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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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† These authors contribute equally to this work.

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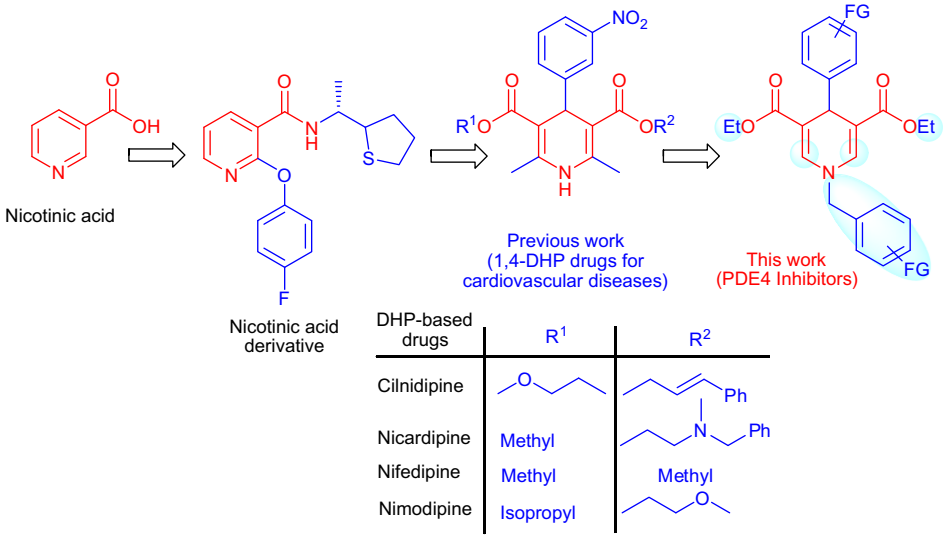
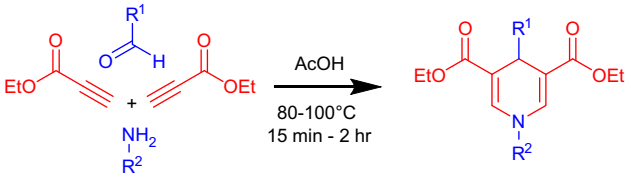


Figure 1. Nicotinic acid and dihydropyridine derivatives.



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

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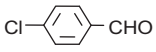
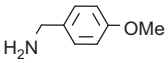
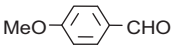
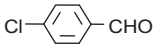
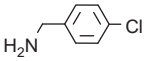
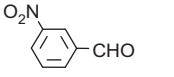
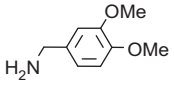
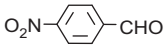
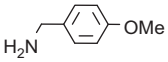
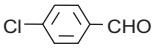
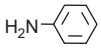
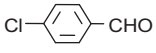
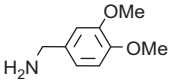
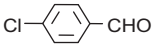
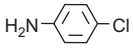
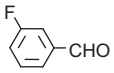
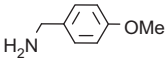
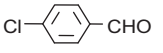
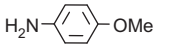
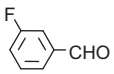
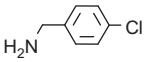
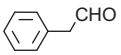
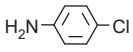
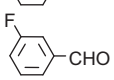
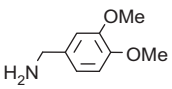
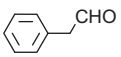
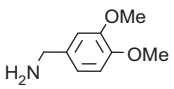
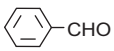
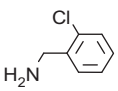
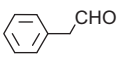
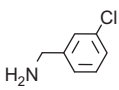
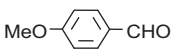
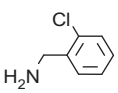
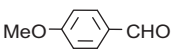
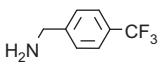
1			30/75	**16**			30/72
2			30/76	**17**			15/67
3			30/77	**18**			30/84
4			45/80	**19**			30/77
5			30/83	**20**			30/84
6			30/84	**21**			30/73
7			45/87	**22**			30/73
8			15/75	**23**			30/71
9			15/80	**24**			15/74

