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New 2-arylnaphthalenediols and triol inhibitors of HIV-1 integrase—Discovery of a new polyhydroxylated antiviral agent

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ABSTRACT

A series of 13 hydroxylated 2-arylnaphthalenes have been synthesized and evaluated as HIV-1 integrase inhibitors. 7-(3,4,5-Trihydroxyphenyl)naphthalene-1,2,3-triol **1c** revealed chemical instability upon storage, leading to the isolation of a dimer **5c** which was also tested. In the 2-arylnaphthalene series, all compounds were active against HIV-1 IN with IC_{50}'s within the 1–10 μM range, except for **1c** and **5c** which displayed submicromolar activity. Antiviral activity against HIV-1 replication was measured on **1b–c** and **5c**. Amongst the tested molecules, only **5c** was found to present antiviral properties with a low cytotoxicity on two different cell lines.

1. Introduction

Combination therapy, comprising at least three anti-human immunodeficiency virus (anti-HIV) drugs, has become the standard treatment of AIDS. Virtually all drugs that have been licensed for clinical use in the treatment of HIV infections fall into one of the following five categories: (i) nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), (ii) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (iii) protease inhibitors (PIs), (iv) entry inhibitors, and (v) integrase inhibitors.[1] Highly active antiretroviral therapy (HAART) strategy still suffers from issues of patient compliance, cost, deleterious side effects, and emerging drug resistance.

Although integrase (IN) has been pursued for many years as a potential target for the development of new anti-HIV compounds, the first integrase inhibitor licensed for clinical use, raltegravir (Scheme 1), was only approved in October 2007. Multiple resistant mutations have since surfaced in both treatment-experienced and treatment-naïve patients.[2] This viral resistance most often results from the substitution of one of three amino acids—Y143, Q148, or N155—usually in combination with at least one other mutation.[3] Other integrase inhibitor under recent clinical trials (i.e., elvitegravir in phase III, GSK-364735 and BMS-707035 halted in phase II) present strong cross-resistance with raltegravir[4–6] and the development of these compounds may yield a relatively low amount of clinical success.[7] Therefore, it is highly relevant to develop a second generation of integrase inhibitors with a new mechanism of action.

IN catalyzes the two-steps of the integration process, namely 3′-processing and strand transfer reactions in the presence of a divalent cation (while Mn^{2+} has been widely used for in vitro assays, Mg^{2+} is thought to be the cation acting as a cofactor of the enzyme in vivo).[8] In the past several years, numerous compounds with various structural features have been reported as IN inhibitors, the most developed of which are β-ketoenol derivatives and polyphenols.[9] Raltegravir and other integrase inhibitors under clinical trials are more or less derived from the diketoacid derivatives family and selectively inhibit the strand transfer reaction. A plethora of IN inhibitors has arised from the polyphenol family, however very few of them actually inhibit viral replication. They are generally non-selective integrase inhibitors and inhibiting both the 3′-processing and the strand transfer reactions in the same magnitude.

We previously reported the synthesis and IN inhibition evaluation of a first series of catechol and bis-catechol derivatives, two of which were found to be active against IN and five presented moderate antiviral activity with a relatively high toxicity.[10] In the present work, we prepared a series of new hydroxylated 2-arylnaphthalenes **1a–n**.

Regarding the first 2-phenylnaphthalene series, we had previously demonstrated that (i) the *ortho*-dihydroxy substitution must be born by the naphthalenyl moiety, (ii) a 1,3-dimethyl substitution (on the naphthalene nucleus) is not recommended for HIV-1 IN inhibitory activity, (iii) catechols on the ancillary aromatic units

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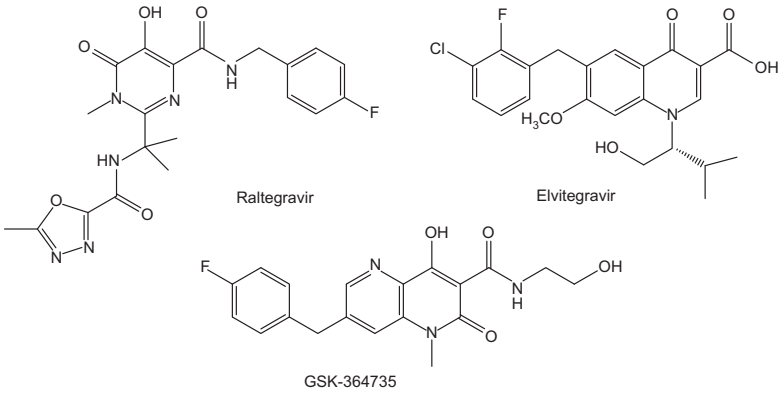


Scheme 1.

