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

This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/1731 since 2015-12-22T12:16:26Z

Published version:
DOI:10.1021/jm0510530

Terms of use:
Open Access
Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)
This is an author version of the contribution published on:
Questa è la versione dell’autore dell’opera:

The definitive version is available at:
La versione definitiva è disponibile alla URL:
[pubs.acs.org/jmc]
NO-Donor Phenols: A New Class of Products

Endowed with Antioxidant and Vasodilator Properties

Donatella Boschi, a Gian Cesare Tron, b Loretta Lazzarato, a Konstantin Chegaev, a Clara Cena, a Antonella Di Stilo, a Marta Giorgis, a Massimo Bertinaria, a Roberta Fruttero a and Alberto Gasco a

a Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via Pietro Giuria 9, 10125 Torino, Italy.

b Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale, Via Bovio 6, 28100 Novara, Italy.

* To whom correspondence should be addressed:

Dipartimento di Scienza e Tecnologia del Farmaco
Via P. Giuria, 9
I-10125 Torino – Italy
Telephone: 0039 011 6707670
Fax: 0039 011 6707286
E-mail: alberto.gasco@unito.it
Abstract. 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 autooxidation 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, others as antioxidants (24, 32, 72) and the two properties are relatively balanced in 19, 41, 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 disease 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 defences, a situation called oxidative stress arises.\(^2b\)\(^{-}\)\(^2d\) 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\(_2^\cdot\)) 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\(^\cdot\)) (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 which 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\(_2^\cdot\) 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, the OH\(^\cdot\) and the nitrogen dioxide radical (NO\(_2^\cdot\)). In addition, O\(_2^\cdot\), when present in high concentrations, can react with thiol residues of proteins which are normally involved in S-nitrosylation, preventing this reaction from occurring.\(^4b\),\(^4c\) The result is the perturbation of this signaling mechanism with the consequent decrease of vessel responsiveness to NO\(^\cdot\). 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, 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 drugs for the treatment of complex diseases such as CD. The risk-benefit profile in the use of a multi-target drug in therapy compared to the use of a mono-target 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, characterised 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 Company\(^8a\) (CHF 2363) and the latter by the Cassella-Hoechst Company\(^8b\) (CAS 1609). The reason for choosing these reference models to use in our chemical hybridisation 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 action of AgNO\(_3\) on the 4-(3-bromopropyl)phenol (12) in acetonitrile solution. The analogue 2,6-dimethoxy substituted 19 was synthesised 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 CH₂Cl₂ 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 CH₂Cl₂ 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 (Bu₄N⁺NO₃⁻) in refluxing benzene to yield 18, that was transformed, in CH₂Cl₂ 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, in the same conditions used to prepare 17, to obtain 21. Subsequently, the phenol group of 21 was Boc-protected with di-tert-butyldicarbonate (Boc₂O) 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 CH₂Cl₂ 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 synthesised starting from 25, that was obtained by treatment of the carboxylic acid Trolox® with ethanol in the presence of p-toluensulfonic acid (p-TSA). The free phenol hydroxy group was MEM-protected using 2-methoxyethoxymethyl chloride (MEMCl) to give 26. Subsequent reduction of the ester group by LiAlH₄ 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 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, 41 were prepared through a common pathway (Scheme 3) which implies the use of the appropriate protected p-allylphenols 33, 15, 39. These products were transformed into the corresponding protected dinitrooxy derivatives 34, 36, 40 by an old procedure to prepare nitric esters of which little use has been made. This procedure involves treating the unsaturated starting materials with iodine and AgNO₃ in acetonitrile. The expected vicinal dinitrooxy substituted compounds were obtained in modest yields. Cleavage of the protection gave the expected final products 35, 37, 41. We also submitted 28 to this procedure
but the related final dinitrooxy substituted obtained structure was unstable when deprotected. The preparation of the phenol substituted furoxans 60-62, 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, 44 were MEMprotected using MEMCl in 1,2-dichloroethane solution in the presence of N,N-diisopropylethylamine (DIPEA) to give the corresponding derivatives 46, 47. The products were subjected to the modified Wittig reaction in the presence of phosphonoacetic acid triethyl ester and t-BuO\(\text{K}^+\) in THF solution to afford the corresponding \(\alpha,\beta\)-unsaturated esters 48-50. Reduction of these products using first \(\text{H}_2\), Pd/C and then LiAlH\(_4\), gave, first the related esters 51-53, and then 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 in 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 MEMprotected ester 53 was transformed, by action of methylamine, into the N-methylcarboxamide 65, that 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\(_2\)Cl\(_2\), the final product 68. The same sequence of reactions was used to prepare the furoxancarboxamide 72 from 26, through the intermediate formation of 69, 70, 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 autooxidation. 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. All the NO-donor phenols proved to inhibit in a concentration dependent manner the generation of TBARS. Selected examples of this behaviour are reported in Figure 1. The potencies (IC\textsubscript{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 respectively. 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, 64 containing as a substructure the 6-hydroxy-2,2,5,7,8-pentamethylchroman 4, followed by models 68, 62 containing as a substructure the 2,6-di-\textit{tert}-butyl-\textit{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 \textit{p}-cresol 1. This could be due to the ability of the product to directly scavenge radicals and/or 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. 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 which operate in this new class of antioxidants is in progress. Preliminary results seem to indicate that the antioxidant potency (log 1/IC\textsubscript{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. 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 behaviour 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, 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, 1H-[1,2,4]oxadiazo-[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 behaviour of some compounds (13, 35, 37, 60-62, 64) is principally vasodilatory, others (24, 32, 72) are primarily antioxidants while the compounds 19, 41, 68 trigger these two activities in a relatively balanced manner. This aspect 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 which 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), $^1$H 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 x 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) and the results, available in supporting information, are within ± 0.4 % of the theoretical, unless otherwise stated. Structures 10, 11, 15, 20, 25, 30, 38 were synthesized according to methods described in the literature. The phenol 20 was further purified by gradient flash chromatography (eluents PE/CH2Cl2) until a 80 % purity. The products 5 and 6 were synthesized from n-propanol and 1,2-propanediol respectively according to the procedure described in literature. The product 9 was synthesized according to the procedure described for the preparation of the diethyl analogue (Mp = 128-129 °C dec. (from iPrOH); anal. (C6H10N3O3) C, H, N). All of the NO-donor phenols were kept in freezer and their stability was checked (HPLC) over three months. They were stable (> 95 %) over this period. Tetrahydrofuran (THF) was distilled immediately before use from Na and benzophenone under a positive atmosphere of N2. When needed the reactions were performed in flame- or oven-dried glassware under a positive pressure of dry N2. 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 2mm diameter shielded microsensor ISO-NOP and a ISO-NO Mark II data recording system from World Precision Instrument (Sarasota, FL, USA).

3-(4-Hydroxyphenyl)propyl nitrate (13). AgNO3 (4.74 g, 28.0 mmol) was added to a stirred solution of 12 (5.00 g, 23.3 mmol) in CH3CN (50 mL), 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, 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$_2$CH$_2$ONO$_2$), 2.65 (t, 2H, -CH$_2$CH$_2$CH$_2$ONO$_2$, $^3$J$_{HH}$ = 8.0 Hz), 4.42 (t, 2H, -CH$_2$ONO$_2$, $^3$J$_{HH}$ = 6.5 Hz), 5.92 (s, 1H, -OH), 6.79 (d, 2H, AA’BB’ system), 7.03 (d, 2H, AA’BB’ system); MS (El) m/z 197 (M)$^+$. Anal. (C$_9$H$_{11}$NO$_4$) calc: C: 54.82, H: 5.62, N: 7.10, found: C: 54.45, H: 5.62, N: 6.68.

4-[(2,6-Dimethoxyphenyl)acetate (15). To a stirred solution of 14 (2.00 mL, 10.3 mmol) in CH$_2$Cl$_2$ (20 mL) TEA (2.86 mL, 20.5 mmol) and DMAP (0.04 g, 0.29 mmol) were added. The mixture was cooled at 0 °C and Ac$_2$O (1.93 mL, 20.5 mmol) was added dropwise. Then the mixture was allowed to reach room temperature (r.t.) and stirred for 20 min. The solution was then diluted with CH$_2$Cl$_2$, 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 colourless oil that became solid on standing. Yield 97 %. Mp 43-44 °C.

1H-NMR (CDCl$_3$) δ 2.33 (s, 3H, C$_t$H$_3$COO-), 3.36 (d, 2H, -C$_t$H$_2$CH=CH$_2$, $^3$J$_{HH}$ = 6.8 Hz), 3.80 (s, 6H, -OC$_t$H$_3$), 5.09-5.15 (m, 2H, C$_t$H$_2$=CH-), 5.91-6.00 (m, 1H, C$_6$H$_2$); MS (EI) m/z 236 (M)$^+$. Anal. (C$_{13}$H$_{18}$O$_5$) C, H.

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$_2$O$_2$ 30 % (13.5 mL) were slowly added. The resulting mixture was allowed to reach r.t. and stirred for 2 h. The excess of H$_2$O$_2$ was destroyed adding sodium bisulphite. 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 iPr$_2$O).

1H-NMR (CDCl$_3$) δ 1.63 (s, 1H, OH), 1.84-1.93 (m, 2H, -CH$_2$CH$_2$OH), 2.33 (s, 3H, CH$_3$COO-), 2.64-2.70 (m, 2H, -CH$_2$CH$_2$CH$_2$OH), 3.66-3.70 (m, 2H, -CH$_2$OH), 3.80 (s, 6H, -OCH$_3$), 6.45 (s, 2H, C$_6$H$_2$); MS (El) m/z 254 (M)$^+$. Anal. (C$_{12}$H$_{18}$O$_5$) C, H.

3-[[[(2,6-Dimethoxyphenyl)acetate-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$_2$CH$_2$OH), 2.06 (s, 3H,
ArCH₃), 2.13 (s, 3H, ArCH₃), 2.16 (s, 3H, ArCH₃), 2.58 (m, 2H, 4-H₂), 3.40 (s, 3H, CH₂O–), 3.44 (d AB system, 1H, 2-CH₃H₆O–, 3JHH = 9.3 Hz), 3.48 (d AB system, 1H, 2-CH₃H₆O–, 3JHH = 9.3 Hz), 3.61 (m, 2H, -OCH₂CH₂O–), 3.68-3.82 (m, 4H, -OCH₂CH₂CH₂OH), 3.95 (m, 2H, -OCH₂CH₂O–), 4.93 (s, 2H, -OCH₂O–); MS (ESI) m/z 405 (M+Na)+, drying conditions: 40 °C, 48 h, pressure < 1 mmHg. Anal. (C₂₁H₄₄O₆) C, H.

**General procedure for 17, 21, 30.** To a solution of the appropriate alcohol 16, 20, 29 (6.17 mmol) in CH₂Cl₂ TEA (1.7 mL, 12.3 mmol), DMAP (0.75 g, 6.17 mmol) and TsCl (2.34 g, 12.3 mmol) were added. The mixture was stirred for 2-3 h and then diluted with CH₂Cl₂ and 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. ¹H-NMR (CDCl₃) δ 1.90-2.00 (m, 2H, -CH₂CH₂OSO₂–), 2.32 (s, 3H, CH₃COO–), 2.44 (s, 3H, CH₃C₆H₄–), 2.60-2.66 (m, 2H, -CH₂CH₂CH₂OSO₂–), 3.77 (s, 6H, CH₃O–), 4.00-4.06 (m, 2H, -CH₂OSO₂–), 6.37 (s, 2H, C₆H₂), 7.34 (d, 2H, AA’BB’ system), 7.78 (d, 2H, AA’BB’ system); MS (EI) m/z 408 (M)+. Anal. (C₂₀H₂₃O₇) C, H.

