Articles

Novel Selective PDE4 Inhibitors. 1. Synthesis, Structure−Activity Relationships, and Molecular Modeling of 4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-ones and Analogues

Margaretha Van der Mey,*[,†,§] Armin Hatzelmann,[‡] Ivonne J. Van der Laan,[§] Geert J. Sterk,[§] Ulrich Thibaut,[‡] and Hendrik Timmerman[†]

Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands; Byk Nederland, Zwanenburg, The Netherlands; and Byk Gulden, Konstanz, Germany

Received February 7, 2001

A number of 6-(3,4-dimethoxyphenyl)-4,5-dihydro-2*H*-pyridazin-3-ones and a novel series of 4-(3,4-dimethoxyphenyl)-2*H*-phthalazin-1-ones were prepared and tested on the cGMP-inhibited phosphodiesterase (PDE3) and cAMP-specific phosphodiesterase (PDE4) enzymes. All tested compounds were found to specifically inhibit PDE4 except for pyridazinone **3b**, which showed moderate PDE4 ($pIC_{50} = 6.5$) as well as PDE3 ($pIC_{50} = 6.6$) inhibitory activity. In both the pyridazinone and phthlazinone series it was found that *N*-substitution is beneficial for PDE4 inhibition, whereas in the pyridazinone series it also accounts for PDE4 selectivity. In the phthalazinone series, the *cis*-4a,5,6,7,8,8a-hexahydrophthalazinones and their corresponding 4a,5,8,8a-tetrahydro analogues showed potent PDE4 inhibitory potency (**10**/**11c**,**d**: $pIC_{50} = 7.6-8.4$). A molecular modeling study revealed that the *cis*-fused cyclohexa(e)ne rings occupy a region in space different from that occupied by the other fused (un)saturated hydrocarbon rings applied; we therefore assume that the steric interactions of these rings with the binding site play an important role in enzyme inhibition.

Introduction

Asthma is one of the most common chronic diseases,[1] worldwide and antiasthma medications are widely prescribed. In fact, asthma treatments account for 1−2% of the total health budget in industrialized countries.[2] Despite advancements in treatment, the incidences of asthma, asthma-related deaths, and hospitalizations for asthma have increased significantly during the past decade.

Asthma is characterized by a reversible airway obstruction, ongoing cellular inflammation, and nonspecific hyper-responsiveness to a variety of challenges. Both acute and long-term manifestations of asthma are believed to be a consequence of various inflammatory mediators released by activated inflammatory and immune cells.[3−6] Therefore, the ability to suppress activation of these cells is an essential activity for a compound to have a therapeutic effect on asthma.

Four major classes of compounds are currently used in the treatment of asthma, including bronchodilators (particularly β-adrenoceptor agonists), immunosuppressive agents (corticosteroids), antiallergic agents for prophylactic use (e.g., disodium cromoglycate), and xanthines (e.g., theophylline),[7] which appear to possess bronchodilatory and anti-inflammatory as well as immunomodulatory properties. Newer drugs include leukotriene antagonists such as montelukast.[8]

To date, much research has been directed toward the discovery of new antiasthmatic agents with high selectivity and efficacy and a reduced side effect profile. Phosphodiesterases (PDEs),[9] enzymes involved in the intracellular degradation of cAMP and cGMP to their corresponding 5′-monophosphate counterparts, have received a considerable amount of attention as molecular targets for the treatment of asthma.

Currently, a number of PDE isoenzyme families have been identified, which have been classified according to their substrate affinities and specificities (cAMP versus cGMP), kinetic characteristics (K_m and V_{max}), subcellular distributions (soluble versus membrane-bound), and regulatory properties (e.g., activation by calcium/calmodulin (CaM)).[10−16] During the past few years molecular biological methods have revealed an even higher complexity by the demonstration that most of these PDE families include more than one, and as many as four, distinct gene products (subtypes) as well as multiple splice variants within one gene family.[17] Currently, major interest centers on selective inhibitors of PDE4,[18−20] mainly due to the fact that PDE4 is the prominent isoenzyme present in inflammatory cells thought to be important in asthma[21−23] and because inhibitors of PDE4 are effective in attenuating the activity of these inflammatory cells.[24−26] PDE4 is also

* Address correspondence to this author at the Radionuclidencentrum, Vrije Universiteit, De Boelelaan 1085c, 1081 HV Amsterdam, The Netherlands (telephone +31 20 4449720; fax +31 20 4449121; e-mail mmeij@rnc.vu.nl).
† Vrije Universiteit.
§ Byk Nederland.
‡ Byk Gulden.

10.1021/jm010837k CCC: $20.00
Published on Web 07/03/2001

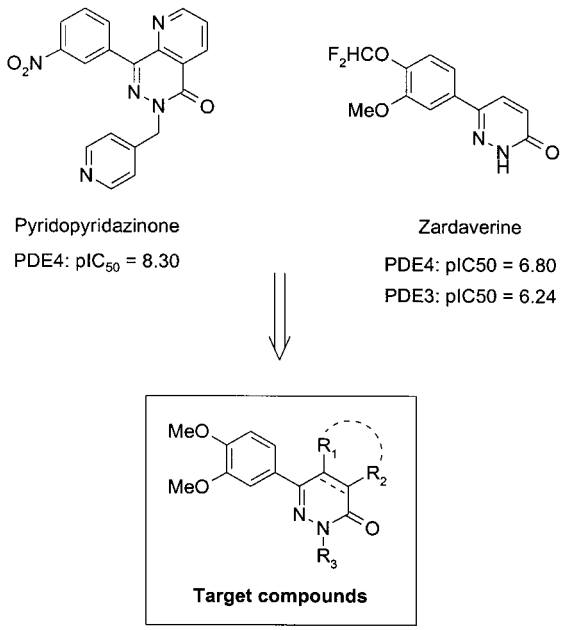


Figure 1.

involved in the regulation of airway smooth muscle tone, together with PDE3, which is the major PDE present in airway smooth muscle. Consistent with the presence of large amounts of PDE3 and PDE4, studies with human isolated bronchi have demonstrated that selective inhibitors of either isoenzyme partially reverse spontaneous tone and elicit bronchorelaxation,[27,28] PDE3 inhibitors being somewhat more effective.[28] Interestingly, either a combination of PDE3 and PDE4 inhibitors or dual PDE3/4 inhibitors produce a much larger bronchorelaxant effect than individual isoenzyme-selective agents alone,[29,30] suggesting that these isoenzymes act in an synergistic manner in human airway smooth muscle.

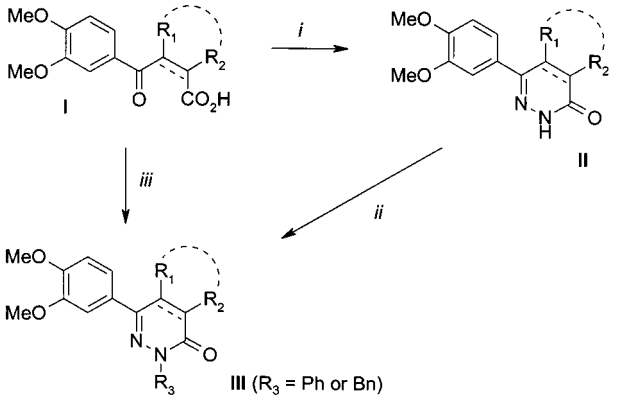
In our search for new lead structures for selective PDE4 or dual PDE3/4 inhibitors (Figure 1) we combined structural elements of the pyridazinone zardaverine,[31] which has been found to be active on PDE3 (pIC_{50} = 6.24; human platelet) and PDE4 (pIC_{50} = 6.80; canine trachea), and a pyridopyridazinone analogue,[32] a potent and selective inhibitor of PDE4 (pIC_{50} = 8.30; human lymphocyte). The target compounds contain the pyridazinone nucleus present in both zardaverine and the pyridopyridazinone compound and a catechol ether moiety, which was found to be important for inhibition in many PDE4 inhibitors.[33]

This paper describes the synthesis, structure−activity relationships (SAR), and molecular modeling studies for a series of pyridazinones and phthalazinones[34,35] among which several potent PDE4 inhibitors are present.

Chemistry

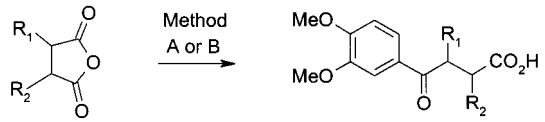
General Procedures for Synthesis of the Target Compounds. The target compounds were synthesized according to the procedures depicted in Scheme 1. The γ-keto acids **I** readily underwent cyclization upon treatment with hydrazine hydrate in EtOH to give the corresponding pyridazinones or phthalazinones **II**, which afforded the desired *N*-benzylated analogues **III** in high yields upon treatment with NaH followed by benzyl chloride.

Scheme 1[a]



[a] Reagents: (*i*) H_2NNH_2, EtOH, reflux; (*ii*) 1, NaH, DMF; 2, BnCl; (*iii*) $PhNHNH_2$, toluene, reflux.

Scheme 2[a]



2a: $R_1 = R_2 = H$
2b: $R_1 = CH_3$, $R_2 = H$
2c: $R_1 = H$, $R_2 = CH_3$
2d: $R_1 = R_2 = CH_3$

[a] Reagents: method A (**2a**); 1,2-dimethoxybenzene, $AlCl_3$, CH_2Cl_2, reflux; method B (**2c**, **2d**); 3,4-dimethoxyphenylmagnesium bromide (**1**), THF.

Condensation of phenylhydrazine with γ-keto acids **I** in toluene at reflux temperature provided the *N*-phenyl pyridazinones and phthalazinones **III** in variable yields.

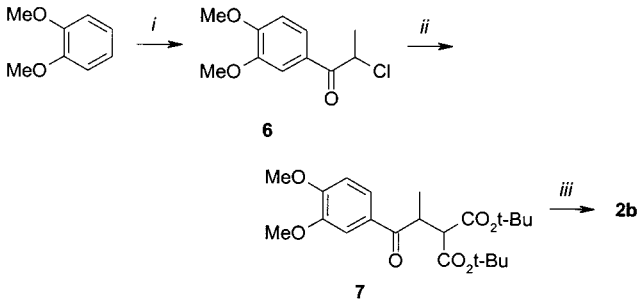
The target compounds were purified by crystallization. If (re)crystallization was not sufficient to give pure products, the compounds were purified by flash column chromatography, followed by crystallization. The overall yields of the *N*-substituted derivatives **III** were strongly influenced by the crystallization procedures.

Synthesis of the 4-Oxobutyric Acids and 4,5-Dihydro-2*H*-pyridazin-3-ones. The γ-keto acid **2a**[36,37] was prepared by a Friedel−Crafts reaction between 1,2-dimethoxybenzene and succinic anhydride in the presence of aluminum chloride (Scheme 2).

The Friedel−Crafts reaction using methylsuccinic anhydride usually leads to a preponderance of the α-methylketo acids.[38] For this reason, the β-methylketo acid **2b**[39] was synthesized analogously to literature procedures[40] using an alternate pathway (Scheme 3). The Friedel−Crafts acylation of 1,2-dimethoxybenzene with 2-chloropropionyl chloride in the presence of aluminum chloride led to the α-chloroketone **6**. Displacement of chloride with *tert*-butyl sodiomalonate in DMF gave the required γ-keto diester **7**. After workup, the crude diester was hydrolyzed by treatment with TFA, followed by decarboxylation of the resulting diacid in refluxing acetic acid to give the easily isolable γ-keto acid **2b**.

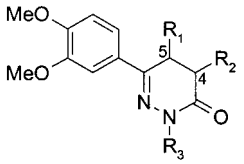
To synthesize α-methylketo acid **2c**,[41] methylsuccinic anhydride was treated with 3,4-dimethoxyphenylmagnesium bromide (**1**) in a Grignard reaction. Workup and subsequent crystallization from diethyl ether gave an inseparable mixture of two regioisomers (ratio **2c**/**2b** = 6:4), the minor component being identical to β-meth-

Scheme 3[a]



[a] Reagents: method C; (*i*) $CH_3ClCHC(O)Cl$, $AlCl_3$, $ClCH_2CH_2Cl$, reflux; (*ii*) sodiomalonic acid *tert*-butyl ester, DMF; (*iii*) 1, TFA, CH_2Cl_2, reflux; 2, AcOH, reflux.

