Synthesis and Structure−Activity Relationships of *cis*-Tetrahydrophthalazinone/Pyridazinone Hybrids: A Novel Series of Potent Dual PDE3/PDE4 Inhibitory Agents

Margaretha Van der Mey,*,†,§ Kirsten M. Bommelé,§ Hildegard Boss,‡ Armin Hatzelmann,‡ Mike Van Slingerland,§ Geert J. Sterk,§ 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 January 13, 2003

In this study, the synthesis and in vitro and in vivo pharmacological investigations of a new series of phthalazinone/pyridazinone hybrids with both PDE3 and PDE4 inhibitory activities are described. These compounds combine the pharmacophores of recently discovered 4a,5,8,-8a-tetrahydro-2*H*-phthalazin-1-one-type inhibitors of PDE4 and the well-known 2*H*-pyridazin-3-one-type PDE3 inhibitors such as the tetrahydrobenzimidazoles. Most of the synthesized compounds are pharmacologically spoken PDE3/PDE4 hybrids. All hybrids show potent PDE4 inhibitory activity ($pIC_{50} = 7.0-8.7$), whereas the pIC_{50} values for inhibition of PDE3 vary from 5.4 to 7.5. In general, analogues with a 5-methyl-4,5-dihydropyridazinone moiety exhibit the highest PDE3 inhibitory activities. The highest in vivo antiinflammatory activity is displayed by phthalazinones **43** and **44** showing, at a dose of 30 μmol/kg po, 46% inhibition of arachidonic acid (AA) induced mouse ear edema. No correlation was found between the in vitro PDE3 and/or PDE4 inhibitory activity and the in vivo antiinflammatory capacity after oral dosing.

Introduction

Dual cGMP-inhibited phosphodiesterase (PDE3) and cAMP-specific phosphodiesterase (PDE4) inhibitors are being pursued as drug therapy for bronchial asthma. Interest in these compounds stems from the potential of elevating cAMP levels in the airway smooth muscle and inflammatory cells involved in asthmatic response, thereby achieving both relaxation and antiinflammatory activity.

PDE3 and PDE4 are involved in the regulation of airway smooth muscle tone. 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.[1,2] PDE3 inhibitors are somewhat more potent.[2] Interestingly, either a combination of PDE3 and PDE4 inhibitors or dual PDE3/PDE4 inhibitors produce a much larger bronchorelaxant effect than individual isoenzyme-selective agents alone.[3,4] The PDE3 and PDE4 isoenzymes apparently act in a synergistic manner in human airway smooth muscle. In addition, PDE4 is the prominent isoenzyme present in the inflammatory cells, thought to be important in asthma.[5,6] Inhibitors of PDE4 are effective in attenuating inflammatory activity.[7,8]

Since no selective clinical agent significantly produces both PDE3/PDE4 pharmacological effects, combining the bronchodilatory and antiinflammatory activities in a dual PDE3/PDE4 inhibitor has the potential to provide a drug that is markedly more effective in the treatment of bronchial asthma.

By far the most thoroughly studied group of PDE3 inhibitors is the 2*H*-pyridazin-3-ones. These agents are especially used for the treatment of congestive heart failure.[9−13] The structures of three of these selective PDE3 inhibitors LY264233,[14] LY197055,[14] and tetrahydrobenzimidazole **II**[15] are shown in Figure 1. There are only two common features of the PDE3 inhibitors synthesized thus far: an amide (−NHCO−) functionality and a near-planar topography of the molecule.[9,16−19] In addition, the introduction of a small lipophilic moiety (the size of a methyl group) at the 5-position of the pyridazinone ring as in LY197055 has been shown to significantly increase the PDE3 inhibitory potency in some compounds.[17]

Recently we reported the synthesis and structure−activity relationships for a novel series of hexa- and 4a,5,8,8a-tetrahydrophthalazinones as PDE4 inhibitors (e.g., phthalazinone **I**, Figure 1).[20−26] Numerous *cis*-4-arylphthalazinones with a large variation in substituents at N2 were found to exhibit high PDE4 inhibitory activity.[25,26] Moreover, the unsaturated fused hydrocarbon ring of the 4a,5,8,8a-tetrahydrophthalazinones was shown to be essential for potent in vivo antiinflammatory activities in a mouse ear edema assay.[24]

To develop mixed PDE3/PDE4 inhibitors, we combined structural features of the well-known pyridazinone-type selective PDE3 inhibitors such as LY264233,[14] LY197055,[14] and tetrahydrobenzimidazole **II**[15] with those of tetrahydrophthalazinone **I**,[26] a potent PDE4

* To whom correspondence should be addressed. Phone: +31 20 4449720. Fax: +31 20 4449121. E-mail: mmeij@rnc.vu.nl. Current address: Vrije Universiteit, Radionuclidencentrum, De Boelelaan 1085c, 1081 HV Amsterdam, The Netherlands.
† Vrije Universiteit.
§ Byk Nederland.
‡ Byk Gulden.

10.1021/jm030776l CCC: $25.00
Published on Web 04/12/2003

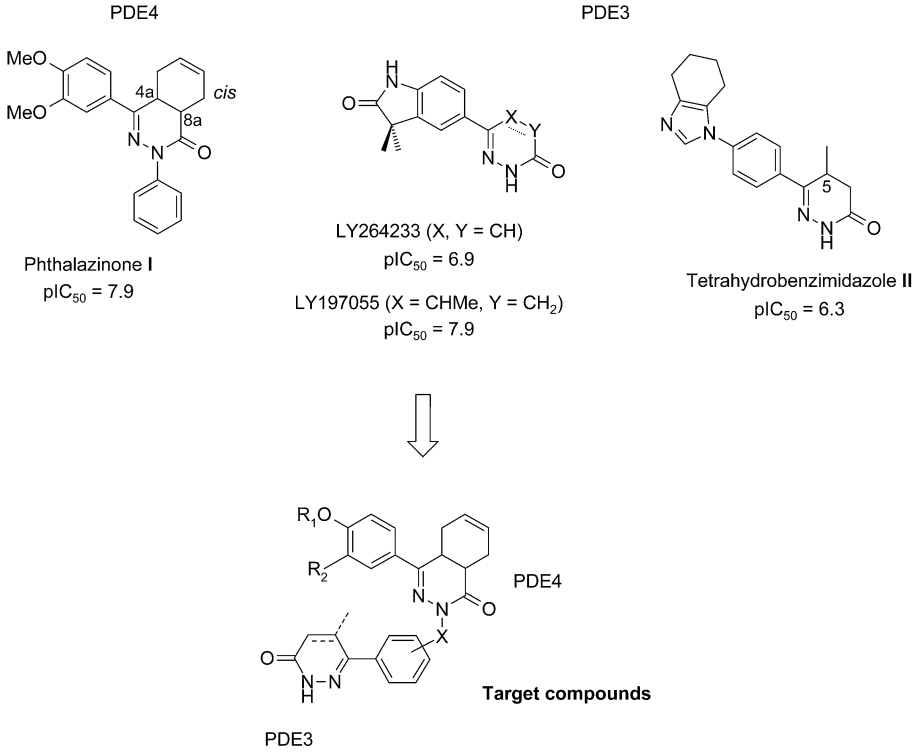


Figure 1. Development of target compounds by combination of structural elements of PDE4 inhibitor phthalazinone **I**[26] with PDE3 blockers LY264233,[14] LY197055,[14] and tetrahydrobenzimidazole **II**.[15]

inhibitor, leading to target compounds with a general structure as shown in Figure 1.[27,28] In agreement with the SAR for both the pyridazinones and phthalazinones, the aromatic ring of the phenylpyridazinone subunit was coupled to N2. Each of these phthalazinone/pyridazinone hybrids possesses an overall flat topography and an amide (−NHCO−) functionality required for potent PDE3 inhibition[9,16−19] as well as a catechol ether moiety common to many PDE4 inhibitors.[29] The present paper describes the synthesis and in vitro and in vivo pharmacological evaluation of these new compounds.

Chemistry

Optimization of the target compounds (Figure 1) involves variation of the 4-aryl substituent of the phthalazinone subunit, modification of the molecular nature and position of linker X, and changes in the pyridazinone subunit. The structures of the target compounds are listed in Table 1. The *N*-phenyl-substituted phthalazinones **28**,[26] **31**, **33**, and **35** were used for pharmacological comparison.

