# 6-Substituted Benzopyrans as Potassium Channel Activators: Synthesis, Vasodilator Properties, and Multivariate Analysis

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During the last 10 years compounds have been discovered which can activate or block $K_{ATP}$ channels. In particular, K channel activators (KCA) have been found to be smooth muscle relaxants with their main utility in hypertension and bronchodilation. In this paper we describe the synthesis of new KCA of the benzopyran type with a fixed 4-substituent and a systematic variation in the 6-position. The relaxant potency in rat aorta and trachea was used for biological characterization of the benzopyrans. In both biological test systems, they exhibit potency ranges of more than 3 log units. Structure−activity relationships are investigated by principal component analysis (PCA) and partial least-squares (PLS) analysis. Most striking outliers in an initial PLS analysis of the entire database were the unsubstituted 6-H compound **13** as well as **34** and **35**. For the remaining set of 31 compounds, a 3-component PLS model explains the variance in biological activity to 81% in the aortic and to 82% in the tracheal test system. 6-Substituents influence affinity by a direct (presumably dipolar) interaction with the receptor site. According to the 2D-plot of the partial PLS weights, a strong electronegativity as well as high values for the integy moment and for the heat of formation in water dominate the first component; low values for substituent size (as defined by globularity or surface) are in addition favorable for high potency. High lipophilicity and low minimum energies of interaction dominate the second component. Chemical descriptors for the biological potency of the test set in rat aorta and rat trachea are very similar according to the almost identical projection of the *Y*-variables onto the *X*-component space.

## Introduction

Potassium channels comprise the most diverse group of ion channels. Molecular biology has defined three families of K channels.[1] The first group belongs to the S4 channel superfamily[2] and mainly comprises the voltage-gated K channels. Another group consists of channels formed by monomers with a single membrane-spanning region (minK channels); the third group represents the inward rectifiers containing two membrane-spanning regions. Members of this group are K channels gating of which is sensitive to [ATP]. These $K_{ATP}$ channels, first detected by Noma[3] in heart muscle, are dimers with a pore-forming α-subunit and a *β*-subunit, labeled SUR, due to its binding region for sulfonylureas.

During the last 10 years compounds have been discovered which can activate or block these $K_{ATP}$ channels. In particular, K channel activators have been found to be smooth muscle relaxants with their main utility in hypertension and bronchodilation. The putative binding region for the KCA is attributed to the *β*-subunit.[4]

There are at least seven classes of KCA,[5] of which the main four are the benzopyrans, the thioformamides, the cyanoguanidines, and the organic nitrates. Best investigated subgroup is the benzopyrans. Structure−activity studies mainly focus on variations in the 4-position of the benzopyran nucleus.[6]

From literature[5,6] it is known that 6-substituents have an outstanding impact on modulating the biological activity of benzopyran KCA. Small and highly electronegative 6-substituents were viewed as optimal. 6-Substituents could contribute to receptor affinity either by a direct interaction with the receptor site or indirectly by withdrawing electrons from the phenyl moiety of the benzopyran nucleus and thereby optimizing charge-transfer interactions of the aromate with the receptor.

To better understand the molecular meaning of 6-substituents for the biological activity, we synthesized new benzopyrans with extensive chemical variation within the 6-position, measured their dilator properties in rat aorta and trachea, defined structure−activity relationships on the basis of principal component analysis (PCA) and partial least-squares (PLS) analysis, and looked for a putative tissue selectivity.

## Chemistry

Synthesis of benzopyran-type potassium channel openers was accomplished according to following procedures: best results were obtained by the method of Kawase[7] (Scheme 1) with the corresponding salicyl aldehydes **1** and **2** as starting material and cyclization

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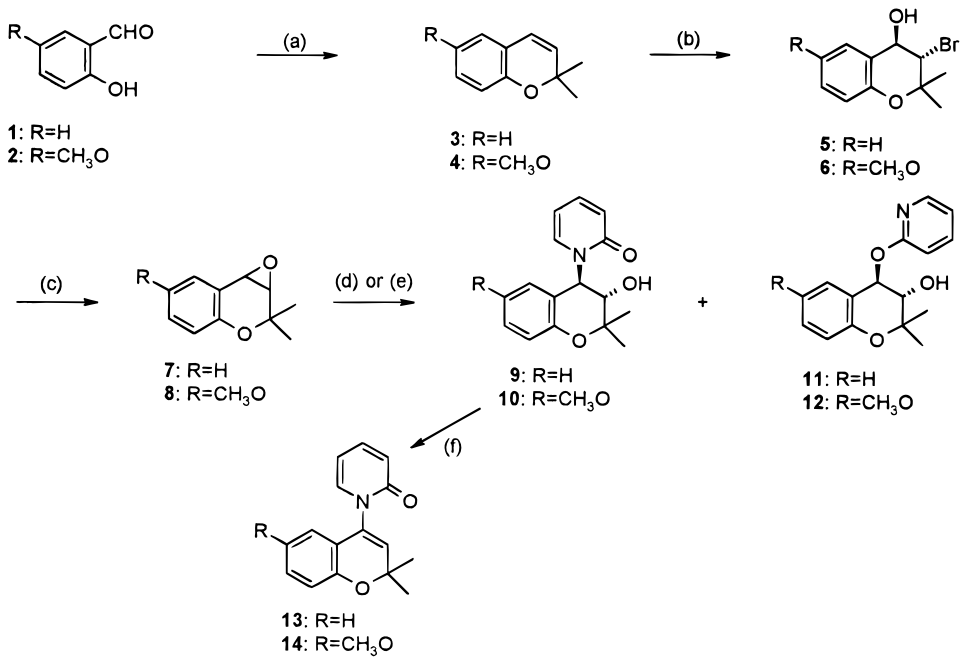
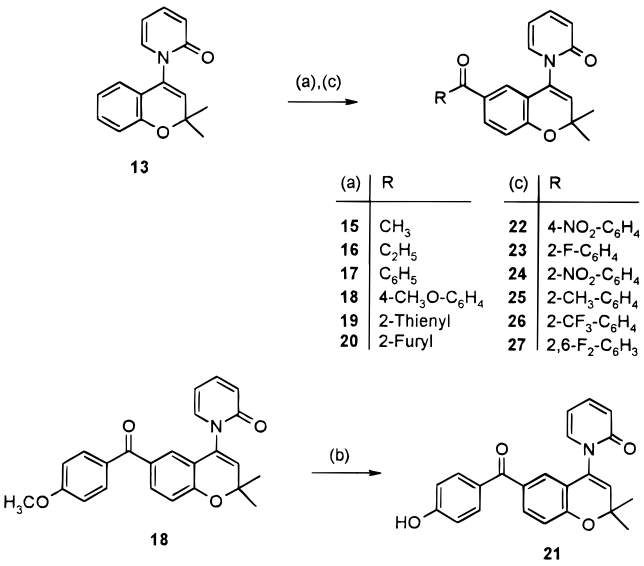
**Scheme 1**[a]




[a] Reagents and conditions: (a) $C(CH_3)_2$=CH−COOEt, $K_2CO_3$, DMF, 150 °C, 15 h; (b) NBS; (c) NaOH (pellets), $Et_2O$; (d) 2-pyridinol, EtOH, pyridine, reflux; (e) 2-pyridinol, $K_2CO_3$, toluene, 2 h, reflux; (f) NaOH (microlayer; Merck cat. no. 1.01564), dioxane, reflux.

**Scheme 2**[a]



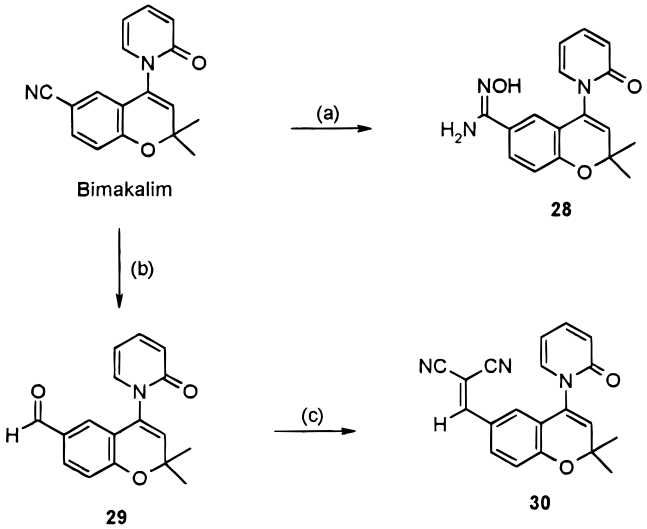

| (a) | R | (c) | R |
|---|---|---|---|
| 15 | $CH_3$ | 22 | 4-$NO_2$-$C_6H_4$ |
| 16 | $C_2H_5$ | 23 | 2-F-$C_6H_4$ |
| 17 | $C_6H_5$ | 24 | 2-$NO_2$-$C_6H_4$ |
| 18 | 4-$CH_3O$-$C_6H_4$ | 25 | 2-$CH_3$-$C_6H_4$ |
| 19 | 2-Thienyl | 26 | 2-$CF_3$-$C_6H_4$ |
| 20 | 2-Furyl | 27 | 2,6-$F_2$-$C_6H_3$ |

[a] Reagents and conditions: (a) for compounds **15**−**20**, RCOCl, $AlCl_3$, 1,2-dichloroethane; (b) for compound **21**, pyridine-HCl, 170 °C; (c) for compounds **22**−**27**; RCOCl, Ag-triflate, 1,2-dichloroethane, reflux.

with dimethylacrylate in DMF/potassium carbonate at about 150 °C. The chromenes **3** and **4** were separated from the reaction mixture on distillation in vacuo. Direct epoxidation of these chromenes with 3-chloroperbenzoic acid failed to give the desired oxirans **7** and **8**, which were prepared by alkaline dehydrohalogenation of *trans*-bromohydrins **5** and **6**; they were in turn obtained from chromenes **3** and **4** with *N*-bromosuccinimide (NBS). Further reactions were similar to the route of Bergmann and Gericke[8] (addition of 2-pyridinol to the epoxides with catalytic amounts of pyridine in refluxing ethanol). Unfortunately it was necessary to separate the resulting mixtures of the pyridones (**9**, **10**) and the (pyridyloxy)-chromanols (**11**, **12**) by silica gel chromatography. To avoid this procedure we boiled the components with potassium carbonate in toluene, and the *trans*-configurated pyridones were the only reaction products in almost quantitative yield. Dehydration of **9** and **10** leads to chromenes **13** and **14**, which were used as starting material for the desired compounds.