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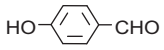
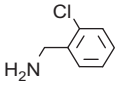
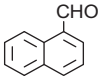
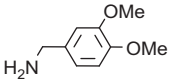
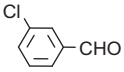
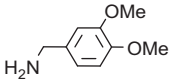
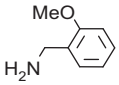
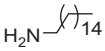
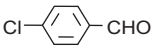
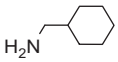
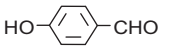
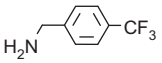
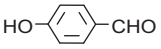
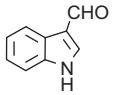
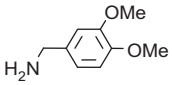
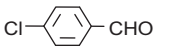
10			20/79	**25**			15/64
11			30/71	**26**			30/92
12			15/69	**27**			30/89
13			15/73	**28**			15/73
14			30/65	**29**			30/77
15			120/53	**30**			30/79

[a] Reaction time in minutes.
[b] Isolated yield in %.

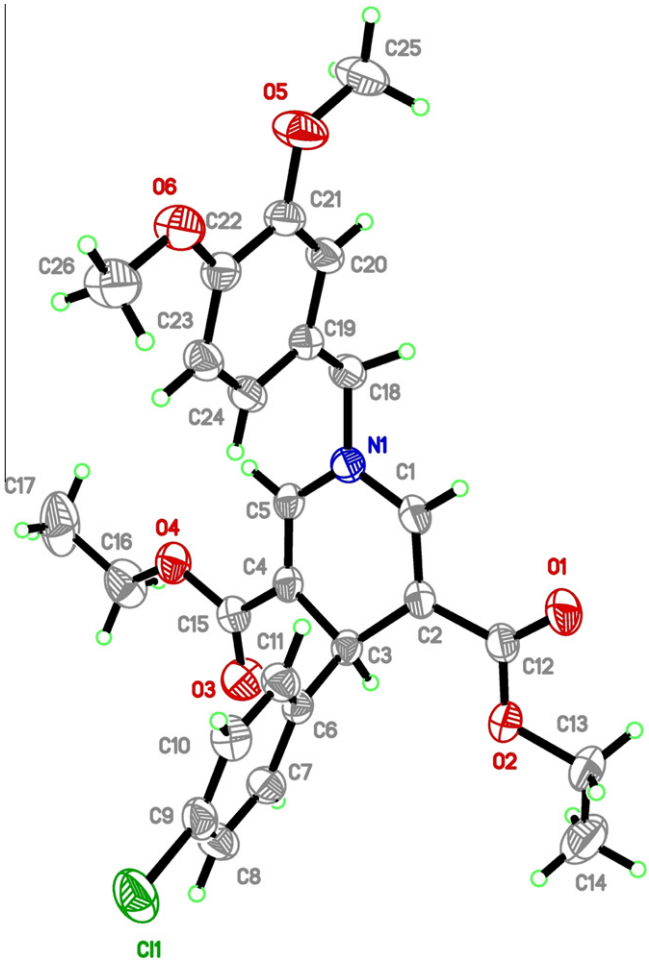


Figure 2. ORTEP representation of the compound **4**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