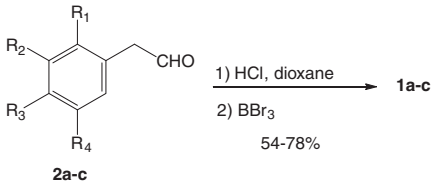
may be replaced by a trifluoromethyl group. We therefore designed a second set of 13 hydroxylated 2-arylnaphthalenes where the substitution on the ancillary phenyl ring was chosen on the basis of our own experience (incorporation of a CF_3 group) and on the facts that lead HIV-1 IN inhibitors comprise a fluorophenyl unit and that the presence of at least one hydroxy group is favorable.

Finally, we serendipitously found that 7-(3,4,5-trihydroxyphenyl)naphthalene-1,2,3-triol **1c** is sensitive to oxidation thus leading to isolation of dimer **5c**. Whereas **1c** was found to be toxic, **5c** revealed good antiviral properties.

2. Results and discussion

2.1. Chemistry

2-Phenylnaphthalenes **1a–c** were prepared by an acid-promoted dimerization of di (tri)methoxyphenylethanals **2a–c**,[11] followed by an exhaustive demethylation of the methyl ethers[11] using boron tribromide (Scheme 2) (yields = 54–78%). 2-Phenylnaphthalenes **1d–n** were synthesized in a two-steps procedure using the Suzuki coupling reaction of 2-bromo-5,6-dimethoxynaphthalene[12] **6** with conveniently substituted phenylboronic acids **3d–n** (yields = 30–85%) leading to the methoxylated derivatives **4d–n** followed by demethylation of the methoxy groups using boron tribromide (Scheme 3) (yields = 47–95%). In our hands, solutions of **1c** (in acetone, ethyl acetate, DMSO) were found to present an unexpected instability with time. Prolonged storage of a solid, dry sample of **1c** also resulted in darkness leading ultimately to a black solid **5c** which was isolated, characterized and tested as IN inhibitor. Its structure (Scheme 4) was established on the basis of spectroscopic data. The ^{1}H NMR spectra of **5c** in DMSO-d_6 and acetone-d_6 indicate the presence of two 1,2,4 trisubstituted aromatic patterns and three singlets (respectively, integrating for one, two and two protons each). The dimerization is comforted by the observation of 28 peaks (four of them corresponding to two carbons) on the ^{13}C spectrum. The deshielded peaks on the ^{13}C NMR spectra can be attributed to a tetraoxygenated *o*-naphthoquinone ring. Both in ^{1}H and ^{13}C NMR spectroscopy, the FID's were found to be very short, denoting a rapid relaxation phenomenon.



Scheme 2.

Synthetic polymers obtained from the oxidation of caffeic acid with hydrogen peroxide were found to be active against HIV-1 and 2.[13] As in the case of **5c**, at the solid state, they gave ESR signals attributed to semiquinonic radical. Our previous experience[14] of radical organic material led us to record the ESR spectrum of *o*-naphthaquinone dimer **5c**. This spectrum shown in Figure 1 is a result of two paramagnetic signals composed by three lines and centered at $g = 2.006$. The signal intensities suggest two types of radical species in the sample. The central signal is assigned to a majority of monoradical ($S = 1/2$) typical of a semiquinonic radical anion. The doublet with a splitting of 46.8 mT corresponds to a minority of biradical triplet spin state ($S = 1$). The dipole spin–spin interaction of the biradical allows us to calculate the distance between radical centers. This distance r_{AB} which separates the radical pairs can be attributed by the dipole splitting term, D.

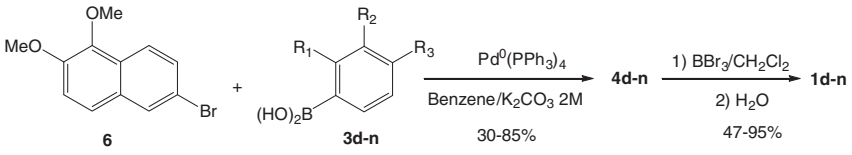
$$D = (\beta^2 g_A g_B / \hbar r_{AB}^3)(1 - 3\cos^2\theta_{AB})$$

θ_{AB} is the angle between the pair director and the external field. The other terms have their usual meanings. For $\theta_{AB} = \pi/2$, r_{AB} (nm) = $(52.04/D\ (\mathrm{MHz}))^{1/3}$. The D value extracted from ESR spectra was around 1310 MHz and the distance r_{AB} deduced was approximately 3.4 ± 0.5 Å.

