Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure−Activity Relationships of 4-Aryl-Substituted *cis*-Tetra- and *cis*-Hexahydrophthalazinones

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Received February 7, 2001

A series of 4-aryl-substituted *cis*-4a,5,8,8a-tetra- and *cis*-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-ones with high inhibitory activity toward cAMP-specific phosphodiesterase (PDE4) was synthesized. To study structure−activity relationships various substituents were introduced to the 2-, 3-, and 4-positions of the 4-phenyl ring. Substitution at the 4-position of the phenyl ring was restricted to a methoxy group, probably due to unfavorable steric interactions of larger groups with the binding site. The introduction of many alkoxy substituents including distinct ring systems and functional groups was allowed to the 3-position. It was found that in general the *cis*-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-ones are more potent than their hexahydrophthalic counterparts, the best activity residing in (4-imidazol-1-yl-phenoxy)butoxy analogue **16o** (pIC_{50} = 9.7).

Introduction

The cyclic nucleotide phosphodiesterases (PDEs) are enzymes that regulate cellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) through hydrolysis of these second messengers. PDE isoenzyme families have been classified on the basis of their substrate specificities (cAMP or cGMP), kinetic characteristics (K_m and V_{max}), and their regulation by specific inhibitors or activators.[1−7] In a wide range of immune and inflammatory cells, including neutrophils, T-lymphocytes, macrophages, and eosinophils, inhibition of cellular responses is associated with elevated levels of cAMP. It has been shown that among the classic PDE families,[1] PDE4 (cAMP-specific) is the predominant PDE isotype in such cells.[8−16] Inhibition of PDE4 in inflammatory cells influences many of the cell-specific responses including the production and/or release of proinflammatory mediators, cytokines, and active oxygen species, both in vitro and in vivo.[17−19] Chronic and acute inflammatory diseases, such as asthma and rheumatoid arthritis, could potentially be treated by the application of selective and potent PDE4 inhibitors,[20−23] because the presence and activation of multiple types of inflammatory cells characterize sites of inflammation.

In a previous paper we have described the discovery of *cis*-4a,5,8,8a-tetra- and *cis*-4a,5,6,7,8,8a-hexahydrophthalazinones[24,25] as interesting classes of PDE4 inhibitors.[26] Structure−activity relationship studies on known catechol ether containing PDE4 inhibitors have revealed that modification of the catechol ether part can have a dramatic effect on the activity.[27−29]

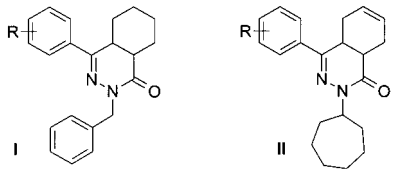

Figure 1. Optimization of the 4-aryl moiety of the *cis*-phthlalazinone lead compounds.

This paper describes the structural requirements of the 4-aryl moiety with respect to potent PDE4 inhibition. For optimization of the hexahydrophthalazinone series, an *N*-benzyl-substituted parent structure (**I**) was used, whereas for the class of tetrahydrophthalazinones the parent molecule (**II**) was substituted with a cycloheptyl ring at the 2-position (Figure 1). After the synthesis of hexahydrophthalazinones **I**, preliminary studies showed that replacement of the benzyl group by a cycloheptyl substituent led to an increase in PDE4 inhibitory activity; therefore, the tetrahydrophthlazinones were substituted with this cycloalkyl moiety. Subsequent investigations are planned to explore this unexpected increase in inhibitory capacity.

The synthesis, pharmacological screening, and structure−activity relationships (SAR) of these novel 4-aryl-substituted phthalazinones[24,25,30] are presented. Furthermore, the SAR of the 3,4-dialkoxyphenyl subunit of the compounds are compared with those of other known specific PDE4 inhibitors such as rolipram[31,32] and other catechol ethers.[27,28,33−35]

Chemistry

The synthetic procedures used for the preparation of the 4-aryl-substituted hexahydrophthalazinones and some of the 4a,5,8,8a-tetrahydrophthalazinones (**3a**−**j** and **3k**−**o**, respectively) are depicted in Scheme 1. Condensation of γ-keto acids **1a**−**o** with hydrazine monohydrate yielded phthalazinones **2a**−**o**, which were

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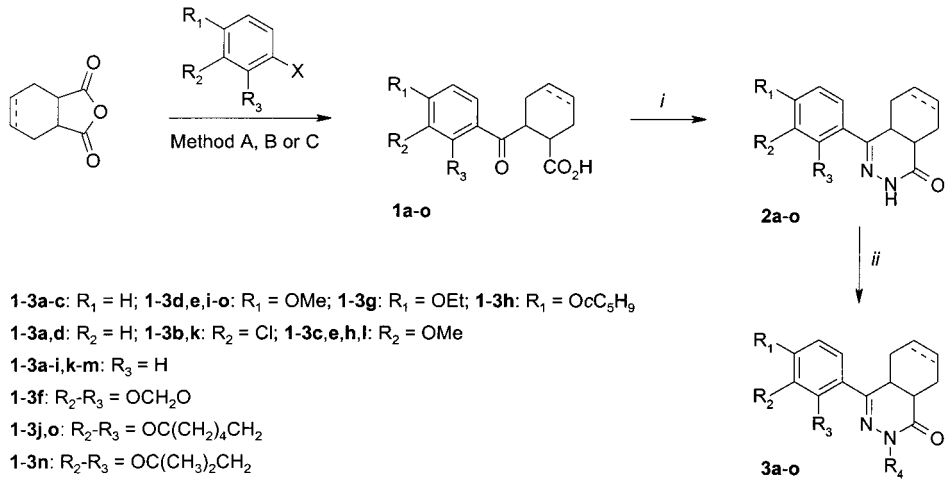
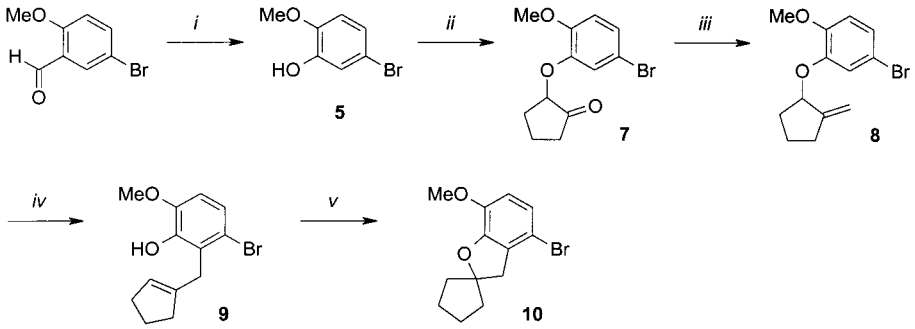
10.1021/jm010838c CCC: $20.00
Published on Web 07/04/2001

Scheme 1[a]



[a] Reagents: method A (**1a**,**d**,**g**,**k**; X = H); $AlCl_3$, CH_2Cl_2; method B (**1b**,**h**−**j**; X = Br); 1, BuLi, THF, −90 °C; 2, anhydride, THF, −80 °C; method C (**1c**,**e**,**f**,**l**−**o**; X = Br); 1, Mg, THF, reflux; 2, anhydride, THF; (*i*) H_2NNH_2, EtOH, reflux; (*ii*) 1, NaH, DMF; 2, R_4X.

Scheme 2[a]



[a] Reagents: (*i*) MCPBA, CH_2Cl_2; (*ii*) 2-chlorocyclopentanone, K_2CO_3, DMF, 60 °C; (*iii*) 1, KOtBu, $MeP(Ph)_3Br$, THF; 2, **7**, THF; (*iv*) 180 °C; (*v*) Amberlyst 15 ion-exchange resin, toluene, 80 °C.

deprotonated with sodium hydride and subsequently alkylated with the selected alkyl halide to afford the corresponding *N*-alkyl-4-aryl-substituted phthalazinones (**3a**−**j**, R_4 = Bn; and **3k**−**o**, R_4 = cycloheptyl). The γ-keto acids employed were synthesized from either *cis*-1,2-cyclohexanedicarboxylic or *cis*-1,2,3,6-tetrahydrophthalic anhydride and the suitable aromatic compound using one of the following methods: Friedel−Crafts acylation (method A), *n*-BuLi-mediated coupling (method B), or Grignard reaction (method C).

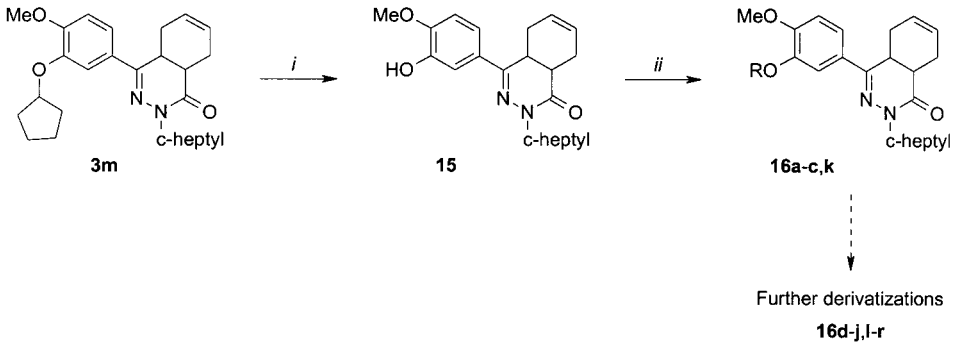
The aromatic bromides used for the preparation of γ-keto acids **1h**−**j** and **1m**−**o** are not commercially available. The synthesis of bromide **10**, a precursor for γ-keto acids **1j** and **1o**, is shown in Scheme 2. Baeyer−Villiger oxidation of commercially available 5-bromo-2-methoxybenzaldehyde using *m*-chloroperoxybenzoic acid (step 1)[36] followed by alkylation of the resulting phenol **5** provided ketone **7**. This ketone was converted into the corresponding alkene **8** by a Wittig reaction involving triphenylphosphonium methylide, which was prepared in situ from (methyl)triphenylphosphonium bromide and potassium *tert*-butoxide. Claisen rearrangement of allyl ether **8** at 180 °C afforded *o*-allyl phenol **9**. Nucleophilic addition of the phenol oxygen to the cyclopentenyl C1 was catalyzed by an acidic ion-exchange resin yielding dihydrobenzofuran **10**. 4-Bromo-2,3-dihydro-2,2-dimethyl-7-methoxybenzofuran (**14**, not shown), used for the preparation of γ-keto acid **1n**, was synthesized analogously to **10** (Scheme 2), using chloro-2-propanone as the alkylating agent.

Alkylation of phenol **5** (Scheme 2) with cyclopentyl bromide afforded the desired catechol ether compound (**6**, not shown), used for the synthesis of **1i** and **1m**. The aromatic bromide employed for **1h** was synthesized in an analogous manner to **6** from 4-bromo-2-methoxyphenol.

Phenol **15** was obtained by hydrolysis of compound **3m** using *p*-toluenesulfonic acid (Scheme 3).

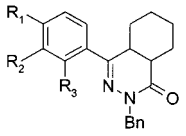
The 4-(3-alkoxy-4-methoxyphenyl)phthalazinones **16a**−**r** (Table 2) were prepared by alkylation of phenol **15** (method D, Scheme 3), generally followed by further derivatization. Treatment of phenol **15** with the suitable alkyl halides yielded phthalazinones **16a**,**b** and **16k**. Alkylation of phenol **15** with ethylene carbonate gave phthalazinone **16c**. Carboxylic acids **16d**−**f** were prepared by hydrolysis of the corresponding ethyl esters, which were formed upon treatment of phenol **15** with the appropriate ω-bromoalkyl esters. A 1:1 adduct formed from triphenylphosphine and bromine was used to convert alcohol **16c** into a bromide, which upon treatment with dimethylamine provided phthalazinone **16g**. To synthesize the remainder (**16h**−**j** and **16l**−**r**), phenol **15** was alkylated with the suitable α,ω-dibromoalkanes to yield the respective 4-(3-ω-bromo-*n*-alkoxy-4-methoxyphenyl)phthalazinones (n = 4 or 6), which were then reacted with the nucleophiles of choice. Analogues **16m** and **16q** were obtained by hydrolysis of the corresponding ethyl esters. Tetrazole **16n** was prepared by a 1,3-dipolar cycloaddition of sodium azide to nitrile **16l**.