Table 1. 6-(3,4-Dimethoxyphenyl)-4,5-dihydro-2*H*-pyridazin-3-ones and Their PDE3 and PDE4 Inhibitory Activities



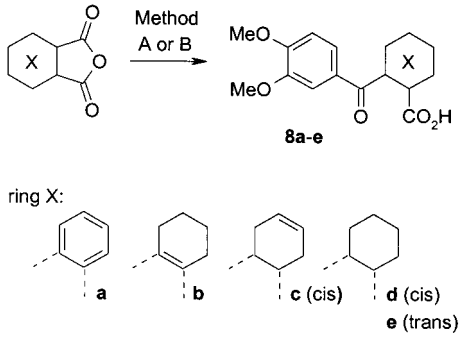
compd	R_1	R_2	R_3	conf C4−C5	PDE3 pIC_{50}[a]	PDE4 pIC_{50}[a]
3a	H	H	H		5.6	5.9
3b	Me	H	H		6.6	6.5
3d	Me	Me	H	cis	<5.0	6.7
3e	Me	Me	H	trans	5.4	6.2
4a	H	H	Ph		<5.0	6.4
4b	Me	H	Ph		<5.0	6.8
4c	H	Me	Ph		<5.0	6.9
4d	Me	Me	Ph	cis	<5.0	7.3
5a	H	H	Bn		5.3	7.1
Zardaverine					6.2	6.8

[a] $pIC_{50} = -\log IC_{50}$. Inhibition of PDE4 was investigated in the cytosol of human neutrophils, and activity on PDE3 was determined in homogenates of human blood platelets. The data are means of two independent determinations in triplicate.

ylketo acid **2b**. The major acylation product **2c** was assigned the α-methyl configuration on the basis of ^{1}H NMR spectroscopy. The α-methylketo acids can be differentiated from the corresponding β-methyl derivatives due to the position of the ^{1}H NMR signal of the methine proton.[42] In the β-methyl series this proton is further downfield and separated from the methylene protons in contrast to the methine proton in the α-methyl analogues. After condensation of the mixture of γ-keto acids **2b** and **2c** with phenylhydrazine, the pyridazinones **4b** and **4c** (Table 1) were isolated in yields of 46 and 7%, respectively.

A mixture of D,L- and meso-2,3-dimethylsuccinic acid was, according to literature procedures, refluxed in acetic anhydride to give a mixture of *cis*- and *trans*-2,3-dimethylsuccinic anhydride.[43] Synthesis of the 2,3-dimethyl-4-oxobutyric acids **2d**[44] (up to four stereoisomers are possible) was effected by a Grignard reaction using the *cis*−*trans* mixture of 2,3-dimethylsuccinic anhydride and Grignard reagent **1** (Scheme 2). The mixture of stereoisomeric γ-keto acids **2d** was then treated with phenylhydrazine, and subsequent purification of the reaction products using flash column chromatography resolved the mixture of *N*-phenyl-4,5-dimethylpyridazinones **4d** (*cis*) and **4e** (*trans*, Table 1). Comparison of the yields indicated that the *trans* compound was predominantly formed in a ratio of 1:7 (**4d**/**4e**). Although analogue **4e** was pure according to TLC and NMR, it could not be obtained in crystalline form.

Scheme 4[a]



[a] Reagents: method A (**8a**,**c**−**e**); 1,2-dimethoxybenzene, $AlCl_3$, CH_2Cl_2, reflux; method B (**8b**−**d**); **1**, THF.

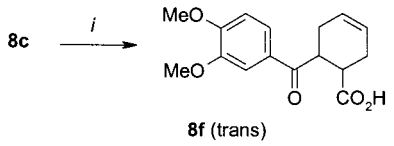
The stereoisomeric mixture of γ-keto acids **2d** was also treated with hydrazine monohydrate to yield the 4,5-dimethylpyridazinones **3d** (*cis*) and **3e** (*trans*) in a ratio of 1:8. The two product ratios obtained agree with the findings that in the dimethylsuccinic series, the open-chain compounds (γ-keto acids) are stable in the meso-forms and the corresponding heterocyclic derivatives (pyridazinones) in the DL(*trans*)-forms.[45]

The configuration of the 4,5-dimethylpyridazinones was determined by NOE (nuclear Overhauser enhancement) measurements. Upon saturation the H4 proton of analogue **4d**, the NOE difference spectrum showed NOEs on the 4-methyl group and the H5 proton (weak). The 4-methyl group was then saturated, and interaction with the H4 proton and 5-methyl group was observed. From these experiments it was concluded that this compound possesses a *cis* configuration. In the case of derivative **4e** the H4 proton was saturated and strong NOEs were observed on the 4- and 5-methyl groups as well as the H5 proton. In a second experiment the NOE spectrum showed, upon saturation of the H5 proton, nearly the same strong NOE on the H4 proton, the 4- and 5-methyl groups, and both ortho-hydrogen atoms of the 6-phenyl ring. On the basis of these results a *trans* configuration was assigned to analogue **4e**.

Synthesis of the Cyclic γ-Keto Acids and 4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-ones. γ-Keto acids **8a**[46] and **8c**−**e** (Scheme 4) were prepared in moderate yields (30−40%) from the corresponding phthalic anhydrides by Friedel−Crafts acylations with 1,2-dimethoxybenzene as described above for 4-oxobutyric acid **2a**. Nucleophilic addition of Grignard reagent **1** to *cis*-1,2,3,6-tetrahydrophthalic and *cis*-1,2-cyclohexanedicarboxylic anhydride also afforded compounds **8c** and **8d**, respectively, but in somewhat higher yields (40 versus 30%). Derivative **8b** was synthesized via a Grignard reaction because Friedel−Crafts acylation of 1,2-dimethoxybenzene with 3,4,5,6-tetrahydrophthalic anhydride was unsuccessful.

In the tetra- and hexahydrophthalic series, γ-keto acids having a *cis* configuration (e.g., **8c** and **8d**) are less conformationally stable than the corresponding *trans* diastereomers.[42,47] Therefore, γ-keto acid **8c** was subjected to aqueous base-mediated epimerization to give the *trans* analogue **8f** as a single diastereomer in 90% yield (Scheme 5).

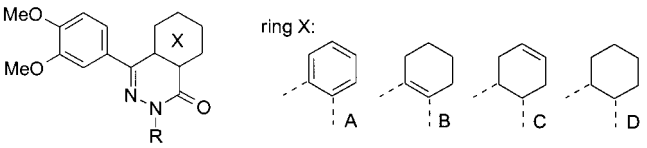
Scheme 5[a]



8f (trans)

[a] Reagents: method D; (*i*) 2 N KOH.

Table 2. 4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-ones and Their PDE4 Inhibitory Activities[a]



compd	ring X	conf C4a−C8a	R	PDE4 pIC_{50}[b]
9a	A		H	5.8
9b	B		H	5.2
9c	C	cis	H	7.0
9d	D	cis	H	6.4
9e	D	trans	H	5.3
10a	A		Ph	5.8
10b	B		Ph	5.3
10c	C	cis	Ph	7.9
10f	C	trans	Ph	6.1
10d	D	cis	Ph	7.6
10e	D	trans	Ph	5.1
11a	A		Bn	6.5
11b	B		Bn	5.8
11c	C	cis	Bn	8.4
11d	D	cis	Bn	8.1
Ariflo				7.0

[a] The compounds show no substantial PDE3 inhibitory activity ($pIC_{50} < 5.4$); the activities are therefore not listed. [b] See footnote *a* of Table 1.

The target phthalazinones **9**−**11** (Table 2) were prepared analogously to the procedures depicted in Scheme 1.

Configurational Analysis of the 4a,5,8,8a-Tetra- and 4a,5,6,7,8,8a-Hexahydrophthalazinones. For the 4a,5,8,8a-tetra- and 4a,5,6,7,8,8a-hexahydrophthalazinones described in this paper, several (up to four) stereoisomers are possible. As the *cis* or *trans* fusion of the cyclohex(a)ene and heterocycle (pyridazinone ring) depends on the reaction conditions during syntheses, the configurations of the starting materials (γ-keto acids) and the products (phthalazinones) can differ. This knowledge emphasizes the importance of determination of the stereostructures of the reaction products. Information about the configurations of the phthalazinones **9c**−**e**, **10c**−**f**, and **11c**,**d** (Table 2) was obtained by the application of different NMR techniques. The configurational assignments of the investigated compounds are based on their homo- and heteronuclear correlation spectra (HH- and CH-COSY, respectively) as well as their attached proton test (APT) and NOE difference spectra.

For hexahydrophthalazinone **10d**, the signals of the two annealed carbon atoms (i.e., C4a and C8a) at 36.11 and 37.12 ppm were identified by APT, and the ^{1}H NMR signals corresponding to these resonances, 3.20 and 2.93 ppm, respectively, were located in the CH-COSY spectrum. NOE measurements were used to determine the position of the methine protons and the configuration of the compound under investigation. Saturation of the methine signal at 3.20 ppm caused enhancement of the signals of the ortho-hydrogen atoms of the 4-phenyl ring, thus indicating their vicinity to the methine hydrogen atom, which could then be assigned as H4a. The strong NOE between the two annealed hydrogen atoms proved their *cis* position.

The NMR data for the hexahydrophthalazinones **10d** and **10e** differ significantly. A *cis* to *trans* change in the structure causes significantly weaker shielding on the cyclohexane carbon atoms. The signals of the annealed hydrogen atoms of analogue **10e** were therefore appreciably upfield-shifted, whereas the overall shift for the six cyclohexane carbon atoms was 16 ppm more than for **10d**, which was regarded as evidence for the *trans* annealation. The absence of an NOE between the two annealed hydrogen atoms once again confirmed their *trans* arrangement.

The configurations of phthalazinones **9c**−**e**, **10c**,**f**, and **11c**,**d** were determined in a similar way. The results indicated that in this series of compounds, the *cis* and *trans* configurations of the γ-keto acids were stable under the conditions used during condensation and alkylation reactions.

Finally, the ^{1}H NMR spectra of phthalazinones **9**−**11** showed that H8′ is strongly deshielded because of its coplanarity with the carbonyl bond, and the anisotropic effect of the latter causes downfield shifts of their signals.

Pharmacology

The pyridazinone and phthalazinone analogues (Tables 1 and 2) were tested for their PDE3 and PDE4 inhibitory activities. PDE3 inhibition was determined in homogenates of human blood platelets.[31] PDE4 inhibition was investigated in the cytosol of human neutrophils.[48] The tests were carried out according to the method of Bauer and Schwabe.[49] In this assay, the PDE reaction with ^{3}H-labeled cAMP in the absence or presence of test compound (different concentrations) is carried out in the first step. In a second step, the resultant 5′-monophosphate is then further hydrolyzed to the uncharged nucleoside by a snake venom 5′-nucleotidase from *Crotalus atrox*. In the third step, the nucleoside is separated from the remaining charged substrate on ion-exchange columns. The radioactivity of the elute is measured and corrected by the corresponding blank values. IC_{50} values, which are the drug concentrations at which the enzyme activity is reduced to 50%, are calculated from the drug concentration−inhibition curves by nonlinear regression analysis. The $-\log IC_{50}$ (= pIC_{50}) values determined for the compounds are summarized in Tables 1 and 2.

PDE Inhibition and SAR

Inhibition of PDE3. Among the pyridazinones with variations at the 2-, 4-, and 5-positions of the heterocyclic ring (Table 1), only 5-methylpyridazinone **3b** shows reasonable PDE3 inhibitory activity. Comparison of **3b** with **3a**,**d** and **3e** reveals that removal of the 5-methyl group or addition of a methyl substituent at the 4-position of the pyridazinone subunit leads to a substantial decrease in activity. Also, the introduction of a phenyl ring at the nitrogen of the pyridazinone moiety (compare **3b** with **4b**) diminishes the potency

dramatically. These results agree with findings of other research groups.[50,51] The phthalazinones (Table 2) show no substantial PDE3 inhibitory activity ($pIC_{50} < 5.4$); the activities are therefore not listed.

