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# Syntheses and Evaluation of Pyrido[2,3-*d*]pyrimidine-2,4-diones as PDE 4 Inhibitors

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**Abstract**—The syntheses and in vitro evaluation of a new series of pyrido[2,3-*d*]pyrimidine-2,4-diones bearing substituents at C-3 and/or C-4 positions on the pyridine ring are described. Some of these compounds, especially **5l** and **6f**, were found to be potent phosphodiesterase 4 (PDE 4) inhibitors exhibiting improved ratio of PDE 4 inhibitory activity:rolipram binding assay (RBA).


The phosphodiesterase (PDE) family[1] is particularly abundant in immunocompetent cells, where an increase of cAMP leads to the inhibition of the synthesis and the release of pro-inflammatory mediators.[2] Due to their crucial role in regulation of cell function, PDEs have become good clinical targets for the treatment of inflammation,[3] asthma,[4] erectile dysfuncion,[5] etc. Persistent efforts and desire to elucidate the active site of PDEs make possible to solve the three-dimensional structure of the catalytic domain of phosphodiesterase 4 (PDE 4).[6] Since the discovery of rolipram,[7] the first PDE 4 inhibitor, a number of compounds such as SB-207499 have been synthesized to increase the activity and to reduce side effects such as vomiting, nausea, etc.[8,9] Despite much progress in the development of PDE 4 inhibitors, the search for new scaffolds to reduce side effects is worth continuing as well.

It has recently been reported that a number of compounds such as RS-25344[10] and CP-77059[11] bearing the pyridopyrimidine moiety exhibited excellent PDE 4 inhibitory activity (Fig. 1). However, there has been no report on the evaluation of pyridopyrimidine analogues having substitutents on the pyridine ring for PDE 4

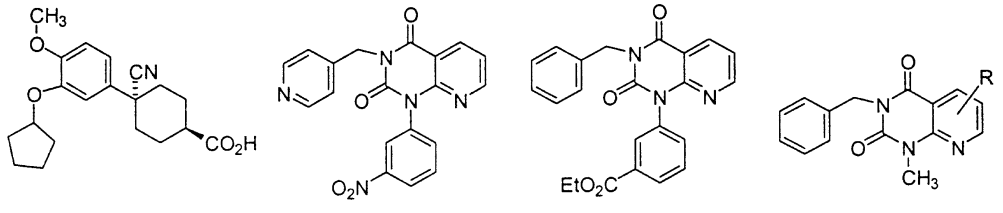


**Figure 1.**

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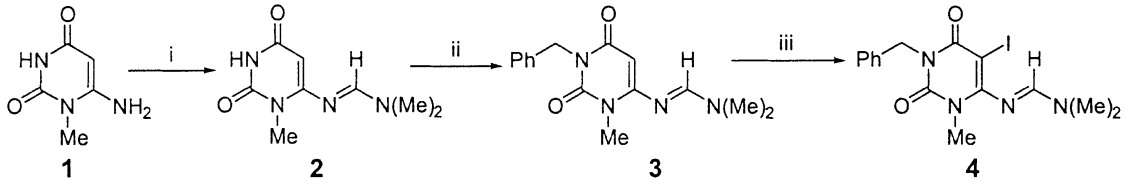
inhibitors so far. In this paper, we wish to report the syntheses of new pyridopyrimidine derivatives represented by compound A and the evaluation for PDE 4 inhibitory activity and rolipram binding affinity.

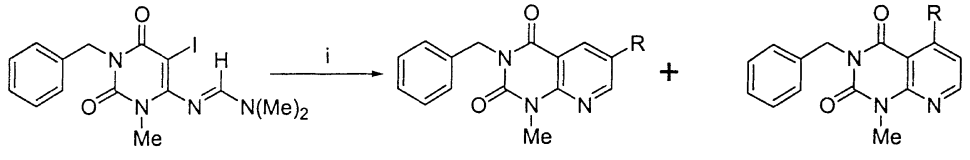
## Chemistry

The compounds **A** were synthesized using palladium catalyzed Heck coupling reaction of **4**, followed by ring cyclization according to our reported procedure.[12] The key intermediate **4** was easily prepared by the reaction of commercially available aminouracil **1** with DMF–DMA, followed by *N*-benzylation of the resultant product **2** with benzylchloride affording **3** and vinyl iodination of **3** with *N*-iodosuccinimide in MeOH (Scheme 1).

