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# Synthesis, biological activity and structure–activity relationship of 4,5-dimethoxybenzene derivatives inhibitor of rhinovirus 14 infection

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ABSTRACT

Human rhinoviruses are a common cause of respiratory infections, and thus constitute an important target for medicinal chemistry. Still, no drug has been approved for clinical use. We report herein the discovery of dibenzenic derivatives with potent and specific *in vitro* anti-rhinoviral 14 activity. A total of 99 structural analogues were synthesized by an original synthesis method, i.e. through one organic agent Tetrakis(DimethylAmino)Ethylene (TDAE) and a structure–activity relationship was established. It was shown that 4,5-dimethoxy scaffold and the presence of a C-4 substituted aromatic moiety were necessary to the *in vitro* activity of these original agents. However, modifications on liker were not convincing. The benzonitrile derivative **23** was identified as the most potent and selective inhibitor of rhinovirus replication in these series ($EC_{50}$ of 2 ± 0.5 μM, $CC_{50}$ of 184 μM, selectivity index of 92).


## 1. Introduction

Human rhinoviruses (HRV) are single-stranded, positive-sense RNA viruses of the Picornaviridae family. They are responsible for at least 50% of the common colds [1,2], a mild, self-limiting upper respiratory tract illness, nonetheless with major economic impact through loss of productivity [1,3,4]. Furthermore, rhinovirus infections have frequently been associated with more severe lower respiratory tract disease such as exacerbations of asthma or chronic obstructive pulmonary disease (COPD) [5,6]. Prevention through vaccination is not feasible because there exist more than 150 different rhinovirus types with low antibody cross-reactivity [7]. To lower the burden of rhinovirus infection in patients with asthma or COPD, urgent development of agents with broad-spectrum antiviral activity against the three genetic clades of HRV (A, B and C) is needed [8]. In the past, several small-molecule inhibitors have been in (clinical) development to treat the common cold [9–11]. However, none of these candidates reached the market because the side-effects of the treatment did not outweigh the burden of a common cold itself or no efficacy was observed in a setting with natural occurring rhinovirus infections [12,13]. Currently, capsid binder vapendavir (BTA-798, Biota Pharmaceuticals Incorporated) is under clinical development for the treatment of asthma exacerbations and has completed phase II clinical trials with a positive outcome [14].

In this paper, we explore the use of Tetrakis(DimethylAmino) Ethylene (TDAE)-based chemistry in a medicinal setting [15,16] (Chart 1). TDAE is an organic reducing agent [17] which reacts with haloalkyl derivatives to generate an anion under mild conditions via two sequential transfers of one electron (Scheme 1) [18]. This carbanion is able to react with various electrophiles such as aromatic aldehydes, α-ketoester, ketomalonate, α-ketolactam and sulfonimine derivatives [19–27]. Since the development of TDAE methodology, a chemical library was constituted and evaluated for the antiviral effect in a virus-cell-based assay on different viruses. This first screening revealed a specificity of the compounds for HRV.

For the initial structure–activity relationship, we evaluated the inhibitory activity of the compounds in a virus-cell-based assay for HRV 14. Subsequently, active compounds from this SAR were evaluated against a panel of 13 genetically diverse human rhinovirus strains.

## 2. Results and discussion

### 2.1. First topological exploration with nitrobenzyl chloride derivatives

The first homogenous series of compounds that have been evaluated for antiviral activity, were the products derived from the

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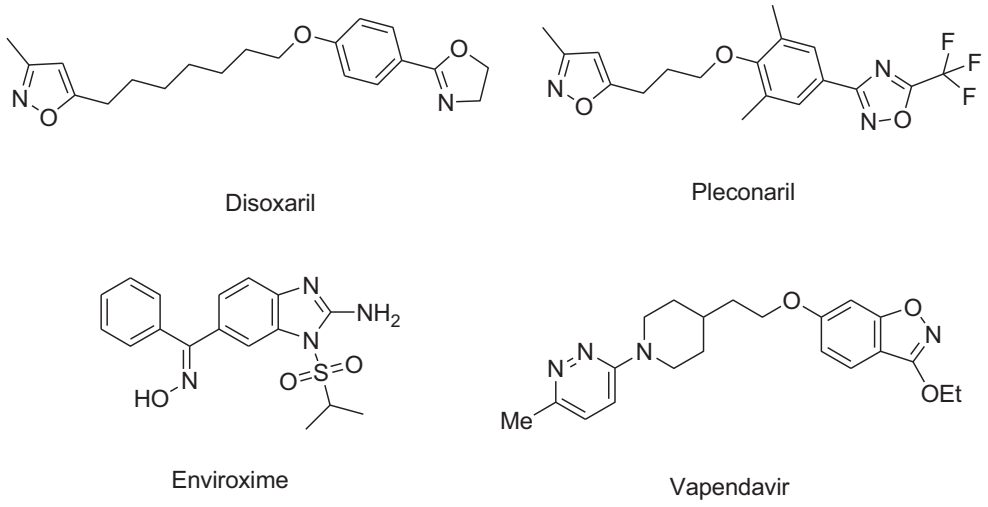
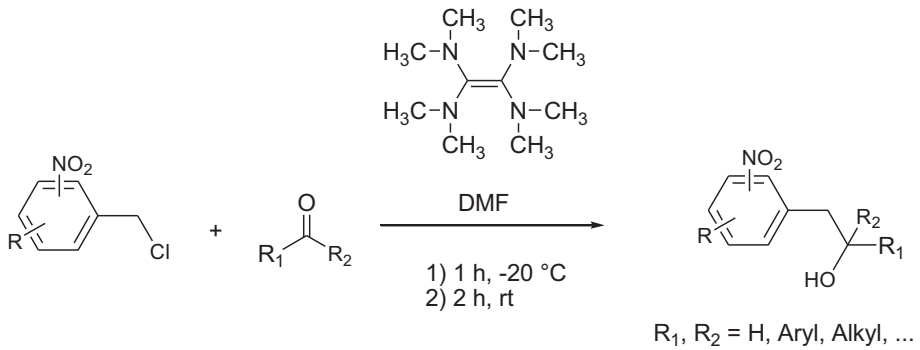



**Chart 1.** Molecules with anti-HRV activity.



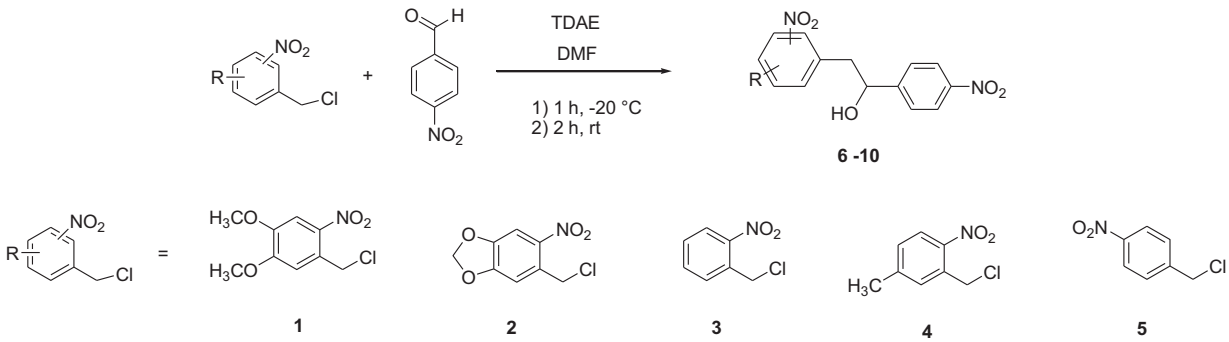

**Scheme 1.** TDAE methodology: general procedure.

TDAE-initiated reaction of various nitrobenzyl chloride derivatives (**1**–**5**) with *p*-nitrobenzaldehyde (most reactive aldehyde) of which the reaction scheme is shown in Scheme 2 and of which the yield of the reaction products together with the antiviral activity against HRV 14 are listed in Table 1.

In this homogenous series, the most active compound was the 2-(4,5-dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanol **6**, which was formed from TDAE-initiated reaction on 1-(chloromethyl)-4,5-dimethoxy-2-nitrobenzene **1**. This compound **6** proved to be a selective ($EC_{50}$ of 4.3 ± 1.0 μM, $CC_{50}$ of 95 μM, selectivity index of 23) inhibitor of virus replication. These first results led us to direct our research towards the 4,5-dimethoxy-2-nitrobenzene derivatives, seeking to produce other compounds with higher activity and less toxicity, as well as to define a structure–activity relationship (SAR). Our strategy involved a topological exploration of the diarylethanol derivative described, examining three targets of this molecule: the linker, $R_1$ and $R_2$ substituents (Chart 2).

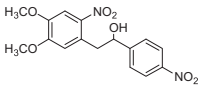
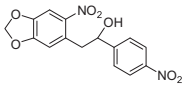
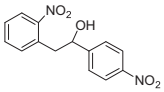
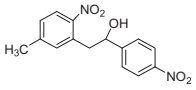
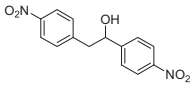
### 2.2. Pharmacomodulation of substituent $R_1$

First, we changed electrophiles, selecting aldehydes with different physicochemical and steric characters. Thus, the synthesis started with the reaction of 1-(chloromethyl)-4,5-dimethoxy-2-nitrobenzene **1** with various aldehydes under classical TDAE




**Scheme 2.** First homogenous series with *p*-nitrobenzaldehyde.

**Table 1**
SAR of the first homogenous series.[a,b]

| No | Code | Structure | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **6** | W6 |  | 85% | 95.1 ± 16.2 | 4.3 ± 1.02 | 8.8 ± 0.9 |
| **7** | M0126[18b] |  | 65% | 11.4 | >301 | >301 |
| **8** | M0168 |  | 85% | 347 | >347 | >347 |
| **9** | M0186 |  | 68% | 67.8 | >331 | >331 |
| **10** | M0174[18a] |  | 85% | 134 | >347 | >347 |

$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.

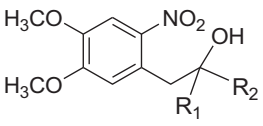


**Chart 2.** First topological exploration of 4,5-dimethoxy-2-nitrobenzene derivative.

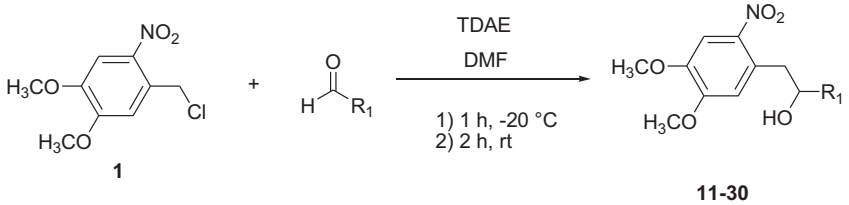
conditions [19] i.e. with 3 equiv of aldehyde in the presence of 1.1 equiv of TDAE in DMF, at −20 °C for 1 h followed by 2 h at room temperature and yielded diarylethanols **11**–**30** in 35%–85% yield (Scheme 3). Yields varied according to functional group of electrophiles. As observed in previous studies [19–30], an electron-withdrawing group in *ortho* or *para* positions promotes the attack of carbanion, thus increasing yield. The biological activities of these molecules are described in Table 2.