Hybrids **29**, **30**, **32**, **34**, and **36** were synthesized as depicted in Scheme 1. In this approach, 6-(4-aminophenyl)-2*H*-pyridazin-3-one (**1**, R_3 = A) and 6-(4-aminophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone[30] (**2**, R_3 = B) were converted into the corresponding arylhydrazines **3** and **4** by treatment with nitrous acid, which was generated in situ from sodium nitrite, and by subsequent reduction of the resulting aryldiazonium ions with tin(II) chloride according to literature procedures.[31] Condensation of arylhydrazine **3** with 6-(3,4-dimethoxybenzoyl)cyclohex-3-enecarboxylic acid (**5**) in pyridine at reflux temperature provided hybrid **29** in good yield. Analogously, compounds **30**, **32**, **34**, and **36** were prepared from arylhydrazine **4** and the corresponding γ-keto acids (**5**−**8**).

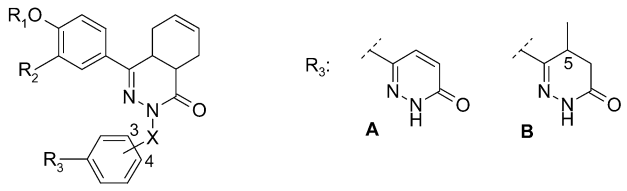
The synthesis of γ-keto acids **5**−**8** has already been described in previous articles.[20,25,26] Aniline **1** was prepared from 6-(4-nitrophenyl)-2*H*-pyridazin-3-one,[32] which was obtained according to literature procedures by reduction of the nitro group with Fe in a mixture of butanol, water, and HCl. The synthesis of aniline **2** has also been described in the literature.[30]

Scheme 2 shows the general synthetic procedure for analogues **37**−**41** containing an amide linker. Phthalazinone **9**[26] was treated with sodium hydride and ethyl bromoacetate to afford ester **10**, which was hydrolyzed without further purification in a mixture of 2 N KOH, THF, and MeOH, yielding the acetic acid derivative **11**. The pentanoic acid **12** was prepared from phthalazinone **9** by alkylation with 5-bromovaleric acid using 2 equiv of sodium hydride. Carboxylic acids **11** and **12** were converted into the corresponding acid chlorides with phosphorus pentachloride and subsequently coupled with selected aniline **1**, **2**, or **20** (**20** is only coupled with **11**) to give hybrids **37**−**41**.

The synthesis of aniline **20** is illustrated in Scheme 3. Bromination of 1-(3-nitrophenyl)propan-1-one[33] in acetic acid using bromine yielded α-bromopropan-1-one **13**. This bromide was reacted with diethyl sodiomalonate to afford ethyl ester **15**, which was hydrolyzed and decarboxylated by treatment with 6 N HCl under reflux. Condensation of γ-keto acid **17** with hydrazine in ethanol gave 4-(3-nitrophenyl)pyridazinone **19**. Reduction of the nitro group of compound **19** with Fe in a mixture of ethanol, water, and HCl provided pyridazinone **20**.

The 4-(4-methoxyphenyl)pyridazinone **21** (Scheme 3) was obtained in good yield following the same route as described above for the preparation of pyridazinone **20**. Pyridazinone **21** was converted into phenol **22** by treatment with aluminum chloride in dichloromethane.

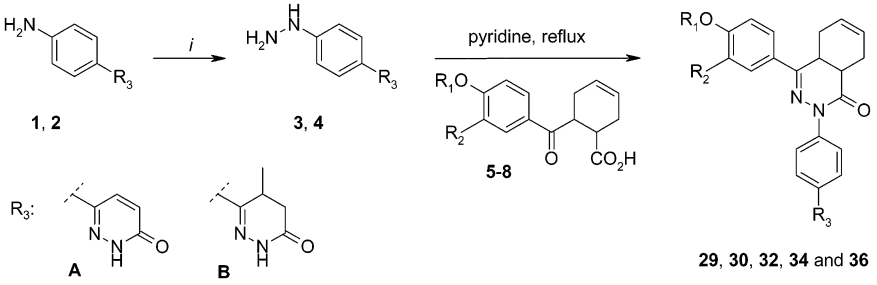
Table 1. Pyridazinones and Their in Vitro PDE3/PDE4 Inhibitory and in Vivo Antiinflammatory Activities



compd	R_1	R_2	X	position	R_3	PDE3 pIC_{50} [a]	PDE4 pIC_{50} [a]	% inhibition of AA-induced mouse ear edema (n)[b]
28	Me	OMe			H	<5.0	7.9	13 (1)
29	Me	OMe		4	A	5.4	8.1	8 (1)
30	Me	OMe		4	B	6.7	8.4	34 (2)
31	Me	OcC_5H_9			H	<5.0	7.8	ND[c]
32	Me	OcC_5H_9		4	B	6.3	7.8	18 (1)
33	Et	OEt			H	<5.0	7.7	ND[c]
34	Et	OEt		4	B	6.6	8.1	42 (2)
35	Me	Cl			H	<5.0	7.1	ND[c]
36	Me	Cl		4	B	7.1	7.0	35 (2)
37	Me	OMe	CH_2CONH	4	A	5.9	8.1	31 (1)
38	Me	OMe	CH_2CONH	4	B	6.7	8.4	13 (2)
39	Me	OMe	CH_2CONH	3	B	5.8	8.4	ND[c]
40	Me	OMe	$(CH_2)_4CONH$	4	A	6.1	8.2	27 (1)
41	Me	OMe	$(CH_2)_4CONH$	4	B	7.0	8.2	26 (3)
42	Me	OMe	$(CH_2)_4O$	4	B	7.1	8.7	32 (1)
43	Et	OEt	$(CH_2)_4O$	4	B	6.7	8.6	46 (2)
44	Me	Cl	$(CH_2)_4O$	4	B	7.5	7.8	47 (2)
zardaverine						6.2	6.8	22
ariflo						<5.0	7.0	33

[a] $pIC_{50} = -\log IC_{50}$. Inhibition of PDE3 was investigated in homogenates from human platelets, and the activity against PDE4 was determined in the cytosol of human neutrophils. The data are the mean of two independent determinations in triplicate. [b] Percent inhibition of the formation of AA-induced mouse ear edema after pretreatment with the target compound (1 h before AA) at a drug concentration of 30 μmol/kg po. [c] ND: not determined.

Scheme 1[a]

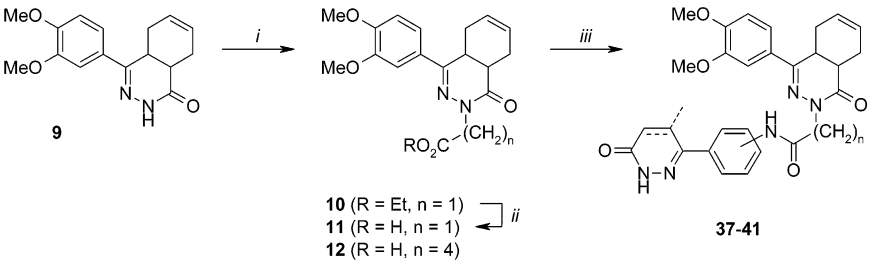


1, **3** (R_3 = A); **2**, **4** (R_3 = B)

5, **6**, **8** (R_1 = Me); **7** (R_1 = Et); **5** (R_2 = OMe), **6** (R_2 = OcC_5H_9), **7** (R_2 = OEt), **8** (R_2 = Cl)

[a] Reagents: (i) (1) $NaNO_2$, 2 N HCl, −2 to 0 °C, 30 min; (2) $SnCl_2$, concentrated HCl, −2 to 0 °C, 1 h.

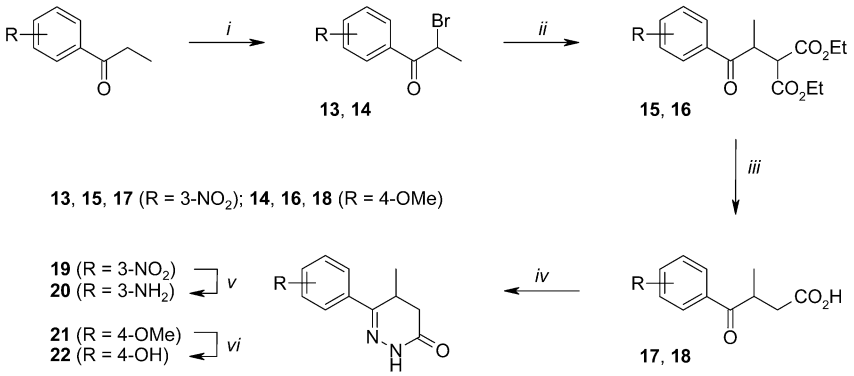
Scheme 2[a]



[a] Reagents: (i) (1) NaH, DMF, (2) $Br(CH_2)_nCO_2R$; (ii) 2 N KOH, THF, MeOH; (iii) (1) PCl_5, CH_2Cl_2, (2) aniline **1**, **2**, or **20**, DMAP, pyridine.