Scheme 3[a]



[a] Reagents: (*i*) pTosOH, toluene, reflux; (*ii*) method D; RX, K_2CO_3, NMP/DMF.

Table 1. 4-Aryl Substituted 4a,5,6,7,8,8a-Hexahydro-2*H*-phthalazin-1-ones and Their PDE4 Blocking Activities



compd	R_1	R_2	R_3	PDE4 pIC_{50}[a]
3a	H	H	H	< 5.0
3b	H	Cl	H	< 5.0
3c	H	OMe	H	5.6
3d	OMe	H	H	5.9
3e	OMe	OMe	H	8.1
3f	OCH_2O		H	5.8
3g	OEt	OEt	H	7.8
3h	O*c*C_5H_9	OMe	H	< 5.0
3i	OMe	O*c*C_5H_9	H	8.0
3j	OMe			8.6
Ariflo				7.0
(-)-Rolipram				7.3

[a] $pIC_{50} = -\log IC_{50}$. Inhibition of PDE4 was investigated in the cytosol of human neutrophils. The data are means of two independent determinations in triplicate.

Pharmacology

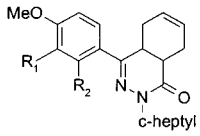
The structures as well as the PDE3 and PDE4 inhibitory activities (pIC_{50} values) of the 4-aryl-substituted hexa- and 4a,5,8,8a-tetrahydrophthalazinones under study are summarized in Tables 1 and 2, respectively. The activities were determined as described previously.[26] SAR for the two series of 4-aryl-substituted phthalazinones are discussed below.

PDE Inhibition and SAR

PDE3 Inhibition. The hexa- and tetrahydrophthalazinones listed in Tables 1 and 2 exhibit no significant PDE3 inhibitory activities ($pIC_{50} < 5.5$); the pIC_{50} values are therefore not listed.

PDE4 Inhibition. The effect of variations at the 2-, 3-, and 4-positions of the aromatic ring, attached to the 4-position of the phthalazinone subunit, on the PDE4 inhibitory activity is studied. The 4-(3,4-dimethoxyphe-

Table 2. 4-Aryl Substituted 4a,5,8,8a-Tetrahydro-2*H*-phthalazin-1-ones and Their PDE4 Blocking Activities



compd	R_1	R_2	PDE4 pIC_{50}[a]
3k	Cl	H	8.0
3l	OMe	H	9.1
16a	$OCHF_2$	H	8.8
16b	OCH_2*c*Pr	H	9.0
3m	O*c*C_5H_9	H	8.9
3n			9.0
3o			9.2
15	OH	H	7.4
16c	$O(CH_2)_2OH$	H	8.4
16d	OCH_2CO_2H	H	5.6
16e	$O(CH_2)_3CO_2H$	H	7.2
16f	$O(CH_2)_4CO_2H$	H	7.8
16g	$O(CH_2)_2N(Me)_2$	H	7.2
16h	$O(CH_2)_4N(Me)_2$	H	7.4
16i	$O(CH_2)_4$imidazol-1-yl	H	8.1
16j	$O(CH_2)_4$purin-7-yl	H	7.6
16k	$O(CH_2)_5Ph$	H	8.3
16l	$O(CH_2)_4O$-4-NCC_6H_4	H	8.6
16m	$O(CH_2)_4O$-4-$HO_2CC_6H_4$	H	9.5
16n	$O(CH_2)_4O$-4-(2*H*-tetrazol-5-yl)C_6H_4	H	9.2
16o	$O(CH_2)_4O$-4-imidazol-1-ylC_6H_4	H	9.7
16p	$O(CH_2)_6OPh$	H	8.0
16q	$O(CH_2)_6O$-4-$HO_2CC_6H_4$	H	8.7
16r	$O(CH_2)_6O$-4-$H_2NCOC_6H_4$	H	9.5

[a] See Table 1 footnote.

nyl)phthalazinone **3e** is one of the first phthalazinones with high PDE4 inhibitory activity synthesized by us and was subsequently used as a lead for further optimization of the catechol ether part (Table 1; hexahydro series). Comparison of **3a**−**d** and **3e** reveals that the 3,4-dialkoxy pattern is essential for potent enzyme inhibition. These results agree with earlier findings of other research groups studying catechol ether containing selective PDE4 inhibitors.[27,28,33−35] In several publications it is assumed that these catechol ether oxygen atoms are involved in hydrogen bonding.

Replacing the 3,4-dimethoxy substituents by a 3,4-dioxymethylene group (**3f**) leads to a 225-fold decrease in potency as compared to **3e**. This result indicates that one or both methyl groups are important for activity and/or that the oxygen lone-pairs in 3,4-dioxymethylene derivative **3f** are in a position unfavorable for interaction with the enzyme as was previously suggested for rolipram analogues.[29] Upon modification of the 4-methoxy group to a cyclopentyloxy moiety (**3h**) a complete loss of activity is observed, which is probably caused by unfavorable steric interactions of the large alkyl ring with the receptor site. Comparison of **3i** with **3e** shows that bulky alkoxy groups are well tolerated at the 3-position of the aromatic ring. This result is in agreement with the SAR of other known selective PDE4 inhibitors; however, the activity of such compounds is increased up to 100-fold by this modification.[27,28,33,34] The 3,4-diethoxy derivative **3g** is slightly less potent than **3e**, which may be due to the steric bulk of the 4-ethoxy substituent. Finally, in analogue **3j** the 3-cyclopentyloxy group is rigidified, leading to a 4-fold increase in activity as compared to **3i**. Thus, it can be concluded that substitution at the 2-position is allowed and that the enhanced activity is a result of either the reduction of the conformational freedom of the 3-cyclopentyloxy group, fixing it in the bioactive conformation, or an increase in lipophilicity.

To further examine the influence of substitutions at the 4-aromatic ring, especially at the 3-position, a large number of 4-aryl-substituted *N*-cycloheptyl-4a,5,8,8a-tetrahydrophthalazinones was prepared and tested. The PDE4 inhibitory activities of these compounds are listed in Table 2. Phthalazinones **3l**−**o** and **16a**,**b** with 3-(cyclo)alkoxy moieties have excellent activities in the nanomolar range. The various sizes and lipophilicities of these alkoxy substituents do not seem to alter the activity. Replacement of the 3-methoxy group in **3l** by a chlorine atom (**3k**) or a hydroxy moiety (**15**) causes a significant decrease in activity.

Next, the effect of alkyl chains substituted with a functional group, aromatic ring, and/or heterocyclic ring on enzyme inhibition was investigated. Comparison of analogues **16c**−**h** with **3l** shows that the introduction of hydrophilic hydroxy, carboxy or *N*,*N*-(dimethyl)amino alkyl moieties causes a considerable reduction in activity.

Derivatives **16i**−**k** and **16p** containing an imidazolyl-, purinyl-, phenyl-, or phenoxyalkyl moiety are ∼10-fold less potent than **3l**. Finally, changing the 3-methoxy group (**3l**) to a tetrazolylphenoxybutoxy moiety (**16n**) does not affect the activity, whereas substitution with a cyano- or carboxyphenoxyalkoxy group (**16l** and **16q**) leads to a 2.5−3-fold reduction of the inhibitory capacity. Phthalazinones **16m**, **16o**, and **16r** with, respectively, a carboxy-, imidazolyl-, or carbamoylphenoxyalkoxy substituent are 2.5−4 times more potent than analogue **3l**. In the latter cases the optimum alkyl chain length seems to be four carbon atoms (compare **16m** with **16q**). The most potent compound in the current class of tetrahydrophthalazinones is the (4-imidazol-1-yl-phenoxy)butoxy analogue **16o**, with a pIC_{50} value of 9.7.

A similar change in PDE4 inhibitory capacity is observed upon replacement of the 3-methoxy group of the 4-aryl-substituted hexa- and tetrahydrophthalazinones (**3e** vs **3i** vs **3j** and **3l** vs **3m** vs **3o**), indicating that such compounds may have the same binding mode.

Regression Analyses

A classical QSAR method was used to establish a possible correlation between the PDE4 inhibitory activity of tetrahydrophthalazinones **3k**−**m**, **15**, and **16a**−**r** (Table 2) and lipophilic (hydrophobic fragment constant *f* of Rekker[37] and Hansch parameter π), steric (Taft parameter E_s and multidimensional Sterimol parameters L, B_1, and B_5), and electronic parameters (Hammett σ constants, σ^* of Taft, and Swain and Lupton parameters F and R). The classical physicochemical parameters (except the Rekker constants) were taken from Hansch.[38] However, no statistically significant correlations were found, which may have been caused by the relatively small number of classical physicochemical parameters available for the R_1 substituents of compounds **3k**−**m**, **15**, and **16a**−**r** (Table 2) as well as the large diversity in structure. Similarly, QSAR analyses employing smaller subsets (e.g., R_1 of analogues **3l**,**m**, **15**, **16a**−**h**, and **16h**−**o**, respectively) gave no significant correlations.

Conclusion

In this paper we describe a novel series of 4-aryl-substituted *cis*-4a,5,8,8a-tetra- and *cis*-4a,5,6,7,8,8a-hexahydrophthalazinones with high inhibitory activity toward PDE4 (nanomolar range). In both series the 4-(3,4-dialkoxyphenyl) pattern is essential for potent PDE4 inhibition, suggesting a crucial role for the catechol ether oxygen atoms in binding to the enzyme. The catechol ether oxygen atom at the 3-position seems to be involved in hydrogen bonding as the 3-hydroxy derivative (**15**) is 50-fold less potent than compound **3l**. Furthermore, substitution at the 4-position of the phenyl ring is restricted to small lipophilic groups (preferably methoxy), whereas numerous alkoxy substituents are allowed at the 3-position. The introduction of polar moieties close to the 4-phenyl ring is, however, unfavorable for PDE4 inhibition. Presumably, the substituents at the 4-position occupy a small lipophilic pocket. In contrast, the 3-substituents either fill a large hydrophobic cavity or are located near the surface of the enzyme. In general, these findings are in accordance with the SAR established for 3,4-dialkoxyphenyl-substituted PDE4 inhibitors such as rolipram[28,29] and RP 73401.[27] Nevertheless, replacement of a 3-methoxy group by larger hydrophobic moieties usually leads to a considerable increase in PDE4 inhibitory activity. For example, modification of a 3-methoxy group by a 3-cyclopentyloxy substituent gave a 10−100-fold enhancement in potency for rolipram and RP 73401, respec-

tively. In the phthalazinone series a similar alteration does not affect the activity. Because of their high activity and easy accessibility, 4-(3,4-dimethoxyphenyl)-substituted hexa- and tetrahydrophthalazinone parent structures were used to explore the influence of *N*-substitution on potency as will be discussed in a future paper. Furthermore, the resolution of various potent *cis*-phthalazinone racemates will be investigated to determine the pharmacological profile of the individual enantiomers.

Experimental Section

(I) Chemistry. General Methods and Materials. THF was freshly distilled from $LiAlH_4$ before use. DMF and NMP were 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, BuLi-mediated couplings, 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 or on an Electrothermal IA9200 apparatus 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). 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) or DMSO-d_6 (δ = 39.5 ppm). Abbreviations used in the 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 singlet. 2D NMR (H−H, 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. The synthesis of phthalazinones **2l** and **3e** is described in a previous paper.[26]

Method A. General Procedure for Friedel—Crafts Acylation. A selected aromatic compound (100 mmol) was slowly added to an ice-cooled suspension of anhydrous aluminum chloride (13.3 g, 100 mmol) in CH_2Cl_2 (400 mL). After complete addition, *cis*-1,2-cyclohexanedicarboxylic anhydride or *cis*-1,2,3,6-tetrahydrophthalic anhydride (100 mmol) was added to the reaction mixture. The resulting solution was refluxed until TLC showed completion of the reaction (4−16 h). The mixture was poured into ice−water, the organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The oil thus obtained was dissolved in CH_2Cl_2 and filtered over silica gel to remove the dicarboxylic acid formed during workup. The γ-keto acids obtained were crystallized from diethyl ether as white solids. Experimental data for the separate compounds are listed below.