Inhibition of PDE4. In the pyridazinone series, a general trend was observed regarding inhibition of PDE4. An increase in the number of methyl substituents (**3a** vs **3b** vs **3d** and **4a** vs **4b**,**c** vs **4d**) leads to more potent analogues. This tendency is most obvious in the *N*-phenyl series **4**.

The diastereomers **3d** (*cis*) and **3e** (*trans*) possess the same lipophilic and electronic features; nevertheless, the *cis* isomer is more active than the *trans* analogue; therefore, steric interactions of the methyl groups with the binding site presumably play a more important role than lipophilicity.

The introduction of a phenyl group at the pyridazinone nitrogen leads to a 2−4-fold increase in PDE4 inhibitory activity (**3a** vs **4a**, **3b** vs **4b** and **3d** vs **4d**). Moreover, the *N*-benzyl-substituted analogue **5a** is even 14 times more potent than **3a**. Thus, lipophilic and aromatic moieties at the 2-position of the pyridazinone subunit enhance enzyme inhibition.

The PDE4 inhibitory activities of phthalazinones **9**−**11** with variations in ring X are shown in Table 2. Comparison of compounds **9**−**11** reveals that analogues in which ring X is an aromatic ring (**9a**, **10a**, and **11a**), a cyclohex-1-ene ring (**9b**, **10b**, and **11b**), a *trans*-cyclohexane ring (**9e** and **10e**), or a *trans*-cyclohex-3-ene ring (**10f**) are only weakly to moderately active regardless of the *N*-substituents. However, cyclohex(a)-ene derivatives **9c**,**d**, **10c**,**d**, and **11c**,**d**, having a *cis* configuration, exhibit high activities. In fact, analogues **10c** and **10d** are up to 350-fold more potent than the corresponding *trans* diastereomers **10f** and **10e**. This may be due to unfavorable steric interactions of the *trans* compounds with the binding site. The latter rationale probably also holds true for **9a**,**b**, **10a**,**b**, and **11a**,**b**. Finally, phthalazinones with a *cis*-cyclohex-3-ene ring are optimal for PDE4 inhibition (**9c**, **10c**, and **11c** vs **9d**, **10d**, and **11d**, respectively).

The activities of the *cis*-annealed phthalazinones generally parallel those of the pyridazinone series (Table 1) with respect to substitutions at the 2-position of the heterocycle. The *N*-phenyl-substituted compounds **10c** and **10d** exhibit activities up to an order of 16 greater than those of the nonsubstituted analogues **9c** and **9d**, respectively. Again, the introduction of a benzyl group at N2 increases potency even more (**11c** vs **9c** and **11d** vs **9d**), the best activity residing in the *N*-benzyl analogue **11c**.

Molecular Modeling

Molecular modeling studies were carried out especially to examine the marked difference in PDE4 inhibitory activity upon changes in the structure of the fused hydrocarbon ring of the phthalazinones under investigation (Table 2). The *N*-phenyl-substituted series (analogues **10a**−**f**) was used for this purpose. Both the *cis* and *trans* enantiomers of compounds **10c**−**f** were taken into account because only the racemates have been synthesized and tested.

Methods of Geometry Optimization of 3D Structures. All structures under study were built in SYBYL 6.3.2[52] on a Silicon Graphics Indigo2 (R10.000 under IRIX 6.2) workstation and after a preliminary minimization with the TRIPOS force field using MAXIMIN II submitted to full-energy minimization with MOPAC 6.0.[53] A systematic conformational search was performed on the rotable bonds using an increment of 10° or 15° followed by full-geometry optimization using MOPAC 6.0 to identify low-energy conformations.

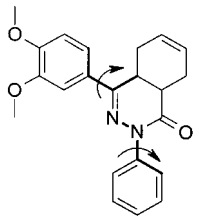


Figure 2. Phthalazinone inter-ring dihedral angles Φ (bold).

Conformational Aspects and Selection of Starting Geometries. The rotational barrier of the two phenyl-phthalazinone inter-ring bonds (Figure 2) is very low with respect to all molecules studied. Therefore, the origin of the difference in PDE4 inhibition of phthalazinones **10a**−**f** should lie in the phthalazinone part of the molecules. In the minimum-energy conformations, the cyclohex(a)ene rings adapt the chair conformation, in which the carbonyl groups are at the axial position as reported previously for analogous compounds.[54]

Analogue **10c** was chosen as the template because of its high affinity. The minimum-energy conformer having a catechol−heterocycle inter-ring dihedral angle of ∼15° (Figure 2) was selected as the template for the molecular overlay of derivatives **10a**,**b**,**d**−**f**. The molecules were aligned via root-mean-square (RMS) fit of (a) the catechol oxygen atoms, (b) the nitrogen atom in position 2, and (c) the two annealed carbon atoms. Low-energy conformers of the molecules were chosen for optimal overlap with one another, under the assumption that the catechol and pyridazinone rings always occupy the same cavity in the enzyme.

Results and Discussion

The final superposition of phthalazinones **10a**−**f** is displayed in Figure 3a,b. These pictures show that the annealed aromatic ring (**10a**), cyclohex-1-ene ring (**10b**), *trans*-cyclohex-3-ene ring (**10f**, both enantiomers), and *trans*-cyclohexane ring (**10e**, both enantiomers) occupy the same region in space; that is, the mean plane of ring X is nearly coplanar with the heterocyclic ring (Figure 3a). However, the *cis*-cyclohex(a)ene rings of analogues **10c** and **10d** are not coplanar with the pyridazinone ring; in fact, they fill a completely different area in space (Figure 3b). Furthermore, Figure 3b clearly shows that the A-rings of the (4a*S*,8a*R*)- and (4a*R*,8a*S*)-enantiomers of these structures point to opposite directions.

As the electronic features of the active *cis* and corresponding inactive *trans* analogues are most likely the same (**10c** vs **10f** and **10d** vs **10e**) and because no significant correlation was found between the PDE4 inhibitory activity and the lipophilicity of ring X, as mentioned earlier, variance in activity is mainly caused by steric interactions. With regard to compounds **10a**,**b**,**e** and **10f** this means a steric unfavorable interaction of ring X with the binding site, explaining the strong

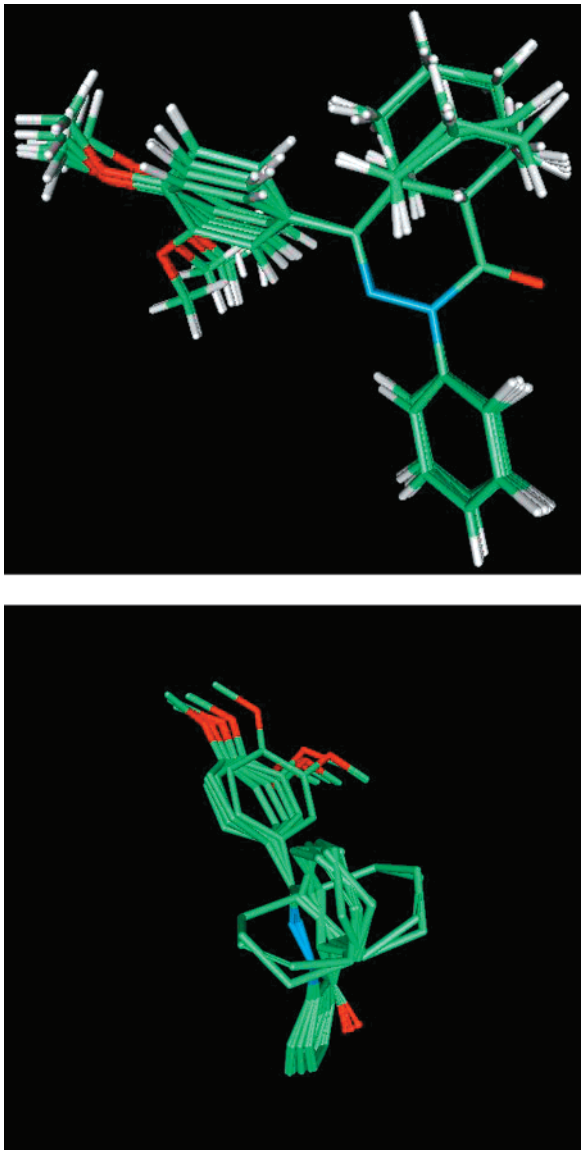


Figure 3. (a, top) Superimposition of phthalazinones **10a**−**f** (Table 2). The heterocycle in the center is more or less coplanar with ring X of compounds **10a**,**b**,**e**,**f**. (b, bottom) Superimposition of phthalazinones **10a**−**f** as shown in (a), however, displayed from a different angle. The cis-fused hydrocarbon rings of derivatives **10c** and **10d** are obviously not coplanar with the heterocycle, which is almost perpendicular to the plane of the paper. The fused hydrocarbon rings of the separate *cis*-enantiomers point to opposite directions. Hydrogen atoms have been omitted for clarity.

decrease of PDE inhibition. Further research will concentrate on the synthesis of both *cis*-enantiomers, which may lead to two new areas of space to explore.

Conclusion

We describe a number of pyridazinones and a novel series of phthalazinones with potent PDE4 inhibitory activities. All compounds prepared are selective PDE4 inhibitors except for 5-methylpyridazinone **3b**, which in addition shows PDE3 inhibitory activity as does zardaverine. SAR studies indicate the importance of the presence of a methyl group at the 5-position of the pyridazinone subunit and a nonsubstituted amide moiety (−NHCO−) for potent PDE3 inhibition, in accordance with literature examples.

In both the pyridazinone and phthlazinone series *N*-substitution is beneficial for PDE4 inhibition. This effect is in agreement with the SAR developed for well-known PDE4 inhibitors such as nitraquazone.[55,56] Particularly the *cis*-4a,5,6,7,8,8a-hexa- and *cis*-4a,5,8,8a-tetrahydrophthalazinones show high PDE4 inhibitory activities. Molecular modeling studies revealed that these *cis*-fused cyclohexa(e)ne rings occupy a region in space different from that occupied by the fused rings of the other phthalazinones studied. Thus, exciting new areas of space have been identified for further exploration in enantiomerically pure *cis*-fused series.

With **11c** and **11d** we have discovered new lead structures for the development of selective PDE4 inhibitors. The resolution of some *cis*-fused hexa- and tetrahydrophthalazinone racemates and optimization of the 4-aryl moiety and *N*-substituent will be the aim of further research.

Experimental Section

I. Chemistry. General Methods and Materials. THF was freshly distilled from $LiAlH_4$ before use. DMF was stored over 4 Å molecular sieves. All other solvents were used as received. Starting materials were commercially available. Reactions were performed under anhydrous conditions unless noted otherwise. Grignard reactions and Friedel−Crafts acylations were performed under an N_2 atmosphere. Reactions were followed by TLC analysis on Merck TLC aluminum sheets Silicagel 60 F254. Flash column chromatography was performed on silica gel, 30−60 μm (J. T. Baker). Melting points were measured on a Mettler FP-5 + FP-052 apparatus equipped with a microscope and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (^{1}H NMR, δ 200.1 MHz; ^{13}C NMR, δ 50.29 MHz), unless stated otherwise. ^{1}H NMR (400.1 MHz) and ^{13}C NMR (100.6 MHz) were recorded on a Bruker 400 MSL spectrometer. The ^{1}H NMR chemical shifts (δ) are expressed in parts per million values relative to $CDCl_3$ (δ = 7.26 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C NMR chemical shifts (δ) are reported in parts per million values relative to $CDCl_3$ (δ = 77.0 ppm). Abbreviations used in description of NMR spectra are as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, m = multiplet, and bs = broad singulet. 2D NMR (H−H and C−H) COSY techniques were frequently used to support interpretation of 1D spectra. All phthalazinones had an elemental analysis (C, H, and N) within ±0.4% of the theoretical value.