Table 2
Inhibition of PDE4 with 1,4-DHP derivatives

Compound	R^1	R^2	% of PDE4B inhibition[a]
1	4-ClC_6H_4	4-$OMeCH_2C_6H_4$	23
2	4-ClC_6H_4	4-$ClCH_2C_6H_4$	15
3	4-$NO_2C_6H_4$	4-$OMeCH_2C_6H_4$	38
4	4-ClC_6H_4	3,4-$(OMe)_2CH_2C_6H_3$	80
5	3-FC_6H_4	4-$OMeCH_2C_6H_4$	28
6	3-FC_6H_4	4-$ClCH_2C_6H_4$	8
7	3-FC_6H_4	3,4-$(OMe)_2CH_2C_6H_3$	86
8	C_6H_5	2-$ClCH_2C_6H_4$	33
9	4-$OMeC_6H_4$	2-$ClCH_2C_6H_4$	58
10	4-OHC_6H_4	2-$ClCH_2C_6H_4$	49
11	3-ClC_6H_4	3,4-$(OMe)_2CH_2C_6H_3$	78
12	Cyclopropyl	2-$OMeCH_2C_6H_4$	48
13	4-ClC_6H_4	Ethylcyclohexane	28
14	4-OHC_6H_4	5-Ethylbenzodioxole	72
15	Indolyl	3,4-$(OMe)_2CH_2C_6H_3$	95
16	4-$OMeC_6H_4$	5-Ethylbenzodioxole	42
17	3-$NO_2C_6H_4$	3,4-$(OMe)_2CH_2C_6H_3$	88
18	4-ClC_6H_4	C_6H_5	30.5
19	4-ClC_6H_4	4-ClC_6H_4	23
20	4-ClC_6H_4	4-$OMeC_6H_4$	33
21	$-CH_2C_6H_4$	4-ClC_6H_4	57.5
22	$-CH_2C_6H_4$	3,4-$(OMe)_2CH_2C_6H_3$	79
23	$-CH_2C_6H_4$	3-$ClCH_2C_6H_4$	31
24	4-$OMeC_6H_4$	4-$CF_3CH_2C_6H_4$	21
25	Napthyl	3,4-$(OMe)_2CH_2C_6H_3$	75
26	4-$OMeC_6H_4$	Octyl	25
27	4-$OMeC_6H_4$	Hexadecyl	17
28	4-OHC_6H_4	4-$CF_3CH_2C_6H_4$	35
29	4-OHC_6H_4	Vinyl	51.5
30	4-ClC_6H_4	Vinyl	49.5

[a] All the compounds were tested at a 30 μM concentration.

derivatives (**1**–**30**) and assessment of their PDE4 inhibitory activities revealed the importance of the substituents at the pendant phenyl ring and pyridine nitrogen position of the DHP structure on PDE4 inhibition. A comparison of the structure–activity relationships (SARs) for a number of compounds containing the dihydropyridine ring were investigated for the in vitro inhibition of PDE4. The most practical route for the synthesis of these com-

