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Synthesis and Biological Activities of 1-Pyridylisoquinoline and 1-Pyridyldihydroisoquinoline Derivatives as PDE4 Inhibitors

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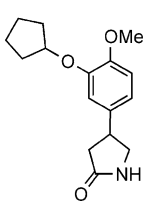
Abstract—A novel series of 1-pyridylisoquinoline and 1-pyridyldihydroisoquinoline derivatives has been prepared. These compounds showed potent PDE4 inhibitory activities and a broad margin between the K_i value of the rolipram binding affinity and the IC_{50} value of PDE4 inhibition. They also exhibited potent inhibitory activities toward LPS-induced TNF-α production in mice.

Cyclic nucleotide phosphodiesterases (PDEs) play a key role in the metabolism of purine cyclic nucleotides, cAMP and cGMP. PDEs have been classified into eleven structurally, biochemically, and pharmacologically distinct families.[1] Among them, cAMP-PDE (PDE4), consisting of four gene products (PDE4A to PDE4D), is characterized by selective, high-affinity hydrolysis of cAMP.[2] The inhibition of PDE4 results in the increase in cellular levels of cAMP, which contributes to both the relaxation of airway smooth muscle and the prevention of proinflammatory cell activation.[3] In particular, this type of manipulation brings about a marked reduction in the release of the proinflammatory cytokine TNF-α into the blood.[4] These observations have generated considerable interest in the use of PDE4 inhibitors for the treatment of various immunological disorders, including asthma, COPD (chronic obstructive pulmonary disease), and rheumatoid arthritis.[5]

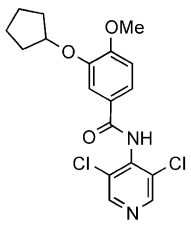
With a considerable amount of interest and excitement, the novel structural classes of PDE4 inhibitors such as benzofuran, benzodiazepine, naphthyridine, etc. have recently been reported as second generation inhibitors.[6] We have already reported 1-pyridylnaphthalene derivatives as a new structural class of selective PDE4 inhibitors.[7] In connection with our efforts in search of a new scaffold to improve pharmacokinetic properties and oral in vivo activities by the introduction of an additional heteroatom to the naphthalene ring of 1-pyridylnaphthalene derivatives, we now disclose 1-pyridylisoquinoline and 1-pyridyldihydroisoquinoline derivatives having potent PDE4 inhibitory activities and a broad margin between the K_i value of the rolipram binding affinity and the IC_{50} value of PDE4 inhibition. They also exhibited potent inhibitory activities toward lipopolysaccaride (LPS)-induced TNF-α production in mice.

Chemistry

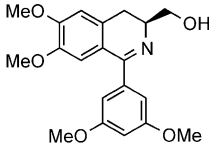
In order to introduce an additional heteroatom to the naphthalene ring of 1-pyridylnaphthalene derivatives, we designed compounds **4**, **5a**, and **6a**, which were analogues of compound **3a** and **3b**, as shown in Scheme 1. In terms of a dihydroisoquinoline scaffold, we selected the *S*-stereoisomer, because it was reported that SDZ



1: Rolipram



2: RP 73401



SDZ ISQ 844

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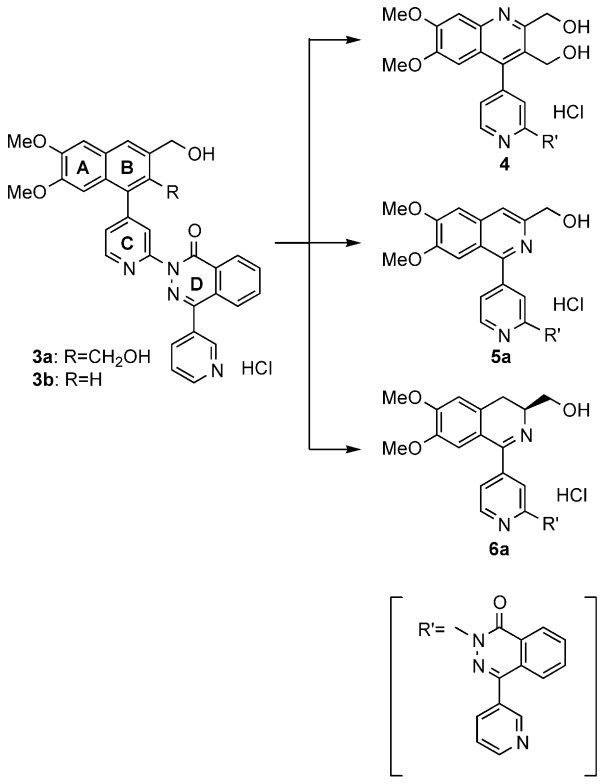


