NO-Donor Phenols: A New Class of Products Endowed with Antioxidant and Vasodilator Properties

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The synthesis and study of the antioxidant and vasodilator properties of a new class of phenols able to release nitric oxide are described. The products were designed through a symbiotic approach using selected phenols and selected nitrooxy and furoxan NO-donors as reference models. The antioxidant activities of the hybrid products were assessed by detecting the 2-thiobarbituric acid reactive substances (TBARS) produced in the ferrous salt/ascorbate-induced autoxidation of lipids present in microsomial membranes of rat hepatocytes. The vasodilator activity was assessed on rat aortic strips precontracted with phenylephrine. Some of the products (**13**, **35**, **37**, **60**−**62**, **64**) behave principally as vasodilators and others as antioxidants (**24**, **32**, **72**), and the two properties are relatively balanced in **19**, **41**, and **68**. Further in vivo studies should clarify whether some of these products may become preclinical candidates for the treatment of cardiovascular disease underpinned by atheroma.

Introduction

Cardiovascular disease (CD) is the major cause of morbidity and mortality in developed countries.[1] Many forms of CD involve atherosclerotic vascular changes, a desease process in which reactive oxygen species (ROS) are heavily implicated. ROS are produced in cellular metabolism through different pathways, but in healthy individuals, they are rapidly eliminated by a wide range of antioxidant systems designed to prevent their harmful effects.[2a] When the prooxidant/antioxidant balance is perturbed, due to either an abnormal production of ROS or depletion of antioxidant defenses, a situation called oxidative stress arises.[2b−d] Continued oxidative stress leads to cellular damage, due to alteration of lipids, enzymes, proteins, and DNA. In the atherosclerotic vascular changes there is an abnormal production of superoxide anion ($O_2^{-\bullet}$) by the endothelium.[2b,3] Hydrogen peroxide is formed from this radical, under the action of the superoxide dismutase (SOD). Hydrogen peroxide is a source of the very toxic hydroxyl radical ($OH^\bullet$) (Fenton and Haber−Weiss reaction). Low density lipoproteins (LDL), accumulated in the subendothelial space, are subject to oxidative modifications under the action of this radical. This is the first step in a complex process that leads first to the formation of foam cells, then of the fatty streak, and ultimately to atherosclerotic plaque.[3] In an atherosclerotic vessel, the excess $O_2^{-\bullet}$ induces alterations in the nitric oxide (NO) signaling system.[4a] In fact, superoxide anion traps NO to generate peroxynitrite (^-OONO) that, in turn, can afford two very reactive and toxic radicals: $OH^\bullet$ and the nitrogen dioxide radical ($NO_2^\bullet$). In addition, $O_2^{-\bullet}$, when present in high concentrations, can react with thiol residues of proteins that are normally involved in *S*-nitrosylation, preventing this reaction from occurring.[4b,c] The result is the perturbation of this signaling mechanism with the consequent decrease of vessel responsiveness to $NO^\bullet$. By contrast, the responsiveness to the vasodilator actions of exogenous NO released by NO donors, such as glyceryl trinitrate and nitroprusside, is largely preserved. This is probably due to the relatively high doses of the compounds used in the experiments. There is also some evidence that in an atherosclerotic vessel the production of NO (EDRF) by the endothelial cells could be decreased.[4d] On these bases, we have designed and synthesized a large series of compounds in which appropriate NO-donor substructures, such as nitrooxy and substituted furoxan moieties, were linked to different antioxidants such as phenols, vitamin C, melatonin, isoflavones, and 1,4-dihydropyridines. These products are examples of multitarget drugs, namely, single chemical entities able to simultaneously modulate more than one target. Today, there is interest in the use of this kind of drug for the treatment of complex diseases such as CD. The risk−benefit profile in the use of a multitarget drug in therapy compared to the use of a monotarget drug cocktail has been discussed.[5] A down side in the use of a polyvalent drug is certainly the difficulty to adjust the ratio of activities against different targets. Advantages seem to be a more predictable pharmacokinetic profile, lower risk of drug−drug interactions, and major compliance by the patient. Here we report the conclusive results of a study on the capacity of inhibiting the ferrous salt/ascorbate-induced peroxidation of membrane lipids of rat hepatocytes and in vitro vasodilator properties obtained with a series of NO-donor phenols.[6] These products were formally obtained by joining the phenols **1**−**4**, characterized by extensively modulated antioxidant properties,[7] with appropriate NO-donor moieties (Chart 1). The NO-donor moieties that we used were nitrooxy-substituted alkyl moieties, which are present in simple nitric esters **5** and **6**, as well as the 3-phenylsulfonylfuroxan-4-yloxy substructure present in the 4-ethoxy-3-phenylsulfonylfuroxan (**7**) and the 3-carbamoylfuroxan-4-ylmethyl substructure present in the 4-hydroxymethyl-3-furoxancarboxamide (**8**) and in its nitrogen analogue **9** (Chart 1). These reference NO donors show extensively modulated in vitro NO-dependent vasodilator properties. Products **7** and **8** are also orally active vasodilators, the former developed by the Chiesi Co.[8a] (CHF 2363) and the latter by the Cassella-Hoechst

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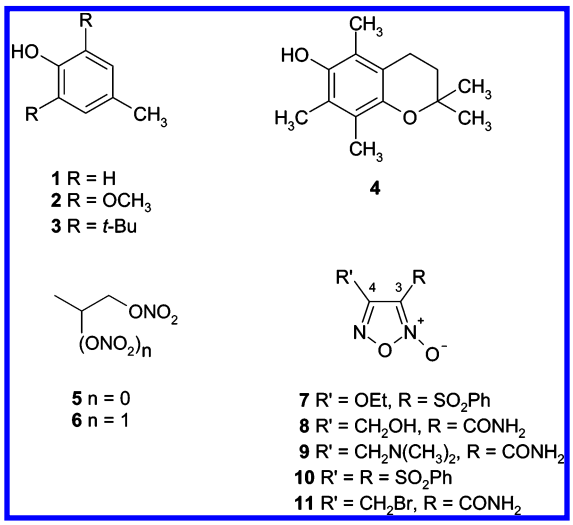
Chart 1

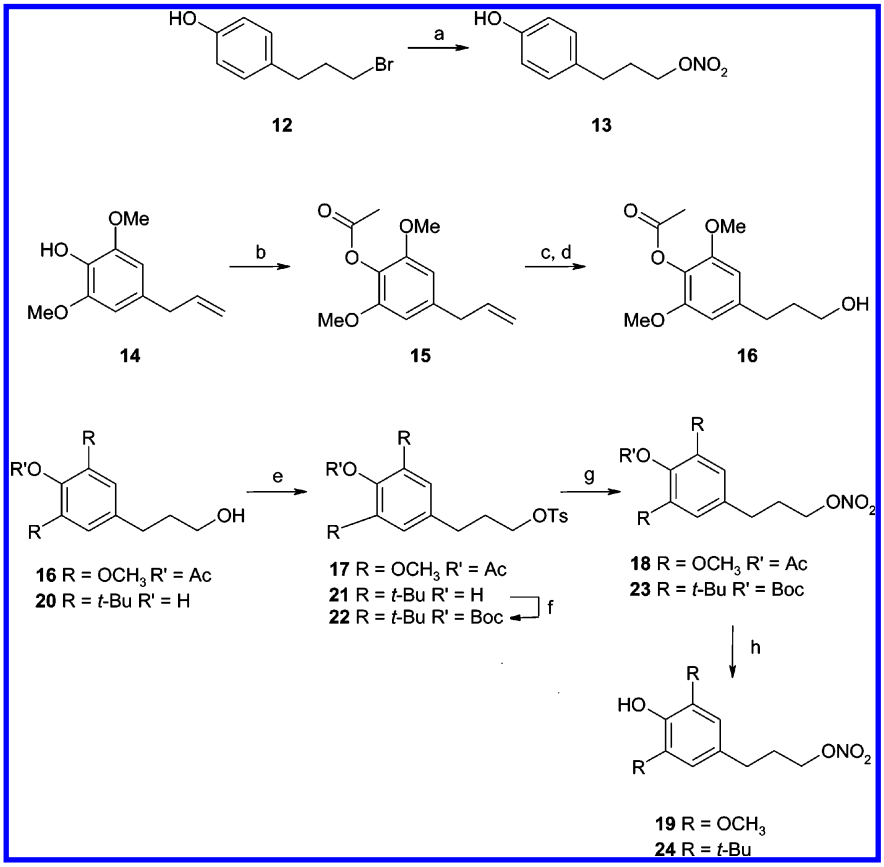


Co.[8b] (CAS 1609). The reason for choosing these reference models to use in our chemical hybridization approach was to obtain final hybrids endowed with extensively modulated antioxidant and vasodilator potencies in order to have a flexible tool for future in vivo studies.

Results and Discussion

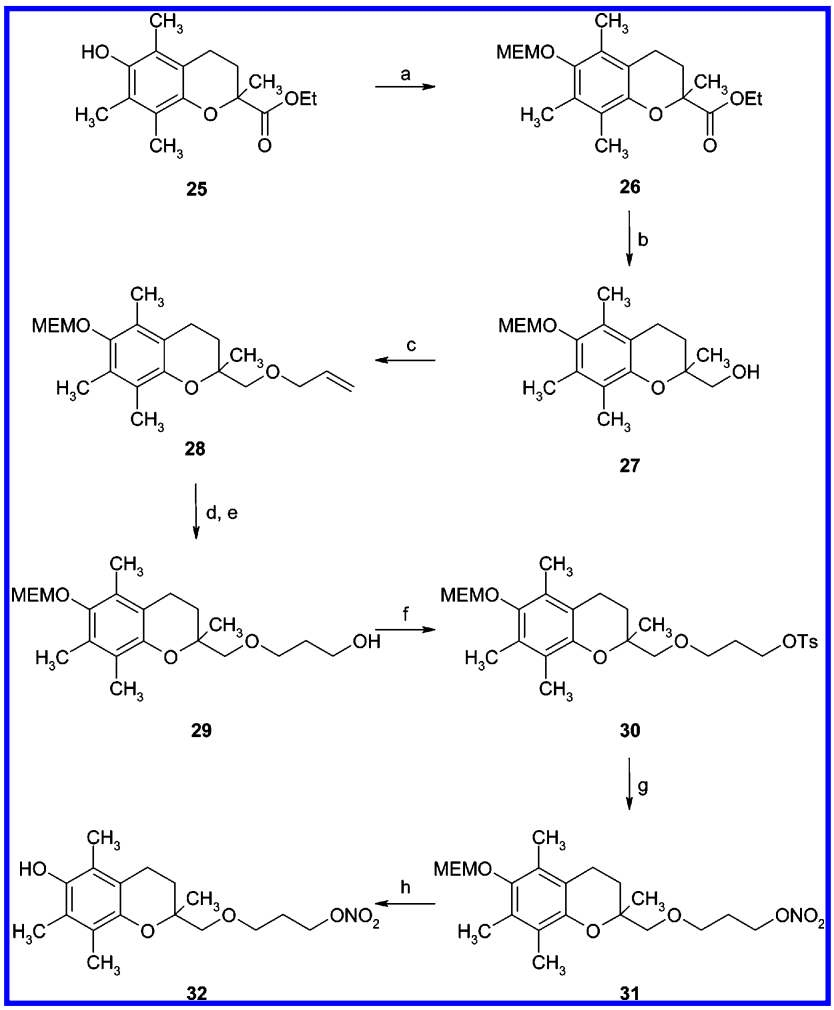
Chemistry. The products containing only one nitrooxy function were prepared according to the procedure reported in Scheme 1. The simple mononitrooxy derivative **13** was obtained by the action of $AgNO_3$ on the 4-(3-bromopropyl)phenol (**12**) in acetonitrile solution. The analogue 2,6-dimethoxy-substituted **19** was synthesized starting from the 4-allyl-2,6-dimethoxyphenol (**14**) that was transformed into the corresponding acetate **15** by acetic anhydride in the presence of triethylamine (TEA) and 4-*N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 solution. The action on **15** of 9-borabicyclo[3.3.1]nonane (9-BBN) in THF and then of 30% hydrogen peroxide and sodium acetate gave the propanol derivative **16**. The hydroxy group of this product was tosylated in CH_2Cl_2 solution with tosyl chloride (TsCl), in the presence of TEA and DMAP, to afford **17**. This latter product was left to react with tetrabutylammonium nitrate ($Bu_4N^+NO_3^-$) in refluxing benzene to yield **18**, which was transformed, in CH_2Cl_2 solution, in the presence of pyrrolidine, into the final compound **19**. To prepare **24**, the alcoholic group of 2,6-di-*tert*-butyl-4-(3-hydroxypropyl)phenol (**20**) was left to react with TsCl, under the same conditions used to prepare **17**, to obtain **21**. Subsequently, the phenol group of **21** was Boc-protected with di-*tert*-butyl dicarbonate (Boc_2O) and the resulting product **22** was transformed into the analogue nitrooxy derivative **23** through the same procedure used to prepare **18** from **17**. The Boc protection was cleaved with trifluoroacetic acid (TFA) in CH_2Cl_2 to give the final product **24**. Compound **32** (Scheme 2), in which the 6-hydroxy-2,2,5,7,8-pentamethylchroman (**4**, Chart 1) substructure of vitamin E is present, was synthesized starting from **25**, which was obtained by treatment of the carboxylic acid Trolox with ethanol in the presence of *p*-toluensulfonic acid (*p*-TSA).[9] The free phenol hydroxy group was MEM-protected using 2-methoxyethoxymethyl chloride (MEMCl) to give **26**. Subsequent reduction of the ester group by $LiAlH_4$ in THF afforded the corresponding alcohol **27**. Reaction of **27** with allyl bromide in DMF, in the presence of NaH, yielded the allyl ether **28**. This latter product was left to

Scheme 1[a]



[a] (a) $AgNO_3$, CH_3CN, 60 °C; (b) Ac_2O, TEA, DMAP, CH_2Cl_2, 0 °C; (c) 9-BBN, dry THF; (d) NaOAc, H_2O_2 30%, 0 °C; (e) TsCl, TEA, DMAP, CH_2Cl_2; (f) Boc_2O, DMAP, CH_2Cl_2; (g) $Bu_4N^+NO_3^-$, benzene, reflux; (h) pyrrolidine, CH_3CN, 0 °C for **18**, TFA, dry CH_2Cl_2, 0 °C for **23**.