**3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propyl tosylate (21).** The crude product was purified by crystallization from iPr₂O to give a white solid. Yield 56 %. Mp 96-97 °C. ¹H-NMR (CDCl₃) δ 1.42 (s, 18H, -C(CH₃)₃), 1.88-1.98 (m, 2H, -CH₂CH₂OSO₂–), 2.45 (s, 3H, CH₃C₆H₄–), 2.54-2.59 (m, 2H, -CH₂CH₂CH₂OSO₂–), 4.05-4.09 (m, 2H, -CH₂OSO₂–), 5.08 (s, 1H, OCH), 6.92 (s, 2H, C₆H₂), 7.35 (d, 2H, AA’BB’ system), 7.81 (d, 2H, AA’BB’ system); MS (EI) m/z 418 (M)+. Anal. (C₃₂H₃₄O₄S) 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 %. ¹H-NMR (CDCl₃) δ 1.17 (s, 3H, 2-CH₃), 1.62-1.71 (m, 1H, 3-H₃H₆), 1.80-1.90 (m, 3H, 3-H₃H₆/OCH₂CH₂CH₂OTs), 2.03 (s, 3H, ArCH₃), 2.13 (s, 3H, ArCH₃), 2.16 (s, 3H, ArCH₃), 2.42 (s, 3H, CH₃C₆H₄), 2.53 (m, 2H, 4-H₂), 3.29 (d AB system, 1H, 2-CH₃H₆O–, 3JHH = 9.9 Hz), 3.37 (d AB system, 1H, 2-CH₃H₆O–, 3JHH = 9.9 Hz), 3.40 (s, 3H, CH₃O–), 3.49-3.54 (m, 2H, -
OCH₂CH₂CH₂O-), 3.60 (m, 2H, -OCH₂CH₂O-), 3.96 (m, 2H, -OCH₂CH₂O-), 4.13 (m, 2H, -OCH₂CH₂CH₂O-), 4.93 (s, 2H, -OCH₂O-), 7.31 (d, 2H, AA’BB’ system), 7.77 (d, 2H, AA’BB’ system); MS (ESI) m/z 559 (M+Na)+. Anal. (C₂₈H₄₀O₈S) C, H.

**General procedure for 18, 23, 31.** Tetrabutyl ammonium nitrate (2.70 g, 8.9 mmol) was added to a solution of the appropriate tosylate 17, 21, 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 %. ¹H-NMR (CDCl₃) δ 2.00-2.10 (m, 2H, -CH₂CH₂ONO₂), 2.33 (s, 3H, CH₃COO-), 2.67-2.72 (m, 2H, -CH₂CH₂CH₂ONO₂), 3.80 (s, 6H, CH₃O-), 4.45-4.49 (m, 2H, -CH₂ONO₂), 6.42 (s, 2H, C₆H₂); MS (EI) m/z 299 (M⁺).

Tert-butyl 2,6-di-tert-butyl-4-(3-nitroxypropyl)phenyl carbonate (23). Eluent: PE/EtOAc 95/5. Yield 90 %. ¹H-NMR (CDCl₃) δ 1.34-1.36 (s, 18H, -C(CH₃)₃), 1.53 (s, 9H, -OC(CH₃)₃), 2.00-2.10 (m, 2H, -CH₂CH₂ONO₂), 2.66-2.72 (m, 2H, -CH₂CH₂CH₂ONO₂), 4.45-4.50 (m, 2H, -CH₂ONO₂), 7.10 (s, 2H, C₆H₂); 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 %. ¹H-NMR (CDCl₃) δ 1.26 (s, 3H, 2-CH₃), 1.70-1.78 (m, 1H, 3-H₃H₃b), 1.88-1.98 (m, 3H, 3-H₃aH₃b/-OCH₂CH₂CH₂ONO₂), 2.06 (s, 3H, ArCH₃), 2.14 (s, 3H, ArCH₃), 2.17 (s, 3H, ArCH₃), 2.58 (m, 2H, 4-H₂), 3.40 (s, 3H, CH₃O-), 3.40 (d AB system, 1H, 2-CH₃H₂O⁻, 3JHH = 9.9 Hz), 3.48 (d AB system, 1H, 2-CH₃H₂O⁻, 3JHH = 9.9 Hz), 3.58-3.64 (m, 4H, -OCH₂CH₂O⁻/-OCH₂CH₂CH₂ONO₂), 3.96 (m, 2H, -OCH₂CH₂O⁻), 4.57 (t, 2H, -OCH₂CH₂CH₂ONO₂, 3JHH = 6.3 Hz), 4.94 (s, 2H, -OCH₂O⁻); MS (ESI) m/z 450 (M+Na)+.

**General procedure for 19, 35, 37.** Pyrrolidine (0.95 mL, 11.5 mmol) was added to a stirred solution of the appropriate acetate 18, 34, 36 (0.86 g, 2.9 mmol) in CH₃CN (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 2N and brine, then 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$_6$) $\delta$ 1.90-2.00 (m, 2H, -CH$_2$CH$_2$ONO$_2$), 2.54-2.59 (m, 2H, -CH$_2$CH$_2$CH$_2$ONO$_2$), 3.74 (s, 6H, CH$_3$-), 4.48-4.52 (m, 2H, -CH$_2$ONO$_2$), 6.47 (s, 2H, C$_6$H$_2$), 8.14 (s, 1H, OH); 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. Colourless oil. Yield 35 %. $^1$H-NMR (CDCl$_3$) $\delta$ 2.86-3.06 (m, 2H, -CH$_2$CH(ONO$_2$)-), 4.38-4.44 (dd, 1H, -CH$_3$H$_6$ONO$_2$), 4.68-4.73 (dd, 1H, -CH$_3$H$_6$ONO$_2$), 5.37-5.43 (m, 1H, -CH(ONO$_2$)CH$_2$-), 5.26 (s br, 1H, OH), 6.81 (d, 2H, AA`BB’ system), 7.10 (d, 2H, AA`BB’ system); MS (EI) m/z 258 (M)$^+$. Anal. (C$_9$H$_{10}$N$_2$O$_7$) C, H, N.

3-(4-Hydroxy-3,5-dimethoxyphenyl)prop-1,2-diyl dinitrate (37). Eluent (PE/EtOAc 70/30). White solid. Yield 72 %. Mp 65-66 °C. $^1$H-NMR (CDCl$_3$) $\delta$ 2.87-3.07 (m, 2H, -CH$_2$CH(ONO$_2$)-), 3.88 (s, 6H, -OCH$_3$), 4.41-4.47 (dd, 1H, -CH$_3$H$_6$ONO$_2$), 4.71-4.76 (dd, 1H, -CH$_3$H$_6$ONO$_2$), 5.40-5.50 (m, 1H, -CH(ONO$_2$)CH$_2$-), 5.51 (s br, 1H, OH), 6.44 (s, 2H, C$_6$H$_2$); MS (EI) m/z 318 (M)$^+$. Anal. (C$_{11}$H$_{14}$N$_2$O$_8$) C, H, N.

3-(4-(tert-Butoxycarbonyloxy)-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, kept under inert atmosphere, of 21 (2.24 g, 5.3 mmol) in dry CH$_2$Cl$_2$ (25 mL), 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$_3$) $\delta$ 1.33 (s, 18H, -C(CH$_3$)$_3$), 1.52 (s, 9H, -OC(CH$_3$)$_3$), 1.88-1.96 (m, 2H, -CH$_2$CH$_2$OSO$_2$-), 2.44 (s, 3H, CH$_3$C$_6$H$_4$-), 2.55-2.62 (m, 2H, -CH$_2$CH$_2$CH$_2$OSO$_2$-), 4.02-4.07 (m, 2H, -CH$_2$OSO$_2$-), 7.02 (s, 2H, C$_6$H$_2$), 7.34 (d, 2H, AA`BB’ system), 7.80 (d, 2H, AA`BB’ system); MS (Cl) 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$_3$) $\delta$ 1.37 (s, 18H, -C(CH$_3$)$_3$), 1.54 (s,
9H, -OC(CH₃)₃, 3.36 (d, 2H, -CH₂CH=CH₂, 3J_HH = 6.9 Hz), 5.07-5.16 (m, 2H, CH₂=CH-), 5.93-6.05 (m, 1H, CH₂=CH-), 7.13 (s, 2H, C₆H₂); MS (Cl) m/z 347 (M+1)+.

**General procedure for 24, 32, 41, 62, 64, 68, 72.** TFA (0.75 mL, 14.7 mmol) was added to a stirred solution, kept under inert atmosphere, of the appropriate protected phenol 23, 31, 40, 59, 63, 67, 71 (2.9 mmol) in dry CH₂Cl₂ (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 NaHCO₃ and brine, dried and evaporated. The crude product was purified like 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. ¹H-NMR (CDCl₃) δ 1.43 (s, 18H, -C(CH₃)₃), 1.96-2.06 (m, 2H, -CH₂CH₂ONO₂-), 2.62-2.67 (m, 2H, -CH₂CH₂CH₂ONO₂-), 4.45-4.49 (m, 2H, -CH₂ONO₂-), 5.10 (s, 1H, OH), 6.96 (s, 2H, C₆H₂); MS (EI) m/z 309 (M)+. Anal. (C₁₇H₂₇NO₄) 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 %. ¹H-NMR (CDCl₃) δ 1.26 (s, 3H, 2-CH₃), 1.72-1.79 (m, 1H, 3-H₄H₉b), 1.92-2.03 (m, 3H, 3-H₄H₁d/-OCH₂CH₂CH₂ONO₂), 2.09 (s, 3H, ArCH₃), 2.11 (s, 3H, ArCH₃), 2.15 (s, 3H, ArCH₃), 2.61 (m, 2H, 4-H₂), 3.41 (d AB system, 1H, 2-CH₃H₁bO-), 3.47 (d AB system, 1H, 2-CH₃H₁bO-, 3J_HH = 9.8 Hz), 3.58-3.63 (m, 2H, -OCH₂CH₂CH₂ONO₂), 4.19 (s, 1H, OH), 4.57 (t, 2H, -OCH₂CH₂CH₂ONO₂, 3J_HH = 6.5 Hz); MS (ESI) m/z 362 (M+Na)+. Anal. (C₁₉H₂₃NO₄) 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 %. ¹H-NMR (CDCl₃) δ 1.42 (s, 18H, -C(CH₃)₃), 2.86-3.04 (m, 2H, -CH₂CH(ONO₂)-), 4.42-4.48 (dd, 1H, -CH₃H₁bONO₂), 4.70-4.74 (dd, 1H, -CH₃H₁bONO₂), 5.36-5.44 (m, 1H, -CH₂CH(ONO₂)-), 5.20 (s br, 1H, OH), 6.99 (s, 2H, C₆H₂); MS (EI) m/z 370 (M)+. Anal. (C₁₇H₂₆N₂O₇) C, H, N.