Method A. General Procedure for Friedel—Crafts Acylation of 1,2-Dimethoxybenzene. 1,2-Dimethoxybenzene (0.10−1.0 mol) was added slowly to an ice-cooled suspension of aluminum chloride (1 equiv) in CH_2Cl_2 (0.10−1.0 L). After complete addition, the desired cyclic anhydride (1 equiv) was added to the reaction mixture. The resulting solution was refluxed until TLC showed completion of the reaction (4−8 h). The mixture was poured into ice−water (0.10−1.0 L), the organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and filtered over silica gel to remove the dicarboxylic acid formed during workup. The product was crystallized from diethyl ether. Experimental data for the separate compounds are listed below.

4-(3,4-Dimethoxyphenyl)-4-oxobutyric acid[36,37] **(2a)** was prepared according to method A using succinic anhydride: yield 53%; mp 159−161 °C; ^{1}H NMR ($CDCl_3$) δ 2.81 (t, 2H, ^3J = 6.6 Hz, CH_2CO$_2$H), 3.29 (t, 2H, ^3J = 6.6 Hz, CH$_2$C(O)), 3.94 (s, 3H, OCH$_3$), 3.96 (s, 3H, OCH$_3$), 6.90 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.54 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.62 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom).

2-(3,4-Dimethoxybenzoyl)benzoic acid[46] **(8a)** was prepared according to method A using phthalic anhydride: yield

38%; mp 233−235 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 6H, OCH_3), 6.61 (d, 1H, ^3J = 8.4 Hz, H-arom), 6.90 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H-arom), 7.08−7.19 (dd, 1H H-arom), 7.28−7.50 (m, 3H, H-arom), 7.81−7.92 (dd, 1H, H-arom).

***trans*-2-(3,4-Dimethoxybenzoyl)cyclohexanecarboxylic acid (8e)** was prepared according to method A using *trans*-1,2-cyclohexanedicarboxylic anhydride: yield 40%; mp 202−205 °C; ^{1}H NMR (DMSO-d_6) δ 1.15−1.61 (m, 4H, H-cyclohexane), 1.70−2.30 (m, 4H, H-cyclohexane), 2.81−3.01 (m, 1H, H1), 3.40−3.60 (m, 1H, H2), 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.50 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.61 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom).

3,4-Dimethoxyphenylmagnesium Bromide (1, 0.29 M in THF). A solution of 1-bromo-3,4-dimethoxybenzene (8.5 mL, 59 mmol) in THF (50 mL) was added dropwise to a suspension of magnesium powder (1.43 g, 58.8 mmol) in THF (150 mL) at such a rate as to maintain a gentle reflux. After the addition was complete, the resulting red mixture was stirred for an additional 5 h at 60 °C.

Method B. General Procedure for Grignard Addition of 1 to Cyclic Anhydrides. A solution of 3,4-dimethoxyphenylmagnesium bromide (**1**) (20−100 mmol, 0.29 M) in THF was added dropwise to an ice-cooled solution of the desired cyclic anhydride (1 equiv) in THF (50−250 mL). After the addition was complete, the resulting mixture was stirred for another 30 min at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. Next, the reaction was quenched by the addition of a saturated NH_4Cl solution, and the product was extracted with diethyl ether. The organic layer was washed with water and subsequently extracted with 1 N NaOH. The combined aqueous extract was acidified with concentrated HCl and extracted with ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remainder was dissolved in CH_2Cl_2 and filtered over silica gel to remove the dicarboxylic acid formed during workup. The product was crystallized from diethyl ether.

4-(3,4-Dimethoxyphenyl)-2-methyl-4-oxobutyric Acid (Mixture of 2b and 2c). 2-Methylsuccinic anhydride (2.9 g, 25 mmol) was treated with Grignard reagent **1** (0.62 M, 25 mmol) as described above to give an inseparable mixture of the regioisomers **2b** and **2c** (ratio 4:6). The mixture was crystallized from ethyl acetate/petroleum ether (60−80): yield 1.9 g (31%); mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, ^3J = 7.2 Hz, CH_3-**2c**), 1.31 (d, 3H, ^3J = 6.9 Hz, CH_3-**2d**), 2.50 (dd, 1H, ^3J = 5.6 Hz, ^2J = 17.0 Hz, H2-**2c**), 2.92−3.26 (m, 3H, H2′-**2c**, H2-**2d**, H3-**2d**), 3.43 (dd, 1H, ^3J = 7.1 Hz, ^2J = 16.7 Hz, H3′-**2d**), 3.80−4.03 (m, 13H, H3-**2c**, OCH_3-**2c**, OCH_3-**2d**), 6.89 (d, 1H, ^3J = 8.4 Hz, H5-arom-**2d**), 6.91 (d, 1H, ^3J = 8.4 Hz, H5-arom-**2c**), 7.50−7.69 (m, 4H, H2-arom-**2c,d**, H6-arom-**2c,d**).

4-(3,4-Dimethoxyphenyl)-2,3-dimethyl-4-oxobutyric Acid (2d). A mixture of 2,3-dimethylsuccinic acid (D,L and meso, 5.0 g, 34 mmol) and acetic anhydride (6.4 mL, 68 mmol) was refluxed for 4 h. The reaction mixture was then concentrated in vacuo and coevaporated with toluene to give the crude product, which crystallized upon cooling to room temperature. The crystals were washed carefully with dry diethyl ether, filtered off, and dried in vacuo to yield 2.8 g (22 mmol) of the anhydride. The product thus obtained was used in a Grignard reaction with compound **1** (22 mmol), following the general procedure: yield 2.6 g (45%); mp 163−166 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (d, 3H, ^3J = 7.2 Hz, 3-CH_3), 1.26 (d, 3H, ^3J = 7.3 Hz, 2-CH_3), 2.99 (dq, 1H, ^3J = 7.3 Hz, H2), 3.72 (dq, 1H, ^3J = 7.3 Hz, H3), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.90 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.53 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.26 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom).

2-(3,4-Dimethoxybenzoyl)cyclohex-1-enecarboxylic acid (8b) was prepared according to method B using 3,4,5,6-tetrahydrophthalic anhydride: yield 56%; mp 180−181 °C; ^{1}H NMR ($CDCl_3$) δ 1.52−2.55 (m, 8H, CH_2), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.86 (d, 1H, ^3J = 8.5 Hz, H5-arom), 6.92−7.22 (m, 2H, H2-arom, H6-arom).

***cis*-6-(3,4-Dimethoxybenzoyl)cyclohex-3-enecarboxylic acid (8c)** was prepared according to method B using *cis*-1,2,3,6-tetrahydrophthalic anhydride: yield 39%; mp 110−112 °C; ^{1}H NMR ($CDCl_3$) δ 2.32−2.68 (m, 3H, CH_2, C*H*H′), 2.72−3.10 (m, 2H, CH*H*′, H1), 3.75−4.06 (m, 7H, OCH_3, H6), 5.52−5.85 (m, 2H, CH=CH), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.42−7.57 (m, 2H, H2-arom, H6-arom).

***cis*-2-(3,4-Dimethoxybenzoyl)cyclohexanecarboxylic acid (8d)** was prepared according to method B using *cis*-1,2-cyclohexanedicarboxylic anhydride: yield 38%; mp 171−175 °C; ^{1}H NMR ($CDCl_3$) δ 1.18−2.36 (m, 8H, CH_2), 2.68 (dt, 1H, ^3J = 4.5 Hz, H1), 3.81−4.06 (m, 7H, OCH_3, H2), 6.87 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.42−7.58 (m, 2H, H2-arom, H6-arom).

Method C. Preparation of 2b. 2-Chloro-1-(3,4-dimethoxyphenyl)propan-1-one (6). Aluminum chloride (31.0 g, 232 mmol) was added to a solution of 1,2-dimethoxybenzene (30.0 mL, 235 mmol) and 2-chloropropionyl chloride (23.0 mL, 237 mmol) in dichloroethane (250 mL). The resulting mixture was refluxed for 28 h. After cooling, the reaction mixture was poured into ice−water, and the product was extracted with CH_2Cl_2. The combined organic extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent in vacuo yielded the crude product, which was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80) 4:7 to obtain 32.9 g (61%) of **6** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.74 (d, 3H, ^3J = 6.7 Hz, CH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 5.25 (q, 1H, ^3J = 6.7 Hz, CHCl), 6.92 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.58 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.66 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom).

2-[2-(3,4-Dimethoxyphenyl)-1-methyl-2-oxoethyl]malonic Acid Di(*tert*-butyl) Ester (7). Malonic acid di(*tert*-butyl) ester (30.0 g, 139 mmol) was added dropwise to a suspension of sodium hydride (60% dispersion in oil, 5.60 g, 140 mmol) in DMF (300 mL), and the mixture was stirred at room temperature overnight. Under ice cooling, a solution of α-chloroketone **6** (32.9 g, 144 mmol) in DMF (100 mL) was added dropwise to the reaction mixture. The resulting mixture was stirred at room temperature for 1 h and then heated to 50 °C for 4 h. The reaction mixture was poured into ice−water and the product was extracted with CH_2Cl_2. After the combined organic extract was washed with water and dried over $MgSO_4$, the solvent was removed in vacuo to obtain the desired crude product as an oily material: yield 35.0 g (81%); ^{1}H NMR ($CDCl_3$) δ 1.18 (d, 3H, ^3J = 7.1 Hz, CH_3), 1.36 (s, 6H, CH_3-*tert*-butyl), 1.47 (s, 6H, CH_3-*tert*-butyl), 1.52 (s, 6H, CH_3-*tert*-butyl), 3.82 (d, 1H, ^3J = 10.9 Hz, C(O)CHC(O)), 3.88−4.10 (m, 1H, C*H*CH_3), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.92 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.55 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.70 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom).

4-(3,4-Dimethoxyphenyl)-3-methyl-4-oxobutyric Acid (2b). TFA (80 mL) was added to a solution of malonic acid di(*tert*-butyl) ester **7** (35.0 g, 112 mmol) in CH_2Cl_2 (500 mL). The reaction mixture was stirred at room temperature for 1.5 h and then refluxed for 3 h. After removal of the solvent in vacuo, acetic acid (400 mL) was added to the residue and the mixture was refluxed for 3 h. The acetic acid was removed under reduced pressure, and the product was obtained by crystallization from diethyl ether: yield 19.4 g (69%); mp 118−123 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, ^3J = 7.2 Hz, CH_3), 2.50 (dd, 1H, ^3J = 5.6 Hz, ^2J = 17.0 Hz, H2), 2.99 (dd, 1H, ^3J = 8.4 Hz, ^2J = 17.0 Hz, H2′), 3.79−4.02 (m, 7H, OCH_3, H3), 6.91 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.54 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.63 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom).

Method D. Epimerization of γ-Keto Acid 8c. *trans*-6-(3,4-Dimethoxybenzoyl)cyclohex-3-enecarboxylic Acid (8f). A solution of compound **8c** (10.0 g, 34.5 mmol) in 2 N KOH (200 mL) was stirred at room temperature for 3 days. The reaction mixture was acidified with concentrated HCl, and the precipitate was filtered off and washed carefully with water to give the pure *trans* isomer: yield 8.01 g (80%); mp 226−230 °C; ^{1}H NMR ($CDCl_3$) δ 1.96−2.72 (m, 4H, H2, H5), 3.10 (dt, 1H, ^3J = 5.6 Hz, ^3J = 11.1 Hz, H1), 3.81 (dt, 1H, ^3J = 5.3 Hz, ^3J = 11.1 Hz, H6), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.68−5.89 (m, 2H, H3, H4), 6.92 (d, 1H, ^3J = 8.4 Hz, H5-arom),

7.54 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.68 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom).

General Procedure for Condensation of γ-Keto Acids with Hydrazine. A mixture of the desired γ-keto acid (**2** or **8**, 10−100 mmol) and hydrazine monohydrate (2 equiv) in EtOH (50−500 mL) was refluxed for 4 h. If, upon cooling to room temperature, the product crystallized from the reaction mixture, the crude product was filtered off and washed with water and EtOH to yield the pure product. Otherwise, the bulk of EtOH was removed in vacuo and the remainder was dissolved in ethyl acetate. The solution was washed with water, dilute $NaHCO_3$, and 1 N HCl and dried over $MgSO_4$. Evaporation of the solvent yielded the crude product, which was purified by crystallization or flash column chromatography and subsequent crystallization. Experimental data for the separate compounds are listed below.

