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Synthesis of 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridine-6-yl)-benzoic Acid: a Potent and Selective Phosphodiesterase Type 4D Inhibitor

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Abstract—The synthesis of a 6,8-disubstituted 1,7-naphthyridine **1** and its characterization as a potent and selective phosphodiesterase type 4D inhibitor ($IC_{50} = 1.5$nM) are described. The compound inhibited TNFα-release from human peripheral blood mononuclear cells and was orally active in a model of adjuvant-induced arthritis in rats.

Introduction

Phosphodiesterase type 4 (PDE4) belongs to a family of at least 10 structurally, biochemically and pharmacologically distinct isoenzymes that catalyze the hydrolysis of the second messengers adenosine 3′, 5′-cyclic monophosphate (cAMP) or guanosine 3′, 5′-cyclic monophosphate (cGMP) to the corresponding inactive 5′-nucleotide products.[1,2] PDE4 is mainly expressed in lymphocytes, monocytes, neutrophils, eosinophils and mast cells and, therefore, is the most important member of the PDE family in regulating immune and inflammatory responses.[3] The anti-inflammatory effect of PDE4 inhibitors has been demonstrated in various animal models and, consequently, inhibition of PDE4 has been proposed as a new therapeutic approach for the treatment of a variety of chronic inflammatory diseases such as asthma, chronic obstructive pulmonary diseases (COPD) and rheumatoid arthritis.[3,4] Four different isogenes and splice variants of human PDE4 were described (PDE4A-D). The enzymes are characterized by their selective, high affinity hydrolysis of cAMP and sensitivity to inhibition by rolipram, an archetype PDE4 inhibitor. With the exception of PDE4C mRNAs of all isoforms are expressed in the majority of cells of the immune system.[5] Nevertheless, the precise function and the relevance of the PDE4 subtypes remain still to be established. A common side effect of PDE4 inhibitors is nausea and emesis. Although the mechanism which leads to the induction of this untoward effect is not fully understood, one hypothesis is that binding of inhibitors to the so-called rolipram high-affinity binding site might play an important role.[6] Ariflo™ (SB 207499, cilomilast), which is the most advanced PDE4 inhibitor and is currently undergoing clinical trials for asthma and COPD, was apparently selected based on an optimized ratio of PDE4 catalytic activity relative to affinity to the rolipram high-affinity binding site.[7,8]

The drug seems to have an acceptable therapeutic window.

In contrast to many other companies, we focused our efforts on finding PDE4D subtype selective compounds. We recently reported the discovery of 6,8-disubstituted 1,7-naphthyridines as a novel class of potent and selective PDE4D inhibitors with strong anti-inflammatory activity in an in vivo model of allergic asthma.[9] The most interesting compound of this series was the benzoic acid substituted 1,7-naphthyridine **2**.

Although this compound displayed a very promising biological profile it contained a sterically non-hindered aromatic nitro functionality. Aromatic amines and nitro groups represent a clear structural alert and such compounds are known to be potentially mutagenic and carcinogenic.[10,11] Consequently, we were looking for an appropriate replacement of the nitro group. Herein, we describe the synthesis of the 6-benzo[1,2,5]oxadiazole substituted 1,7-naphthyridine **1** and demonstrate that the

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compound potently and selectively inhibited PDE4D and thus, had a similar profile as its nitro analogue **2** (Chart 1).

Chemistry

The title compound **1** was synthesized by two alternative routes using palladium-catalyzed cross-coupling reactions as key steps. The necessary tin or boronic acid benzofurazan reagents **7** and **8** were synthesized in good overall yields from the commercially available amine **3** (Scheme 1). Bromination of **3** followed by cyclization afforded the *N*-oxide **5** which was easily reduced to the benzofurazan **6**. Palladium-catalyzed stannylation led to the tin compound **7**. Formation of the boronic acid **8** was more tricky and using organolithium- or Grignard reagents followed by quenching with triethyl borate gave complex mixtures when using standard reaction conditions. Very low-temperature, addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and, particularly, in-situ trapping of the organolithium intermediate by triethyl borate were mandatory to prepare compound **8** in acceptable yield.

A first synthesis of compound **1** is depicted in Scheme 2, using bromide **9**[9] and either the easily available but potentially toxic tin compound **7** or, alternatively, the more difficult to prepare boronic acid **8**. In both cases, standard reaction conditions for Suzuki[12] or Stille-type couplings[13] were applied. Intermediate **10** was transformed to the corresponding triflate **11** which was then coupled to 4-carboxyphenylboronic acid by a second Suzuki-type reaction.

Alternatively, the benzoic acid moiety was attached to the 1,7-naphthyridine ring first as depicted in Scheme 3. In this case regioselective cyclization of the dinitrile **12** gave the amine **13** which after transformation into the corresponding triflate, was subjected to the first Suzuki coupling. The ether **14** was readily converted into the bromide **15** which was then coupled to the boronic acid **8** under standard Suzuki conditions. In this way, multi-gram quantities of **1** were synthesized. Interestingly, the free acid **1** could be transformed into the water-soluble *N*-methyl-D-glucamine salt **1b** by crystallization from methanol.