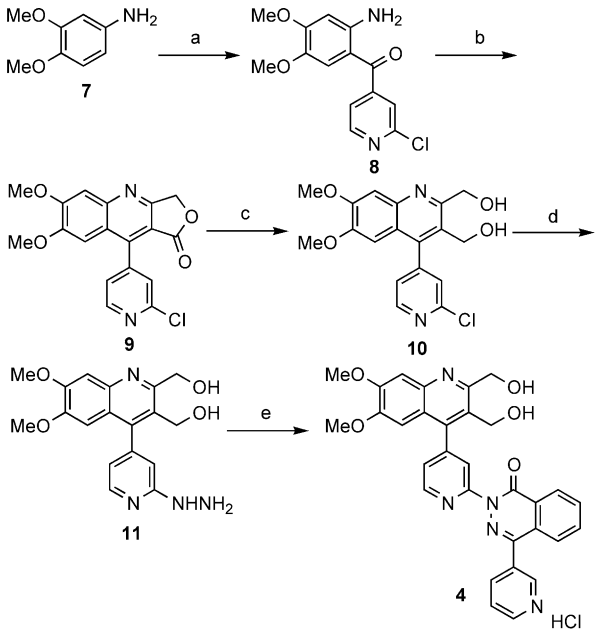
Scheme 1.

ISQ 844 was a PDE3/4 dual inhibitor and its *S*-stereoisomer was more potent than *R*-stereoisomer.[8] In this approach, (1) the naphthalene part (A,B-ring) was transformed to a quinoline, isoquinoline, or dihydroisoquinoline part, (2) 3-hydroxymethyl group was kept, (3) the heterocyclic compound having a carbonyl group (D-ring) was introduced, and (4) the pyridyl group (C-ring) was fixed from the previous SAR study.[7]

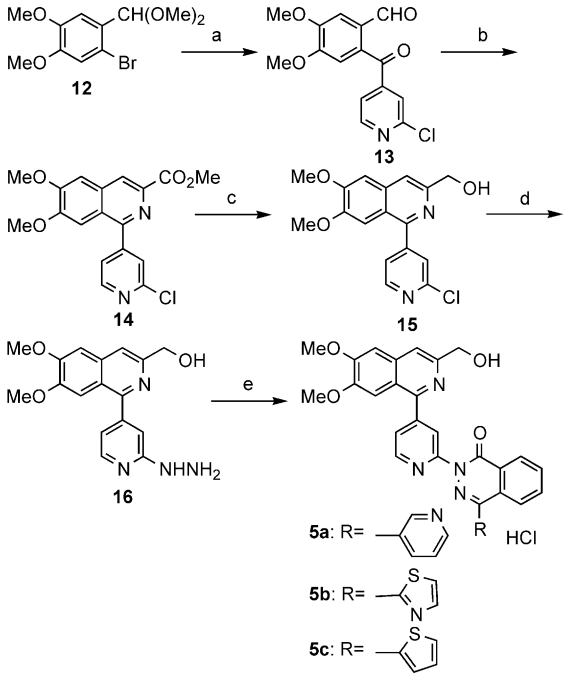
Quinoline derivative **4** was prepared in five steps from 4-aminoveratrole **7** (Scheme 2). 1-Pyridylquinoline intermediate **9** was synthesized by the Friedel-Crafts acylation of **7** with 2-chloro-4-cyanopyridine, followed by acid catalyzed cyclization of **8** with tetronic acid. Lactone **9** was converted to alcohol **10** by reduction with Red-Al®. Quinoline derivative **4** was synthesized by the reaction of chloride **10** with hydrazine hydrate, followed by cyclization with 2-(3-pyridinoyl)benzoic acid.

Isoquinoline derivatives **5a–c** were prepared in five steps from bromo acetal **12**[9] (Scheme 3). Benzaldehyde **13** was synthesized by nucleophilic addition of lithium salt of **12** to 2-chloro-*N*,*N*-dimethylisonicotinamide, followed by deprotection of acetal in acidic media. 1-Pyridylisoquinoline intermediate **14** was obtained by cyclization of **13** with methyl isocyanoacetate and NaH. Isoquinoline derivatives **5a–c** were synthesized by reduction of ester **14** with Red-Al®, followed successively by the reaction with hydrazine hydrate and by cyclization with 2-(heteroarylcarbonyl)benzoic acid.