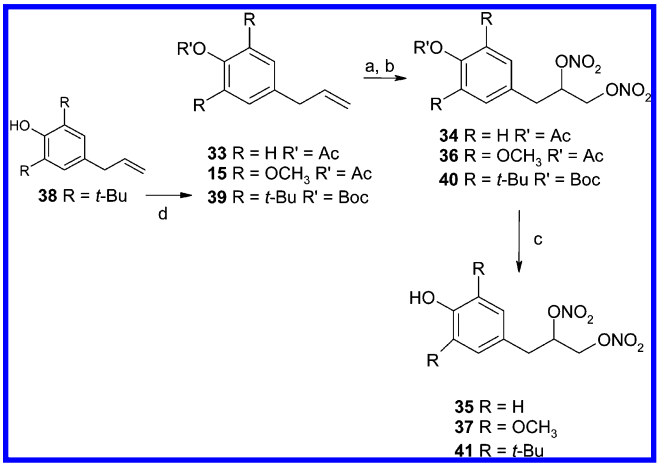
Scheme 2[a]



[a] (a) MEMCl, NaH, dry THF; (b) $LiAlH_4$, dry THF; (c) allyl bromide, NaH, DMF; (d) 9-BBN, dry THF; (e) NaOAc, H_2O_2 30%, 0 °C; (f) TsCl, TEA, DMAP, CH_2Cl_2; (g) $Bu_4N^+NO_3^-$, benzene, reflux; (h) TFA, CH_2Cl_2.

react under the same conditions used to transform **15** into **16** to give the propanol derivative **29**. The corresponding tosylate **30**, obtained under the same conditions used to prepare the tosylate **21**, was transformed into the final nitrooxy derivative **32**, through the intermediate formation of **31**, following the same procedures as those used to transform **22** into **24**. Dinitrooxy-substituted compounds **35**, **37**, and **41** were prepared through a common pathway (Scheme 3), which implies the use of the appropriate protected *p*-allylphenols **33**, **15**, and **39**. These products were transformed into the corresponding protected dinitrooxy derivatives **34**, **36**, and **40** by an old procedure to prepare nitric esters of which little use has been made.[10] This procedure involves treating the unsaturated starting materials with iodine and $AgNO_3$ in acetonitrile. The expected vicinal dinitrooxy-substituted compounds were obtained in modest yields. Cleavage of the protection gave the expected final products **35**, **37**, and **41**. We also submitted **28** to this procedure, but the related final dinitrooxy-substituted structure obtained was unstable when deprotected. The preparation of the phenol-substituted furoxans **60**−**62** and **64** bearing at the 3-position of the furoxan the phenylsulfonyl group is outlined in Scheme 4. The hydroxy group of the *p*-hydroxybenzaldehyde (**42**) was TBDMS-protected using *tert*-butyldimethylsilyl chloride (TBDMSCl) in THF solution in the presence of NaH to give **45**. By contrast, the hydroxy groups of the other aldehydes **43** and **44** were MEM-protected using MEMCl in 1,2-dichloroethane solution in the presence of *N*,*N*-diisopropylethylamine

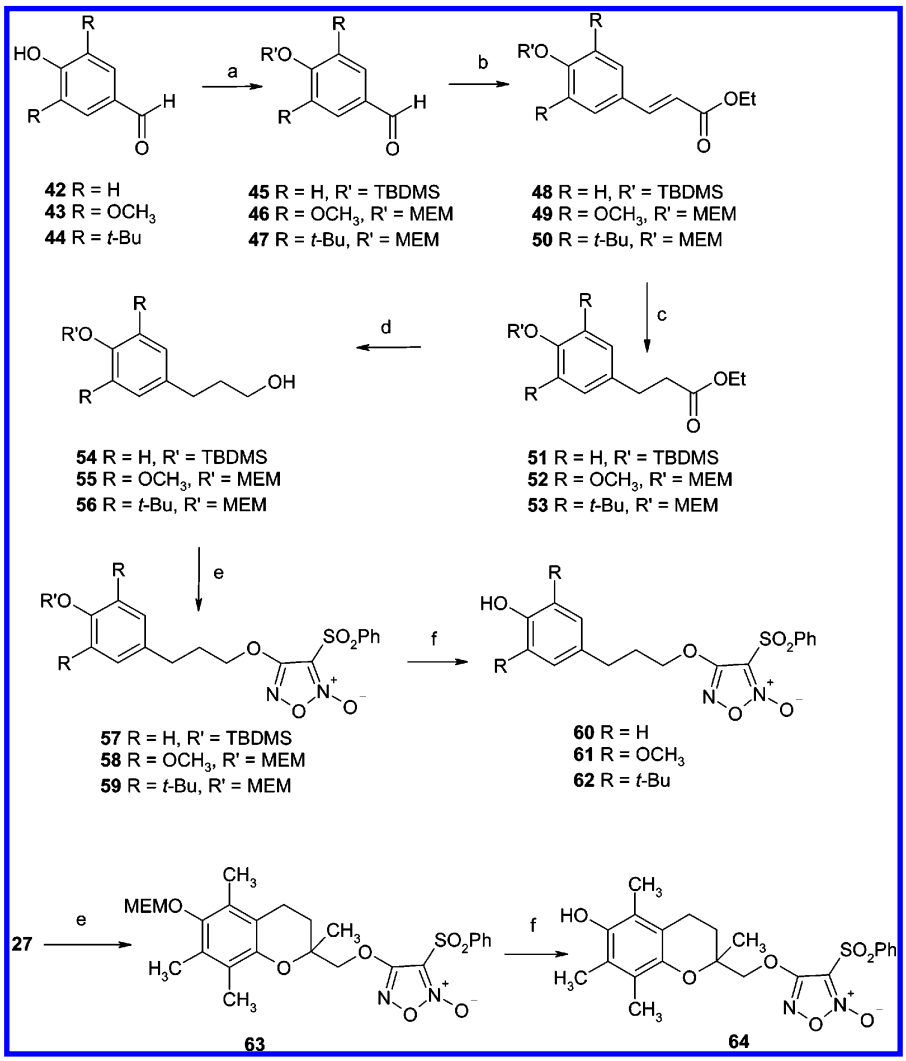
Scheme 3[a]



[a] (a) $AgNO_3$, I_2, CH_3CN, 0 °C, 2.5 h; (b) $AgNO_3$, CH_3CN, reflux; (c) pyrrolidine, CH_3CN, 0 °C for **34** and **36**; TFA, dry CH_2Cl_2, 0 °C for **40**; (d) Boc_2O, DMAP, CH_2Cl_2.

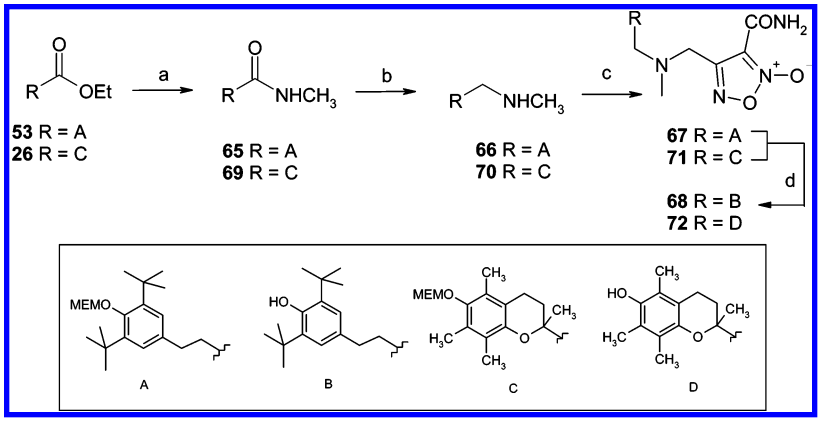
(DIPEA) to give the corresponding derivatives **46** and **47**. The products were subjected to the modified Wittig reaction in the presence of phosphonoacetic acid triethyl ester and *t*-BuO^-K^+ in THF solution to afford the corresponding α,*β*-unsaturated esters **48**−**50**. Reduction of these products using first H_2, Pd/C, and then $LiAlH_4$ gave first the related esters **51**−**53** and then

Scheme 4[a]



[a] (a) NaH, TBDMSCl, dry THF for **42**; DIPEA, MEMCl, $ClCH_2CH_2Cl$ for **43**, **44**; (b) *t*-BuO^-K^+, $(EtO)_2POCH_2COOEt$, dry THF; (c) H_2, Pd/C, EtOH; (d) $LiAlH_4$, dry THF; (e) **10**, NaH, dry THF; (f) HCl 37%, 1,4-dioxane for **57**; 1 M HCl, THF for **58**; TFA, CH_2Cl_2 for **59**, **63**.

Scheme 5[a]



[a] (a) $MeNH_2$ 40%, 1,4-dioxane, 120 °C; (b) $LiAlH_4$, dry THF, 72 °C; (c) **11**, $KHCO_3$, acetone; (d) TFA, CH_2Cl_2.

the saturated alcohols **54**−**56**. Finally, the selective displacement by these products of the 4-phenylsulfonyl group of the 3,4-diphenylsulfonylfuroxan (**10**, Chart 1) yielded the final protected products **57**−**59**. Cleavage of the protection under acidic conditions produced the expected compounds **60**−**62**. Compound **64** was obtained by treating **27** under the same conditions used to prepare **60**−**62** from the corresponding propanol derivatives. The models bearing the 3-carbamoylfuroxan substructure were obtained as reported in Scheme 5. The MEM-protected ester **53** was transformed, by action of methylamine, into the *N*-methylcarboxamide **65**, which was subsequently reduced to related secondary amine **66**, under the action of $LiAlH_4$ in THF. This product was left to react with the 4-bromomethyl-3-furoxancarboxamide (**11**, Chart 1) in acetone, in the presence of $KHCO_3$, to produce the protected carboxamide **67** and then, by action of TFA in CH_2Cl_2, the final product **68**.

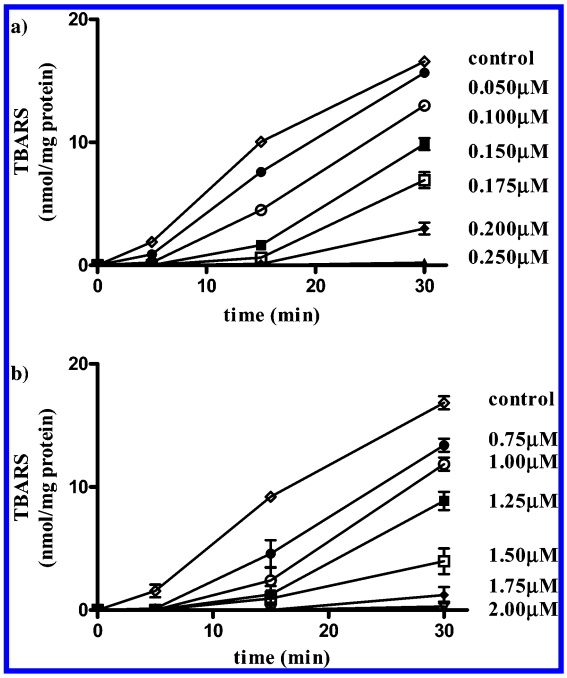


Figure 1. Effect of compounds **32** (a) and **68** (b) on time course of lipid peroxidation.