4-(3-(3-Benzensulfonylfuroxan-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). ¹H-NMR (DMSO-d₆) δ 1.33 (s, 18H, -C(CH₃)₃), 1.99 (m, 2H, -CH₂CH₂CH₂O-), 2.57 (t, 2H,
-CH₂CH₂CH₂O-, ³JHH = 7.2 Hz), 4.33 (t, 2H, -CH₂CH₂CH₂O-, ³JHH = 5.9 Hz), 6.74 (s br, 1H, OH), 6.86 (s, 2H, C₆H₂), 7.72-8.05 (m, 5H, C₆H₅SO₂-); MS (EI) m/z 488 (M)⁺. Anal. (C₂₅H₃₂N₂O₆S) C, H, N.

2-(3-Benzene sulfonylfuroxan-4-yl oxymethyl)-2,5,7,8-tetramethylchroman-6-ol (64). The crude product was purified by preparative HPLC (Lichrospher 250-25 C₁₈, CH₃CN/H₂O 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/H₂O). ¹H-NMR (DMSO-d₆) δ 1.28 (s, 3H, 2-CH₃), 1.85 (s, 3H, ArCH₃), 1.90 (m, 2H, 3-H₂), 2.05 (s, 6H, ArCH₃), 2.60 (m, 2H, 4-H₂), 4.45 (m, 2H, 2-CH₂O-), 7.48 (s br, 1H, OH), 7.60-7.95 (m, 5H, C₆H₅SO₂); MS (EI) m/z 460 (M)⁺. Anal. (C₂₂H₂₄N₂O₇S) 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/iPrOH 90/10) to give a white solid. Yield 69 %. Mp 103-105 °C (from hexane). ¹H-NMR (DMSO-d₆) δ 1.36 (s, 18H, -C(CH₃)₃), 1.70 (m, 2H, -NCH₂CH₂CH₂-), 2.25 (s, 3H, -NCH₃), 2.40-2.50 (m, 4H, -NCH₂CH₂CH₂-), 3.81 (s, 2H, -CH₂Fx), 6.67 (s, 1H, OH), 6.89 (s, 2H, C₆H₂), 8.27 (s br, 1H, -CONH₂); MS (Cl) m/z 419 (M+1)⁺. Anal. (C₂₂H₂₄N₂O₄) 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/iPrOH 90/10) to give a pale yellow solid. Yield 80 %. Mp 132-135 °C dec (from CH₂Cl₂/CH₂Cl₂). ¹H-NMR (DMSO-d₆) δ 1.12 (s, 3H, 2-CH₃), 1.59-1.64 (m, 1H, 3-H₂H₆), 1.77-1.82 (m, 1H, 3-H₂H₆), 1.93 (s, 3H, ArCH₃), 2.01 (s, 3H, ArCH₃), 2.03 (s, 3H, ArCH₃), 2.43 (s, 3H, -NCH₃), 2.51 (s br, 2H, 4-H₂), 2.66 (m, 2H, 2-CH₂N-), 3.91 (d AB system, 1H, -CH₂H₆Fx), 3.96 (d AB system, 1H, -CH₂H₆Fx), 7.39 (s br, 1H, OH), 8.33 (s br, 2H, -CONH₂); MS (EI) m/z 390 (M)⁺, drying conditions: 40 °C, 48 h, pressure < 1 mmHg. Anal. (C₁₉H₂₆N₂O₅ · 0.5 EtOAc) 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, kept under inert atmosphere at 20 °C, of NaH 60 % (0.38 g, 9.4 mmol) in dry THF (5 mL). 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 %. 1H-NMR (CDCl3) δ 1.17 (t, 3H, -COOCH2CH3, 3JHH = 7.1 Hz ), 1.60 (s, 3H, 2-CH3), 1.80-1.88 (m, 1H, 3-HaHb), 2.10 (s, 3H, ArCH3), 2.16 (s, 3H, ArCH3), 2.18 (s, 3H, ArCH3), 2.40-2.65 (m, 3H, 3-HaHb, 4-H2), 3.40 (s, 3H, CH3O-), 3.60 (m, 2H, -OCH2CH2O-), 3.95 (m, 2H, -OCH2CH2O-), 4.12 (q, 2H, -COOCH2CH3, 3JHH = 7.1 Hz), 4.93 (s, 2H, -OCH2O-); MS (EI) m/z 366 (M)⁺.

2-Allyloxyethyl-6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchromane (28). NaH 60 % (0.28 g, 6.9 mmol) was added portion wise to a solution of 27 (1.50 g, 4.6 mmol) in dry DMF (15 mL) kept under inert atmosphere. Then allylbromide (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 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 %. 1H-NMR (CDCl3) δ 1.28 (s, 3H, 2-CH3), 1.72-1.80 (m, 1H, 3-HaHb), 1.94-2.04 (m, 1H, 3-HaHb), 2.07 (s, 3H, ArCH3), 2.14 (s, 3H, ArCH3), 2.17 (s, 3H, ArCH3), 2.58 (m, 2H, 4-H2), 3.40 (d AB system, 1H, 2-CHaHbO-, 2JHH = 9.6 Hz), 3.48 (d AB system, 1H, 2-CHaHbO-, 2JHH = 9.6 Hz), 3.40 (s, 3H, CH3O-), 3.61 (m, 2H, -OCH2CH2O-), 3.95 (m, 2H, -OCH2CH2O-), 4.05 (m, 2H, -OCH2CH=CH2), 4.94 (s, 2H, -OCH2O-), 5.15-5.30 (m, 2H, -OCH2CH=CH2), 5.84-5.95 (m, 1H, -OCH2CH=CH2); MS (ESI) m/z 387 (M+Na)⁺. Anal. (C21H32O5) 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 %. 1H-NMR (CDCl3) δ 2.32 (s, 3H, CH3COO-), 3.37 (d, 2H, -CH2CH=CH2, 3JHH = 6.6 Hz), 5.05-5.11 (m, 2H, -CH2=CH-), 5.87-6.02 (m, 1H, CH2=CH-), 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, 40. To a stirred solution of the appropriate allyl derivative 33, 15, 38 (11.3 mmol) and AgNO3 (2.32 g, 13.6 mmol) in CH3CN (20 mL) kept at -15 °C, a solution of iodine (3.46 g, 13.6 mmol) in CH3CN (30 mL) was added dropwise. At the end of the addition the mixture
was allowed to reach r.t. AgNO\textsubscript{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\textsuperscript{®}. The filtrate was diluted with EtOAc and washed with water and brine, dried and evaporated. The crude product was purified by chromatography to give the title compound as a colourless oil.

4-(2,3-Dinitrooxypropyl)phenyl acetate (34). Reaction time 14 h. Eluent: PE/EtOAc 90/10 . Yield 21 %. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \(\delta\) 2.30 (s, 3H, \(CH\textsubscript{3}COO\textsuperscript{-}\)), 2.96-3.04 (m, 2H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 4.40-4.46 (dd, 1H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 4.71-4.76 (dd, 1H, -CH\textsubscript{2}H\textsubscript{6}ONO\textsubscript{2}), 5.38-5.46 (m, 1H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 7.07 (d, 2H, AA’BB’ system), 7.25 (d, 2H, AA’BB’ system); MS (EI) m/z 300 (M\textsuperscript{+}).

4-(2,3-Dinitrooxypropyl)-2,6-dimethoxyphenyl acetate (36). Reaction time 24 h. Eluent: PE/EtOAc 80/20 . Yield 65 %. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \(\delta\) 2.33 (s, 3H, \(CH\textsubscript{3}COO\textsuperscript{-}\)), 2.91-3.10 (m, 2H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 3.81 (s, 6H, -OCH\textsubscript{3}), 4.44-4.50 (dd, 1H, -CH\textsubscript{2}H\textsubscript{6}ONO\textsubscript{2}), 4.74-4.79 (dd, 1H, -CH\textsubscript{2}H\textsubscript{6}ONO\textsubscript{2}), 5.43-5.46 (m, 1H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 6.46 (s, 2H, C\textsubscript{6}H\textsubscript{2}); MS (EI) m/z 360 (M\textsuperscript{+}).

4-(2,3-Dinitrooxypropyl)-2,6-di-tert-butylphenyl tert-butyl carbonate (40). Reaction time 14 h. Eluent: PE/EtOAc 90/10 . Yield 35 %. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \(\delta\) 1.35 (s, 18H, -C(CH\textsubscript{3})\textsubscript{3}), 1.53 (s, 9H, -OC(CH\textsubscript{3})\textsubscript{3}), 2.90-3.10 (m, 2H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 4.42-4.48 (dd, 1H, -CH\textsubscript{2}H\textsubscript{6}ONO\textsubscript{2}), 4.72-4.77 (dd, 1H, -CH\textsubscript{2}H\textsubscript{6}ONO\textsubscript{2}), 5.39-5.46 (m, 1H, -CH\textsubscript{2}CH(ONO\textsubscript{2})\textsuperscript{-}), 7.14 (s, 2H, C\textsubscript{6}H\textsubscript{2}); MS (Cl) m/z 471 (M+1\textsuperscript{+}).

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\textsubscript{2}, a solution of 4-hydroxybenzaldehyde (0.50 g, 4.0 mmol) in dry THF (6 mL) was slowly added. To the mixture so obtained a solution of TBDMSCI (0.84 g, 5.6 mmol) in dry THF (3 mL) was then slowly added. The reaction was completed in 1h. The mixture was poured into 2 M NaOH (10 mL) and extracted with EtOAc. The organic layers were washed with brine, then dried and evaporated. The product so obtained was used in the next synthetic step without further purification. Yield 93 %. \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \(\delta\) 0.26 (s, 6H, -Si(CH\textsubscript{3})\textsubscript{2}), 1.01 (s, 9H, -C(CH\textsubscript{3})\textsubscript{3}), 6.96 (d, 2H, AA’BB’ system), 7.80 (d, 2H, AA’BB’ system), 9.90 (s, 1H, -CHO); MS (EI) m/z 236 (M\textsuperscript{+}).
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), then the mixture was heated at reflux for 2 h. The mixture was washed with a saturated solution of NH₄Cl, NaOH 0.1 M and brine, was dried and evaporated. The product so obtained was used in the next synthetic step without further purification. Yield 100 %. ¹H-NMR (CDCl₃) δ 3.36 (s, 3H, -OCH₂CH₂OCH₃), 3.56 (m, 2H, -OCH₂CH₂O-), 3.91 (s, 6H, -OCH₃), 3.99 (m, 2H, -OCH₂CH₂O-), 5.30 (s, 2H, -OC₆H₄O-), 7.13 (s, 2H, C₆H₅), 9.87 (s, 1H, -CHO); 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 %. ¹H-NMR (CDCl₃) δ 1.48 (s, 18H, -C(C₆H₃)₃), 3.43 (s, 3H, -OCH₂CH₂OCH₃), 3.66 (m, 2H, -OCH₂CH₂O-), 4.00 (m, 2H, -OCH₂CH₂O-), 5.04 (s, 2H, -OCH₂O-), 7.81 (s, 2H, C₆H₅), 9.92 (s, 1H, -CHO); MS (Cl) 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-BuOK⁺ (1.60 g, 14.3 mmol) in dry THF (15 mL) kept under 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 r.t. and stirred for 1 h. The mixture was poured into a saturated solution of NH₄Cl and extracted with EtOAc. The organic layers were washed with brine, dried and evaporated.