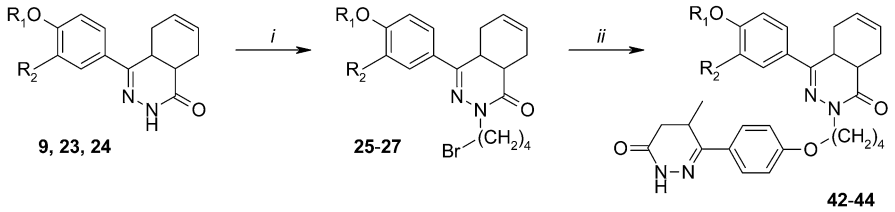
The synthesis of the hybrids containing an alkoxy linker is shown in Scheme 4. Phthalazinones **25**, **26**, and **27** were prepared starting from phthalazinones **9**, **23**, and **24**,[25] respectively, by successive treatment with sodium hydride and the corresponding α,ω-dibromoalkane. Subsequently, alkylbromides **25**−**27** were used

Scheme 3[a]



[a] Reagents: (i) Br_2, AcOH; (ii) $NaHC(CO_2Et)_2$, DMF; (iii) 6 N HCl; (iv) H_2NNH_2, H_2O/EtOH, reflux; (v) Fe, HCl, EtOH, H_2O, reflux; (vi) $AlCl_3$, CH_2Cl_2.

Scheme 4[a]



9, **25**, **42** (R_1 = Me, R_2 = OMe); **23**, **26**, **43** (R_1 = Et, R_2 = OEt); **24**, **27**, **44** (R_1 = Me, R_2 = Cl)

[a] Reagents: (i) (1) NaH, DMF, (2) $Br(CH_2)_nBr$; (ii) phenol **22**, K_2CO_3, KI, DMF, 60 °C.

to alkylate phenol **22** in the presence of base and a catalytic amount of potassium iodide, yielding compounds **42**−**44**, respectively.

Pharmacology

Table 1 summarizes the results of the pharmacological screening of compounds **28**−**44**. The in vitro PDE3 and PDE4 inhibitory activities and in vivo antiinflammatory properties using a mouse ear edema assay have been determined as specified earlier.[24,26] The dual inhibitor zardaverine[34] was tested for pharmacological comparison.

Structure−Activity Relationships for in Vitro Enzyme Inhibition. Modification of the phenyl substituent for a phenylpyridazinone subunit (**A** or **B**, Table 1) connected via different linkers to N2 of the target phthalazinones does not affect the PDE4 inhibitory activity significantly, whereas PDE3 inhibition is strongly influenced (compare **28** with **29** and **30**, **31** with **32**, **33** with **34**, etc.). Inhibition of PDE3 is only observed for compounds that contain a 5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (**B**) or 2*H*-pyridazin-3-one (**A**) moiety. Replacement of the pyridazinone **A** subunit by **B** yields a 6- to 20-fold increase in potency with respect to inhibition of the PDE3 isoenzyme (**37** vs **38**; **29** vs **30**). This enhancement in activity is in agreement with the known SAR of other pyridazinone-type PDE3 inhibitors.[9,17,18] The 5-methyl group is believed to fit into a small lipophilic pocket located in the active site of the PDE3 enzyme. Another explanation may be that a better interaction of the aromatic ring with the active site is achieved, since the methyl group disrupts the coplanar arrangement of the aromatic and pyridazinone rings.[18,19]

The effect of the linker (X) connecting the phthalazinone and phenylpyridazinone subunits on PDE inhibition was also examined. Comparison of the individual 3,4-dimethoxyphenyl analogues **30**, **38**, **41**, and **42**, the 3,4-diethoxyphenyl derivatives **34** and **43**, and the 3-chloro-4-mehoxyphenyl analogues **36** and **44** reveals that the linker has no significant impact on PDE3 and PDE4 inhibition.

Attachment of an acetamide linker to the meta position instead of the para position of the pyridazinonephenyl moiety results in a 10-fold reduction of PDE3 inhibitory activity, while the ability to inhibit of PDE4 remains unchanged (**38** vs **39**). Usually, the pyridazinone-type PDE3 inhibitors contain an electron-rich partial structure in the para position of the phenyl ring.

Subsequently, the role of the catechol moiety was investigated. In general, 3-chloro-4-methoxyphenyl-substituted derivatives are more potent PDE3 inhibitors than the corresponding 3,4-dialkoxyphenyl analogues (compare **36** with **30**, **32**, **34** and compare **44** with **42**, **43**). However, phthalazinones **36** and **44** are the least potent PDE4 inhibitors of the present series. As was discussed in a previous paper,[25] the optimum structures for inhibition of PDE4 contain a 3,4-dialkoxyphenyl moiety.

In the present series, all compounds with a 5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (**B**) part at the para position of the pyridazinonephenyl moiety are more potent PDE3 and PDE4 inhibitors than zardaverine, with pIC_{50} values of 6.3−7.5 and 7.0−8.7, respectively.

In Vivo Antiinflammatory Activity after Oral Administration. Direct evidence for the potential antiinflammatory activity of PDE4 inhibitors by inhibition of mediator release is derived from animal studies. A much used model is the formation of arachidonic acid (AA) induced ear edema in mice.[24] In this in vivo assay,

the suppression of the formation of arachidonic acid (AA) induced mouse ear edema was measured after oral administration of the drug. Two hours after oral administration of the target compound and 1 h after provocation and application of a solution of AA to the mouse ear, the percentage of inhibition of edema formation was determined with respect to the provoked nontreated control animals. The maximal possible inhibition of edema in this model is 80%.

Many of the final compounds prepared were tested in this assay (Table 1). The 4-(3,4-diethoxyphenyl)-phthalazinones **34** and **43** and 4-(3-chloro-4-methoxyphenyl) derivative **44** exhibit the most effective inhibitory activity in vivo with 42−47% inhibition of mouse ear edema formation at a concentration of 30 μmol/kg po. Under the same conditions, the reference compounds zardaverine and ariflo were less potent (22% and 33% inhibition, respectively).

Single and multiple regression analyses were performed to correlate the PDE3 and/or PDE4 inhibitory activity with in vivo antiinflammatory activity; however, no statistically significant correlations were found.

Conclusion

Most of the investigated compounds show moderate to high PDE3 inhibitory activity and are potent inhibitors of PDE4 as well. The SAR determined for our compounds regarding PDE inhibition is widely consistent with that already observed for analogous pyridazinones and phthalazinones. The in vivo data suggest that several of these compounds are potent antiinflammatory drugs (**34**, **43**, and **44**). No correlation was found between the antiinflammatory activity after oral administration and the PDE3 and/or PDE4 inhibitory activity. Whether the combination of both PDE3 and PDE4 inhibitory activity in one drug offers advantages with respect to dosage, route of administration, and pharmacokinetics over the single or combined application of both PDE3 and PDE4 inhibitors remains to be investigated.

Experimental Section

DMF and pyridine were stored over 4 Å molecular sieves. All the other solvents were used as received. Starting materials were commercially available. Reactions were performed under anhydrous conditions unless noted otherwise. Reactions were followed by TLC analysis on Merck TLC aluminum sheets with silica gel 60 F254. Flash column chromatography was performed on silica gel, 30−60 μm (J. T. Baker). Melting points were measured on an Electrothermal IA9200 and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (^{1}H NMR, 200.1 MHz) spectrometer. The ^{1}H NMR chemical shifts (δ) are expressed in ppm values relative to $CDCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm). Abbreviations used in description of NMR spectra are the following: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, m = multiplet, and bs = broad singulet. All phthalazinones had an elemental analysis (C, H and N) results within ±0.4% of the theoretical value.

6-(4-Aminophenyl)-2*H*-pyridazin-3-one Hydrochloride (1). 6-(4-Nitrophenyl)-2*H*-pyridazin-3-one[32] (23.0 g, 106 mmol) was dissolved in a mixture of butanol (1000 mL) and water (250 mL) and heated to reflux temperature. Fe (80.0 g, 1.43 mol) and 2 N HCl (15 mL) were added sequentially, and the reaction mixture was refluxed for 5 h. After the suspension was cooled to room temperature, the solids were filtered off and washed with hot ethanol. Upon concentration of the filtrate in vacuo, the title compound precipitated. The yellow solids were collected by filtration and washed with diethyl ether. Yield: 21.6 g (91%). Mp, 208 °C. ^{1}H NMR (DMSO-d_6): δ 5.48 (bs, 2H, NH_2), 6.60 (d, 2H, ^3J = 8.6 Hz, H-arom), 6.86 (d, 1H, ^3J = 9.9 Hz, *H*C═CH), 7.53 (d, 2H, ^3J = 8.6 Hz, H-arom), 7.88 (d, 1H, ^3J = 9.9 Hz, HC═C*H*), 12.93 (bs, 1H, NH).