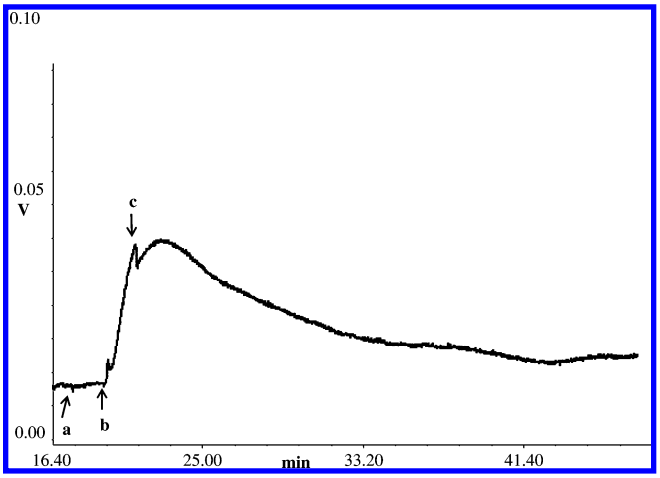
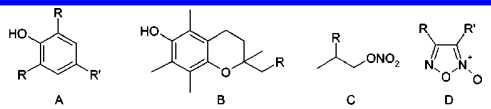


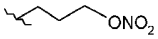
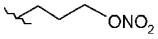
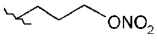
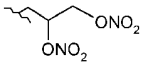
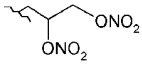
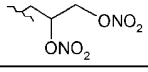
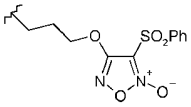
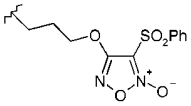
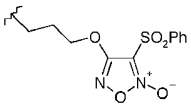
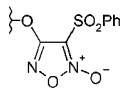
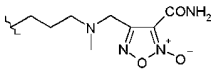
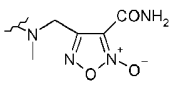
Figure 2. Release of NO from **7** measured during the antioxidant activity assay. The NO electrode was inserted into a 10 mL (final volume) aliquot of a pH 7.4 buffered suspension of rat hepatic microsomes (2 mg prot/mL). Arrows indicate the time points of consecutive additions of ascorbate (100 μM) (a), **7** (100 μM) (b), and $FeSO_4$ (2.5 μM) (c). The peak is obtained after 3 min and corresponds to a maximal NO concentration of ca. 0.1−0.2 μM.

The same sequence of reactions was used to prepare the furoxancarboxamide **72** from **26**, through the intermediate formation of **69**−**71**.

Biological Results. All the final compounds were assessed as inhibitors of ferrous salt/ascorbate-induced lipidic peroxidation of membrane lipids of rat hepatocytes. The parent phenols **1**−**4** and the NO-donor reference compounds **5**−**9** were also considered for comparison. The TBA (2-thiobarbituric acid) assay was used to follow the progress of the autoxidation. This procedure involves the detection of the final metabolites of the autoxidation, 2-thiobarbituric acid reactive substances (TBARS), by visible spectroscopy. This is at present the most commonly used procedure, even though the reaction is not very specific and experimental conditions can contribute to the colorimetric signal.[11] All the NO-donor phenols proved to inhibit in a concentration dependent manner the generation of TBARS. Selected examples of this behavior are reported in Figure 1. The potencies (IC_{50}) of the products as antioxidants are collated in Table 1, along with those of the reference compounds. In the nitrooxy series, the antioxidant potencies follow the sequence **32** > **24** ≅ **41** > **37** ≅ **19** > **13** ≅ **35**, which parallels the antioxidant potencies of the reference phenols **1**−**4**. The potencies of the hybrids **13**, **35** and **19**, **37** are just a little higher than those of the reference phenols **1** and **2**, respectively, while the potencies of **24**, **41**, and **32** are close to those of references **3** and **4**. Once again, in the furoxan series there is a parallelism between the antioxidant properties of the products and those of the reference phenols. However, product **60** is surprisingly a rather more potent antioxidant than the reference phenol **1**. The most potent antioxidants are models **72** and **64** containing as a substructure the 6-hydroxy-2,2,5,7,8-pentamethylchroman **4**, followed by models **68** and **62** containing as a substructure the 2,6-di-*tert*-butyl-*p*-methylphenol **3**. Worthy of note is the finding that the reference furoxan **7**, unlike the 4-(hydroxymethyl)-furoxan-3-carboxamide **8**, its nitrogen analogue **9**, and the simple nitric ester models **5** and **6**, displays by itself an antioxidant action, 2−3-fold higher than that of the *p*-cresol **1**. This could be due to the ability of the product to scavenge directly radicals and/or due to small amounts of NO released by the product under the experimental conditions used for the evaluation of the antioxidant activity. It is known that low concentrations of NO display antioxidant actions through mechanisms not complete disclosed.[12] Indeed, we were able to detect, using a Clark-type electrode, significant release of NO from **7** (Figure 2), but not from the other NO-donor reference compounds, when the products were incubated with microsomial membranes, ascorbate, and ferrous salt. Further studies are necessary to clarify this point. A close investigation of the structure−activity relationships that operate in this new class of antioxidants is in progress. Preliminary results seem to indicate that the antioxidant potency (log $1/IC_{50}$) is well-predicted by a linear combination of CLOGP and log *Z*. The latter is a kinetic parameter, derived from the initial rates of the reaction between a phenol and the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical. Ideally, it should only be influenced by hydroxyl hydrogen abstraction in the reaction. These results are in line with those obtained by other researchers on other phenol derivatives.[13] All the NO-donor phenols and the related NO-donor simple models were tested for their ability to relax rat aorta strips precontracted with phenylephrine. It was demonstrated that the compounds dilated the contracted strips in a concentration dependent manner; an example of this behavior is reported in Figure 3. The vasodilator potencies (EC_{50}) of the products are collected in Table 1. Generally speaking, in the nitrooxy series, when other factors are equal, the dinitrooxy-substituted products were more potent than the respective mononitrooxy ones. In the furoxan series, the most potent products were those bearing the 3-phenylsulfonylfuroxan moiety present in **7**. The two products **68** and **72** bearing the 3-carbamoylfuroxan-4-ylmethyl substructure were less potent, and this parallels what happens in the simple reference models **7** with respect to **8** and **9**. The vasorelaxant properties of all the tested compounds are cGMP-dependent because the well-known inhibitor of the sGC, 1*H*-[1,2,4]-oxadiazolo[4,3-*a*]quinoxalin-1-one (ODQ), caused a significant reduction in the vasodilator potencies of the compounds (Table 1). This suggests an involvement of NO in the vasodilating action. The analysis of data collected in Table 1 indicates that the behavior of some compounds (**13**, **35**, **37**, **60**−**62**, **64**) is principally vasodilatory and others (**24**, **32**, **72**) are primarily antioxidants, while the compounds **19**, **41**, and **68** trigger these two activities in a relatively balanced manner. This aspect

Table 1. Antioxidant and Vasodilating Activity of the NO-Donor Phenols, of the Phenols **1**−**4**, and NO-Donor Parents **5**−**9**



	Compd	Struct.	R	R'	Antioxidant activity[a] IC50 (95% CL) μM	Vasodilating activity[b] EC50 ± SE, μM	Vasodilating activity[b] +1 μM ODQ [% relaxation][c]
Phenol and NO-Donor Parents	**1**	A	H	CH_3	290 (260-324)	-	-
	2	A	OCH_3	CH_3	18 (17-20)	-	-
	3	A	*t*-Bu	CH_3	1.7 (1.6-1.9)	-	-
	4	B	H	-	0.17 (0.16-0.17)	-	-
	5	C	H	-	-[d]	41 ± 6	[4.6 ± 0.6]
	6	C	ONO_2	-	-[d]	0.24 ± 0.03	[10 ± 2]
	7	D	OEt	SO_2Ph	110 (98-122)	0.012 ± 0.002	1.2 ± 0.2
	8	D	CH_2OH	$CONH_2$	-[d]	6.3 ± 0.8	[21 ± 7]
	9	D	$CH_2N(CH_3)_2$	$CONH_2$	-[d]	3.1 ± 0.3	[17 ± 3]
Nitrooxy Phenols	**13**	A	H		143 (133-153)	1.0 ± 0.2	[38 ± 9]
	19	A	OCH_3		5.9 (5.5-6.4)	4.3 ± 0.6	[33 ± 3]
	24	A	*t*-Bu		2.0 (1.9-2.1)	40 ± 1	[15 ± 5]
	32	B		-	0.15 (0.15-0.16)	1.2 ± 0.1	10 ± 1
	35	A	H		185 (176-195)	0.13 ± 0.03	65 ± 4
	37	A	OCH_3		5.4 (5.0-5.8)	0.64 ± 0.09	49 ± 4
	41	A	*t*-Bu		2.6 (1.9-3.5)	3.3 ± 0.4	[24 ± 4[e]]
Furoxan Phenols	**60**	A	H		47 (45-48)	0.012 ± 0.001	0.36 ± 0.09
	61	A	OCH_3		3.4 (3.2-3.5)	0.022 ± 0.003	0.50 ± 0.13
	62	A	*t*-Bu		2.0 (1.9-2.0)	0.11 ± 0.03	4.8 ± 0.5
	64	B		-	0.49 (0.48-0.50)	0.044 ± 0.004	0.67 ± 0.09
	68	A	*t*-Bu		1.2 (1.1-1.2)	0.41 ± 0.08	7.4 ± 1.1
	72	B			0.14 (0.14-0.14)	1.5 ± 0.1	19 ± 1

[a] Values are the means of at least five experiments. [b] Values are the means of at least six experiments. [c] When EC_{50} could not be calculated, percent relaxation was evaluated at the maximal concentration tested (100 μM). [d] Inactive at 1 mM. [e] Percent relaxation was evaluated at 30 μM, the maximal concentration tested due to insolubility limits.

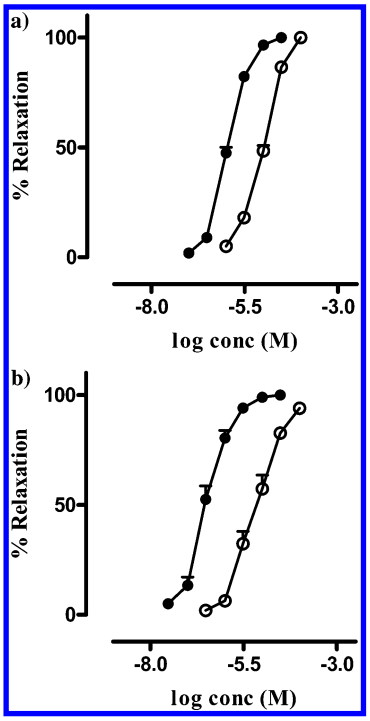


Figure 3. Concentration−response curves for vasodilating activity of compound **32** (a) and **68** (b) in the absence (solid circle) and in the presence (open circle) of ODQ.

renders the class of products here reported a flexible tool for further investigation in the field of CD. In fact, different pathologies could require different balance degree between the two activities. In conclusion, we have described a new series of phenols containing NO-donor nitrooxy and furoxan moieties that simultaneously display extensively modulated antioxidant and vasodilator activities. Further studies in animal models should clarify whether some of these products may become preclinical candidates for the treatment of some forms of CD.