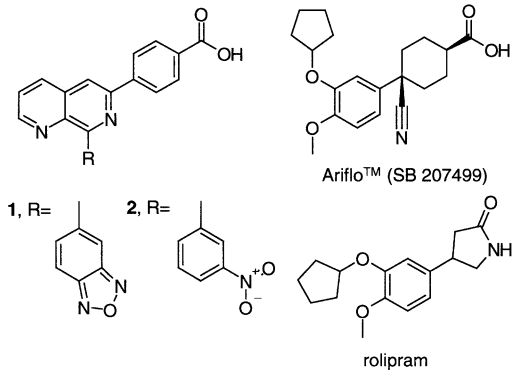
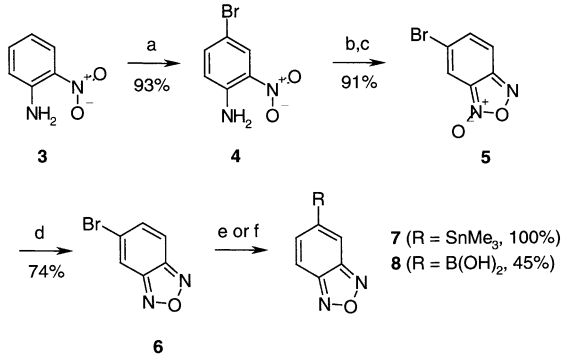
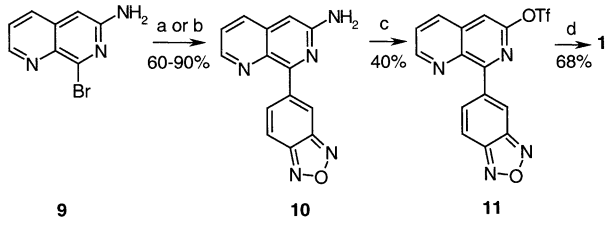


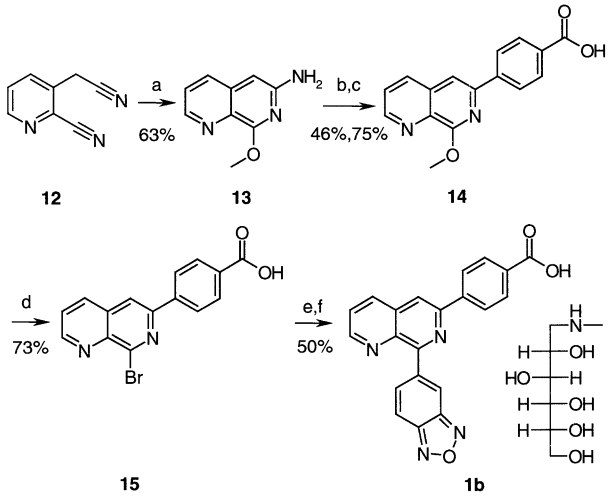
Chart 1.



Scheme 1. Synthesis of 5-trimethylstannanyl-benzo[1,2,5]oxadiazole **7** and 5-benzo[1,2,5]oxadiazole boronic acid **8**. Reaction conditions: (a) *N*-bromosuccinimide, AcOH, 60 °C, 2 h; (b) KOH, EtOH, 60 °C, 1 h; (c) aq NaOCl, 0 °C, 1 h; (d) $P(Ph)_3$, xylene, 140 °C, 3 h, (e) hexamethyl-distannane, $Pd(dba)_2$, $P(Ph)_3$, toluene, 110 °C, 3 h; (f) n-BuLi, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, $B(OEt)_3$, THF/*n*-pentane, −100 °C, 5 min.



Scheme 2. Synthesis of 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridine-6-yl)-benzoic acid **1**: (a) 7, $Pd(dba)_2$, $P(Ph)_3$, DMF, 120 °C, 3 h; (b) **8**, $Pd(dba)_2$, $P(o\text{-tol})_3$, toluene/DMF, 2 N Na_2CO_3, 110 °C, 3 h; (c) $NaNO_2$, CF_3SO_3H/DMF, rt 3 h; (d) 4-carboxyphenylboronic acid, $Pd(dba)_2$, $P(Ph)_3$, 2 N Na_2CO_3, DMF, 80 °C, 2 h.



Scheme 3. Alternative synthesis of 4-(8-benzo[1,2,5]oxadiazol-5-yl-[1,7]naphthyridine-6-yl)-benzoic acid *N*-methyl-D-glucamine salt **1b**: (a) Na, MeOH, rt, 16 h; (b) aq $NaNO_2$, CF_3SO_3H/H_2O, 0 °C, 3 h; (c) 4-carboxyphenylboronic acid, $Pd(dba)_2$, $P(Ph)_3$, 2 N Na_2CO_3, DMF, 80 °C, 2 h; (d) PBr_3, DMF, 100 °C, 30 min; (e) **8**, $Pd(dba)_2$, $P(o\text{-tol})_3$, 2 N Na_2CO_3, DMF, 110 °C, 2 h; (f) *N*-methyl-D-glucamine, MeOH.

