (%) <sup>a</sup> |
|-------|--------------------|--------------------|-----------------------|------------|-------------------------|
| 1     | 4-CH <sub>3</sub>  | H                  | <b>4a</b>             | 119-120    | 85                      |
| 2     | 4-F                | H                  | <b>4b</b>             | 118-120    | 82                      |
| 3     | 4-Cl               | H                  | <b>4c</b>             | 146-148    | 87                      |
| 4     | 2-Cl               | H                  | <b>4d</b>             | 120-122    | 86                      |
| 5     | 4-Cl               | 4-OCH <sub>3</sub> | <b>4e</b>             | 148-149    | 89                      |
| 6     | 4-CH <sub>3</sub>  | 4-OCH <sub>3</sub> | <b>4f</b>             | 128-129    | 87                      |
| 7     | 4-Br               | H                  | <b>4g</b>             | 153-155    | 82                      |
| 8     | 4-OCH <sub>3</sub> | 4-OH               | <b>4h</b>             | 180-182    | 87                      |

<sup>a</sup>Isolated yields. <sup>b</sup>Melting points of 4a-h are in good agreement with those reported earlier. <sup>[30]</sup>

**Table 2** 2-(2, 4-dioxothiazolidin-5-yl)-N-(4, 6-diphenylpyrimidin-2-yl) acetamides (**6a-h**)

| Entry | R <sub>1</sub>     | R <sub>2</sub>     | Products  | M. P. (°C) | Yields (%) <sup>a</sup> |
|-------|--------------------|--------------------|-----------|------------|-------------------------|
| 1     | 4-CH <sub>3</sub>  | H                  | <b>6a</b> | 183-185    | 73                      |
| 2     | 4-F                | H                  | <b>6b</b> | 125-127    | 71                      |
| 3     | 4-Cl               | H                  | <b>6c</b> | 119-121    | 74                      |
| 4     | 2-Cl               | H                  | <b>6d</b> | 165-167    | 72                      |
| 5     | 4-Cl               | 4-OCH <sub>3</sub> | <b>6e</b> | 122-123    | 77                      |
| 6     | 4-CH <sub>3</sub>  | 4-OCH <sub>3</sub> | <b>6f</b> | 138-139    | 76                      |
| 7     | 4-Br               | H                  | <b>6g</b> | 132-133    | 74                      |
| 8     | 4-OCH <sub>3</sub> | 4-OH               | <b>6h</b> | 201-202    | 78                      |

<sup>a</sup>Isolated yields.

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