Biological assays showed five molecules (**6**, **13**, **14**, **23**, **24**) with interesting anti-HRV 14 activities ($EC_{50}$ around 2 μM). These molecules were also selective (selectivity index from 6 to 92). All these products presented a phenyl group moiety as R1. The substitution and various replacements of the C-4 phenyl group (compounds **6**, **14**, **23** and **24**) of $R_1$ moiety led to slightly more active derivatives (isosteric and non isosteric). In addition, $R_1$ biphenyl structure 1-(biphenyl-4-yl)-2-(4,5-dimethoxy-2-nitrophenyl)ethanol **13** increased the lipophilic character and provided good activity, with a $EC_{50}$ of 1.97 ± 0.13 μM. Moreover, the substitution and various replacements of the C-3 phenyl (compounds **17**, **18** and **22**) or C-2 phenyl (like compound **16** for example) group of $R_1$ substitutions of chemical entities decreased or abolished the hRV 14 activity *in vitro*. The 4-[1-hydroxy-2-(4,5-dimethoxy-2-nitrophenyl)-1-hydroxyethyl]benzonitrile **23** was identified as the most potent ($EC_{50}$ of 2.19 ± 0.49 μM) and selective ($CC_{50}$ of 184 ± 30 μM, selectivity index of 92) inhibitor of virus replication.

### 2.3. Secondary alcohol function explorations

For the purposes of the SAR study and to confirm our hit scaffold, we investigated the importance of the secondary alcohol function. Thus, we synthesized and evaluated a series of tertiary alcohols prepared under initial TDAE procedure from **1** and ketone derivatives such as α-ketoesters [21], α-diketones [29], acetophenones and isatine [28] as electrophiles (Scheme 4 and Table 3). Tertiary alcohols **31**–**37** were obtained in 28%–87% yield.

All modifications on scaffold, presented in Table 3, clearly showed the importance of secondary alcohol versus tertiary alcohol. In fact, modifications of C–OH substituents for compounds **31**–**37** greatly affected biological activity, suggesting that steric hindrance is correlated with activity. Moreover, the modification of the more active compounds **6** and **23** by a methyl group as $R_2$ (compounds **33** and **34**) led to a total loss of inhibitory activity against HRV 14.




**Scheme 3.** Pharmacomodulation of $R_1$.

**Table 2**
SAR: nature of $R_1$.[a,b]

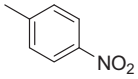
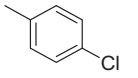
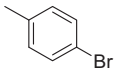
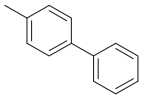
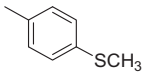
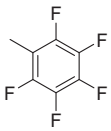
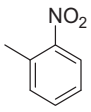
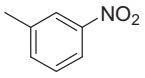
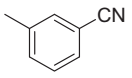
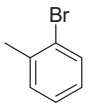
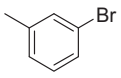
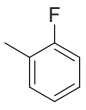
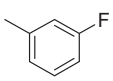
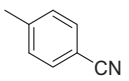
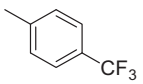
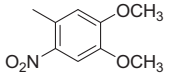
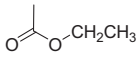
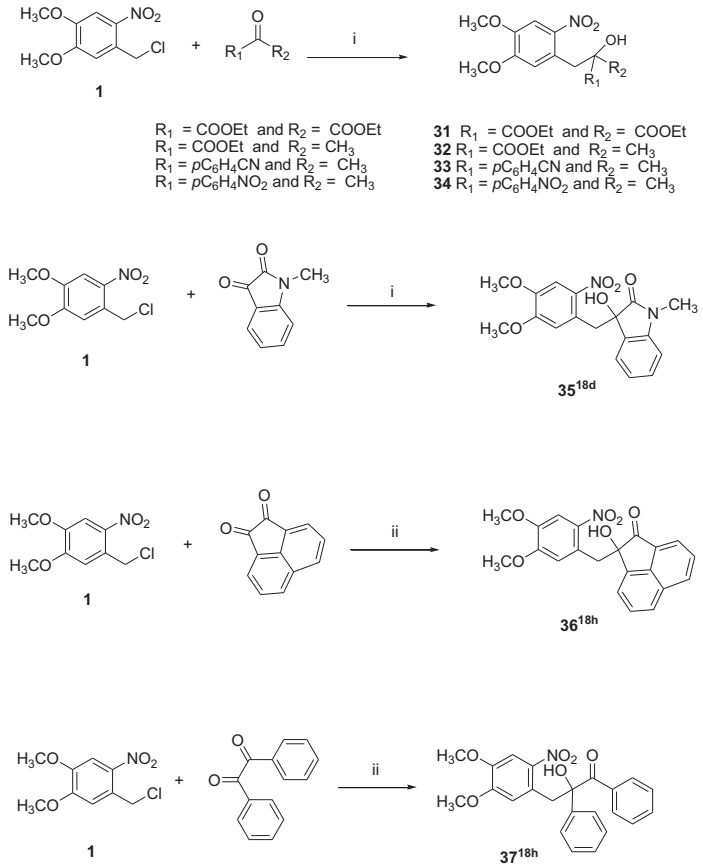
| No | Code | $R_1$ | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **6** | W6 |  | 85% | 95.1 ± 16.2 | 4.3 ± 1.0 | 8.8 ± 0.9 |
| **11** | M090 |  | 68% | 78.7 ± 12.7 | 9.8 ± 0.1 | 15.7 ± 0.3 |
| **12** | M092 |  | 50% | 65.8 ± 4.1 | 6.0 ± 0.5 | 10.3 ± 1.1 |
| **13** | M0108 |  | 70% | 12 ± 5.6 | 1.97 ± 0.1 | 3.13 ± 0.1 |
| **14** | M0110 |  | 35% | 56 ± 16.0 | 2.8 ± 0.6 | 5.2 ± 1.1 |
| **15** | M0122 |  | 25% | ND | >254 | >254 |
| **16** | M0140 |  | 36% | ND | >287 | >287 |
| **17** | M0142 |  | 52% | 380 | 15.8 ± 3.3 | 27.5 ± 5.4 |
| **18** | M0144 |  | 70% | 160 ± 38.8 | 29 ± 6.9 | 66.7 ± 11.8 |
| **19** | M0146 |  | 50% | ND | >262 | >262 |
| **20** | M0148 |  | 39% | 52.4 ± 13.5 | 28.1 ± 3.1 | 33.3 |
| **21** | M0164 |  | 85% | 98.7 ± 11.4 | >311 | >311 |
| **22** | M0166 |  | 85% | 89.8 ± 9.6 | 43.2 ± 1.3 | ND |
| **23** | W5 |  | 81% | 184 ± 30 | 2.19 ± 0.4 | 3.83 ± 0.8 |
| **24** | W46 |  | 85% | 49.7 ± 18.1 | 2.04 ± 0.1 | 3.28 ± 0.1 |
| **25** | W47 |  | 62% | 112 | 60.4 ± 9.3 | 134 ± 15 |

**Table 2** (*continued*)

| No | Code | $R_1$ | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **26** | W48 |  | 49% | ND | >306 | >306 |
| **27** | M0130 |  | 86% | 171 ± 44.4 | 58.9 ± 3.4 | 100 ± 2.7 |
| **28** | M0132 |  | 33% | 221 ± 32.9 | 117 ± 28.8 | 313 |
| **29** | M0134 |  | 70% | 276 | >329 | >329 |
| **30** | M052 |  | 85% | ND | >334 | >334 |

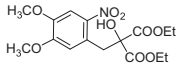
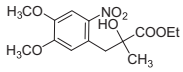
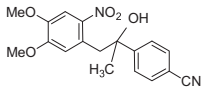
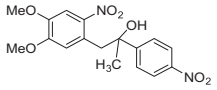
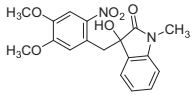
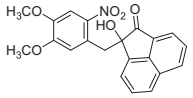
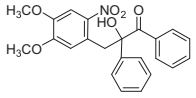
ND = not determined.
$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.




[a] All yields refer to the chromatographically isolate products and are relative to substrate.
[b] Reagents and conditions: (i) electrophile (3 equiv), TDAE (1.1 equiv), extra dry DMF, -20 °C,1 h; rt, 2 h; $H_2O$; **31** (72%), **32** (59%), **33** (78%), **34** (34%), **35** (87%), (ii) electrophile (3 equiv), TDAE (1.0 equiv), extra dry DMF, -20 °C,1 h; 80°C, 2 h; $H_2O$; **36** (32 %), **37** (28%).

**Scheme 4.** Pharmacomodulation of $R_1$ and $R_2$.[a,b]

**Table 3**
SAR: $R_1$ and $R_2$ modification.[a,b]

| No | Code | Structure | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **31** | OUA34 |  | 72% | ND | >269 | >269 |
| **32** | M056 |  | 59% | ND | >319 | >319 |
| **33** | M096 |  | 78% | 107 | >292 | >292 |
| **34** | M0112 |  | 34% | 138 | >276 | >276 |
| **35** | W0018[18d] |  | 87% | 152 ± 44.9 | >279 | >279 |
| **36** | W0037[18h] |  | 32% | ND | >329 | >329 |
| **37** | W0038[18h] |  | 28% | ND | 301 | >307 |

ND = not determined.
$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.

### 2.4. Linker modifications

Next, variations on the linker moiety were introduced to further expand the SAR. Different approaches were considered: effect of linker elongation, modification of hydroxyl group and linker rigidification (Scheme 5). However, TDAE methodology was not sufficient for all these purposes: our first strategy was to somewhat modify the TDAE methodology (substrate, experimental conditions) to obtain products with a modified linker.

The reaction of chloride **1** and *p*-nitrobenzaldehyde under classical TDAE conditions but with heating at 70 °C for 2 h in the second phase of the protocol enabled us to isolate the (*E*)-1,2-dimethoxy-4-nitro-5-(4-nitrostyryl)benzene **38** in 15% yield. In parallel, the reaction of chloride **5** with 3 equiv of 4,5-dimethoxy-2-nitrobenzaldehyde under classical TDAE conditions [19] led to 1-(4,5-dimethoxy-2-nitrophenyl)-2-(4-nitrophenyl)ethanol **39** in 36% yields. In this case, the position of OH group was modified compared with hit **6**.

Moreover, a carbonyl function in the linker should promote rigidifying. So, a solution of 4-[1-hydroxy-2-(4,5-dimethoxy-2-nitrophenyl)-1-hydroxyethyl]benzonitrile **23** in acetone was treated with 3 equiv $CrO_3$ solubilized in 10 equiv of $H_2SO_4$. The reaction was stirred during 0.5 h to obtain ketone 2-(4,5-dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanone **40** in 80% yield. To explore more linker modifications, we synthesized product 1-(4,5-dimethoxy-2-nitrophenyl)-4-(4-nitrophenyl)but-3-yn-1-ol **42** in 32% yield from the reaction of 1-(3-chloroprop-1-ynyl)-4-nitrobenzene **41** (prepared via a Sonogashira cross coupling reaction) [27] with 3 equiv of 4,5-dimethoxy-2-nitrobenzaldehyde in the presence of 1.1 equiv of TDAE in DMF, at −50 °C for 1 h followed by 2 h at 60 °C [20].

The reaction of the 1-(dichloromethyl)-4,5-dimethoxy-2-nitrobenzene **43** with 3 equiv of aldehydes (presented in Scheme 5) in the presence of 1.1 equiv of TDAE in DMF, at −20 °C for 1 h, followed by 2 h at rt yielded oxirane derivatives **44**–**49** in 35%–80% yield. These reactions were performed under light catalysis (Table 4).

OH functional group reversal was explored with the biological evaluation of compound **39**. The potent activity was abolished in the case of inversion of the OH functional group position on the linker. Moreover, the expected effect of rigidifying the linker was to decrease the number of conformations and thus potentially increase selectivity. Product 1-(4,5-dimethoxy-2-nitrophenyl)-4-(4-nitrophenyl)but-3-yn-1-ol **42** presented interesting anti-rhinoviral activity but also significant toxicity on the Hela cells ($CC_{50}$ = 17.2 μM). An increased linker length might be more interesting without a triple bond. Rigidification without elongation (**38**, **40**, **44**–**49**) led to a complete loss of anti-HRV 14 activity.