Results and Discussion

Compound **1** was measured against a panel of human phosphodiesterases (Table 1). As predicted, **1** selectively inhibited PDE4D ($IC_{50} = 1.5$ nM) and was 23-, 400-, and 820-fold less potent on PDE4B, PDE4A, and

Table 1. Inhibition of human phosphodiesterase activity, [^{3}H]-rolipram binding and inhibition of TNFα release from human peripheral blood mononuclear cells by compounds **1**, **2** and SB207499

	1 (nM)[a]	**2** (nM)[a]	SB207499 (nM)[a]
PDE4A[b]	602 (±25)	88 (±14)	398 (±7)
PDE4B	34 (±0.5)	49 (±7)	288 (±7)
PDE4C	1230 (±39)	68 (±9)	813 (±13)
PDE4D	1.5 (±0.1)	1.0 (±0.2)	63 (±2)
PDE1	>10,000	—	>10,000
PDE2	>10,000	—	>10,000
PDE3	>10,000	>10,000	>10,000
PDE5	>10,000	—	>10,000
[^{3}H]-rolipram[c]	1.0 (±0.3)	0.6 (±0.2)	40 (±13)
TNFα-release[d]	68 (±1)	115	3467 (64)

[a]Data indicated as mean IC_{50} of at least three experiments; S.E. mean is given in parentheses.
[b]Inhibition of PDE activity, see ref 9.
[c]Inhibition of [3H]-rolipram binding.
[d]Inhibition of LPS/interferon γ stimulated TNFα release from human peripheral blood mononuclear cells.

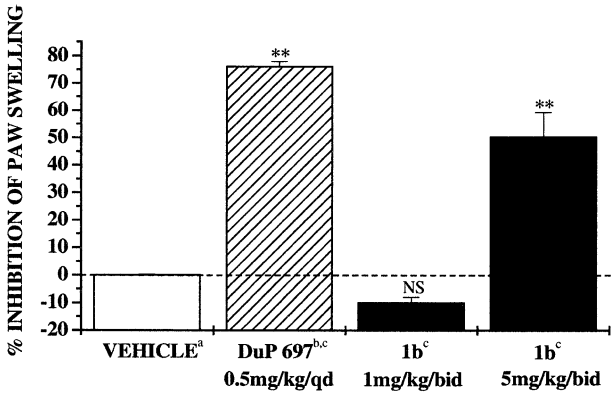


Figure 1. Activity of **1b** in adjuvant-induced arthritis in rats. [a]Water. [b]Control compound DuP 697; 5-bromo-2-(4-fluoro-phenyl)-3-(4-methanesulfonyl-phenyl)-thiophene. [c]The compounds were given orally for 17 days at the indicated dose and schedule, from the day of adjuvant injection; $^{**}P<0.01$ ANOVA followed by Dunnett's test post hoc. NS, not significant.

PDE4C, respectively. Furthermore, at a concentration of 10 μM, **1** did not inhibit a variety of other phosphodiesterase family members (PDE1, 2, 3 and 5). Thus, compound **1** had virtually the same activity profile against all measured PDEs as the nitro analogue **2**. Compared to the reference compound SB 207499, **1** was 40-fold more potent in inhibiting PDE4D and showed a significant better selectivity profile toward the other PDE4 subtypes. Both compounds, **1** and **2** were not selective in terms of inhibition of PDE4D catalytic activity versus their ability to block the high-affinity [^{3}H]-rolipram binding site. In this respect, compound **1** had a very similar profile to SB 207499 which was also not selective in our hands. On the cellular level, **1** potently inhibited LPS/interferon-gamma stimulated TNFα-release from human peripheral blood mononuclear cells ($IC_{50}=68$ nM). Thus again, the compound was roughly equipotent to the nitro-analogue **2**. It is noteworthy that the reference compound SB 207499 was significantly less active in this assay.

Since the subtype non-selective, archetype PDE4 inhibitor rolipram was reported to be active in a model of rheumatoid arthritis[14] we tested our PDE4D selective compound **1b** in a rat model of adjuvant-induced arthritis (Fig. 1). When dosed for 17 days after adjuvant injection (5 mg/kg bid, po), compound **1b** inhibited paw swelling by 50%. The control compound, a COX-2 inhibitor, was very potent in this model which is known to be very sensitive to this class of compounds.

Conclusion

We have demonstrated that the 6-benzo[1,2,5]oxadiazole substituted 1,7-naphthyridine **1** could be readily prepared by two alternative synthetic routes using palladium-catalyzed cross-coupling reactions as key steps. In vitro, compound **1** potently and selectively inhibited PDE4D and thus had a very similar profile to its nitro analogue **2**. Compound **1** was negative in in vitro assays of mutagenicity and genotoxicity. Oral anti-inflammatory activity of **1** was demonstrated in a rat model of adjuvant-induced arthritis where it dose-dependently inhibited paw-swelling. The full therapeutic potential of **1**, particularly its effect in models of other chronic inflammatory diseases such as asthma and COPD, will be reported elsewhere.

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