6-(3,4-Dimethoxyphenyl)-4,5-dihydro-2*H*-pyridazin-3-one (3a) was prepared from γ-keto acid **2a** according to the general procedure and crystallized from ethyl acetate: yield 63%; mp 164−167 °C (mp 168−170 °C[57]); ^{1}H NMR ($CDCl_3$) δ 2.53−2.68 (m, 2H, H4), 2.92−3.06 (m, 2H, H5), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.87 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.19 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.4 Hz, H6-arom), 7.42 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.77 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 22.19 (5-CH_2), 26.22 (4-CH_2), 55.74, 55.78 (OCH_3), 107.92 (C2-arom), 110.17 (C5-arom), 119.07 (C6-arom), 128.08 (C1-arom), 148.99, 150.15, 150.56 (C3-arom, C4-arom, C=N), 167.80 (C=O). Anal. Calcd ($C_{12}H_{14}N_2O_3$): C, H, N.

6-(3,4-Dimethoxyphenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (3b) was prepared from γ-keto acid **2b** according to the general procedure and crystallized from EtOH: yield 80%; mp 188−191 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3H, ^3J = 7.4 Hz, CH_3), 2.47 (dd, 1H, ^3J = 1.4 Hz, ^2J = 16.9 Hz, H4), 2.72 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, H4′), 3.36 (dq, 1H, ^3J = 7 Hz, H5), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.22 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.4 Hz, H6-arom), 7.46 (d, 1H, ^4J = 2.1 Hz, H2-arom), 8.78 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.25 (CH_3), 27.69 (C5), 33.70 (C4), 55.73, 55.77 (OCH_3), 108.11 (C2-arom), 110.20 (C5-arom), 118.91 (C6-arom), 127.06 (C1-arom), 149.11, 150.58 (C3-arom, C4-arom), 153.60 (C=N), 166.82 (C=O). Anal. Cacld ($C_{13}H_{16}N_2O_3$): C, H, N.

***cis*-6-(3,4-Dimethoxyphenyl)-4,5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (3d).** γ-Keto acid **2d** was treated with hydrazine monohydrate according to the general procedure to give two products (R_f 0.51 and 0.66) as indicated by TLC analysis (ethyl acetate). Upon concentration of the organic layer after workup, the two diastereomers crystallized. The white solids were filtered off and purified by flash column chromatography using ethyl acetate/petroleum ether (60−80) 6:4 to afford the minor compound **3d** (*cis*), which was crystallized from diethyl ether: yield 3%; mp 154−155 °C; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, 3H, ^3J = 7.3 Hz, 5-CH_3), 1.28 (d, 3H, ^3J = 7.1 Hz, 4-CH_3), 2.73 (dq, 1H, ^3J = 7 Hz, H4), 3.15 (dq, 1H, ^3J = 7 Hz, H5), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.85 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.18 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.42 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.47 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 9.41 (5-CH_3), 9.80 (4-CH_3), 32.73 (C5), 34.59 (C4), 55.47, 55.53 (OCH_3), 108.11 (C2-arom), 110.20 (C5-arom), 119.06 (C6-arom), 126.90 (C1-arom), 148.91, 150.41 (C3-arom, C4-arom), 155.66 (C=N), 170.83 (C=O). Anal. Calcd ($C_{14}H_{18}N_2O_3$): C, H, N.

***trans*-6-(3,4-Dimethoxyphenyl)-4,5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (3e).** Further elution of the column material (see **3d**) with ethyl acetate/petroleum ether (60−80) 6:4 gave the *trans* isomer **3e**. This compound was crystallized from diethyl ether: yield 25%; mp 178−180 °C; ^{1}H NMR ($CDCl_3$) δ 1.19[a], 1.23[b] (overlapping d, 3H each, ^3J = 7.6 Hz, [a]4-CH_3, [b]5-CH_3), 2.51 (q, 1H, ^3J = 7.5 Hz, H4), 3.06 (q, 1H, ^3J = 7.4 Hz, H5), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.21 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.47 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.64 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 16.34, 16.41 (CH_3), 35.40 (C5), 39.35 (C4), 55.85, 55.92 (OCH_3), 108.16 (C2-arom), 110.31 (C5-arom), 119.06 (C6-arom), 127.88 (C1-arom), 149.24, 150.75 (C3-arom, C4-arom), 152.91 (C=N), 170.34 (C=O). Anal. Calcd ($C_{14}H_{18}N_2O_3$): C, H, N.

4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-one (9a) was prepared from γ-keto acid **8a** according to the general procedure and crystallized from EtOH: yield 81%; mp 244−249 °C (mp 251−252 °C[58]); ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.02 (d, 1H, ^3J = 8.0 Hz, H5-arom), 7.08−7.22 (m, 2H, H2-arom, H6-arom), 7.71−7.87 (m, 3H, H5-phth, H6-phth, H7-phth), 8.48−8.60 (m, 1H, H8-phth), 10.54 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 55.89 (OCH_3), 110.79 (C5-arom), 112.19 (C2-arom), 122.01 (C6-arom), 126.79, 126.98 (CH-phth), 127.30, 128.21, 129.74 (C1-arom, C4a, C8a), 131.40, 133.28 (CH-phth), 147.93, 148.96, 149.74 (C3-arom, C4-arom, C=N), 159.96 (C=O). Anal. Calcd ($C_{16}H_{14}N_2O_3$): C, H, N.

4-(3,4-Dimethoxyphenyl)-5,6,7,8-tetrahydro-2*H*-phthalazin-1-one (9b) was prepared from γ-keto acid **8b** according to the general procedure and crystallized from MeOH: yield 82%; mp 214−215 °C; ^{1}H NMR ($CDCl_3$) δ 1.64−1.96 (m, 4H, H6, H7), 2.40−2.58 (m, 2H, H5), 2.62−2.70 (m, 2H, H8), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.86−7.03 (m, 3H, H-arom), 11.70 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 20.70 (C7), 21.34 (C6), 22.95 (C8), 27.64 (C5), 55.73 (OCH_3), 110.60 (C5-arom), 111.79 (C2-arom), 121.25 (C6-arom), 127.94 (C1-arom), 137.84, 140.76 (C4a, C8a), 148.51, 148.91, 149.23 (C3-arom, C4-arom, C=N), 161.67 (C=O). Anal. Calcd ($C_{16}H_{18}N_2O_3$): C, H, N.

***cis*-4-(3,4-Dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (9c)** was prepared from γ-keto acid **8c** according to the general procedure and crystallized from EtOH: yield 86%; mp 173−174 °C; ^{1}H NMR ($CDCl_3$) δ 2.08−2.37 (m, 3H, H5, H8), 2.85 (t, 1H, ^3J = 6.0 Hz, H8a), 2.91−3.11 (m, 1H, H8′), 3.42 (dt, 1H, ^3J = 8.7 Hz, ^3J = 5.5 Hz, H4a), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.63−5.88 (m, 2H, H6, H7), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.24 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.48 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.77 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.35 (C8), 23.05 (C5), 31.09 (C4a), 33.90 (C8a), 55.75, 55.77 (OCH_3), 107.85 (C2-arom), 110.18 (C5-arom), 119.01 (C6-arom), 124.06 (C6), 125.42 (C7), 127.23 (C1-arom), 149.13, 150.59 (C3-arom, C4-arom), 154.31 (C=N), 169.69 (C=O). Anal. Calcd ($C_{16}H_{18}N_2O_3$): C, H, N.

***cis*-4-(3,4-Dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (9d)** was prepared from γ-keto acid **8d** according to the general procedure and crystallized from EtOH: yield 75%; mp 170 °C; ^{1}H NMR ($CDCl_3$) δ 1.25−1.97 (m, 7H, H5, H6, H7, H8), 2.46−2.67 (m, 1H, H8′), 2.70−2.85 (m, 1H, H8a), 3.06−3.26 (m, 1H, H4a), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.87 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.20 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.45 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.60 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 21.87, 23.20, 24.37, 25.46 (C5, C6, C7, C8), 35.66 (C4a), 36.04 (C8a), 55.76 (OCH_3), 108.02 (C2-arom), 110.13 (C5-arom), 118.91 (C6-arom), 127.26 (C1-arom), 149.10, 150.48 (C3-arom, C4-arom), 153.55 (C=N), 169.72 (C=O). Anal. Calcd ($C_{16}H_{20}N_2O_3$): C, H, N.

***trans*-4-(3,4-Dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (9e)** was prepared from γ-keto acid **8e** according to the general procedure and crystallized from EtOH: yield 70%; mp 143−146 °C; ^{1}H NMR ($CDCl_3$) δ 0.97−1.48 (m, 4H, H-cyclohexane), 1.70−1.96 (m, 2H, H-cyclohexane), 2.03−2.22 (m, 2H, H-cyclohexane), 2.42−2.75 (m, 2H, H-cyclohexane), 3.92 (s, 6H, OCH_3), 6.88 (m, 3H, H2-arom, H5-arom, H6-arom), 8.72 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 24.90, 25.27 (C6, C7), 25.59 (C8), 29.89 (C5), 38.62 (C4a), 40.14 (C8a), 55.76, 55.80 (OCH_3), 110.33 (C5-arom), 110.75 (C2-arom), 120.29 (C6-arom), 128.48 (C1-arom), 148.50, 149.41 (C3-arom, C4-arom), 157.50 (C=N), 169.70 (C=O). Anal. Calcd ($C_{16}H_{20}N_2O_3$): C, H, N.

General Procedure for Condensation of γ-Keto Acids with Phenylhydrazine. A mixture of γ-keto acid **2** or **8** (5.0 mmol) and phenylhydrazine (2 equiv) in toluene (50 mL) was refluxed until TLC showed completion of the reaction (8−16 h). After the mixture had cooled to room temperature, the bulk of toluene was removed in vacuo and the residue was dissolved

in ethyl acetate. The solution was washed with water, aqueous HCl (1 N), and dilute $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent yielded the crude product, which was purified by crystallization or flash column chromatography and subsequent crystallization. The experimental data for the respective compounds are listed below.

6-(3,4-Dimethoxyphenyl)-2-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (4a) was prepared from γ-keto acid **2a** according to the general procedure and crystallized from MeOH: yield 56%; mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 2.71−2.85 (m, 2H, H4), 3.02−3.17 (m, 2H, H5), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.89 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.22−7.36 (m, 2H, H6-arom, H−Ph), 7.38−7.50 (m, 3H, H2-arom, H−Ph), 7.55−7.68 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 22.61 (C5), 27.95 (C4), 55.82 (OCH_3), 108.34 (C2-arom), 110.27 (C5-arom), 119.39 (C6-arom), 124.80 (CH−Ph), 126.37 (CH−Ph), 128.07 (C1-arom), 128.36 (CH−Ph), 141.15 (C1−Ph), 148.96, 150.72, 151.22 (C3-arom, C4-arom, C=N), 165.23 (C=O). Anal. Calcd ($C_{18}H_{18}N_2O_3$): C, H, N.

6-(3,4-Dimethoxyphenyl)-5-methyl-2-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (4b) was prepared from γ-keto acid **2b** according to the general procedure, purified by flash column chromatography using ethyl acetate/petroleum ether (60−80) 6:4, and crystallized from ethyl acetate/petroleum ether: yield 57%; mp 71−72 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (d, 3H, ^3J = 7.3 Hz, CH_3), 2.65 (dd, 1H, ^3J = 1.3 Hz, ^2J = 16.9 Hz, H4), 2.90 (dd, 1H, ^3J = 6.4 Hz, ^2J = 16.9 Hz, H4′), 3.45 (dq, 1H, H5), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.89 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.23−7.38 (m, 2H, H6-arom, H−Ph), 7.40−7.50 (m, 2H, H−Ph), 7.51 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.58−7.68 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 16.34 (CH_3), 28.07 (C5), 35.31 (C4), 55.80 (OCH_3), 108.49 (C2-arom), 110.35 (C5-arom), 119.33 (C6-arom), 124.67 (CH−Ph), 126.34 (CH−Ph), 126.99 (C1-arom), 128.37 (CH−Ph), 141.04 (C1−Ph), 149.08, 150.77 (C3-arom, C4-arom), 154.82 (C=N), 164.57 (C=O). Anal. Calcd ($C_{19}H_{20}N_2O_3$·0.4H_2O): C, H, N.