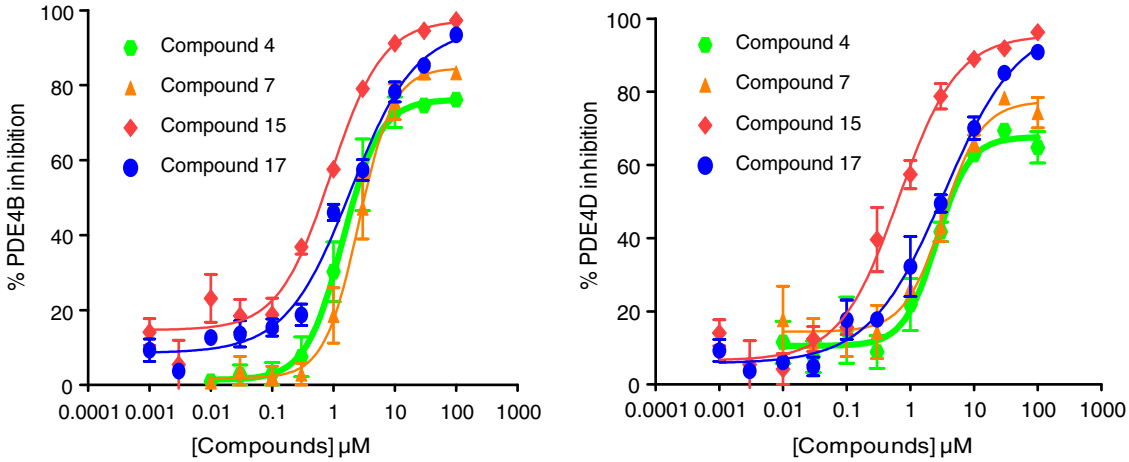


Figure 3. Dose–response curves of **4**, **7**, **15** and **17** with PDE4B and PDE4D.

Table 3
IC_{50} of selected compounds (greater than 50% inhibition)

Compound	R^1	R^2	PDE4B IC_{50}	PDE4D IC_{50}
4	3,4-$(OMe)_2CH_2C_6H_3$	4-ClC_6H_4	3.71	2.78
7	3,4-$(OMe)_2CH_2C_6H_3$	3-FC_6H_4	4.22	3.33
15	3,4-$(OMe)_2CH_2C_6H_3$	Indolyl	0.54	0.65
17	3,4-$(OMe)_2CH_2C_6H_3$	3-$NO_2C_6H_4$	1.57	2.89

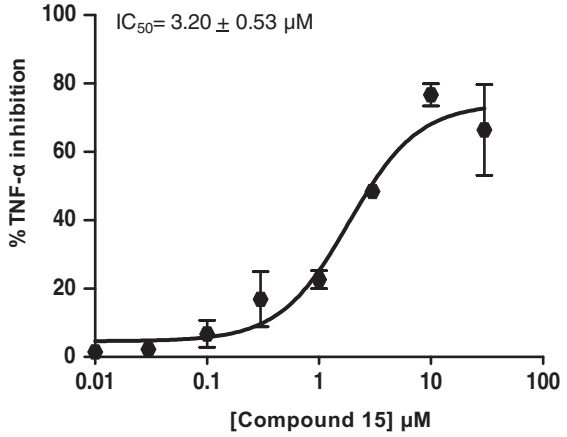


Figure 4. TNF-α inhibition with compound **15**.

Table 4
Docking scores of synthesized inhibitors along with AMP and SI-15x

S. No.	Compound ID	PDE4B	PDE4D
1	AMP	−11.4	−11.0
2	SI-15x	−10.6	−8.2
3	**4**	−7.5	−5.7
4	**7**	−6.9	−6.4
5	**11**	−6.8	−5.8
6	**14**	−7.8	−6.8
7	**15**	−8.1	−7.0
8	**17**	−7.6	−6.5

pounds incorporated the diversity at single-step stage, as shown in Scheme 1, by treatment of aldehydes and with the appropriate substituted primary amines.

The classical synthesis of symmetrical 1,4-DHPs is the three-component cyclocondensation of aldehyde, β-ketoester and ammonia in acetic acid or in alcohol, which was reported by Hantzsch.[15] Despite the long history, sustaining interests in more advanced synthetic methodology of 1,4-DHPs have been triggered by the prolific pharmacological properties imbedded in 1,4-DHPs.[16] Recently much effort has been expanded to develop more efficient methods for the preparation of 1,4-DHPs such as using microwave,[17] solvent free,[18] metal triflates as catalyst,[19] boronic acids,[20] ceric ammonium nitrate,[21] and silica-supported acids.[22] Here, the synthesis of substituted 1,4-dihydropyridines shown in Table 1 was accomplished by modification of the classical Hantzsch reaction. Thus, three-component, one-pot cyclocondensation between aldehyde, ethyl propiolate and the amine, heated at 80 °C in glacial acetic acid afford the title compounds. In order to obtain substitution at the C4-position, the aldehyde component, was varied. Substitution at the N1-position was achieved by varying the benzylamine component. Good yields of the 1,4-DHPs were obtained using a 15–30 min reaction time at 80 °C. All compounds were purified through silica gel column chromatography and were fully characterized by IR, ^1H, ^{13}C NMR and mass spectral analysis (Supplementary data). Further, the single crystal X-ray diffraction studies of four unambiguously confirmed their molecular structures (Fig. 2).