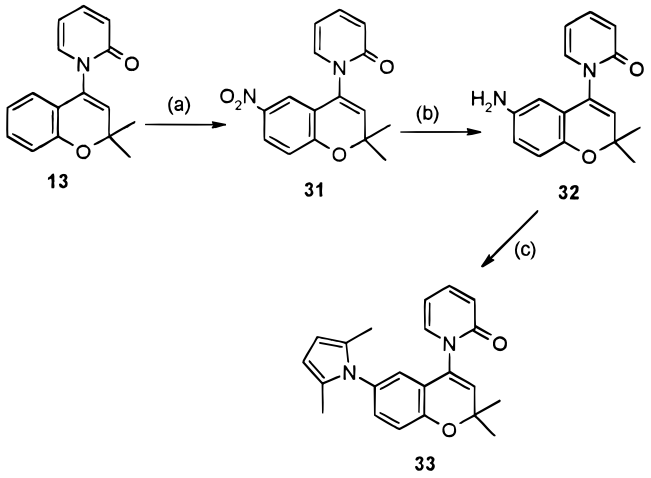
Acylation of **13** (Scheme 2) under normal Friedel−Crafts conditions was only successful for the preparation of **15**−**20**, whereas the substituted aryl ketones **22**−**27** were not accessible in this way due to a simultaneous transformation of the benzopyran to an indene ring system.[9] Therefore we used the method of Effenberger et al.[10] with silver triflate and the corresponding acyl chlorides to produce the mixed carboxylic−sulfuric−anhydrides in situ. Acceptable yields were obtained for compounds **22**−**26** in refluxing 1,2-dichloroethane, and

**Scheme 3**[a]




[a] Reagents and conditions: (a) $NH_2OH$·HCl, $Na_2CO_3$, $H_2O$, 60 °C; (b) $NaH_2PO_2$, $H_2O$, AcOH, pyridine, Raney nickel; (c) $CH_2(CN)_2$, AcOH, piperidine, toluene, reflux.

**Scheme 4**[a]




[a] Reagents and conditions: (a) $NO_2BF_4$, $CH_2Cl_2$; (b) iron/$H_2SO_4$; (c) acetonylacetone, reflux.

only the difluoro ketone **27** required higher temperatures (150 °C in nitrobenzene).

Further 6-substituted benzopyrans were prepared as derivatives of bimakalim[8] by common procedures (Scheme 3). Excellent yields of amidoxime **28** and aldehyde[8] **29** were obtained after treatment of the nitrile with either hydroxylamine or Raney nickel and sodium hypophosphite,[11] respectively. **29** was condensed with malononitrile to form **30** in high yield.

Preparation of the chromene **33** is shown in Scheme 4. Nitration of **13** with nitronium tetrafluoroborate in dry dichloromethane afforded **31**,[8] which was reduced to the amine **32**. Cyclocondensation with acetonylacetone by the conventional Paal–Knorr method[12] gave the pyrrole **33**.

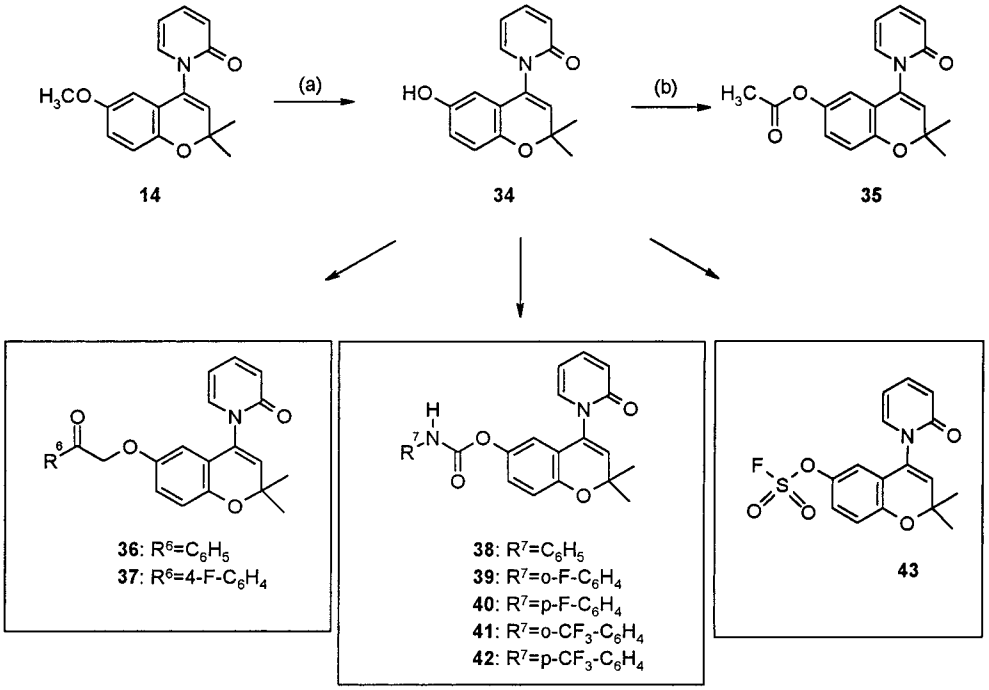
Methods for preparation of 6-O-substituted benzopyrans are summarized in Scheme 5. Cleavage of the methyl ether **14** with pyridine-HCl[13] at 170 °C or with boron tribromide at −10 °C afforded the phenol **34**, which was converted to the acetate **35**, the phenacyl ethers[14] **36** and **37**, and with the corresponding isocyanates to a series of urethanes[15] (**38**–**42**). The fluorosulfonate **43** was prepared from phenol **34** with fluorosulfonyl chloride in absolute pyridine[16] at 0 °C. Bimakalim (**44**) and compounds **45**–**48** (Table 1) were kindly provided by E. Merck, Darmstadt, Germany, and are described in the literature;[8] **44**–**48** are included in our test assays to allow a direct comparison of biological activities of the new benzopyrans with reference compounds.

## Results and Discussion

Structure–activity relationships (SAR) for KCA of the benzopyran-type, so far available in the literature,[5,6] stem from in vitro data (dilation of aortic rings or strips) or from in vivo experiments in spontaneously hypertensive rats (blood pressure-lowering effect). The great majority of SAR analyses deal with variations in the 4-position; investigations on 6-substituted benzopyrans are rather limited with the exception of data on a set of 13 4-carbothioamidobenzopyrans with 6-variation of intermediate chemical diversity.[17,18] According to these QSAR studies, electronic properties, in particular hydrogen bond acceptor properties of the 6-substituent, are assumed to determine the in vitro potency of the benzopyrans.

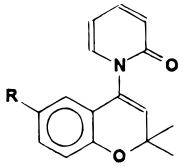
Here we describe the synthesis ($n = 29$) and derive multivariate SAR analyses ($n = 34$) for a database of 6-substituted benzopyrans with extensive chemical variation in the 6-position. For biological characterization of the 34 KCA, their relaxant potency in rat aorta and trachea was measured according to a protocol, described in the Experimental Section. Half-maximal potency was derived from dose–response curves as

**Scheme 5**[a]




[a] Reagents and conditions: (a) pyridine-HCl/170 °C or $BBr_3$/−10 °C; (b) acetyl chloride, triethylamine, toluene, reflux; (c) $R^6COCH_2Br$, $K_2CO_3$, acetone; (d) $R^7NCO$, triethylamine, toluene, reflux; (e) $SO_2ClF$, pyridine, 0 °C.