6-(4-Hydrazinophenyl)-2*H*-pyridazin-3-one Hydrochloride (3). Compound 3 was prepared analogously to the synthesis of 6-(4-hydrazinophenyl)-4,5-dihydro-2*H*-pyridazin-3-one hydrochloride[31] from 6-(4-aminophenyl)pyridazinone **1** (11.2 g, 50.1 mmol). Yield: 9.51 g (80%). Mp, >200 °C. ^{1}H NMR (DMSO-d_6): δ 6.96 (d, 1H, ^3J = 9.9 Hz, *H*C═CH), 7.05 (d, 2H, ^3J = 8.6 Hz, H-arom), 7.79 (d, 2H, ^3J = 8.6 Hz, H-arom), 8.00 (d, 1H, ^3J = 9.9 Hz, HC═C*H*), 10.41 (bs, 3H, NH_3^+), 13.10 (bs, 1H, NH).

6-(4-Hydrazinophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one Hydrochloride (4). 6-(4-Aminophenyl)-4,5-dihydro-5-methyl-3(2*H*)-pyridazinone[30] (**2**) (10.2 g, 50.2 mmol) was mixed with 2 N HCl (100 mL) and cooled to −2 to 0 °C. Sodium nitrite (3.50 g, 50.1 mmol) was dissolved in water (10 mL). The solution was added dropwise while keeping the temperature below 0 °C, and 30 min after the last addition, tin(II) chloride dihydrate (28.0 g, 124 mmol) in concentrated HCl (20.5 mL) was added at the same temperature. One hour later, the solids that appeared in the reaction mixture were filtered off and the product was extracted from the filtrate with *n*-butanol. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crystals that were formed upon stirring the oily remainder with dichloromethane were filtered off to afford the title compound as an orange solid. Yield: 83%. Mp, 198 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (d, 3H, ^3J = 7.2 Hz, CH_3), 2.22 (d, 1H, ^2J = 16.5 Hz, C*H*H′-pyr), 2.66 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.7 Hz, CH*H*′-pyr), 3.29−3.48 (m, 1H, C*H*CH_3), 6.97 (d, 2H, ^3J = 8.6 Hz, H-arom), 7.72 (d, 2H, ^3J = 8.6 Hz, H-arom), 8.49 (bs, 1H, NH), 10.25 (bs, 3H, NH_3^+), 10.87 (s, 1H, NH).

***cis*-2-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]acetic Acid (11).** Sodium hydride (60% dispersion in mineral oil, 0.92 g, 23 mmol) was added to a suspension of *cis*-4-(3,4-dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (**9**) (6.00 g, 21.0 mmol) in DMF (100 mL). After the reaction mixture was stirred for 1 h, ethyl bromoacetate (3.84 g, 23.0 mmol) was added and the resulting 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 layers were washed with water and brine and dried over $MgSO_4$. Removal of the solvent in vacuo yielded the crude ethyl ester **10**, which was stirred for 3 h in a mixture of 2 N KOH (50 mL), THF (50 mL), and methanol (50 mL). The reaction mixture was concentrated to a volume of 50 mL, diluted with water, and acidified with concentrated HCl. The product was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was crystallized from diethyl ether. Yield: 5.02 g (69%). Mp, 178−180 °C. ^{1}H NMR ($CDCl_3$): δ 2.08−2.50 (m, 3H, H5, H8), 2.83−3.10 (m, 2H, H8a, H8′), 3.30−3.50 (m, 1H, H4a), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.67 (AB, 2H, NCH_2), 5.63−5.88 (m, 2H, HC═CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.25 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.44 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-5-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]pentanoic Acid (12). Compound 12** was prepared as described for acetic acid **11** using 5-bromopentanoic acid as the alkylating agent and 2.2 equiv of NaH. The title compound was crystallized from diethyl ether. Yield: 50%. Mp, 107−108 °C. ^{1}H NMR ($CDCl_3$/CD_3-OD): δ 1.59−1.90 (m, 4H, $(CH_2)_2$), 1.95−2.33 (m, 3H, H5, H8), 2.41 (t, 2H, ^3J = 6.9 Hz, CH_2COOH), 2.72−2.86 (m, 1H, H8a), 2.90−3.10 (m, 1H, H8′), 3.24−3.43 (m, 1H, H4a), 3.70−4.10 (m, 8H, OCH_3, NCH_2), 5.60−5.88 (m, 2H, HC═CH), 6.87 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.25 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.47 (d, 1H, ^4J = 2.0 Hz, H2-arom).

2-Bromo-1-(4-methoxyphenyl)propan-1-one (14). Bromine (48.9 g, 0.31 mol) was added dropwise to a solution of 4-methoxypropiophenone (50.2 g, 0.31 mol) in acetic acid (500 mL). After the reaction mixture was decolorized, the solution was concentrated in vacuo. The oily residue was dissolved in ethyl acetate and washed with 2 N HCl and aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remainder was dissolved in dichloromethane and filtered over silica. After concentration of the filtrate, the title compound was obtained as an oil. Yield: 73.3 g (99%). ^{1}H NMR ($CDCl_3$): δ 1.86 (d, 3H, ^3J = 6.6 Hz, CH_3), 3.84 (s, 3H, OCH_3), 5.27 (q, 1H, ^3J = 6.6 Hz, C*H*CH_3), 6.88−7.00 (m, 2H, H-arom), 7.91−8.05 (m, 2H, H-arom).

Ethyl 2-Ethoxycarbonyl-3-(4-methoxybenzoyl)butanoate (16). Diethyl malonate (31.9 g, 199 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 7.40 g, 185 mmol) in DMF (300 mL), keeping the temperature below 30 °C. The reaction mixture was stirred overnight at room temperature, α-bromoketone **14** (43.8 g, 180 mmol) was added, and the reaction mixture was heated at 110 °C for 4 h. After cooling, the solution was concentrated in vacuo. The residual oil was diluted with ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford the title compound as a yellow oil that was hydrolyzed without further purification as described below. ^{1}H NMR ($CDCl_3$): δ 1.10−1.39 (m, 9H, CH_2CH_3, $CHCH_3$), 3.87 (s, 3H, OCH_3), 3.93−4.38 (m, 6H, COCHCO, CH_2CH_3, C*H*CH_3), 6.89−7.02 (m, 2H, H-arom), 7.93−8.08 (m, 2H, H-arom).

4-(4-Methoxyphenyl)-3-methyl-4-oxobutyric Acid (18). A mixture of malonic ester **16** (maximum of 180 mmol) and 6 N HCl (600 mL) was heated under reflux for 6 h. The solution was concentrated in vacuo to a volume of 400 mL and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was obtained as a yellow oil. Yield: 32.5 g (81%). ^{1}H NMR ($CDCl_3$): δ 1.22 (d, 3H, ^3J = 6 Hz, CH_3), 2.47 (dd, 1H, ^3J = 4 Hz, ^2J = 16 Hz, C*H*H′-pyr), 2.98 (dd, 1H, ^3J = 9 Hz, ^2J = 16 Hz, CH*H*′-pyr), 3.78−3.95 (m, 1H, C*H*CH_3), 3.85 (s, 3H, OCH_3), 6.95 (d, 2H, ^3J = 6 Hz, H-arom), 7.98 (d, 2H, ^3J = 6 Hz, H-arom).

6-(4-Methoxyphenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (21). A mixture of γ-keto acid **18** (33.8 g, 152 mmol) and hydrazine monohydrate (19.7 g, 394 mmol) in water (200 mL) was refluxed for 10 h. After the mixture was cooled to room temperature, the product was extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Subsequently the title compound was crystallized from diethyl ether. Yield: 15.2 g (46%). Mp, 190−192 °C. ^{1}H NMR ($CDCl_3$): δ 1.25 (d, 3H, ^3J = 7.4 Hz, CH_3), 2.46 (d, 1H, ^3J = 1.1 Hz, ^2J = 16.9 Hz, C*H*H′-pyr), 2.72 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 3.25−3.46 (m, 1H, C*H*CH_3), 3.85 (s, 3H, OCH_3), 6.88−7.00 (m, 2H, H-arom), 7.65−7.78 (m, 2H, H-arom), 8.79 (bs, 1H, NH).