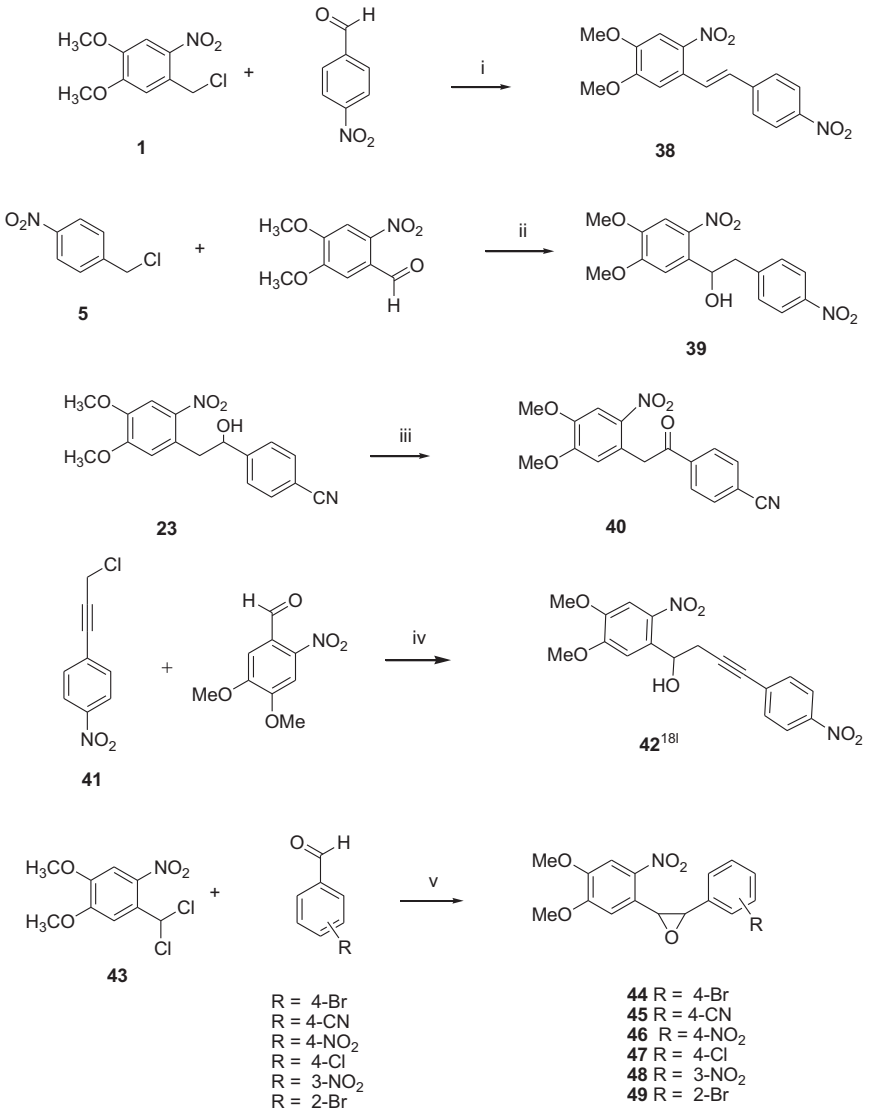
The next step in our pharmacomodulation process was the derivatization of the linker. All substitutions are described in Scheme 6 [31–35]. The substitution reactions were carried out for products **6**, **13**, **23** and **28** by the action of 3 equiv of thionyl chloride in $CH_2Cl_2$, for 4 h. This reaction led to chloride derivatives **50**–**53** in 90%–95% yield. 1-(Azido-2-(4-nitrophenyl)ethyl)-4,5-dimethoxy-2-nitrobenzene **54** and 4-(1-azido-2-(4,5-dimethoxy-2-nitrophenyl)ethyl)benzonitrile **55** were obtained by using 3 equiv of $NaN_3$ and respectively the 1-(2-chloro-2-(4-nitrophenyl)ethyl)-4,5-dimethoxy-2-nitrobenzene **50** and the 4-(1-chloro-2-(4,5-dimethoxy-2-nitrophenyl)ethyl)biphenyl **51** in solution in ethanol for 6 h (Yields: **54**, 37%; **55**, 30%). The conversion of 1-(azido-2-(4-nitrophenyl)ethyl)-4,5-dimethoxy-2-nitrobenzene **54** to 2-(4,5-dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanamine **56** was accomplished by treatment with 1 equiv of $PPh_3$ according to Staudinger reaction conditions.

4-[2-(4,5-Dimethoxy-2-nitrophenyl)-1-hydroxy-ethyl]benzonitrile **23** was then treated with diethylaminosulfur trifluoride to yield the 4-(2-(4,5-dimethoxy-2-nitrophenyl)-1-fluoroethyl)benzonitrile **57**. To check the effect of steric hindrance in this scaffold moiety on biological activity, mesylation of the hydroxyl group of 4-[2-(4,5-dimethoxy-2-nitrophenyl)-1-hydroxy-ethyl]benzonitrile **23** was performed with 1.5 equiv of methane sulfonyl chloride in chloroform at 60 °C for 48 h leading to 1-(4-cyanophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethyl methanesulfonate **58** in 25% yield (Table 5).

Modification of hydroxyl function changed the biological activity but not significantly. In fact, in the case of **50**, **51**, **52**, **56** and **57**, anti-HRV 14 activity was retained. However, modification of steric hindrance significantly decreased $EC_{50}$ value. In fact, 1-(4-cyanophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethyl methanesulfonate **58** did not show any antiviral activity *in vitro*.

### 2.5. First C-2 substituent exploration

Our final aim here was to determine the real impact of the C-2 group on biological activity. This group, present on dimethoxybenzene substrate, is very important for TDAE reactivity. From a biological point of view, it is very lipophilic and promotes membrane crossing. The effect of "nitro" substituent at the 2- position of the dimethoxybenzene core on anti-HRV 14 activity was examinated by comparison with unsubstituted or acetamido derivatives.




[a] Reagents and Conditions: (i) *p*-nitrobenzaldehyde (3 equiv), TDAE (1.1 equiv), extra dry DMF, -20° C,1 h; 70 °C, 2 h; $H_2O$; **38** (15%). (ii) 4,5-dimethoxy-2-nitrobenzaldehyde (3 equiv), TDAE (1.1 equiv), extra dry DMF, -20 °C, 1 h; rt, 2 h; $H_2O$; **39** (36%). (iii) $CrO_3$ (3 equiv) in $H_2SO_4$ (10 equiv), $C_3H_6O$, rt, 0.5 h; **40** (80%). (iv) 4,5-dimethoxy-2-nitrobenzaldehyde (3 equiv), TDAE (1.1 equiv), extra dry DMF, -50 °C,1 h; 60 °C, 2 h; $H_2O$; **42** (32%). (v) electrophile (3 equiv), TDAE (1.1 equiv), extra dry DMF, -20 °C, 1 h, hν; rt, 2 h, hν.; $H_2O$; **44** (52%), **45** (40%), **46** (58%), **47** (40%), **48** (40%), **49** (38%).
[b] All yields refer to the chromatographically isolate products and are relative to substrate.

**Scheme 5.** Modifications of the linker.[a,b]

The preparation of the non-nitrated analogue 4-(2-(3,4-dimethoxyphenyl)-1-hydroxyethyl)benzonitrile **60** of compound **23** was realized from 4-[2-(4,5-dimethoxy-2-nitrophenyl)-1-hydroxy-ethyl]benzonitrile **23** via a reduction of the nitro group, diazotation of amine and reduction of diazonium salt by hypophosphorus acid ($H_3PO_2$). In this context, the formation of 4-(2-(3,4-dimethoxyphenyl)-1-hydroxyethyl)benzonitrile **60** (10%) was accompanied by *N*-(2-(2-(4-cyanophenyl)-2-hydroxyethyl)-4,5-dimethoxyphenyl)acetamide **59** (15%). This procedure is presented in Scheme 7.

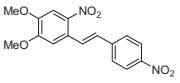
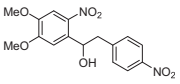
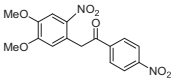
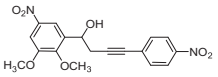
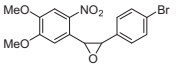
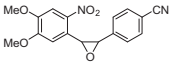
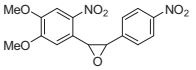
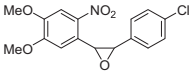
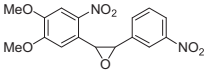
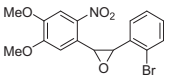
As **60** showed some activity (Table 6), the "nitro" group seems to promote anti-HRV 14 activity. Moreover, steric hindrance at this position significantly decreased $EC_{50}$ value which is evident from compound **59** that did not present any antiviral activity *in vitro*.

### 2.6. Integrated SAR guidelines

The aim of the present study was to provide some elements to analyse the effect of different structural elements on *in vitro* activity. To date, all these results could be summarized; the guidelines of integrated SAR and following synthesis strategy are represented in Scheme 8.

Subsequently, a subset of compounds that were selected based on their potency against HRV 14 were evaluated for selective antiviral activity in virus-cell-based assays of thirteen HRV serotypes, including major and minor group serotypes (HRV 2, HRV 9, HRV 15, HRV 29, HRV 41, HRV 59, HRV 63, HRV 85 and HRVA89 from HRV clade A; HRV 42, HRV 70, HRV 72 and HRV 86 from HRV clade B). This analysis revealed that the antiviral activity of

**Table 4**
SAR: linker modifications.[a,b]

| No | Code | Structure | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **38** | M3036 |  | 65% | 152 | >303 | >303 |
| **39** | W36[18a] |  | 36% | ND | >359 | >359 |
| **40** | OM1616 |  | 10% | ND | >306 | >306 |
| **42** | M3110[18l] |  | 32% | 17.2 ± 3.5 | 6.8 ± 1.1 | 9.7 |
| **44** | W1 |  | 52% | ND | >263 | >263 |
| **45** | W2 |  | 40% | ND | >306 | >306 |
| **46** | W22 |  | 58% | ND | >289 | >289 |
| **47** | W21 |  | 40% | 109 | >298 | >298 |
| **48** | W4 |  | 40% | 144 ± 55.6 | 98.3 | ND |
| **49** | W3 |  | 38% | ND | >263 | >263 |

ND = not determined.
$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.

this class of compounds was highly specific against HRV 14 (Table 7).

## 3. Conclusion

A new compound library was established by using original TDAE methodology. A total of 99 molecules were synthesized and evaluated for selective antiviral activity in a virus-cell-based assay for HRV 14 replication. Exploration of the SAR of this class of compounds showed that the dibenzenic structure was allowed to possess various groups on the C-4 phenyl moiety. The compound 4-[1-hydroxy-2-(4,5-dimethoxy-2-nitrophenyl)-1-hydroxyethyl] benzonitrile **23** was identified as the most potent and selective inhibitor of the replication of this virus. Currently, studies are ongoing to unravel the precise molecular mechanism-of-action of this compound.

## 4. Experimental section

### 4.1. Chemistry

Reagents were purchased from Sigma Aldrich Chemical Co., Fisher Scientific SAS and Alfa Aesar Co. VWR international and Carlo Erba grade solvents were routinely used. Melting points were determinated on a Buchi capillary melting point apparatus and are uncorrected. Elemental analysis or Mass spectrometries were performed by Spectropole centre, Aix-Marseille University. The $^1H$ and $^{13}C$ NMR spectra were determinated on a Bruker AC 200 spectrometer. The $^1H$ chemical shifts are reported as parts per million downfield from tetramethylsilane ($Me_4Si$), the $^{13}C$ chemical shifts were referenced to the solvent peak. ($CDCl_3$: 76.9 ppm and $Me_2SO$-$d_6$ 39.6 ppm.) Coupling constants ($J$) are in Hertz.

