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Discovery of novel 1,4-dihydropyridine-based PDE4 inhibitors

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ABSTRACT

Substituted 1,4-dihydropyridines were discovered as a novel and potent series of phosphodiesterase 4 (PDE4) inhibitors. Structure–activity relationships within this series have been carried out and studies revealed that the dihydropyridine core, with indole moiety and 3,4-dimethoxybenzyl group, is a potent analogue for PDE4 inhibition. These novel series of compounds were prepared via a 3-component reaction in a single pot. In vitro biological activity, modeling studies and crystallography data are also reported.

Phosphodiesterase 4 (PDE4) is a member of PDE enzyme family and is responsible for the regulation of intracellular cyclic adenosine monophosphate (cAMP).[1] The PDE4s are characterized by selective, hydrolytic degradation of cyclic AMP and sensitivity to inhibition by a wide selection of inhibitors. A number of inhibitors of the PDE4s have been discovered in recent years, and beneficial pharmacological effects resulting from PDE4 inhibition have been shown in a variety of disease models.[2] Therefore, considerable interest continues in the discovery of potent and selective inhibitors of PDE4.

To pursue our investigation on PDE4 inhibiting compounds, we started with the information that derivatives of nicotinic acid possess PDE4 inhibiting properties. Recently, nicotinamide derivatives are claimed as selective inhibitors of PDE4 which may be useful for the treatment of inflammatory diseases such as asthma, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), rheumatoid arthritis and psoriasis, as well as central nervous system (CNS) disorders such as depression.[3] Thus, we decided to explore further on the nicotinamide derivatives and related structural cores for the design of novel compounds, potentially active inhibitors for PDE4 (Fig. 1).

Nitrogen heterocyclic frameworks are prevalent in pharmaceuticals and biologically functional molecules. 1,4-Dihydropyridines (1,4-DHPs) are widely known class of biologically active nitrogen heterocycles as well as analogues of NADH coenzymes. 1,4-DHP scaffold is one of the most versatile pharmacophores since it has been found as the central core in many pharmaceuticals.[4] The well-known marketed drugs are the series of 1,4-DHP-based calcium channel blockers such as cilnidipine, nicardipine, nifedipine, and nimodipine (Fig. 1), which are widely used for the treatment of hypertension and cardiovascular diseases.[4,5] 1,4-DHPs have been considered as prototypical calcium channel blockers to modulate calcium current at the voltage-dependent calcium channels (VDCCs), and widely used in clinic. Cilnidipine is a potent dual blocker for N/L-type VDCCs and is currently used for the treatment of hypertension. Nimodipine and nicardipine are also calcium channel blockers, and inhibited the cyclic AMP phosphodiesterase (PDE) activity of purified PDE in a cell-free preparation. 1,4-DHPs have been reported with miscellaneous new functions in recent years, including antitumor,[6] and anti-diabetic agents,[7] HIV protease inhibitors,[8] and drugs in the treatment of a number of other diseases.[9–11] In addition, the results obtained from the study with 1,4-DHPs as inhibition and activation of Sirtuins,[12] inhibition of cytochrome P450,[13] ACE inhibition, and blood pressure control on chronic, non-diabetic nephropathies.[14]

Thus, designing and screening compounds, searching for novel biological activity of 1,4-DHPs is highly desirable work. To the best of our knowledge, this is the first report of new function of 1,