Experimental Section

Chemistry. Melting points were measured with a capillary apparatus (Büchi 540) and are uncorrected. Melting points with decomposition were determined after introducing the sample into the bath at a temperature 10 °C lower than the melting point. A heating rate of 3 °C min^{-1} was used. All the compounds were routinely checked by IR (Shimadzu FT-IR 8101-M and FT-IR Thermo-Nicolet Avatar), ^1H and ^{13}C NMR (Bruker Avance 300 and JEOL ECP300), and mass spectrometry (Finnigan-Mat TSQ-700 and Thermofinnigan LCQ-deca XP-PLU). The following abbreviations were used to indicate the peak multiplicity: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Column chromatography was performed on Merck Kieselgel 60, 70−230 mesh ASTM or 230−400 mesh ASTM using the indicated eluents. Thin-layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm. HPLC analyses were performed using a diode array UV detector (Shimadzu LC10A). Anhydrous magnesium sulfate was used as drying agent for the organic phases. Analysis (C, H, N) of the new compounds dried at 20 °C, pressure < 10 mmHg for 24 h, was performed by REDOX (Monza, Italy) and the results, available as Supporting Information, are within ±0.4% of the theoretical, unless otherwise stated. Structures **10**,[14] **11**,[15] **20**,[16] **25**,[10] and **38**[17] were synthesized according to methods described in the literature. The phenol **20** was further purified by gradient flash chromatography (eluents PE/CH_2Cl_2) until a 80% purity. The products **5** and **6** were synthesized from *n*-propanol and 1,2-propandiol, respectively, according to the procedure described in the literature.[18] The product **9** was synthesized according to the procedure described for the preparation of the diethyl analogue[19] (mp = 128−129 °C dec (from *i*PrOH). Anal. ($C_6H_{10}N_3O_3$) C, H, N). All of the NO-donor phenols were kept in a freezer and their stability was checked (HPLC) over 3 months. They were stable (>95%) over this period. Tetrahydrofuran (THF) was distilled immediately before use from Na and benzophenone under a positive atmosphere of N_2. When needed the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N_2. All reactions were carried out three times without any attempts to optimize the yields. NO released was measured by means of an ISO-NO meter equipped with a 2 mm diameter shielded microsensor ISO-NOP and a ISO-NO Mark II data recording system from World Precision Instrument (Sarasota, FL).

3-(4-Hydroxyphenyl)propyl Nitrate (13). $AgNO_3$ (4.74 g, 28.0 mmol) was added to a stirred solution of **12** (5.00 g, 23.3 mmol) in CH_3CN (50 mL) and then the mixture was heated at 60 °C for 24 h. After cooling, the mixture was filtered and diluted with EtOAc (50 mL). The organic layer was washed with water and brine, dried, and evaporated. The resulting residue was purified by chromatography (PE/EtOAc 90/10), yielding the pure compound as a pale yellow oil: yield 68%; ^1H NMR ($CDCl_3$) δ 1.95−2.04 (m, 2H, CH_2CH_2ONO$_2$), 2.65 (t, 2H, CH_2CH_2CH_2ONO$_2$, $^3J_{HH}$ = 8.0 Hz), 4.42 (t, 2H, CH_2ONO$_2$, $^3J_{HH}$ = 6.5 Hz), 5.92 (s br, 1H, O*H*), 6.79 (d, 2H, AA′BB′ system), 7.03 (d, 2H, AA′BB′ system); MS (EI) *m/z* 197 $(M)^+$. Anal. Calcd ($C_9H_{11}NO_4$): C, 54.82; H, 5.62; N, 7.10. Found: C, 54.45; H, 5.62; N, 6.68.

4-Allyl-2,6-dimethoxyphenyl Acetate (15). To a stirred solution of **14** (2.00 mL, 10.3 mmol) in CH_2Cl_2 (20 mL) were added TEA (2.86 mL, 20.5 mmol) and DMAP (0.04 g, 0.29 mmol). The mixture was cooled at 0 °C and Ac_2O (1.93 mL, 20.5 mmol) was added dropwise. Then the mixture was allowed to reach room temperature and stirred for 20 min. The solution was then diluted with CH_2Cl_2, washed with water and brine, dried, and evaporated. The crude product was purified by chromatography (PE/EtOAc 95/5) to give the title compound as a colorless oil that became solid on standing: yield 97%; mp 43−44 °C; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H, CH_3COO), 3.36 (d, 2H, CH_2CH=CH_2, $^3J_{HH}$ = 6.8 Hz), 3.80 (s, 6H, OCH_3), 5.09−5.15 (m, 2H, CH_2=CH), 5.91−6.00 (m, 1H, CH_2=C*H*), 6.44 (s, 2H, C_6H_2); MS (EI) *m/z* 236 $(M)^+$.

4-(3-Hydroxypropyl)-2,6-dimethoxyphenyl Acetate (16). A solution of 9-BBN (0.5 M) in THF (44.7 mL, 22.3 mmol) was slowly added to a magnetically stirred solution of **15** (2.64 g, 11.2 mmol) in dry THF (20 mL) kept under inert atmosphere. After 22 h the mixture was cooled at 0 °C and a solution of sodium acetate (3 N, 26 mL) and H_2O_2 (30%, 13.5 mL) were slowly added. The resulting mixture was allowed to reach room temperature and stirred for 2 h. The excess of H_2O_2 was destroyed adding sodium bisulfite. The mixture was then concentrated under reduced pressure and dissolved in EtOAc. The obtained organic layer was washed with water and brine, dried, and evaporated. The crude product was purified by chromatography (PE/EtOAc 60/40) to give the title compound as a white solid: yield 92%; mp 79−80 °C (from *i*Pr_2O); ^1H NMR ($CDCl_3$) δ 1.63 (s, 1H, O*H*), 1.84−1.93 (m, 2H, CH_2-CH_2OH), 2.33 (s, 3H, CH_3COO), 2.64−2.70 (m, 2H, CH_2CH_2CH_2-OH), 3.66−3.70 (m, 2H, CH_2OH), 3.80 (s, 6H, OCH_3), 6.45 (s, 2H, C_6H_2); MS (EI) *m/z* 254 $(M)^+$. Anal. ($C_{13}H_{18}O_5$) C, H.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propan-1-ol (29). The title compound was obtained as **16** starting from **28**: eluent Hex/EtOAc 70/30; yield 70%; ^1H NMR ($CDCl_3$) δ 1.26 (s, 3H, 2-CH_3), 1.70−1.98 (m, 4H, 3-H_2, OCH$_2$CH_2CH_2OH), 2.06 (s, 3H, ArCH_3), 2.13 (s, 3H, ArCH_3), 2.16 (s, 3H, ArCH_3), 2.58 (m, 2H, 4-H_2), 3.40 (s, 3H, CH_3O), 3.44 (d AB system, 1H, 2-C$H_a$$H_b$O, $^2J_{HH}$ = 9.3 Hz), 3.48 (d AB system, 1H, 2-C$H_a$$H_b$O, $^2J_{HH}$ = 9.3 Hz), 3.61 (m, 2H, OCH_2CH_2O), 3.68−3.82 (m, 4H, OCH_2CH_2CH_2OH), 3.95 (m, 2H, OCH$_2$CH_2O), 4.93 (s, 2H, OCH_2O); MS (ESI) *m/z* 405 $(M + Na)^+$, drying conditions: 40 °C, 48 h, pressure < 1 mmHg. Anal. ($C_{21}H_{34}O_6$) C, H.

General Procedure for 17, 21, and 30. To a solution of the appropriate alcohol **16**, **20**, or **29** (6.17 mmol) in CH_2Cl_2 were added TEA (1.7 mL, 12.3 mmol), DMAP (0.75 g, 6.17 mmol), and TsCl (2.34 g, 12.3 mmol). The mixture was stirred for 2−3 h; diluted

with CH_2Cl_2; washed with water, HCl (2 N), and brine; dried; and evaporated. The crude product was purified as described.

2,6-Dimethoxy-4-(3-tosylpropyl)phenyl Acetate (17). The crude product was purified by chromatography (PE/EtOAc 70/30) to give a white solid: yield 59%; mp 70−71 °C; ^{1}H NMR ($CDCl_3$) δ 1.90−2.00 (m, 2H, CH_2CH$_2$OSO$_2$), 2.32 (s, 3H, CH_3COO), 2.44 (s, 3H, CH_3C$_6$H$_4$), 2.60−2.66 (m, 2H, CH_2CH$_2$CH$_2$OSO$_2$), 3.77 (s, 6H, CH_3O), 4.00−4.06 (m, 2H, CH_2OSO$_2$), 6.37 (s, 2H, C$_6H_2$), 7.34 (d, 2H, AA′BB′ system), 7.78 (d, 2H, AA′BB′ system); MS (EI) *m/z* 408 (M)$^+$. Anal. ($C_{20}H_{23}O_7$) C, H.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl Tosylate (21). The crude product was purified by crystallization from *i*Pr$_2$O to give a white solid: yield 56%; mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H, C(CH_3)$_3$), 1.88−1.98 (m, 2H, CH_2CH$_2$OSO$_2$), 2.45 (s, 3H, CH_3C$_6$H$_4$), 2.54−2.59 (m, 2H, CH_2CH$_2$CH$_2$OSO$_2$), 4.05−4.09 (m, 2H, CH_2OSO$_2$), 5.08 (s, 1H, O*H*), 6.92 (s, 2H, C$_6H_2$), 7.35 (d, 2H, AA′BB′ system), 7.81 (d, 2H, AA′BB′ system); MS (EI) *m/z* 418 (M)$^+$. Anal. ($C_{24}H_{34}O_4S$) C, H.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl Tosylate (30). The crude product was purified by chromatography (Hex/EtOAc 80/20) to give a pale yellow oil: yield 68%; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 3H, 2-CH_3), 1.62−1.71 (m, 1H, 3-H_aH$_b$), 1.80−1.90 (m, 3H, 3-H$_a$$H_b$/OCH$_2CH_2$-CH$_2$OTs), 2.03 (s, 3H, ArC$H_3$), 2.13 (s, 3H, ArC$H_3$), 2.16 (s, 3H, ArC$H_3$), 2.42 (s, 3H, C$H_3C_6H_4$), 2.53 (m, 2H, 4-$H_2$), 3.29 (d AB system, 1H, 2-CH_aH$_b$O, $^2J_{HH}$ = 9.9 Hz), 3.37 (d AB system, 1H, 2-CH$_a$$H_b$O, $^2J_{HH}$ = 9.9 Hz), 3.40 (s, 3H, CH_3O), 3.49−3.54 (m, 2H, OCH_2CH$_2$CH$_2$O), 3.60 (m, 2H, OCH_2CH$_2$O), 3.96 (m, 2H, OCH$_2$CH_2O), 4.13 (m, 2H, OCH$_2$CH$_2$CH_2O), 4.93 (s, 2H, OCH_2O), 7.31 (d, 2H, AA′BB′ system), 7.77 (d, 2H, AA′BB′ system); MS (ESI) *m/z* 559 (M + Na)$^+$. Anal. ($C_{28}H_{40}O_8S$) C, H.

General Procedure for 18, 23, and 31. Tetrabutylammonium nitrate (2.70 g, 8.9 mmol) was added to a solution of the appropriate tosylate **17**, **21**, or **30** (3.5 mmol) in benzene (14 mL), and the mixture was heated at reflux until the disappearance of the tosylate by TLC. The mixture was concentrated under reduced pressure and the crude product was purified by chromatography to give the title compound as pale yellow oil.

2,6-Dimethoxy-4-(3-nitroxypropyl)phenyl Acetate (18). Eluent PE/EtOAc 70/30; yield 81%; ^{1}H NMR ($CDCl_3$) δ 2.00−2.10 (m, 2H, CH_2CH$_2$ONO$_2$), 2.33 (s, 3H, CH_3COO), 2.67−2.72 (m, 2H, CH_2CH$_2$CH$_2$ONO$_2$), 3.80 (s, 6H, CH_3O), 4.45−4.49 (m, 2H, CH_2-ONO$_2$), 6.42 (s, 2H, C$_6H_2$); MS (EI) *m/z* 299 (M)$^+$.

***tert*-Butyl 2,6-di-*tert*-butyl-4-(3-nitrooxypropyl)phenyl Carbonate (23).** Eluent PE/EtOAc 95/5; yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.34−1.36 (s, 18H, C(CH_3)$_3$), 1.53 (s, 9H, OC(CH_3)$_3$), 2.00−2.10 (m, 2H, CH_2CH$_2$ONO$_2$), 2.66−2.72 (m, 2H, CH_2CH$_2$CH$_2$-ONO$_2$), 4.45−4.50 (m, 2H, CH_2ONO$_2$), 7.10 (s, 2H, C$_6H_2$); MS (EI) *m/z* 409 (M)$^+$.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl Nitrate (31). Eluent Hex/EtOAc 90/10; yield 94%; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H, 2-CH_3), 1.70−1.78 (m, 1H, 3-H_aH$_b$), 1.88−1.98 (m, 3H, 3-H$_a$$H_b$/OCH$_2$-C$H_2CH_2ONO_2$), 2.06 (s, 3H, ArC$H_3$), 2.14 (s, 3H, ArC$H_3$), 2.17 (s, 3H, ArC$H_3$), 2.58 (m, 2H, 4-$H_2$), 3.40 (s, 3H, C$H_3$O), 3.40 (d AB system, 1H, 2-CH_aH$_b$O, $^2J_{HH}$ = 9.9 Hz), 3.48 (d AB system, 1H, 2-CH$_a$$H_b$O, $^2J_{HH}$ = 9.9 Hz), 3.58−3.64 (m, 4H, OCH_2CH$_2$O/OCH_2CH$_2$CH$_2$ONO$_2$), 3.96 (m, 2H, OCH$_2$CH_2O), 4.57 (t, 2H, OCH$_2$CH$_2$CH_2ONO$_2$, $^3J_{HH}$ = 6.3 Hz), 4.94 (s, 2H, OCH_2O); MS (ESI) *m/z* 450 (M + Na)$^+$.