**Table 1.** Biological Activity in Rat Aorta and Trachea, Expressed as Reciprocal Half-Maximal Potency (log 1/*C* ± SD)




| compd | R | log 1/*C* aorta | log 1/*C* trachea |
|---|---|---|---|
| **13** | H | 5.43 (±0.06) | 5.05 (±0.08) |
| **14** | methoxy | 6.55 (±0.05) | 5.99 (±0.11) |
| **15** | acetyl | 7.37 (±0.05) | 6.65 (±0.01) |
| **16** | propionyl | 6.63 (±0.10) | 5.85 (±0.07) |
| **17** | benzoyl | 6.61 (±0.07) | 6.21 (±0.07) |
| **18** | 4-methoxybenzoyl | 6.15 (±0.13) | 5.72 (±0.03) |
| **19** | 2-thienoyl | 6.40 (±0.10) | 5.84 (±0.08) |
| **20** | 2-furoyl | 6.49 (±0.05) | 5.92 (±0.04) |
| **21** | 4-hydroxybenzoyl | 6.65 (±0.03) | 5.87 (±0.12) |
| **22** | 4-nitrobenzoyl | 6.20 (±0.13) | 6.09 (±0.11) |
| **23** | 2-fluorobenzoyl | 7.08 (±0.13) | 6.34 (±0.12) |
| **24** | 2-nitrobenzoyl | 6.17 (±0.05) | 5.64 (±0.04) |
| **25** | 2-methylbenzoyl | 6.83 (±0.09) | 6.25 (±0.08) |
| **26** | 2-(trifluoromethyl)benzoyl | 6.76 (±0.14) | 5.78 (±0.16) |
| **27** | 2,6-difluorobenzoyl | 6.97 (±0.09) | 5.99 (±0.06) |
| **28** | aminohydroxyiminomethyl | 5.99 (±0.06) | 5.51 (±0.06) |
| **29** | formyl | 6.91 (±0.05) | 6.14 (±0.03) |
| **30** | 2,2-dicyanoethenyl | 6.95 (±0.08) | 6.30 (±0.07) |
| **33** | 2,5-dimethyl-1-pyrrolyl | 7.27 (±0.08) | 6.78 (±0.06) |
| **34** | hydroxy | 5.44 (±0.05) | 5.31 (±0.05) |
| **35** | acetoxy | 5.60 (±0.03) | 4.97 (±0.05) |
| **36** | phenacyloxy | 5.05 (±0.03) | 4.69 (±0.07) |
| **37** | 4-fluorophenacyloxy | 4.63 (±0.04) | 4.77 (±0.14) |
| **38** | phenylcarbamoyloxy | 5.30 (±0.03) | 4.89 (±0.08) |
| **39** | 2-fluorophenylcarbamoyloxy | 5.38 (±0.02) | 4.22 (±0.16) |
| **40** | 4-fluorophenylcarbamoyloxy | 5.30 (±0.02) | 4.37 (±0.33) |
| **41** | 2-(trifluoromethyl)phenylcarbamoyloxy | 5.58 (±0.09) | 5.19 (±0.04) |
| **42** | 4-(trifluoromethyl)phenylcarbamoyloxy | 5.10 (±0.04) | 4.54 (±0.04) |
| **43** | fluorosulfonyloxy | 7.95 (±0.05) | 7.22 (±0.04) |
| **44** | cyano | 7.67 (±0.10) | 7.10 (±0.08) |
| **45** | 4-pyridyl | 6.68 (±0.10) | 6.32 (±0.12) |
| **46** | thiocarboxamido | 6.21 (±0.12) | 5.96 (±0.06) |
| **47** | bromo | 7.84 (±0.08) | 7.53 (±0.23) |
| **48** | trifluoromethyl | 7.61 (±0.12) | 7.37 (±0.05) |

$pEC_{50}$ value (Table 1). In both test systems the KCA exhibit potency ranges of more than 3 log units. In rat aorta the spectrum ranges from a $pEC_{50}$ value of 7.95 for **43** to 4.63 for **37**; in rat trachea the highest potency ($pEC_{50} = 7.53$) is observed for the 6-bromo derivative **47**, and the compound with the weakest potency is **39** with a $pEC_{50}$ of 4.22.

Results of a PLS analysis ($t-u$ score plot) of the 34 KCA are shown in Figure 1. A $t-u$ score plot displays the observations in the projected $X$ ($t$) and $Y$ ($u$) space and shows how well the $Y$ space (biological activity) correlates to the $X$ space (chemical descriptors). Most striking outlier in this plot is the 6-unsubstituted compound **13**, encircled in the figure. For receptor binding, this finding might indicate an essential role of 6-substitution, lack of which results in the significant reduction of potency as observed for **13**. A first inspection of the influence of 6-substituents on biological activity indicates a strong potency increase by preferentially small, electronegative, and rather rigid substituents (arrow 1), an intermediate increase by C═O-linked moieties (arrow 2), and a sustained or even reduced activity by oxygen-bridged groups (arrow 3) with **13** as reference. In addition to **13**, further strong outliers are **34** and **35**; they are primarily responsible for unexplained variance. Due to their pronounced outlier behavior, we excluded **13**, **34**, and **35** from the further PLS analysis.

The variance in biological activity of the remaining 31 benzopyrans is explained by a 3-component model to 81% in the aortic and to 82% in the tracheal test systems. Corresponding PLS plots for the 3 components are comparatively shown in Figure 2. The model tries to explain the remaining molecular pattern after the first by the second component and so forth. Characteristic descriptors dominating the respective components are shown in a color-coded manner with red coding for high values and green coding for low values of the corresponding descriptor. Thus, low molecular volume is dominating the first, high lipophilicity the second, and high LUMO values the third component.

The overall quality of the obtained PLS model is summarized in Figure 3, plotting the experimental versus the recalculated biological activity data for the aortic (a) and the tracheal (b) test systems. This figure elucidates the strong similarity in the SAR for both test systems and the slight superiority of the model for tracheal data as compared to the aortic test system.

The 2D-plot of the partial PLS weights in Figure 4 for the second versus the first component displays the correlation between $X$-variables and $u$ ($Y$). The $w$'s are the weights that combine the $X$-variables to the scores

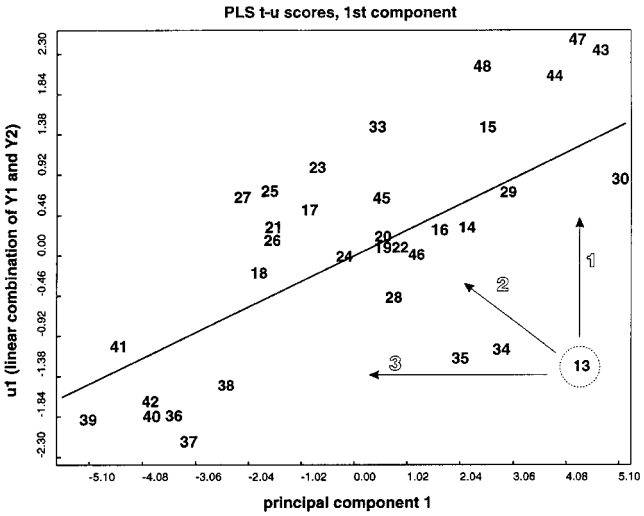



**Figure 1.** Initial PLS analysis of the entire database: most striking outlier in this plot is the 6-unsubstituted **13**, encircled in the figure. A first inspection of the influence of 6-substituents on biological activity indicates a strong potency increase by small, electronegative, and rigid substituents (arrow 1), an intermediate increase by C═O-linked moieties (arrow 2), and a sustained or reduced activity by oxygen-bridged groups (arrow 3) with **13** as the reference.

*t*, so as to maximize their correlation with *Y*. *X*-variables with high *w*'s are highly correlated with *u* (*Y*). A strong electronegativity (Ela) and high values for the integy moment $I_2$ (calculated at −0.5 kcal/mol) and for the heat of formation in water ($HF_w$) dominate the first component; low values (projection onto the negative part of the *X*-component) for substituent size (as defined by globularity *G* or surface *S*+) are in addition favorable for high potency. High lipophilicity (log *P*) and low minimum energies of interaction ($E_{min}$) likewise dominate the second component.

This pattern of dominating variables might serve as an explanation for the outlier behavior of the phenol **34**, which exhibits strong electron-donating properties instead of the advantageous electron-withdrawing properties (see first component) and an extraordinarily low lipophilicity (see second component). Corresponding explanations for the other outlier **35** (chemically quite different from **34**) are lacking.

The almost coinciding positioning of the *Y*-variables in the PLS weights plot indicates very similar chemical descriptors for the biological potency of the entire set of the 6-substituted benzopyrans in both rat aorta and rat trachea.

Two striking features in our SAR results were treated in some more detail: (i) the pronounced reduction in potency when exchanging 6-acetyl in **15** by 6-propionyl in **16** and (ii) the high activity of **43** exhibiting a 6-fluorosulfonyloxy substituent.

An attempt to explain the potency loss of **16** is given in Figure 5. Molecules **15** and **16** are superimposed in order to comparatively show their integy moment vectors. Integy moments measure the imbalance between the center of mass of a molecule and the position of the hydrophilic regions around it. Integy moments are vectors centered in the molecular center of mass. If the integy moment is high, there is a clear concentration of hydrated regions in only one part of the molecular surface. The regions of interaction are calculated with