Heck coupling of **4** with appropriate vinyl substrates, followed by ring cyclization formed the regio-isomeric mixture of pyridopyrimidine compounds **5** and **6**. It has been found that the ratio of **5** and **6** is dependent on the substituents R. In the case of the reaction with *n*-butylvinyl ether was obtained only **6a**. However, the reactions with acrylonitrile, ethyl acrylate, 2-trifluorostyrene and 3-nitrostyrene afforded only the C-3 substituted isomers **5b**, **5c**, **5i** and **5j**, respectively. All other



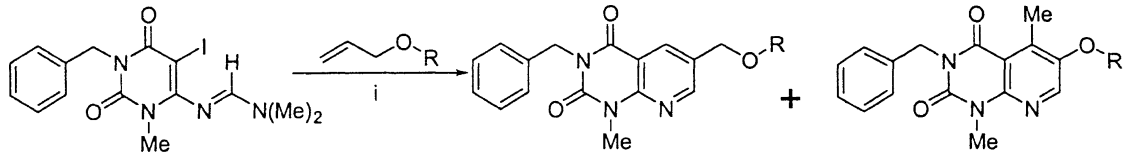

**Scheme 1.** (i) DMF–DMA, MeOH, reflux, 88%; (ii) benzylchloride, $K_2CO_3$, DMF, reflux, 70%; (iii) NIS, MeOH, reflux, 93%.




| R | O-*n*-Bu | CN | $CO_2Et$ | Ph | Ph(4-Cl) | Ph(4-F) |
|---|---|---|---|---|---|---|
| **5** (%) | — | **5b** (73) | **5c** (78) | **5d** (28) | **5e** (45) | **5f** (78) |
| **6** (%) | **6a** (74) | — | — | **6d** (11) | **6e** (55) | **6f** (22) |

| R | Ph(4-OEt) | Ph(2-F) | Ph(2-$CF_3$) | Ph(3-$NO_2$) | Ph(3-$CF_3$) | $CH_2Ph$ |
|---|---|---|---|---|---|---|
| **5** (%) | **5g** (45) | **5h** (41) | **5i** (30) | **5j** (70) | **5k** (61) | **5l** (42)) |
| **6** (%) | **6g** (38) | **6h** (38) | — | — | **6k** (34) | **6l** (20) |

**Scheme 2.** (i) $CH_2$=CH-R, $Pd(OAc)_2$ (5 mol%), $K_2CO_3$ (2 equiv), $PPh_3$ (0.1 equiv), DMF, 120 °C.




| R | **7** (%) | **8** (%) |
|---|---|---|
| *n*-Pr | **7a** (17) | **8a** (9) |
| Ph | **7b** (25) | -- |
| Bn | **7c** (22) | **8c** (12) |