Ethyl 3-((tert-butyl(dimethyl)silyloxy)phenyl)acrylate (48). The crude product was purified by flash chromatography (PE/Et₂O 95/5) to give the title compound as a colourless oil. Yield 62 %. ¹H-NMR (CDCl₃) δ 0.22 (s, 6H, -Si(CH₃)₂), 0.99 (s, 9H, -C(CH₃)₃), 1.34 (t, 3H, CH₃CH₂O-, ³J_HH = 7.1 Hz ), 4.25 (q, 2H, CH₃CH₂O-, 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. (C₁₇H₂₆O₃Si) C, H.
Ethyl 3-(3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)acrylate (49). The crude product was purified by crystallization from iPr₂O to give the title compound as a white solid. Yield 94 %. Mp 51-54 °C (from iPr₂O). ¹H-NMR (CDCl₃) δ 1.34 (t, 3H, CH₃CH₂O-, 3JHH = 7.1 Hz), 3.36 (s, 3H, -OCH₂CH₂OCH₃), 3.56 (m, 2H, -OCH₂CH₂O-), 3.86 (s, 6H, -OCH₃), 3.99 (m, 2H, -OCH₂CH₂O-), 4.26 (q, 2H, CH₃CH₂O-, 3JHH = 7.1 Hz), 5.23 (s, 2H, -OCH₂O), 6.35 (d, 1H, -COCH=CH-, 3JHH = 15.9 Hz), 6.75 (s, 2H, C₆H₂), 7.60 (d, 1H, -COCH=CH-, 3JHH = 15.9 Hz); MS (EI) m/z 340 (M)+. Anal. (C₁₇H₂₄O₇) 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/Et₂O 90/10) to give the title compound as pale yellow oil. Yield 94 %. ¹H-NMR (CDCl₃) δ 1.34 (t, 3H, CH₂CH₂O-, 3JHH = 7.1 Hz), 1.44 (s, 18H, -C(CH₃)₃), 3.42 (s, 3H, -OCH₂CH₂OCH₃), 3.65 (m, 2H, -OCH₂CH₂O-), 3.99 (m, 2H, -OCH₂CH₂O-), 4.26 (q, 2H, CH₂CH₂O-, 3JHH = 7.1 Hz), 5.00 (s, 2H, -OCH₂O), 6.34 (d, 1H, -COCH=CH-, 3JHH = 16.0 Hz), 7.44 (s, 2H, C₆H₂), 7.64 (d, 1H, -COCH=CH-, 3JHH = 16.0 Hz); MS (EI) m/z 392 (M)+. Anal. (C₂₃H₃₆O₃) 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 H₂ for 3 h. Then the mixture was filtered through Celite® and evaporated. The product so obtained, a colourless 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 (CDCl₃) δ 0.19 (s, 6H, -Si(CH₃)₂), 1.00 (s, 9H, -C(CH₃)₃), 1.24 (t, 3H, CH₃CH₂O-, 3JHH = 7.1 Hz), 2.59 (t, 2H, 3JHH = 7.5 Hz), 2.89 (t, 2H, 3JHH = 7.5 Hz) (-COCH₂CH₂-), 4.13 (q, 2H, CH₂CH₂O-, 3JHH = 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 (CDCl₃) δ 1.25 (t, 3H, CH₂CH₂O-, 3JHH = 7.1 Hz), 2.60 (t, 2H, 3JHH = 7.5 Hz), 2.89 (t, 2H, 3JHH = 7.5 Hz) (-COCH₂CH₂-), 3.37 (s, 3H, -OCH₂CH₂OCH₃), 3.56 (m, 2H, -OCH₂CH₂O-), 3.86 (s, 6H, -
OCH$_3$), 4.00 (m, 2H, -OCH$_2$CH$_2$O-), 4.14 (q, 2H, CH$_3$CH$_2$O-, $^3$J$_{HH} = 7.1$ Hz), 5.16 (s, 2H, -OCH$_2$O-), 6.41 (s, 2H, C$_6$H$_2$); MS (El) 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$_3$CH$_2$O-, $^3$J$_{HH} = 7.1$ Hz), 1.42 (s, 18H, -C(CH$_3$)$_3$), 2.59 (t, 2H, $^3$J$_{HH} = 7.5$ Hz), 2.88 (t, 2H, $^3$J$_{HH} = 7.5$ Hz) (-COCH$_2$CH$_2$-), 3.42 (s, 3H, -OCH$_2$CH$_2$OCH$_3$), 3.66 (m, 2H, -OCH$_2$CH$_2$O-), 3.98 (m, 2H, -OCH$_2$CH$_2$O-), 4.14 (q, 2H, CH$_3$CH$_2$O-, $^3$J$_{HH} = 7.1$ Hz), 4.97 (s, 2H, -OCH$_2$O-), 7.07 (s, 2H, C$_6$H$_2$); MS (El) m/z 394 (M$^+$. General procedure for 27, 54-56. A solution of the appropriate ethyl ester 26, 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 r.t. and stirred for 1.5 h. The mixture was poured into a saturated solution of NH$_4$Cl and extracted with EtOAc. The organic layers were washed with water and brine, then dried and evaporated. The crude product so obtained was purified by flash chromatography to give a colourless 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$_2$H$_6$), 1.89 (s br, 1H, OH), 1.94-2.01 (m, 1H, 3-H$_2$H$_6$), 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$_2$CH$_2$O-/2-CH$_2$OH, overlapped signals), 3.95-3.98 (m, 2H, -OCH$_2$CH$_2$O-), 4.95 (s, 2H, -OCH$_2$O-); MS (El) m/z 324 (M$^+$. Anal. (C$_{18}$H$_{28}$O$_5$) C, H, N.

3-(4-((tert-Butyl(dimethyl)silyloxy)phenyl)propan-1-ol (54). Eluent: Hexane/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$_2$CH$_2$CH$_2$OH), 2.66 (t, 2H, -CH$_2$CH$_2$CH$_2$OH, $^3$J$_{HH} = 7.4$ Hz), 3.68 (t, 2H, -CH$_2$CH$_2$CH$_2$OH, $^3$J$_{HH} = 6.4$ Hz), 6.77 (d, 2H, AA′BB’ system), 7.06 (d, 2H, AA′BB’ system); MS (El) m/z 266 (M$^+$. Anal. (C$_{15}$H$_{26}$O$_2$Si) C, H.

3-(3,5- Dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (55). Yield 92 %. Because the product was unstable it was used directly in the next synthetic step without further purification. ¹H-NMR (CDCl$_3$) δ 1.76 (s br, 1H, OH), 1.87 (m, 2H, -CH$_2$CH$_2$CH$_2$OH), 2.64 (t, 2H, -
CH$_2$CH$_2$CH$_2$OH, $^3$J$_{HH}$ = 7.5 Hz), 3.37 (s, 3H, -OCH$_2$CH$_2$OCH$_3$), 3.57 (m, 2H, -OCH$_2$CH$_2$O-), 3.68 (t, 2H, -CH$_2$CH$_2$CH$_2$OH, $^3$J$_{HH}$ = 6.4 Hz), 3.81 (s, 6H, -OCH$_3$), 4.00 (m, 2H, -OCH$_2$CH$_2$O), 5.16 (s, 2H, -OCH$_2$O-), 6.41 (s, 2H, C$_6$H$_2$); MS (EI) m/z 300 (M)$^+$. 

3-(3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (56). Eluent: Hexane/EtOAc 80/20. Yield 90%. $^1$H-NMR (CDCl$_3$) δ 1.38 (s, 1H, OH), 1.43 (s, 18H, -C(CH$_3$)$_3$), 1.87 (m, 2H, -CH$_2$CH$_2$CH$_2$OH), 2.62 (t, 2H, -CH$_2$CH$_2$CH$_2$OH, $^3$J$_{HH}$ = 7.5 Hz), 3.42 (s, 3H, -OCH$_2$CH$_2$OCH$_3$), 3.63-3.71 (m, 4H), 3.98 (m, 2H) (-OCH$_2$CH$_2$O/-CH$_2$CH$_2$CH$_2$OH overlapped signals), 4.98 (s, 2H, -OCH$_2$O-), 7.07 (s, 2H, C$_6$H$_2$); MS (EI) m/z 352 (M)$^+$. Anal. (C$_{21}$H$_{36}$O$_4$) C, H.

General procedure for 57-59, 63. A solution of the appropriate alcohol 54-56, 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 by TLC. Then the mixture was poured into a saturated solution of NH$_4$Cl and extracted with Et$_2$O. The organic layers were washed with brine, dried and evaporated. The crude product was purified by flash chromatography to give the title compound.

3-Benzencesulfonyl-4-(3-(4-(tert-butyl(dimethyl)silyl)oxy)phenyl)propoxy)furoxan (57). Eluent: PE/EtOAc 95/5. Yield 54%. $^1$H-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$_2$CH$_2$CH$_2$O-), 2.74 (t, 2H, -CH$_2$CH$_2$CH$_2$O-, $^3$J$_{HH}$ = 7.3 Hz), 4.40 (t, 2H, -CH$_2$CH$_2$CH$_2$O-, $^3$J$_{HH}$ = 6.4 Hz), 6.77 (d, 2H, AA’BB’ system), 7.05 (d, 2H, AA’BB’ system), 7.60-8.09 (m, 5H, C$_6$H$_5$SO$_2$-); MS (EI) m/z 491 (M+1)$^+$. 

3-Benzencesulfonyl-4-(3-(3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propoxy)furoxan (58). Eluent: CH$_2$Cl$_2$/EtOAc 95/5. Yield 52%. $^1$H-NMR (CDCl$_3$) δ 2.19 (m, 2H, -CH$_2$CH$_2$CH$_2$O-), 2.77 (t, 2H, -CH$_2$CH$_2$CH$_2$O-, $^3$J$_{HH}$ = 7.2 Hz), 3.37 (s, 3H, -OCH$_2$CH$_2$OCH$_3$), 3.57 (m, 2H, -OCH$_2$CH$_2$O-), 3.82 (s, 6H, OCH$_3$), 4.01 (m, 2H, -OCH$_2$CH$_2$O), 4.43 (t, 2H, -CH$_2$CH$_2$CH$_2$O-, $^3$J$_{HH}$ = 6.3 Hz), 5.18 (s, 2H, -OCH$_2$O-), 6.44 (s, 2H, C$_6$H$_2$), 7.56-8.09 (m, 5H, C$_6$H$_5$SO$_2$-); MS (EI) m/z 524 (M)$^+$. 

3-Benzencesulfonyl-4-(3-(3,5-di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propoxy)furoxan (59). Eluent: PE/EtOAc 9/1 Yield 54%. $^1$H-NMR (CDCl$_3$) δ 1.42 (s, 18H, -C(CH$_3$)$_3$), 2.17
(m, 2H, -CH₂CH₂CH₂O⁻), 2.73 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 7.2 Hz), 3.42 (s, 3H, -OCH₂CH₂OCH₃), 3.65 (m, 2H, -OCH₂CH₂O⁻), 3.99 (m, 2H, -OCH₂CH₂O), 4.42 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 6.4 Hz), 4.99 (s, 2H, -OCH₂O⁻), 7.06 (s, 2H, C₆H₂), 7.59-8.10 (m, 5H, C₆H₅SO₂⁻); 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 %. ¹H-NMR (CDCl₃) δ 1.39 (s, 3H, 2-CH₃), 1.99 (s, 3H, ArCH₃), 2.13 (s, 3H, ArCH₃), 2.16 (s, 3H, ArCH₃), 1.93-2.16 (m, 2H, 3-H₂), 2.68 (m, 2H, 4-H₂) 3.41 (s, 3H, -OCH₃), 3.59 (m, 2H, -OCH₂CH₂O⁻), 3.97 (m, 2H, -OCH₂CH₂O⁻), 4.39 (d AB system, 1H, 2-CH₃H₂O⁻, ³JHH = 10.5 Hz), 4.46 (d AB system, 1H, 2-CH₃H₂O⁻, ³JHH = 10.5 Hz), 4.95 (s, 2H, -OCH₂O⁻), 7.47-8.00 (m, 5H, C₆H₅SO₂⁻); MS (EI) m/z 548 (M⁺).