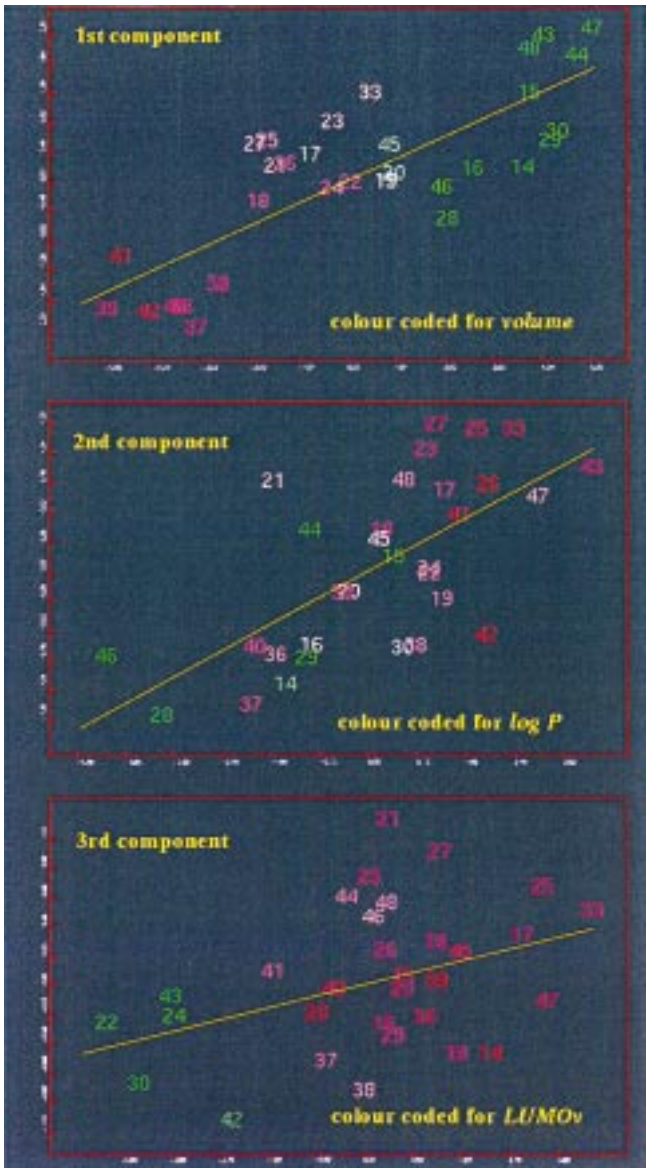



**Figure 2.** PLS plots for the 3 components of the second PLS ($n = 31$). The model tries to explain remaining "noise" of the first by the aid of the second component and so forth. Characteristic descriptors dominating the respective components are shown by color coding (red = high values and green = low values of the corresponding descriptor). Accordingly, low volume dominates the first, high log *P* the second, and high LUMO values the third component.

GRID using the water probe. The contour level shown is at −5 kcal/mol. The integy vectors start from the positive baricenters of the molecules and point toward the negative baricenters. The two integies for **15** and **16** differ regarding module and direction of the vector; this comparison indicates a strong sensitivity of the KCA activity to the directionality of charge distribution within the 6-varied test compounds.

Comparison of the score and loading plots in Figure 6, obtained from PCA, hints at some chemical interpretation of the high dilator activity of **43**. The pattern of chemical descriptors for **43** exhibits significant differences from the remaining compounds as far as the second component is concerned (see score plot); from the loading plot this difference can be mainly attributed to a significantly increased electronegativity which in turn seems to improve receptor affinity. Contribution of

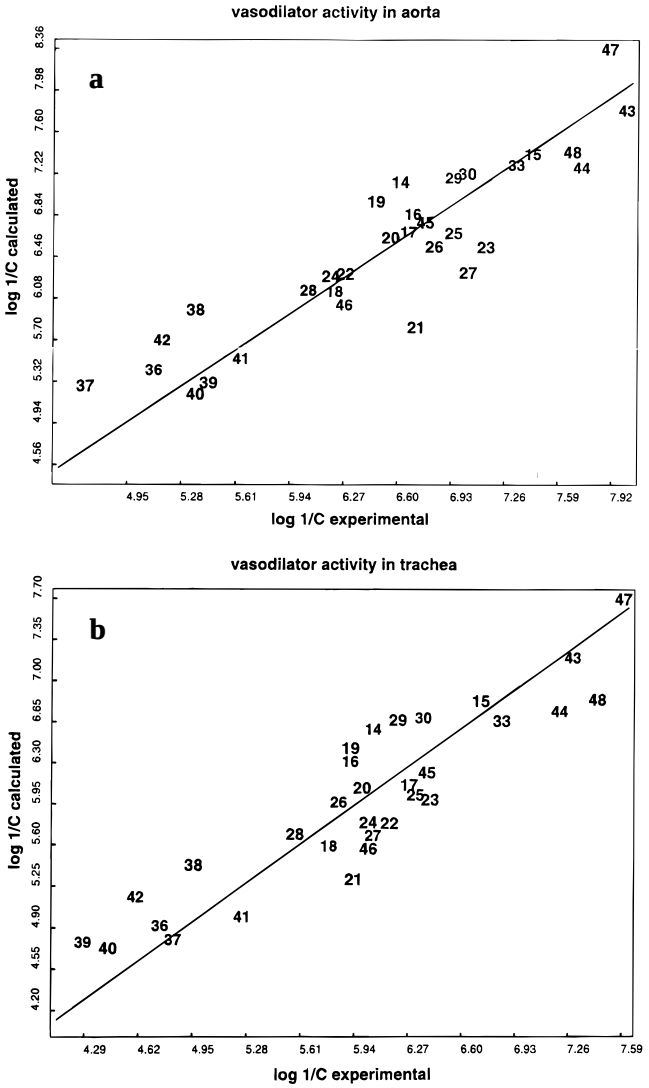



**Figure 3.** Plot of experimental versus recalculated biological activity data for the aortic (a) and tracheal (b) test systems. The figure elucidates the strong similarity in the SAR for both test systems and the slight superiority of the model for tracheal data.

6-substituents to receptor affinity could be either by a direct (presumably dipolar) interaction with the receptor site or indirectly by withdrawing electrons from the attached phenyl moiety and thereby optimizing charge-transfer interactions of the aromate. The high potency of **43** with its fluorosulfonyloxy substituent strongly favors the first alternative.

In summary, our multivariate analysis provides the following results: (1) 6-Substituents represent part of the benzopyran pharmacophore; i.e., they directly bind to the receptor site. KCA activity is strongly sensitive to the directionality of charge distribution within the 6-substituent; it seems to be particularly favorable for the 6-fluorosulfonyloxy derivative **43**. 6-Substituents containing a sulfonyl moiety could represent an interesting lead for further optimizing new benzopyrans. (2) 6-Substituents should exhibit a strong electronegativity and high values for the integy moment, low volume, high lipophilicity, and low minimum energies of interaction for optimized dilator potency. (3) Tissue selectivity is not achievable with variation of substitution pattern in the 6-position.

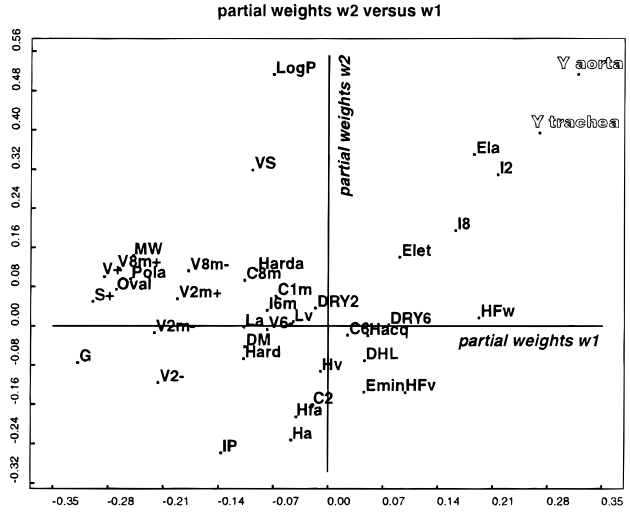



**Figure 4.** 2D-plot of the partial weights for the second versus the first component. A strong electronegativity as well as high values for the integy moment $I_2$ (calculated at −0.5 kcal/mol) dominate the first component; low values (projection onto the negative part of the *X*-component) for substituent size (as defined by globularity *G* or positive surface *S*+) are in addition favorable for high potency. High lipophilicity (log *P*) and low minimum energies of interaction ($E_{min}$) likewise dominate the second component.

**Figure 5.** **15** and **16** are superimposed to compare their integy moment vectors. The regions of interaction are calculated with GRID using the water probe (contour level −5 kcal/mol). Integy vectors start from the positive baricenters of the molecules and point toward the negative baricenters. The two integies for **15** (light gray) and **16** (dark gray) differ regarding module and direction of the vector.

The present model can be used as a test case to guide further synthesis. For the simple exchange of F in **43** by Cl, a log 1/*C* of 7.3 for the aorta and 6.95 for trachea are predicted. As a more complex alternative $-O-CH_2-SO_2-Ph$ was selected yielding predictions of 7.2 and 6.5, respectively. This could be an interesting candidate because a limited loss in activity is coupled with a reduction of lipophilicity, in turn improving its profile as a putative drug candidate.