6-(3,4-Dimethoxyphenyl)-4-methyl-2-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (4c). The mixture of **2b** and **2c** (0.74 g, 2.9 mmol) was treated with phenylhydrazine as described above, resulting in two products (R_f 0.33 and 0.49) as indicated by TLC analysis [ethyl acetate/petroleum ether (60−80) 1:1]. The remaining oil after workup was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80) 6:4 to give the major compound **4c**, which was crystallized from MeOH: yield 0.44 g (46%); mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 1.38 (d, 3H, ^3J = 6.4 Hz, CH_3), 2.69−2.91 (m, 2H, H4, H5), 3.06−3.30 (m, 1H, H5′), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.22−7.33 (m, 2H, H6-arom, H−Ph), 7.38−7.50 (m, 3H, H2-arom, H−Ph), 7.55−7.65 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 15.32 (CH_3), 30.21 (C5), 32.18 (C4), 55.82 (OCH_3), 108.28 (C2-arom), 110.28 (C5-arom), 119.38 (C6-arom), 124.81 (CH−Ph), 126.26 (CH−Ph), 128.30 (CH−Ph), 128.39 (C1-arom), 141.37 (C1−Ph), 148.96, 150.67, 150.93 (C3-arom, C4-arom, C=N), 168.67 (C=O). Anal. Calcd ($C_{19}H_{20}N_2O_3$): C, H, N.

Further elution with ethyl acetate/petroleum ether (60−80) 6:4 gave **4b**. This compound was crystallized from ethyl acetate/petroleum ether: yield 70 mg (7%).

***cis*-6-(3,4-Dimethoxyphenyl)-4,5-dimethyl-2-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (4d).** The γ-keto acid **2d** (0.80 g, 3.0 mmol) was treated with phenylhydrazine according to the general procedure to give two products (R_f 0.49 and 0.66) as indicated by TLC analysis [ethyl acetate/petroleum ether (60−80) 1:1]. The oil obtained after workup was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80) 6:4 to afford the minor compound **4d** (*cis*), which crystallized after concentration of the elute. The white solid was recrystallized from diethyl ether and dried in vacuo: yield 60 mg (6%); mp 144−145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.18 (d, 3H, ^3J = 7.3 Hz, 5-CH_3), 1.35 (d, 3H, ^3J = 7.0 Hz, 4-CH_3), 2.92 (dq, 1H, ^3J = 7.0 Hz, ^3J = 5.5 Hz, H4), 3.22 (dq, 1H, ^3J = 7.3 Hz, ^3J = 5.6 Hz, H5), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.22−7.33 (m, 2H, H6-arom, H−Ph), 7.37−7.45 (m, 2H, H−Ph), 7.50 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.55−7.61 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.25 (5-CH_3), 11.01 (4-CH_3), 33.34 (C5), 36.16 (C4), 55.80 (OCH_3), 108.42 (C2-arom), 110.33 (C5), 119.30 (C6), 124.51 (CH−Ph), 126.08 (CH−Ph), 127.06 (C1-arom), 128.26 (CH−Ph), 141.22 (C1−Ph), 149.09, 150.73 (C3-arom, C4-arom), 156.09 (C=N), 168.27 (C=O). Anal. Calcd ($C_{20}H_{22}N_2O_3$·0.5H_2O): C, H, N.

***trans*-6-(3,4-Dimethoxyphenyl)-4,5-dimethyl-2-phenyl-4,5-dihydro-2*H*-pyridazin-3-one (4e).** Further elution of the column material (see **4d**) with ethyl acetate/petroleum ether (60−80) 6:4 yielded *trans* isomer **4e**. The pure compound was obtained as an oil and could not be crystallized: yield 40%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, ^3J = 7.4 Hz, 4-CH_3), 1.30 (d, 3H, ^3J = 7.4 Hz, 5-CH_3), 2.68 (dq, 1H, ^3J = 7.4 Hz, ^3J = 1.4 Hz, H4), 3.11 (dq, 1H, ^3J = 7.4 Hz, ^3J = 1.4 Hz, H5), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.89 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.25−7.31 (m, 2H, H6-arom, H−Ph), 7.38−7.46 (m, 2H, H−Ph), 7.51 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.56−7.60 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.07, 16.54 (CH_3), 35.44 (C5), 40.55 (C4), 55.77 (OCH_3), 108.47 (C2-arom), 110.39 (C5), 119.36 (C6), 124.71 (CH−Ph), 126.32 (CH−Ph), 127.74 (C1-arom), 128.34 (CH−Ph), 141.20 (C1−Ph), 149.06, 150.79 (C3-arom, C4-arom), 153.65 (C=N), 168.18 (C=O).

4-(3,4-Dimethoxyphenyl)-2-phenyl-2*H*-phthalazin-1-one (10a) was prepared from γ-keto acid **8a** according to the general procedure and crystallized from MeOH: yield 60%; mp 220−221 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 7.01 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.16 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.21 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.2 Hz, H6-arom), 7.31−7.58 (m, 3H, H−Ph), 7.67−7.78 (m, 2H, H−Ph), 7.79−7.93 (m, 3H, H5-phth, H6-phth, H7-phth), 8.55−8.68 (m, 1H, H8-phth); ^{13}C NMR ($CDCl_3$) δ 55.89, 55.93 (OCH_3), 110.88 (C5-arom), 112.45 (C2-arom), 122.20 (C6-arom), 125.70 (CH−Ph), 126.77 (CH-phth), 127.42 (Cq), 127.47 (CH−Ph), 127.51 (C8-phth), 128.55 (CH−Ph), 128.73 (Cq), 129.10 (Cq), 131.46, 133.00 (CH-phth), 141.84 (C1−Ph), 147.26, 148.89, 149.76 (C3-arom, C4-arom, C=N), 158.71 (C=O). Anal. Calcd ($C_{22}H_{18}N_2O_3$): C, H, N.

4-(3,4-Dimethoxyphenyl)-2-phenyl-5,6,7,8-tetrahydro-2*H*-phthalazin-1-one (10b) was prepared from γ-keto acid **8b** according to the general procedure, subjected to flash column chromatography using ethyl acetate/petroleum ether (60−80) 1:5 > ethyl acetate, and crystallized from diethyl ether: yield 18%; mp 155−156 °C; ^{1}H NMR ($CDCl_3$) δ 1.67−1.94 (m, 4H, H6, H7), 2.41−2.56 (m, 2H, H5), 2.66−2.80 (m, 2H, H8), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.92 (d, 1H, ^3J = 8.2 Hz, H5-arom), 6.95 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.01 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.2 Hz, H6-arom), 7.30−7.53 (m, 3H, H−Ph), 7.61−7.72 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 21.06 (C7), 21.48 (C6), 23.81 (C8), 27.64 (C5), 55.82, 55.85 (OCH_3), 110.68 (C5-arom), 111.93 (C2-arom), 121.40 (C6-arom), 125.49 (CH−Ph), 127.62 (CH−Ph), 128.23 (C1-arom), 128.46 (CH−Ph), 138.64, 139.03 (C4a, C8a), 141.72 (C1−Ph), 147.94, 148.60, 149.33 (C3-arom, C4-arom, C=N), 159.74 (C=O). Anal. Calcd ($C_{22}H_{22}N_2O_3$): C, H, N.

***cis*-4-(3,4-Dimethoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (10c)** was prepared from γ-keto acid **8c** according to the general procedure and crystallized from diethyl ether: yield 50%; mp 134−135 °C; ^{1}H NMR ($CDCl_3$) δ 2.18−2.40 (m, 3H, H5, H8), 2.93−3.17 (m, 2H, H8′, H8a), 3.33−3.55 (m, 1H, H4a), 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.52−5.88 (m, 2H, H6, H7), 6.89 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.18−7.50 (m, 4H, H6-arom, H−Ph), 7.52 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.57−7.65 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 22.27 (C8), 23.61 (C5), 31.55 (C4a), 35.18 (C8a), 55.84 (OCH_3), 108.22 (C2-arom), 110.31 (C5-arom), 119.36 (C6-arom), 123.61 (C6), 124.63 (CH−Ph), 125.80 (C7), 126.16 (CH−Ph), 127.22 (C1-arom), 128.26 (CH−Ph), 141.34 (C1−Ph), 149.14, 150.82 (C3-arom, C4-arom), 155.22 (C=N), 167.06 (C=O). Anal. Calcd ($C_{22}H_{22}N_2O_3$): C, H, N.

***trans*-4-(3,4-Dimethoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (10f)** was prepared from γ-keto acid **8f** according to the general procedure and subjected to flash column chromatography using ethyl acetate/petroleum

ether (60−80) 1:5 > 2:3 > 1:1 to give the product as a colorless oil, which was crystallized from diethyl ether: yield 34%; mp 170−171 °C; ^{1}H NMR ($CDCl_3$) δ 1.85−2.10 (m, 1H, H5), 2.23−2.91 (m, 4H, H5′, H8, H8a), 3.04−3.28 (m, 1H, H4a), 3.91 (s, 6H, OCH_3), 5.61−5.92 (m, 2H, H6, H7), 5.61−5.75 (m, 1H, H7), 5.77−5.92 (m, 1H, H6), 6.89 (d, 1H, ^3J = 8.9 Hz, H5-arom), 6.95−7.07 (m, 2H, H2-arom, H6-arom), 7.20−7.31 (m, 1H, H−Ph), 7.32−7.45 (m, 2H, H−Ph), 7.50−7.62 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 26.32 (C8), 30.55 (C5), 34.89 (C4a), 37.77 (C8a), 55.82, 55.87 (OCH_3), 110.43 (C5), 110.64 (C2), 120.19 (C6), 124.68 (CH−Ph), 124.82 (C7), 125.77 (C6), 126.31 (CH−Ph), 128.32 (CH−Ph), 128.75 (C1-arom), 140.97 (C1−Ph), 148.57, 149.64 (C3-arom, C4-arom), 156.44 (C═N), 166.87 (C═O). Anal. Calcd ($C_{22}H_{22}N_2O_3$) C, H, N.

***cis*-4-(3,4-Dimethoxyphenyl)-2-phenyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (10d)** was prepared from γ-keto acid **8d** according to the general procedure and crystallized from ethyl acetate/petroleum ether (60−80): yield 47%; mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 1.33−1.98 (m, 7H, H5, H6, H7, H8), 2.53−2.69 (m, 1H, H8′), 2.85−3.00 (m, 1H, H8a), 3.11−3.28 (m, 1H, H4a), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.19−7.33 (m, 2H, H6-arom, H−Ph), 7.37−7.49 (m, 2H, H−Ph), 7.51 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.55−7.68 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 21.73, 23.91[a], 24.98, 25.61 (C5, C6, C7, [a]C8), 36.11 (C4a), 37.12 (C8a), 55.82 (OCH_3), 108.41 (C2-arom), 110.25 (C5-arom), 119.25 (C6-arom), 124.76 (CH−Ph), 126.14 (CH−Ph), 127.27 (C1-arom), 128.26 (CH−Ph), 141.42 (C1−Ph), 149.08, 150.67 (C3-arom, C4-arom), 154.14 (C═N), 167.25 (C═O). Anal. Calcd ($C_{22}H_{24}N_2O_3$): C, H, N.

***trans*-4-(3,4-Dimethoxyphenyl)-2-phenyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (10e)** was prepared from γ-keto acid **8e** according to the general procedure and crystallized from diethyl ether: yield 41%; mp 139−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.03−1.52 (m, 4H, H5, H6, H7, H8), 1.73−2.01 (m, 2H, H6′, H7′), 2.11−2.40 (m, 2H, H5′, H8a), 2.43−2.61 (m, 1H, H8′), 2.65−2.86 (m, 1H, H4a), 3.90 (m, 3H, OCH_3), 3.91 (m, 3H, OCH_3), 6.82−6.99 (m, 3H, H2-arom, H5-arom, H6-arom), 7.16−7.29 (m, 1H, H−Ph), 7.30−7.43 (m, 2H, H−Ph), 7.50−7.61 (m, 2H, H−Ph); ^{13}C NMR ($CDCl_3$) δ 24.84, 25.13 (C6, C7), 26.13 (C8), 30.08 (C5), 38.50 (C4a), 41.13 (C8a), 55.80, 55.88 (OCH_3), 110.40 (C5-arom), 111.00 (C2-arom), 120.52 (C6-arom), 124.67 (CH−Ph), 126.20 (CH−Ph), 128.30 (CH−Ph), 128.57 (C1-arom), 140.99 (C1−Ph), 148.45, 149.48 (C3-arom, C4-arom), 158.31 (C═N), 167.70 (C═O). Anal. Calcd ($C_{22}H_{24}N_2O_3$): C, H, N.