***cis*-2-Benzoylcyclohexanecarboxylic acid (1a)** was prepared via method A using *cis*-1,2-cyclohexanedicarboxylic anhydride and benzene: yield 4.65 g (20%); mp 130−132 °C (mp 138−140 °C[39]); ^{1}H NMR ($CDCl_3$) δ 1.12−2.38 (m, 8H, CH_2), 2.61−2.82 (m, 2H, H1), 3.82−3.99 (m, 1H, H2), 7.33−7.62 (m, 3H, H3-arom, H4-arom, H5-arom), 7.78−7.91 (m, 2H, H2-arom, H6-arom).

***cis*-2-(4-Methoxybenzoyl)cyclohexanecarboxylic acid (1d)** was prepared via method A using anisole and *cis*-1,2-cyclohexanedicarboxylic anhydride: yield 7.34 g (28%); mp 110−112 °C (mp 112−114 °C[40]); ^{1}H NMR ($CDCl_3$) δ 1.21−2.39 (m, 8H, CH_2), 2.60−2.78 (dq, 1H, H1), 3.80−3.97 (m, 4H, H2, OCH_3), 6.85−6.99 (m, 2H, H3-arom, H5-arom), 7.80−7.93 (m, 2H, H2-arom, H6-arom), 10.25 (COOH).

***cis*-2-(3,4-Diethoxybenzoyl)cyclohexanecarboxylic acid (1g)** was prepared via method A using 1,2-diethoxybenzene and *cis*-1,2-cyclohexanedicarboxylic anhydride: yield 7.69 g (24%); mp 180−182 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.39 (m, 14H, CH_2-cyclohexane, CH_2CH_3), 2.60−2.78 (m, 1H, H1), 3.80−3.98 (m, 1H, H2), 4.04−4.25 (m, 4H, OCH_2), 6.86 (d, 1H, ^3J = 8.9 Hz, H5-arom), 7.40−7.55 (m, 2H, H2-arom, H6-arom).

***cis*-6-(3-Chloro-4-methoxybenzoyl)cyclohex-3-enecarboxylic acid (1k)** was prepared via method A using *cis*-1,2,3,6-tetrahydrophthalic anhydride and 2-chloroanisole: yield 18.27 g (62%); mp 207−210 °C; ^{1}H NMR ($CDCl_3$) δ 2.27−2.58 (m, 3H, H-cyclohexene), 2.59−2.81 (m, 1H, H-cyclohexene), 2.81−2.98 (m, 1H, H1), 3.73−3.97 (m, 4H, H6, OCH_3), 5.47−5.75 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.6 Hz, H5-arom), 7.68 (dd, 1H, ^4J = 2.2 Hz, ^3J = 8.6 Hz, H6-arom), 7.78 (d, 1H, ^4J = 2.1 Hz, H2-arom).

Method B. BuLi-Mediated Synthesis of γ-Keto Acids (as for 1b). *cis*-2-(3-Chlorobenzoyl)cyclohexanecarboxylic Acid (1b). 3-Bromochlorobenzene (14.4 g, 75.2 mmol) was dissolved in THF (200 mL) and cooled with an ethanol/nitrogen(l) bath to −90 °C. BuLi (1.6 M in hexane, 51.5 mL, 82.4 mmol) was added dropwise while the temperature was kept below −80 °C. After the last addition, the mixture was stirred for another 15 min. Under a nitrogen atmosphere the reaction mixture was then quickly added to a cooled solution (−90 °C) of *cis*-1,2-cyclohexanedicarboxylic anhydride (13.8 g, 89.5 mmol) in THF (200 mL). After 2 h at −80 °C, the reaction was quenched with solid ammonium chloride and the mixture was allowed to warm slowly to room temperature. Water (300 mL) was added, and after separation of the two layers, the aqueous layer was extracted with EtOAc (200 mL). The combined organic extract was washed with water (300 mL) and brine (2 × 300 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The title compound was crystallized from diethyl ether as a white solid: yield 9.60 g (48%); mp 117−121 °C; ^{1}H NMR ($CDCl_3$) δ 0.95−2.30 (m, 8H, CH_2), 2.49−2.75 (m, 1H, H1), 3.61−3.90 (m, 1H, H2), 7.11−7.85 (m, 4H, H-arom).

***cis*-2-(4-Cyclopentyloxy-3-methoxybenzoyl)cyclohexanecarboxylic acid (1h)** was prepared in a similar way as described for **1b** using bromide **4** (16.3 g, 60.1 mmol), BuLi (41.0 mL, 65.6 mmol), and *cis*-1,2-cyclohexanedicarboxylic anhydride (11.1 g, 72.0 mmol). After workup, the remainder was dissolved in CH_2Cl_2 and purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 1:1. The title compound was crystallized from ethyl acetate as a white solid: yield 5.97 g (29%); mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−2.41 (m, 16H, CH_2), 2.62−2.78 (m, 1H, H1), 3.82−4.02 (m, 4H, H2, OCH_3), 4.78−4.92 (m, 1H, OCH), 6.87 (d, 1H, ^3J = 8.1 Hz, H5-arom), 7.43−7.54 (m, 2H, H2-arom, H6-arom).

***cis*-2-(3-Cyclopentyloxy-4-methoxybenzoyl)cyclohexanecarboxylic acid (1i)** was prepared in a similar way as described for **1b** using bromide **6** (16.3 g, 60.1 mmol), BuLi (41.0 mL, 65.6 mmol), and *cis*-1,2-cyclohexanedicarboxylic anhydride (11.1 g, 72.0 mmol). After workup, the residue was dissolved in CH_2Cl_2 and purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 7:13. The title compound was crystallized from petroleum ether (60−80)/ethyl acetate as a white solid: yield 10.1 g (49%); mp 120−121 °C; ^{1}H NMR ($CDCl_3$) δ 1.24−2.41 (m, 16H, CH_2), 2.63−2.78 (m, 1H, H1), 3.81−4.01 (m, 4H, H2, OCH_3), 4.77−4.90 (m, 1H, OCH), 6.86 (d, 1H, ^3J = 8.1 Hz, H5-arom), 7.42−7.57 (m, 2H, H2-arom, H6-arom).

***cis*-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentane-4-carbonyl)cyclohexanecarboxylic acid (1j)** was prepared in a similar way as described for **1b** using bromide **10** (20.3 g, 71.7 mmol), BuLi (49.0 mL, 78.4 mmol), and *cis*-1,2-cyclohexanedicarboxylic anhydride (13.3 g, 86.3 mmol). After workup, the remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 1:1. The title compound was crystallized from petroleum ether (60−80)/ethyl acetate: yield 17.9 g (70%); mp 161−163 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.38 (m, 16H, CH_2), 2.62−2.80 (quintet, 1H, $CHCO_2H$), 3.49 (AB, 2H, CH_2-benzofuran), 3.72−3.99 (m, 4H, OCH_3, CHC=O), 6.75 (d, 1H, ^3J = 8.6 Hz, H-arom), 7.30 (d, 1H, ^3J = 8.6 Hz, H-arom).

Method C. Synthesis of γ-Keto Acids Using Grignard Conditions (as for 1c). *cis*-2-(3-Methoxybenzoyl)cyclohexanecarboxylic Acid (1c). A solution of 3-bromoanisole (9.34 g, 49.9 mmol) in THF (30 mL) was added slowly to a suspension of magnesium (1.45 g, 59.6 mmol) in THF (120 mL). Subsequently, the mixture was refluxed for 4 h and stirred at room temperature for an additional 18 h. The reaction mixture was then added dropwise to an ice-cooled solution of *cis*-1,2-cyclohexanedicarboxylic anhydride (8.00 g, 51.9 mmol) in THF (100 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 combined organic extract was washed with water and subsequently extracted with 1 N NaOH. The combined basic extracts were acidified with concentrated HCl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and filtered over silica gel to remove the dicarboxylic acid formed during workup. The product was recrystallized from ethyl acetate: yield 4.00 g (31%); mp 128−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−2.40 (m, 8H, CH_2), 2.66−2.80 (dq, 1H, H1), 3.77−4.02 (m, 4H, H2, OCH_3), 7.03−7.15 (m, 1H, H-arom), 7.29−7.51 (m, 3H, H-arom).

***cis*-2-(Benzo[1,3]dioxole-5-carbonyl)cyclohexanecarboxylic acid (1f)** was synthesized analogously to the preparation of **1c** using 4-bromo-1,2-(methylenedioxy)benzene (10.0 g, 49.7 mmol), Mg (1.34 g, 55.1 mmol), and *cis*-1,2-cyclohexanedicarboxylic anhydride (9.00 g, 58.4 mmol). The title compound was crystallized from ethyl acetate: yield 7.98 g (58%); mp 152−154 °C (mp 168−169 °C[41]); ^{1}H NMR ($CDCl_3$) δ 1.12−2.35 (m, 7H, 3 × CH_2, C*H*′H), 2.58−2.93 (m, 2H, H1, CH′*H*), 3.76−3.92 (m, 1H, H2), 6.04 (s, 2H, OCH_2O), 6.85 (d, 1H, ^3J = 8.0 Hz, H-arom), 7.34 (d, 1H, ^4J = 4.5 Hz, H-arom), 7.49 (d, 1H, ^3J = 8.2 Hz, H-arom).

***cis*-6-(3-Cyclopentyloxy-4-methoxybenzoyl)cyclohex-3-enecarboxylic acid (1m)** was synthesized analogously to the preparation of **1c** using bromide **6** (58.4 g, 215 mmol), Mg (5.76 g, 237 mmol), and *cis*-1,2,3,6-tetrahydrophthalic anhydride (36.0 g, 237 mmol). The crude product was crystallized from petroleum ether (60−80)/ethyl acetate and was recrystallized from diethyl ether to yield the title compound as a white solid: yield 36.6 g (49%); mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 1.46−2.11 (m, 7H, H-cyclohexene, H-cyclopentyl), 2.26−2.71 (m, 4H, H-cyclopentyl), 2.72−3.15 (m, 2H, H-cyclohexene, H1), 3.80−4.03 (m, 4H, H6, OCH_3), 4.75−4.90 (m, 1H, OCH), 5.56−5.86 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.40−7.57 (m, 2H, H2-arom, H6-arom).

***cis*-6-(2,3-Dihydro-2,2-dimethyl-7-methoxybenzofuran-4-carbonyl)cyclohex-3-enecarboxylic acid (1n)** was synthesized analogously to the preparation of **1c** using bromide **14** (25.7 g, 99.9 mmol), Mg (2.92 g, 120 mmol), and *cis*-1,2,3,6-tetrahydrophthalic anhydride (16.7 g, 110 mmol). The title compound was crystallized from diethyl ether: yield 15.2 g (46%); mp 127−129 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 6H, CH_3), 2.32−2.60 (m, 3H, H-cyclohexene), 2.69−2.91 (m, 1H, H-cyclohexene), 2.93−3.09 (m, 1H, H1), 3.34 (AB, 2H, CH_2), 3.84−4.00 (m, 4H, OCH_3, H6), 5.59−5.86 (m, 2H, HC=CH), 6.77 (d, 1H, ^3J = 8.6 Hz, H-arom), 7.33 (d, 1H, ^3J = 8.6 Hz, H-arom).

***cis*-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentane-4-carbonyl)-1,2,3,6-tetrahydrobenzoic acid (1o)** was synthesized analogously to the preparation of **1c** using bromide **10** (35.0 g, 124 mmol), Mg (3.48 g, 143 mmol), and *cis*-1,2,3,6-tetrahydrophthalic anhydride (18.8 g, 124 mmol). After workup, the remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate/acetic acid 3:1:0.1. The title compound was crystallized from diethyl ether: yield 22.7 g (52%); mp 132−135 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−2.22 (m, 8H, CH_2-cyclopentane), 2.31−2.62 (m, 3H, H-cyclohexene), 2.70−2.94 (m, 1H, H-cyclohexene), 2.95−3.09 (m, 1H, H1), 3.32−3.64 (AB, 2H, CH_2-benzofuran), 3.85−4.04 (m, 4H, H6, OCH_3), 5.58−5.83 (m, 2H, HC=CH), 6.79 (d, 1H, ^3J = 8.6 Hz, H5-arom), 7.32 (d, 1H, ^3J = 8.6 Hz, H6-arom).

