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ARYL SULFONAMIDES AS SELECTIVE PDE4 INHIBITORS

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Abstract: A series of novel selective phosphodiesterase 4 (PDE4) inhibitors has been developed which displays activity both *in vitro* and *in vivo*. These compounds possess good selectivity for the catalytic site of PDE4 over the high affinity Rolipram binding site. *In vivo* studies demonstrate a reduced propensity to display the emetic side effects which are commonly observed with PDE4 inhibitors.

Introduction

Asthma is a chronic, debilitating and often fatal disease whose incidence is increasing, primarily in the Western World. Current therapies are based upon inhaled β-agonists[1] to treat bronchoconstriction and steroids to treat the underlying inflammation, the latter of which has associated side effects. There is thus a requirement for an oral anti-inflammatory agent to treat the underlying disease; in recent years, the interest in this field has grown at a rapid pace, leading to the development of many orally active compounds that are able to selectively inhibit the PDE4 enzyme.[2]

Cyclic adenosine monophosphate (cAMP) is converted by phosphodiesterase enzymes (PDEs) into the inactive acyclic 5'-adenosine monophosphate (5'-AMP). Inhibition of PDE activity thus causes the cellular levels of cAMP to be potentiated, thereby activating the protein kinases responsible for decreasing inflammatory cell activity and airway smooth muscle tone.[3] Seven families of PDEs have been identified to date;[4] PDE4 is cAMP specific and is found in airway smooth muscle, all inflammatory cells and the vascular endothelium. Selective inhibitors of PDE4 have shown anti-inflammatory activity in animal models.[5] The anti-inflammatory action stems from the inhibition of cell function and cytokine liberation (e.g. TNF_{α}, IL-2, IL-5, IFN), leading to the inhibition of cell adhesion and proliferation.

The archetypal PDE4 inhibitor, Rolipram (1),[6] although possessing potent PDE4 inhibitory activity, causes emesis in ferrets even at doses as low as 0.1 mg/kg p.o.. The reason for this side-effect is not clear, but evidence suggests that Rolipram binds to the PDE4 enzyme at both the catalytic site and a high affinity binding site whose nature is not completely understood.[7] However there is increasing support for the hypothesis that binding to this high affinity site (Rolipram binding activity, RBA) correlates with the observed side-effects.[8]

Results

Our objective was to identify an orally active PDE4 inhibitor which does not cause nausea/emesis in man whilst maintaining the full spectrum of beneficial biological actions. Based on available literature SAR, database mining was used to select structurally diverse molecules. These compounds were screened in

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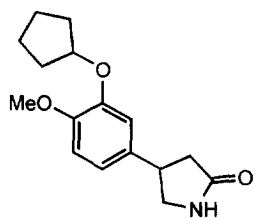
primary *in vitro* assays; the initial 'hits' are exemplified below (**2,3**) and were found to be selective for PDE4 over other PDE isoforms (Table 1).



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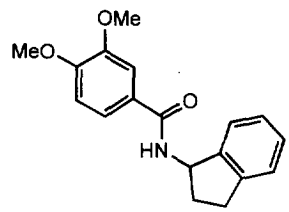

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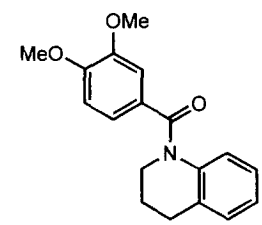


3

Compound	PDE1	PDE2	PDE3	PDE4[a]	PDE5	RBA[b]	Ratio PDE4/RBA
1 Rolipram	>200μM	28% (200μM)	27% (200μM)	3.5	200	0.02	175
2	14%	37%	53%	11	24%	3	3.7
3	14%	21%	31%	20	12%	15% (10μM)	<1

Values shown are IC_{50}s (μM) or percent inhibitions at 20μM unless otherwise stated.

Table 1. PDE selectivity profile of initial amide hits.

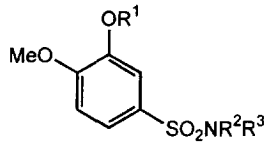
Although the absolute potency of compounds **2** and **3** against the PDE4 isozyme was only modest, the ratio of PDE4 catalytic activity to high-affinity Rolipram binding activity (RBA) was far superior to that observed for Rolipram, suggesting that these compounds would possess a therapeutic advantage.