General Procedure for Benzylation of Pyridazinones and Phthalazinones. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv) was added to a suspension of the desired pyridazinone **3** or phthalazinone **9** (3.0−5.0 mmol) in DMF (30−50 mL). After the reaction mixture had been stirrred for 3 h, benzyl chloride (1.1 equiv) was added and the mixture was stirred for another 4 h. The reaction mixture was poured into water, and the product was extracted with ethyl acetate. The combined organic extract was washed with water and brine and dried over $MgSO_4$. After removal of the solvent, crystallization or flash column chromatography followed by crystallization yielded the pure products. The experimental data for the separate compounds are listed below.

2-Benzyl-6-(3,4-dimethoxyphenyl)-4,5-dihydro-2*H*-pyridazin-3-one (5a) was prepared from pyridazinone **3a** according to the general procedure, subjected to flash column chromatography using ethyl acetate/petroleum ether (60−80) 1:1, and crystallized from diethyl ether: yield 49%; mp 128−130 °C; ^{1}H NMR ($CDCl_3$) δ 2.55−2.69 (m, 2H, H4), 2.88−3.00 (m, 2H, H5), 3.91 (s, 6H, OCH_3), 5.03 (s, 2H, CH_2−Bn), 6.85 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.19 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.4 Hz, H6-arom), 7.24−7.48 (m, 6H, H2-arom, H−Bn); ^{13}C NMR ($CDCl_3$) δ 22.58 (C5), 27.03 (C4), 52.04 (CH_2−Bn), 55.69, 55.79 (OCH_3), 108.20 (C2-arom), 110.20 (C5-arom), 119.08 (C6-arom), 127.17 (CH−Bn), 127.87 (C1-arom), 128.21, 128.29 (CH−Bn), 137.53 (C1−Bn), 148.87, 150.05, 150.51 (C3-arom, C4-arom, C═N), 165.09 (C═O). Anal. Calcd ($C_{19}H_{20}N_2O_3$): C, H, N.

2-Benzyl-4-(3,4-dimethoxyphenyl)-2*H*-phthalazin-1-one (11a) was prepared from phthalazinone **9a** according to the general procedure and crystallized from ethyl acetate at 0 °C: yield 61%; mp 151−154 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.45 (s, 2H, CH_2−Bn), 6.98 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.07 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.13 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.2 Hz, H6-arom), 7.20−7.37 (m, 3H, CH−Bn), 7.42−7.57 (m, 2H, CH−Bn), 7.64−7.83 (m, 3H, H5-phth, H6-phth, H7-phth), 8.45−8.54 (m, 1H, H8-phth); ^{13}C NMR ($CDCl_3$) δ 54.77 (CH_2−Bn), 55.88 (OCH_3), 110.85 (C5-arom), 112.47 (C2-arom), 122.10 (C6-arom), 126.55 (CH-phth), 127.14 (C8-phth), 127.50 (CH−Bn), 127.61, 128.23 (Cq-phth, Cq-phth/C1-arom), 128.31 (CH−Bn), 128.62 (CH−Bn), 129.19 (Cq-phth/C1-arom), 131.16, 132.63 (CH-phth), 136.85 (C1−Bn), 146.71, 148.84, 149.69 (C3-arom, C4-arom, C═N), 158.82 (C═O). Anal. Calcd ($C_{23}H_{20}N_2O_3$): C, H, N.

2-Benzyl-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydro-2*H*-phthalazin-1-one (11b) was prepared from phthalazinone **9b** according to the general procedure, subjected to flash column chromatography using ethyl acetate/petroleum ether (60−80) 1:3, and crystallized from diethyl ether: yield 57%; mp 137−139 °C; ^{1}H NMR ($CDCl_3$) δ 1.53−1.87 (m, 4H, H6, H7), 2.35−2.50 (m, 2H, H5), 2.57−2.73 (m, 2H, H8), 3.90 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.36 (s, 2H, CH_2−Bn), 6.85−7.01 (m, 3H, H2-arom, H5-arom, H6-arom), 7.21−7.40 (m, 3H, CH−Bn), 7.43−7.58 (m, 2H, CH−Bn); ^{13}C NMR ($CDCl_3$) δ 21.01 (C7), 21.44 (C6), 23.70 (C8), 27.51 (C5), 55.12 (CH_2−Bn), 55.79 (OCH_3), 110.66 (C5-arom), 111.99 (C2-arom), 121.35 (C6-arom), 127.52 (CH−Bn), 128.26 (CH−Bn), 128.40 (C1-arom), 125.73 (CH−Bn), 136.52, 137.71, 138.83 (C4a, C8a, C1−Bn), 147.33, 148.54, 149.26 (C3-arom, C4-arom, C═N), 159.83 (C═O). Anal. Calcd ($C_{23}H_{24}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-(3,4-dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (11c)** was prepared from phthalazinone **9c** according to the general procedure, subjected to flash column chromatography using ethyl acetate/petroleum ether (60−80) 1:3, and crystallized from diethyl ether: yield 61%; mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.81−2.35 (m, 3H, H5, H8), 2.82 (t, 1H, ^3J = 5.8 Hz, H8a), 2.93−3.11 (m, 1H, H8′), 3.34 (dt, 1H, ^3J = 11.5 Hz, ^3J = 5.9 Hz, H4a), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.04 (AB, 2H, CH_2−Bn), 5.55−5.87 (m, 2H, H6, H7), 6.85 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.14−7.48 (m, 7H, H2-arom, H6-arom, H−Bn); ^{13}C NMR ($CDCl_3$) δ 22.08 (C8), 23.20 (C5), 31.37 (C4a), 34.34 (C8a), 52.41 (CH_2−Bn), 55.70, 55.78 (OCH_3), 108.10 (C2-arom), 110.29 (C5-arom), 119.06 (C6-arom), 123.81 (C6), 125.68 (C7), 127.13 (CH−Bn), 127.33 (C1-arom), 128.20, 128.30 (CH−Bn), 137.72 (C1−Bn), 149.05, 150.59 (C3-arom, C4-arom), 153.90 (C═N), 167.13 (C═O). Anal. Calcd ($C_{23}H_{24}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-(3,4-dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (11d)** was prepared from phthalazinone **9d** according to the general procedure, subjected to flash column chromatography using ethyl acetate/petroleum ether (60−80) 2:3, and crystallized from diethyl ether/petroleum ether (60−80): yield 53%; mp 117−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.19−1.93 (m, 7H, H5, H6, H7, H8), 2.50−2.68 (m, 1H, H8′), 2.69−2.79 (m, 1H, H8a), 3.00−3.18 (m, 1H, H4a), 3.91 (s, 6H, OCH_3), 5.05 (AB, 2H, CH_2−Bn), 6.84 (d, 1H, ^3J = 8.3 Hz, H5-arom), 7.13−7.48 (m, 7H, H2-arom, H6-arom, H−Bn); ^{13}C NMR ($CDCl_3$) δ 21.89, 23.77[a], 24.58, 25.55 (C5, C6, C7, [a]C8), 35.91 (C4a), 36.37 (C8a), 52.23 (CH_2−Bn), 55.67, 55.75 (OCH_3), 108.26 (C2-arom), 110.21 (C5-arom), 118.92 (C6-arom), 127.05 (CH−Bn), 127.39 (C1-arom), 128.17, 128.24 (CH−Bn), 137.88 (C1−Bn), 148.99, 150.44 (C3-arom, C4-arom), 152.83 (C═N), 169.72 (C═O). Anal. Calcd ($C_{23}H_{26}N_2O_3$): C, H, N.

II. Pharmacology. Methods. In Vitro Assay of PDE Inhibition. The PDE activity was determined according to the method of Thompson et al.,[59] with some modifications.[49] The assay mixture contained 50 mM Tris-HCl (pH 7.4), 5 mM $MgCl_2$, 0.5 μM cAMP, [^{3}H]cAMP (∼30000 cpm/assay), the indicated concentration of the inhibitor, and an aliquot of the enzyme solution (see further) at a final assay volume of 200 μL.

Stock solutions of 2 mM were prepared in DMSO and diluted 1:100 (v/v) in the Tris-HCl buffer mentioned above; appropriate dilutions were prepared in 1% (v/v) DMSO/Tris-HCl, which were diluted 1:2 (v/v) in the assays to obtain the desired final concentrations of the inhibitors at a DMSO concentration of 0.5% (v/v). None of the PDE activities were affected by DMSO itself.

After preincubation for 5 min at 37 °C, the reaction was started by the addition of substrate (cAMP), and the assays were incubated for a further 15 min at 37 °C. The reaction was terminated by the addition of 50 μL of 0.2 N HCl, and the assays were left on ice for ~10 min. Following incubation with 25 μg of 5′-nucleotidase (snake venom from *Crotalus atrox*) for 10 min at 37 °C, the assays were loaded on QAE Sephadex A-25 columns (Econo Columns, Bio-Rad, 1 mL bed volume). The columns were eluted with 2 mL of 30 mM ammonium formiate (pH 6.0). The radioactivity of the elute was measured and corrected for the corresponding blank values (measured in the presence of denatured protein), which were below 5% of total radioactivity. The amount of cAMP hydrolyzed did not exceed 30% of the original substrate concentration.

PDE3 was investigated in homogenates from human blood platelets as described by Schudt et al.[31]

PDE4 was investigated in the cytosol of human polymorphonuclear leukocytes (PMNL) (isolated from leukocyte concentrates);[48] the PDE3-specific inhibitor motapizone (1 μM) was included to suppress PDE3 activity originating from contaminating platelets.

Statistics. The IC_{50} values were calculated from the concentration−inhibition curves by nonlinear regression analysis using the GraphPad Prism program (version 2.00, 1995). The data are means of two independent determinations in triplicate: the variance is <0.3 log unit.