## Experimental Section

**A. Chemistry.** Melting points were taken on a Lindstroem apparatus and are uncorrected. $^1H$ and H-decoupled $^{13}C$ NMR

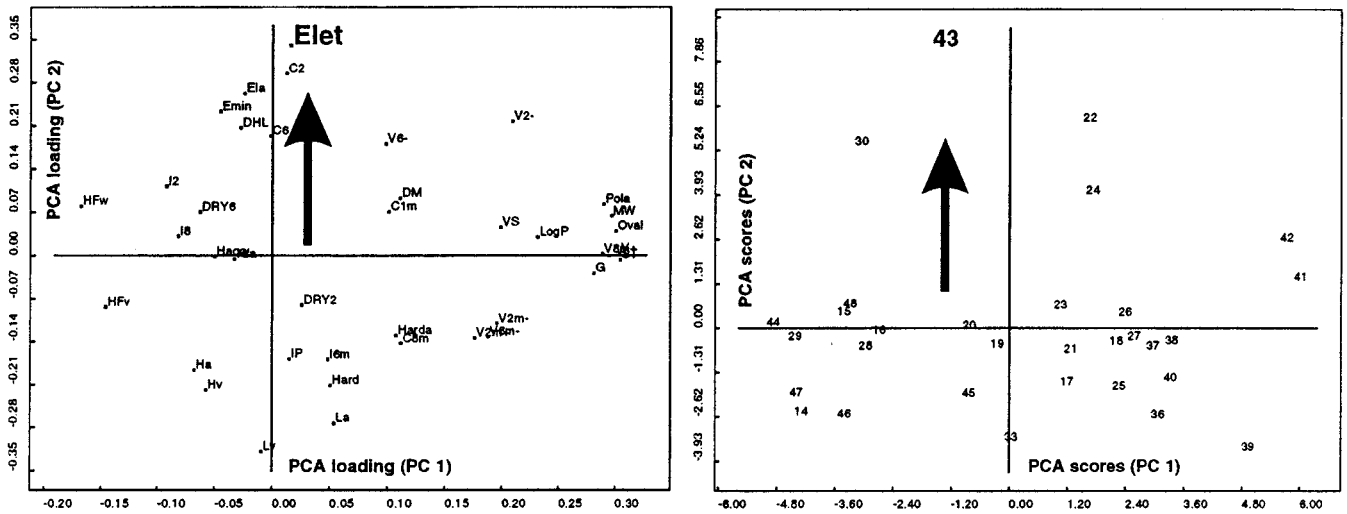



**Figure 6.** Principal component analysis ($n = 31$). Chemical descriptors for **43** differ from the other compounds in the second component (see score plot); from the loading plot this difference can be mainly attributed to a significantly increased electronegativity which in turn seems to improve receptor affinity.

spectra were recorded on a Bruker AC-200 spectrometer. IR and MS spectra were measured on a Perkin-Elmer 1600 FT-IR spectrometer and a Finnigan 4000 spectrometer. Elemental analyses (C, H, N) were carried out in the microanalytical center (Heinrich-Heine-Universität, Düsseldorf) with a Perkin-Elmer PE2400 CHN elemental analyzer and were within ±0.3% of the calculated values. Solvents were all of anhydrous grade and were obtained from commercial suppliers; 1,2-dichloroethane was distilled from $P_2O_5$ just prior to use.

**Synthesis of the Benzopyrans 3 and 4.** A mixture of the corresponding aldehyde (12.2 g, 0.1 mol salicyl aldehyde; 15.3 g, 0.1 mol 2-hydroxy-5-methoxybenzaldehyde; Aldrich Chemicals), anhydrous potassium carbonate (40 g), and 80 mL DMF was heated at 150 °C for 15 h. The resulting dark-brown mixture was allowed to cool and evaporated to remove DMF. The residue was partitioned between ether and water, and the aqueous phase was discarded. The organic layer was successively washed with 1 N HCl, 1 N NaOH, and water, dried ($MgSO_4$), evaporated, and distilled in vacuo.

**2,2-Dimethyl-2*H*-1-benzopyran (3):** colorless oil[7] (3.8 g, 24%); $bp_{19}$ 110 °C; MS 161 (7, M + 1), 160 (16, M), 145 (100).

**6-Methoxy-2,2-dimethyl-2*H*-1-benzopyran (4):** yellowish oil[7] (2.63 g, 46%); $bp_{0.05}$ 58−60 °C; MS 190 (35, M), 175 (100), 160 (6), 135 (86).

**Synthesis of the Bromohydrins 5 and 6.** The appropriate chromene (0.05 mol, 8.01 g of **3** or 9.51 g of **4**, respectively) was dissolved in a mixture of 40 mL DMSO and water (0.9 g, 0.05 mol). This solution was treated successively with NBS (9.8 g, 0.055 mol). The mixture was stirred for 0.5 h and then poured into 500 mL water and extracted with ethyl acetate. The organic layer was washed with water to remove DMSO and finally dried ($MgSO_4$). Evaporation followed by trituration with hexane gave the bromohydrins.

**3-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (5):** colorless crystals (10.4 g, 81%); mp 82 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.41 (s, 3H), 1.61 (s, 3H), 2.49 (d, $J = 4.8$ Hz, OH), 4.16 (d, $J = 9.4$ Hz, 1H), 4.94 (dd, $J = 9.4$ and 4.8 Hz, after add. of $D_2O$ d, $J = 9.4$ Hz, 1H), 6.8 ('d', $J = 7.8$ Hz, 1H), 7.00 ('t', $J = 7.8$ Hz, 1H), 7.20 ('t', $J = 7.8$ Hz, 1H) 7.39 ('d', $J = 7.8$ Hz, 1H); IR (KBr) 3407, 2985, 1608, 1586, 1483, 1454, 754 cm$^{-1}$; MS 258 (11), 256 (11), 161 (10), 122 (100). Anal. ($C_{11}H_{13}$BrO) C, H.

**3-Bromo-3,4-dihydro-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran-4-ol (6):** colorless crystals (12.9 g, 90%); mp 123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.38 (s, 3H), 1.58 (s, 3H), 2.52 (d, $J = 4.8$ Hz, OH), 3.78 (s, 3H), 4.41 (d, $J = 9.5$ Hz, 1H), 4.89 (dd, $J = 9.5$ and 5.0 Hz, after add. of $D_2O$ d, $J = 9.5$ Hz, 1H), 6.72 (d, $J = 8.90$ Hz, 1H), 6.80 (dd, $J = 8.9$ and 2.9 Hz, 1H), 7.00 (d, $J = 2.9$ Hz, 1H); IR (KBr) 3181, 2978, 1496, 1368, 1263, 1222, 904 cm$^{-1}$; MS 288 (20), 286 (21), 271 (2), 269 (2), 255 (2), 253 (2), 189 (7), 175 (4), 152 (100), 137 (43), 125 (29). Anal. ($C_{12}H_{15}$BrO$_3$) C, H.

**Synthesis of Epoxides 7 and 8.** The appropriate bromochromanol (0.02 mol, 5.12 g of **5** or 5.74 g of **6**, respectively) was stirred with a suspension of powdered KOH (5.7 g, 0.1 mol) in 100 mL dry ether for 2 days at room temperature. Filtration and evaporation gave the crude epoxides, which were used without further purification.

**3,4-Epoxy-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (7):** colorless oil (3.28 g, 93%); $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (s, 3H), 1.58 (s, 3H), 3.47 (d, $J = 4.6$ Hz, 1H), 3.90 (d, $J = 4.6$ Hz, 1H), 6.81 ('d', $J = 8$ Hz, 1H), 6.92 ('t', $J = 7.5$ Hz, 1H), 7.24 (td, $J = 8.0$ and 1.6 Hz, 1H), 7.34 (dd, $J = 7.5$ and 1.6 Hz, 1H); IR ($CHCl_3$) 2973, 1646, 1385, 1369, 1255 cm$^{-1}$; MS 176 (5, M), 161 (20), 139 (15), 121 (25), 43 (100).

**3,4-Epoxy-3,4-dihydro-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran (8):** colorless crystals (3.71 g, 90%); mp 82−83 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.22 (s, 3H), 1.57 (s, 3H), 3.47 (d, $J = 4.3$ Hz, 1H), 3.78 (s, 3H), 3.86 (d, $J = 4.3$ Hz, 1H), 6.74 (d, $J = 8.7$ Hz, 1H), 6.80 (dd, $J = 8.7$ and 2.7 Hz, 1H), 6.89 (d, $J = 2.7$ Hz, 1H); IR (KBr) 2977, 2833, 1616, 1499, 1368, 1260, 871 cm$^{-1}$; MS 206 (61, M), 191 (5), 163 (19), 150 (100), 137 (32), 122 (12). Anal. ($C_{12}H_{14}O_3$) C, H.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran (9).** The epoxide ***7*** (3.52 g, 20 mmol) and 2-pyridinol (2.85 g, 30 mmol) were taken in 150 mL toluene. Potassium carbonate (14 g, 0.1 mol) was added, and the mixture was refluxed for 2 h. Inorganic material was filtered off, and the toluene was washed with water to remove unreacted 2-pyridinol, then dried ($MgSO_4$), and evaporated. The residue was recrystallized from ethyl acetate to give **9** (5.15 g, 95%): mp 186 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (s, 3H), 1.52 (s, 3H), 3.86 (dd, $J = 9.5$ and 4.1 Hz, after add. of $D_2O$ d, $J = 9.5$ Hz, 1H), 4.29 (d, OH), 6.21 ('t', $J = 6.8$ Hz, 1H), 6.31 (d, $J = 9.5$ Hz, 1H), 6.68 ('d', $J = 9.0$ Hz, 1H), 6.77 ('d', $J = 7.5$ Hz, 1H), 6.90 (m, 2H), 6.98 (dd, $J = 6.9$ and 0.9 Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.38 (m, 1H); IR (KBr) 3164, 2975, 1654, 1568, 1542, 1489, 1255, 767 cm$^{-1}$; MS 253 (21, M−$H_2O$), 238 (75), 159 (37), 43 (100). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

***trans*-3,4-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-3-hydroxy-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran (10).** According to the procedure described for **9** from the epoxide **8** (4.12 g, 20 mmol), 2-pyridinol (2.85 g, 30 mmol), and potassium carbonate (14 g, 0.1 mol) in 150 mL toluene and crystallization of the residue from chloroform/hexane gave **10** (5.54 g, 92%): mp 209 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.31 (s, 3H), 1.50 (s, 3H), 3.66 (s, 3H), 3.85 (dd, $J = 9.5$ and 4.0 Hz, after add. of $D_2O$ d, $J = 9.5$ Hz, 1H), 4.27 (d, OH), 6.23 (m, 3H), 6.68 ('d', $J = 9.9$ Hz, 1H), 6.85 (m, 2H), 7.01 ('dd', $J = 8.7$ Hz, and 1.9 Hz, 1H), 7.38