6-(4-Hydroxyphenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (22). Aluminum chloride (197 g, 1.48 mol) was added to a solution of methoxyphenyl analogue **21** (15.2 g, 69.6 mmol) in dichloromethane (500 mL). The reaction mixture was stirred overnight, the dichloromethane layer was decanted, and the remainder was poured into ice/water and extracted with THF. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Diethyl ether was added to the crystalline residue, and the solids were filtered off to yield the title compound as a white solid. Yield: 11.9 g (84%). Mp, 265−266 °C. ^{1}H NMR (DMSO-d_6): δ 1.05 (d, 3H, ^3J = 7.3 Hz, CH_3), 2.19 (d, 1H, ^2J = 16.7 Hz, C*H*H′-pyr), 2.64 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.7 Hz, CH*H*′-pyr), 3.22−3.48 (m, 1H, C*H*CH_3), 6.80 (d, 2H, ^3J = 8.7 Hz, H-arom), 7.62 (d, 2H, ^3J = 8.7 Hz, H-arom), 9.83 (bs, 1H, NH), 10.79 (bs, 1H, OH).

2-Bromo-1-(3-nitrophenyl)propan-1-one (13). Synthesized as described for the preparation of bromide **14** from 1-(3-nitrophenyl)propan-1-one[33] (17.2 g, 96.0 mmol). After workup, petroleum ether (60−80 °C) was added to the resulting solids, which were collected by filtration. Yield: 22.1 g (89%). Mp, 62−64 °C. ^{1}H NMR ($CDCl_3$): δ 1.95 (d, 3H, ^3J = 6.6 Hz, CH_3), 5.31 (q, 1H, ^3J = 6.6 Hz, CHBr), 7.73 (t, 1H, ^3J = 8.0 Hz, H-arom), 8.31−8.40 (m, 1H, H-arom), 8.41−8.51 (m, 1H, H-arom), 8.85 (t, 1H, ^4J = 1.9 Hz, H-arom).

5-Methyl-6-(3-nitrophenyl)-4,5-dihydro-2*H*-pyridazin-3-one (19). Compound 19 was prepared in a similar way as described for phthalazinone **21**. 2-Bromo-1-(3-nitrophenyl)-propan-1-one (**13**) (37.0 g, 143 mmol) was used as a starting material for the synthesis of the title compound. Intermediates have not been isolated. Condensation with hydrazine was performed in ethanol. After the ethanol was removed in vacuo, the title compound was crystallized from diethyl ether. The overall yield was 14.6 g (44%). Mp, 193−195 °C. ^{1}H NMR ($CDCl_3$/D_2O): δ 1.30 (d, 3H, ^3J = 6.6 Hz, CH_3), 2.53 (dd, 1H, ^3J = 2.5 Hz, ^2J = 17.0 Hz, C*H*H′-pyr), 2.79 (dd, 1H, ^3J = 6.7 Hz, ^2J = 17.0 Hz, CH*H*′-pyr), 3.32−3.52 (m, 1H, C*H*CH_3), 7.62 (t, 1H, ^3J = 8.0 Hz, H-arom), 8.07−8.18 (m, 1H, H-arom), 8.20−8.32 (m, 1H, H-arom), 8.60 (t, 1H, ^2J = 1.9 Hz, H-arom).

6-(3-Aminophenyl)-5-methyl-4,5-dihydro-2*H*-pyridazin-3-one (20). 4-Nitrophenyl analogue **19** (8.00 g, 34.3 mmol) was dissolved in a mixture of ethanol (275 mL) and water (75 mL), and the resulting mixture was heated to reflux temperature. Fe (25.0 g, 0.45 mol) and 2 N HCl (5 mL) were added successively, and the reaction mixture was refluxed for 2 h. After the suspension was cooled to room temperature, the solids were filtered off and washed with hot ethanol. The filtrate was concentrated in vacuo, and the residual oil was diluted with ethyl acetate and washed with 1 N HCl and aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was crystallized from diethyl ether. Yield: 5.51 g (79%). Mp, 144−146 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, ^3J = 6.6 Hz, CH_3), 2.46 (dd, 1H, ^3J = 2.5 Hz, ^2J = 17.0 Hz, C*H*H′-pyr), 2.71 (dd, 1H, ^3J = 6.7 Hz, ^2J = 17.0 Hz, CH*H*′-pyr), 3.22−3.41 (m, 1H, C*H*CH_3), 3.81 (bs, 2H, NH_2), 6.69−6.80 (m, 1H, H-arom), 7.04−7.29 (m, 3H, H-arom), 8.93 (bs, 1H, NH).

***cis*-4-(3,4-Diethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (23).** A mixture of 6-(3,4-diethoxybenzoyl)-cyclohex-3-enecarboxylic acid (**7**) (10.0 g, 31.4 mmol) and hydrazine monohydrate (3.20 g, 63.9 mmol) in ethanol (125 mL) was refluxed for 4 h. When the mixture cooled, the title compound crystallized from the reaction mixture. Yield: 9.30 g (94%). Mp, 145−147 °C. ^{1}H NMR ($CDCl_3$): δ 1.39−1.58 (m, 6H, CH_3), 2.10−2.37 (m, 3H, H5, H8), 2.77−2.90 (m, 1H, H8a), 2.90−3.10 (m, 1H, H8′), 3.29−3.49 (m, 1H, H4a), 4.02−4.27 (m, 4H, OCH_2), 5.61−5.88 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.22 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.4 Hz, H6-arom), 7.44 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.58 (bs, 1H, NH).

***cis*-2-(4-Bromobutyl)-4-(3,4-dimethoxyphenyl)-4a,5,8,-8a-tetrahydro-2*H*-phthalazin-1-one (25).** Sodium hydride (60% dispersion in oil, 1.54 g, 38.5 mmol) was added to a solution of phthalazinone **9** (10.0 g, 34.9 mmol) in DMF (250 mL). After the mixture was stirred for 30 min, 1,4-dibromobutane (19.7 g, 91.2 mmol) was added. Another 30 min later, the reaction mixture was poured into water and the product was extracted with diethyl ether. The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The remainder was purified by flash column chromatography using dichloromethane. The title compound was crystallized from petroleum ether (60−80 °C). Yield: 80%. Mp, 105−106 °C. ^{1}H NMR ($CDCl_3$): δ 1.78−2.32 (m, 7H, H5, H8, $(CH_2)_2$), 2.79 (t, 1H, ^3J = 5.7 Hz, H8a), 2.90−3.11 (m, 1H, H8′), 3.28−3.55 (m, 3H, H4a, CH_2Br), 3.75−4.10 (m, 5H, NCH_2, OCH_3), 5.62−5.89 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.26 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.48 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-2-(4-Bromobutyl)-4-(3,4-diethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (26).** Prepared as described for bromide **25** from phthalazinone **23** (9.30 g, 29.6 mmol). The residue was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:4. The title compound was crystallized from methanol/water. Yield:

12.5 g (94%). Mp, 73−74 °C. ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3H, ^3J = 7.0 Hz, CH_3), 1.49 (t, 3H, ^3J = 7.0 Hz, CH_3), 1.77−2.33 (m, 7H, H5, H8, $(CH_2)_2$), 2.78 (t, 1H, ^3J = 5.8 Hz, H8a), 2.89−3.11 (m, 1H, H8′), 3.22−3.41 (m, 1H, H4a), 3.47 (t, 2H, ^3J = 6.2 Hz, CH_2Br), 3.71−4.25 (m, 6H, NCH_2, OCH_2), 5.60−5.88 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.25 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 Hz, H6-arom), 7.46 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-2-(4-Bromobutyl)-4-(3-chloro-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (27). Compound 27** was prepared as described for bromide **25** from 4-(3-chloro-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (**24**) (20.0 g, 68.8 mmol). Purification by flash column chromatography using dichloromethane yielded the title compound as a colorless oil. Yield: 17.1 g (58%). ^{1}H NMR ($CDCl_3$): δ 1.74−2.32 (m, 7H, H5, H8, $(CH_2)_2$), 2.71−2.85 (m, 1H, H8a), 2.88−3.10 (m, 1H, H8′), 3.21−3.40 (m, 1H, H4a), 3.40−3.52 (m, 2H, CH_2Br), 3.71−4.09 (m, 5H, NCH_2, OCH_3), 5.59−5.87 (m, 2H, HC=CH), 6.96 (d, 1H, ^3J = 8.7 Hz, H5-arom), 7.65 (dd, 1H, ^4J = 2.2 Hz, ^3J = 8.7 Hz, H6-arom), 7.86 (d, 1H, ^4J = 2.2 Hz, H2-arom).

General Procedure for the Condensation of γ-Keto Acids with Arylhydrazines. A mixture of γ-keto acid (4.0 mmol) and arylhydrazine hydrochloride **3** or **4** (6.0 mmol) in pyridine (50 mL) was refluxed for several hours until TLC analysis showed completion of the reaction. The reaction mixture was concentrated in vacuo, and the remainder was dissolved in ethyl acetate and washed with 1 N HCl, aqueous $NaHCO_3$, and water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The isolation of the individual products is described below.