General Procedure for Condensation of γ-Keto Acids with Hydrazine. A mixture of γ-keto acid (7.5−60 mmol) and hydrazine monohydrate (3 equiv) in ethanol (40−300 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 ethanol to yield the pure product. Otherwise, the bulk of ethanol was removed in vacuo and the residue was dissolved in ethyl acetate. The solution was washed with water, 1 N HCl, and aqueous $NaHCO_3$ 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. Experimental data for the separate compounds are listed below.

***cis*-4-Phenyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2a)** was prepared from γ-keto acid **1a** (4.00 g, 17.2 mmol) according to the general procedure and crystallized from methanol: yield 3.54 g (90%); mp 170−172 °C (mp 173−174 °C[42]); ^{1}H NMR ($CDCl_3$) δ 1.22−1.93 (m, 7H, H5, H6, H7, H8), 2.45−2.69 (m, 1H, H8′), 2.70−2.84 (m, 1H, H8a), 3.07−3.26 (m, 1H, H4a), 7.32−7.50 (m, 3H, H3-arom, H4-arom, H5-arom), 7.69−7.82 (m, 2H, H2-arom, H6-arom), 8.86 (bs, 1H, NH).

***cis*-4-(3-Chlorophenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2b)** was prepared from γ-keto acid **1b** (7.86 g, 29.5 mmol) according to the general procedure. The title compound crystallized upon concentration of the reaction mixture: yield 3.18 g (41%); mp 161−162 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−1.98 (m, 7H, H5, H6, H7, H8), 2.42−2.69 (m, 1H, H8′), 2.70−2.85 (m, 1H, H8a), 3.00−3.21 (m, 1H, H4a), 7.29−7.46 (m, 2H, H-arom), 7.56−7.70 (m, 1H, H-arom), 7.76 (s, 1H, H2-arom), 8.71 (bs, 1H, NH).

***cis*-4-(3-Methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2c)** was prepared from γ-keto acid **1c** (4.00 g, 15.2 mmol) according to the general procedure and crystallized from methanol: yield 2.46 g (63%); mp 136−137 °C; ^{1}H NMR ($CDCl_3$) δ 1.23−1.95 (m, 7H, H5, H6, H7, H8), 2.48−2.69 (m, 1H, H8′), 2.71−2.84 (m, 1H, H8a), 3.04−3.22 (m, 1H, H4a), 3.85 (s, 3H, OCH_3), 6.90−7.02 (m, 1H, H-arom), 7.26−7.41 (m, 3H, H-arom), 8.50 (bs, 1H, NH).

***cis*-4-(4-Methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2d)** was prepared from γ-keto acid **1d** (2.00 g, 7.62 mmol) according to the general procedure and crystallized from methanol: yield 1.69 g (86%); mp 158−159 °C; ^{1}H NMR ($CDCl_3$) δ 1.29−1.95 (m, 7H, H5, H6, H7, H8), 2.45−2.69 (m, 1H, H8′), 2.70−2.83 (m, 1H, H8a), 3.05−3.22 (m, 1H, H4a), 3.85 (s, 3H, OCH_3), 6.89−7.00 (m, 2H, H3-arom, H5-arom), 7.66−7.79 (m, 2H, H2-arom, H6-arom), 8.64 (bs, 1H, NH).

***cis*-4-Benzo[1,3]dioxol-5-yl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2f)** was prepared from γ-keto acid **1f** (7.48 g, 27.1 mmol) according to the general procedure. The product crystallized upon concentration of the reaction mixture in vacuo: yield 6.04 g (82%); mp 140−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−1.91 (m, 7H, H5, H6, H7, H8), 2.48−2.63 (m, 1H, H8′), 2.68−2.80 (m, 1H, H8a), 3.02−3.18 (m, 1H, H4a), 6.01 (s, 2H, OCH_2O), 6.83 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.20 (dd, 1H, ^4J = 1.6 Hz, ^3J = 8.2 Hz, H6-arom), 7.33 (d, 1H, ^4J = 1.6 Hz, H2-arom), 8.50 (bs, 1H, NH).

***cis*-4-(3,4-Diethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2g)** was prepared from γ-keto acid **1g** (4.01 g, 12.5 mmol) according to the general procedure, purified by flash column chromatography using CH_2Cl_2, and crystallized from ethyl acetate: yield 3.55 g (90%); mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 1.27−1.92 (m, 13H, H5, H6, H7, H8, CH_3), 2.43−2.69 (m, 1H, H8′), 2.69−2.82 (m, 1H, H8a), 3.02−3.21 (m, 1H, H4a), 4.04−4.24 (m, 4H, OCH_2), 6.86 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.19 (dd, 1H, ^4J = 2.0, ^3J = 8.4 Hz, H6-arom), 7.44 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.77 (bs, 1H, NH).

***cis*-4-(4-Cyclopentyloxy-3-methoxyphenyl)-4a,5,6,7,8,-8a-hexahydro-2*H*-phthalazin-1-one (2h)** was prepared from γ-keto acid **1h** (3.00 g, 8.66 mmol) according to the general

procedure: yield 2.63 g (89%); mp 152−153 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.12 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentyl), 2.43−2.67 (m, 1H, H8′), 2.69−2.81 (m, 1H, H8a), 3.03−3.21 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 4.73−4.90 (m, 1H, OCH), 6.86 (d, 1H, ^3J = 8.5 Hz, H6-arom), 7.18 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, H5-arom), 7.43 (d, 1H, ^4J = 2.1 Hz, H2-arom), 8.54 (bs, 1H, NH).

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,6,7,8,-8a-hexahydro-2*H*-phthalazin-1-one (2i)** was prepared from γ-keto acid **1i** (2.99 g, 8.63 mmol) according to the general procedure. When the reaction mixture cooled to room temperature, compound **2i** (2.42 g, 82%) crystallized. The filtrate was concentrated to yield another 0.43 g (15%) of **2i** as a white solid. The combined solids were recrystallized from ethanol: final yield 92%; mp 175−176 °C; ^{1}H NMR ($CDCl_3$) δ 1.21−2.13 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentyl), 2.45−2.68 (m, 1H, H8′), 2.69−2.82 (m, 1H, H8a), 3.02−3.20 (m, 1H, H4a), 3.88 (s, 3H, OCH_3), 4.77−4.93 (m, 1H, OCH), 6.85 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.20 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, H6-arom), 7.43 (d, 1H, ^4J = 2.0 Hz, H2-arom), 8.58 (bs, 1H, NH).

***cis*-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (2j)** was prepared from γ-keto acid **1j** (5.02 g, 14.0 mmol) according to the general procedure and crystallized from ethanol: yield 4.50 g (91%); mp 185−186 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−2.29 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentane), 2.42−2.68 (m, 1H, H8a), 2.69−2.83 (m, 1H, H8′), 3.02−3.21 (m, 1H, H4a), 3.43 (s, 1H, CH_2-benzofuran), 3.90 (s, 3H, OCH_3), 6.76 (d, 1H, ^3J = 8.5 Hz, H-arom), 7.00 (d, 1H, ^3J = 8.6 Hz, H-arom), 8.46 (bs, 1H, NH).

***cis*-4-(3-Chloro-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (2k)** was prepared from γ-keto acid **1k** (15.1 g, 51.2 mmol) according to the general procedure: yield 12.6 g (84%); mp 198−204 °C; ^{1}H NMR ($CDCl_3$) δ 2.07−2.34 (m, 3H, H5, H8), 2.78−3.09 (m, 2H, H8a, H8′), 3.26−3.45 (m, 1H, H4a), 3.95 (s, 3H, OCH_3), 5.61−5.87 (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), 7.83 (d, 1H, ^4J = 2.2 Hz, H2-arom).

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (2m)** was prepared from γ-keto acid **1m** (20.0 g, 58.1 mmol) according to the general procedure: yield 11.7 g (59%); mp 166−168 °C; ^{1}H NMR ($CDCl_3$) δ 1.50−2.39 (m, 11H, H5, H8, CH_2-cyclopentyl), 2.84 (t, 1H, ^3J = 6.0 Hz, H8a), 2.90−3.10 (m, 1H, H8′), 3.29−3.48 (m, 1H, H4a), 3.89 (s, 3H, OCH_3), 4.79−4.91 (m, 1H, OCH), 5.63−5.88 (m, 2H, HC=CH), 6.86 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.22 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 Hz, H6-arom), 7.45 (d, 1H, ^4J = 2.1 Hz, H2-arom), 8.59 (bs, 1H, NH).

***cis*-4-(7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4-yl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (2n)** was prepared from γ-keto acid **1n** (10.0 g, 30.3 mmol) according to the general procedure and crystallized from ethyl acetate/diethyl ether/petroleum ether (60−80); yield 7.31 g (74%); mp 243 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.10−2.37 (m, 3H, H5, H8), 2.84 (t, 1H, ^3J = 5.6, H8a), 2.90−3.08 (m, 1H, H8′), 3.26−3.48 (m, 3H, CH_2-benzofuran, H4a), 3.91 (s, 3H, OCH_3), 5.64−5.88 (m, 2H, HC=CH), 6.77 (d, 1H, ^3J = 8.6 Hz, H-arom), 7.04 (d, 1H, ^3J = 8.6 Hz, H-arom), 8.69 (bs, 1H, NH).

***cis*-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (2o)** was prepared from γ-keto acid **1o** (7.99 g, 22.4 mmol) according to the general procedure and crystallized from ethyl acetate: yield 6.87 g (87%); mp 193−194 °C; ^{1}H NMR ($CDCl_3$) δ 1.62−2.32 (m, 11H, H5, H8, CH_2-cyclopentane), 2.78−3.06 (m, 2H, H8′, H8a), 3.28−3.50 (m, 3H, H4a, CH_2-benzofuran), 3.90 (s, 3H, OCH_3), 5.63−5.87 (m, 2H, HC=CH), 6.77 (d, 1H, ^3J = 8.6 Hz, H5-arom), 7.04 (d, 1H, ^3J = 8.6 Hz, H-arom), 8.83 (bs, 1H, NH).

General Procedure for the *N*-Alkylation of Phthalazinones. Sodium hydride (60% dispersion in mineral oil, 1.1 equiv) was added to a suspension of the selected phthalazinone (2.8−75 mmol) in DMF (10−750 mL). After the reaction mixture had been stirred for 3 h, the preferred alkyl halide (1.1 equiv) was added and the reaction 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. Experimental data for the separate compounds are listed below.

***cis*-2-Benzyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3a)** was synthesized following the general procedure using **2a** (2.00 g, 8.76 mmol) and benzyl chloride as the alkylating agent and crystallized from methanol: yield 1.28 g (46%); mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−1.88 (m, 7H, H5, H6, H7, H8), 2.43−2.70 (m, 1H, H8′), 2.70−2.84 (m, 1H, H8a), 3.02−3.22 (m, 1H, H4a), 5.05 (AB, 2H, CH_2−Bn), 7.13−7.55 (m, 8H, H−Ph, H−Bn), 7.66−7.88 (m, 2H, H−Ph). Anal. Calcd ($C_{21}H_{22}N_2O$): C, H, N.

***cis*-2-Benzyl-4-(3-chlorophenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3b)** was synthesized following the general procedure using **2b** (1.50 g, 5.71 mmol) and benzyl chloride as the alkylating agent, purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 3:1, and crystallized from petroleum ether (60−80) and methanol: yield 1.30 g (65%); mp 67−68 °C; ^{1}H NMR ($CDCl_3$) δ 1.19−1.95 (m, 7H, H5, H6, H7, H8), 2.43−2.69 (m, 1H, H8′), 2.69−2.81 (m, 1H, H8a), 2.95−3.19 (m, 1H, H4a), 4.90−5.17 (AB, 2H, CH_2−Bn), 7.18−7.44 (m, 7H, H4-arom, H5-arom, H−Bn), 7.53−7.69 (m, 1H, H6-arom), 7.69−7.80 (m, 1H, H2-arom). Anal. Calcd ($C_{21}H_{21}N_2OCl$): C, H, N.