**Table 2.** Chemical Data of Ketones **15**−**27**

| compd | yield, % | prep method | mp, °C | recryst solvent | formula ($M_r$) |
|---|---|---|---|---|---|
| **15** | 93 | a | 141 | ether | $C_{18}H_{17}NO_3$ (295.3) |
| **16** | 91 | a | 131 | $CH_2Cl_2$/hexane | $C_{19}H_{19}NO_3$ (309.4) |
| **17** | 84 | a | 107 | EtOAc/hexane | $C_{23}H_{19}NO_3$ (357.4) |
| **18** | 92 | a | 138 | ether | $C_{24}H_{21}NO_4$ (387.4) |
| **19** | 66 | a | 168 | EtOAc/hexane | $C_{21}H_{17}NO_3S$ (363.4) |
| **20** | 33 | a | 145 | EtOAc/hexane | $C_{21}H_{17}NO_4$ (347.4) |
| **21** | 25 | b | 305 | ether | $C_{23}H_{19}NO_4$ (373.4) |
| **22** | 55 | c | 75 | EtOAc/hexane | $C_{23}H_{18}N_2O_5$ (402.4) |
| **13** | 88 | c | 67 | ether | $C_{23}H_{18}FNO_3$ (375.4) |
| **14** | 10 | c | 79 | EtOAc/hexane | $C_{23}H_{18}N_2O_5$ (402.4) |
| **15** | 59 | c | 146 | EtOAc/hexane | $C_{24}H_{21}NO_3$ (371.4) |
| **16** | 25 | c | 132 | ether | $C_{24}H_{18}F_3NO_3$ (425.4) |
| **27** | 19 | d | 68 | EtOAc/hexane | $C_{23}H_{17}F_2NO_3$ (393.4) |

(m, 1H); IR (KBr) 3322, 2975, 1654, 1579, 1498, 1378, 1151, 864 $cm^{-1}$; MS 301 (1, M), 283 (29), 185 (36), 137 (11), 121 (9). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-(2-pyridyloxy)-2*H*-1-benzopyran (11).** From epoxide **7** (3.52 g, 20 mmol) and 2-pyridinol (2.85 g, 30 mmol) according to the procedure of Bergmann and Gericke[8] (ethanol, pyridine) and silica gel chromatography (toluene, 35/$CH_2Cl_2$, 60/2-propanol, 5) gave **11** (0.89 g, 16%) as a white solid: mp 178 °C (from ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 1.34 (s, 3H), 1.55 (s, 3H), 3.99 (d, $J$ = 8 Hz, 1H), 5.80 (d, $J$ = 8 Hz, 1H), 6.68 (s, OH), 6.90 (m, 4H), 7.22 (m, 1H), 7.35 ('d', $J$ = 7.8 Hz, 1H), 7.70 (m, 1H), 8.16 (m, 1H); IR (KBr) 3279, 2979, 1600, 1583, 1572, 1470, 1433, 1306, 754 $cm^{-1}$; MS 253 (3, M − $H_2O$), 238 (24), 43 (100). Anal. ($C_{16}H_{17}NO_3$) C, H, N.

***trans*-3,4-Dihydro-3-hydroxy-6-methoxy-2,2-dimethyl-4-(2-pyridyloxy)-2*H*-1-benzopyran (12).** According to the procedure described for **11** from the epoxide **8** (4.12 g, 20 mmol) and 2-pyridinol (2.85 g, 30 mmol) and recrystallization from ethyl acetate gave **12** (0.36 g, 6%) as a white solid: mp 85 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.32 (s, 3H), 1.53 (s, 3H), 3.76 (s, 3H), 3.98 (d, $J$ = 7.9 Hz, 1H), 5.76 (d, $J$ = 7.9 Hz, 1H), 6.63 (s, OH), 6.84 (m, 3H), 7.00 (m, 2H), 7.71 (m, 1H), 8.14 ('dd', $J$ = 5.2 and 1.2 Hz, 1H); IR (KBr) 3196, 2835, 1604, 1569, 1493, 1281, 1147 $cm^{-1}$; MS 301 (2, M), 283 (9), 268 (42), 168 (8), 150 (11), 43 (100). Anal. ($C_{17}H_{19}NO_4$) C, H, N.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (13).** The benzopyranol **9** (5.43 g, 20 mmol) was dissolved in 300 mL dioxane, and sodium hydroxide on microlayer (10 g; Merck 1.01564) was added. The suspension was refluxed for 2 h and filtered, and the filtrate was evaporated. The residual white solid was recrystallized from ether to yield **13** (3.59 g, 71%): mp 114 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.53 (s, 1H), 1.58 (s, 3H), 5.70 (s, 1H), 6.21 (td, $J$ = 6.9 and 1.3 Hz, 1H), 6.61 (m, 2H), 6.80 (m, 2H), 7.20 (m, 2H), 7.41 (m, 1H); IR (KBr) 3058, 2976, 1677, 1590, 1532, 760 $cm^{-1}$; MS 253 (21, M), 238 (100), 159 (38). Anal. ($C_{16}H_{15}NO_2$) C, H, N.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-6-methoxy-2,2-dimethyl-2*H*-1-benzopyran (14).** According to the procedure described for **13**, the benzopyranol **10** (5.66 g, 20 mmol) was dissolved in 300 mL dioxane, and sodium hydroxide on microlayer (10 g; E. Merck 1.01564) was added. The residual white solid was recrystallized from ethyl acetate to yield **14** (3.68 g, 65%): mp 119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 1.51 (s, 3H), 1.56 (s, 3H), 3.67 (s, 3H), 5.74 (s, 1H), 6.21 (m, 2H), 6.64 ('d', $J$ = 9.2 Hz, 1H), 6.72 (dd, $J$ = 8.8 and 2.8 Hz, 1H), 6.81 (d, $J$ = 8.8 Hz, 1H), 7.17 ('dd', $J$ = 7.0 and 2.0 Hz, 1H), 7.41 (m, 1H); IR (KBr) 2978, 1673, 1593, 1577, 1267, 862 $cm^{-1}$; MS 283 (33, M), 268 (100), 225 (6), 189 (43), 173 (17), 145 (19). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

**General Procedures for the Synthesis of Benzopyran Ketones (Table 2). Method a for the Preparation of Ketones 15**−**20.** The appropriate acid chloride was freshly prepared by refluxing (3 h) the corresponding acid (0.01 mol) in thionyl chloride (11.9 g, 0.1 mol). The excess $SOCl_2$ was distilled off, and the residue was dried in an exsiccator over KOH pellets. This material was used in the next step without further purification. The acid chloride was taken in 100 mL absolute 1,2-dichloroethane, and this solution was dropped into a stirred suspension of anhydrous $AlCl_3$ (1.32 g, 0.01 mol) in 100 mL 1,2-dichloroethane at 0 °C. Finally, the solution of benzopyran **13** (2.53 g, 0.01 mol) in 50 mL 1,2-dichloroethane was added slowly at 0 °C. After stirring at room temperature overnight the reaction mixture was poured on crashed ice. The organic layer was washed with 2 N HCl, 0.1 N NaOH, and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized as described.

**Method b for the Preparation of 21.** Compound **18** (0.39 g, 1 mmol) was heated with pyridine HCl (1.1 g, 0.01 mol) at 170 °C for 6 h and allowed to cool. The mixture was diluted with 2 N HCl and extracted with ether. The phenol was separated from the organic phase with 0.5 N NaOH and reextracted with ether after acidification of the aqueous layer. After drying ($MgSO_4$) and evaporation of the ether extract remained a white solid of **21**.

**Method c for the Preparation of Ketones 22**−**26.** The acid chlorides (2 mmol) were prepared from the corresponding acids and thionyl chloride as described in method a. Each was taken in 50 mL 1,2-dichloroethane, and silver triflate (0.9 g, 3.5 mmol) was added in several portions. After addition of the benzopyran **13** (0.51 g, 2 mmol) in 50 mL 1,2-dichloroethane, the mixture was refluxed for 3 h. After cooling and dilution with 150 mL ether, 10 mL 2 N KOH was added and the mixture vigorously stirred for 2 h, at room temperature. The organic phase was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography (if necessary) and crystallized as described (Table 2).

**Method d for the Preparation of 27.** Nitrobenzene was used as solvent instead of 1,2-dichloroethane, as described in method c, and the reaction temperature was raised to 160 °C. The filtrate was distilled in vacuo and the residue purified by silica gel chromatography with toluene/$CH_2Cl_2$/2-propanol (35/60/5).

**6-(Aminohydroxyiminomethyl)-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (28).** Bimakalim (**44**)[8] (280 mg, 1 mmol) was dissolved in ethanol and mixed up with a solution of hydroxylamine hydrochloride (0.42 g, 6 mmol) and sodium carbonate (0.32 g, 3 mmol) in 25 mL water. The mixture was kept on a water bath at 60 °C for 2 h, cooled, acidified with 2 N HCl, and extracted with ether. The aqueous layer was neutralized with $NH_4OH$ and saturated with $(NH_4)_2SO_4$. This solution was extracted with ethyl acetate, which was dried ($MgSO_4$) and evaporated to yield a white solid of **28** (0.27 g, 87%): mp 205−207 °C (cyclohexane); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.46 (s, 3H), 1.51 (s, 3H), 5.72 (s, $NH_2$), 5.90 (s, 1H), 6.33 (m, 1H), 6.47 (dd, $J$ = 8.9 and 0.9 Hz, 1H), 6.87 (d, $J$ = 8.4 Hz, 1H), 6.94 (d, $J$ = 2.0 Hz, 1H), 7.47 (dd, $J$ = 8.4 and 2.0 Hz, 1H), 7.57 (m, 2H), 9.52 (s, OH); IR (KBr) 3566, 3338, 1658. 1273 $cm^{-1}$; MS 311 (11, M), 296 (32), 263 (12), 217 (19). Anal. ($C_{17}H_{17}N_3O_3 \cdot 0.5H_2O$) C, H, N.