Absorptions are reported with the following notations: s, singlet; d, doublet; t, triplet; q, quartet; m, a more complex multipletor overlapping multiplets. The following absorbents were used for column chromatography: silica gel 60 (Merck, particle size 0.0063–0.200, 70–230 mesh ASTM).

TLC was performed on 5 cm × 10 cm aluminium plates coated with silica gel 60 F-254 (Merck) in an appropriate solvent.

#### 4.1.1. General procedure for TDAE reaction with various electrophiles

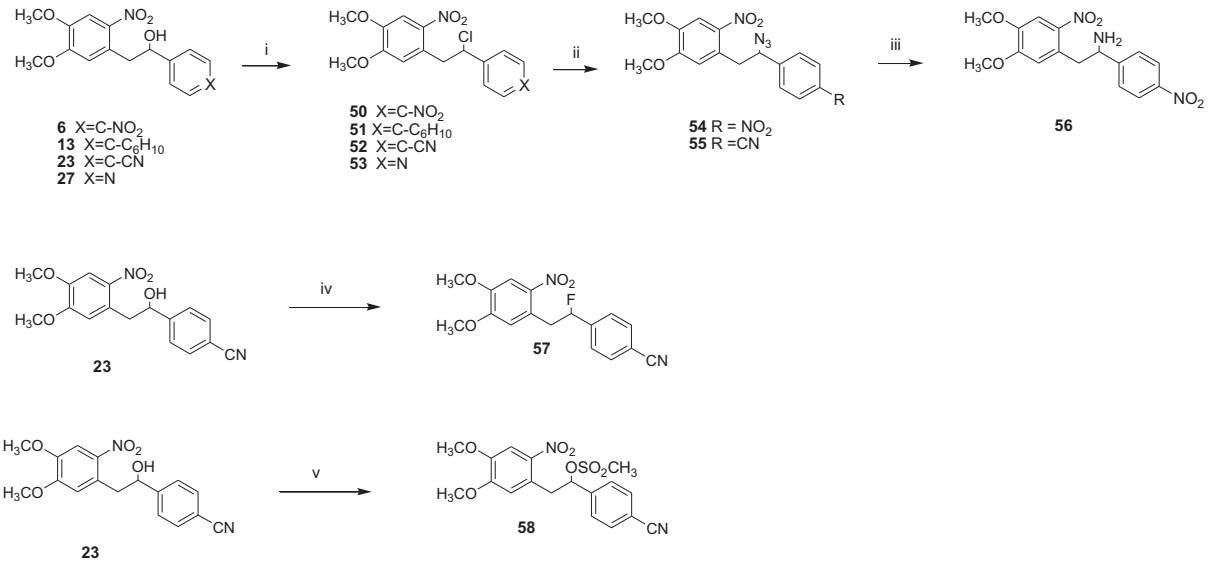
All materials were dried for one day at 120 °C. Chloride and carbonyl derivatives were introduced into a Schlenk of 30 mL. Products were put *in vacuo*, then under nitrogen. An appropriate volume of anhydrous DMF was added after 10 min of nitrogen bubbling. The solution was vigorously stirred for 20 min at −20 °C. TDAE was added slowly under inert atmosphere. The reaction was stirred for one hour. The second reaction phase was performed at rt or at temperature according to procedure of synthesis. The reaction was hydrolysed with distilled water after TLC analysis clearly showed that the chloride **1** had been totally consumed. The aqueous solution was extracted with dichloromethane and the combined organic layers washed with brine then dried on $MgSO_4$.

*4.1.1.1. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanol (**6**).* Yellow solid. Yield, 85%. Mp (recrystallized from ethanol) 157 °C. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.24 (d, 2H, $J$ = 8.7), 7.66 (s, 1H), 7.64 (d, 2H, $J$ = 8.7), 6.66 (s, 1H), 5.21 (dd, 1H, $J$ = 8.8, 3.6), 3.96 (s, 3H), 3.90 (s, 3H), 3.53 (dd, 1H, $J$ = 13.5, 3.6), 3.04 (dd, 1H, $J$ = 13.5, 8.8), 2.42 (s, 1H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 152.9, 151.4, 147.9, 147.3, 141.4, 127.9, 126.5, 123.6, 115.0, 108.2, 73.1, 56.4, 56.3, 43.8. Anal ($C_{16}H_{16}N_2O_7$) C, H, N.

*4.1.1.2. 2-(2-Nitrophenyl)-1-(4-nitrophenyl)ethanol (**8**).* Yellow solid. Yield, 85%. Mp 122 °C. $^1H$ MR (200 MHz, $CDCl_3$) $\delta$ 8.19 (d, 1H, $J$ = 8.8), 7.98 (m, 1H), 7.58 (d, 2H, $J$ = 8.8), 7.29–7.55 (m, 3H), 5.20 (m, 1H), 3.42 (dd, 1H, $J$ = 13.3, 3.8), 3.11 (dd, 1H, $J$ = 13.3, 8.6), 2.46 (d, 1H, $J$ = 3.8). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 151.0, 149.7, 147.5, 133.7, 133.1, 132.5, 128.2, 126.5, 125.1, 123.8, 73.3, 43.0. Anal ($C_{14}H_{12}N_2O_5$) C, H, N.

*4.1.1.3. 2-(5-Methyl-2-nitrophenyl)-1-(4-nitrophenyl)ethanol (**9**).* Yellow solid. Yield, 68%. Mp 132 °C. $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 8.24–8.20 (m, 2H), 7.95 (d, 1H, $J$ = 8.4), 7.62 (d, 2H, $J$ = 8.4), 7.25–7.21 (m, 1H), 7.13 (s, 1H), 5.20–5.16 (m, 1H), 3.45 (dd, 1H, $J$ = 13.4, 3.5), 3.03 (dd, 1H, $J$ = 13.4, 9.0), 2.41 (s, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$) $\delta$ 151.1, 147.4, 147.2, 144.5, 134.2, 132.7, 128.8, 126.5, 125.4, 123.7, 73.3, 43.3, 21.4. Anal ($C_{15}H_{12}N_2O_5$) C, H, N.

*4.1.1.4. 1-(4-Chlorophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethanol (**11**).* Brown solid. Yield, 68%. Mp 108 °C. $^1H$ NMR (200 MHz, $CDCl_3$)




[a]All yields refer to the chromatographically isolate products and are relative to substrate.
[b]Reagents and conditions: (i) $SOCl_2$ (3 equiv), $CH_2Cl_2$, 0 °C then 50 °C, 4 h, (**50- 53**) 85-95%; (ii) $NaN_3$ (2 equiv), EtOH, 70 °C, 24 h, 37% (**54**), 30% (**55**); (iii) 1) $PPh_3$ (1 equiv), 2) $H_2O$ (2mL), THF, rt, 24 h, (**73**) 20%; (iv) $N(Et)_2SF_3$ (1.5 equiv), $N_2$, $CH_2Cl_2$, 0 °C then rt, 10 min, (**57**) 90%; (v) Methane sulfonylchloride (1.5 equiv), $CHCl_3$, 60 °C, 48 h, (**58**) 25 %.

**Scheme 6.** Synthesis of 50–58 and evaluation of the OH substitution.[a,b]

δ 7.58 (s, 1H), 7.30 (s, 4H), 6.51 (s, 1H), 5.01 (dd, 1H, $J$ = 8.2, 4.3), 3.91 (s, 3H), 3.82 (s, 3H), 3.38 (dd, 1H, $J$ = 13.3, 4.3), 3.10 (dd, 1H, $J$ = 13.3, 8.2), 2.36 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.7, 147.7, 142.4, 141.6, 133.3, 128.6, 128.3, 127.2, 115.0, 108.2, 73.5, 56.3, 73.4, 43.7. Anal ($C_{16}H_{16}ClNO_5$) C, H, N.

*4.1.1.5. 1-(4-Bromophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethanol (**12**).* Brown solid. Yield, 50%. Mp 134 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.47 (d, 2H, $J$ = 8.4), 7.27 (d, 2H, $J$ = 8.4), 6.52 (s, 1H), 5.03 (dd, 1H, $J$ = 8.1, 4.3), 3.93 (s, 3H), 3.84 (s, 3H), 3.39 (dd, 1H, $J$ = 13.3, 4.3), 3.10 (dd, 1H, $J$ = 13.3, 8.1), 2.11 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.7, 147.7, 142.9, 141.6, 131.5, 128.2, 127.5, 121.4, 114.9, 108.2, 73.5, 56.3, 43.7. Anal ($C_{16}H_{16}BrNO_5$) C, H, N.

*4.1.1.6. 1-(Biphenyl-4-yl)-2-(4,5-dimethoxy-2-nitrophenyl)ethanol (**13**).* Brown solid. Yield, 70%. Mp 101 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.61–7.55 (m, 5H), 7.47–7.31 (m, 5H), 6.54 (s, 1H), 5.10 (dd, 1H, $J$ = 8.0, 4.6), 3.91 (s, 3H), 3.79 (s, 3H), 3.45 (dd, 1H, $J$ = 13.2, 4.6), 3.25 (dd, 1H, $J$ = 13.2, 8.0), 2.53 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.5, 147.5, 142.9, 141.6, 140.6, 140.5, 128.7, 128.4, 127.3, 127.0, 126.9, 126.2, 114.9, 108.0, 73.8, 56.2, 43.5. HRMS for $C_{22}H_{21}NO_2$ $[M + NH_4]^+$ = 397.1758. Found: $[M + H]^+$ = 397.1758.

*4.1.1.7. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-[4-(methylthio)phenyl] ethanol (**14**).* Brown solid. Yield, 35%. Mp 96 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.25 (dd, 4H, $J$ = 15.9, 8.4), 6.51 (s, 1H), 5.10 (dd, 1H, $J$ = 8.0, 4.5), 3.90 (s, 3H), 3.80 (s, 3H), 3.35 (dd, 1H, $J$ = 13.2, 4.6), 3.15 (dd, 1H, $J$ = 13.2, 8.0), 2.45 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.6, 147.6, 141.6, 140.9, 137.8, 128.5, 126.6, 126.3, 115.0, 108.1, 73.7, 56.3, 43.5, 15.9. Anal ($C_{17}H_{19}NO_5S$) C, H, N.

*4.1.1.8. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(perfluorophenyl)ethanol (**15**).* Yellow solid. Yield, 25%. Mp 87 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.74 (s, 1H), 5.40–5.42 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.35 (dd, 1H, $J$ = 13.2, 8.0), 3.15 (dd, 1H, $J$ = 13.2, 4.6). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.2, 148.1, 141.6, 127.1, 114.2, 108.3, 66.5, 56.5, 56.4, 40.4. HRMS $m/z$ calcd for $C_{16}H_{12}F_5NO_5$, 394.0708, (M + H); found: 394.0714.

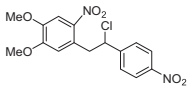
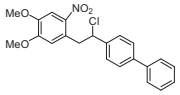
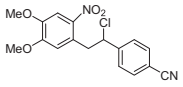
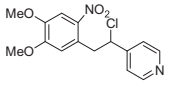
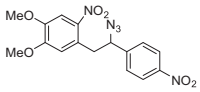
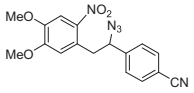
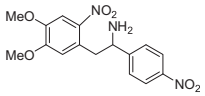
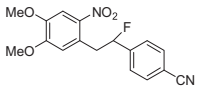
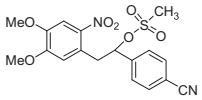
*4.1.1.9. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(2-nitrophenyl)ethanol (**16**).* Brown solid. Yield, 36%. Mp 121 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.0 (dd, 1H, $J$ = 8.1, 1.1), 7.90–7.86 (m, 1H), 7.73–7.65 (m, 1H), 7.52 (s, 1H), 7.53–742 (m, 1H), 6.88 (s, 1H), 5.62–5.56 (m, 1H), 3.94 (s, 6H), 3.50 (dd, 1H, $J$ = 13.3, 8.8), 3.06 (dd, 1H, $J$ = 13.7, 3.7), 1.58 (bs, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.2, 147.8, 142.6, 139.6, 133.8, 128.5, 128.5, 127.7, 124.6, 113.7, 107.9, 71.1, 56.4, 40.6. Anal ($C_{16}H_{16}N_2O_7$) C, H, N.