Dihydroisoquinoline derivatives **6a–e** were prepared in six steps from L-DOPA derivative **17**[10] (Scheme 4). Compound **19** was synthesized by the condensation of **17** with 2-bromo-isonicotinic acid, followed by reduction of ester **18** with $NaBH_4$–MeOH.[11] Phthalazinone or isoquinolone moiety was introduced into **19** to give compounds **20a–e** by the Ullmann condensation in the presence of a catalytic amount of CuI.[12] Dihydroisoquinoline derivatives **6a–e** were synthesized by

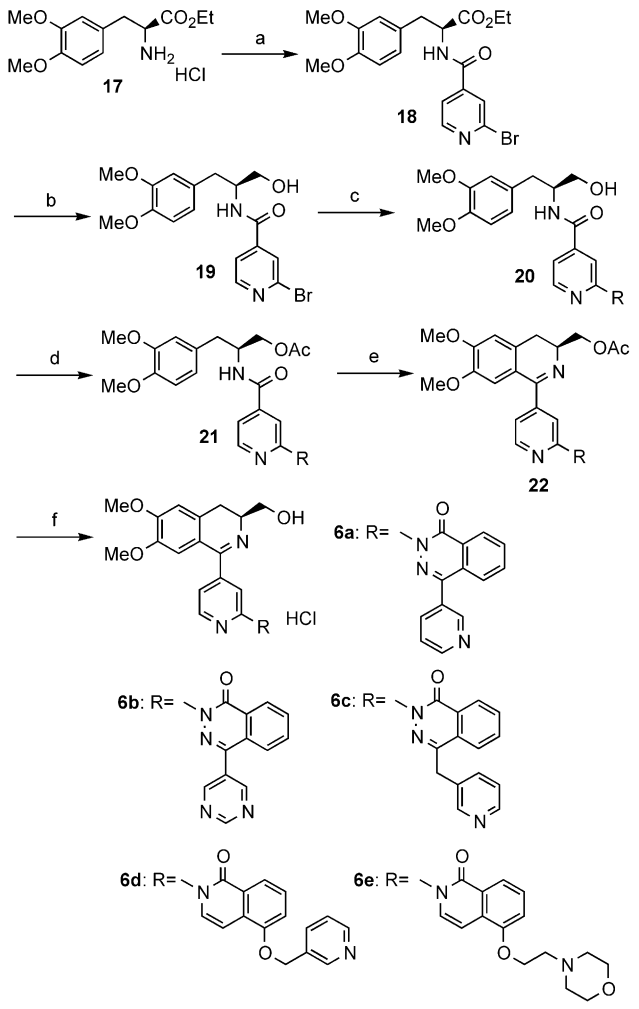


Scheme 2. Reagents and conditions: (a) 2-chloro-4-cyanopyridine, BCl_3/$ClCH_2CH_2Cl$, reflux: (b) tetronic acid, TFA/toluene-AcOH, reflux; (c) Red-Al/THF, 0 °C; (d) $NH_2NH_2{\cdot}H_2O$, reflux: (e) (1) 2-(3-pyridinoyl)benzoic acid/ethylene glycol, 150 °C, (2) 2N aqueous HCl/$CHCl_3$–MeOH.



Scheme 3. Reagents and conditions: (a) (1) *n*-BuLi, 2-chloro-*N*,*N*-dimethylisonicotinamide/THF, −70 °C, (2) concd HClaq; (b) methyl isocyanoacetate, NaH/DMF, 50 °C; (c) Red-Al/THF, 0 °C; (d) $NH_2NH_2{\cdot}H_2O$, reflux; (e) (1) 2-(heteroarylcarbonyl)benzoic acid/ethylene glycol, 150 °C, (2) 2N aqueous HCl/$CHCl_3$–MeOH.

acetylation of hydroxy group of compounds **20a–e**, followed successively by the Bischler-Napieralski cyclization of compounds **21a–e** with $POCl_3$ and by deprotection of acetyl group with aqueous LiOH.



Scheme 4. Reagents and conditions: (a) DCC, HOBt, 2-bromo-isonicotinic acid/CH_2Cl_2, 25 °C; (b) $NaBH_4$/THF-MeOH, reflux; (c) RH, CuI, K_2CO_3/DMF, 120 °C; (d) Ac_2O, Et_3N/CH_2Cl_2, 25 °C; (e) $POCl_3$/CH_3CN, reflux; (f) (1) LiOH·H_2O/MeOH, 25 °C, (2) 2N aqueous HCl/$CHCl_3$–MeOH.