**6-Formyl-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (29).** Bimakalim (**44**)[8] (1.39 g, 5 mmol) and 2 g sodium hypophosphite were dissolved in a mixture of 40 mL water/acetic acid/pyridine (1/1/2); 0.5 g Raney nickel was added, and the whole mixture was stirred for 2 h at 45 °C. The catalyst was filtered off, and the filtrate was diluted with 100 mL water and extracted with ether. The organic phase was washed with 2 N HCl, sodium bicarbonate, and water, dried, and evaporated. The residue was crystallized from ether to give a white solid (1.20 g, 85%): mp 172 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.52 (s, 3H), 1.55 (s, 3H), 6.13 (s, 1H), 6.38 (m, 1H), 6.51 (dd, $J$ = 9.7 and 1.0 Hz, 1H), 7.06 (m, 2H), 7.60 (m, 2H), 7.78 (dd, $J$ = 8.4 and 2.0 Hz, 1H), 9.77 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 190.36, 161.78, 158.59, 140.44, 137.64, 134.30, 132.55, 130.01, 129.11, 124.64, 121.97, 118.38, 117.55, 106.30, 78.43, 28.32, 28.14; IR (KBr) 1682, 1666, 1596 $cm^{-1}$; MS 281 (14, M), 266 (53), 187 (52), 115 (19), 78 (100). Anal. ($C_{17}H_{15}NO_3$) C, H, N.

**6-(2,2-Dicyanoethenyl)-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (30).** The aldehyde **29** (0.84 g, 3 mmol) and malononitrile (0.2 g, 3 mmol) were dissolved

in 50 mL toluene. After addition of each 1 drop of acetic acid and piperidine, the mixture was boiled on a water separator for 2 h. The toluene phase was washed with 2 N HCl and then with sodium bicarbonate and water, dried, and evaporated. The residue was crystallized from ethyl acetate/hexane to give a yellow solid of **30** (0.87 g, 88%): mp 202−204 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.53 (s, 3H), 1.56 (s, 3H), 6.16 (s, 1H), 6.35 (m, 1H), 6.46 (dd, $J$ = 9.8 and 1.0 Hz, 1H), 7.11 (d, $J$ = 8.6 Hz, 1H), 7.36 (d, $J$ = 2.2 Hz, 1H), 7.56 (m, 2H), 7.84 (dd, $J$ = 8.6 and 2.2 Hz, 1H), 8.36 (s, 1H); IR (KBr) 2224, 1666, 1582, 1226 cm$^{-1}$; MS 329 (3, M), 314 (15), 235 (19), 78 (100). Anal. ($C_{20}H_{15}N_3O_2$) C, H, N.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-nitro-2*H*-1-benzopyran (31).** This compound is already described by Bergmann and Gericke,[8] but we used another method for preparation. The benzopyran **13** (0.5 g, 2 mmol) was dissolved in dry dichloromethane (50 mL), and nitronium tetrafluoroborate (0.3 g, 2.2 mmol) was added. After stirring under anhydrous conditions for 24 h at room temperature, the solvent was washed with sodium bicarbonate and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized from ethyl acetate to yield a nearly colorless solid of **31** (0.36 g, 60%): mp 164 °C (lit.[8] mp 156−158 °C); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.54 (s, 3H), 1.57 (s, 3H), 6.25 (s, 1H), 6.41 (m, 1H), 6.54 (d, $J$ = 9.3 Hz, 1H), 7.09 (d, $J$ = 9.0 Hz, 1H), 7.32 (d, $J$ = 2.6 Hz, 1H), 7.65 (m, 2H), 8.11 (dd, $J$ = 9.0 and 2.6 Hz, 1H); IR (KBr) 1666, 1594, 1534, 1517, 1481 cm$^{-1}$; MS 298 (1, M), 283 (21), 238 (73), 159 (38). Anal. ($C_{16}H_{14}N_2O_4$) C, H, N.

**6-Amino-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (32).** The nitro compound **31** (0.9 g, 3 mmol) was reduced with an excess of elementary iron powder (0.3 g) in 100 mL 5 N $H_2SO_4$ at room temperature for 3 h. The remaining solution was filtered and neutralized with NaOH to pH 7, and tartaric acid was added. This solution was extracted several times with ethyl acetate, which after drying and evaporation gave the amine **32** as a light-brown solid (0.52 g, 65%): mp 157 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.38 (s, 3H), 1.43 (s, 3H), 4.67 (s, $NH_2$), 5.83 (s, 1H), 5.84 (s, 1H), 6.30 (m, 1H), 6.40 (dd, $J$ = 8.5 and 2.6 Hz, 1H), 6.45 (d, $J$ = 8.5 Hz, 1H), 6.57 (d, $J$ = 8.5 Hz, 1H), 7.52 (m, 2H); IR (KBr) 3423, 3336, 1663, 1590, 1274 cm$^{-1}$; MS 268 (63, M), 253 (100), 173 (78). Anal. ($C_{16}H_{16}N_2O_2$) C, H, N.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-6-(2,5-dimethyl-1-pyrrolyl)-2,2-dimethyl-2*H*-1-benzopyran (33).** The amine ***32*** (0.54 g, 2 mmol) was mixed with 10 mL acetonylacetone and kept at 160 °C for 2 h. The excess of diketone was distilled in vacuo and the residue purified by silica gel chromatography with toluene/acetone (60/40); yellowish solid from methanol/water (0.4 g, 58%); mp 146 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 1.51 (s, 3H), 1.55 (s, 3H), 1.88 (s, 6H), 5.71 (s, 2H), 6.07 (s, 1H), 6.24 (d, $J$ = 2.3 Hz, 1H), 6.31 (m, 1H), 6.46 (d, $J$ = 9.2 Hz, 1H), 6.96 (d, $J$ = 8.5 Hz, 1H), 7.09 (dd $J$ = 8.5 and 2.3 Hz, 1H), 7.55 (m, 2H); IR (KBr) 1662, 1593, 1533 cm$^{-1}$; MS 346 (14, M), 331 (13), 252 (17), 236 (11), 208 (53). Anal. ($C_{22}H_{22}N_2O_2$) C, H, N.

**Synthesis of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-6-hydroxy-2,2-dimethyl-2*H*-1-benzopyran (34). Method a:** The benzopyran **14** (5.67 g, 20 mmol) was melted with pyridine hydrochloride (6.93, 60 mmol) at 170 °C for 2 h. The hot solution was poured in 150 mL sulfuric acid (2%), and the product was extracted with methylene chloride. The organic layer was dried ($MgSO_4$), and evaporation followed by crystallization from methanol gave the phenol **34** (2.21 g, 41%).

**Method b:** 5.67 g (20 mmol) of compound **14** was dissolved in 40 mL dry dichloromethane and cooled to −10 °C. A mixture of (25 g, 0.1 mol) boron tribromide and 30 mL dichloromethane was slowly added, and the solution was stirred for 1 h. Subsequently the solution was poured into water, and the product was extracted three times with ethyl acetate. The combined ethyl acetate phases were dried ($MgSO_4$) and evaporated. The residue was washed with ether, and the crystalline solid was purified by recrystallization from methanol to give the phenol derivative **34** (3.12 g, 58%): colorless crystals; mp 238 °C (from methanol); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.41 (s, 3H), 1.46 (s, 3H), 5.91 (s, 1H), 5.99 (d, $J$ = 2.7 Hz, 1H), 6.32 ('dt', $J$ = 6.5 and 1.0 Hz, 1H), 6.47 ('d', $J$ = 9.0 Hz, 1H), 6.57 (dd $J$ = 8.6 and 2.7 Hz, 1H), 6.69 (d, $J$ = 8.6 Hz, 1H), 7.55 (m, 2H), 8.97 (s, OH); IR (KBr) 3126, 1658, 1652, 1570, 1537, 1150 cm$^{-1}$; MS 269 (23, M), 254 (100), 175 (33), 147 (6), 131 (10), 115 (10). Anal. ($C_{16}H_{15}NO_3$) C, H, N.

