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SUBSTITUTED FURANS AS INHIBITORS OF THE PDE4 ENZYME

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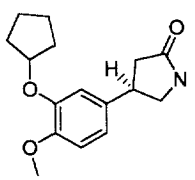
Abstract: The synthesis and in vitro activity of a series of substituted furans as a novel structural class of PDE4 inhibitors is described. Comparison of emetic threshold with known PDE4 inhibitors is presented.

It has been established that PDE4 is responsible for the breakdown of cAMP in many types of inflammatory cells.[1a] PDE4 inhibitors block inflammatory mediator release, such as LPS induced TNFα and eicosanoid release in whole blood. Furthermore, elevation of cAMP in airway smooth muscle has an antispasmolytic effect and consequently PDE4 inhibitors are currently being developed as potential drugs for the treatment of asthma, by virtue of their ability to block both inflammation and bronchoconstriction.[1b]

The design of PDE4 inhibitors for the treatment of inflammatory diseases such as asthma, has met with limited success to date. Rolipram (**1**),[2] one of the first clinically evaluated PDE4 inhibitors, unfortunately causes emesis as a side effect at or near its effective dose. More recently, discovered PDE4 inhibitors[3,4] such as CDP 840 (**2**) and SB207499 (Ariflo, **3**) are less emetic than Rolipram.



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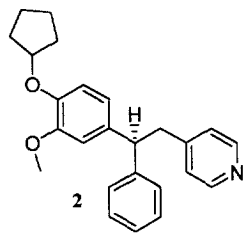

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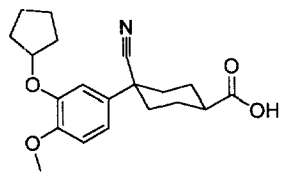

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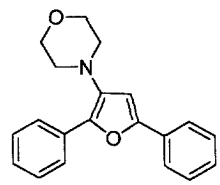

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In order to identify a new PDE4 inhibitor structural lead our strategy has been to select compounds for screening from our sample collection using a topological similarity search program. Using this technique, a novel class of inhibitors based on the lead compound **4**[5] (IC_{50} = 2.3μM) has been discovered. We describe herein the SAR obtained by further screening of compounds selected from our sample collection as well as newly synthesized analogs.

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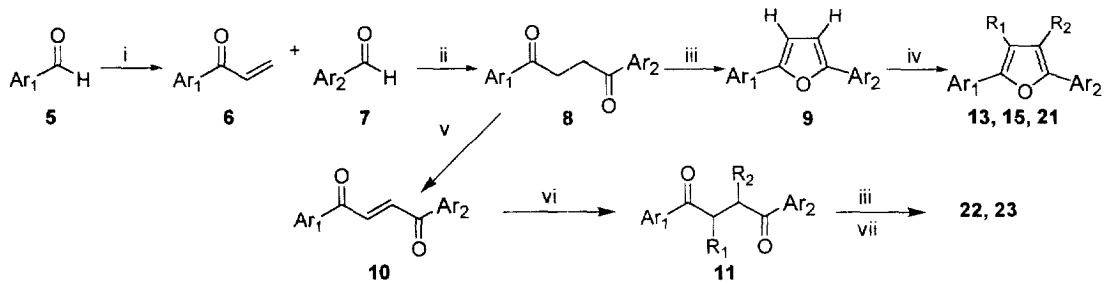


Scheme 1. (Ar_1, Ar_2, R_1 and R_2 are shown in Table 1). *Reagents & conditions:* (i) (1) Vinyl magnesium bromide, THF, 0 °C (2) MnO_2, EtOAc; (ii) Ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide, NEt_3, 90 °C, 2 h. (iii) TsOH, toluene, 100 °C; (iv) (1) BuLi, THF, –78 °C, then PhCHO or MeCHO; (2) MnO_2, EtOAc; (v) (1) TMSCl , KHMDS; (2) Br_2; (vi) Thiophenol, Na_2CO_3, EtOH; (vii) Oxone, MeOH, H_2O.

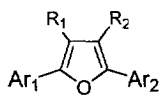
The chemistry used in the preparation of the compounds is described in Scheme 1. Grignard addition of vinyl magnesium bromide to the aldehyde **5** followed by manganese dioxide oxidation gave compound **6**. Coupling of this vinyl ketone with ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide[6] and aldehyde **7** afforded **8**. Cyclization of the diketone **8** with *p*-toluenesulfonic acid gave the 2,5-disubstituted furan **9**. Further substitution of **9** was achieved by treatment with butylithium followed by an aldehyde to give a single regioisomer of the secondary alcohol, as demonstrated by NOE experiment. After manganese dioxide oxidation, the desired trisubstituted acylated furans **13**, **15**, or **21** were obtained. The phenyl sulfone compounds **22** and **23** were prepared by non-regioselective addition of an electrophile to olefin **10**, obtained from an addition elimination reaction on compound **8**, to give **11**. Cyclization and the oxidation afforded **22** and **23**.