**Scheme 3.** (i) $Pd(OAc)_2$ (5 mol%), $K_2CO_3$ (2 equiv), $PPh_3$ (0.1 equiv), DMF, 110 °C.

**Table 1.** PDE 4 inhibitory activity of pyridopyrimidine derivatives **5**–**8**

| | PDE 4 inhibition (μM) (A)[a,13] | | | | | | RBA[b], $IC_{50}$[14] (μM) (B) | B/A |
|---|---|---|---|---|---|---|---|---|
| Compounds | 10 μM | 3 μM | 1 μM | 0.3 μM | 0.1 μM | $IC_{50}$ (μM) | | |
| **5b** | 44.6 | 29.9 | 21.9 | ND[c] | ND | >10 | ND | |
| **5c** | 48.3 | 43 | 30.3 | ND | ND | >10 | ND | |
| **5d** | 40.4 | 31.3 | 17.4 | ND | ND | >10 | ND | |
| **5e** | 49.0 | 47.8 | 35.5 | ND | ND | >10 | ND | |
| **5f** | 55.1 | 44 | 41.4 | ND | ND | 5.75 | ND | |
| **5g** | 32.6 | 30.2 | 31.5 | ND | ND | >10 | ND | |
| **5h** | 48.0 | 46.4 | 40.7 | ND | ND | >10 | ND | |
| **5i** | 65.4 | 53.7 | 38.1 | ND | ND | 2.31 | ND | |
| **5j** | 36.0 | 23.5 | 17.4 | ND | ND | >10 | ND | |
| **5k** | 42.4 | 37.6 | 31.7 | ND | ND | >10 | ND | |
| **5l** | 72.9 | 68.2 | 60.3 | 54.7 | ND | 0.11 | 23.4 | 212.73 |
| **6a** | 35.9 | 28.2 | 25.6 | 22.6 | ND | >10 | ND | |
| **6d** | 83.7 | 67.6 | 59.8 | 45.7 | ND | 0.43 | 1.01 | 2.35 |
| **6f** | 83.9 | 72.1 | 63.6 | 57.6 | ND | 0.07 | 0.755 | 10.79 |
| **6g** | 38.6 | 35.1 | 19.3 | ND | ND | >10 | ND | |
| **6h** | 89.7 | 69.7 | 66.8 | 53.2 | ND | 0.24 | 0.491 | 2.05 |
| **6k** | 62.3 | 54.3 | 50.2 | 52.3 | ND | 0.95 | 0.95 | 1.00 |
| **6l** | 59.5 | 57.1 | 49.3 | ND | ND | 3.34 | ND | |
| **7a** | 58.7 | 46.7 | 38.2 | ND | ND | 4.48 | ND | |
| **7b** | 53.4 | 45.1 | 39.4 | ND | ND | 6.11 | ND | |
| **7c** | 63.5 | 49.8 | 42.1 | ND | ND | 3.05 | ND | |
| **8a** | 58.0 | 43.5 | 41.7 | ND | ND | 5.15 | ND | |
| **8c** | 51.3 | 49.2 | 41.5 | ND | ND | 4.75 | ND | |
| SB-207499 | ND | 72.2 | 69.1 | 54 | 45.8 | 0.11 | 0.18 | 1.64 |
| Rolipram | 67.8 | ND | 43.8 | 35 | 29.7 | 1.8 | 0.002 | 0.001 |

[a]Isolated from rat liver.
[b]Rolipram binding assay (isolated from rat brain).
[c]ND = not determined.

substrates afforded a mixture of **5** and **6**[15] (Scheme 2). The pyridopyrimidines **7** and **8**[15] were also prepared by the reactions of **4** with allyl ethers (Scheme 3).

## Biological Properties

Table 1 shows the PDE 4 inhibitory activity and rolipram binding affinity of the compounds **5**–**8**. It has been found that all of the C-4 substituted pyridopyrimidine derivatives **6** except the benzyl substituted compound **6l** exhibited more potent inhibitory activity than the corresponding C-3 substituted compounds **5**. The compound **5l** having a benzyl group at the C-3 position exhibited 33 times more potent activity than the C-4 substituted compound **6l**. The compounds **7** and **8** showed also moderate PDE 4 inhibitory activities. For evaluation in high rolipram binding site, we selected five compounds (**5l**, **6d**, **6f**, **6h** and **6k**), of which the activity for PDE 4 was submicromolar. Biological data of **6f** for PDE 4 inhibitory activity and rolipram binding affinity is superior to those of SB-207499.[9b] The inhibitory value of **6f** for PDE 4 is more potent than that of **5l**. Nevertheless, the compound **5l** showed more promising rolipram binding assay data and B/A value. This compound **5l** is under further investigations for anti-inflammatory effect and inhibitory activity for TNF-α production.

## Acknowledgements

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15. Representative procedure for the synthesis of **5**–**8**: The compound **4** (150 mg, 0.36 mmol) was reacted with acrylonitrile (47.3 μL, 0.72 mmol), $K_2CO_3$ (99.3 mg, 0.72 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.018 mmol) in DMF (4 mL) at 120 °C for 5 h in a sealed tube. The resulting mixture was filtered through Celite and extracted with methylene chloride (30 mL×3), washed with water and dried over $Na_2SO_4$. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc:*n*-hexane = 1:3) to give **5b** (76.3 mg, 73%) as a white solid; mp 146–147 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 5.22 (s, 2H), 7.27 (m, 3H), 7.48 (d, $J$ = 7.45 Hz, 2H), 8.71 (d, $J$ = 2.13 Hz, 1H), 8.89 (d, $J$ = 2.13 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 30.26, 45.68, 104.78, 110.98, 116.09, 127.94, 128.34, 129.37, 136.17, 141.76, 151.03, 152.92, 156.90, 159.96, 163.41; IR (KBr pellet, $cm^{-1}$) 3455, 3106, 2947, 2368, 2249, 1720, 1671, 1616, 1491, 1461, 1391, 1347, 1277, 1112, 948, 788, 704, 614.