4-(3-(3-Benzensulfonylfuroxan-4-yl)oxy)propyl)phenol (60). To a solution of 57 (1.84 g, 3.7 mmol) in 1,4-dioxane (26 mL) HCl 37 % (1.4 mL) was added 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). ¹H-NMR (DMSO-d₆) δ 2.00 (m, 2H, -CH₂CH₂CH₂O⁻), 2.57 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 7.5 Hz), 4.34 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 6.2 Hz), 6.69 (d, 2H, AA’BB’ system), 6.99 (d, 2H, AA’BB’ system), 7.74-8.07 (m, 5H, C₆H₅SO₂⁻), 9.19 (s br, 1H, OH); MS (EI) m/z 376 (M⁺). Anal. (C₁₇H₁₆N₂O₆S) C, H, N.

4-(3-(3-Benzensulfonylfuroxan-4-yl)oxy)propyl)-2,6-dimethoxyphenol (61). To a solution of 58 (1.06 g, 2.0 mmol) in THF (15 mL) HCl 1M (12 mL) was added and the solution was stirred at r.t. for 4h. The mixture was poured into water and extracted twice with CH₂Cl₂. The organic layers were dried and evaporated to give the title compound as a white solid. Yield 89 %. Mp 116-117 °C (from EtOH). ¹H-NMR (DMSO-d₆) δ 2.04 (m, 2H, -CH₂CH₂CH₂O⁻), 2.58 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 7.3 Hz), 3.71 (s, 6H, -OCH₃), 4.34 (t, 2H, -CH₂CH₂CH₂O⁻, ³JHH = 6.1 Hz), 6.43 (s, 2H, C₆H₂), 7.72-8.05 (m, 5H, C₆H₅SO₂⁻), 8.11 (s br, 1H, OH); MS (EI) m/z 436 (M⁺). Anal. (C₁₉H₂₀N₂O₈S) 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) MeNH₂ 40 % (4.55 mL, 40 eq) was
added and the solution was heated to 120 °C for 24 h in the Parr® reactor. Then the solution was concentrated and the residue dissolved in water and extracted with CH₂Cl₂. The organic layers were dried and evaporated. The crude product was purified by flash chromatography (PE/iPrOH 95/5) to give the title compound as a white solid. Yield 51 %. Mp 86-89 °C (from iPrOH). ¹H- NMR (CDCl₃) δ 1.42 (s, 18H, -C(CH₃)₃), 2.44 (t, 2H, ³J_HH = 7.4 Hz), 2.89 (t, 2H, ³J_HH = 7.4 Hz) (-COCH₂CH₂-), 2.79 (d, 3H, -NHCH₃), 3.42 (s, 3H, -OCH₂CH₂OCH₃), 3.64 (m, 2H, -OCH₂CH₂O-), 3.97 (m, 2H, -OCH₂CH₂O-), 4.97 (s, 2H, -OCH₂O-), 5.45 (s br, 1H, -NH-), 7.07 (s, 2H, C₆H₂); MS (EI) m/z 379 (M⁺). Anal. (C₂₂H₃₇NO₄) 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/iPrOH 95/5. Yield 50 %. Mp 80-81 °C (from iPr₂O). ¹H-NMR (DMSO-d₆) δ 1.37 (s, 3H, 2-CH₃), 1.69-1.74 (m, 1H, 3-H₆H₆), 2.04 (s, 3H, ArCH₃), 2.11 (s, 3H, ArCH₃), 2.14 (s, 3H, ArCH₃), 2.21 (m, 1H, 3-H₆H₆), 2.40-2.51 (m, 2H, 4-H₂), 2.59 (d, 3H, -NHCH₃, ³J_HH = 4.7 Hz), 3.25 (s, 3H, CH₃O-), 3.48 (m, 2H, -OCH₂CH₂O-), 3.81 (m, 2H, -OCH₂CH₂O-), 4.85 (s, 2H, -OCH₂O-), 7.41 (m, 1H, -NH-); MS (EI) m/z 351 (M⁺). Anal. (C₁₉H₂₉NO₅·H₂O) 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 LiAlH₄ (0.19 g, 4.9 mmol) in dry THF (3 mL) stirred under N₂. The mixture was heated at 72 °C for 24 h. To the mixture first water (30 mL), than 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/iPrOH 90/10) to give the title compound as yellow oil (yield 66 %). An analytical sample was prepared adding a saturated solution of H₂C₂O₄ in acetone to a saturated solution of product in acetone and filtering the white solid so obtained. Mp 153-154 °C dec (from acetone). ¹H- NMR (DMSO-d₆) δ 1.40 (s, 18H, -C(CH₃)₃), 1.86 (m, 2H, -NHCH₂CH₂CH₂-), 2.52-2.58 (m, 5H, -NHCH₂CH₂CH₂-, -NHCH₃), 2.89 (t, 2H, -CH₂CH₂CH₂NH-, ³J_HH = 7.3 Hz), 3.29 (s, 3H, -OCH₂CH₂OCH₃), 3.55 (m, 2H, -OCH₂CH₂O-), 3.88
(m, 2H, -OCHO₂H₂O⁻), 4.90 (s, 2H, -OCHO₂O⁻), 7.09 (s, 2H, C₆H₂), 9.00 (s vb, 3H, -NH•H₂CO₄); MS (EI) m/z 365 (M)⁺. Anal. (C₂₄H₄₁NO₇) 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: CH₂Cl₂/7 N NH₃ in MeOH 98/2. Yield 78 %. Mp 167-168 °C dec (from acetone). ¹H-NMR (DMSO-d₆) δ 1.24 (s, 3H, 2-CH₃), 1.84 (m, 2H, 3-H₂), 2.05 (s, 3H, ArCH₃), 2.08 (s, 3H, ArCH₃), 2.10 (s, 3H, ArCH₃), 2.50-2.64 (m, 7H, 4-H₂, -CH₂NH₂-, -NHCH₃), 3.25 (s, 3H, CH₃O⁻), 3.49 (m, 2H, -OCHO₂CH₂O⁻), 3.82 (m, 2H, -OCHO₂CH₂O⁻), 4.86 (s, 2H, -OCHO₂O⁻), H₂CO₄ signal not detectable; MS (Cl) m/z 338 (M+1)⁺. Anal. (C₂₁H₃₃NO₈ · 0.5 H₂O) 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) a solution of KHCO₃ 0.5 N (4 mL) and slowly a solution of 11 (0.15 g, 0.37 mmol) in acetone (2 mL) were added. Then the mixture was stirred for 24 h and KHCO₃ 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. ¹H- NMR (CDCl₃) δ 1.42 (s, 18H, -C(CH₃)₃), 1.85 (m, 2H, -NCH₂CH₂CH₂-), 2.39 (s, 3H, -NCH₃⁻), 2.50-2.63 (m, 4H, -NCH₂CH₂CH₂-), 3.42 (s, 3H, -OCHO₂CH₂OCH₃), 3.65 (m, 2H, -OCHO₂CH₂O⁻), 3.89 (s, 2H, -CH₂Fx), 3.98 (m, 2H, -OCHO₂CH₂O⁻), 4.98 (s, 2H, -OCHO₂O⁻), 5.90 (s br, 1H, -CONHCH₃), 7.04 (s, 2H, C₆H₂), 8.81 (s br, 1H, -CONHCH₃); 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/iPrOH 95/5. Yield 85 %. Mp 109-110 °C. ¹H-NMR (CDCl₃) δ 1.20 (s, 3H, 2-CH₃), 1.64-1.71 (m, 1H, 3-H₃H₃b), 1.87-1.96 (m, 1H, 3-H₃H₃b), 2.03 (s, 3H, ArCH₃), 2.14 (s, 3H, ArCH₃), 2.17 (s, 3H, ArCH₃), 2.55 (s, 3H, -NCH₃⁻), 2.61 (m, 2H, 4-H₂), 2.76 (d AB system, 1H, 2-CH₃H₃bN⁻, JHH = 14.1 Hz), 2.79 (d AB system, 1H, 2-CH₃H₃bN⁻, JHH = 14.1 Hz), 3.40 (s, 3H, CH₃O-
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 mMpH 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 FeSO₄ (2.5 µM) in HPLC-grade water (50 µL) were performed via a gas-tight syringe. Final volume of the tested mixture was 10 mL. Change in the current was recorded as function of time and data were elaborated with a MacLab SysteMpowerLab®. Experiments were run at least in triplicate after appropriate calibration of the electrode with NaNO₂.

Biological experiments.

Antioxidant activity. Hepatic microsomal membranes from male Wistar rats (200-250 g) were prepared by differential centrifugation (8000 g, 20 min; 120000 g, 1h) 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 mMpH 7.4) containing microsomal membranes (2 mg prot/mL), sodium ascorbate (100 µM) and DMSO solutions of the tested compounds. An 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 FeSO₄ 2.5 µM. 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 consisting mainly of malondialdehyde (MDA) and TBARS concentrations (expressed in nmol/mg protein) were obtained by interpolation with a MDA standard curve. The antioxidant activity of tested compounds was evaluated as the % of inhibition of TBARS production with respect to control.
samples, using the values obtained after 30 min of incubation. IC\textsubscript{50} values were calculated by non-linear 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 tension in organ baths containing 30 mL of Krebs-bicarbonate buffer with the following composition (mM): NaCl 111.2, KCl 5.0, CaCl\textsubscript{2} 2.5, MgSO\textsubscript{4} 1.2, KH\textsubscript{2}PO\textsubscript{4} 1.0, NaHCO\textsubscript{3} 12.0, glucose 11.1, maintained at 37 °C and gassed with 95 % O\textsubscript{2} 5 % CO\textsubscript{2} (pH = 7.4). The aortic strips were allowed to equilibrate for 120 min and then contracted with 1 \(\mu\)M L-phenylephrine. When the response to the agonist reached a plateau, cumulative concentrations of the vasodilating agent were added. Results are expressed as EC\textsubscript{50} ± SE (\(\mu\)M). The effects of 1 \(\mu\)M ODQ on relaxation were evaluated in a separate series of experiments in which it was added 5 minutes before the contraction. Responses were recorded by an isometric transducer connected to the MacLab SysteMpowerLab®. An addition of the drug vehicle, DMSO, had no appreciable effect on contraction level.
Acknowledgment. This work was supported by a grant from MIUR Studi e Ricerche Finalizzate 40\% Roma and Regione Piemonte Ricerca Scientifico Applicata, 2003.
Supporting Information Available: Table of combustion analysis. $^{13}$C NMR data of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.
References


Table 1. Antioxidant and vasodilating activity of the NO-donor phenols, of the phenol 1-4 and NO-donor 5-9 parents.