*4.1.1.10. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(3-nitrophenyl)ethanol (**17**).* Yellow solid. Yield, 52%. Mp 151 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.15 (dd, 1H, $J$ = 2.2, 1.2), 7.78 (d, 1H, $J$ = 7.9), 7.65 (s, 1H), 7.55 (t, 1H, $J$ = 7.9), 6.68 (s, 1H), 5.25–5.17 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.53 (dd, 1H, $J$ = 13.4, 3.6), 3.08 (dd, 1H, $J$ = 13.4, 3.7), 2.44 (d, 1H, $J$ = 3.6). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.9, 148.5, 148.0, 146.1, 141.5, 132.0, 129.4, 127.8, 122.6, 120.6, 114.9, 108.3, 73.1, 56.4, 43.8. Anal ($C_{16}H_{16}N_2O_7$) C, H, N.

*4.1.1.11. 3-[2-(4,5-Dimethoxy-2-nitrophenyl)-1-hydroxyethyl]benzonitrile (**18**).* Brown solid. Yield, 70%. Mp 148 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.78–7.43 (m, 4H), 7.64 (s, 1H), 6.63 (s, 1H), 5.12 (dd, 1H, $J$ = 8.6, 3.5), 3.94 (s, 3H), 3.89 (s, 3H), 3.48 (dd, 1H, $J$ = 13.4, 3.5), 3.04 (dd, 1H, $J$ = 13.4, 8.6), 2.48 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.9, 147.9, 145.5, 141.5, 131.3, 130.3, 129.3, 127.9, 118.8, 115.0, 112.5, 108.3, 73.1, 56.4, 43.8. Anal ($C_{17}H_{16}N_2O_5$) C, H, N.

*4.1.1.12. 1-(2-Bromophenyl)-2-(4,5-dimethoxy-2-nitrophenyl) ethanol (**19**).* Brown solid. Yield, 50%. Mp 117 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.56–7.48 (m, 2H), 7.53 (s, 1H), 7.38–7.30 (m, 1H), 7.18–7.11 (m, 1H), 6.47 (s, 1H), 5.48–5.40 (m, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.46 (dd, 1H, $J$ = 13.5, 7.2), 3.32 (dd, 1H, $J$ = 13.5, 5.1), 2.88 (d, 1H,

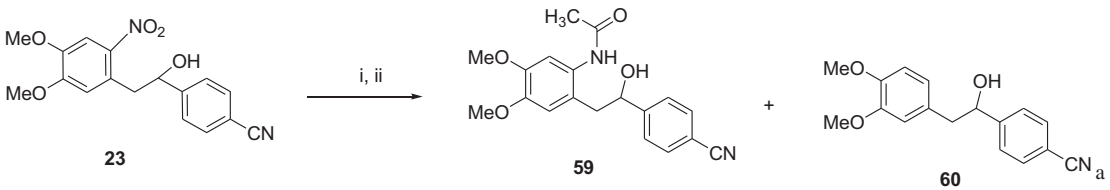
**Table 5**
SAR: evaluation of the OH substitution.[a,b]

| No | Code | Structure | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **50** | M2094 |  | 95% | 137 | 33.1 ± 9.6 | 69 ± 9.9 |
| **51** | M3028 |  | 87% | 14.1 | 3.42 ± 0.7 | ND |
| **52** | M3024 |  | 90% | 145 | 55.1 ± 3.4 | 80.2 |
| **53** | M3026 |  | 85% | 86.6 ± 69.3 | >310 | >310 |
| **54** | M2104 |  | 37% | ND | >268 | >268 |
| **55** | M3054 |  | 30% | 215 | 33 ± 1 | 51.5 ± 0.4 |
| **56** | M3022 |  | 20% | 191 | 49.5 ± 0.1 | 71.6 ± 0.2 |
| **57** | M3100 |  | 90% | 61.9 | 18.1 | 28.5 |
| **58** | M3076 |  | 25% | ND | >308 | >308 |

ND = not determined.
$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.

$J$ = 3.8). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.6, 147.7, 142.4, 132.6, 129.1, 127.9, 127.8, 127.4, 122.1, 114.2, 107.9, 73.3, 56.3, 56.2, 40.4. Anal ($C_{16}H_{16}BrNO_5$) C, H, N.

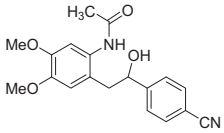
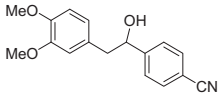
*4.1.1.13. 1-(3-Bromophenyl)-2-(4,5-dimethoxy-2-nitrophenyl) ethanol (**20**).* Brown solid. Yield, 39%. Mp 131 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.45–7.18 (m, 4H), 6.58 (s, 1H), 5.10–5.03 (m, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 3.45 (dd, 1H, $J$ = 13.4, 4.2), 3.32 (dd, 1H, $J$ = 13.5, 8.3), 2.88 (d, 1H, $J$ = 2.8). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.7, 147.8, 146.2, 141.6, 130.7, 130.1, 128.8, 128.1, 124.5, 122.6, 120.1, 114.9, 108.2, 73.4, 56.3, 43.6. Anal ($C_{16}H_{16}BrNO_5$) C, H, N.




[a] All yields refer to the chromatographically isolate products and are relative to substrate.
[b] Reagents and Conditions: (i) Reaction was performed with 35 equiv of Fe, acetic acid, 115 °C, 0.5h; (ii) $H_3PO_2$, 100 °C; 1 equiv of $NaNO_2$, -15 °C; 0 °C 0.75 h, 15% of **59** and 10% of **60**.

**Scheme 7.** Impact of the C-2 group on biological activity.[a,b]

**Table 6**
SAR: C-2 group influence.[a,b]

| No | Code | Structure | Yield | $CC_{50}$ | $EC_{50}$ | $EC_{90}$ |
|---|---|---|---|---|---|---|
| **59** | OM1606 |  | 15% | ND | >294 | >294 |
| **60** | OM1613 |  | 10% | >353 | 96.2 ± 17.8 | >353 |

ND = not determined.
$CC_{50}$ = 50% Cytostatic/Cytotoxic Concentration (concentration at which 50% adverse effect is observed on the host cell).
$EC_{50}$ = 50% Effective Concentration (concentration at which 50% inhibition of virus replication is observed).
$EC_{90}$ = 90% Effective Concentration (concentration at which 90% inhibition of virus replication is observed).
[a] All values are in μM, expressed as median ± Med. Abs. Dev.
[b] In assay conditions: Pleconaril $EC_{50}$ = 0.2 ± 0.1 μM; Pleconaril $CC_{50}$ = 50.2 ± 5 μM.

*4.1.1.14. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(2-fluorophenyl)ethanol (**21**).* Yellow solid. Yield, 85%. Mp 94 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.50–7.42 (m, 1H), 7.32–7.11 (m, 2H), 7.06–6.96 (m, 1H), 6.48 (s, 1H), 5.42–5.34 (m, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.46 (d, 1H, $J$ = 1.88), 3.32 (s, 1H), 2.58 (d, 1H, $J$ = 3.7). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 159.8 (C, d, $J$ = 245), 152.6, 147.6, 142.1, 130.6 (CH, d, $J$ = 13.0), 129.2 (d, CH, $J$ = 8.4), 127.7, 127.6 (d, CH, $J$ = 8.4), 124.7 (d, CH, $J$ = 3.66), 115.3 (d, CH, $J$ = 21.6), 114.5, 108.1, 68.8, 56.3, 41.4. Anal ($C_{16}H_{16}FNO_5$) C, H, N.

*4.1.1.15. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(3-fluorophenyl)ethanol (**22**).* Yellow solid. Yield 85%. Mp 91 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.3–7.29 (m, 1H), 7.19–7.14 (m, 2H), 7.02–6.93 (m, 1H), 6.57 (s, 1H), 5.10–5.06 (m, 1H), 3.94 (s, 3H), 3.85 (s, 3H), 3.45 (dd, 1H, $J$ = 13.3, 4.3), 3.32 (dd, 1H, $J$ = 13.3, 8.3), 2.94 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 163.0 (d, C, $J$ = 246.2), 152.8, 147.7, 146.6 (d, C, $J$ = 6.59), 141.7, 130.0 (d, CH, $J$ = 8.41), 128.2, 121.5 (d, CH, $J$ = 2.9), 114.9, 114.5 (d, CH, $J$ = 21.2), 112.7 (d, CH, $J$ = 21.9), 108.2, 73.6, 56.3, 43.6. Anal ($C_{16}H_{16}FNO_5$) C, H, N.

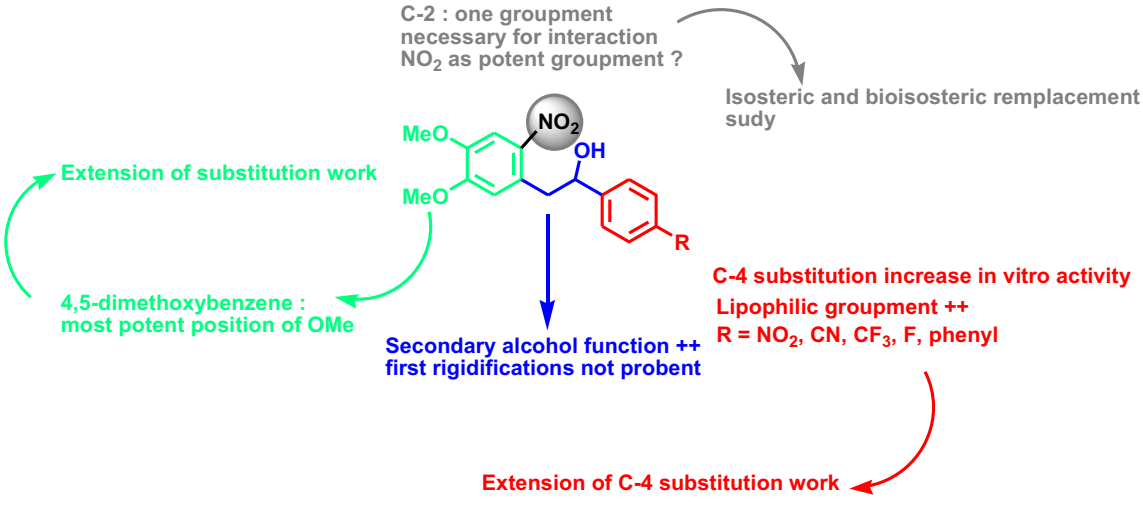
*4.1.1.16. 4-[2-(4,5-Dimethoxy-2-nitrophenyl)-1-hydroxy-ethyl]benzonitrile (**23**).* Yellow solid. Yield, 81%. Mp (recrystallized from ethanol) 159 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, 2H, $J$ = 8.4), 7.58 (s, 1H), 7.52 (d, 2H, $J$ = 8.4), 6.60 (s, 1H), 5.10 (dd, 1H, $J$ = 8.6, 3.6), 3.90 (s, 3H), 3.87 (s, 3H), 3.47 (dd, 1H, $J$ = 13.4, 3.6), 3.03 (dd, 1H, $J$ = 13.4, 8.6), 2.47 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.8, 149.2, 147.9, 141.5, 132.3, 127.8, 126.4, 118.7, 114.9, 111.3, 108.2, 73.3, 56.4, 56.3, 43.7. Anal ($C_{17}H_{16}N_2O_5$) C, H, N.