The synthesized derivatives (**1**–**30**) were tested for their inhibitory potencies against PDE4B and PDE4D using recombinant isoenzymes as described in the supporting information. All the compounds were tested at a fixed concentration (30 μM). The functional group array of the scaffold and the percentage of PDE4B inhibition for all the compounds at this concentration are shown in Table 2. Several of the compounds tested showed promising PDE4B inhibitory activity and dose response studies were undertaken to determine IC_{50} of selected compounds which displayed greater than 50% activity (Fig. 3 and Table 3).

In parallel, we also determined the selectivity of the selected compounds against PDE4D and found that the selected compounds exhibited similar potency against PDE4D as well. Elevation of cAMP levels via inhibition of PDE4B is linked to a variety of anti-inflammatory effects. Thus, compound **15** was tested for its ability to blunt LPS-induced TNF-α production (Fig. 4) and was found to inhibit TNF-α synthesis with an IC_{50} of 3.2 μM. Above set of experiments revealed that compound **15** is the most potent amongst all the compounds tested and is a suitable candidate for further exploration.

To gather SAR information of the synthesized 1,4-DHP derivatives, hit compound **9** was divided into two constituent parts and

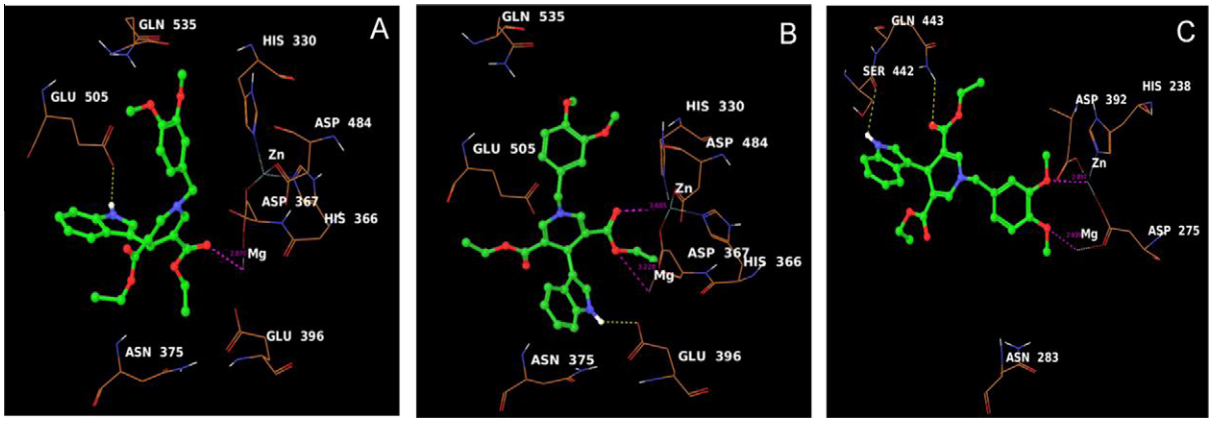


Figure 5. Docked orientations of **15** in PDE4D (panel A and B), and in PDE4B (panel C).