<table>
<thead>
<tr>
<th>Compd</th>
<th>Struct.</th>
<th>R</th>
<th>R'</th>
<th>Antioxidant activity&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Vasodilating activity&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IC&lt;sub&gt;50&lt;/sub&gt;(95% CL) µM</td>
<td>EC&lt;sub&gt;50&lt;/sub&gt; ± SE, µM +1 µM ODQ [% relaxation&lt;sup&gt;c&lt;/sup&gt;]</td>
</tr>
<tr>
<td>1</td>
<td>A</td>
<td>H</td>
<td>CH₃</td>
<td>290 (260-324)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>OCH₃</td>
<td>CH₃</td>
<td>18 (17-20)</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>t-Bu</td>
<td>CH₃</td>
<td>1.7 (1.6-1.9)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>H</td>
<td>-</td>
<td>0.17 (0.16-0.17)</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>H</td>
<td>-</td>
<td>-d</td>
<td>41 ± 6 [4.6 ± 0.6]</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>ONO₂</td>
<td>-</td>
<td>-d</td>
<td>0.24 ± 0.03 [10 ± 2]</td>
</tr>
<tr>
<td>7</td>
<td>D</td>
<td>OEt</td>
<td>SO₂Ph</td>
<td>110 (98-122)</td>
<td>0.012 ± 0.002 1.2 ± 0.2</td>
</tr>
<tr>
<td>8</td>
<td>D</td>
<td>CH₂OH</td>
<td>CONH₂</td>
<td>-d</td>
<td>6.3 ± 0.8 [21 ± 7]</td>
</tr>
<tr>
<td>9</td>
<td>D</td>
<td>CH₃N(CH₃)₂</td>
<td>CONH₂</td>
<td>-d</td>
<td>3.1 ± 0.3 [17 ± 3]</td>
</tr>
<tr>
<td>13</td>
<td>A</td>
<td>H</td>
<td>ONO₂</td>
<td>143 (133-153)</td>
<td>1.0 ± 0.2 [38 ± 9]</td>
</tr>
<tr>
<td>19</td>
<td>A</td>
<td>OCH₃</td>
<td>ONO₂</td>
<td>5.9 (5.5-6.4)</td>
<td>4.3 ± 0.6 [33 ± 3]</td>
</tr>
<tr>
<td>24</td>
<td>A</td>
<td>t-Bu</td>
<td>ONO₂</td>
<td>2.0 (1.9-2.1)</td>
<td>40 ± 1 [15 ± 5]</td>
</tr>
<tr>
<td>32</td>
<td>B</td>
<td>-</td>
<td>ONO₂</td>
<td>0.15 (0.15-0.16)</td>
<td>1.2 ± 0.1 10 ± 1</td>
</tr>
<tr>
<td>35</td>
<td>A</td>
<td>H</td>
<td>ONO₂</td>
<td>185 (176-195)</td>
<td>0.13 ± 0.03 65 ± 4</td>
</tr>
<tr>
<td>37</td>
<td>A</td>
<td>OCH₃</td>
<td>ONO₂</td>
<td>5.4 (5.0-5.8)</td>
<td>0.64 ± 0.09 49 ± 4</td>
</tr>
<tr>
<td>41</td>
<td>A</td>
<td>t-Bu</td>
<td>ONO₂</td>
<td>2.6 (1.9-3.5)</td>
<td>3.3 ± 0.4 [24 ± 4°]</td>
</tr>
<tr>
<td>60</td>
<td>A</td>
<td>H</td>
<td>SO₂Ph</td>
<td>47 (45-48)</td>
<td>0.012 ± 0.001 0.36 ± 0.09</td>
</tr>
<tr>
<td>61</td>
<td>A</td>
<td>OCH₃</td>
<td>SO₂Ph</td>
<td>3.4 (3.2-3.5)</td>
<td>0.022 ± 0.003 0.50 ± 0.13</td>
</tr>
<tr>
<td>62</td>
<td>A</td>
<td>t-Bu</td>
<td>SO₂Ph</td>
<td>2.0 (1.9-2.0)</td>
<td>0.11 ± 0.03 4.8 ± 0.5</td>
</tr>
<tr>
<td>64</td>
<td>B</td>
<td>-</td>
<td>SO₂Ph</td>
<td>0.49 (0.48-0.50)</td>
<td>0.044 ± 0.004 0.67 ± 0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>68</td>
<td>A</td>
<td>r-Bu</td>
<td>![Chemical Structure]</td>
<td>1.2 (1.1-1.2)</td>
<td>0.41 ± 0.08</td>
</tr>
<tr>
<td>72</td>
<td>B</td>
<td>![Chemical Structure]</td>
<td>0.14 (0.14-0.14)</td>
<td>1.5 ± 0.1</td>
<td>19 ± 1</td>
</tr>
</tbody>
</table>

*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, % relaxation was evaluated at the maximal concentration tested (100 μM)

*d* Inactive at 1 mM

*e* % relaxation was evaluated at 30 μM, maximal concentration tested due to insolubility limits.
**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 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 FeSO₄ (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.

**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.
Figure 1.

a) 

b)
Figure 2.
Figure 3.

a) Figure showing the relationship between % Relaxation and log conc (M).

b) Figure showing the relationship between % Relaxation and log conc (M).
Chart 1.

1 \( R = H \)
2 \( R = \text{OCH}_3 \)
3 \( R = \text{t-Bu} \)

\[ \text{(ONO}_2\text{)}_n \]

5 \( n = 0 \)
6 \( n = 1 \)

7 \( R' = \text{OEt}, R = \text{SO}_2\text{Ph} \)
8 \( R' = \text{CH}_2\text{OH}, R = \text{CONH}_2 \)
9 \( R' = \text{CH}_2\text{N(CH}_3)_2\), \( R = \text{CONH}_2 \)
10 \( R' = R = \text{SO}_2\text{Ph} \)
11 \( R' = \text{CH}_2\text{Br}, R = \text{CONH}_2 \)
Scheme 1. a) AgNO$_3$, CH$_3$CN, 60 °C; b) Ac$_2$O, TEA, DMAP, CH$_2$Cl$_2$, 0 °C; c) 9-BBN, dry THF; d) NaOAc, H$_2$O$_2$ 30 %, 0 °C; e) TsCl, TEA, DMAP, CH$_2$Cl$_2$; f) Boc$_2$O, DMAP, CH$_2$Cl$_2$; g) Bu$_4$N$^+$NO$_3^-$, benzene, reflux; h) pyrrolidine, CH$_3$CN, 0 °C for 18, TFA, dry CH$_2$Cl$_2$, 0 °C for 23.
Scheme 1.

12 \[ \text{Br} \] \[ {\rightarrow} \] 13 \[ \text{ONO}_2 \]

b

14 \[ \text{MeO} \] \[ \text{OH} \] \[ \text{R} \] \[ \text{Me} \] \[ \text{OH} \] \[ \text{M} \] \[ \text{e} \] \[ \text{O} \] \[ {\rightarrow} \] 15 \[ \text{MeO} \] \[ \text{OH} \] \[ \text{R} \] \[ \text{Me} \] \[ \text{OH} \] \[ \text{M} \] \[ \text{e} \]

16 \[ \text{R} = \text{OCH}_3, \text{R'} = \text{Ac} \]
17 \[ \text{R} = \text{OCH}_3, \text{R'} = \text{Ac} \]
18 \[ \text{R} = \text{OCH}_3, \text{R'} = \text{Ac} \]
19 \[ \text{R} = \text{OCH}_3 \]
20 \[ \text{R} = \text{t-Bu}, \text{R'} = \text{H} \]
21 \[ \text{R} = \text{t-Bu}, \text{R'} = \text{H} \]
22 \[ \text{R} = \text{t-Bu}, \text{R'} = \text{Boc} \]
23 \[ \text{R} = \text{t-Bu}, \text{R'} = \text{Boc} \]
24 \[ \text{R} = \text{t-Bu} \]
Scheme 2. a) MEMCl, NaH, dry THF; b) LiAlH₄, dry THF; c) allylbromide, NaH, DMF; d) 9-BBN, dry THF; e) NaOAc, H₂O₂ 30 %, 0 °C; f) TsCl, TEA, DMAP, CH₂Cl₂; g) Bu₄N⁺NO₃⁻, benzene, reflux; h) TFA, CH₂Cl₂.
Scheme 2.

25 \[ \xrightarrow{a} \] 26

28 \[ \xrightarrow{c} \] 27

29 \[ \xrightarrow{d, e} \] 30

29 \[ \xrightarrow{f} \] 30

32 \[ \xrightarrow{h} \] \item{31}
Scheme 3. a) AgNO$_3$, I$_2$, CH$_3$CN, 0 °C, 2.5 h; b) AgNO$_3$, CH$_3$CN, reflux; c) pyrrolidine, CH$_3$CN, 0 °C for 34 and 36; TFA, dry CH$_2$Cl$_2$, 0 °C for 40; d) Boc$_2$O, DMAP, CH$_2$Cl$_2$. 
Scheme 3.

38 $R = t$-Bu
33 $R = H \ R' = Ac$
15 $R = OCH_3 \ R' = Ac$
39 $R = t$-Bu $R' = Boc$

34 $R = H \ R' = Ac$
36 $R = OCH_3 \ R' = Ac$
40 $R = t$-Bu $R' = Boc$

35 $R = H$
37 $R = OCH_3$
41 $R = t$-Bu
Scheme 4. a) NaH, TBDMSCl, dry THF for 42; DIPEA, MEMCl, Cl\textsubscript{2}CH\textsubscript{2}Cl\textsubscript{2} for 43, 44; b) t-BuO\textsuperscript{-}K\textsuperscript{+}, (EtO)\textsubscript{2}POCH\textsubscript{2}COOEt, dry THF; c) H\textsubscript{2}, Pd/C, EtOH; d) LiAlH\textsubscript{4}, dry THF; e) 10, NaH, dry THF; f) HCl 37 %, 1,4-dioxane for 57; HCl 1M, THF for 58; TFA, CH\textsubscript{2}Cl\textsubscript{2} for 59, 63.
Scheme 4

42 R = H
43 R = OCH₃
44 R = t-Bu

45 R = H, R' = TBDMS
46 R = OCH₃, R' = MEM
47 R = t-Bu, R' = MEM

48 R = H, R' = TBDMS
49 R = OCH₃, R' = MEM
50 R = t-Bu, R' = MEM

51 R = H, R' = TBDMS
52 R = OCH₃, R' = MEM
53 R = t-Bu, R' = MEM

54 R = H, R' = TBDMS
55 R = OCH₃, R' = MEM
56 R = t-Bu, R' = MEM

57 R = H, R' = TBDMS
58 R = OCH₃, R' = MEM
59 R = t-Bu, R' = MEM

60 R = H
61 R = OCH₃
62 R = t-Bu

27

63

64
Scheme 5. a) MeNH$_2$ 40 %, 1,4-dioxane, 120 °C; b) LiAlH$_4$, dry THF, 72 °C; c) 11, KHCO$_3$, acetone; d) TFA, CH$_2$Cl$_2$. 
Scheme 5.

\[
\begin{align*}
R \text{OEt} & \xrightarrow{a} R - \text{CONHCH}_3, & R \text{NHCH}_3 & \xrightarrow{b} R - \text{NHCH}_3, & R \text{CONH}_2 \text{N}^\cdot \text{O}^\cdot \\
53 & R = A, & 65 & R = A, & 67 & R = A \\
26 & R = C, & 69 & R = C, & 68 & R = B, \\
66 & R = A, & 70 & R = C, & 71 & R = C, \\
68 & R = B, & 72 & R = D, & & \text{d}
\end{align*}
\]
NO-Donor Phenols: A New Class of Products Endowed with Antioxidant and Vasodilator Properties
Donatella Boschi, Gian Cesare Tron, Loretta Lazzarato, Kostantin Chegazev, Clara Cena, Antonella Di Stilo, Marta Giorgis, Massimo Bertinaria, Roberta Fruttero and Alberto Gasco,*
Supporting Information

