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SYNTHESIS AND IN VITRO PROFILE OF A NOVEL SERIES OF CATECHOL BENZIMIDAZOLES. THE DISCOVERY OF POTENT, SELECTIVE PHOSPHODIESTERASE TYPE IV INHIBITORS WITH GREATLY ATTENUATED AFFINITY FOR THE [^{3}H]ROLIPRAM BINDING SITE.

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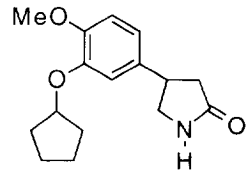
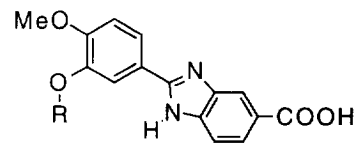
Abstract: The synthesis and biological properties of a novel series of potent and selective phosphodiesterase type IV (PDE IV) inhibitors are described. These catechol benzimidazoles were designed from rolipram and initial compounds reflected a similarly high affinity for the [^{3}H]rolipram binding site (500 to 1000X greater affinity for the [^{3}H]rolipram binding site over the PDE IV inhibitory site). However, SAR studies on the 3-alkoxy position revealed that this [^{3}H]rolipram binding site affinity could be attenuated, while potentiating the PDE IV inhibitory activity. This resulted in the 2-indanyl analog **13** which is a potent, selective PDE IV inhibitor with a 15X differential in favor of PDE IV binding.

As discussed in the preceding paper and in the references cited therein, there has been a vigorous pursuit of selective phosphodiesterase type IV (PDE IV) inhibitors for the treatment of asthma. Much of this work, including our own,[1] has used rolipram **1** as a starting point for SAR development. This compound is a micromolar PDE IV inhibitor (IC_{50} = 3.45 ± 0.91 μM, n = 7)[2] against human PDE IV isolated from lung tissue. Furthermore, there is a high-affinity binding site for rolipram in mouse brain homogenates (IC_{50} = 0.004 ± 0.002 μM, n= 73),[2] known as the [^{3}H]rolipram binding site. Although the physiological significance of this [^{3}H]rolipram binding site is not known, we felt that it would be useful to have compounds that did not exhibit affinity for this site, since not only would such a compound be a more selective agent, but it would also offer the potential of improved therapy with reduced side effects.[1]

A synthetic program with such goals in mind was undertaken and in the preceding paper, we report the synthesis and biological activity of a series of oxindoles which are micromolar PDE IV inhibitors with much reduced affinity for the [^{3}H]rolipram binding site (> 50 μM). In a different series of compounds, we found that by modifying the alkoxy substituents on the phenyl ring of **1**, after changing the pyrrolidone ring to a benzimidazole functionality, we were able to achieve PDE IV



1

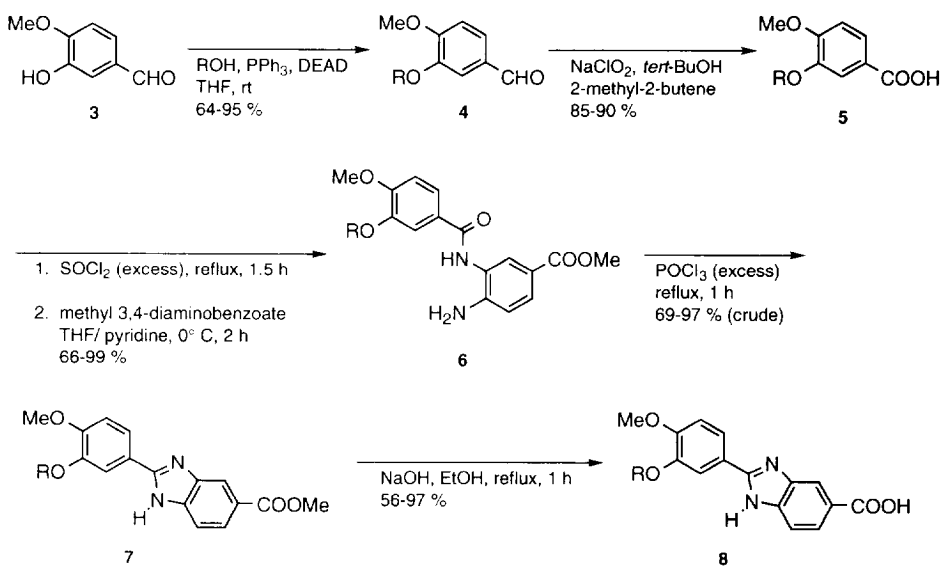


2

potencies in the nanomolar range, while in general they were inactive against PDE III. These compounds with the general structure **2**, proved to still have high affinity for the [^{3}H]rolipram binding site; however, the IC_{50}s were such that now these compounds are 15X more potent as PDE IV inhibitors.[3]

The general scheme for making these compounds is illustrated in Scheme I.[4] Treatment of isovanillin with the appropriate alcohol under Mitsunobu conditions provided 3-alkoxy-4-methoxybenzaldehyde **4**. This material was then oxidized to the acid **5** with sodium chlorite, whereupon it was coupled with methyl 3,4-diaminobenzoate to yield the amide **6**. Cyclization of **6** to the benzimidazole **7** was effected by treatment with phosphorous oxychloride, and the methyl ester was saponified with sodium hydroxide to yield the desired compounds as shown in Table I.