***cis*-2-Benzyl-4-(3-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3c)** was synthesized following the general procedure using **2c** (1.89 g, 7.32 mmol) and benzyl chloride as the alkylating agent, purified by flash column chromatography using CH_2Cl_2, and crystallized from petroleum ether (60−80) at 5 °C: yield 1.63 g (64%); mp 59−60 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−1.85 (m, 7H, H5, H6, H7, H8), 2.47−2.68 (m, 1H, H8′), 2.68−2.81 (m, 1H, H8a), 2.99−3.18 (m, 1H, H4a), 3.83 (s, 3H, OCH_3), 5.02 (AB, 2H, CH_2−Bn), 6.84−7.00 (m, 1H, H-arom), 7.16−7.46 (m, 8H, H-arom). Anal. Calcd ($C_{22}H_{24}N_2O_2$): C, H, N.

***cis*-2-Benzyl-4-(4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3d)** was synthesized following the general procedure using **2d** (2.00 g, 7.74 mmol) and benzyl chloride as the alkylating agent and crystallized from diethyl ether: yield 1.62 g (60%); mp 102−104 °C; ^{1}H NMR ($CDCl_3$) δ 1.16−1.92 (m, 7H, H5, H6, H7, H8), 2.44−2.68 (m, 1H, H8′), 2.68−2.79 (m, 1H, H8a), 2.96−3.18 (m, 1H, H4a), 3.83 (s, 3H, OCH_3), 5.06 (AB, 2H, CH_2−Bn), 6.82−6.98 (m, 2H, H3-arom, H5-arom), 7.19−7.47 (m, 5H, H−Bn), 7.63−7.79 (m, 2H, H2-arom, H6-arom). Anal. Calcd ($C_{22}H_{24}N_2O_2$): C, H, N.

***cis*-4-Benzo[1,3]dioxol-5-yl-2-benzyl-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3f)** was synthesized following the general procedure using **2f** (1.93 g, 7.09 mmol) and benzyl chloride as the alkylating agent, purified by flash column chromatography using CH_2Cl_2, and crystallized from methanol: yield 1.17 g (46%); mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 1.26−1.81 (m, 7H, H5, H6, H7, H8), 2.48−2.65 (m, 1H, H8′), 2.67−2.80 (m, 1H, H8a), 2.95−3.13 (m, 1H, H4a), 5.02 (AB, 2H, CH_2−Bn), 5.99 (s, 2H, OCH_2O), 6.83 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.17 (dd, 1H, ^3J = 8.1 Hz, ^4J = 1.8 Hz, H6-arom), 7.24−7.48 (m, 6H, H2-arom, H−Bn). Anal. Calcd ($C_{22}H_{22}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-(3,4-diethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3g)** was synthesized following the general procedure using **2g** (2.01 g, 6.35 mmol) and benzyl chloride as the alkylating agent and crystallized from petroleum ether (60−80): yield 1.49 g (58%); mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.15−1.98 (m, 13H, H5, H6, H7, H8, CH_3), 2.45−2.79 (m, 2H, H8′, H8a), 2.98−3.18 (m, 1H, H4a), 4.12 (q, 4H, ^3J = 7.0 Hz, OCH_2), 5.03 (AB, 2H, CH_2−Bn), 6.84 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.19 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.22−7.49 (m, 6H, H2-arom, H−Bn). Anal. Calcd ($C_{25}H_{30}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-(4-cyclopentyloxy-3-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3h)** was synthesized following the general procedure using **2h** (1.00 g, 2.92 mmol) and benzyl chloride as the alkylating agent. The title compound was crystallized from petroleum ether (60−80)/diethyl ether as a white solid: yield 0.28 g (22%). After 1 week at 5 °C, another 0.61 g (48%) of compound **3h** had crystallized from the filtrate: total yield 70%; mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 1.20−2.11 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentyl), 2.48−2.65 (m, 1H, H8′), 2.65−2.81 (m, 1H, H8a), 2.99−3.18 (m, 1H, H4a), 3.87 (s, 3H, OCH_3), 4.74−4.88 (m, 1H, OCH), 5.04 (AB, 2H, CH_2−Bn), 6.84 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.18 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, H6-arom), 7.24−7.49 (m, 6H, H2-arom, H−Bn). Anal. Calcd ($C_{27}H_{32}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3i)** was synthesized following the general procedure using **2i** (1.00 g, 2.92 mmol) and benzyl chloride as the alkylating agent. After workup, the remainder was dissolved in CH_2Cl_2 and purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was crystallized from petroleum ether (60−80)/ethyl acetate as a white solid: yield 0.43 g (34%); mp 91−92 °C; ^{1}H NMR ($CDCl_3$) δ 1.19−2.16 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentyl), 2.49−2.67 (m, 1H, H8′), 2.67−2.81 (m, 1H, H8a), 2.98−3.18 (m, 1H, H4a), 3.87 (s, 3H, OCH_3), 4.72−4.87 (m, 1H, OCH), 5.03 (AB, 2H, CH_2−Bn), 6.83 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.18 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.1 Hz, H6-arom), 7.23−7.49 (m, 6H, H2-arom, H−Bn). Anal. Calcd ($C_{27}H_{32}N_2O_3$): C, H, N.

***cis*-2-Benzyl-4-{spiro[cyclopentane-1′,2(3H)-7-methoxybenzofurane]-4-yl}-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one (3j)** was synthesized following the general procedure using **2j** (1.00 g, 2.82 mmol) and benzyl chloride as the alkylating agent. After workup, the residue was dissolved in CH_2Cl_2 and purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was crystallized from petroleum ether (60−80)/ethyl acetate: yield 0.90 g (72%); mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−2.18 (m, 15H, H5, H6, H7, H8, CH_2-cyclopentane), 2.50−2.65 (m, 1H, H8′), 2.69−2.82 (m, 1H, H8a), 2.92−3.21 (m, 3H, H4a, CH_2-benzofuran), 3.88 (s, 3H, OCH_3), 5.02 (AB, 2H, CH_2−Bn), 6.73 (d, 1H, ^3J = 8.5 Hz, H5-arom), 6.96 (d, 1H, ^3J = 8.6 Hz, H6-arom), 7.14−7.41 (m, 5H, H−Bn). Anal. Calcd ($C_{28}H_{32}N_2O_3$): C, H, N.

***cis*-4-(3-Chloro-4-methoxyphenyl)-2-cycloheptyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (3k)** was synthesized following the general procedure using **2k** (2.00 g, 6.88 mmol) and cycloheptyl bromide as the alkylating agent: yield 1.73 g (65%); mp 138−141 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.36 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.72 (t, 1H, ^3J = 5.7 Hz, H8a), 2.90−3.11 (m, 1H, H8′), 3.18−3.35 (m, 1H, H4a), 3.95 (s, 3H, OCH_3), 4.70−4.92 (m, 1H, NCH), 5.60−5.88 (m, 2H, HC=CH), 6.96 (d, 1H, ^3J = 8.7 Hz, H5-arom), 7.67 (dd, 1H, ^4J = 2.2 Hz, ^3J = 8.7 Hz, H6-arom), 7.85 (d, 1H, ^4J = 2.2 Hz, H2-arom). Anal. Calcd ($C_{22}H_{27}N_2O_2Cl$): C, H, N.

***cis*-2-Cycloheptyl-4-(3,4-dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (3l)** was synthesized following the general procedure using 4-(3,4-dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one[26] (2.00 g, 6.98 mmol) and cycloheptyl bromide as the alkylating agent, purified by flash column chromatography, and crystallized from diethyl ether/petroleum ether (60−80); yield 1.74 g (65%); mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 1.41−2.32 (m, 15H, 6 × CH_2-cycloheptyl, H5, H8), 2.68−2.81 (m, 1H, H8a), 2.91−3.13 (m, 1H, H8′), 3.21−3.40 (m, 1H, H4a), 3.93 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.74−4.95 (m, 1H, NCH), 5.60−5.89 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.27 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.53 (d, 1H, ^4J = 2.0 Hz, H-arom). Anal. Calcd ($C_{23}H_{30}N_2O_3$): C, H, N.

***cis*-2-Cycloheptyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (3m)** was synthesized following the general procedure using **2m** (25.0 g, 73.4 mmol) and cycloheptyl bromide as the alkylating agent and crystallized from petroleum ether (60−80): yield 18.0 g (56%); mp 106 °C; ^{1}H NMR ($CDCl_3$) δ 1.29−2.31 (m, 23H, CH_2-cycloheptyl, CH_2-cyclopentyl, H5, H8), 2.72 (t, 1H, ^3J = 5.7 Hz, H8a), 2.90−3.10 (m, 1H, H8′), 3.19−3.38 (m, 1H, H4a), 3.89 (s, 3H, OCH_3), 4.72−4.97 (m, 2H, NCH, OCH), 5.60−5.88 (m, 2H, HC=CH), 6.86 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.24 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.1 Hz, H6-arom), 7.54 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{27}H_{36}N_2O_3$): C, H, N.

***cis*-2-Cycloheptyl-4-(2,3-dihydro-2,2-dimethyl-7-methoxybenzofuran-4-yl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (3n)** was synthesized following the general procedure using **2n** (2.00 g, 6.13 mmol) and cycloheptyl bromide as the alkylating agent, purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 5:1, and crystallized from petroleum ether (60−80)/ethyl acetate: yield 0.60 g (23%); mp 114−115 °C; ^{1}H NMR ($CDCl_3$) δ 1.37−2.32 (m, 21H, CH_2-cycloheptyl, H5, H8, CH_3), 2.68−2.81 (m, 1H, H8a), 2.90−3.10 (m, 1H, H8′), 3.20−3.48 (m, 3H, CH_2, H4a), 3.91 (s, 3H, OCH_3), 4.72−4.92 (m, 1H, NCH), 5.60−5.87 (m, 2H, HC=CH), 6.78 (d, 1H, ^3J = 8.5 Hz, H-arom), 7.04 (d, 1H, ^3J = 8.6 Hz, H-arom). Anal. Calcd ($C_{26}H_{34}N_2O_3$): C, H, N.

***cis*-2-Cycloheptyl-4-(2,3-dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (3o)** was synthesized following the general procedure using **2o** (1.00 g, 2.81 mmol) and cycloheptyl bromide as the alkylating agent. Purification was by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was crystallized from diethyl ether/petroleum ether (60−80): yield 0.81 g (64%); mp 135 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.40 (m, 23H, H5, H8, CH_2-cyclopentane, CH_2-cycloheptyl), 2.68−2.82 (m, 1H, H8a), 2.90−3.12 (m, 1H, H8′), 3.20−3.40 (m, 1H, H4a), 3.42−3.64 (m, 2H, CH_2-benzofuran), 3.91 (s, 3H, OCH_3), 4.72−4.95 (m, 1H, NCH), 5.60−5.89 (m, 2H, HC=CH), 6.77 (d, 1H, ^3J = 8.6 Hz, H6-arom), 7.03 (d, 1H, ^3J = 8.6 Hz, H5-arom). Anal. Calcd ($C_{28}H_{36}N_2O_3$): C, H, N.

4-Bromo-1-cyclopentyloxy-2-methoxybenzene (4). A mixture of 4-bromo-2-methoxyphenol (15.0 g, 73.9 mmol), anhydrous K_2CO_3 (20.4 g, 148 mmol), and cyclopentyl bromide (19.1 g, 128 mmol) in DMF (100 mL) was stirred at 65 °C for 10 h. After cooling to room temperature, the reaction mixture was diluted with diethyl ether, and the solution was washed with 1 M NaOH and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The title compound was obtained as a yellow oil: yield 19.5 g (97%); ^{1}H NMR ($CDCl_3$) δ 1.50−2.03 (m, 8H, CH_2), 3.83 (s, 3H, OCH_3), 4.68−4.80 (m, 1H, OCH), 6.73 (d, 1H, ^3J = 8.2 Hz, H6-arom), 6.93−7.07 (m, 2H, H3-arom, H5-arom).