**NO-Donor Phenols: A New Class of Products**

Endowed with Antioxidant and Vasodilator Properties

*Donatella Boschi, a Gian Cesare Tron, b Loretta Lazzarato, a Konstantin Chegaev, a Clara Cena, a Antonella Di Stilo, a Marta Giorgis, a Massimo Bertinaria, a Roberta Fruttero a and Alberto Gasco* *a*

Combustion analysis Data:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Calculated</th>
<th></th>
<th>Obtained</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%C</td>
<td>%H</td>
<td>%N</td>
<td>%C</td>
</tr>
<tr>
<td>13</td>
<td>C$<em>2$H$</em>{11}$NO$_4$</td>
<td>54.82</td>
<td>5.62</td>
<td>7.10</td>
<td>54.45</td>
</tr>
<tr>
<td>16</td>
<td>C$<em>{13}$H$</em>{18}$O$_5$</td>
<td>61.41</td>
<td>7.13</td>
<td>///</td>
<td>61.33</td>
</tr>
<tr>
<td>17</td>
<td>C$<em>{20}$H$</em>{24}$O$_7$S</td>
<td>58.81</td>
<td>5.92</td>
<td>///</td>
<td>58.87</td>
</tr>
<tr>
<td>19</td>
<td>C$<em>{11}$H$</em>{15}$NO$_6$</td>
<td>51.36</td>
<td>5.88</td>
<td>5.44</td>
<td>51.25</td>
</tr>
<tr>
<td>21</td>
<td>C$<em>{24}$H$</em>{34}$O$_4$S</td>
<td>68.86</td>
<td>8.19</td>
<td>///</td>
<td>68.86</td>
</tr>
<tr>
<td>24</td>
<td>C$<em>{17}$H$</em>{27}$NO$_4$</td>
<td>65.99</td>
<td>8.80</td>
<td>4.53</td>
<td>66.10</td>
</tr>
<tr>
<td>27</td>
<td>C$<em>{18}$H$</em>{28}$O$_5$</td>
<td>66.64</td>
<td>8.70</td>
<td>///</td>
<td>66.77</td>
</tr>
<tr>
<td>28</td>
<td>C$<em>{21}$H$</em>{32}$O$_5$</td>
<td>69.20</td>
<td>8.85</td>
<td>///</td>
<td>68.95</td>
</tr>
<tr>
<td>29</td>
<td>C$<em>{21}$H$</em>{34}$O$_6$</td>
<td>65.94</td>
<td>8.96</td>
<td>///</td>
<td>66.29</td>
</tr>
<tr>
<td>30</td>
<td>C$<em>{28}$H$</em>{40}$O$_8$S</td>
<td>62.66</td>
<td>7.51</td>
<td>///</td>
<td>62.46</td>
</tr>
<tr>
<td></td>
<td>Molecular Formula</td>
<td>C</td>
<td>H</td>
<td>N</td>
<td>O</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-----</td>
<td>-----</td>
<td>-----</td>
<td>-------</td>
</tr>
<tr>
<td>32</td>
<td>C₁₇H₂₅NO₆</td>
<td>60.16</td>
<td>7.42</td>
<td>4.13</td>
<td>60.22</td>
</tr>
<tr>
<td>35</td>
<td>C₉H₁₀N₂O₇</td>
<td>41.87</td>
<td>3.90</td>
<td>10.85</td>
<td>41.84</td>
</tr>
<tr>
<td>37</td>
<td>C₁₃H₁₆N₂O₁₀</td>
<td>41.52</td>
<td>4.43</td>
<td>8.80</td>
<td>41.44</td>
</tr>
<tr>
<td>41</td>
<td>C₁₇H₂₆N₂O₇</td>
<td>55.13</td>
<td>7.08</td>
<td>7.56</td>
<td>55.45</td>
</tr>
<tr>
<td>48</td>
<td>C₁₇H₂₆O₃Si</td>
<td>66.62</td>
<td>8.55</td>
<td>/</td>
<td>66.40</td>
</tr>
<tr>
<td>49</td>
<td>C₁₇H₂₄O₇</td>
<td>59.99</td>
<td>7.11</td>
<td>/</td>
<td>59.86</td>
</tr>
<tr>
<td>50</td>
<td>C₂₃H₃₈O₅</td>
<td>70.38</td>
<td>9.24</td>
<td>/</td>
<td>70.57</td>
</tr>
<tr>
<td>54</td>
<td>C₁₃H₂₆O₂Si</td>
<td>67.62</td>
<td>9.84</td>
<td>/</td>
<td>67.20</td>
</tr>
<tr>
<td>56</td>
<td>C₁₁H₃₆O₄</td>
<td>71.55</td>
<td>10.29</td>
<td>/</td>
<td>71.34</td>
</tr>
<tr>
<td>60</td>
<td>C₁₇H₁₆N₂O₆S</td>
<td>54.25</td>
<td>4.28</td>
<td>7.44</td>
<td>54.16</td>
</tr>
<tr>
<td>61</td>
<td>C₁₉H₂₀N₂O₈S · 0.25 H₂O</td>
<td>51.75</td>
<td>4.69</td>
<td>6.35</td>
<td>51.63</td>
</tr>
<tr>
<td>62</td>
<td>C₂₅H₃₂N₂O₆S · 0.25 H₂O</td>
<td>60.89</td>
<td>6.64</td>
<td>5.68</td>
<td>61.00</td>
</tr>
<tr>
<td>64</td>
<td>C₂₂H₂₄N₂O₇S</td>
<td>57.38</td>
<td>5.25</td>
<td>6.08</td>
<td>57.02</td>
</tr>
<tr>
<td>65</td>
<td>C₂₂H₃₇NO₄</td>
<td>69.62</td>
<td>9.83</td>
<td>3.69</td>
<td>69.33</td>
</tr>
<tr>
<td>66</td>
<td>C₂₄H₄₁NO₇ 0.5 H₂O</td>
<td>62.04</td>
<td>9.11</td>
<td>3.01</td>
<td>62.07</td>
</tr>
<tr>
<td>68</td>
<td>C₂₂H₃₄N₄O₄</td>
<td>63.13</td>
<td>8.19</td>
<td>13.39</td>
<td>63.18</td>
</tr>
<tr>
<td>69</td>
<td>C₁₉H₉₂NO₅ · 0.5 H₂O</td>
<td>63.31</td>
<td>8.39</td>
<td>3.88</td>
<td>63.61</td>
</tr>
<tr>
<td>70</td>
<td>C₂₁H₃₃NO₈ · 0.5 H₂O</td>
<td>57.78</td>
<td>7.85</td>
<td>3.21</td>
<td>57.34</td>
</tr>
<tr>
<td>72</td>
<td>C₁₉H₂₆N₃O₅ · 0.5 EtOAc</td>
<td>58.05</td>
<td>6.96</td>
<td>12.89</td>
<td>58.34</td>
</tr>
</tbody>
</table>

3-(4-Hydroxyphenyl)propyl nitrate (13). $^{13}$C-NMR (CDCl₃) δ 28.5, 30.8, 72.5, 115.5, 129.6, 132.3, 154.1.

4-Allyl-2,6-dimethoxyphenyl acetate (15). $^{13}$C-NMR (CDCl₃) δ 20.5, 40.6, 56.0, 105.0, 116.3, 126.9, 136.9, 138.5, 152.0, 168.9.

4-(3-Hydroxypropyl)-2,6-dimethoxyphenyl acetate (16). $^{13}$C-NMR (CDCl₃) δ 20.5, 32.7, 34.2, 56.0, 62.1, 105.0, 126.7, 140.5, 151.9, 169.0.

2,6-Dimethoxy-4-(3-tosylpropyl)phenyl acetate (17). $^{13}$C-NMR (CDCl₃) δ 20.6, 21.7, 30.6, 32.2, 56.2, 69.6, 105.1, 127.0, 128.0, 130.0, 133.1, 139.0, 144.9, 152.1, 169.0.

2,6-Dimethoxy-4-(3-nitroxypropyl)phenyl acetate (18). $^{13}$C-NMR (CDCl₃) δ 20.6, 28.4, 32.4,
3-(4-Hydroxy-3,5-dimethoxyphenyl)propyl nitrate (19). $^{13}$C-NMR (DMSO-$d_6$) δ 25.9, 29.2, 53.9, 71.3, 103.6, 128.6, 131.7, 146.0.

3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propyl tosylate (21). $^{13}$C-NMR (CDCl$_3$) δ 21.7, 30.4, 31.0, 31.6, 34.4, 70.2, 125.0, 128.0, 130.0, 131.1, 133.3, 136.0, 144.8, 152.2.

3-(4-(tert-Butyloxycarbonyloxy)-3,5-di-tert-butylphenyl)propyl tosylate (22). $^{13}$C-NMR (CDCl$_3$) δ 21.7, 27.9, 30.7, 31.5, 31.8, 35.5, 70.1, 83.0, 126.3, 128.0, 130.0, 133.3, 137.2, 142.7, 144.8.

Tert-butyl 2,6-di-tert-butyl-4-(3-nitrooxypropyl)phenyl carbonate (23). $^{13}$C-NMR (CDCl$_3$) δ 28.5, 31.5, 31.9, 35.5, 72.6, 85.2, 126.3, 128.0, 130.0, 133.3, 137.2, 142.7, 144.8.

Ethyl 6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchromane-2-carboxylate (26). $^{13}$C-NMR (CDCl$_3$) δ 11.9, 12.4, 13.3, 14.1, 20.9, 25.3, 30.4, 59.1, 61.0, 69.2, 71.8, 77.7, 98.3, 117.2, 123.0, 126.0, 128.2, 147.2, 148.1, 173.7.

(6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methanol (27). $^{13}$C-NMR (CDCl$_3$) δ 11.9, 12.5, 13.3, 20.2, 20.5, 27.6, 59.1, 69.2, 69.4, 71.8, 75.3, 98.4, 117.5, 122.9, 126.3, 128.3, 147.0, 147.4.

2-Allyloxyethyl-6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchromane (28). $^{13}$C-NMR (CDCl$_3$) δ 12.0, 12.6, 13.4, 20.4, 22.5, 28.6, 59.2, 69.3, 72.0, 72.7, 75.0, 75.5, 98.5, 116.8, 117.7, 122.9, 126.2, 128.2, 135.0, 146.8, 147.9.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propan-1-ol (29). $^{13}$C-NMR (CDCl$_3$) δ 12.0, 12.6, 13.4, 20.4, 22.2, 28.6, 32.1, 59.3, 62.2, 69.3, 71.4, 71.9, 74.8, 76.7, 98.5, 117.5, 123.0, 126.2, 128.3, 146.9, 147.8.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl tosylate (30). $^{13}$C-NMR (CDCl$_3$) δ 12.0, 12.6, 13.4, 20.4, 21.7, 22.2, 28.4, 29.4, 59.2, 67.1, 67.8, 69.3, 71.9, 74.9, 76.3, 98.5, 117.6, 122.9, 126.2, 128.0, 128.2, 130.0, 133.2, 144.8, 146.8, 147.8.