***cis*-4-(3,4-Dimethoxyphenyl)-2-[4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (29). Compound 29** was prepared according to the general procedure from 6-(3,4-dimethoxybenzoyl)cyclohex-3-enecarboxylic acid (**5**) (1.16 g, 4.00 mmol) and arylhydrazine **3** (1.43 g, 5.99 mmol), and the mixture was refluxed for 5 h. The title compound was crystallized from methanol. Yield: 1.68 g (71%). Mp, 279 °C. ^{1}H NMR (DMSO-d_6): δ 1.93−2.41 (m, 3H, H5, H8), 2.71−2.92 (m, 1H, H8′), 3.10−3.24 (m, 1H, H8a), 3.55−3.72 (m, 1H, H4a), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 5.61−5.86 (m, 2H, HC=CH-phth), 6.95−7.12 (m, 2H, H5-arom, *H*C=CH-pyr), 7.46−7.56 (m, 2H, H6-arom, H2-arom), 7.66 (d, 2H, ^3J = 8.6 Hz, H-arom-pyr), 7.92 (d, 2H, ^3J = 8.6 Hz, H-arom-pyr), 8.07 (d, 1H, ^3J = 9.9 Hz, HC=C*H*-pyr), 13.23 (bs, 1H, NH). Anal. ($C_{26}H_{24}N_4O_4$) C, H, N.

***cis*-4-(3,4-Dimethoxyphenyl)-2-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (30). Compound 30** was prepared according to the general procedure from γ-keto acid **5** (1.16 g, 4.00 mmol) and arylhydrazine **4** (1.53 g, 6.01 mmol), and the mixture was refluxed for 5 h. The title compound was crystallized from methanol. Yield: 1.41 g (65%). Mp, 192−194 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, ^3J = 7.3 Hz, CH_3), 2.13−2.41 (m, 3H, H5, H8), 2.46 (d, 1H, ^2J = 16.9 Hz, C*H*H′-pyr), 2.71 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 2.97−3.19 (m, 2H, H8a, H8′), 3.30−3.60 (m, 2H, H4a, C*H*CH_3), 3.90 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.66−5.92 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.32 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.0 Hz, H6-arom), 7.50 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.65−7.88 (m, 4H, H-arom-pyr), 8.54 (bs, 1H, NH). Anal. ($C_{27}H_{28}N_4O_4$) C, H, N.

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (31). Compound 31** was prepared from 6-(3-cyclopentyloxy-4-methoxybenzoyl)-cyclohex-3-enecarboxylic acid (**6**) (2.02 g, 5.87 mmol) and phenylhydrazine as described before. The title compound was crystallized from methanol. Yield: 1.59 g (65%). Mp, 134−135 °C. ^{1}H NMR ($CDCl_3$): δ 1.50−2.40 (m, 11H, CH_2-cyclopentyl, H5, H8), 2.93−3.16 (m, 2H, H8a, H8′), 3.32−3.50 (m, 1H, H4a), 3.89 (s, 3H, OCH_3), 4.77−4.91 (m, 1H, OCH), 5.64−5.91 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.18−7.67 (m, 7H, H-arom). Anal. ($C_{26}H_{28}N_2O_3$) C, H, N.

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-2-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (32). Compound 32** was prepared according to the general procedure from γ-keto acid **6** (1.38 g, 4.01 mmol) and arylhydrazine **4** (1.53 g, 6.01 mmol), and the mixture was refluxed for 6 h. The title compound was crystallized from diethyl ether. Yield: 1.14 g (68%). Mp, 121−128 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, ^3J = 7.3 Hz, CH_3), 1.49−2.08 (m, 8H, CH_2-cyclopentyl), 2.12−2.40 (m, 3H, H5, H8), 2.49 (d, 1H, ^2J = 16.9 Hz, C*H*H′-pyr), 2.74 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 2.98−3.19 (m, 2H, H8a, H8′), 3.28−3.57 (m, 2H, H4a, C*H*CH_3), 3.90 (s, 3H, OCH_3), 4.78−4.92 (m, 1H, OCH), 5.67−5.92 (m, 2H, HC=CH), 6.89 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.33 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, H6-arom), 7.53 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.67−7.87 (m, 4H, H-arom-pyr), 8.62 (bs, 1H, NH). Anal. ($C_{31}H_{34}N_4O_4$) C, H, N.

***cis*-4-(3,4-Diethoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (33). Compound 33** was prepared from γ-keto acid **7** (2.01 g, 6.32 mmol) and phenylhydrazine as described before. The title compound was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:3, and was subsequently crystallized from methanol. Yield: 0.86 g (35%). Mp, 107−108 °C. ^{1}H NMR ($CDCl_3$): δ 1.38−1.58 (m, 6H, CH_3), 2.12−2.42 (m, 3H, H5, H8), 2.94−3.18 (m, 2H, H8a, H8′), 3.34−3.51 (m, 1H, H4a), 4.02−4.22 (m, 4H, OCH_2), 5.63−5.90 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.19−7.65 (m, 7H, H-arom). Anal. ($C_{24}H_{26}N_2O_3$) C, H, N.

***cis*-4-(3,4-Diethoxyphenyl)-2-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (34). Compound 34** was prepared according to the general procedure from γ-keto acid **7** (1.27 g, 3.99 mmol) and arylhydrazine **4** (1.53 g, 6.01 mmol), and the mixture was refluxed for 7 h. The title compound was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:1, and was subsequently crystallized from diethyl ether. Yield: 1.38 g (70%). Mp, 164−165 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, ^3J = 7.4 Hz, CH_3), 1.41−1.59 (m, 6H, CH_2CH_3), 2.12−2.41 (m, 3H, H5, H8), 2.48 (d, 1H, ^2J = 16.9 Hz, C*H*H′-pyr), 2.74 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 2.98−3.19 (m, 2H, H8a, H8′), 3.31−3.59 (m, 2H, H4a, C*H*CH_3), 4.07−4.25 (m, 4H, OCH_2), 5.66−5.91 (m, 2H, HC=CH), 6.90 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.33 (dd, 1H, ^3J = 8.4 Hz, ^4J = 1.9 Hz, H6-arom), 7.52 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.66−7.88 (m, 4H, H-arom-pyr), 8.51 (bs, 1H, NH). Anal. ($C_{29}H_{32}N_4O_4$) C, H, N.

***cis*-4-(3-Chloro-4-methoxyphenyl)-2-phenyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (35). Compound 35** was prepared from 6-(3-chloro-4-methoxybenzoyl)cyclohex-3-enecarboxylic acid (**8**) (1.89 g, 6.43 mmol) and phenylhydrazine as described before. The reaction mixture was concentrated in vacuo, and the residue was dissolved in dichloromethane and filtered over silica. After evaporation of the solvent under reduced pressure, the title compound was crystallized from diethyl ether and recrystallized from ethanol. Yield: 2.00 g (85%). Mp, 151−152 °C. ^{1}H NMR ($CDCl_3$): δ 2.12−2.40 (m, 3H, H5, H8), 2.95−3.17 (m, 2H, H8a, H8′), 3.32−3.50 (m, 1H, H4a), 3.94 (s, 3H, OCH_3), 5.65−5.91 (m, 2H, HC=CH), 6.95 (d, 1H, ^3J = 8.7 Hz, H5-arom), 7.20−7.32 (m, 1H, H−Ph), 7.35−7.49 (m, 2H, H−Ph), 7.51−7.63 (m, 2H, H−Ph), 7.71 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H6-arom), 7.91 (d, 1H, ^4J = 2.2 Hz, H2-arom). Anal. ($C_{21}H_{19}ClN_2O_2$) C, H, N.

***cis*-4-(3-Chloro-4-methoxyphenyl)-2-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (36). Compound 36** was prepared according to the general procedure from γ-keto acid **8** (1.18 g, 4.00 mmol) and arylhydrazine **4** (1.53 g, 6.01 mmol), and the mixture was refluxed for 5 h. The title compound was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:1, and was subsequently crystallized from diethyl ether. Yield: 1.20 g (71%). Mp, 198−201 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3H, ^3J = 7.4 Hz, CH_3), 2.17−2.42 (m, 3H, H5, H8), 2.49 (d, 1H, ^2J = 17.0 Hz, C*H*H′-pyr), 2.75 (dd, 1H, ^3J = 6.7 Hz, ^2J = 17.0 Hz, CH*H*′-pyr), 2.97−

3.19 (m, 2H, H8a, H8′), 3.30−3.55 (m, 2H, H4a, C*H*CH_3), 3.96 (s, 3H, OCH_3), 5.65−5.92 (m, 2H, HC=CH), 6.98 (d, 1H, ^3J = 8.7 Hz, H5-arom), 7.64−7.88 (m, 5H, H-6-arom, H-arom-pyr), 7.92 (d, 1H, ^4J = 2.2 Hz, H2-arom), 8.56 (bs, 1H, NH). Anal. ($C_{26}H_{25}ClN_4O_3$) C, H, N.