General Procedure for 19, 35, and 37. Pyrrolidine (0.95 mL, 11.5 mmol) was added to a stirred solution of the appropriate acetate **18**, **34**, or **36** (0.86 g, 2.9 mmol) in CH_3CN (8 mL) kept at 0 °C. The reaction was completed in 5 h. The mixture was concentrated under reduced pressure and the obtained residue was dissolved with EtOAc. The organic layer was washed with HCl (2 N) and brine, dried, and evaporated. The crude product was purified by chromatography.

3-(4-Hydroxy-3,5-dimethoxyphenyl)propyl Nitrate (19). Eluent PE/EtOAc 80/20; pale yellow oil; yield 86%; ^{1}H NMR (DMSO-d_6) δ 1.90−2.00 (m, 2H, CH_2CH$_2$ONO$_2$), 2.54−2.59 (m, 2H, CH_2CH$_2$CH$_2$ONO$_2$), 3.74 (s, 6H, CH_3O), 4.48−4.52 (m, 2H, CH_2-ONO$_2$), 6.47 (s, 2H, C$_6H_2$), 8.14 (s, 1H, O*H*); MS (EI) *m/z* 257 (M)$^+$. Anal. ($C_{11}H_{15}NO_6$) C, H, N.

3-(4-Hydroxyphenyl)prop-1,2-diyl Dinitrate (35). Eluent PE/EtOAc 90/10; colorless oil; yield 35%; ^{1}H NMR ($CDCl_3$) δ 2.86−3.06 (m, 2H, CH_2CH(ONO$_2$)), 4.38−4.44 (dd, 1H, CH_aH$_b$ONO$_2$), 4.68−4.73 (dd, 1H, CH$_a$$H_bONO_2$), 5.37−5.43 (m, 1H, C*H*(ONO$_2$)-CH$_2$), 5.26 (s br, 1H, O*H*), 6.81 (d, 2H, AA′BB′ system), 7.10 (d, 2H, AA′BB′ system); MS (EI) *m/z* 258 (M)$^+$. Anal. ($C_9H_{10}N_2O_7$) C, H, N.

3-((4-Hydroxy-3,5-dimethoxy)phenyl)prop-1,2-diyl Dinitrate (37). Eluent PE/EtOAc 70/30; white solid; yield 72%; mp 65−66 °C; ^{1}H NMR ($CDCl_3$) δ 2.87−3.07 (m, 2H, CH_2CH(ONO$_2$)), 3.88 (s, 6H, OCH_3), 4.41−4.47 (dd, 1H, CH_aH$_b$ONO$_2$), 4.71−4.76 (dd, 1H, CH$_a$$H_bONO_2$), 5.40−5.50 (m, 1H, C*H*(ONO$_2$)CH$_2$), 5.51 (s br, 1H, O*H*), 6.44 (s, 2H, C$_6H_2$); MS (EI) *m/z* 318 (M)$^+$. Anal. ($C_{11}H_{14}N_2O_9$) C, H, N.

3-(4-((*tert*-Butoxycarbonyl)oxy)-3,5-di-*tert*-butylphenyl)propyl Tosylate (22). Boc$_2$O (2.55 g, 11.7 mmol) and DMAP (0.62 g, 5.3 mmol) were added to a solution of **21** (2.24 g, 5.3 mmol) that was kept under an inert atmosphere in dry CH_2Cl_2 (25 mL) and then the mixture was stirred for 1.5 h. The mixture was diluted with EtOAc and washed with HCl (2 N) and brine, dried and evaporated. The crude product was purified by chromatography (PE/EtOAc 98/2) to give the title compound as pale yellow solid: yield 68%; mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 18H, C(CH_3)$_3$), 1.52 (s, 9H, OC(CH_3)$_3$), 1.88−1.96 (m, 2H, CH_2CH$_2$OSO$_2$), 2.44 (s, 3H, CH_3C$_6$H$_4$), 2.55−2.62 (m, 2H, CH_2CH$_2$CH$_2$OSO$_2$), 4.02−4.07 (m, 2H, CH_2OSO$_2$), 7.02 (s, 2H, C$_6H_2$), 7.34 (d, 2H, AA′BB′ system), 7.80 (d, 2H, AA′BB′ system); MS (CI) *m/z* 463 (M + 1 − C$_4$H$_8$)$^+$.

4-Allyl-2,6-di-*tert*-butylphenyl Carbonate (39). The title compound was obtained as **22** starting from **38**: eluent PE/EtOAc 98/2; yield 60%; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 18H, C(CH_3)$_3$), 1.54 (s, 9H, OC(CH_3)$_3$), 3.36 (d, 2H, CH_2CH═CH$_2$, $^3J_{HH}$ = 6.9 Hz), 5.07−5.16 (m, 2H, CH_2═CH), 5.93−6.05 (m, 1H, CH$_2$═C*H*), 7.13 (s, 2H, C$_6H_2$); MS (CI) *m/z* 347 (M + 1)$^+$.

General Procedure for 24, **32, 41, 62**, **64, 68, and 72.** TFA (0.75 mL, 14.7 mmol) was added to a stirred solution of the appropriate protected phenol **23**, **31**, **40**, **59**, **63**, **67**, or **71** (2.9 mmol) that was kept under an inert atmosphere in dry CH_2Cl_2 (15 mL) until the disappearance of the starting material, as checked by TLC. Then the mixture was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$ and brine, dried, and evaporated. The crude product was purified as described.

3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl Nitrate (24). The crude product was purified by chromatography (PE) to give a white solid: yield 68%; mp 79 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 18H, C(CH_3)$_3$), 1.96−2.06 (m, 2H, CH_2CH$_2$ONO$_2$), 2.62−2.67 (m, 2H, CH_2CH$_2$CH$_2$ONO$_2$), 4.45−4.49 (m, 2H, CH_2ONO$_2$), 5.10 (s, 1H, O*H*), 6.96 (s, 2H, C$_6H_2$); MS (EI) *m/z* 309 (M)$^+$. Anal. ($C_{17}H_{27}$-NO$_4$) C, H, N.

3-((6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl Nitrate (32). The crude product was purified by chromatography (Hex/EtOAc 90/10) to give a yellow oil: yield 56%; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H, 2-CH_3), 1.72−1.79 (m, 1H, 3-H_aH$_b$), 1.92−2.03 (m, 3H, 3-H$_a$$H_b$/OCH$_2CH_2CH_2ONO_2$), 2.09 (s, 3H, ArC$H_3$), 2.11 (s, 3H, ArC$H_3$), 2.15 (s, 3H, ArC$H_3$), 2.61 (m, 2H, 4-$H_2$), 3.41 (d AB system, 1H, 2-CH_aH$_b$O, $^2J_{HH}$ = 9.8 Hz), 3.47 (d AB system, 1H, 2-CH$_a$$H_b$O, $^2J_{HH}$ = 9.8 Hz), 3.58−3.63 (m, 2H, OCH_2-CH$_2$CH$_2$ONO$_2$), 4.19 (s, 1H, O*H*), 4.57 (t, 2H, OCH$_2$CH$_2$CH_2ONO$_2$, $^3J_{HH}$ = 6.5 Hz); MS (ESI) *m/z* 362 (M + Na)$^+$. Anal. ($C_{17}H_{25}NO_6$) C, H, N.

3-((4-Hydroxy-3,5-di-*tert*-butyl)phenyl)prop-1,2-diyl Dinitrate (41). The crude product was purified by chromatography (PE/EtOAc 98/2) to give a yellow oil: yield 31%; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H, C(CH_3)$_3$), 2.86−3.04 (m, 2H, CH_2CH(ONO$_2$)), 4.42−4.48 (dd, 1H, CH_aH$_b$ONO$_2$), 4.70−4.74 (dd, 1H, CH$_a$$H_bONO_2$), 5.36−5.44 (m, 1H, CH$_2$C*H*(ONO$_2$)), 5.20 (s br, 1H, O*H*), 6.99 (s, 2H, C$_6H_2$); MS (EI) *m/z* 370 (M)$^+$. Anal. ($C_{17}H_{26}N_2O_7$) C, H, N.

4-(3-(3-Benzenesulfonylfuroxan-4-yloxy)propyl)-2,6-di-*tert*-butylphenol (62). The crude product was purified by crystallization from EtOH to give a white solid: yield 88%; mp 110−111 °C (from EtOH); ^{1}H NMR (DMSO-d_6) δ 1.33 (s, 18H, C(CH_3)$_3$), 1.99 (m, 2H, CH$_2$CH_2CH$_2$O), 2.57 (t, 2H, CH_2CH$_2$CH$_2$O, $^3J_{HH}$ = 7.2 Hz), 4.33 (t, 2H, CH$_2$CH$_2$CH_2O, $^3J_{HH}$ = 5.9 Hz), 6.74 (s br, 1H, O*H*), 6.86 (s, 2H, C$_6H_2$), 7.72−8.05 (m, 5H, C$_6H_5$SO$_2$); MS (EI) *m/z* 488 (M)$^+$. Anal. ($C_{25}H_{32}N_2O_6S$) C, H, N.

2-(3-Benzenesulfonylfuroxan-4-yloxymethyl)-2,5,7,8-tetramethylchroman-6-ol (64). The crude product was purified by preparative HPLC (Lichrospher 250−25 C_{18}, CH$_3$CN/H$_2$O 65/35, flow 39 mL/min, λ 224 nm, injection 1 mL, solution 50 mg/mL): yield 60%; mp 68−72 °C dec (from cold MeOH/H$_2$O); ^{1}H NMR (DMSO-d_6) δ 1.28 (s, 3H, 2-CH_3), 1.85 (s, 3H, ArCH_3), 1.90 (m, 2H, 3-H_2), 2.05 (s, 6H, ArCH_3), 2.60 (m, 2H, 4-H_2), 4.45 (m, 2H, 2-CH_2O), 7.48 (s br, 1H, O*H*), *7*.60−7.95 (m, 5H, C$_6$H$_5$SO$_2$); MS (EI) *m/z* 460 (M)$^+$. Anal. ($C_{22}H_{24}N_2O_7S$) C, H, N.

4-((*N*-(3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl)-*N*-methylamino)methyl)furoxan-3-carboxamide (68). The crude product was purified by flash chromatography (PE/*i*PrOH 90/10) to give a white solid: yield 69%; mp 103−105 °C (from hexane); ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 18H, C(CH_3)$_3$), 1.70 (m, 2H, NCH$_2$CH_2-CH$_2$), 2.25 (s, 3H, NCH_3), 2.40−2.50 (m, 4H, NCH_2CH$_2$CH_2), 3.81 (s, 2H, CH_2Fx), 6.67 (s, 1H, O*H*), 6.89 (s, 2H, C$_6H_2$), 8.27 (s br, 1H, CON*H*H), 8.74 (s br, 1H, CONH*H*); MS (CI) *m/z* 419 (M + 1)$^+$. Anal. ($C_{22}H_{34}N_4O_4$) C, H, N.

4-((*N*-((6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl)-*N*-methylamino)methyl)furoxan-3-carboxamide (72). The crude product was purified by flash chromatography (PE/*i*PrOH 90/10) to give a pale yellow solid: yield 80%; mp 132−135 °C dec (from CH$_2$ClCH$_2$Cl); ^{1}H NMR (DMSO-d_6) δ 1.12 (s, 3H, 2-CH_3), 1.59−1.64 (m, 1H, 3-H_aH$_b$), 1.77−1.82 (m, 1H, 3-H$_a$$H_b$), 1.93 (s, 3H, ArC$H_3$), 2.01 (s, 3H, ArC$H_3$), 2.03 (s, 3H, ArC$H_3$), 2.43 (s, 3H, NC$H_3$), 2.51 (s br, 2H, 4-$H_2$), 2.66 (m, 2H, 2-C$H_2$N), 3.91 (d AB system, 1H, CH_aH$_b$Fx), 3.96 (d AB system, 1H, CH$_a$$H_b$Fx), 7.39 (s br, 1H, O*H*), 8.33 (s br, 2H, CONH_2); MS (EI) *m/z* 390 (M)$^+$ (drying conditions, 40 °C, 48 h, pressure < 1 mmHg). Anal. ($C_{19}H_{26}N_4O_5$·0.5EtOAc) C, H, N.