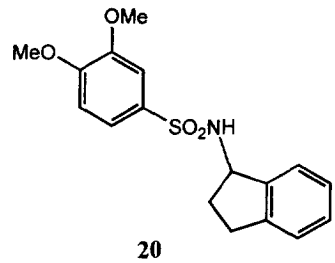
Replacement of the amide moiety with a sulfonamide led to a novel series of compounds possessing improved PDE4 inhibitory activity and a very favorable ratio of PDE4: RBA (Table 2). In this series of compounds, excellent selectivity for the PDE4 enzyme over the PDE3 isoenzyme was also maintained (data not shown). This is important since inhibition of PDE3 may result in cardiotoxicity.[4]

Our initial observation was that replacement of the cyclopentyl moiety with a methyl group in R^1 led to a greatly improved ratio of catalytic to Rolipram binding activity. Examination of these results for compounds **4** - **15** suggests that for optimum potency, R^2 should be CH_2aryl or CH_2heteroaryl together with an alkyl or substituted alkyl substituent with an optimum chain length of 3 or 4 carbon atoms for R^3. Additionally when R^3 represents a sulfone as in compounds **16** - **19**, equally good absolute potency and therapeutic ratio are observed.

Compounds **20**, **22**, **24** - **27** in which the R^2 group has been modified to a substituted indanyl moiety leading to a more conformationally constrained system also demonstrated good potency and selectivity for the catalytic binding site over the Rolipram binding site. Evidence suggests that the aromatic ring present in R^2 is essential for good *in vitro* potency against the PDE4 enzyme, but that a substituted alkyl side chain on the sulfonamide is not an absolute requirement.

An extension of this work led to a series of compounds possessing an endocyclic sulfonamide nitrogen atom, invoking further conformational restriction. Many of these compounds were found to possess both submicromolar activity against PDE4 and an excellent PDE4:RBA ratio and are exemplified by compounds **29-33** in Table 3.

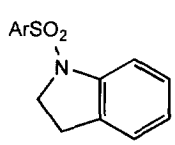




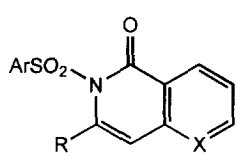
20

Compound	R^1	R^2	R^3	PDE4 IC_{50}	RBA IC_{50}	Ratio PDE4/RBA
1 Rolipram				3.5	0.02	175
4	Me	furan-2-ylmethyl	CH_2CH_2CN	10	37% (10μM)	<1
5	Cp	furan-2-ylmethyl	CH_2CH_2CN	32% (20μM)	10	>1
6	Me	furan-2-ylmethyl	$CH_2CH_2CH_2CN$	9	37% (10μM)	<1
7	Me	furan-2-ylmethyl	CH2CN	30% (20μM)	36% (10μM)	>1
8	Me	furan-2-ylmethyl	CH_2COCH_3	24	35	0.69
9	Me	furan-2-ylmethyl	$CH_2CH_2CH_3$	1.5	15	0.10
10	Me	furan-2-ylmethyl	CH_2CO_2Me	10	23% (100μM)	<1
11	Me	4-(methylamino-carbonyl)phenylmethyl	$CH_2CH_2CH_3$	1.9	4.3	0.44
12	Me	tetrahydrofuran-2-ylmethyl	CH_2CH_2CN	19	112	0.17
13	Me	H	CH_2CH_2CN	17.6	50	0.35
14	Me	pyrid-3-ylmethyl	CH_2Ph	5	8% (10μM)	<1
15	Me	pyrid-3-ylmethyl	H	39% (200μM)	41% (100mM)	>1
16	Me	pyrid-3-ylmethyl	SO_2Me	6	50	0.12
17	Cp	pyrid-3-ylmethyl	SO_2Me	2	4.5	0.44
18	$(CH_2)_5Ph$	pyrid-3-ylmethyl	SO_2Me	1.5	18% (1μM)	<1
19	Me	pyrid-3-ylmethyl	$SO_2(CH_2)_2NHSO_2Ph$	3	24	0.13
20	Me	indan-1-yl	H	6	12% (10μM)	<0.6
21	Me	cyclopentyl	H	100	19% (100μM)	<1
22	Me	indan-1-yl	CH_2CH_2CN	4.1	26% (10μM)	<0.4
23	Me	1,2,3,4-tetrahydro-naphth-1-yl	CH_2CH_2CN	6.4	30% (10μM)	<0.6
24	Me	5-chloroindan-1-yl	H	5.2	12% (10μM)	<0.5
25	Me	6-methoxyindan-1-yl	H	2.5	2% (10μM)	<0.25
26	Me	indan-1-yl	pyrid-3-ylmethyl	9	20% (10μM)	<0.9
27	Me	indan-1-yl	pyrid-2-ylmethyl	5.3	12% (10μM)	<0.5
28	Me	benzyl	pyrid-2-ylmethyl	7.8	5% (10μM)	<0.7

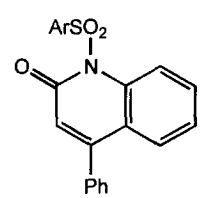
Table 2. *In vitro* activity and selectivity of sulfonamides.
All data are mean values and number of determinants is ≥2.