General Procedure for the Synthesis of Hybrids Linked via an Amide Bond. Phosphorus pentachloride (0.52 g, 2.5 mmol) was added to a solution of carboxylic acid **11** or **12** (2.5 mmol) in dichloromethane (50 mL). After the mixture was stirred for 1 h at room temperature, the reaction mixture was concentrated in vacuo. The acid chlorides were used without further purification.

The selected acid chloride (maximum of 2.5 mmol) was diluted with dichloromethane (10 mL) and added to a solution of aniline **1**, **2**,[30] or **20** (2.5 mmol) in pyridine (75 mL) with a catalytic amount of 4-(dimethylamino)pyridine (DMAP).

***cis*-2-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]-*N*-[4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl]acetamide (37). Compound 37** was prepared according to the general procedure from carboxylic acid **11** (0.86 g) and aniline **1** (0.56 g). The title compound was crystallized from ethyl acetate. Yield: 65%. Mp, 161−162 °C. ^{1}H NMR ($CDCl_3$): δ 2.18−2.45 (m, 3H, H5, H8), 2.90−3.17 (m, 2H, H8a, H8′), 3.37−3.56 (m, 1H, H4a), 3.93 (s, 6H, OCH_3), 4.76 (AB, 2H, NCH_2), 5.65−5.91 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.09 (d, 1H, ^3J = 9.7 Hz, *H*C=CH-pyr), 7.27 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.0 Hz, H6-arom), 7.42−7.80 (m, 6H, H2-arom, HC=C*H*-pyr, H-arom-pyr), 8.62 (bs, 1H, NH). Anal. ($C_{28}H_{27}N_5O_5$) C, H, N.

***cis*-2-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]-*N*-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]acetamide (38). Compound 38** was prepared according to the general procedure from carboxylic acid **11** (0.86 g) and aniline **2** (0.51 g). The title compound was crystallized from diethyl ether. Yield: 47%. Mp, 139−141 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (d, 3H, ^3J = 7.3 Hz, CH_3), 2.18−2.57 (m, 4H, H5, H8, C*H*H′-pyr), 2.70 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 2.91−3.15 (m, 2H, H8a, H8′), 3.22−3.55 (m, 2H, H4a, C*H*CH_3), 3.93 (m, 6H, OCH_3), 4.73 (AB, 2H, NCH_2), 5.65−5.91 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^3J = 8.5 Hz, ^4J = 1.9 Hz, H6-arom), 7.43−7.73 (m, 5H, H2-arom, H-arom-pyr), 8.47 (bs, 1H, NH), 8.74 (bs, 1H, NH). Anal. ($C_{29}H_{31}N_5O_5$) C, H, N.

***cis*-2-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]-*N*-[3-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]acetamide (39). Compound 39** was prepared according to the general procedure from carboxylic acid **11** (0.86 g) and aniline **20** (0.51 g). The title compound was purified by flash column chromatography using ethyl acetate and crystallized from diethyl ether. Yield: 50%. Mp, 136−140 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (d, 3H, ^3J = 7.4 Hz, CH_3), 2.17−2.39 (m, 3H, H5, H8), 2.45 (d, 1H, ^2J = 17.0 Hz, C*H*H′-pyr), 2.70 (dd, 1H, ^3J = 6.7 Hz, ^2J = 17.0 Hz, CH*H*′-pyr), 2.90−3.14 (m, 2H, H8a, H8′), 3.22−3.51 (m, 2H, H4a, C*H*CH_3), 3.93 (m, 6H, OCH_3), 4.72 (AB, 2H, NCH_2), 5.63−5.91 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.3 Hz, H6-arom), 7.35 (d, 1H, ^3J = 7.8 Hz, H-arom-pyr), 7.40−7.58 (m, 3H, H2-arom, H-arom-pyr), 7.90−8.01 (m, 1H, H-arom-pyr), 8.26 (bs, 1H, NH), 8.62 (bs, 1H, NH). Anal. ($C_{29}H_{31}N_5O_5$) C, H, N.

***cis*-5-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]pentanoic Acid [4-(6-oxo-1,6-dihydropyridazin-3-yl)phenyl]amide (40). Compound 40** was prepared according to the general procedure from carboxylic acid **12** (0.97 g) and aniline **1** (0.56 g). The title compound was crystallized from ethyl acetate. Yield: 59%. Mp, 253 °C. ^{1}H NMR (DMSO-d_6): δ 1.50−2.45 (m, 9H, $(CH_2)_3C$=O, H5, H8), 2.62−2.92 (m, 2H, H8a, H8′), 3.38−3.56 (m, 1H, H4a), 3.58−3.98 (m, 8H, OCH_3, NCH_2), 5.53−5.79 (m, 2H, HC=CH), 6.89−7.04 (m, 2H, H5-arom, *H*C=CH), 7.29−7.47 (m, 2H, H6-arom, H2-arom), 7.61−7.86 (m, 4H, H-arom-pyr), 7.99 (d, 1H, ^3J = 9.9 Hz, HC=C*H*), 10.06 (bs, 1H, NH), 13.11 (bs, 1H, NH). Anal. ($C_{31}H_{33}N_5O_5$) C, H, N.

***cis*-5-[4-(3,4-Dimethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]pentanoic Acid [4-(4-Methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenyl]amide (41). Compound 41** was prepared according to the general procedure from carboxylic acid **12** (0.97 g) and aniline **2** (0.51 g). The title compound was crystallized from diethyl ether. Yield: 63%. Mp, 154−157 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, ^3J = 7.3 Hz, CH_3), 1.54−2.63 (m, 10H, $(CH_2)_3C$=O, H5, H8, C*H*H′-pyr), 2.72 (dd, 1H, ^3J = 6.7 Hz, ^2J = 16.9 Hz, CH*H*′-pyr), 2.80−2.92 (m, 1H, H8a), 2.93−3.14 (m, 1H, H8′), 3.27−3.48 (m, 2H, H4a, C*H*CH_3), 3.70−4.24 (m, 8H, OCH_3, NCH_2), 5.54−5.82 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.26 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.0 Hz, H6-arom), 7.48 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.57−7.80 (m, 4H, H-arom-pyr), 8.30 (bs, 1H, NH), 8.73 (bs, 1H, NH). Anal. ($C_{32}H_{37}N_5O_5$) C, H, N.

General Procedure for the Synthesis of Hybrids Linked via Ether Bonds. A mixture of phenol **22** (0.51 g, 2.5 mmol), bromide **25-29** (2.5 mmol), K_2CO_3 (0.69 g, 5.0 mmol), and a catalytic amount of KI in DMF (50 mL) was heated at 60 °C for 3−6 h. The reaction mixture was diluted with water, and the product was extracted with diethyl ether. The combined organic extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure.

***cis*-4-(3,4-Dimethoxyphenyl)-2-{4-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy]butyl}-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (42). Compound 42** was synthesized following the general procedure using bromide **25** (1.05 g). The title compound was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:1, and crystallized from ethyl acetate. Yield: 35%. Mp, 94−97 °C. ^{1}H NMR ($CDCl_3$): δ 1.21 (d, 3H, ^3J = 7.4 Hz, CH_3), 1.71−2.32 (m, 7H, $(CH_2)_2$, H5, H8), 2.42 (d, 1H, ^2J = 16.7 Hz, C*H*H′-pyr), 2.59−2.84 (m, 2H, H8a, CH*H*′-pyr), 2.90−3.11 (m, 1H, H8′), 3.20−3.42 (m, 2H, H4a, C*H*CH_3), 3.72−4.19 (m, 10H, OCH_2, OCH_3, NCH_2), 5.59−5.87 (m, 2H, HC=CH), 6.79−6.97 (m, 3H, H5-arom, H-arom-pyr), 7.24 (dd, 1H, ^4J = 1.8 Hz, ^3J = 8.4 Hz, H6-arom), 7.45 (d, 1H, ^4J = 1.8 Hz, H2-arom), 7.64 (d, 2H, ^3J = 8.9 Hz, H-arom-pyr), 8.47 (bs, 1H, NH). Anal. ($C_{31}H_{36}N_4O_5$) C, H, N.