Ethyl 6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchromane-2-carboxylate (26). A solution of **25** (1.74 g, 6.3 mmol) in dry THF (6 mL) was slowly added to a stirred suspension of NaH 60% (0.38 g, 9.4 mmol) in dry THF (5 mL) that was kept under an inert atmosphere at 20 °C. Then a solution of MEMCl (1.1 mL, 9.4 mmol) in dry THF (3 mL) was added and the solution was stirred for 25 h. The mixture was poured into NaOH (0.1 M) and extracted with EtOAc. The organic layers were washed with brine, dried, and evaporated. The crude product was purified by flash chromatography (PE/EtOAc 90/10) to give the title compound as yellow oil: yield 74%; ^{1}H NMR (CDCl$_3$) δ 1.17 (t, 3H, COOCH$_2$CH_3, $^3J_{HH}$ = 7.1 Hz), 1.60 (s, 3H, 2-CH_3), 1.80−1.88 (m, 1H, 3-H_aH$_b$), 2.10 (s, 3H, ArCH_3), 2.16 (s, 3H, ArCH_3), 2.18 (s, 3H, ArCH_3), 2.40−2.65 (m, 3H, 3-H$_a$$H_b$, 4-$H_2$), 3.40 (s, 3H, C$H_3$O), 3.60 (m, 2H, OC$H_2CH_2$O), 3.95 (m, 2H, OCH$_2CH_2$O), 4.12 (q, 2H, COOC$H_2CH_3$, $^3J_{HH}$ = 7.1 Hz), 4.93 (s, 2H, OCH_2O); MS (EI) *m/z* 366 (M)$^+$.

2-Allyloxymethyl-6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchromane (28). NaH 60% (0.28 g, 6.9 mmol) was added portionwise to a solution of **27** (1.50 g, 4.6 mmol) in dry DMF (15 mL) kept under inert atmosphere. Then allyl bromide (0.6 mL, 6.9 mmol) was added and the mixture was stirred for 16 h. The mixture was diluted with water and filtered through Celite, washed twice with water, and then eluted with EtOAc. The organic layer was washed with brine, dried, and evaporated. The crude product was purified by chromatography (Hex/EtOAc 80/20) to give the title compound as pale yellow oil: yield 60%; ^{1}H NMR (CDCl$_3$) δ 1.28 (s, 3H, 2-CH_3), 1.72−1.80 (m, 1H, 3-H_aH$_b$), 1.94−2.04 (m, 1H, 3-H$_a$$H_b$), 2.07 (s, 3H, ArC$H_3$), 2.14 (s, 3H, ArC$H_3$), 2.17 (s, 3H, ArC$H_3$), 2.58 (m, 2H, 4-$H_2$), 3.40 (d AB system, 1H, 2-CH_aH$_b$O, $^2J_{HH}$ = 9.6 Hz), 3.48 (d AB system, 1H, 2-CH$_a$$H_b$O, $^2J_{HH}$ = 9.6 Hz), 3.40 (s, 3H, CH_3O), 3.61 (m, 2H, OCH_2CH$_2$O), 3.95 (m, 2H, OCH$_2$CH_2O), 4.05 (m, 2H, OCH_2CH=CH$_2$), 4.94 (s, 2H, OCH_2O), 5.15−5.30 (m, 2H, OCH$_2$CH=CH_2), 5.84−5.95 (m, 1H, OCH$_2$C*H*=CH$_2$); MS (ESI) *m/z* 387 (M + Na)$^+$. Anal. ($C_{21}H_{32}O_5$) C, H.

4-Allylphenyl Acetate (33). The title compound was obtained as **15** starting from 4-allylphenol.[20] The crude pale yellow oil obtained was used without further purification: yield 71%; ^{1}H NMR (CDCl$_3$) δ 2.32 (s, 3H, CH_3COO), 3.37 (d, 2H, CH_2CH=CH$_2$, $^3J_{HH}$ = 6.6 Hz), 5.05−5.11 (m, 2H, CH_2=CH), 5.87−6.02 (m, 1H, CH$_2$=C*H*), 6.99 (d, 2H, AA′BB′ system), 7.18 (d, 2H, AA′BB′ system); MS (EI) *m/z* 176 (M)$^+$.

General Procedure for 34, 36, and 40. To a stirred solution of the appropriate allyl derivative **33**, **15**, or **38** (11.3 mmol) and AgNO$_3$ (2.32 g, 13.6 mmol) in CH$_3$CN (20 mL) kept at −15 °C was added a solution of iodine (3.46 g, 13.6 mmol) in CH$_3$CN (30 mL) dropwise. At the end of the addition the mixture was allowed to reach room temperature. AgNO$_3$ (2.32 g, 13.6 mmol) was added and the mixture was heated at reflux for the reported time. After cooling the mixture was filtered through Celite. The filtrate was diluted with EtOAc, washed with water and brine, dried, and evaporated. The crude product was purified by chromatography to give the title compound as a colorless oil.

4-(2,3-Dinitrooxypropyl)phenyl Acetate (34). Reaction time 14 h; eluent PE/EtOAc 90/10; yield 21%; ^{1}H NMR (CDCl$_3$) δ 2.30 (s, 3H, CH_3COO), 2.96−3.04 (m, 2H, CH_2CH(ONO$_2$)), 4.40−4.46 (dd, 1H, CH$_2$CH(ONO$_2$)CH_aH$_b$ONO$_2$), 4.71−4.76 (dd, 1H, CH$_a$$H_b$-ONO$_2$), 5.38−5.46 (m, 1H, CH$_2$C*H*(ONO$_2$)), 7.07 (d, 2H, AA′BB′ system), 7.25 (d, 2H, AA′BB′ system); MS (EI) *m/z* 300 (M)$^+$.

4-(2,3-Dinitrooxypropyl)-2,6-dimethoxyphenyl Acetate (36). Reaction time 24 h; eluent PE/EtOAc 80/20; yield 65%; ^{1}H NMR (CDCl$_3$) δ 2.33 (s, 3H, CH_3COO), 2.91−3.10 (m, 2H, CH_2CH-(ONO$_2$)), 3.81 (s, 6H, OCH_3), 4.44−4.50 (dd, 1H, CH_aH$_b$ONO$_2$), 4.74−4.79 (dd, 1H, CH$_a$$H_bONO_2$), 5.43−5.46 (m, 1H, CH$_2$C*H*-(ONO$_2$)), 6.46 (s, 2H, C$_6H_2$); MS (EI) *m/z* 360 (M)$^+$.

4-(2,3-Dinitrooxypropyl)-2,6-di-*tert*-butylphenyl *tert*-butyl Carbonate (40). Reaction time 14 h; eluent PE/EtOAc 90/10; yield 35%; ^{1}H NMR (CDCl$_3$) δ 1.35 (s, 18H, C(CH_3)$_3$), 1.53 (s, 9H, OC(CH_3)$_3$), 2.90−3.10 (m, 2H, CH_2CH(ONO$_2$)), 4.42−4.48 (dd, 1H, CH_aH$_b$ONO$_2$), 4.72−4.77 (dd, 1H, CH$_a$$H_bONO_2$), 5.39−5.46 (m, 1H, CH$_2$C*H*(ONO$_2$)), 7.14 (s, 2H, C$_6H_2$); MS (CI) *m/z* 471 (M + 1)$^+$.

4-((*tert*-Butyl(dimethyl)silyl)oxy)benzaldehyde (45). To a stirred suspension of NaH (60%, 0.19 g, 4.8 mmol) in dry THF (3 mL), kept under N$_2$, was slowly added a solution of 4-hydroxybenzaldehyde (0.50 g, 4.0 mmol) in dry THF (6 mL). To the mixture so obtained was then slowly added a solution of TBDMSCl (0.84 g, 5.6 mmol) in dry THF (3 mL). The reaction was completed in 1 h. The mixture was poured into NaOH (2 M, 10 mL) and extracted with EtOAc. The organic layers were washed with brine, dried, and evaporated. The product so obtained was used in the next synthetic step without further purification: yield 93%; ^{1}H NMR (CDCl$_3$) δ 0.26 (s, 6H, Si(CH_3)$_2$), 1.01 (s, 9H, C(CH_3)$_3$), 6.96 (d, 2H, AA′BB′ system), 7.80 (d, 2H, AA′BB′ system), 9.90 (s, 1H, C*H*O); MS (EI) *m/z* 236 (M)$^+$.

3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)benzaldehyde (46). DIPEA (3.68 mL, 21.1 mmol) and MEMCl (2.09 mL, 18.3 mmol) were added to a stirred suspension of 4-hydroxy-3,5-dimethoxybenzaldehyde (**43**) (2.57 g, 14.1 mmol) in dichloroethane (34 mL), and then the mixture was heated at reflux for 2 h. The mixture was washed with a saturated solution of NH$_4$Cl, NaOH (0.1 M), and brine, dried, and evaporated. The product so obtained was used in the next synthetic step without further purification: yield 100%; ^{1}H NMR (CDCl$_3$) δ 3.36 (s, 3H, OCH$_2$CH$_2$OCH_3), 3.56 (m, 2H, OCH_2CH$_2$O), 3.91 (s, 6H, OCH_3), 3.99 (m, 2H, OCH$_2$CH_2O), 5.30 (s, 2H, OCH_2O), 7.13 (s, 2H, C$_6H_2$), 9.87 (s, 1H, C*H*O); MS (EI) *m/z* 270 (M)$^+$.

3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)benzaldehyde (47). The title product was prepared as describe for **46** starting from **44** and refluxing for 38 h. The product so obtained was purified by flash chromatography (PE/EtOAc 98/2 → 90/10): yield 72%; ^{1}H NMR (CDCl$_3$) δ 1.48 (s, 18H, C(CH_3)$_3$), 3.43 (s, 3H, OCH$_2$CH$_2$OCH_3), 3.66 (m, 2H, OCH$_2$CH_2O), 4.00 (m, 2H,

OCH_2CH_2O), 5.04 (s, 2H, OCH_2O), 7.81 (s, 2H, C_6H_2), 9.92 (s, 1H, CHO); MS (CI) *m/z* 323 $(M + 1)^+$.

General Procedure for 48−50. A solution of triethylphosphonoacetate (2.25 mL, 13.8 mmol) in dry THF (18 mL) was slowly added to a stirred solution of t-BuO^-K^+ (1.60 g, 14.3 mmol) in dry THF (15 mL) kept under an inert atmosphere at −78 °C. Then a solution of the appropriate aldehyde **45−47** (13.8 mmol) in dry THF (20 mL) was slowly added. After 1 h the mixture was allowed to reach room temperature and stirred for 1 h. The mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic layers were washed with brine, dried, and evaporated.

Ethyl 3-(4-((*tert*-Butyl(dimethyl)silyl)oxy)phenyl)acrylate (48). The crude product was purified by flash chromatography (PE/Et_2O 95/5) to give the title compound as a colorless oil: yield 62%; ^1H NMR ($CDCl_3$) δ 0.22 (s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $C(CH_3)_3$), 1.34 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 4.25 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 6.30 (d, 1H, COCH=CH, $^3J_{HH}$ = 16.0 Hz), 6.83 (d, 2H, AA′BB′ system), 7.41 (d, 2H, AA′BB′ system), 7.63 (d, 1H, COCH=CH, $^3J_{HH}$ = 16.0 Hz); MS (EI) *m/z* 306 $(M)^+$. Anal. ($C_{17}H_{26}O_3Si$) C, H.

Ethyl 3-(3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)acrylate (49). The crude product was purified by crystallization from iPr_2O to give the title compound as a white solid: yield 94%; mp 51−54 °C (from iPr_2O); ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 3.36 (s, 3H, $OCH_2CH_2OCH_3$), 3.56 (m, 2H, OCH_2CH_2O), 3.86 (s, 6H, OCH_3), 3.99 (m, 2H, OCH_2CH_2O), 4.26 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 5.23 (s, 2H, OCH_2O), 6.35 (d, 1H, COCH=CH, $^3J_{HH}$ = 15.9 Hz), 6.75 (s, 2H, C_6H_2), 7.60 (d, 1H, COCH=CH, $^3J_{HH}$ = 15.9 Hz); MS (EI) *m/z* 340 $(M)^+$. Anal. ($C_{17}H_{24}O_7$) C, H.