Ar = 3,4-dimethoxyphenyl
29



30 R = Ph; X = N
31 R = Ph; X = CH
32 R = H; X = CH



33

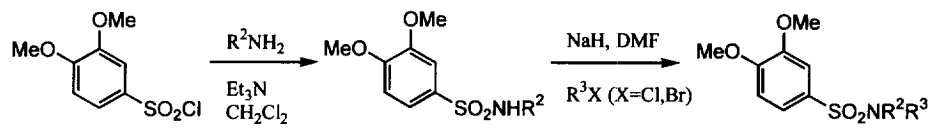
Compound	PDE4 IC_{50} (μM)	RBA IC_{50}	Ratio PDE4/RBA
29	4.3	18% (10μM)	<0.43
30	1.5	20% (10μM)	<0.15
31	0.6	31% (10μM)	<0.06
32	0.5	4.0μM	0.12
33	0.5	14% (10μM)	<0.05

Table 3. Activity profile of sulfonamides prepared from cyclic amines. All data are mean values and number of determinants is ≥2.

The formation of a 'sulfonimide' (**30-33**) increased the absolute PDE4 inibitory activity, while the construction of a highly conjugated system (**30, 31, 33**) afforded a highly favorable PDE4:RBA ratio.

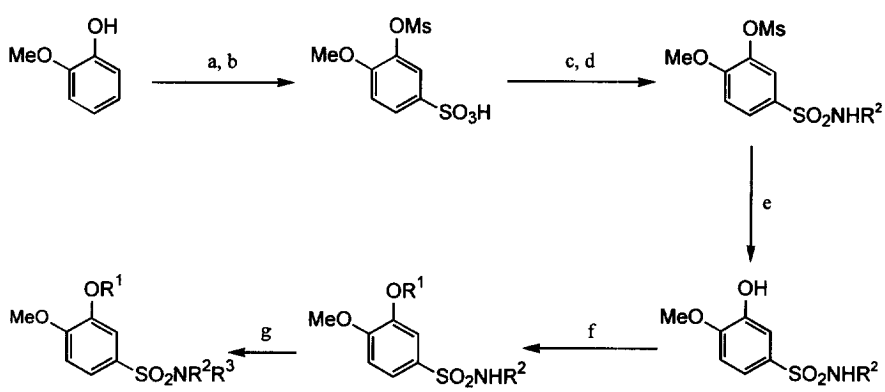
Chemistry

The general synthetic route to these compounds is outlined in Scheme 1 below. Coupling of the appropriate amine with 3,4-dimethoxysulfonyl chloride affords the secondary sulfonamides which are subsequently treated with the appropriate alkylating or sulfonylating agent.

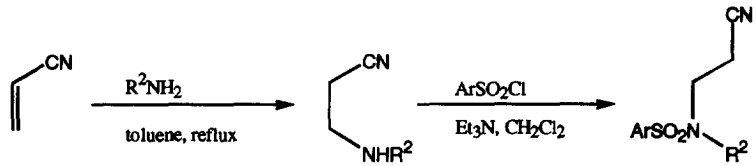


Scheme 1. Sulfonamide preparation.

In cases where R^1 is other than a methyl group, then the sequence shown in Scheme 2 is followed. Directed sulfonylation of the aromatic ring is achieved by using methanesulfonyl-protected 2-methoxyphenol. This is followed by sulfonamide formation, deprotection, *O*-alkylation and *N*-alkylation to form the desired sulfonamides. In cases where R^2 = CH_2CH_2CN, the protocol depicted in Scheme 3 is followed.

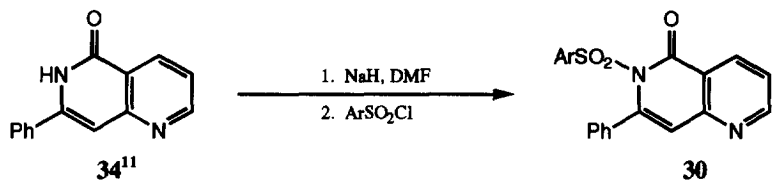


Scheme 2. a) MsCl, Et_3N, CH_2Cl_2; b) $ClSO_3H$; c) $(COCl)_2$, CH_2Cl_2; d) R^2NH_2, Et_3N, CH_2Cl_2; e) NaOH, dioxane, 65°C; f) R^1Br, Cs_2CO_3, DMF; g) R^3X (X=Cl, Br), NaH, DMF.