References

(1) Barnes, P. J. New aspects of asthma. *J. Intern. Med.* **1992**, *231*, 453−461.
(2) Barnes, P. J. Asthma: what is there left to find out? *Br. Med. J.* **1993**, *307*, 814−815.
(3) Adelroth, E.; Rosenhall, L.; Johansson, S. A.; Linden, M.; Venge, P. Inflammatory cells and eosinophilic activity in asthmatics investigated by the bronchoalveolar lavage. *Am. Rev. Respir. Dis.* **1990**, *142*, 91−99.
(4) Holgate, S. T. Inflammatory cells and their mediators in the pathogenesis of asthma. *Postgrad. Med. J.* **1988**, *64*, S82−S95.
(5) Reed, C. E. Basic mechanisms of asthma: role of inflammation. *Chest* **1988**, *94*, 175−177.
(6) Djukanovic, R.; Roche, W. R.; Wilson, J. W.; Beasley, C. R. W.; Twentyman, O. P.; Howarth, P. H.; Holgate, S. T. Mucosal inflammation in asthma. *Am. Rev. Respir. Dis.* **1990**, *142*, 434−457.
(7) Vassallo, R.; Lipsky, J. J. Theophylline: recent advances in the understanding of its mode of action and uses in clinical practice. *Mayo Clin. Proc.* **1998**, *73*, 346−354.
(8) Reques, F. G.; Rodriguez, J. L. E. Tolerability of leukotriene modifiers in asthma−A review of clinical experience. *Biodrugs* **1999**, *11*, 385−394.
(9) Butcher, R. W.; Sutherland, E. W. Adenosine 3′,5′-phosphate in biological materials. I. Purification and properties of cyclic 3′,5′-nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3′,5-phosphate in human urine. *J. Biol. Chem.* **1962**, *237*, 1244−1250.
(10) Beavo, J. A. Cyclic nucleotide phosphodiesterases: functional implications of multiple isoforms. *Physiol. Rev.* **1995**, *75*, 725−748.
(11) Beavo, J. A. Isolation and characterization of a dual-substrate phosphodiesterase gene family: PDE10A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 7071−7076.
(12) Fisher, D. A.; Smith, J. F.; Pillar, J. S.; St. Denis, S. H.; Cheng, J. B. Isolation and characterization of PDE9A, a novel human cGMP-specific phosphodiesterase. *J. Biol. Chem.* **1998**, *273*, 15559−15564.
(13) Fisher, D. A.; Smith, J. F.; Pillar, J. S.; St. Denis, S. H.; Cheng, J. B. Isolation and characterization of PDE8A, a novel human cAMP-specific phosphodiesterase. *Biochem. Biophys. Res. Commun.* **1998**, *246*, 570−577.
(14) Soderling, S. H.; Bayuga, S. J.; Beavo, J. A. Identification and characterization of a novel family of cyclic nucleotide phosphodiesterases. *J. Biol. Chem.* **1998**, *273*, 15553−15558.
(15) Soderling, S. H.; Bayuga, S. J.; Beavo, J. A. Cloning and characterization of a cAMP-specific cyclic nucleotide phosphodiesterase. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8991−8996.
(16) Beavo, J. A.; Conti, M.; Heaslip, R. J. Multiple cyclic nucleotide phosphodiesterases. *Mol. Pharmacol.* **1994**, *46*, 399−405.
(17) Loughney, K.; Ferguson, K. Identification and quantification of PDE isoenzymes and subtypes by molecular biological methods. In *Phosphodiesterase Inhibitors*; Schudt, C., Dent, G., Rabe, K. F., Eds.; Academic Press: San Diego, CA, 1997; pp 1−19.
(18) Norman, P. PDE4 inhibitors 1998. *Exp. Opin. Ther. Patents* **1998**, *8*, 771−784.
(19) Shire, M. G.; Muller, G. W. *Exp. Opin. Ther. Patents* **1998**, *8*, 531−544.
(20) Dyke, H. J.; Montana, J. G. *Exp. Opin. Invest. Drugs* **1999**, *8*, 1301.
(21) Giembycz, M. A.; Dent, G. Prospects for selective cyclic nucleotide phosphodiesterase inhibitors in the treatment of bronchial asthma. *Clin. Exp. Allergy* **1992**, *22*, 337−344.
(22) Torphy, T. J. Phosphodiesterase isozymes. Molecular targets for novel antiasthma agents. *Am. J. Respir. Crit. Care Med.* **1998**, *157*, 351−370.
(23) Torphy, T. J.; Undem, B. J. Phosphodiesterase inhibitors: new opportunities for treatment of asthma. *Thorax* **1991**, *46*, 512−523.
(24) Dent, G.; Giembycz, M. A. Interaction of PDE4 inhibitors with enzymes and cell functions. In *Phosphodiesterase Inhibitors*; Schudt, C., Dent, G., Rabe, K. F., Eds.; Academic Press: San Diego, CA, 1997.
(25) Schmidt, D.; Dent, G.; Rabe, K. F. Selective phosphodiesterase inhibitors for the treatment of bronchial asthma and chronic obstructive pulmonary disease. *Clin. Exp. Allergy* **1999**, *29*, 99−109.
(26) Teixeira, M. M.; Gristwood, R. W.; Cooper, N.; Hellewell, P. G. Phosphodiesterase (PDE)4 inhibitors: anti-inflammatory drugs of the future? *Trends Pharmacol. Sci.* **1997**, *18*, 164−171.
(27) Cortijo, J.; Bou, J.; Beleta, J.; Cardelus, I.; Llenas, J.; Morcillo, E.; Gristwood, R. W. Investigation into the role of phosphodiesterase IV in bronchorelaxation, including studies with human bronchus. *Br. J. Pharmacol.* **1993**, *108*, 562−568.
(28) Rabe, K. F.; Tenor, H.; Dent, G.; Schudt, C.; Liebig, S.; Magnussen, H. Phosphodiesterase isozymes modulating inherent tone in human airways: identification and characterization. *Am. J. Physiol.* **1993**, *264*, L458−L464.
(29) De Boer, J.; Philpott, A. J.; Van Amsterdam, R. G.; Shahid, M.; Zaagsma, J.; Nicholson, C. D. Human bronchial cyclic nucleotide phosphodiesterase isoenzymes: biochemical and pharmacological analysis using selective inhibitors. *Br. J. Pharmacol.* **1992**, *106*, 1028−1034.
(30) Torphy, T. J.; Undem, B. J.; Cieslinski, L. B.; Luttmann, M. A.; Reeves, M. L.; Hay, D. W. P. Identification, characterization and functional role of phosphodiesterase isozymes in human airway smooth muscle. *J. Pharmacol. Exp. Ther.* **1993**, *265*, 1213−1223.
(31) Schudt, C.; Winder, S.; Muller, B.; Ukena, D. Zardaverine as a selective inhibitor of phosphodiesterase isoenzymes. *Biochem. Pharmacol.* **1991**, *42*, 153−162.
(32) Wilhelm, R. S.; Loe, B. E.; Devens, B. H.; Alverez, R.; Martin, M. G. New benzo and pyrido pyridazinones and pyridazinethiones inhibit PDE IV activity for treating inflammatory, asthmatic, allograft rejection graft-versus-host or autoimmune diseases and pain. PCT Int. Appl. WO 9307146, 1993.
(33) Palfreyman, M. N.; Souness, J. E. 1. Phosphodiesterase type IV inhibitors. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: Amsterdam, The Netherlands, 1996; Vol. 33, pp 1−52.
(34) Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Van der Mey, M.; Van der Laan, I. J.; Timmerman, H.; Sterk, G. J. Preparation of phthalazinones as phosphodiesterase IV inhibitors. PCT Int. Appl. WO 9931071, 1999.
(35) Van der Mey, M.; Van der Laan, I. J.; Timmerman, H.; Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Sterk, G. J. Preparation of arylphthalazinones as inhibitors of cyclic nucleotide phosphodiesterase. PCT Int. Appl. WO 9831674, 1998.
(36) Fetter, J.; Lempert, K.; Moller, J.; Nyitrai, J.; Zauer, K. Electron deficient heteroaromatic ammonioamidates. XXIII. Heteroaromatic ammonioamidates with bridge-head ammonium nitrogen. *Acta Chim. Hung.* **1983**, *112*, 43−57.
(37) Fieser, L. F.; Hershberg, E. B. The synthesis of phenanthrene and hydrophenanthrene detivatives. IV. Hydroxylated compounds. *J. Am. Chem. Soc.* **1936**, *58*, 2314−2318.
(38) Robertson, A.; Waters, R. B. Podophyllotoxin. *J. Chem. Soc.* **1933**, 83−86.
(39) Haworth, R. D.; Woodcock, D. The constituents of natural phenolic resins. Part XI. Synthesis of 2- and 3-methyl-6:7-dimethoxy-1-veratrylnaphthalenes. *J. Chem. Soc.* **1938**, 809−813.
(40) Burpitt, B. E.; Crawford, L. P.; Davies, B. J.; Mistry, J.; Mitchell, M. B.; Pancholi, K. D.; Coates, W. J. 6-(Substituted phenyl)-5-methyl-4,5-dihydro-pyridazin-3(2*H*)-ones of medicinal interest. The synthesis of SK&F 94836 and SK&F 95654. *J. Heterocycl. Chem.* **1988**, *25*, 1689−1695.

(41) Fichter, Fr.; Herbrand, A. Ueber eine neue darstellungsweise einiger lactone der fettreihe. *Ber.* **1896**, *29*, 1192−1195.
(42) Curran, W. V.; Ross, A. 6-Phenyl-4,5-dihydro-3(2*H*)-pyridazinones. A series of hypotensive agents. *J. Med. Chem.* **1974**, *17*, 273−281.
(43) Bone; Perkin. The symmetrical dimethylsuccinic acids. B. Behaviour of the dimethylsuccinic acids on distillation at the ordinary atmospheric pressure. *J. Chem. Soc.* **1896**, *69*, 265−267.
(44) Haworth, R. D.; Mavin, C. R. The constituents of guaiacum resin. Part I. Synthesis of pyroguaiacin methyl ether. *J. Chem. Soc.* **1932**, 1485−1488.
(45) Linstead, R. P.; Whalley, M. 1:2-Dicarboxylic acids. Part II. The diastereoisomeric αα′-dimethyl-succinic acids and their derivatives. Effect of conformation on stability. *J. Chem. Soc.* **1954**, 3722−3730.
(46) Lagodzinski, K. Ueber 2,3-dioxyanthracen. *Justus Liebigs Ann. Chem.* **1905**, *342*, 96−98.
(47) Jucker, E.; Suess, R. Darstellung basisch substituierter pyridaz-6-one. *Helv. Chim. Acta* **1952**, *42*, 2506−2514.
(48) Schudt, C.; Winder, S.; Forderkunz, S.; Hatzelmann, A.; Ullrich, V. Influence of selective phosphodiesterase inhibitors on human neutrophil functions and levels of cAMP and Ca. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1991**, *344*, 682−690.
(49) Bauer, A. C.; Schwabe, U. An improved assay of cyclic 3′,5′-nucleotide phosphodiesterase with QAE Sephadex A-25. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *311*, 193−198.
(50) Bristol, J. A.; Sircar, I.; Moos, W. H.; Evans, D. B.; Weishaar, R. E. Cardiotonic agents. 1. 4,5-Dihydro-6-[4-(1*H*-imidazol-1-yl)-phenyl]-3-(2*H*)-pyridazinones: novel positive inotropic agents for the treatment of congestive heart failure. *J. Med. Chem.* **1984**, *27*, 1099−1101.
(51) Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhail, A. T. Cardiotonic agents. 8. Selective inhibitors of adenosine 3′,5′-cyclic phosphate phosphodiesterase. Elaboration of a five-point model for positive inotropic activity. *J. Med. Chem.* **1987**, *30*, 1963−1972.
(52) *SYBYL Molecular Modelling Package*, 6.3.2 ed.; Tripos Associates: St. Louis, MO, 1997.
(53) MOPAC 6.0, QCPE 455.
(54) Sohar, P.; Bernath, G. Stereochemical studies−XIV: cyclic amino alcohols and related compounds−VII. *Org. Magn. Reson.* **1973**, *5*, 159−160.
(55) Glaser, T.; Traber, J. TVX 2706−A new phosphodiesterase inhibitor with antiinflammatory action. Biochemical characterization. *Agents Actions* **1984**, *15*, 341−348.
(56) Lowe, J. A. I.; Archer, R. L.; Chapin, D. S.; Cheng, J. B.; Helwig, D.; Johnson, J. L.; Koe, B. K.; Lebel, L. A.; Moore, P. F.; Nielsen, J. A.; Russo, L. L.; Shirley, J. T. Structure−activity relationships of quinazolinedione inhibitors of calcium-independent phosphodiesterase. *J. Med. Chem.* **1991**, *34*, 624−628.
(57) Hashem, M. M.; Berlin, K. D.; Chesnut, R. W.; Durham, N. N. Novel pyrazolo, isoxazolo, and thiazolo steroidal systems and model analogs containing dimethoxyaryl (or dihydroxylaryl) groups and derivatives. Synthesis, spectral properties, and biological activity. *J. Med. Chem.* **1976**, *19*, 229−239.
(58) Yamaguchi, M.; Kamei, K.; Koga, T.; Akima, M.; Kuroki, T.; Ohi, N. Novel antiasthmatic agents with dual activities of thromboxane A2 synthetase inhibition and bronchodilation. 1. 2-[2-(1-Imidazolyl)alkyl]-1(2*H*)-phthalazinones. *J. Med. Chem.* **1993**, *36*, 4052−4060.
(59) Thompson, W. J.; Terasaki, W. L.; Epstein, P. M.; Strada, S. J. Assay of cyclic nucleotide phosphodiesterase and resolution of multiple molecular forms of the enzyme. *Adv. Cyclic Nucleotide Res.* **1979**, *10*, 69−92.

JM010837K