**Table 3.** Chemical Data of Carbamates **38**−**42**

| compd | yield, % | mp, °C | IR (KBr) (cm$^{-1}$) | formula ($M_r$) |
|---|---|---|---|---|
| **38** | 87 | 195 | 1734, 1665 | $C_{23}H_{20}N_2O_4$ (388.4) |
| **39** | 85 | 171 | 1736, 1666 | $C_{23}H_{19}FN_2O_4$ (406.4) |
| **40** | 86 | 185 | 1734, 1665 | $C_{23}H_{19}FN_2O_4$ (406.4) |
| **41** | 59 | 145 | 1744, 1663 | $C_{24}H_{19}F_3N_2O_4$ (456.4) |
| **42** | 68 | 160 | 1734, 1662 | $C_{24}H_{19}F_3N_2O_4$ (456.4) |

**6-Acetoxy-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran (35).** Phenol **34** (2.69 g, 10 mmol), acetyl chloride (940 mg, 12 mmol), 1−2 drops of trimethylamine, and 100 mL dry toluene was stirred under reflux for 1 h. After evaporation the residue was dissolved in methylene chloride, and the organic layer was washed with 2% sulfuric acid and 2% sodium hydroxide. The organic phase was dried ($MgSO_4$) and evaporated. The residue was crystallized from methylene chloride/hexane to give the ester derivative **35** (2.49 g, 80%): colorless crystals; mp 173 °C from hexane; $^1$H NMR ($CDCl_3$) $\delta$ 1.53 (s, 3H), 1.58 (s, 3H), 2.21 (s, 3H), 5.74 (s, 1H), 6.22 ('dt', $J$ = 6.8 and 1.2 Hz, 1H), 6.41 (d, $J$ = 2.3 Hz, 1H), 6.63 ('d', $J$ = 8.4 Hz, 1H), 6.84 (d $J$ = 8.3 Hz, 1H), 6.90 (dd, $J$ = 8.3 and 2.3 Hz, 1H), 7.18 ('dd', $J$ = 6.9 and 1.9 Hz, 1H), 7.42 (m, 1H); IR (KBr) 2974, 1754, 1674, 1593, 1531, 1218, 764 cm$^{-1}$; MS 311 (6, M), 296 (9), 269 (5), 254 (41), 175 (19), 117 (6), 96 (22), 43 (100). Anal. ($C_{18}H_{17}NO_4$) C, H, N.

**General Procedure for the Synthesis of Ether Derivatives 36−37.** Phenol **34** (2.69 g, 10 mmol) was stirred under reflux with the appropriate phenacyl bromide (11 mmol) and potassium carbonate in acetone for 1 h. The resultant suspension was filtrated and evaporated. The residue was purified by silica gel chromatography (10% acetone/toluene) to give the ethers as colorless crystals.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-(phenacyloxy)-2*H*-1-benzopyran (36):** colorless crystals (1.82 g, 47%); mp 137 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.51 (s, 3H), 1.56 (s, 3H), 5.13 (s, 2H), 5.74 (s, 1H), 6.18 ('dt', $J$ = 6.8 and 1.2 Hz, 1H), 6.32 ('d', $J$ = 1.9 Hz, 1H), 6.59 ('d' $J$ = 9.2 Hz, 1H), 6.77 (m, 2H), 7.14 ('dd', $J$ = 6.9 and 1.9 Hz, 1H), 7.46 (m, 4H), 7.93 (m, 2H); IR (KBr) 2978, 1700, 1672, 1662, 1269, 764 cm$^{-1}$; MS 387 (14, M), 372 (32), 268 (30), 173 (10), 105 (100). Anal. ($C_{24}H_{21}NO_4$) C, H, N.

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-6-(4-fluorophenacyloxy)-2,2-dimethyl-2*H*-1-benzopyran (37):** colorless crystals (2.35 g, 58%); mp 159 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.51 (s, 3H), 1.56 (s, 3H), 5.07 (s, 2H), 5.74 (s, 1H), 6.19 ('dt', $J$ = 6.9 and 1.5 Hz, 1H), 6.31 (d, $J$ = 2.5 Hz, 1H), 6.60 ('d', $J$ = 9.0 Hz, 1H), 6.77 (m, 2H), 7.15 (m, 3H), 7.39 (m, 1H), 7.98 (m, 2H); IR (KBr) 3074, 1704, 1666, 1595, 1138 cm$^{-1}$; MS 405 (8, M), 390 (21), 268 (16), 145 (12), 123 (100). Anal. ($C_{24}H_{20}FNO_4$) C, H, N.

**General Procedure for the Synthesis of Carbamates 38−42.** Phenol **34** (2.69 g, 10 mmol) was dissolved in 50 mL absolute toluene; then 2 drops of triethylamine and 10 mmol of the appropriate isocyanate were added. The mixture was stirred for 1 h under reflux. After the solvent was removed, the residue was crystallized from hexane to give the carbamates **38**−**42** as colorless crystals (Table 3).

**4-(1,2-Dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-2*H*-1-benzopyran-6-yl Fluorosulfonate (43).** A solution of (2.69 g, 10 mmol) phenol **34** in 30 mL pyridine was stirred in a flask fitted with a condenser cooled by solid carbon dioxide. The mixture was chilled to 0 °C, and 1.77 g (15 mmol) of sulfuryl chloride fluoride was introduced. The mixture was slowly warmed and held at 30 °C for 1 h. It was then poured into ice-cold hydrochloric acid, and the product was extracted with

ether. The ethereal extract was washed with water, then with dilute aqueous sodium chloride, and again with water. After evaporation the residue was purified by silica gel chromatography (ethyl acetate) to give nearly colorless crystals (562 mg, 16%): mp 121 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.55 (s, 3H), 1.60 (s, 3H), 5.81 (s, 1H), 6.27 ('dt', $J$ = 6.8 and 1.6 Hz, 1H), 6.65 (m, 2H), 6.90 (d, $J$ = 8.9 Hz, 1H), 7.16 (m, 2H), 7.46 (m, 1H); IR (KBr) 3066, 2980, 1666, 1593, 1534, 1484, 1446, 1232, 1210 cm$^{-1}$; MS 351 (7, M), 336 (24), 268 (8), 257 (18), 149 (15), 127 (14), 117 (12), 78 (100). Anal. ($C_{16}H_{14}FNO_5S$) C, H, N.

**B. Biological Methods. Relaxant Potency in Rat Aorta and Trachea.** For biological characterization of the dilator properties of KCA, male Wistar rats of 250−350 g of body weight were used. After dissection of aorta and trachea, tissues were placed in Krebs solution containing (mmol/L) 120 $Na^+$, 5 $K^+$, 2.25 $Ca^{2+}$, 0.5 $Mg^{2+}$, 98.5 $Cl^-$, 34 $HCO_3^-$, 1$HPO_4^{2-}$, and 0.5 $SO_4^{2-}$, equilibrated with carbogen (95% $O_2$, 5% $CO_2$).

Aortic rings of 5-mm width were prepared and denuded from endothelium, success of which was tested by lacking dilator response to acetylcholine (1 mmol/L). Tracheal strips were prepared by splitting tracheal rings on the opposite side of the ring muscle layer as described by Lemoine and Overlack.[19] Tissues were mounted in a modified Blinks apparatus[20] equipped with 7-mL baths and isometric strain gauge transducers (Swema SG4-45). Pretension of smooth muscle strips was adjusted to 0.5 g. Experiments were performed at 32.5 °C in Krebs solution, supplemented with (mmol/L) fumarate (5.0), pyruvate (5.0), glutarate (5.0), bicarbonate (5.0), and glucose (10.0).

Contractures were induced with 25 mmol/L $K^+$ and 0.6 $\mu$mol/L carbachol in aortic rings and tracheal strips, respectively. After developed force had reached a stable level of contraction, cumulative concentration−effect curves were performed for each test compound.

Compounds were dissolved in stock solutions containing $10^{-2}$ M DMSO; dilutions were performed in distilled water. Final concentration of DMSO in the organ bath did not exceed 2% to avoid dilator effects of the solvent. Dose−response curves were fitted with the software SAS 604; half-maximal potency of the KCA was derived from the curves as $pEC_{50}$ value.

**C. Chemical Descriptors.** Log $P$ data were calculated with the KOWWIN software.[21] The matrix of the other chemical descriptors was built using different modeling programs. Geometry optimization was obtained using Spartan[22] at the AM1-acq level. Molecular descriptors such as heat of formation, ionization potential, dipole moment, HOMO, LUMO, electronegativity, hardness, and polarity were computed by Spartan using the QSAR option. The remaining descriptors were computed from the 3D-interaction energy maps produced by GRID[23] and transformed by VolSurf.[24] GRID force field detects favorable binding sites for chemical probes on the surface of target molecules. For a drug molecule surrounded by the water probe, the trapped water molecules are used to define hydrophilic regions; the hydrophobic probe DRY is applied for defining hydrophobic regions. Area and volume of this envelope vary with the level of interaction energies between probe and target molecule. However, at a fixed isoenergetic contour level, the hydrophilic area and volume are well-defined for each molecule. VolSurf is a program to visualize, quantify, and transform the 3D-energy maps into useful chemical descriptors. From the 3D-interaction energy maps VolSurf is able to compute molecular volume, surface, and globularity, interaction energy moments, and capacity factors. The globularity is defined as $S/Se$, in which $Se$ is the surface area of a sphere of volume $V$, which is the equivalent sphere. Globularity equals 1 for spherical molecules. Moreover VolSurf calculates the integy moment; it is defined similarly to the dipole moment but calculated from the interaction energies. Finally capacity factors are calculated, which are defined as the ratio between the attractive molecular volume and the molecular surface, which is the amount of negative interaction per surface unit. Positive repulsive surfaces and volumes were computed at 0.25 kcal/mol, negative attractive volumes in a range from −0.5 up to −6 kcal/mol. This procedure yields a minimum of 10 descriptor variables. The same procedure was applied to the MEP computed by Spartan, yielding 10 more molecular descriptors. Some of these can be higly correlated. However, their simultaneous use is to be preferred since spourious errors can be better detected and compensated.

**D. Statistical Approaches.** Principal component and PLS analyses[25] were performed with the GOLPE[26] software, version 3.1, on a Silicon Graphics workstation.

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**Supporting Information Available:** Spectroscopic data (IR, $^1$H and $^{13}$C NMR, MS) on ketones **15**−**27** and carbamates **38**−**42**. This material is available free of charge via the Internet at http://pubs.acs.org.

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