*4.1.1.17. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-[4-(trifluoromethyl) phenyl]ethanol (**24**).* Brown oil. Yield, 85%. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.62–7.48 (m, 5H), 6.50 (s, 1H), 5.12 (dd, 1H, $J$ = 8.1, 4.2), 3.91 (s, 3H), 3.80 (s, 3H), 3.44 (dd, 1H, $J$ = 13.1, 4.2), 3.1 (dd, 1H, $J$ = 13.1, 8.1), 2.48 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.7, 147.8, 147.7, 141.5, 129.4 (q, C, $J$ = 75.0), 128.0, 126.0, 125.3 (q, 2CH, $J$ = 3.7), 124.1 (q, $CF_3$, $J$ = 271.9), 114.9, 108.1, 73.4, 56.2, 43.6. Anal ($C_{17}H_{16}F_3NO_5$) C, H, N.

*4.1.1.18. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(4-fluorophenyl)ethanol (**25**).* Brown solid. Yield, 62%. Mp 113 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.38–7.31 (m, 2H), 7.07–6.98 (m, 2H), 6.54 (s, 1H), 5.03 (dd, 1H, $J$ = 8.0, 4.5), 3.92 (s, 3H), 3.83 (s, 3H), 3.38 (dd, 1H, $J$ = 13.4, 4.5), 3.14 (dd, 1H, $J$ = 13.4, 8.0). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 162.2 (d, C, $J$ = 245.5), 152.6, 147.6, 141.6, 139.6, 128.3, 127.4 (d, 2CH, $J$ = 8.0), 115.2 (d, 2CH, $J$ = 21.2), 114.9, 108.1, 73.5, 56.2, 43.7. Anal ($C_{16}H_{16}FNO_5$) C, H, N.

*4.1.1.19. 1,2-Bis(4,5-dimethoxy-2-nitrophenyl)ethanol (**26**).* Brown solid. Yield, 49%. Mp 194 °C (dec). $^1$H NMR (200 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.50 (s, 1H), 7.34 (s, 1H), 7.03 (s, 1H), 5.70 (dd, 1H, $J$ = 8.9, 3.0), 4.01 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.95 (s, 3H), 3.52 (dd, 1H, $J$ = 13.9, 8.9), 3.30 (dd, 1H, $J$ = 5.0, 3.0). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.9, 153.2, 148.0, 147.8, 142.7, 139.4, 135.5, 127.9, 113.6, 109.2, 108.1, 107.8, 71.5, 56.5, 56.4, 56.3, 40.2. Anal ($C_{18}H_{20}N_2O_9$) C, H, N.

*4.1.1.20. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(pyridin-4-yl)ethanol (**27**).* Yellow solid. Yield, 86%. Mp 191 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.60–8.59 (m, 2H), 7.65 (s, 1H), 7.38 (d, 2H, $J$ = 5.4), 6.58 (s, 1H), 5.21 (dd, 1H, $J$ = 8.7, 3.9), 3.96 (s, 3H), 3.87 (s, 3H), 3.53 (dd, 1H, $J$ = 13.4, 3.9), 3.06 (dd, 1H, $J$ = 13.4, 8.7). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.8, 149.8, 147.9, 141.6, 127.8, 120.8, 114.9, 108.3, 72.7, 56.4, 43.4. Anal ($C_{15}H_{16}N_2O_5$) C, H, N.




**Scheme 8.** SAR Guidelines.

**Table 7**
Broad spectrum hRV activities.

| $EC_{50}$ (μM) median ± Med. Abs. Dev. | Human rhinovirus A | | | | | | | | | Human rhinovirus B | | | | | $CC_{50}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A2 | A9 | A15 | A29 | A41 | A59 | A63 | A85 | A89 | B14 | B42 | B70 | B72 | B86 | |
| **11** | >296 | >148 | >148 | >148 | >148 | >148 | >148 | >148 | >148 | 10 ± 0.2 | >148 | >148 | 7 ± 4 | 11 ± 2 | 75 ± 2 |
| **12** | >262 | >131 | >131 | >131 | >131 | >131 | >131 | >131 | >131 | 6 ± 0.6 | >131 | 25 ± 0.1 | 17 ± 2 | 8 ± 0.2 | 66 ± 0 |
| **13** | >132 | >132 | >132 | >132 | >44 | >44 | >44 | >44 | >132 | 2 ± 0.1 | >44 | >132 | 1 ± 0.2 | 1 ± 0.4 | 10 ± 1 |
| **14** | >286 | >143 | >143 | >143 | >143 | ND | >143 | >143 | >143 | 3 ± 0.7 | >143 | ND | 10 ± 1 | 9 ± 0.4 | 72 ± 9 |
| **27** | >329 | 108 ± 4 | >164 | ND | 53 ± 2 | 11 ± 4 | 26 ± 10 | >164 | >164 | 59 ± 3 | >164 | >164 | 22 ± 6 | >55 | 171 ± 44 |
| **17** | >287 | 15 ± 1 | >144 | >287 | >144 | >144 | ND | >144 | >144 | 16 ± 3 | >144 | >144 | 59 ± 16 | >144 | 380 ± 0 |
| **18** | >152 | 53 ± 2 | >152 | 85 ± 3 | >152 | >51 | >152 | >152 | >152 | 29 ± 7 | >152 | >152 | 76 ± 3 | 111 ± 2 | 144 ± 51 |
| **20** | >131 | >131 | >131 | >262 | >131 | >131 | >131 | >131 | >131 | 28 ± 3 | >131 | >131 | 33 ± 5 | 10 ± 5 | 52 ± 13 |
| **22** | >156 | >156 | 37 ± 8 | >156 | >156 | ND | ND | >156 | >156 | 43 ± 1 | >156 | >156 | >52 | >156 | 135 ± 41 |
| **23** | ND | 41 ± 9 | >152 | >152 | >152 | 6 ± 2 | 9 ± 3 | >152 | >152 | 2 ± 0.6 | >152 | 46 ± 2 | 7 ± 0.5 | 4 ± 0.8 | 116 ± 23 |
| **6** | ND | 42 ± 3 | >144 | >287 | >144 | >287 | 20 ± 3 | >144 | >144 | 4 ± 1 | >144 | 66 ± 1 | 7 ± 0.1 | 7 ± 1 | 95 ± 12 |
| **24** | >135 | >135 | >135 | ND | >135 | >135 | >135 | >135 | >135 | 2 ± 0.1 | >135 | ND | 8 ± 5 | 3 ± 1 | 51 ± 17 |
| **25** | >156 | >52 | >156 | ND | >156 | >156 | >156 | >156 | >156 | 60 ± 9 | >156 | >156 | 81 ± 4 | >52 | 104 ± 11 |

*4.1.1.21. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(pyridin-3-yl)ethanol (**28**).* Yellow solid. Yield, 33%. Mp 150 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.60–8.59 (m, 1H), 8.49–8.47 (m, 1H), 7.77–7.73 (m, 1H), 7.62 (s, 1H), 7.31–7.29 (m, 1H), 6.59 (s, 1H), 5.12 (dd, 1H, $J$ = 8.4, 4.2), 3.93 (s, 3H), 3.86 (s, 3H), 3.45 (dd, 1H, $J$ = 13.3, 4.2), 3.06 (dd, 1H, $J$ = 13.3, 8.4). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.8, 148.9, 147.8, 147.6, 141.6, 139.3, 133.6, 128.0, 123.4, 114.9, 108.2, 71.9, 56.4, 43.7. Anal ($C_{15}H_{16}N_2O_5$) C, H, N.

*4.1.1.22. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(pyridin-2-yl)ethanol (**29**).* Brown solid. Yield, 70%. Mp 196 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.57–8.84 (m, 1H), 7.74–7.63 (m, 1H), 7.61 (s, 1H), 7.42–7.38 (m, 1H), 7.24–7.20 (m, 1H), 6.76 (s, 1H), 5.08 (dd, 1H, $J$ = 8.3, 3.2), 3.92 (s, 3H), 3.89 (s, 3H), 3.45 (dd, 1H, $J$ = 13.3, 3.2), 3.06 (dd, 1H, $J$ = 13.3, 8.3), 2.78 (s, 1H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 160.9, 152.7, 148.1, 147.6, 141.4, 136.9, 129.0, 122.7, 121.0, 115.1, 108.1, 72.6, 56.3, 43.3. Anal ($C_{15}H_{16}N_2O_5$) C, H, N.

*4.1.1.23. Ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-2-hydroxypropanoate (**30**).* Yellow solid. Yield, 85%. Mp 102 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.83 (s, 1H), 4.51 (dd, 1H, $J$ = 9.1, 4.5), 4.23 (q, 2H, $J$ = 7.4), 3.96 (s, 3H), 3.94 (s, 3H), 3.60 (dd, 1H, $J$ = 13.6, 4.5), 3.15 (dd, 1H, $J$ = 13.6, 9.1), 1.30 (t, 3H, $J$ = 7.4). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 174.2, 152.7, 147.8, 141.7, 126.9, 114.6, 108.2, 70.3, 62.1, 56.3, 37.9, 14.1. Anal ($C_{13}H_{17}NO_7$) C, H, N.

*4.1.1.24. Diethyl 2-(4,5-dimethoxy-2-nitrobenzyl)-2-hydroxymalonate (**31**).* Yellow solid. Yield, 72%. Mp 102 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.44 (s, 1H), 6.96 (s, 1H), 4.22 (q, 4H, $J$ = 7.2), 3.92 (s, 3H), 3.91 (s, 3H), 3.83 (m, 3H), 1.27 (t, 6H, $J$ = 7.2). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 169.7, 151.9, 147.8, 143.3, 123.7, 114.8, 108.0, 78.7, 63.0, 56.3, 56.2, 35.5, 13.9. Anal ($C_{16}H_{21}NO_9$) C, H, N.

*4.1.1.25. Ethyl 3-(4,5-dimethoxy-2-nitrophenyl)-2-hydroxy-2-methylpropanoate (**32**).* Brown semi-solid. Yield, 59%. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.87 (s, 1H), 4.15 (q, 2H, $J$ = 6.9), 3.93 (s, 3H), 3.91 (s, 3H), 3.57 (d, 1H, $J$ = 13.9), 3.38 (d, 1H, $J$ = 13.9), 1.46 (s, 3H), 1.27 (t, 3H, $J$ = 6.9). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 176.0, 151.9, 147.6, 142.9, 125.2, 114.6, 108.0, 74.8, 62.3, 56.2, 40.7, 26.1, 14.0. Anal ($C_{14}H_{19}NO_7$) C, H, N.

*4.1.1.26. 4-(1-(4,5-Dimethoxy-2-nitrophenyl)-2-hydroxypropan-2-yl)benzonitrile (**33**).* Brown solid. Yield, 78%. Mp 136 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.60 (d, 2H, $J$ = 8.6), 7.52 (d, 2H, $J$ = 8.6), 7.46 (s, 1H), 6.18 (s, 1H), 3.89 (s, 3H), 3.72 (d, 1H, $J$ = 13.8), 3.64 (s, 3H), 3.20 (d, 1H, $J$ = 13.8), 2.71 (s, 1H), 1.65 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.5, 152.0, 147.6, 142.9, 131.9, 126.1, 125.9, 118.6, 114.5, 110.6, 108.0, 75.2, 56.2, 56.0, 45.5, 30.0. HRMS $m/z$ calcd for $C_{18}H_{18}N_2O_5$, 360.1554 (M + Na); found: 360.1555.

*4.1.1.27. 1-(4,5-Dimethoxy-2-nitrophenyl)-2-(4-nitrophenyl)propan-2-ol (**34**).* Brown solid. Yield 34%. Mp 116 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.18 (d, 2 H, $J$ = 8.5), 7.61 (d, 2H, $J$ = 8.5), 7.50 (s, 1H), 6.23 (s, 1H), 3.92 (s, 3H), 3.75 (d, 1H, $J$ = 13.8), 3.65 (s, 3H), 3.26 (d, 1H, $J$ = 13.8), 2.89 (s, 1H), 1.7 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.5, 152.2, 147.7, 146.8, 142.9, 126.3, 125.9, 123.3, 114.5, 108.2, 75.2, 56.3, 56.1, 45.6, 30.2. Anal ($C_{17}H_{18}N_2O_7$) C, H, N.