3-((6-((2-Methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl nitrate
(31). $^{13}$C-NMR (CDCl$_3$) $\delta$ 12.0, 12.6, 13.4, 20.4, 22.3, 27.5, 28.5, 59.2, 67.4, 69.3, 70.6, 71.9, 74.9, 76.5, 98.5, 117.6, 122.9, 126.3, 128.3, 146.8, 147.8.

3-((6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy)propyl nitrate (32). $^{13}$C-NMR (CDCl$_3$) $\delta$ 11.4, 11.9, 12.3, 20.4, 22.2, 27.5, 28.7, 67.4, 70.6, 74.9, 76.5, 117.4, 118.6, 121.2, 122.6, 144.9, 145.2.

4-Allylphenyl acetate (33). $^{13}$C-NMR (CDCl$_3$) $\delta$ 21.1, 39.6, 116.1, 121.5, 129.5, 137.1, 137.6, 149.0, 169.7.

4-(2,3-Dinitrooxypropyl)phenyl acetate (34). $^{13}$C-NMR (CDCl$_3$) $\delta$ 21.2, 35.0, 70.0, 79.4, 122.4, 130.4, 131.7, 150.2, 169.5.

3-(4-Hydroxyphenyl)prop-1,2-diyl dinitrate (35). $^{13}$C-NMR (CDCl$_3$) $\delta$ 34.8, 70.2, 79.8, 116.0, 126.3, 130.6, 155.1.

4-(2,3-Dinitrooxypropyl)-2,6-dimethoxyphenyl acetate (36). $^{13}$C-NMR (CDCl$_3$) $\delta$ 20.4, 36.0, 56.2, 70.1, 79.3, 105.8, 128.2, 132.6, 152.5, 168.7.

3-((4-Hydroxy-3,5-dimethoxy)phenyl)prop-1,2-diyl dinitrate (37). $^{13}$C-NMR (CDCl$_3$) $\delta$ 35.7, 56.4, 70.2, 79.6, 105.8, 125.0, 134.3, 147.4.

4-Allyl-2,6-di-tert-butylphenyl carbonate (39). $^{13}$C-NMR (CDCl$_3$) $\delta$ 27.9, 31.5, 35.5, 40.4, 82.9, 115.9, 126.5, 136.7, 137.6, 142.6.

4-(2,3-Dinitrooxypropyl)-2,6-di-tert-butylphenyl tert-butyl carbonate (40). $^{13}$C-NMR (CDCl$_3$) $\delta$ 27.9, 29.4, 31.4, 35.6 (2C), 70.2, 79.6, 83.4, 127.1, 131.0, 143.8, 148.0, 152.9.

3-((4-Hydroxy-3,5-di-tert-butyl)phenyl)prop-1,2-diyl dinitrate (41). $^{13}$C-NMR (CDCl$_3$) $\delta$ 30.3, 34.4, 35.5, 70.3, 80.0, 124.7, 125.8, 136.7, 153.3.

4-((tert-Butyl(dimethyl)silyl)oxy)benzaldehyde (45). $^{13}$C-NMR (CDCl$_3$) $\delta$ -4.5, 18.1, 25.4, 119.8, 130.3, 131.8, 161.4, 190.8.

3,5-Dimethoxy-4-((2-methoxyethoxy)methoxy)benzaldehyde (46). $^{13}$C-NMR (CDCl$_3$) 56.2, 59.0, 68.7, 71.6, 96.9, 106.5, 132.2, 140.0, 153.8, 191.1.

3,5-Di-tert-butyl 4-((2-methoxyethoxy)methoxy)benzaldehyde (47). $^{13}$C-NMR (CDCl$_3$) 31.8, 35.9, 59.1, 69.3, 71.6, 99.9, 128.5, 131.6, 145.7, 160.2, 192.1.
Ethyl 3-((tert-butyl(dimethyl)silyloxy)phenyl)acrylate (48). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 4.4, 14.4, 18.2, 25.6, 60.4, 115.9, 120.5, 127.8, 129.6, 144.3, 157.8, 167.3.

Ethyl 3-(3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)acrylate (49). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 14.3, 55.9, 58.9, 60.5, 68.5, 71.7, 96.9, 105.4, 117.6, 130.4, 136.3, 144.6, 153.5, 166.9.

Ethyl 3-(3,5-di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)acrylate (50). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 14.3, 31.9, 35.8, 59.1, 60.4, 69.1, 71.6, 99.6, 116.7, 126.6, 129.2, 145.1, 156.5, 167.2.

Ethyl 3-(4-((tert-butyl(dimethyl)silyloxy)phenyl)propanoate (51). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 4.4, 14.2, 18.2, 25.7, 30.3, 36.2, 60.3, 120.0, 129.2, 133.3, 154.0, 172.9.

Ethyl 3-(3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propanoate (52). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 14.2, 31.4, 36.1, 55.9, 58.9, 60.5, 68.4, 71.7, 96.9, 105.1, 132.6, 136.8, 153.2, 172.9.

Ethyl 3-(3,5-di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propanoate (53). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 14.2, 30.9, 32.6, 34.3, 59.1, 60.4, 68.9, 71.7, 99.3, 126.4, 134.8, 144.2, 152.5, 173.1.

3-(4-((tert-Butyl(dimethyl)silyloxy)phenyl)propan-1-ol (54). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 4.2, 18.6, 25.7, 31.30, 34.4, 62.3, 120.0, 129.3, 134.4, 153.7.

3-(3,5- Dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (55). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 32.6, 34.3, 55.9, 59.0, 62.2, 68.4, 71.8, 96.9, 105.2, 132.3, 138.1, 153.2.

3-(3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propan-1-ol (56). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 32.1, 34.5, 35.6, 59.1, 62.6, 68.8, 71.7, 99.3, 126.5, 136.1, 144.1, 152.2.

3-Benzencesulfonyl-4-(3-(4-(tert-butyl(dimethyl)silyloxy)phenyl)propoxy)furoxan (57). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) -4.2, 18.6, 26.1, 30.5, 31.1, 70.9, 110.5, 120.6, 129.0, 129.8, 130.1, 133.3, 136.0, 138.6, 154.5, 159.4.

3-Benzencesulfonyl-4-(3-(3,5-dimethoxy-4-((2-methoxyethoxy)methoxy)phenyl)propoxy)furoxan (58). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 29.9, 31.9, 56.0, 59.0, 68.4, 70.4, 71.8, 96.9, 105.3, 110.5, 128.5, 129.9, 132.7, 135.7, 136.5, 138.1, 153.4, 159.0.

3-Benzencesulfonyl-4-(3-(3,5-di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propoxy)furoxan
furoxan (59). $^{13}$C-NMR (CDCl$_3$) $\delta$ 30.0, 31.4, 32.0, 35.7, 59.1, 68.9, 70.7, 71.7, 99.4, 110.5, 126.5, 128.5, 129.7, 134.6, 135.6, 138.2, 144.4, 152.6, 159.0.

4-(3-(3-Benzenesulfonylfuroxan-4-yloxy)propyl)phenol (60). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 29.7, 29.9, 70.5, 110.4, 115.1, 128.2, 129.1, 130.0, 130.5, 136.0, 137.2, 137.8, 148.5, 159.6.

4-(3-(3-Benzenesulfonylfuroxan-4-yloxy)propyl)-2,6-dimethoxyphenol (61). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 30.2, 31.6, 35.3, 71.4, 111.3, 125.2, 129.1, 130.9, 132.2, 137.0, 138.1, 140.1, 152.8, 159.8.

3-Benzensulfonyl-4-((6-(2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methoxy)furoxan (63). $^{13}$C-NMR (CDCl$_3$) $\delta$ 11.8, 12.5, 13.4, 20.1, 21.6, 28.1, 59.1, 69.3, 71.8, 73.6, 75.2, 98.5, 110.4, 116.8, 123.1, 126.3, 128.3, 128.4, 129.6, 135.5, 138.2, 147.1, 147.3, 159.1.

2-(3-Benzenesulfonylfuroxan-4-yloxymethyl)-2,5,7,8-tetramethylchroman-6-ol (64). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 11.5, 11.9, 12.8, 19.5, 20.9, 27.6, 73.3, 74.9, 110.5, 116.5, 120.5, 121.1, 122.9, 128.0, 130.0, 136.1, 143.7, 145.7, 159.1.

3-(3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)-N-methylpropanamide (65). $^{13}$C-NMR (CDCl$_3$) $\delta$ 26.3, 31.8, 32.0, 35.7, 38.8, 59.1, 68.9, 71.7, 99.3, 126.4, 135.2, 144.3, 152.5, 173.0.

3-(3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)-N-methylpropan-1-amine oxalate (66). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 27.3, 31.7, 31.8, 32.3, 35.2, 47.8, 58.0, 68.5, 71.0, 99.2, 126.2, 135.0, 143.4, 151.9, 164.4.

4-((N-((3-(3,5-Di-tert-butyl-4-((2-methoxyethoxy)methoxy)phenyl)propyl)-N-methyl)amino)methyl)furoxan-3-carboxamide (67). $^{13}$C-NMR (CDCl$_3$) $\delta$ 28.7, 32.1, 33.4, 35.6, 41.8, 52.6, 57.0, 59.1, 68.8, 71.7, 99.3, 110.3, 126.4, 135.8, 144.1, 152.3, 154.5, 156.2.

4-((N-(3-(3,5-Di-tert-butyl-4-hydroxyphenyl)propyl)-N-methylamino)methyl)furoxan-3-carboxamide (68). $^{13}$C-NMR (DMSO-d$_6$) $\delta$ 29.5, 31.3, 33.7, 35.3, 42.1, 52.8, 57.0, 111.5, 125.0,
6-((2-Methoxyethoxy)methoxy)-N,2,5,7,8-pentamethylchromane-2-carboxamide (69). $^{13}$C-NMR (DMSO-d$_6$) δ 13.0, 13.1, 14.1, 20.8, 25.1, 26.9, 30.0, 59.0, 69.4, 72.1, 78.5, 98.7, 118.5, 123.0, 126.6, 128.4, 147.6, 147.9, 174.4.

N-((6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)methyl)-N-methylamine oxalate (70). $^{13}$C-NMR (DMSO-d$_6$) δ 11.9, 12.2, 13.1, 19.3, 21.0, 28.2, 34.2, 56.0, 58.0, 68.5, 71.1, 72.5, 97.8, 116.9, 122.2, 125.9, 127.7, 146.2, 147.0, 164.1.

4-(N-methyl-N-((6-((2-methoxyethoxy)methoxy)-2,5,7,8-tetramethylchroman-2-yl)amino)methyl)furoxan-3-carboxamide (71). $^{13}$C-NMR (CDCl$_3$) δ 12.1, 12.5, 13.4, 20.4, 22.0, 29.6, 44.5, 54.3, 59.1, 65.2, 69.2, 71.8, 76.0, 98.4, 110.5, 117.1, 122.7, 126.3, 128.3, 146.9, 147.5, 155.3, 156.1.

4-((N-((6-Hydroxy-2,5,7,8-tetramethylchroman-2-yl)methyl)-N-methylamino)methyl)furoxan-3-carboxamide (72). $^{13}$C-NMR (DMSO-d$_6$) δ 11.7, 11.8, 12.6, 19.8, 21.5, 29.5, 43.7, 53.4, 63.8, 75.3, 110.7, 116.4, 120.2, 120.7, 122.6, 144.1, 145.1, 155.6, 155.7.