Ethyl 3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)phenyl)acrylate (50). The crude product was purified by flash chromatography (PE/Et_2O 90/10) to give the title compound as pale yellow oil: yield 84%; ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 1.44 (s, 18H, $C(CH_3)_3$), 3.42 (s, 3H, $OCH_2CH_2OCH_3$), 3.65 (m, 2H, OCH_2CH_2O), 3.99 (m, 2H, OCH_2CH_2O), 4.26 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 5.00 (s, 2H, OCH_2O), 6.34 (d, 1H, COCH=CH, $^3J_{HH}$ = 16.0 Hz), 7.44 (s, 2H, C_6H_2), 7.64 (d, 1H, COCH=CH, $^3J_{HH}$ = 16.0 Hz); MS (EI) *m/z* 392 $(M)^+$. Anal. ($C_{23}H_{36}O_5$) C, H.

General Procedure for 51−53. A solution of the appropriate intermediate **48−50** (12.7 mmol) in EtOH (40 mL) was added to a suspension of 10% palladium on charcoal catalyst (0.38 g) in EtOH (20 mL), and the mixture was stirred under atmospheric pressure of H_2 for 3 h. Then the mixture was filtered through Celite and evaporated. The product so obtained, a colorless oil, was used in the next synthetic step without further purification.

Ethyl 3-(4-((*tert*-Butyl(dimethyl)silyl)oxy)phenyl)propanoate (51). Yield 96%; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 1.24 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 2.59 (t, 2H, $^3J_{HH}$ = 7.5 Hz), 2.89 (t, 2H, $^3J_{HH}$ = 7.5 Hz) ($COCH_2CH_2$), 4.13 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 6.76 (d, 2H, AA′BB′ system), 7.05 (d, 2H, AA′BB′ system); MS (EI) *m/z* 308 $(M)^+$.

Ethyl 3-(3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propanoate (52). Yield 94%; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 2.60 (t, 2H, $^3J_{HH}$ = 7.5 Hz), 2.89 (t, 2H,$^3J_{HH}$ = 7.5 Hz) ($COCH_2CH_2$), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.56 (m, 2H, OCH_2CH_2O), 3.86 (s, 6H, OCH_3), 4.00 (m, 2H, OCH_2CH_2O), 4.14 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 5.16 (s, 2H, OCH_2O), 6.41 (s, 2H, C_6H_2); MS (EI) *m/z* 342 $(M)^+$.

Ethyl 3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propanoate (53). Yield 90%; ^1H NMR ($CDCl_3$) δ 1.23 (t, 3H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 1.42 (s, 18H, $C(CH_3)_3$), 2.59 (t, 2H, $^3J_{HH}$ = 7.5 Hz), 2.88 (t, 2H, $^3J_{HH}$ = 7.5 Hz) ($COCH_2CH_2$), 3.42 (s, 3H, $OCH_2CH_2OCH_3$), 3.66 (m, 2H, OCH_2CH_2O), 3.98 (m, 2H, OCH_2CH_2O), 4.14 (q, 2H, CH_3CH_2O, $^3J_{HH}$ = 7.1 Hz), 4.97 (s, 2H, OCH_2O), 7.07 (s, 2H, C_6H_2); MS (EI) *m/z* 394 $(M)^+$.

General Procedure for 27 and 54−56. A solution of the appropriate ethyl ester **26** and **51−53** (10.2 mmol) in dry THF (25 mL) was slowly added to a suspension, stirred under N_2 at 0 °C, of $LiAlH_4$ (0.41 g, 10.2 mmol). Then the mixture was allowed to reach room temperature and stirred for 1.5 h. The mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic layers were washed with water and brine, dried, and evaporated. The crude product so obtained was purified by flash chromatography to give a colorless oil.

(6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methanol (27). Eluent PE/EtOAc 80/20; yield 84%; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3H, 2-CH_3), 1.68−1.77 (m, 1H, 3-H_aH_b), 1.89 (s br, 1H, OH), 1.94−2.01 (m, 1H, 3-H_aH_b), 2.08 (s, 3H, $ArCH_3$), 2.15 (s, 3H, $ArCH_3$), 2.17 (s, 3H, $ArCH_3$), 2.61−2.66 (m, 2H, 4-H_2), 3.40 (s, 3H, OCH_3), 3.56−3.67 (m, 4H, OCH_2CH_2O/2-CH_2OH, overlapped signals), 3.95−3.98 (m, 2H, OCH_2CH_2O), 4.95 (s, 2H, OCH_2O); MS (EI) *m/z* 324 $(M)^+$. Anal. ($C_{18}H_{28}O_5$) C, H, N.

3-(4-((*tert*-Butyl(dimethyl)silyl)oxy)phenyl)propan-1-ol (54). Eluent Hex/EtOAc 95/5 → 80/20; yield 100%; ^1H NMR ($CDCl_3$) δ 0.20 (s, 6H, $Si(CH_3)_2$), 1.00 (s, 9H, $C(CH_3)_3$), 1.40 (s br, 1H, OH), 1.88 (m, 2H, $CH_2CH_2CH_2OH$), 2.66 (t, 2H, $CH_2CH_2CH_2OH$, $^3J_{HH}$ = 7.4 Hz), 3.68 (t, 2H, $CH_2CH_2CH_2OH$, $^3J_{HH}$ = 6.4 Hz), 6.77 (d, 2H, AA′BB′ system), 7.06 (d, 2H, AA′BB′ system); MS (EI) *m/z* 266 $(M)^+$. Anal. ($C_{15}H_{26}O_2Si$) C, H.

3-(3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (55). Because the product was unstable it was used directly in the next synthetic step without further purification: yield 92%; ^1H NMR ($CDCl_3$) δ 1.76 (s br, 1H, OH), 1.87 (m, 2H, $CH_2CH_2CH_2OH$), 2.64 (t, 2H, $CH_2CH_2CH_2OH$, $^3J_{HH}$ = 7.5 Hz), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.57 (m, 2H, OCH_2CH_2O), 3.68 (t, 2H, $CH_2CH_2CH_2OH$, $^3J_{HH}$ = 6.4 Hz), 3.81 (s, 6H, OCH_3), 4.00 (m, 2H, OCH_2CH_2O), 5.16 (s, 2H, OCH_2O), 6.41 (s, 2H, C_6H_2); MS (EI) *m/z* 300 $(M)^+$.

3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (56). Eluent Hex/EtOAc 80/20; yield 90%; ^1H NMR ($CDCl_3$) δ 1.38 (s, 1H, OH), 1.43 (s, 18H, $C(CH_3)_3$), 1.87 (m, 2H, $CH_2CH_2CH_2OH$), 2.62 (t, 2H, $CH_2CH_2CH_2OH$, $^3J_{HH}$ = 7.5 Hz), 3.42 (s, 3H, $OCH_2CH_2OCH_3$), 3.63−3.71 (m, 4H), 3.98 (m, 2H) (CH_2CH_2O/$CH_2CH_2CH_2OH$ overlapped signals), 4.98 (s, 2H, OCH_2O), 7.07 (s, 2H, C_6H_2); MS (EI) *m/z* 352 $(M)^+$. Anal. ($C_{21}H_{36}O_4$) C, H.

General Procedure for 57−59 and 63. A solution of the appropriate alcohol **54-56** and **27** (7.3 mmol) in dry THF (4 mL) was slowly added to a suspension of NaH (60%, 0.44 g, 11.0 mmol) in dry THF (4 mL), stirred under N_2 at 0 °C. After 30 min **10** (2.69 g, 7.3 mmol) was added and the mixture was stirred at 30 °C until the disappearance of the alcohol as shown by TLC. Then the mixture was poured into a saturated solution of NH_4Cl and extracted with Et_2O. The organic layers were washed with brine, dried, and evaporated. The crude product was purified by flash chromatography to give the title compound.

3-Benzenesulfonyl-4-(3-(4-(*tert*-butyl(dimethyl)silyl)oxy)phenyl)propoxy)furoxan (57). Eluent PE/EtOAc 95/5; yield 54%; ^1H NMR ($CDCl_3$) δ 0.19 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $C(CH_3)_3$), 2.16 (m, 2H, $CH_2CH_2CH_2O$), 2.74 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 7.3 Hz), 4.40 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 6.4 Hz), 6.77 (d, 2H, AA′BB′ system), 7.05 (d, 2H, AA′BB′ system), 7.60−8.09 (m, 5H, $C_6H_5SO_2$); MS (CI) *m/z* 491 $(M + 1)^+$.

3-Benzenesulfonyl-4-(3-(3,5-dimethoxy-4-((2-methoxyethoxy)-methoxy)phenyl)propoxy)furoxan (58). Eluent CH_2Cl_2/EtOAc 95/5; yield 52%; ^1H NMR ($CDCl_3$) δ 2.19 (m, 2H, $CH_2CH_2CH_2O$), 2.77 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 7.2 Hz), 3.37 (s, 3H, $OCH_2CH_2OCH_3$), 3.57 (m, 2H, OCH_2CH_2O), 3.82 (s, 6H, OCH_3), 4.01 (m, 2H, OCH_2CH_2O), 4.43 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 6.3 Hz), 5.18 (s, 2H, OCH_2O), 6.44 (s, 2H, C_6H_2), 7.56−8.09 (m, 5H, $C_6H_5SO_2$); MS (EI) *m/z* 524 $(M)^+$.

3-Benzenesulfonyl-4-(3-(3,5-di-*tert*-butyl-4-((2-methoxyethoxy)-methoxy)phenyl)propoxy)furoxan (59). Eluent PE/EtOAc 9/1; yield 54%; ^1H NMR ($CDCl_3$) δ 1.42 (s, 18H, $C(CH_3)_3$), 2.17 (m, 2H, $CH_2CH_2CH_2O$), 2.73 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 7.2 Hz), 3.42 (s, 3H, $OCH_2CH_2OCH_3$), 3.65 (m, 2H, OCH_2CH_2O), 3.99 (m, 2H, OCH_2CH_2O), 4.42 (t, 2H, $CH_2CH_2CH_2O$, $^3J_{HH}$ = 6.4 Hz), 4.99 (s, 2H, OCH_2O), 7.06 (s, 2H, C_6H_2), 7.59−8.10 (m, 5H, $C_6H_5SO_2$); MS (EI) *m/z* 576 $(M)^+$.

3-Benzensulfonyl-4-((6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)furoxan (63). Eluent PE/EtOAc 85/15; yield 60%; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 3H, 2-CH_3), 1.99 (s, 3H, ArCH_3), 2.13 (s, 3H, ArCH_3), 2.16 (s, 3H, ArCH_3), 1.93−2.16 (m, 2H, 3-H_2), 2.68 (m, 2H, 4-H_2) 3.41 (s, 3H, OCH_3), 3.59 (m, 2H, OCH_2CH$_2$O), 3.97 (m, 2H, OCH$_2$CH_2O), 4.39 (d AB system, 1H, 2-CH_aH$_b$O, $^2J_{HH}$ = 10.5 Hz), 4.46 (d AB system, 1H, 2-CH$_a$$H_b$O, $^2J_{HH}$ = 10.5 Hz), 4.95 (s, 2H, OCH_2O), 7.47−8.00 (m, 5H, C$_6H_5$SO$_2$); MS (EI) *m/z* 548 (M)$^+$.

4-(3-(3-Benzenesulfonylfuroxan-4-yloxy)propyl)phenol (60). To a solution of **57** (1.84 g, 3.7 mmol) in 1,4-dioxane (26 mL) was added HCl (37%, 1.4 mL) and the solution stirred for 22 h. Then the solution was evaporated and the solid so obtained was triturated with ice-cold EtOH and filtered to give the title compound as white solid: yield 44%; mp 92−93 °C (from EtOH); ^{1}H NMR (DMSO-d_6) δ 2.00 (m, 2H, CH$_2$CH_2CH$_2$O), 2.57 (t, 2H, CH_2CH$_2$-CH$_2$O, $^3J_{HH}$ = 7.5 Hz), 4.34 (t, 2H, CH$_2$CH$_2$CH_2O, $^3J_{HH}$ = 6.2 Hz), 6.69 (d, 2H, AA′BB′ system), 6.99 (d, 2H, AA′BB′system), 7.74−8.07 (m, 5H, C$_6H_5$SO$_2$), 9.19 (s br, 1H, O*H*); MS (EI) *m/z* 376 (M)$^+$. Anal. ($C_{17}H_{16}N_2O_6S$) C, H, N.