modifications were systematically done at C4 and N1 positions. Table 2 summarizes PDE4 inhibition data of C4 and N1-substituted 1,4-DHPs and clearly showed that 3,4-dimethoxybenzyl group (**4**, **7**, **11**, **15**, **17**, **22**, and **25**, >80% inhibition) were superior to other substituents. In this series, the indole (**15**) and 3-nitrophenyl (**17**) moieties at C4 position (IC_{50} = 0.54 and 1.57 μM, respectively) were more potent compounds. From the evaluated 1,4-DHPs, we concluded that 4-phenyl and *N*-benzyl substitution of 1,4-DHPs were important for PDE4 inhibitory activity, and we thus mainly modified the R^1 and R^2 groups of the 1,4-DHP core. We found that *N*-phenyl group abrogated PDE4 inhibition potency (**18**, **19** and **20**). The conclusion was that an additional H-bond donor/acceptor at R^1 or R^2 positions was required for potent PDE4 inhibitory activity, and this was supported by the lack of inhibition by **2**, **6** and **27** (<20% inhibition), underscoring the assumption that an H-acceptor at the N1-benzyl position were apparently required.

In order to gain further insight into the binding mode of 1,4-DHPs with PDE4 enzymes, docking studies were carried out with help of the Glide module Maestro (ver. 9.2), Schrodinger Inc. according to the procedure described in the Supplementary data. Studies were focused only on those compounds which showed considerable inhibition on PDE4. Docking studies of the synthesized inhibitors reveal significant understanding as to how they inhibit PDE4B and PDE4D enzymes. Table 4 reflects the docking scores of the highest docking pose that has good conformational consensus of AMP, standard inhibitor (SI-15x), and synthesized compounds. It is apparent that the docking scores of most of these molecules from Table 4 fall in similar range (i.e. within −5.7 to −8.2) with PDE4B and PDE4D enzymes, thus giving evidence that these compounds may serve as non-selective inhibitors.

The variations within the measured activity may not be reflected from the docking scores; nevertheless, a greater understanding of relative inhibitory potency of the synthesized inhibitors lies in their critical interactions within the enzyme—while the differences among the active sites and shapes of PDE4B and PDE4D determine selectivity. The docked orientations of some synthesized inhibitors along with the SI-15x are given in Supplementary data.

Inhibitor **15** gave best docking score in PDE4B (−8.1) and PDE4D (−7.0) among other inhibitors its relative sensitivity towards inhibition of these two enzymes, as shown in Table 4. Figure 5 depicts the two possible docked orientations of **15** in PDE4D (panels A and B), while a single possible interacting orientation in PDE4B (panel C). The indole moiety of **15** forms two possible orientations in PDE4D, and in both cases, it makes a stronger hydrogen bond with the residues Glu396 or Glu505 of PDE4D, while its orientation in PDE4B is completely different than that in PDE4D. The dimethoxy group interacts with the metal atoms in PDE4B, while it is expected to interact with Gln443. The Gln535 in PDE4D interacts with the dimethoxy group of **15**. The indole moiety of **15** in PDE4D makes strong H-bonding interactions with Glu505 or Glu396 (in two possible orientations), while in PDE4B, the same moiety is shown to interact in a H-bonded manner with Ser442 backbone. This additional interaction of indole moiety will make it a better inhibitor than the rest of the synthesized inhibitors. The docking scores of **15** are marginally better (i.e. lower) than the rest of the inhibitors, while further rigorous molecular modeling studies may strengthen this observation.

In conclusion, we have reported the first investigation of dihydropyridine-based compounds on the PDE4 inhibition activity. The dihydropyridine motif, bearing the dimethoxybenzyl and indole groups form multiple interactions with the metal ion binding site of PDE4, may also provide a new insights for the design of PDE4 inhibitors. Further studies are ongoing to improve the selectivity on PDE4 inhibition activity of our *N*-dimethoxybenzyl and indole DHPs to optimize the inhibition profile.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.11.121.