Biological Results and Discussion

The IC_{50} value of PDE4 inhibition, the K_i value of binding affinity for the rolipram binding site, and the ratio of both values are summarized in Table 1. Transformation of the naphthalene part to quinoline, isoquinoline, or dihydroisoquinoline part was first examined. Quinoline derivative **4** proved to have a rather weak PDE4 inhibitory activity despite its structural resemblance to **3a** (**4**, $IC_{50}=70$ nM; **3a**, $IC_{50}=0.7$ nM). On the other hand, isoquinoline **5a** and dihydroisoquinoline derivative **6a** exhibited almost the same activities as **3a** and **3b** (**5a**, $IC_{50}=0.6$ nM; **6a**, $IC_{50}=1.0$ nM; **3b**, $IC_{50}=0.7$ nM). Next we paid attention to the transformation of the D-ring to further increase the PDE4 inhibitory activity. Among their compounds, compounds **5b**, **c**, and **6b–e** exhibited almost the same activities ($IC_{50}=0.3$–3 nM) as **3a** and **b**. The affinities for the high-affinity rolipram binding site were also investigated. All compounds **5a–c** and **6a–e** exhibited comparatively lower affinities than **2** for the high affinity rolipram binding site (K_i value (nM); **5a–c** and **6a–e**: 1.4–6.5, **2**: 0.85). In particular, compounds **5b**, **5c**, **6a**, **6d**, and **6e** showed broader margin between the K_i value of the rolipram binding affinity and the IC_{50} value of PDE4 inhibition (ratio 0.15–0.28, respectively) than **2** (ratio 0.35).

Table 1. PDE4 Inhibitory activities and rolipram binding affinity

Compd	PDE4 inhibition, IC_{50}, nM[a], (A)	[^{3}H]-Rolipram binding, K_i, nM[a], (B)	Ratio A/B
1 (Rolipram)	500	3.8	132
2 (RP 73401)	0.3	0.85	0.35
3a	0.7	3.5	0.20
3b	0.7	3.0	0.23
4	70	120	0.58
5a	0.6	1.4	0.43
5b	0.3	1.7	0.18
5c	0.3	1.4	0.21
6a	1	6.5	0.15
6b	3	5.4	0.56
6c	2	3.1	0.65
6d	0.4	1.5	0.27
6e	0.5	1.8	0.28

[a]IC_{50} and K_i values were determined from the logarithmic concentration–inhibition curve (at least four points). The value is given as the mean of three experiments, where the variation from the mean value is 20% or less.

Next we selected five compounds on the basis of PDE4 inhibitory potency ($IC_{50}<1$ nM) and broad margin (ratio <0.35) between the K_i value of the rolipram binding affinity and the IC_{50} value of PDE4 inhibition, for further evaluation of their ability to inhibit LPS-induced TNF-α production in mice, as shown in Table 2. Compounds **5b**, **6a**, and **6e** proved to be more potent than **2** (**5b**, $ED_{50}=0.26$ mg/kg; **6a**, $ED_{50}=0.52$ mg/kg; **6e**, $ED_{50}=0.13$ mg/kg; **2**, $ED_{50}=0.72$ mg/kg). On the other hand, **5c** and **6d** led to a decrease in potency (**5c**, $ED_{50}=1.6$ mg/kg; **6d**, $ED_{50}=2.4$ mg/kg). For example, **5c** exhibited lower inhibition of LPS-induced TNF-α production than **5b** in spite of the same potencies for PDE4 inhibition (**5b**, $IC_{50}=0.3$ nM; **5c**, $IC_{50}=0.3$ nM), in 1-pyridylisoquinoline derivatives. Furthermore, **6d** also exhibited lower inhibition of LPS-induced TNF-α

Table 2. Inhibition of LPS-induced TNF-α production

Compd	TNF-α, ED_{50}, mg/kg, po[a]
1 (Rolipram)	2.6
2 (RP 73401)	0.72
3a	1.2
5b	0.26
5c	1.6
6a	0.52
6d	2.4
6e	0.13

[a]ED_{50} values were determined from dose-response curves of TNF-α inhibition. Compounds were administered orally to mice 30min prior to LPS challenge.

production than **6a** and **6e** in spite of almost the same potencies for PDE4 inhibition (**6a**, $IC_{50} = 1.0$ nM; **6d**, $IC_{50} = 0.4$ nM; **6e**, $IC_{50} = 0.5$ nM), in 1-pyridyldihydroisoquinoline derivatives. More lipophilic derivatives **5c** and **6d** showed less potencies than **5b**, **6a**, and **6e** in this assay [calculated log D at pH 6.5: **5c**; 3.47 vs **5b**; 2.38 (1-pyridylisoquinoline derivatives): **6d**; 1.94 vs **6a**; 1.26, **6e**; 1.40 (1-pyridyldihydroisoquinoline derivatives)]. These findings might be ascribed to the differences of physicochemical properties (cell permeability, water solubility) among these compounds.