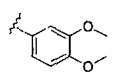
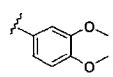
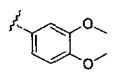
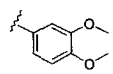
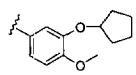
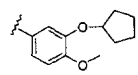
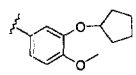
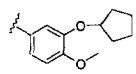
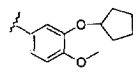
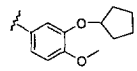
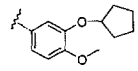
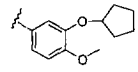
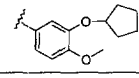
The potency of the inhibitors against PDE4 was determined by titration against human recombinant purified GST-PDE4A_{248} using the Amersham's PDE-SPA assay kit (cat #RPNQ-0150). For IC_{50} determination, 2 μL of DMSO solution of the testing compound (in threefold serial dilution) was mixed with 190 μL of the assay buffer (0.1 μM cAMP (0.15 μCi ^{3}H-AMP) in 50 mM Tris, 1mM EDTA, and 10 mM $MgCl_2$ at pH 7.5). The reaction was initiated by the addition of 10 μL of GST-PDE4A_{248} (~1 ng) and terminated after 10 min at 30°C by the addition of 50 μL of the SPA bead suspension. The amount of ^{3}H-AMP generated was determined on a Wallac's Microbeta 96-well plate counter. The IC_{50} values were calculated from the nonlinear regression fit of a 10 point dose–response curve in duplicate with the four parameter equation. The results are summarized in Table 1.

Removal of the morpholino group from compound **4**, leading to **12**, resulted in a total loss of potency. However, replacement of the morpholino by an other polar group such as a phenyl ketone as in compound **13**, increased the potency by eightfold. Introduction of methoxy groups on both phenyl rings gave compound **14** with an IC_{50} of 0.56 μM, a fourfold increase in potency from **4**. Combining a polar group (methyl ketone) as R^1 or R^2 and the methoxy subtitution on the phenyl rings resulted in a further fourfold increase in potency (**15**, IC_{50}

= 0.12μM). Introduction of the rolipram like 3-methoxy-4-cyclopentoxy moiety on both phenyl rings gave compound **16** (IC_{50} = 0.043μM), which is ten times more potent than the corresponding compound **14** with methoxy groups. Replacement of one of the dialkoxyaryl groups on compound **16** with a 2-pyridyl group gave a further twofold increase in potency (**17**, IC_{50} = 0.025μM). The 4-pyridyl group (**18**) as in CDP 840, the 3-pyridyl group (**19**) or a quinolinyl (**20**) were all less potent than compound **17**. Introduction of a phenyl ketone group on compound **17** decreased the potency (**21**, IC_{50} = 0.59μM) contrary to what could be expected from the SAR of compound **13**. Introduction of phenyl sulfone (**22** and **23**) as R^1 or R^2 also failed to improve the potency.

Table 1. Potency of Inhibitors on GST-PDE4A_{248}



Compound	R^1	R^2	Ar^1	Ar^2	IC_{50}(μM)
4	N-Morpholinyl	H	Phenyl	Phenyl	2.3
12	H	H	Phenyl	Phenyl	>10
13	Benzoyl	H	Phenyl	Phenyl	0.34
14	H	H			0.56
15	Acetyl	H			0.12
16	H	H			0.044
17	H	H		2-Pyridinyl	0.025
18	H	H		3-Pyridinyl	0.37
19	H	H		4-Pyridinyl	0.065
20	H	H		2-Quinolinyl	0.19
21	Benzoyl	H		2-Pyridinyl	0.59
22	Phenylsulfonyl	H		2-Pyridinyl	0.77
23	H	Phenylsulfonyl		2-Pyridinyl	0.74

The emetic threshold of **17** was determined using the ferret emesis model.[7] Administration of 3 mg/kg po was followed by a two hour observation period during which no effect was observed. Subsequent administration of 10 mg/kg of **17** caused emesis within 1 h after administration. Comparison of the emetic threshold in the ferret of compound **17**, CDP840 and (-) Rolipram and their GST- $PDE4A_{248}$ enzyme inhibition potency is shown in Table 2. Compound **17** was more emetic then CDP 840 (threefold lower dose) while being less potent on the enzyme. On the other hand, **17** is less emetic than rolipram (30-fold higher dose) but it is also less potent on the enzyme.

Table 2. Emesis and PDE4A Potency.

Compound	Emetic threshold	GST- $PDE4A_{248}$ (IC_{50}, nM)
CDP 840	30 mg/kg	5
(–)Rolipram	0.3 mg/kg	4
17	10 mg/kg	25

In conclusion, we have identified a series of substituted furans as potent inhibitors of PDE4. Substitution of the furan by both a 2-pyridyl and a 3-methoxy-4-cyclopentyloxy group led to **17** (GST- $PDE4A_{248}$ IC_{50} = 25 nM), which is a 100-fold more potent than the lead compound **4**.

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