5-Bromo-2-methoxyphenol (5). A solution of 5-bromo-2-methoxybenzaldehyde (50.0 g, 233 mmol) in CH_2Cl_2 (150 mL) was cooled with an ice bath to 0 °C, and subsequently 3-chloroperoxybenzoic acid (70−75% purity) (68.1 g, 276 mmol) in CH_2Cl_2 (500 mL) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred for 72 h. The white solid was filtered off, and the filtrate was stirred for 2 h with 2 M $Na_2S_2O_3$ (200 mL). The organic layer was concentrated in vacuo, and the remainder was dissolved in diethyl ether and washed with 1 M Na_2SO_3 and a half saturated $NaHCO_3$ solution. The organic phase was extracted with 2 M NaOH. The combined basic extract was acidified (pH 3−4) with concentrated HCl and extracted with diethyl ether. The combined organic extract was dried over $MgSO_4$, and the solvent was removed under reduced pressure to give the title compound as a pale brown solid: yield 43.5 g (92%); mp 61−64 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OCH_3), 5.67 (s, 1H, OH), 6.70 (d, 1H, ^3J = 8.6 Hz, H3-arom), 6.96 (dd, 1H, ^4J = 2.3 Hz, ^3J = 8.6 Hz, H4-arom), 7.06 (d, 1H, ^4J = 2.3 Hz, H6-arom).

4-Bromo-2-cyclopentyloxy-1-methoxybenzene (6) was prepared analogously to the preparation of **4** except using phenol **5** (12.4 g, 61.1 mmol). After workup, the residue was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 7:3, yielding bromide **6** as a yellow oil: yield 16.3 g (99%); ^{1}H NMR (DMSO-d_6) δ 1.50−2.16 (m,

8H, CH_2), 3.82 (s, 3H, OCH_3), 4.68−4.81 (m, 1H, OCH), 6.72 (d, 1H, ^3J = 8.7 Hz, H6-arom), 6.94−7.08 (m, 2H, H3-arom, H5-arom).

2-(5-Bromo-2-methoxyphenoxy)cyclopentanone (7). A mixture of phenol **5** (25.2 g, 124 mmol), 2-chlorocyclopentanone (17.6 g, 148 mmol), and K_2CO_3 (34.3 g, 248 mmol) in DMF (250 mL) was stirred for 2.5 h at 60 °C. The reaction mixture was concentrated in vacuo, and the remainder was diluted with diethyl ether and washed with 1 M NaOH and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The remaining oil was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 7:3 to yield the title compound, which crystallized after removal of the solvent under reduced pressure: yield 24.4 g (69%); ^{1}H NMR ($CDCl_3$) δ 1.78−2.60 (m, 6H, CH_2), 3.83 (s, 3H, OCH_3), 4.52−4.68 (m, 1H, OCH), 6.75 (d, 1H, ^3J = 8.8 Hz, H3-arom), 7.02−7.17 (m, 2H, H4-arom, H6-arom).

3-Bromo-2-cyclopent-1-enylmethyl-6-methoxyphenol (9). Potassium *tert*-butoxide (10.6 g, 94.5 mmol) was added slowly to a solution of (methyl)triphenylphosphonium bromide (33.7 g, 94.3 mmol) in THF (250 mL). After the reaction mixture was stirred for 2 h, a solution of ketone **7** (22.4 g, 78.6 mmol) in THF (200 mL) was added dropwise in 45 min. The resulting mixture was stirred for another hour, diluted with diethyl ether, and washed with water. The organic phase was reduced in volume under reduced pressure, dried over $MgSO_4$, and then fully concentrated in vacuo. Next, the residue, containing compound **8**, was heated at 180 °C for 45 min. The remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 8:2 to give the title compound as a yellow oil: yield 20.3 g (91%); ^{1}H NMR($CDCl_3$) δ 1.78−1.97 (m, 2H, CH_2), 2.20−2.41 (m, 4H, CH_2), 3.55 (AB, 2H, CH_2−Ph), 3.87 (s, 3H, OCH_3), 5.13−5.24 (m, 1H, HC=C), 5.79 (s, 1H, OH), 6.63 (d, 1H, ^3J = 8.7 Hz, H-arom), 7.06 (d, 1H, ^3J = 8.7 Hz, H-arom).

4-Bromo-2,3-dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentane (10). A mixture of compound **9** (20.3 g, 71.7 mmol) and Amberlyst 15 ion-exchange resin (18.8 g) in toluene (250 mL) was heated at 80 °C for 3 h. Subsequently, the Amberlyst 15 was filtered off and the filtrate concentrated in vacuo to give pure **10** as a yellow oil: yield 19.3 g (95%); ^{1}H NMR ($CDCl_3$) δ 1.62−2.31 (m, 8H, CH_2), 3.19 (s, 2H, CH_2-benzofuran), 3.84 (s, 3H, OCH_3), 6.63 (d, 1H, ^3J = 8.6 Hz, H-arom), 6.90 (d, 1H, ^3J = 8.6 Hz, H-arom).

1-(5-Bromo-2-methoxyphenoxy)propan-2-one (11) was synthesized analogously to the preparation of **7** using phenol **5** (50.0 g, 246 mmol), chloro-2-propanone (30.0 g, 324 mmol), and K_2CO_3 (48.0 g, 347 mmol). The mixture was heated for 6 h. After workup, the remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 3:1, yielding the title compound as a yellow oil: yield 38.9 g (61%); ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, CH_3C=O), 3.86 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2), 6.78 (d, 1H, ^3J = 8.6 Hz, H5-arom), 6.88 (d, 1H, ^4J = 2.3 Hz, H2-arom), 7.09 (dd, 1H, ^4J = 2.3 Hz, ^3J = 8.6 Hz, H6-arom).

3-Bromo-6-methoxy-2-(2-methylallyl)phenol (13) was synthesized analogously to the preparation of **9** except using ketone **11** (38.0 g, 148 mmol). After workup, the remaining oil was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 10:1. The title compound was obtained as a yellow oil: yield 25.5 g (67%); NMR spectrum not available.

4-Bromo-2,3-dihydro-2,2-dimethyl-7-methoxybenzofuran (14) was synthesized analogously to the preparation of **10** except using compound **13** (25.0 g, 97.2 mmol). After workup, the product was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 30:1. The title compound was obtained as a yellow oil: yield 16.8 (67%); ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 6H, CH_3), 3.04 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 6.63 (d, 1H, ^3J = 8.6 Hz, H-arom), 6.91 (d, 1H, ^3J = 8.6 Hz, H-arom).

***cis*-2-Cycloheptyl-4-(3-hydroxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (15).** A mixture of compound **3m** (20.0 g, 45.8 mmol) and *p*-toluenesulfonic acid monohydrate (10.0 g, 52.6 mmol) in toluene (250 mL) was refluxed for 3 h. Subsequently, the toluene was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was crystallized from diethyl ether: yield 12.0 g (71%); mp 171 °C; ^{1}H NMR ($CDCl_3$) δ 1.39−2.30 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.71 (t, 1H, ^3J = 5.7 Hz, H8a), 2.89−3.10 (m, 1H, H8′), 3.19−3.36 (m, 1H, H4a), 3.94 (s, 3H, OCH_3), 4.71−4.90 (m, 1H, NCH), 5.60−5.88 (m, 3H, HC=CH, OH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.48 (d, 1H, ^4J = 2.1 Hz, H2-arom). Anal. Calcd ($C_{22}H_{28}N_2O_3$): C, H, N.

***cis*-2-Cycloheptyl-4-(3-difluoromethoxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one(16a).** A solution of phenol **15** (2.00 g, 5.43 mmol), tetraethylammonium bromide (0.12 g, 0.57 mmol), and NaOH (0.65 g, 16 mmol) in water (1 mL) and dioxane (14 mL) was heated to 80 °C and saturated with chlorodifluoromethane for 30 min. After the reaction mixture had cooled to room temperature, the organic layer was decanted and concentrated in vacuo. The remainder was dissolved in ethyl acetate and washed with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining oil was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The product was crystallized from dichloromethane/petroleum ether (60−80): yield 1.45 g (64%); mp 83 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.33 (m, 15H, H-cycloheptyl, H5, H8), 2.67−2.80 (m, 1H, H8a), 2.90−3.11 (m, 1H, H8′), 3.18−3.33 (m, 1H, H4a), 3.93 (s, 3H, OCH_3), 4.71−4.91 (m, 1H, NCH), 5.58−5.88 (m, 2H, HC=CH), 6.60 (t, 1H, ^2J = 75.0 Hz, F_2CHO), 6.99 (d, 1H, ^3J = 8.3 Hz, H5-arom), 7.62 (dd, 1H, ^4J = 2.2 Hz, ^3J = 8.6 Hz, H6-arom), 7.68 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{23}H_{28}N_2O_3F_2$) C, H, N.

***cis*-2-Cycloheptyl-4-(3-cyclopropylmethoxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one(16b).** A mixture of phenol **15** (1.40 g, 3.80 mmol), chloromethylcyclopropane (0.40 g, 4.4 mmol), potassium iodide (0.10 g, 0.60 mmol), and K_2CO_3 (0.60 g, 4.3 mmol) in NMP (100 mL) was heated at 60 °C for 5 days. The reaction mixture was diluted with diethyl ether and washed with water. The organic layer was dried over $MgSO_4$ and concentrated, and the residue was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The product was crystallized from petroleum ether (60−80): yield 0.15 g (9%); mp 102−103 °C; ^{1}H NMR ($CDCl_3$) δ 0.33−0.48 (m, H-cyclopropyl), 0.60−0.75 (m, H-cyclopropyl), 1.24−2.32 (m, 16H, H-cycloheptyl, H5, H8, CH-cyclopropyl), 2.67−2.79 (m, 1H, H8a), 2.90−3.10 (m, 1H, H8′), 3.20−3.38 (m, 1H, H4a), 3.84−4.01 (m, 5H, OCH_3, OCH_2), 4.73−4.93 (m, 1H, NCH), 5.60−5.86 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.28 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.4 Hz, H6-arom), 7.51 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{26}H_{34}N_2O_3$): C, H, N.

***cis*-2-Cycloheptyl-4-[3-(2-hydroxyethoxy)-4-methoxyphenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one(16c)**. A mixture of phenol **15** (1.00 g, 2.71 mmol), ethylene carbonate (0.50 g, 5.7 mmol), and K_2CO_3 (0.80 g, 5.8 mmol) in NMP (20 mL) was heated to 125 °C for 4 h. After the reaction mixture had cooled to room temperature, water was added and the product was extracted with diethyl ether. The combined organic extract was dried over $MgSO_4$ and concentrated. The remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 1:1. The title compound was crystallized from diethyl ether/petroleum ether (60−80): yield 1.01 g (90%); mp 75 °C; ^{1}H NMR (DMSO-d_6) δ 1.40−2.30 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.72 (t, 1H, ^3J = 5.7 Hz, H8a), 2.90−3.11 (m, 1H, H8′), 3.20−3.38 (m, 1H, H4a), 3.91 (s, 3H, OCH_3), 3.92−4.07 (m, 2H, CH_2OH), 4.20 (t, 2H, ^3J = 4.1/8 Hz, OCH_2), 4.72−4.91 (m, 1H, NCH), 5.60−5.88 (m, 2H, HC=CH), 6.90 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.34 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 Hz, H6-arom), 7.54 (d, 1H, ^4J = 2.1 Hz, H2-arom). Anal. Calcd ($C_{24}H_{32}N_2O_4$): C, H, N.