Scheme 3. Ar = 3,4-dimethoxyphenyl

Compound **29** was prepared simply by treating the appropriate amine with 3,4-dimethoxybenzenesulfonyl chloride in the presence of triethylamine. Compounds **30-33** were prepared by treating the appropriate amide with sodium hydride then 3,4-dimethoxybenzenesulfonyl chloride, as exemplified in Scheme 4.



34[11] **30**

Scheme 4. Ar = 3,4-dimethoxyphenyl

***In vivo* assay**

A guinea pig skin eosinophilia model was developed to assess the efficacy of these compounds *in vivo*.[12] Compound **20**, having a similar *in vitro* PDE4 activity to Rolipram but a better ratio, demonstrates an average 51% inhibition of eosinophilia at 5mg/kg ip, compared to Rolipram which gives 72% inhibition (Figure 1). However, in a model of ferret emesis,[13] Rolipram produces CNS effects at 0.1mg/kg i.p. and retching and vomiting at 3.0mg/kg i.p. (Figure 2), whereas compound **20** displays none of these side effects up to the highest dose tested (10 mg/kg i.p.). This demonstrates that an improvement of the *in vitro* ratio of catalytic PDE4 activity to Rolipram binding activity can translate to an improved *in vitro* profile.

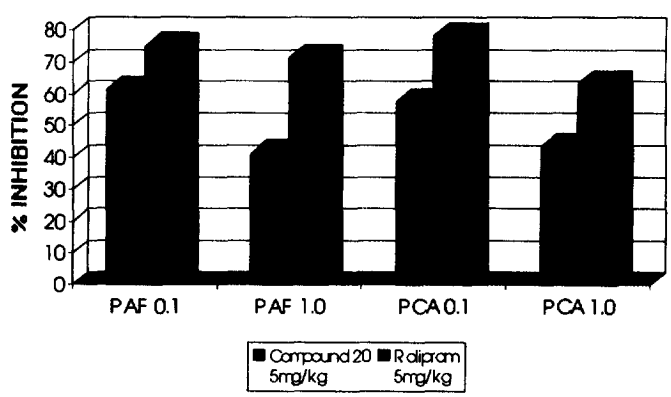


Figure 1. Inhibition of skin eosinophilia in the guinea pig by compound **20** and Rolipram.

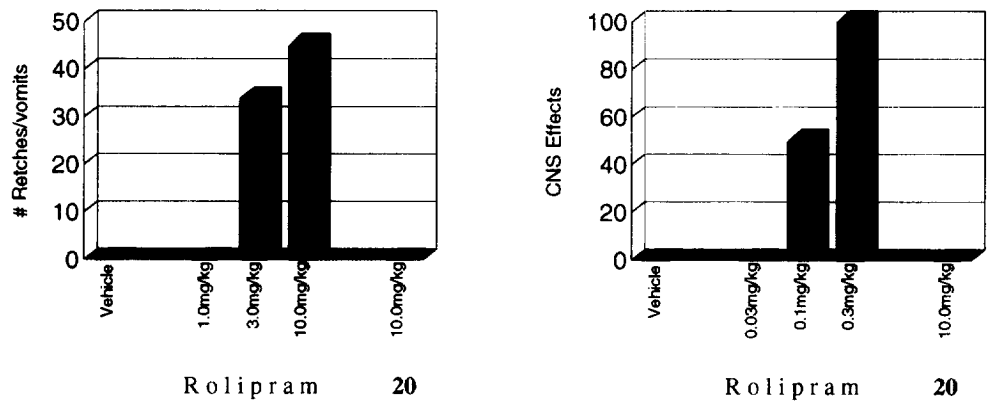


Figure 2. Retching and vomiting and CNS effects observed in ferrets by Rolipram and compound **20**. CNS effects are a compilation of mouth scratching, head burrows and salivation.

Conclusions

The initial hits demonstrated that adequate PDE4 potency could be achieved with a good catalytic site to high affinity site binding ratio. Subsequent generation of SAR led to several sulfonamide series that provided significant improvements in potency and/or selectivity. Additionally these compounds exhibit a good *in vivo* profile and strong support is lent to the hypothesis that Rolipram binding activity (RBA) is responsible for the observed emetic side effects so often associated with PDE4 inhibitors. The sulfonamide **20** exhibits no such side effects at efficacious doses. Work is ongoing to further improve these compounds which will be reported in due course.

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