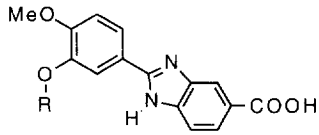
Scheme I

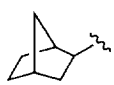
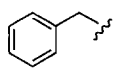
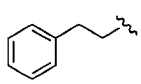
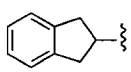


3 4 5 6 7 8

Our first analog in this series, compound **9**, was a very exciting lead. In this structure, the pyrrolidone ring of **1** was replaced by a benzimidazole ring, while retaining the methyl and cyclopentyl

Table I. Pharmacological Profile of Catechol Benzimidazoles[a]



Example	R	PDE IV IC_{50} (μM)[5]	[^{3}H]Rolipram IC_{50} (μM)[6]
9		0.071	0.078 ± 0.023 (2)
10		0.103	0.13 ± 0.09 (2)
11		6.77 ± 8.3 (2)	5.91
12		0.081	0.22 ± 0.05 (2)
13		0.002 ± 0.002 (2)	0.032 ± 0.022 (3)

[a] Values are individual determinations unless otherwise noted. See footnotes for variability of the reference agents.

ethers of the catechol functionality. This substitution effected a remarkable potentiation of the PDE IV inhibitory activity and attenuation of the [^{3}H]rolipram binding activity, both by roughly 50X so that the IC_{50}s were now roughly equipotent. Since this was a highly desirable development, we decided to continue in this series and explore the SAR around the catechol ether moiety of **9**.

In a previous series of compounds,[7] it had been found that the norbornyl functionality was a very effective bioisostere for the cyclopentyl group. It also proved to be effective in our series, although compound **10** showed no advantage over **9**, being only equipotent with respect to the PDE IV and [^{3}H]rolipram binding activity. The benzyl derivative **11** was considerably less potent than **9**, but when we synthesized the ethyl phenyl analog **12**, we were very excited to find that we had regained the PDE IV potency of **9**. At the same time, the [^{3}H]rolipram binding activity of **12** had been attenuated once again, so that there was now a modest 3X differential. We were intrigued by the structural similarities between the cyclopentyl and the ethyl phenyl groups, and thus decided to append the indanyl functionality to yield compound **13**. As can be seen, we achieved another

potentiation of the PDE IV activity, so that the potency of **13** is now in the nanomolar range. Although the [^{3}H]rolipram binding was also potentiated somewhat from **12**, the [^{3}H]rolipram binding IC_{50} is now 15X weaker than the PDE IV IC_{50}. Furthermore, compound **13** was found to have *in vivo* activity in the aerosolized antigen induced airway obstruction model (78% inhibition at 10 mg/kg, p.o., 1 h post dose).[8]

In summary, by manipulating the SAR around **1**, we were able to realize a 1000X increase in the potency of PDE IV antagonist activity. At the same time, the [^{3}H]rolipram binding has been significantly attenuated to yield a compound which is 15X more selective for PDE IV antagonist activity over [^{3}H]rolipram binding. Such compounds are invaluable tools for evaluating the role of [^{3}H]rolipram binding on PDE IV inhibitors and are being evaluated further pharmacologically.

References and Notes

1. Masamune, H.; Cooper, K.; Eggler, J. F.; Marfat, A.; Tickner, J. E.; Vazquez, E.; Cheng, J. B.; Marshall, S. C.; Shirley, J. T.; Umland, J. P. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue.
2. Pfizer data.
3. A similar approach to influencing the binding activity was undertaken in Koe, K. B.; Lebel, L. A.; Nielsen, J. A.; Russo, L. L.; Saccomano, N. A.; Vinick, F. J.; Williams, I. H. *Drug Dev. Res.* **1990**, *21*, 135.
4. All chiral compounds described in this paper are racemates. All yields are unoptimized.
5. Reeves, M. L.; Leigh, B. K.; England, P. J. *Biochem. J.* **1987**, *241*, 535. Data on reference standards, CP-76,593 (the racemate of CP-80,633 **2**) and milrinone (Harrison, S.A.; *Mol. Pharmacol.* **1986**, *29*, 506), illustrate the confidence limits for the PDE IV and PDE III screens, respectively. For the PDE IV assay, CP-76,593 gave an IC_{50} of 1.5 ± 12 μM (n = 150). For the guinea pig PDE III assay, milrinone gave an IC_{50} of 8.5 ± 2.5 μM (n = 3). For the human PDE III assay, milrinone gave an IC_{50} of 3.3 ± 1.3 μM (n = 41). Statistics were done with a Student's *t* test.
6. See reference 1. For this screen, rolipram gave an IC_{50} of 0.004 ± 0.002 μM (n = 73). Statistics were done with a Student's *t* test.
7. Saccomano, N. A.; Vinick, F. J.; Koe, B. K.; Nielsen, J. A.; Whalen, W. M.; Meltz, M.; Phillips, D.; Thadieo, P. F.; Jung, S.; Chapin, D. S.; Lebel, L. A.; Russo, L. L.; Helweg, D. A.; Johnson, J. L.; Ives, J. L.; Williams, I. H. *J. Med. Chem.* **1991**, *34*, 291.
8. Watson, J.W.; Conklyn, M.; Showell, H.J. *Am. Rev. Respir. Dis.* **1990**, *142*, 1093.

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