***cis*-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]acetic Acid Ethyl Ester (16.1d).** A mixture of compound **15** (1.00 g, 2.71 mmol), ethyl bromoacetate (0.50 g, 3.0 mmol), and K_2CO_3 (0.40 g, 2.9 mmol) in NMP (100 mL) was heated to 60 °C for 6 h. After the addition of water, the product was extracted with diethyl ether. The combined organic extract was washed with saturated $NaHCO_3$ and dried over $MgSO_4$, and the solvent was evaporated to yield the title compound as a yellow oil: yield 1.01 g (82%); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H, ^3J = 7.1 Hz, CH_2CH_3), 1.40−2.30 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.71 (t, 1H, ^3J = 5.9 Hz, H8a), 2.88−3.11 (m, 1H, H8′), 3.18−3.35 (m, 1H, H4a), 3.93 (s, 3H, OCH_3), 4.28 (q, 2H, ^3J = 7.1 Hz, CH_2CH_3), 4.68−4.90 (m, 3H, NCH, CH_2C=O), 5.58−5.87 (m, 2H, HC=CH), 6.91 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.33 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.46 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]acetic acid (16d).** Ester **16.1d** (1.00 g, 2.20 mmol) was stirred in a mixture of THF (100 mL), MeOH (100 mL), and 2 N KOH (200 mL) for 2 h. The reaction mixture was concentrated in vacuo, the residue was diluted with ethyl acetate, and the product was extracted with 1 M NaOH. The combined aqueous extract was acidified with concentrated HCl and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, and after removal of the solvent under reduced pressure, the title compound was crystallized from the remainder as a white solid using diethyl ether: yield 0.47 g (50%); mp 143 °C; ^{1}H NMR ($CDCl_3$) δ 1.37−2.35 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.72 (t, 1H, ^3J = 5.7 Hz, H8a), 2.89−3.10 (m, 1H, H8′), 3.18−3.35 (m, 1H, H4a), 3.94 (s, 3H, OCH_3), 4.70−4.91 (m, 3H, NCH, OCH_2), 5.58−5.85 (m, 2H, HC=CH), 6.93 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.38 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.5 Hz, H6-arom), 7.53 (d, 1H, ^4J = 1.9 Hz, H2-arom). Anal. Calcd ($C_{24}H_{30}N_2O_5$): C, H, N.

***cis*-4-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]butyric acid (16e).** The ethyl ester of compound **16e** was prepared as described for **16.1d** using ethyl 4-bromobutyrate (0.60 g, 3.1 mmol). Hydrolysis of the ethyl ester was performed analogously to the preparation of **16d** except the reaction mixture was stirred for 30 min. The product was crystallized from diethyl ether as a white solid: yield 0.48 g (39%); mp 121 °C; ^{1}H NMR ($CDCl_3$) δ 1.38−2.32 (m, 17H, CH_2-cycloheptyl, H5, H8, H−Pr), 2.56−2.80 (m, 3H, H8a, CH_2C=O), 2.90−3.11 (m, 1H, H8′), 3.19−3.38 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 4.14 (t, 2H, ^3J = 6.1 Hz, OCH_2), 4.72−4.93 (m, 1H, NCH), 5.59−5.85 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.30 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.49 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{26}H_{34}N_2O_5$): C, H, N.

***cis*-5-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]pentanoic acid (16f).** The ethyl ester of compound **16f** was prepared as described for **16.1d** using ethyl 5-bromovalerate (0.60 g, 2.9 mmol) and heating for 12 h. Hydrolysis of the ethyl ester was performed analogously to the preparation of **16d** except the reaction mixture was stirred for 30 min. The title compound was obtained as a white solid by crystallization from ethyl acetate: yield 0.74 g (58%); mp 161 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.32 (m, 19H, CH_2-cycloheptyl, H5, H8, H-pentyl), 2.48 (t, 2H, ^3J = 6.9 Hz, CH_2C=O), 2.73 (t, 1H, ^3J = 5.6 Hz, H8a), 2.90−3.12 (m, 1H, H8′), 3.18−3.39 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 4.11 (t, 2H, ^3J = 6.0 Hz, OCH_2), 4.72−4.94 (m, 1H, NCH), 5.60−5.87 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.49 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{27}H_{36}N_2O_5$): C, H, N.

***cis*-4-[3-(2-Bromoethoxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16.1g).** A solution of bromine (4.00 g, 25.0 mmol) in dichloromethane (10 mL) was added dropwise to an ice-cooled solution of triphenylphosphine (6.56 g, 25.0 mmol) in dichloromethane (50 mL) under a nitrogen atmosphere. Subsequently, a solution of compound **16c** (10.3 g, 25.0 mmol) in dichloromethane (25 mL) was added to the reaction mixture while the temperature was maintained at 0 °C. After the last addition, the mixture was allowed to reach room temperature and was stirred for another 2 h. The reaction was quenched by the addition of aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The title compound was crystallized from the residue as a white solid using methanol: yield 7.73 g (65%); mp 92−94 °C; ^{1}H NMR (DMSO-d_6) δ 1.49−2.32 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.72 (t, 1H, ^3J = 5.8 Hz, H8a), 2.91−3.11 (m, 1H, H8′), 3.20−3.37 (m, 1H, H4a), 3.69 (t, 2H, ^3J = 6.7 Hz, CH_2Br), 3.92 (s, 3H, OCH_3), 4.41 (t, 2H, ^3J = 6.7 Hz, OCH_2), 4.74−4.94 (m, 1H, NCH), 5.60−5.85 (m, 2H, HC=CH), 6.90 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.33 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 HZ, H6-arom), 7.55 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-2-Cycloheptyl-4-[3-(2-dimethylaminoethoxy)-4-methoxyphenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one hemifumarate (16g).** Bromide **16.1 g** (1.00 g, 2.10 mmol) was stirred in a 30% solution of dimethylamine in ethanol (30 mL) for 4 h. The reaction mixture was diluted with saturated $NaHCO_3$, and the product was extracted with diethyl ether. The combined organic extract was dried over $MgSO_4$ and concentrated in vacuo. The desired product was crystallized as the hemifumarate from ethyl acetate/diethyl ether/fumaric acid: yield 0.99 g (95%); mp 163 °C; ^{1}H NMR ($CDCl_3$) δ 1.39−2.31 (m, 15H, CH_2-cycloheptyl, H5, H8), 2.65−2.84 (m, 7H, H8a, NCH_3), 2.89−3.11 (m, 1H, H8′), 3.18−3.39 (m, 3H, H4a, NCH_2), 3.89 (s, 3H, OCH_3), 4.37 (t, 2H, ^3J = 5.9 Hz, OCH_2), 4.71−4.90 (m, 1H, NCH), 5.60−5.86 (m, 2H, HC=CH), 6.78 (s, 1H, HC=CH−fumaric acid), 6.89 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.36 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 Hz, H6-arom), 7.50 (d, 1H, ^4J = 2.0 Hz, H2-arom). Anal. Calcd ($C_{26}H_{37}N_3O_3.C_4H_4O_4$): C, H, N.

***cis*-4-[3-(4-Bromobutoxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16.1h).** A mixture of **15** (4.01 g, 10.9 mmol), 1,4-dibromobutane (7.50 g, 34.7 mmol), and K_2CO_3 (2.71 g, 19.6 mmol) in NMP (100 mL) was heated to 60 °C for 4 h. Workup was performed as described for **16.1d**. The remaining oil was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was obtained as a white solid by crystallization from petroleum ether (60−80)/ethyl acetate: yield 3.82 g (70%); mp 101−103 °C; ^{1}H NMR ($CDCl_3$) δ 1.42−2.32 (m, 19H, CH_2-cycloheptyl, H5, H8, H−Bu), 2.66−2.79 (m, 1H, H8a), 2.91−3.11 (m, 1H, H8′), 3.21−3.38 (m, 1H, H4a), 3.52 (t, 2H, ^3J = 6.3 Hz, CH_2Br), 3.91 (s, 3H, OCH_3), 4.13 (t, 2H, ^3J = 5.9 Hz, OCH_2), 4.71−4.93 (m, 1H, NCH), 5.60−5.87 (m, 2H, HC=CH), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.50 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-2-Cycloheptyl-4-[3-(4-dimethylaminobutoxy)-4-methoxyphenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one hemifumarate (16h)** was prepared from bromide **16.1h** (1.00 g, 1.99 mmol) analogously to the preparation of **16g**. After workup, the title compound was crystallized as the hemifumarate from diethyl ether/fumaric acid: yield 0.96 g (92%); mp 146 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.32 (m, 19H, CH_2-cycloheptyl, H5, H8, H−Bu), 2.65−2.81 (m, 7H, H8a, NCH_3), 2.88−3.16 (m, 3H, H8′, NCH_2), 3.19−3.37 (m, 1H, H4a), 3.89 (s, 3H, OCH_3), 4.04−4.19 (m, 2H, OCH_2), 4.72−4.92 (m, 1H, NCH), 5.59−5.87 (m, 2H, HC=CH), 6.78 (s, 1H, HC=CH−fumaric acid), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.30 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.45 (d, 1H, ^4J = 1.9 Hz, H2-arom), 11.07 (bs, 1H, COOH−fumaric acid). Anal. Calcd ($C_{28}H_{41}N_3O_3.C_4H_4O_4$): C, H, N.

***cis*-2-Cycloheptyl-4-[3-(4-imidazol-1-yl-butoxy)-4-methoxyphenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one hydrochloride (16i)** was synthesized from bromide **16.1h** (1.00 g, 1.99 mmol), imidazole (0.20 g, 2.9 mmol), and K_2CO_3 (0.50 g, 3.6 mmol) as described for **16.1d**. The product was crystallized as the hydrochloride from ethyl acetate/HCl: yield 0.51 g (49%); mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 1.35−2.33 (m, 19H, CH_2-cycloheptyl, H5, H8, H−Bu), 2.65−2.80 (m, 1H, H8a),

2.90−3.12 (m, 1H, H8′), 3.21−3.39 (m, 1H, H4a), 3.96 (s, 3H, OCH_3), 4.08−4.24 (t, 2H, OCH_2), 4.45−4.66 (t, 2H, NCH_2), 4.70−4.92 (m, 1H, NCH), 5.58−5.87 (m, 2H, HC═CH), 6.91 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.30 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.5 Hz, H6-arom), 7.41 (d, 2H, ^4J = 11.8 Hz, HC═CH−imidazolyl), 7.47 (d, 1H, ^4J = 1.9 Hz, H2-arom), 9.57 (s, 1H, CH-imidazolyl), 15.13 (s, 1H, HCl). Anal. Calcd ($C_{29}H_{38}N_4O_3$.HCl): C, H, N.

***cis*-2-Cycloheptyl-4-[4-methoxy-3-(4-purin-7-yl-butoxy)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16j)** was synthesized from bromide **16.1h** (1.00 g, 1.99 mmol) and purine (0.27 g, 2.2 mmol) as described for **16.1d**, purified by flash column chromatography using ethyl acetate/methanol 3:1, and crystallized from methanol at −20 °C: yield 0.43 g (40%); mp 110−111 °C; ^{1}H NMR ($CDCl_3$) δ 1.38−2.34 (m, 19H, CH_2-cycloheptyl, CH_2−Bu, H5, H8), 2.73 (t, 1H, ^3J = 5.6 Hz, H8a), 2.92−3.11 (m, 1H, H8′), 3.20−3.39 (m, 1H, H4a), 3.92 (s, 3H, OCH_3), 4.16 (t, 2H, ^3J = 5.7 Hz, NCH_2), 4.50 (t, 2H, ^3J = 6.9 Hz, OCH_2), 4.72−4.92 (m, 1H, NCH), 5.60−5.88 (m, 2H, HC═CH), 6.90 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.30 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.5 Hz, H6-arom), 7.49 (d, 1H, ^4J = 1.9 Hz, H2-arom), 8.35 (s, 1H, H-purine), 8.99 (s, 1H, H-purine), 9.16 (s, 1H, H-purine). Anal. Calcd ($C_{31}H_{38}N_6O_3$): C, H, N.

(5-Bromopentyl)benzene (16.1k). A solution of 5-phenylpentan-1-ol (2.00 g, 12.2 mmol) and PBr_3 (3.31 g, 12.2 mmol) in diethyl ether (150 mL) was refluxed for 6 h. The reaction was quenched with water, and the mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield the desired bromide as an oil: yield 1.11 g (40%); ^{1}H NMR ($CDCl_3$) δ 1.28−1.92 (m, 6H, CH_2), 2.56 (t, 2H, ^3J = 7.8 Hz, CH_2−Ph), 3.33 (t, 2H, ^3J = 6.8 Hz, CH_2−Br), 7.00−7.28 (m, 5H arom).