4-(3-(3-Benzenesulfonylfuroxan-4-yloxy)propyl)-2,6-dimethoxyphenol (61). To a solution of **58** (1.06 g, 2.0 mmol) in THF (15 mL) was added HCl (1 M, 12 mL) and the solution was stirred at room temperature for 4 h. The mixture was poured into water and extracted twice with CH_2Cl_2. The organic layers were dried and evaporated to give the title compound as a white solid: yield 89%; mp 116−117 °C (from EtOH); ^{1}H NMR (DMSO-d_6) δ 2.04 (m, 2H, CH$_2$CH_2CH$_2$O), 2.58 (t, 2H, CH_2CH$_2$CH$_2$O, $^3J_{HH}$ = 7.3 Hz), 3.71 (s, 6H, OCH_3), 4.34 (t, 2H, CH$_2$CH$_2$CH_2O, $^3J_{HH}$ = 6.1 Hz), 6.43 (s, 2H, C$_6H_2$), 7.72−8.05 (m, 5H, C$_6H_5$SO$_2$), 8.11 (s br, 1H, O*H*); MS (EI) *m/z* 436 (M)$^+$. Anal. ($C_{19}H_{20}N_2O_8S$) C, H, N.

3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)phenyl)-*N*-methylpropanamide (65). To a stirred solution of **53** (1.3 g, 3.29 mmol) in 1,4-dioxane (13 mL) was added MeNH$_2$ (40%, 4.55 mL, 40 equiv) and the solution was heated at 120 °C for 24 h in the Parr reactor. Then the solution was concentrated and the residue dissolved in water and extracted with CH_2Cl_2. The organic layers were dried and evaporated. The crude product was purified by flash chromatography (PE/*i*PrOH 95/5) to give the title compound as a white solid: yield 51%; mp 86−89 °C (from *i*PrOH); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H, C(CH_3)$_3$), 2.44 (t, 2H, $^3J_{HH}$ = 7.4 Hz), 2.89 (t, 2H, $^3J_{HH}$ = 7.4 Hz) (COCH_2CH_2), 2.79 (d, 3H, NHCH_3), 3.42 (s, 3H, OCH$_2$CH$_2$OCH_3), 3.64 (m, 2H, OCH$_2$CH_2O), 3.97 (m, 2H, OCH_2CH$_2$O), 4.97 (s, 2H, OCH_2O), 5.45 (s br, 1H, N*H*), 7.07 (s, 2H, C$_6H_2$); MS (EI) *m/z* 379 (M)$^+$. Anal. ($C_{22}H_{37}NO_4$) C, H, N.

6-((2-Methoxyethoxy)methoxy)-*N*,2,5,7,8-pentamethylchromane-2-carboxamide (69). The title compound was obtained as **65** starting from **26**: eluent PE/*i*PrOH 95/5; yield 50%; mp 80−81 °C (from *i*Pr$_2$O); ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 3H, 2-CH_3), 1.69−1.74 (m, 1H, 3-H_aH$_b$), 2.04 (s, 3H, ArCH_3), 2.11 (s, 3H, ArCH_3), 2.14 (s, 3H, ArCH_3), 2.21 (m, 1H, 3-H$_a$$H_b$), 2.40−2.51 (m, 2H, 4-$H_2$), 2.59 (d, 3H, NHC$H_3$, $^3J_{HH}$ = 4.7 Hz), 3.25 (s, 3H, CH_3O), 3.48 (m, 2H, OCH_2CH$_2$O), 3.81 (m, 2H, OCH$_2$CH_2O), 4.85 (s, 2H, OCH_2O), 7.41 (m, 1H, N*H*); MS (EI) *m/z* 351 (M)$^+$. Anal. ($C_{19}H_{29}NO_5$·H$_2$O) C, H, N.

3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)phenyl)-*N*-methylpropan-1-amine (66) Oxalate. A solution of **65** (0.65 g, 1.6 mmol) in dry THF (3 mL) was slowly added to a suspension of $LiAlH_4$ (0.19 g, 4.9 mmol) in dry THF (3 mL) stirred under N_2. The mixture was heated at 72 °C for 24 h. To the mixture first water (30 mL), then NaOH 15% (20 mL), and finally water (20 mL) were added. This mixture was extracted twice with EtOAc. The organic layers were dried and evaporated. The crude product was purified by flash chromatography (PE/*i*PrOH 90/10) to give the title compound as yellow oil (yield 66%). An analytical sample was prepared by adding a saturated solution of $H_2C_2O_4$ in acetone to a saturated solution of product in acetone and filtering the white solid so obtained: mp 153−154 °C dec (from acetone); ^{1}H NMR (DMSO-d_6) δ 1.40 (s, 18H, C(CH_3)$_3$), 1.86 (m, 2H, NHCH$_2$CH_2-CH$_2$), 2.52−2.58 (m, 5H, NHCH$_2$CH$_2$CH_2, NHCH_3), 2.89 (t, 2H, CH$_2$CH$_2$CH_2NH, $^3J_{HH}$ = 7.3 Hz), 3.29 (s, 3H, OCH$_2$CH$_2$OCH_3), 3.55 (m, 2H, OCH$_2$CH_2O), 3.88 (m, 2H, OCH_2CH$_2$O), 4.90 (s, 2H, OCH_2O), 7.09 (s, 2H, C$_6H_2$), 9.00 (s vb, 3H, N*H*·H$_2$C$_2$O$_4$); MS (EI) *m/z* 365 (M)$^+$. Anal. ($C_{24}H_{41}NO_7$) C, H, N.

***N*-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methyl)-*N*-methylamine (70) Oxalate.** The title compound was obtained as **66** starting from **69**: eluent CH_2Cl_2/7 N NH$_3$ in MeOH 98/2; yield 78%; mp 167−168 °C dec (from acetone); ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 3H, 2-CH_3), 1.84 (m, 2H, 3-H_2), 2.05 (s, 3H, ArCH_3), 2.08 (s, 3H, ArCH_3), 2.10 (s, 3H, ArCH_3), 2.50−2.64 (m, 7H, 4-H_2, CH_2NH, NHCH_3), 3.25 (s, 3H, CH_3O), 3.49 (m, 2H, OCH_2CH$_2$O), 3.82 (m, 2H, OCH$_2$CH_2O), 4.86 (s, 2H, OCH_2O), $H_2C_2O_4$ signal not detectable; MS (CI) *m/z* 338 (M + 1)$^+$. Anal. ($C_{21}H_{33}NO_8$·0.5 H$_2$O) C, H, N.

4-((*N*-((3-(3,5-Di-*tert*-butyl-4-((2-methoxyethoxy)methoxy)-phenyl)propyl)-*N*-methyl)amino)methyl)furoxan-3-carboxamide (67). To a solution of **66** (0.27 g, 0.74 mmol) in acetone (6 mL) were added a solution of $KHCO_3$ (0.5 N, 4 mL) and slowly a solution of **11** (0.15 g, 0.37 mmol) in acetone (2 mL). Then the mixture was stirred for 24 h and $KHCO_3$ (0.5 N) was added until basic pH and the solution was extracted with EtOAc. The organic layers were washed with brine, dried, and evaporated. The crude product was purified by flash chromatography (PE/EtOAc 80/20) to give the title compound as a yellow solid: yield 90%; mp 84−86 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H, C(CH_3)$_3$), 1.85 (m, 2H, NCH$_2$CH_2CH$_2$), 2.39 (s, 3H, NCH_3), 2.50−2.63 (m, 4H, NCH_2-CH$_2$CH_2), 3.42 (s, 3H, OCH$_2$CH$_2$OCH_3), 3.65 (m, 2H, CH$_2$CH_2O), 3.89 (s, 2H, CH_2Fx), 3.98 (m, 2H, OCH_2CH$_2$O), 4.98 (s, 2H, OCH_2O), 5.90 (s br, 1H, CON*H*H), 7.04 (s, 2H, C$_6H_2$), 8.81 (s br, 1H, CONH*H*); MS (EI) *m/z* 506 (M)$^+$.

4-(*N*-Methyl-*N*-((6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)amino)methyl)furoxan-3-carboxamide (71). The title compound was obtained as **67** starting from **70**: eluent PE/*i*PrOH 95/5; yield 85%; mp 109−110 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H, 2-CH_3), 1.64−1.71 (m, 1H, 3-H_aH$_b$), 1.87−1.96 (m, 1H, 3-H$_a$$H_b$), 2.03 (s, 3H, ArC$H_3$), 2.14 (s, 3H, ArC$H_3$), 2.17 (s, 3H, ArC$H_3$), 2.55 (s, 3H, NC$H_3$), 2.61 (m, 2H, 4-$H_2$), 2.76 (d AB system, 1H, 2-CH_aH$_b$N, $^2J_{HH}$ = 14.1 Hz), 2.79 (d AB system, 1H, 2-CH$_a$$H_b$N, $^2J_{HH}$ = 14.1 Hz), 3.40 (s, 3H, CH_3O), 3.61 (m, 2H, OCH_2CH$_2$O), 3.96 (m, 2H, OCH$_2$CH_2O), 4.06 (s, 2H, CH_2Fx), 4.94 (s, 2H, OCH_2O), 5.91 (s br, 1H, CON*H*H), 8.38 (s br, 1H, CONH*H*); MS (EI) *m/z* 478 (M)$^+$.

Amperometric Detection of NO Release from Derivative 7. The membrane-covered tip of the measuring electrode was inserted into a solution containing Tris-HCl/KCl (100 mM/150 mM, pH 7.4) buffer either in the absence (control experiments) or in the presence of hepatocytes microsomial fraction (2 mg prot/mL). The suspension was constantly mixed by a magnetic stirrer and kept at 37 °C in a closed glass vial. The current was recorded for 15 min to allow for baseline stabilization. Consecutive additions of sodium ascorbate (100 μM) in HPLC-grade water (50 μL), reference furoxan **7** (100 μM) in DMSO (1% in final solution), and $FeSO_4$ (2.5 μM) in HPLC-grade water (50 μL) were performed via a gastight syringe. The final volume of the tested mixture was 10 mL. Change in the current was recorded as a function of time, and data were elaborated with a MacLab System PowerLab. Experiments were run at least in triplicate after appropriate calibration of the electrode with $NaNO_2$.[21]

Biological Experiments. Antioxidant Activity. Hepatic microsomal membranes from male Wistar rats (200−250 g) were prepared by differential centrifugation (8000*g*, 20 min; 120 000*g*, 1 h) in a HEPES/sucrose buffer (10 mM, 250 mM, pH 7.4) and stored at −80 °C. Incubation was performed at 37 °C in a Tris-HCl/KCl (100 mM/150 mM, pH 7.4) containing microsomal membranes (2 mg prot/mL), sodium ascorbate (100 μM), and DMSO solutions of the tested compounds. Addition of DMSO alone (maximal amount 5%) did not change significantly the extent of peroxidation in the control experiments. Lipid peroxidation was initiated by adding 2.5 μM $FeSO_4$. Aliquots were taken from the incubation mixture at 5, 15, and 30 min and treated with trichloroacetic acid (TCA) 10% w/v. Lipid peroxidation was assessed by spectrophotometric (543 nm) determination of the TBARS consist-

ing mainly of malondialdehyde (MDA), and TBARS concentrations (expressed in nmol/mg protein) were obtained by interpolation with a MDA standard curve.[22] The antioxidant activity of tested compounds was evaluated as the percent inhibition of TBARS production with respect to control samples, using the values obtained after 30 min of incubation. IC_{50} values were calculated by nonlinear regression analysis.

Vasodilator Activity. Thoracic aortas were isolated from male Wistar rats weighting 180−200 g. As few animals as possible were used. The purposes and the protocols of our studies have been approved by the Ministero della Salute, Rome, Italy. The endothelium was removed, and the vessels were helically cut: three strips were obtained from each aorta. The tissues were mounted under 1.0 g of tension in organ baths containing 30 mL of Krebs−bicarbonate buffer with the following composition (mM): NaCl (111.2), KCl (5.0), $CaCl_2$ (2.5), $MgSO_4$ (1.2), KH_2PO_4 (1.0), $NaHCO_3$ (12.0), glucose (11.1). The tissues were maintained at 37 °C and gassed with 95% O_2 5% CO_2 (pH 7.4). The aortic strips were allowed to equilibrate for 120 min and then contracted with 1 μM L-phenylephrine. When the response to the agonist reached a plateau, cumulative concentrations of the vasodilating agent were added. Results are expressed as $EC_{50} \pm$ SE (μM). The effects of 1 μM ODQ on relaxation were evaluated in a separate series of experiments in which it was added 5 min before the contraction. Responses were recorded by an isometric transducer connected to the MacLab System PowerLab. Addition of the drug vehicle, DMSO, had no appreciable effect on contraction level.

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Supporting Information Available: Combustion analysis data and ^{13}C NMR data of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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