References and notes

1. (a) Banner, K. H.; Moriggi, E.; Da Ros, B.; Schioppacassi, G.; Semeraro, C.; Page, C. P. *Br. J. Pharmacol.* **1996**, *119*, 1255; (b) Hatzelmann, A.; Schudt, C. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 26.
2. (a) Kodimuthali, A.; Jabaris, S. S. L.; Pal, M. *J. Med. Chem.* **2008**, *51*, 5471; (b) Dastidar, S. G.; Rajagopal, D.; Ray, A. *Curr. Opin. Investig. Drugs* **2007**, *85*, 364.
3. Mathias, J. P.; Nicotinamide derivatives useful as PDE4 inhibitors, **2006**, US 7,153,870 B2 and **2005**, US 0,026,952 A1.
4. For related reviews, see: (a) Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug Res.* **1987**, *16*, 309; (b) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141; (c) Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.
5. (a) Varache-Lemebge, M.; Nuhrich, A.; Zemb, V.; Devaux, G.; Vacher, P.; Vacher, A. M.; Dufy, B. *Eur. J. Med. Chem.* **1996**, *31*, 547; (b) Alker, D.; Campbell, S. F.;

Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1990**, *33*, 585.
6. Abbas, H. A. S.; El Sayed, W. A.; Fathy, N. M. *Eur. J. Med. Chem.* **2010**, *45*, 973.
7. Briede, J.; Stivrina, M.; Vigante, B.; Stoldere, D.; Dubur, G. *Cell Biochem. Funct.* **2008**, *26*, 238.
8. Hilgeroth, A. *Mini Rev. Med. Chem.* **2002**, *2*, 235.
9. Letelier, M. E.; Entrala, P.; Lopez-Alarcon, C.; Gonzalez-Lira, V.; Molina-Berríos, A.; Cortes-Troncoso, J.; Jara-Sandoval, J.; Santander, P.; Nunez-Vergara, L. *Toxicol. In Vitro* **2007**, *21*, 1610.
10. Marco, C. J.; Leon, R.; de Los Rios, C.; Guglietta, A.; Terencio, J.; Lopez, M. G.; Villarroya, M. *J. Med. Chem.* **2006**, *49*, 7607.
11. Bretzel, R. G.; Bollen, C. C.; Maeser, E.; Federlin, K. F. *Am. J. Kidney Dis.* **1993**, *21*, 53.
12. Mai, A.; Valente, S.; Meade, S.; Carafa, V.; Tardungo, M.; Nebbioso, A.; Galmozzi, A.; Mitro, N.; Fabiani, E. D.; Altucci, L.; Kazantsev, A. *J. Med. Chem.* **2009**, *52*, 5496.
13. Xia, Z.; Wang, M.; Zou, S.; Chen, R. *Eur. J. Drug Meta. Pharmacokinet.* **2012**, *37*, 211.
14. Ruggenenti, P.; Perna, A.; Benini, R.; Remuzzi, G. *J. Am. Soc. Nephrol.* **1998**, *9*, 2096.
15. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *1*, 215.
16. For alternative synthesis of Hantsch-type 1,4-DHP, see: (a) Cui, S. L.; Wang, J.; Lin, X. F.; Wang, Y. G. *J. Org. Chem.* **2007**, *72*, 7779; (b) Kikuchi, S.; Iwai, M.; Murayama, H.; Fukuzawa, S. *Tetrahedron Lett.* **2008**, *49*, 114.
17. (a) Osberg, L.; Westman, J. *Synlett* **2001**, 1298; (b) Salehi, H.; Guo, Q. *Synth. Commun.* **2004**, *34*, 4349.
18. Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, 827.
19. Wang, L. M.; Sheng, J.; Zhang, L.; Han, J. W.; Fan, Z. Y.; Tian, H.; Qian, C. T. *Tetrahedron* **2005**, *61*, 1539.
20. Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Synlett* **2008**, 509.
21. Ko, S.; Yao, C. F. *Tetrahedron* **2006**, *62*, 7293.
22. Gupta, R.; Gupta, R.; Paul, S.; Loupy, A. *Synthesis* **2007**, 2835.