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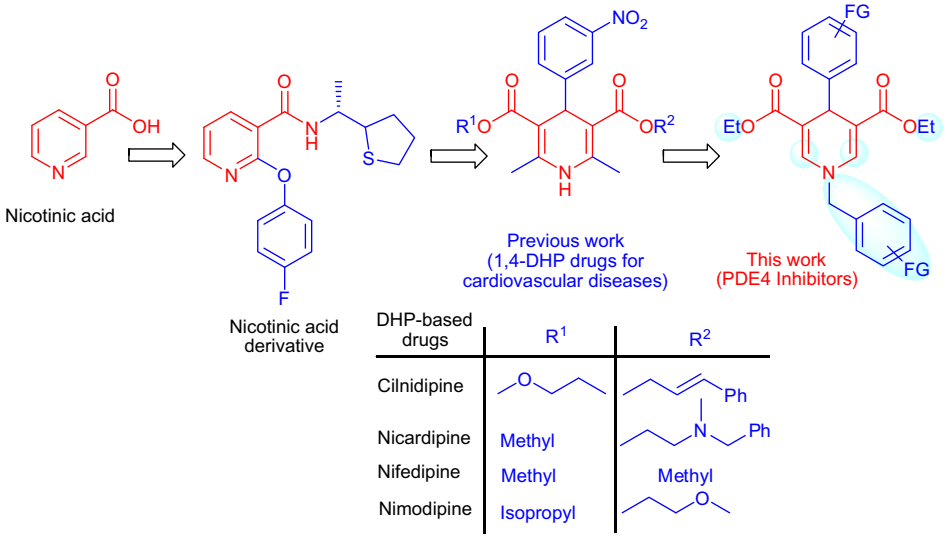
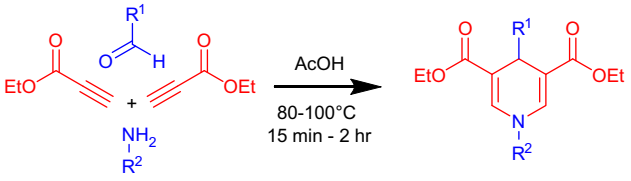


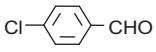
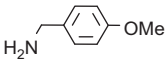
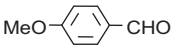
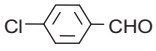
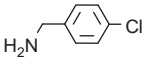
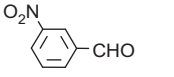
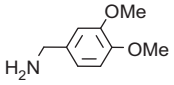
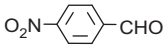
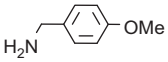
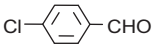
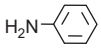
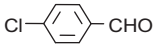
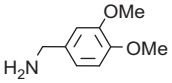
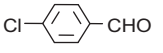
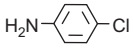
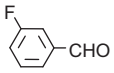
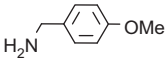
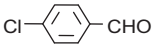
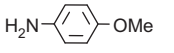
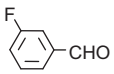
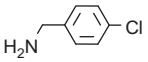
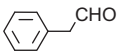
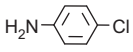
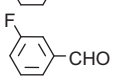
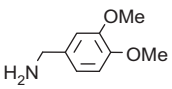
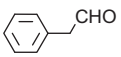
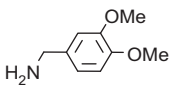
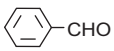
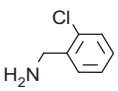
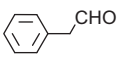
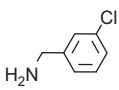
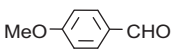
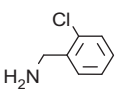
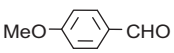
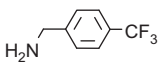
Figure 1. Nicotinic acid and dihydropyridine derivatives.



Scheme 1. Synthesis of substituted 1,4-dihydropyridine derivatives.

4-DHPs. Here, we examined the potential of the previously unexplored dihydropyridine scaffold in developing PDE4 inhibitors; we have screened our in-house compound collection in search of novel class of inhibitors. To our surprise, compound **9** displayed reasonable inhibition of PDE4 (58% inhibition at 30 μM). This result has prompted our use of **9** as a starting point for improving the potency for PDE4. We targeted two of the major regions of **9** for synthetic explorations: (1) the pendant phenyl ring, and (2) the pyridine nitrogen. Accordingly, we prepared a series of 1,4-DHP

Table 1
Synthesis of substituted 1,4-dihydropyridine derivatives

Entry	Aldehyde	Amine	Time[a]/Yield[b]	Entry	Aldehyde	Amine	Time[a]/Yield[b]
1			30/75	**16**			30/72
2			30/76	**17**			15/67
3			30/77	**18**			30/84
4			45/80	**19**			30/77
5			30/83	**20**			30/84
6			30/84	**21**			30/73
7			45/87	**22**			30/73
8			15/75	**23**			30/71
9			15/80	**24**			15/74

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