In conclusion, 1-pyridylisoquinoline and 1-pyridyldihydroisoquinoline derivatives were disclosed as novel structural classes of PDE4 inhibitors with improved oral in vivo activities. Among these analogues, compounds **5b**, **6a**, and **6e** were found to be potent inhibitors against both the inhibitory activities of PDE4 and LPS-induced TNF-α production, and also showed a broad margin between the K_i value of the rolipram binding affinity and the IC_{50} value of PDE4 inhibition. Further studies on this interesting class of PDE4 inhibitors are in progress.

References and Notes

1. (a) Francis, S. H.; Turko, I. V.; Corbin, J. D. *Prog. Nucleic Acid Res. Mol. Biol.* **2000**, *65*, 1. (b) Beavo, J. A.; Conti, M.; Heaslip, R. J. *Mol. Pharmacol.* **1994**, *46*, 399. (c) Beavo, J. A. *Physiol. Rev.* **1995**, *75*, 725. (d) Juilfs, D. M.; Soderling, S.; Burns, F.; Beavo, J. A. *Rev. Physiol. Biochem. Pharmacol.* **1999**, *135*, 67. (e) Conti, M.; Jin, S.-L. C. *Prog. Nucleic Acid Res. Mol. Biol.* **2000**, *63*, 1. (f) Fujishige, K.; Kotera, J.; Michibata, H.; Yuasa, K.; Takebayashi, S.; Okumura, K.; Ohmori, K. *J. Biol. Chem.* **1999**, *274*, 18438. (g) Fawcett, L.; Baxendale, R.; Stacey, P.; McGrouther, C.; Harrow, I.; Soderling, S.; Hetman, J.; Beavo, J. A.; Phillips, S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 3702.
2. Müller, T.; Engels, P.; Fozard, J. R. *Trends Pharmacol. Sci.* **1996**, *17*, 294.
3. (a) Torphy, T. J. *Agents Actions* **1988**, *23*, S37. (b) Giembycz, M. A.; Dent, G. *Clin. Exp. Allergy* **1992**, *22*, 337. (c) Torphy, T. J.; Livi, G. P.; Christensen, S. B. *Drug News Perspect.* **1993**, *6*, 203.
4. (a) Schade, F. U.; Schudt, C. *Eur. J. Pharmacol.* **1993**, *230*, 9. (b) Semmler, J.; Endres, S. *Int. J. Immunopharmac.* **1993**, *15*, 409. (c) Prabhakar, U.; Lipschutz, D.; Bartus, J.; O'Leary Slivjak, M. J.; Smith, E. F., III; Lee, J. C.; Esser, K. M. *Int. J. Immunopharmac.* **1994**, *16*, 805.
5. (a) de Brito, F. B.; Souness, J. E.; Warne, P. *J. Emerging Drugs* **1997**, *2*, 249. (b) Marriot, J. B.; Westby, M.; Dalgleish, A. G. *Drug Develop. Today* **1997**, *2*, 273. (c) Nyman, U.; Mussener, A.; Larsson, E.; Lorentzen, J.; Klareskog, L. *Clin. Exp. Immunol.* **1997**, *108*, 415. (d) Wolda, S. L. *Emerging Drugs* **2000**, *5*, 309. (e) Palfreyman, M. N. *Drugs Future* **1995**, *20*, 793.
6. Norman, P. *Exp. Opin. Ther. Pat.* **1999**, *9*, 1101.
7. Ukita, T.; Sugahara, M.; Terakawa, Y.; Kuroda, T.; Wada, K.; Nakata, A.; Ohmachi, Y.; Kikkawa, H.; Ikezawa, K.; Naito, K. *J. Med. Chem.* **1999**, *42*, 1088.
8. Neaf, R. Eur. Pat. Appl. EP 91-810954.
9. (a) Rodrigo, R. *J. Org. Chem.* **1980**, *45*, 4538. (b) Forsey, S. P.; Rajapaksa, D.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1989**, *54*, 4280.
10. Tsuda, Y.; Hosoi, S.; Ishida, K.; Sangai, M. *Chem. Pharm. Bull.* **1994**, *42*, 204.
11. Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948.
12. Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719.