***cis*-4-(3,4-Diethoxyphenyl)-2-{4-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy]butyl}-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (43). Compound 43** was synthesized following the general procedure using bromide **26** (1.12 g). The title compound was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80 °C), 1:1, and crystallized from petroleum ether (60−80 °C). Yield: 28%. Mp, 73−78 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, ^3J = 7.3 Hz, CH_3), 1.39−1.57 (m, 6H, OCH_2CH_3), 1.72−2.32 (m, 7H, $(CH_2)_2$, H5, H8), 2.45 (d, 1H, ^2J = 16.9 Hz, C*H*H′-pyr), 2.61−2.87 (m, 2H, H8a, CH*H*′-pyr), 2.90−3.11 (m, 1H, H8′), 3.21−3.42 (m, 2H, H4a, C*H*CH_3), 3.73−4.23 (m, 8H, OCH_2, NCH_2), 5.60−5.88 (m, 2H, HC=CH), 6.81−6.98 (m, 3H, H5-arom, H-arom-pyr), 7.25 (dd, 1H, ^4J = 1.8 Hz, ^3J = 8.4 Hz, H6-arom), 7.46 (d, 1H, ^4J = 1.8 Hz, H2-arom), 7.66 (d, 2H, ^3J = 8.8 Hz, H-arom-pyr), 8.47 (bs, 1H, NH). Anal. ($C_{33}H_{40}N_4O_5$) C, H, N.

***cis*-4-(3-Chloro-4-methoxyphenyl)-2-{4-[4-(4-methyl-6-oxo-1,4,5,6-tetrahydropyridazin-3-yl)phenoxy]butyl}-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (44). Compound 44** was synthesized following the general procedure using bromide **27** (1.06 g). The title compound was crystallized from a mixture of ethyl acetate and MeOH. Yield: 21%. Mp, 105−106 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (d, 3H, ^3J = 7.4 Hz, CH_3), 1.71−2.32 (m, 7H, $(CH_2)_2$, H5, H8), 2.45 (d, 1H, ^2J = 16.9 Hz, C*H*H′-pyr), 2.61−2.85 (m, 2H, H8a, CH*H*′-pyr), 2.90−3.10 (m, 1H, H8′), 3.20−3.41 (m, 2H, H4a, C*H*CH_3), 3.74−4.14 (m, 7H, OCH_2, OCH_3, NCH_2), 5.59−5.88 (m, 2H, HC=CH), 6.84−6.99 (m, 3H, H5-arom, H-arom-pyr), 7.58−7.71 (m, 3H, H6-arom, H-arom-pyr), 7.87 (d, 1H, ^4J = 2.2 Hz, H2-arom), 8.46 (bs, 1H, NH). Anal. ($C_{30}H_{33}ClN_4O_4$) C, H, N.

References

(1) 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.

(2) 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.

(3) 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.

(4) 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.

(5) 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.

(6) Torphy, T. J.; Undem, B. J. Phosphodiesterase inhibitors: new opportunities for treatment of asthma. *Thorax* **1991**, *46*, 512−523.

(7) 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, 1997.

(8) 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.

(9) 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.

(10) Kauffman, R. F.; Crowe, V. G.; Utterback, B. G.; Robertson, D. W. LY195115: a potent, selective inhibitor of cyclic nucleotide phosphodiesterase located in the sarcoplasmic reticulum. *Mol. Pharmacol.* **1986**, *30*, 609−616.

(11) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F.; Hayes, J. S. Dihydropyridazinone cardiotonics: synthesis and inotropic activity of 5′-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)spiro[cycloalkane-1,3′-[3H]indol]-2′(1′*H*)-ones. *J. Med. Chem.* **1987**, *30*, 824−829.

(12) Sircar, I.; Duell, B. L.; Bobowski, G.; Bristol, J. A.; Evans, D. B. Cardiotonic agents. 2. Synthesis and structure−activity relationships of 4,5-dihydro-6-[4-(1*H*-imidazol-1-yl)phenyl]-3(2*H*)-pyridazinones: a new class of positive inotropic agents. *J. Med. Chem.* **1985**, *28*, 1405−1413.

(13) Weishaar, R. E.; Cain, M. H.; Bristol, J. A. A new generation of phosphodiesterase inhibitors: multiple molecular forms of phosphodiesterase and the potential for drug selectivity. *J. Med. Chem.* **1985**, *28*, 537−545.

(14) Robertson, D. W.; Boyd, D. B. Structural requirements for potent and selective inhibition of low-*Km*, cyclic-AMP-specific phosphodiesterases. In *Advances in Second Messenger and Phosphoprotein Research*; Strada, S. J. a. H. H., Ed.; Raven Press: New York, 1992; Vol. 25, pp 321−340.

(15) Weishaar, R. E.; Bristol, J. A. Selective inhibitors of phosphodiesterases. *Compr. Med. Chem.* **1990**, *2*, 501−514.

(16) Davis, A.; Warrington, B. H.; Vinter, J. G. Strategic Approaches to Drug Design. II. Modeling Studies on Phosphodiesterase Substrates and Inhibition. *J. Comput.-Aided Mol. Des.* **1987**, *1*, 97−120.

(17) Erhardt, P. W.; Hagedorn, A. A. d.; Sabio, M. Cardiotonic agents. 3. A topographical model of the cardiac cAMP phosphodiesterase receptor. *Mol. Pharmacol.* **1987**, *33*, 1−13.

(18) Erhardt, P. W.; Chou, Y. L. A topographical model for the c-AMP phosphodiesterase III active site. *Life Sci.* **1991**, *49*, 553−568.

(19) 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.

(20) Van der Mey, M.; Boss, H.; Couwenberg, D.; Hatzelmann, A.; Sterk, G. J.; Goubitz, K.; Schenk, H.; Timmerman, H. Novel Selective PDE4 Inhibitors. 4. Resolution, Absolute Configuration, and PDE4 Inhibitory Activity of *cis*-Tetra and *cis*-Hexahydrophthalazinones. *J. Med. Chem.* **2002**, *45*, 2526−2533.

(21) 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. Patent WO 9831674, 1998.

(22) 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. Patent WO 9931071, 1999.

(23) Thibaut, U.; Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Timmerman, H.; Van der Laan, I. J.; Ulrich, W. R.; Sterk, G. J.; Van der Mey, M. Preparation of phthalazinyldihydrobenzofurans as cyclic nucleotide phosphodiesterase inhibitors. Patent WO 9931090, 1999.

(24) Van der Mey, M.; Boss, H.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Timmerman, H. Novel Selective PDE4 Inhibitors. 3. In Vivo Anti-Inflammatory Activity of a New Series of *N*-Substituted *cis*-Tetra- and *cis*-Hexahydrophthalazinones. *J. Med. Chem.* **2002**, *45*, 2520−2525.

(25) Van der Mey, M.; Hatzelmann, A.; Van Klink, G. P. M.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Ulrich, W. R.; Timmerman, H. Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure−Activity Relationships of 4-Aryl-Substituted *cis*-Tetra- and *cis*-Hexahydrophthalazinones. *J. Med. Chem.* **2001**, *44*, 2523−2535.

(26) Van der Mey, M.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H. Novel Selective PDE4 Inhibitors. 1. Synthesis, Structure−Activity Relationships, and Molecular Modeling of 4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-ones and Analogues. *J. Med. Chem.* **2001**, *44*, 2511−2522.

(27) Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Van der Laan, I. J.; Timmerman, H.; Sterk, G. J.; Van der Mey, M. Preparation of arylphthalazinones as phosphodiesterase III/IV inhibitors. Patent WO 9947505, 1999.

(28) Sterk, G. J.; Van der Mey, M. Phthalazinone PDE III/IV inhibitors. U.S. Patent 6,255,303, 2001.

(29) 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 B. V.: Amsterdam, The Netherlands, 1996; Vol. 33, pp 1−52.

(30) 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.

(31) Mertens, A.; Friebe, W. G.; Müller-Beckmann, B.; Kampe, W.; Kling, L.; von der Saal, W. Nonsteroidal cardiotonics. 3. New 4,5-dihydro-6-(1*H*-indol-5-yl)pyridazin-3(2*H*)-ones and related compounds with positive inotropic activities. *J. Med. Chem.* **1990**, *33*, 2870−2875.

(32) Coates, W. J.; McKillop, A. One-pot preparation of 6-substituted 3(2*H*)-pyridazinones from ketones. *Synthesis* **1993**, 334−342.

(33) Leonard, N. J.; Boyd, S. N. Cinnolines. I. Synthesis of aminoacetophenones and aminopropiophenones. *J. Org. Chem.* **1946**, *11*, 405−418.

(34) Schudt, C.; Winder, S.; Muller, B.; Ukena, D. Zardaverine as a selective inhibitor of phosphodiesterase isoenzymes. *Biochem. Pharmacol.* **1991**, *42*, 153−162.

JM030776L