*4.1.1.28. (E)-1,2-Dimethoxy-4-nitro-5-(4-nitrostyryl)benzene (**38**).* Yellow solid, Yield, 65%. Mp 186 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, 2H, $J$ = 8.7), 7.93 (d, 1H, $J$ = 16.1), 7.67 (d, 2H, $J$ = 8.7), 7.66 (s, 1H), 7.08 (s, 1H), 6.98 (d, 1H, $J$ = 16.1), 4.05 (s, 3H), 3.99 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.3, 149.1, 147.3, 143.1, 140.7, 129.8, 129.5, 127.4, 127.2, 124.2, 109.5, 108.0, 56.5. HRMS $m/z$ calcd for $C_{16}H_{14}N_2O_6$, 331.025 (M + H); found: 331.0924.

*4.1.1.29. trans-2-(4-Bromophenyl)-3-(4,5-dimethoxy-2-nitrophenyl) oxirane (**44**).* Yellow solid. Yield, 52%. Mp 153 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.54 (d, 2H, $J$ = 8.2), 7.31 (d, 2H, $J$ = 8.2), 7.14 (s, 1H), 4.50 (d, 1H, $J$ = 1.7), 4.02 (s, 3H), 3.98 (s, 3H), 3.74 (d, 1H, $J$ = 1.7). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.3, 148.4, 135.3, 131.8, 129.3, 128.7, 127.5, 122.6, 108.0, 107.8, 61.5, 60.5, 56.6, 56.5. Anal ($C_{16}H_{14}BrNO_5$) C, H, N.

*4.1.1.30. trans-4-(3-(4,5-Dimethoxy-2-nitrophenyl)oxiran-2-yl)benzonitrile (**45**).* Yellow solid. Yield, 40%. Mp 188 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.71 (d, 2H, $J$ = 8.2), 7.52 (d, 2H, $J$ = 8.2), 7.14 (s, 1H), 4.47 (d, 1H, $J$ = 1.6), 4.02 (s, 3H), 3.98 (s, 3H), 3.84 (d, 1H, $J$ = 1.7). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.3, 148.6, 141.7, 139.9, 132.5, 128.1, 126.4, 118.6, 112.3, 108.0, 107.8, 61.1, 61.0, 56.6, 56.5. Anal ($C_{17}H_{14}N_2O_5$) C, H, N.

*4.1.1.31. trans-2-(4,5-Dimethoxy-2-nitrophenyl)-3-(4-nitrophenyl) oxirane (**46**).* Yellow solid. Yield, 58%. Mp 202 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.28 (d, 2H, $J$ = 8.2), 7.77 (s, 1H), 7.58 (d, 2H, $J$ = 8.2), 7.15 (s, 1H), 4.49 (d, 1H, $J$ = 1.6), 4.03 (s, 3H), 3.99 (s, 3H), 3.88 (d, 1H, $J$ = 1.6). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.4, 148.7, 148.1, 143.6, 139.9, 128.0, 126.6, 123.9, 108.9, 107.8, 61.1, 60.8, 56.6, 56.5. Anal ($C_{16}H_{14}N_2O_7$) C, H, N.

*4.1.1.32. trans-2-(4-Chlorophenyl)-3-(4,5-dimethoxy-2-nitrophenyl) oxirane (**47**).* Yellow solid. Yield, 40%. Mp 146 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.37 (m, 4H), 7.14 (s, 1H), 4.50 (d, 1H, $J$ = 1.8), 4.02 (s, 3H), 3.98 (s, 3H), 3.75 (d, 1H, $J$ = 1.8). $^{13}$C NMR

(50 MHz, $CDCl_3$) δ 154.3, 148.4, 134.8, 134.4, 128.9, 128.7, 127.2, 108.1, 107.8, 61.4, 60.5, 56.6, 56.5. Anal ($C_{16}H_{14}ClO_5$) C, H, N.

*4.1.1.33. trans-2-(4,5-Dimethoxy-2-nitrophenyl)-3-(3-nitrophenyl) oxirane (**48**).* Brown solid. Yield, 40%. Mp 175 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.28–8.21 (m, 2H), 7.77 (s, 1H), 7.63–7.55 (m, 2H), 7.15 (s, 1H), 4.53 (d, 1H, *J* = 1.8), 4.03 (s, 3H), 3.99 (s, 3H), 3.88 (d, 1H, *J* = 1.8). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.4, 148.6, 140.0, 138.7, 131.8, 129.7, 128.1, 123.5, 120.8, 108.1, 107.8, 61.0, 60.7, 56.6, 56.5. Anal ($C_{16}H_{14}N_2O_7$) C, H, N.

*4.1.1.34. trans-2-(2-Bromophenyl)-3-(4,5-dimethoxy-2-nitrophenyl) oxirane (**49**).* Yellow solid. Yield, 38%. Mp 162 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.61–7.57 (m, 1H), 7.41–7.37 (m, 2H), 7.23 (s, 1H), 7.18 (s, 1H), 4.52 (m, 1H), 4.07 (m, 1H), 4.03 (s, 3H), 3.98 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 154.2, 148.4, 140.2, 135.6, 132.6, 129.7, 128.4, 127.7, 126.1, 123.1, 108.1, 108.0, 61.7, 60.2, 56.6, 56.5. Anal ($C_{16}H_{14}BrNO_5$) C, H, N.

*4.1.2. Procedure for chlorination of linker hydroxyl group*

To a solution of products **13**, **23**, **6** or **27** in dichloromethane (10 mL), 3 equiv of thionyl chloride was added slowly at 0 °C. The mixture was stirred at 50 °C for 4 h. After this time TLC analysis (dichloromethane) clearly showed that the diarylethanol was totally consumed. Solution was neutralized with $Na_2CO_3$ solution and the organic phase, after washing with brine was dried with $MgSO_4$. Purification by silica gel led to corresponding chloride products.

*4.1.2.1. 1-(2-Chloro-2-(4-nitrophenyl)ethyl)-4,5-dimethoxy-2-nitrobenzene (**50**).* Brown solid. Yield, 95%. Mp 144 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.24 (d, 2H, *J* = 8.7), 7.68 (s, 1H), 7.66 (d, 2H, *J* = 8.7), 6.70 (s, 1H), 5.34 (dd, 1H, *J* = 9.4, 4.3), 3.95 (s, 3H), 3.90 (s, 3H), 3.77 (dd, 1H, *J* = 13.8, 4.3), 3.04 (dd, 1H, *J* = 13.8, 9.4). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.0, 148.3, 148.1, 147.7, 141.1, 127.9, 126.9, 123.9, 115.4, 108.3, 58.3, 56.4, 56.3, 44.8. Anal ($C_{16}H_{15}ClN_2O_6$) C, H, N.

*4.1.2.2. 4-(1-Chloro-2-(4,5-dimethoxy-2-nitrophenyl)ethyl)biphenyl (**51**).* Brown solid. Yield, 87%. Mp 112 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.61–7.36 (m, 9H), 6.58 (s, 1H), 5.30 (dd, 1H, *J* = 5.6, 8.3), 3.94 (s, 3H), 3.82 (s, 3H), 3.72 (dd, 1H, *J* = 13.6, 5.6), 3.55 (dd, 1H, *J* = 13.6, 8.3). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.7, 147.0, 141.5, 141.4, 140.5, 140.2, 128.9, 127.8, 127.5, 127.4, 127.1, 115.4, 108.2, 62.6, 56.3, 44.9. Anal ($C_{22}H_{20}ClNO_4$) C, H, N.

*4.1.2.3. 4-(1-Chloro-2-(4,5-dimethoxy-2-nitrophenyl)ethyl)benzonitrile (**52**).* Brown solid. Yield, 90%. Mp 140 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.65 (d, 2H, *J* = 8.2), 7.65 (s, 1H), 7.57 (d, 2H, *J* = 8.2), 6.63 (s, 1H), 5.31–5.24 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.70 (dd, 1H, *J* = 14.0, 5.0), 3.35 (dd, 1H, *J* = 14.0, 9.0). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.0, 148.3, 146.2, 141.1, 132.5, 127.8, 127.0, 118.4, 115.4, 112.2, 108.3, 61.7, 56.4, 44.8. Anal ($C_{17}H_{15}ClN_2O_4$) C, H, N.

*4.1.2.4. 4-(1-Chloro-2-(4,5-dimethoxy-2-nitrophenyl)ethyl)pyridine (**53**).* Brown semi-solid. Yield, 85%. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.60 (d, 2H, *J* = 6.0), 7.66 (s, 1H), 7.39 (d, 2H, *J* = 6.0), 6.60 (s, 1H), 5.21 (dd, 1H, *J* = 9.0, 4.6), 3.92 (s, 3H), 3.86 (s, 3H), 3.7 (dd, 1H, *J* = 13.6, 4.6), 3.32 (dd, 1H, *J* = 13.6, 9.0). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 162.4, 152.8, 150.0, 148.2, 141.1, 126.8, 121.7, 115.3, 108.2, 60.8, 56.3, 44.6. Anal ($C_{15}H_{15}ClN_2O_4$) C, H, N.

*4.1.3. Procedure of azide derivative formation*

Ten equivalents of natrium azide were added to a solution of chloride derivative **50** or **52** in ethanol (20 mL). The mixture was heated to 60 °C and was stirred for 24 h. After this time, TLC analysis (dichloromethane) clearly showed that the diarylethanol was totally consumed. Solvent evaporation led to a brown product. The residue was solubilized with dichloromethane (10 mL) and washed with saturated NaCl (20 mL) and dried with $MgSO_4$. Purification by flash column chromatography using $CH_2Cl_2$ gave 100 mg of corresponding azido derivative **54** (37%) or **55** (30%).

*4.1.3.1. 1-[Azido-2-(4-nitrophenyl)ethyl]-4,5-dimethoxy-2-nitrobenzene (**54**).* Yellow semi-solid. Yield, 37%. $^1$H NMR (200 MHz, $CDCl_3$) δ 8.25 (d, 2H, *J* = 8.7), 7.70 (s, 1H), 7.68 (d, 2H, *J* = 8.7), 6.70 (s, 1H), 5.35 (dd, 1H, *J* = 9.4, 4.3), 3.96 (s, 3H), 3.92 (s, 3H), 3.77 (dd, 1H, *J* = 13.8, 4.3), 3.04 (dd, 1H, *J* = 13.8, 9.4). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.1, 148.2, 148.0, 146.8, 141.1, 127.6, 127.1, 124.0, 115.0, 108.4, 65.5, 56.4, 41.9. HRMS *m*/*z* calcd for $C_{16}H_{15}N_5O_6$, 391.1361 (M + Na); found: 391.1361.

*4.1.3.2. 4-[1-Azido-2-(4,5-dimethoxy-2-nitrophenyl)ethyl]benzonitrile (**55**).* Yellow solid. Yield, 30%. 99 °C (dec). $^1$H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, 2H, *J* = 8.3), 7.66 (s, 1H), 7.50 (d, 2H, *J* = 8.3), 6.60 (s, 1H), 5.12 (dd, 1H, *J* = 9.1, 4.4), 3.93 (s, 3H), 3.89 (s, 3H), 3.40 (dd, 1H, *J* = 13.3, 4.4), 3.05 (dd, 1H, *J* = 13.3, 9.2). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.0, 148.2, 144.8, 141.1, 132.6, 127.3, 127.0, 118.3, 115.0, 112.1, 108.3, 65.7, 56.4, 56.3, 41.9. HRMS *m*/*z* calcd for $C_{17}H_{15}N_5O_4$, 371.1462 (M + $NH_4$); 371.1466.