***cis*-2-Cycloheptyl-4-[4-methoxy-3-(5-phenylpentyloxy)-phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16k).** A mixture of bromide **16.1k** (0.50 g, 2.2 mmol), **15** (0.82 g, 2.2 mmol), and K_2CO_3 (0.31 g, 2.2 mmol) in NMP (100 mL) was heated at 60 °C for 5 h. Subsequently, the mixture was diluted with diethyl ether and washed with water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo, and the remainder was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was crystallized as a white solid from diethyl ether at −20 °C: yield 0.80 g (72%); mp 59−60 °C; ^{1}H NMR ($CDCl_3$) δ 1.36−2.33 (m, 21H, 6 × CH_2-cycloheptyl, H5, H8, 6 × H-hexyl), 2.64−2.79 (m, 3H, H8a, CH_2−Ph), 2.89−3.11 (m, 1H, H8′), 3.18−3.37 (m, 1H, H4a), 3.88 (s, 3H, OCH_3), 4.06 (t, 2H, ^3J = 6.8 Hz, OCH_2), 4.71−4.93 (m, 1H, NCH), 5.59−5.84 (m, 2H, HC═CH), 6.85 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.05−7.40 (m, 6H, H6-arom, H−Ph), 7.49 (d, 1H, ^4J = 1.9 Hz, H2-arom). Anal. Calcd ($C_{33}H_{42}N_2O_3$): C, H, N.

cis-4-{4-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]butoxy}benzonitrile (16l) was synthesized from bromide **16.1h** (2.00 g, 3.97 mmol) and 4-hydroxybenzonitrile (0.53 g, 4.4 mmol) as described for **16.1d**. After workup, compound **16l** was crystallized from methanol as a white solid: yield 2.13 g (99%); mp 131−133 °C; ^{1}H NMR (DMSO-d_6) δ 1.40−2.32 (m, 19H, CH_2-cycloheptyl, H5, H8, CH_2−Bu), 2.67−2.82 (m, 1H, H8a), 2.90−3.10 (m, 1H, H8′), 3.20−3.39 (m, 1H, H4a), 3.89 (s, 3H, OCH_3), 4.05−4.29 (m, 4H, OCH_2), 4.73−4.93 (m, 1H, NCH), 5.60−5.88 (m, 2H, HC═CH), 6.83−7.02 (m, 3H, H5-arom, H-benzonitrile), 7.28 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.4 Hz, H6-arom), 7.48−7.68 (m, 3H, H2-arom, H-benzonitrile). Anal. Calcd ($C_{33}H_{39}N_3O_4$): C, H, N.

***cis*-4-{4-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]butoxy}benzoic acid (16m).** The ethyl ester of compound **16m** was prepared as described for **16.1d** using bromide **16.1h** (1.00 g, 1.99 mmol), ethyl 4-hydroxybenzoate (0.36 g, 2.2 mmol), and K_2CO_3 (0.50 g, 3.6 mmol) and heating for 5 h. Hydrolysis of the ethyl ester was performed analogously to the preparation of **16d**. The title compound was obtained as a white solid by crystallization from diethyl ether: yield 0.78 g (70%); mp 142−143 °C; ^{1}H NMR ($CDCl_3$) δ 1.41−2.32 (m, 19H, 6 × CH_2-cycloheptyl, H5, H8, 4 × H−Bu), 2.65−2.79 (m, 1H, H8a), 2.90−3.11 (m, 1H, H8′), 3.20−3.38 (m, 1H, H4a), 3.87 (s, 3H, OCH_3), 4.02−4.31 (m, 4H, OCH_2), 4.74−4.96 (m, 1H, NCH), 5.61−5.89 (m, 2H, HC═CH), 6.85 (d, 1H, ^3J = 8.5 Hz, H5-arom), 6.91 (d, 2H, ^3J = 9.0 Hz, H-benzoic), 7.26 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.49 (d, 1H, ^4J = 1.9 Hz, H2-arom), 8.03 (d, 2H, ^3J = 8.9 Hz, H-benzoic). Anal. Calcd ($C_{33}H_{40}N_2O_6$): C, H, N.

***cis*-2-Cycloheptyl-4-(4-methoxy-3-{4-[4-(2H-tetrazol-5-yl)-phenoxy]butoxy}phenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16n).** A mixture of benzonitrile **16l** (1.50 g, 2.77 mmol), NaN_3 (1.81 g, 27.8 mmol), and NH_4Cl (1.50 g, 28.0 mmol) in DMF (50 mL) was heated for 10 h at 120 °C. The reaction mixture was cooled to room temperature and concentrated, and the residue was dissolved in ethyl acetate and washed with 1 N HCl. The organic layer was dried over $MgSO_4$ and concentrated in vacuo, and the remaining oil was purified by flash column chromatography using ethyl acetate/petroleum ether (60−80)/acetic acid 2:2:0.2. The title compound was crystallized from ethyl acetate: yield 0.97 g (60%); mp 153−155 °C; ^{1}H NMR (DMSO-d_6) δ 1.32−2.34 (m, 19H, CH_2-cycloheptyl, H5, H8, CH_2−Bu), 2.71−2.87 (m, 1H, H8a), 2.91−3.13 (m, 1H, H8′), 3.21−3.41 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 4.04−4.29 (m, 4H, OCH_2), 4.75−4.94 (m, 1H, NCH), 5.54−5.83 (m, 2H, HC═CH), 6.89 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.00 (d, 2H, ^3J = 8.8 Hz, H-arom), 7.29 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.5 Hz, H6-arom), 7.53 (d, 1H, ^4J = 1.9 Hz, H2-arom), 8.10 (d, 2H, ^3J = 8.7 Hz, H-arom). Anal. Calcd ($C_{33}H_{40}N_6O_4$): C, H, N.

***cis*-2-Cycloheptyl-4-{3-[4-(4-imidazol-1-yl-phenoxy)butoxy]-4-methoxyphenyl}-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one hydrochloride (16o)** was synthesized from bromide **16.1h** (1.00 g, 1.99 mmol) and 4-(imidazol-1-yl)phenol (0.35 g, 2.19 mmol) as described for **16.1d**, purified by flash column chromatography using ethyl acetate, and crystallized from ethyl acetate/dichloromethane/HCl as the hydrochloride: yield 0.49 g (40%); mp 146−149 °C; ^{1}H NMR ($CDCl_3$) δ 1.35−2.30 (m, 19H, CH_2-cycloheptyl, CH_2−Bu, H5, H8), 2.68−2.80 (m, 1H, H8a), 2.91−3.11 (m, 1H, H8′), 3.22−3.39 (m, 1H, H4a), 3.91 (s, 3H, OCH_3), 4.06−4.29 (m, 4H, OCH_2), 4.73−4.93 (m, 1H, NCH), 5.60−5.88 (m, 2H, HC═CH), 6.89 (d, 1H, ^3J = 8.4 Hz, H5-arom), 7.08 (d, 2H, ^3J = 8.9 Hz, H−Ph), 7.29 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom), 7.44 (d, 2H, ^4J = 13.2 Hz, HC═CH−imidazole), 7.50−7.63 (m, 3H, H2-arom, H−Ph), 9.29 (s, 1H, H-imidazole). Anal. Calcd ($C_{35}H_{42}N_4O_4$·HCl): C, H, N.

***cis*-4-[3-(6-Bromohexyloxy)-4-methoxyphenyl]-2-cycloheptyl-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16.1p)** was prepared in a similar way as described for bromide **16.1h** except using 1,6-dibromohexane (8.47 g, 34.7 mmol). The remaining oil was purified by flash column chromatography using petroleum ether (60−80)/ethyl acetate 4:1. The title compound was obtained as a white solid by crystallization from petroleum ether (60−80)/ethyl acetate: yield 4.61 g (80%); mp 104−105 °C; ^{1}H NMR ($CDCl_3$) δ 1.49−2.30 (m, 23H, CH_2-cycloheptyl, CH_2-hexyl, H5, H8), 2.66−2.79 (m, 1H, H8a), 2.91−3.10 (m, 1H, H8′), 3.20−3.38 (m, 1H, H4a), 3.52 (t, 2H, ^3J = 6.3 Hz, $BrCH_2$), 3.91 (s, 3H, OCH_3), 4.13 (t, 2H, ^3J = 5.9 Hz, OCH_2), 4.75−4.93 (m, 1H, NCH), 5.60−5.89 (m, 2H, HC═CH), 6.88 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.28 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.50 (d, 1H, ^4J = 2.0 Hz, H2-arom).

***cis*-2-Cycloheptyl-4-[4-methoxy-3-(6-phenoxyhexyloxy)phenyl]-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one (16p).** Compound **16p** was prepared in a similar way as described for **16.1d** except using bromide **16.1p** (1.00 g, 1.88 mmol) and phenol (0.20 g, 2.1 mmol) and heating for 12 h. After workup, the product was crystallized from 2-propanol at −20 °C: yield 0.36 g (35%); mp 77−78 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.33 (m, 23H, CH_2-cycloheptyl, CH_2-hexyl, H5, H8), 2.67−2.80 (m, 1H, H8a), 2.91−3.10 (m, 1H, H8′), 3.20−3.39 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 3.97 (t, 1H, ^3J = 6.4 Hz, OCH_2), 4.11 (t, 1H, ^3J = 6.7 Hz, OCH_2), 4.74−4.93 (m, 1H, NCH), 5.59−5.89 (m, 2H, HC═CH), 6.78−7.00 (m, 4H, H5-arom, H−Ph), 7.17−7.33 (m, 3H, H6-arom, H−Ph), 7.51 (d, 1H, ^4J = 1.8 Hz, H2-arom). Anal. Calcd ($C_{34}H_{44}N_2O_4$): C, H, N.

***cis*-4-{6-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]hexyloxy}benzoic acid (16q)** was synthesized analogously to the preparation of **16m** except using bromide **16.1p** (1.00 g, 1.88 mmol). The title compound was crystallized from diethyl ether: yield 0.39 g (35%). mp 141−142 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−2.35 (m, 23H, CH_2-cycloheptyl, CH_2-hexyl, H5, H8), 2.66−2.80 (m, 1H, H8a), 2.90−3.13 (m, 1H, H8′), 3.20−3.39 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 3.97−4.22 (m, 4H, OCH_2), 4.73−4.95 (m, 1H, NCH), 5.60−5.89 (m, 2H, HC=CH), 6.80−7.01 (m, 3H, H5-arom, H3−Ph, H5−Ph), 7.27 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.4 Hz, H6-arom), 7.52 (d, 1H, ^4J = 1.9 Hz, H2-arom), 8.05 (m, 2H, H2−Ph, H6−Ph). Anal. Calcd ($C_{35}H_{44}N_2O_6$): C, H, N.

***cis*-4-{6-[5-(3-Cycloheptyl-4-oxo-3,4,4a,5,8,8a-hexahydrophthalazin-1-yl)-2-methoxyphenoxy]hexyloxy}benzamide (16r)** was synthesized analogously to the preparation of **16.1d** except using bromide **16.1p** (1.00 g, 1.88 mmol) and 4-hydroxybenzamide (0.29 g, 2.1 mmol). The title compound was crystallized from ethyl acetate/petroleum ether (60−80): yield 0.44 g (40%); mp 124−125 °C; ^{1}H NMR (DMSO-d_6) δ 1.31−2.31 (m, 23H, CH_2-cycloheptyl, CH_2-hexyl, H5, H8), 2.67−2.78 (m, 1H, H8a), 2.91−3.10 (m, 1H, H8′), 3.20−3.38 (m, 1H, H4a), 3.90 (s, 3H, OCH_3), 4.02 (t, 2H, ^3J = 6.4 Hz, OCH_2), 4.11 (t, 2H, ^3J = 6.6 Hz, OCH_2), 4.73−4.93 (m, 1H, NCH), 5.59−5.89 (6.11) (m, 2/4H, NH_2, HC=CH), 6.81−6.98 (m, 3H, H6-arom, H−Ph), 7.26 (dd, 1H, ^4J = 1.9 Hz, ^3J = 8.5 Hz, H6-arom), 7.52 (d, 1H, ^4J = 1.9 Hz, H2-arom), 7.77 (d, 2H, ^3J = 8.8 Hz, H−Ph). Anal. Calcd ($C_{35}H_{45}N_3O_5$): C, H, N.

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JM010838C