*4.1.4. Synthesis of amino derivative **56***

One equivalent of $PPh_3$ was added to a solution of azido derivative **54** in THF (10 mL). Then distillate water (2 mL) was added. The reaction mixture was stirred at 70 °C over 24 h. After this time, TLC analysis (dichloromethane) clearly showed that the formation of amino derivative. The concentrate was treated with saturated NaCl solution (20 mL) and was extracted with dichloromethane (3 × 10 mL). The aqueous layer basified with 2 M NaOH (2 mL), and extracted with EtOAc (10 mL) and was dried with $MgSO_4$. Solvent was removed *in vacuo*, providing 120 mg of **56** (20%) as yellow oil.

*4.1.4.1. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanamine (**56**).* Yellow solid. Yield, 20%. 190 °C (dec). $^1$H NMR (200 MHz, $CDCl_3$) δ 8.17 (d, 2H, *J* = 8.7), 7.65 (s, 1H), 7.55 (d, 2H, *J* = 8.7), 6.47 (s, 1H), 4.49–4.43 (m, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.35 (dd, 1H, *J* = 13.1, 5.5), 3.04 (dd, 1H, *J* = 13.1, 7.94), 1.93 (bs, 2H). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 152.8, 152.6, 147.8, 147.2, 141.3, 131.9, 128.4, 127.4, 123.7, 114.5, 108.5, 56.3, 55.8, 44.3. HRMS *m*/*z* calcd for $C_{16}H_{17}N_3O_6$, 348.1190 (M + H); found: 348.1189.

*4.1.5. Synthesis of fluoro compound **57***

To a solution of 1.5 equiv of $N(Et)_2SF_3$ in dichloromethane (10 mL) under nitrogen atmosphere, 1 equiv of product **23** was added slowly at 0 °C using a syringe. The mixture was stirred at rt for 15 min. After this time, TLC analysis (dichloromethane) clearly showed that the diarylethanol was totally consumed. Solution was neutralized with $Na_2CO_3$ solution and the organic phase, after washing with brine was dried with $MgSO_4$. Purification by flash silica gel using $CH_2Cl_2$ gave 90 mg of corresponding fluorinate derivative **57** (90%).

*4.1.5.1. 4-[2-(4,5-Dimethoxy-2-nitrophenyl)-1-fluoroethyl]benzonitrile (**57**).* Yellow solid. Yield, 90%. Mp 152 °C. $^1$H NMR (200 MHz, $CDCl_3$) δ 7.72–7.64 (m, 3H), 7.56 (d, 2H, *J* = 8.5), 6.73 (s, 1H), 5.12 (dd, 1H, *J* = 9.2, 2.5), 3.96 (s, 6H), 3.65 (dd, 1H, *J* = 14.2, 2.5), 3.05 (dd, 1H, *J* = 14.2, 9.2). $^{13}$C NMR (50 MHz, $CDCl_3$) δ 153.1, 148.2, 145.2, 144.7, 141.2, 129.9 (d, CH, *J* = 296.4), 129.5 (d, CH, *J* = 81.2), 132.4, 126.7, 125.6 (d, CH, *J* = 8.0), 115.3 (d, C, *J* = 313.9), 111.6 (d, CH, *J* = 336.6), 108.8 (d, CH, *J* = 73.9), 92.9 (d, CH, *J* = 176.0), 56.4, 42.4

(d, $CH_2$, $J$ = 23.1). HRMS $m/z$ calcd for ($C_{17}H_{15}FN_2O_4$), 353.0908 (M + Na); found: 353.0910.

#### 4.1.6. Synthesis of sulfonyl compound **58**

Two equivalents of methane sulfonyl chloride and 1 equiv of pyridine was added to a solution of diarylethanol derivative **23** in chloroform (20 mL). The mixture was heated to 60 °C and was stirred for 48 h. After this time, TLC analysis (dichloromethane) clearly showed the formation of sulfonyl derivative. Solvent evaporation led to a brown product. The concentrate was washed with saturated NaCl solution (20 mL) and was extracted with dichloromethane (3 × 10 mL). Solvent was removed *in vacuo*, purification by flash column chromatography using $CH_2Cl_2$ gave 90 mg of corresponding sulfonyl derivative **58** (25%).

*4.1.6.1. 1-(4-Cyanophenyl)-2-(4,5-dimethoxy-2-nitrophenyl)ethyl methanesulfonate (**58**).* Yellow solid. Yield, 25%. Mp 134 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.70 (d, 2H, $J$ = 8.3), 7.66 (s, 1H), 7.60 (d, 2H, $J$ = 8.3), 6.65 (s, 1H), 5.34–5.27 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.74 (dd, 1H, $J$ = 13.7, 4.4), 3.05 (dd, 1H, $J$ = 13.7, 9.2), 3.00 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 152.9, 148.3, 146.2, 141.2, 132.6, 127.8, 127.0, 118.4, 115.4, 112.3, 108.4, 66.2, 56.4, 56.3, 44.8, 37.5. HRMS $m/z$ calcd for ($C_{18}H_{18}N_2O_7S$), 429.0726 (M + Na); found: 429.0727.

#### 4.1.7. Synthesis of carbonyl derivative **40**

A solution of $CrO_3$ (3 equiv) in $H_2SO_4$ (10 equiv) was added slowly to a solution of diarylethanol derivative **23** (1 equiv) in acetone (20 mL). The mixture was stirred for 0.5 h at rt. After this time, TLC analysis (dichloromethane) clearly showed that the diarylethanol was totally consumed. The solution was extracted with dichloromethane (3 × 10 mL) and was washed with saturated NaCl solution (20 mL). The organic phase was dried with $MgSO_4$. Solvent was removed *in vacuo*, purification by flash column chromatography using $CH_2Cl_2$ gave 150 mg of corresponding **40** (80%).

*4.1.7.1. 2-(4,5-Dimethoxy-2-nitrophenyl)-1-(4-nitrophenyl)ethanone (**40**).* Yellow solid. Yield, 10%. Mp 190 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.12 (d, 2H, $J$ = 8.2), 7.81 (d, 2H, $J$ = 8.2), 7.78 (s, 1H), 6.73 (s, 1H), 4.65 (s, 2H), 3.93 (s, 6H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 194.7, 153.5, 148.4, 140.8, 139.7, 132.6, 128.6, 124.8, 117.9, 116.6, 114.9, 108.6, 56.4, 44.7. HRMS $m/z$ calcd for ($C_{17}H_{14}N_2O_5$), 327.0975 (M + H); found: 327.76.

#### 4.1.8. Formation of products **59** and **60**

Thirty five equivalents of iron were added to a solution of diarylethanol derivative **23** (1.52 mol) in acetic acid (20 mL). The mixture was heated to 115 °C and was stirred for 0.5 h. Solvent evaporation led a brown product. This product was dissolved in 1.5 mL of $H_3PO_2$ at 100 °C, then, 1 equiv of $NaNO_2$ was added at −15 °C. The mixture was stirred at 0 °C for 0.75 h. The solution was extracted with dichloromethane (3 × 10 mL) and was washed with saturated NaCl solution (20 mL). The organic phase was dried with $MgSO_4$. Solvent was removed *in vacuo*, purification by flash column chromatography using $CH_2Cl_2$ gave 65 mg of derivative **59** (15%) and 52 mg of corresponding amido derivative **60** (10%).

*4.1.8.1. N-[2-(2-(4-Cyanophenyl)-2-hydroxyethyl)-4,5-dimethoxyphenyl]acetamide (**59**).* Brown solid. Yield, 10%. Mp 76 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 8.83 (s, 1H), 7.54 (d, 2H, $J$ = 8.1), 7.33 (d, 2H, $J$ = 8.1), 7.14 (s, 1H), 6.27 (s, 1H), 4.93 (dd, 1H, $J$ = 7.4, 3.5), 3.74 (s, 3H), 3.65 (s, 3H), 2.85 (dd, 1H, $J$ = 14.4, 3.5), 2.73 (dd, 1H, $J$ = 14.4, 7.4), 2.06 (s, 3H). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 169.3, 149.3, 147.6, 146.2, 132.0, 129.8, 129.5, 126.3, 126.1, 122.2, 118.6, 113.3, 110.9, 108.5, 75.1, 56.0, 41.0, 23.9. HRMS for $C_{19}H_{20}N_2O_4$ $[M + H]^+$ = 341.1496. Found: $[M + H]^+$ = 341.1497.

*4.1.8.2. 4-[2-(3,4-Dimethoxyphenyl)-1-hydroxyethyl]benzonitrile (**60**).* Yellow solid. Yield, 15%. Mp 100 °C. $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 7.62 (d, 2H, $J$ = 8.4), 7.44 (d, 2H, $J$ = 8.4), 6.82 (d, 1H, $J$ = 8.2), 6.70 (dd, 1H, $J$ = 8.2, 1.8), 6.60 (d, 2H, $J$ = 1.8), 4.92 (dd, 1H, $J$ = 8.2, 5.0), 3.86 (s, 3H), 3.82 (s, 3H), 2.98 (dd, 1H, $J$ = 13.7, 5.0), 2.84 (dd, 1H, $J$ = 13.7, 8.2). $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 149.0, 148.0, 132.1, 129.1, 126.6, 121.5, 118.8, 112.5, 111.3, 111.1, 74.4, 55.8, 45.6. HRMS $m/z$ calcd for ($C_{16}H_{17}NO_5$), 301.1547 (M + Na); found: 301.1547.

### 4.2. Biology

#### 4.2.1. Cells and virus

HeLa Rh cells were grown in MEM Rega3 (Gibco) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Integro), 2 mM L-glutamine (Gibco) and 0.075% $NaHCO_3$ (Gibco). Cells were grown at 37 °C in a 5% $CO_2$ incubator at 95–99% relative humidity. Human Rhinoviruses (HRV 2, HRV 9, HRV 15, HRV 29, HRV 41, HRV 59, HRV 63, HRV 85 and HRVA89 from HRV clade A; HRV 14, HRV 42, HRV 70, HRV 72 and HRV 86 from HRV clade B), kindly provided by K. Andries (Janssen Pharmaceutica, Beerse, Belgium), were cultivated in HeLa Rh cells in the presence of 30 mM $MgCl_2$.

#### 4.2.2. Virus-cell-based antiviral assay

The antiviral activity of the synthesized compounds was evaluated in an MTS [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium]-based live virus-cell-based assay. In this assay, the (residual) metabolic activity of treated, infected cells is quantified which is representative for cell survival or reduction of virus-induced cytopathic effects (CPE), and thus the antiviral effect of a compound. Rhinovirus assays were performed in 96-well plate format, using MEM Rega3 supplemented with 2% FBS, 2 mM L-glutamine, 0.075% $NaHCO_3$ and 30 mM $MgCl_2$. Briefly, a serial dilution of the compound was added to cells grown to confluence in 96-well microtiter plates, followed by infection with a virus inoculum containing as few infectious virus particles as possible that still causes 100% cytopathic effect after the desired incubation time (this was determined in advance by titration of the available virus stock). The cultures were incubated for 3 days at 35 °C until complete CPE was observed in the untreated, infected virus control condition (VC). After removal of the medium from each well, 100 μL of a 5% MTS-phenazine solution in phenol red-free MEM was added. Following incubation for at least 1 h, a time at which the optical density at 498 nm reaches values between 0.6 and 0.8, raw OD values were collected using a microtiter plate reader (Safire$^2$, Tecan). Values were converted to percentage of controls and the 50% effective concentration ($EC_{50}$, defined as the concentration of compound that should offer 50% protection against virus-induced CPE), was calculated from the dose–response curve using logarithmic interpolation. In addition, the assays were inspected by light microscope and the adverse effect of the compound on the cells was quantified by scoring of the cells from which the $CC_{50}$ (concentration at which 50% cytotoxic effect is observed) was calculated using logarithmic interpolation.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.034.

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