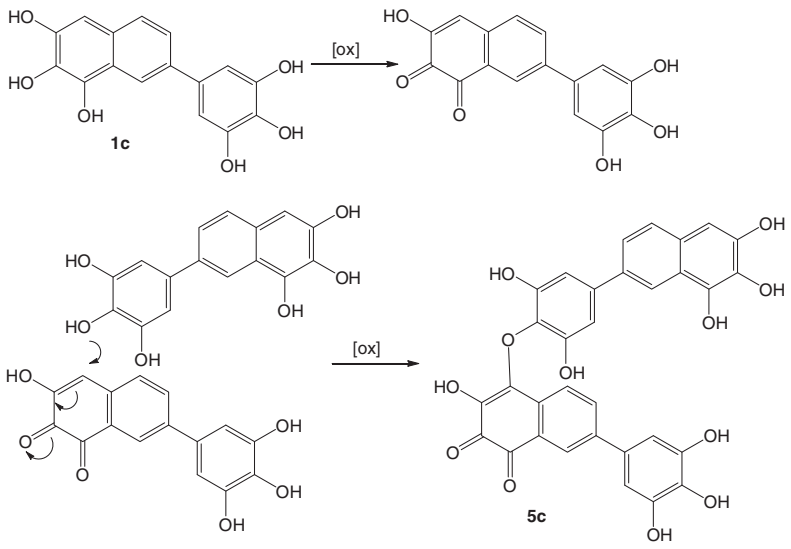
This very short distance cannot be explained on the basis of intramolecular interactions due to the absence of folding of the bulky dimeric molecule **5c**. We therefore suppose that this inter-radical distance may provide from intermolecular interactions.

2.2. Antiintegrase activity

Compounds **1a–n** and **5c** were screened for inhibitory activities against purified HIV-1 IN on the overall reaction, that is, both Mg^{2+}-dependent 3′-processing and strand transfer reactions (Table 1). In the case of **5c**, the IC_{50}'s on the two reactions catalyzed by IN were measured. In our previous paper on a first series of 2-phenylnaphthalene derivatives,[10] we found that best integrase inhibition was obtained when the *ortho*-dihydroxy moiety was born by the naphthalene nucleus and the two aromatic rings were not orthogonal (no substitution on the positions ortho of the phenyl ring). In the present work, a series of 7-arylnaphthalene-1,2-diols was synthesized displaying good IN inhibitory action with IC_{50} ranging between 1 and 10 μM. However there is a slight difference between the bis-catechols **1b** and **1d** and the naphthalene-1,2-diols **1e–n**. Bis-catechols **1b** and **1d** gave the same result on IN than **1a** showing that the relative position of the catechol



Scheme 3.



Scheme 4.

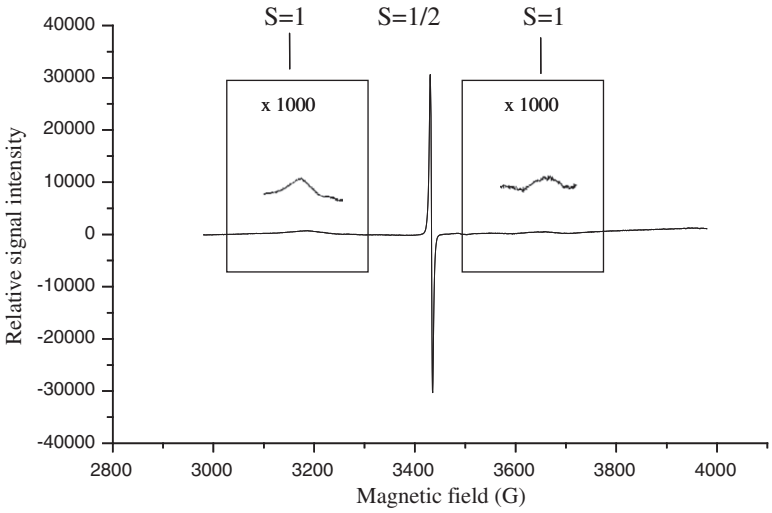


Figure 1. ESR_CW spectrum at room temperature of **5c** powder with $g = 2.006$.

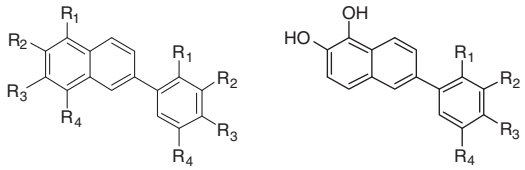
moiety is not critical and confirming the importance of the presence of two catechols. In deep contrast with our previous results, the substitution of the phenyl ring is practically ineffective to give SAR information possibly because this part of the inhibitor does not participate in the interaction with the enzyme. The linker between the two aromatic moieties (absent in the present case) has to be modified, that is, by adding one or more sp^3 atom in order to increase to degree of freedom and allow this part of the inhibitor to interact with the enzyme. Adding a third hydroxyl group did not significantly increase the inhibition of IN (IC_{50} of 0.5 μM for **1c** vs 1–2 μM for **1a–b** and **1d**).

The dimer **5c** strongly inhibited the overall activity of IN (IC_{50} = 0.85 μM) with no significant selectivity toward the strand transfer reaction (IC_{50} (3′-P) = 450 nM and IC_{50} (ST) = 170 nM). In deep contrast with chicoric acid[13] which inhibits selectively the 3′-processing step, **5c** inhibits both catalyzed reactions in the same magnitude with a slight difference in favor of ST.

2.3. Antiviral activity

Synthetic polyphenols and natural tannins are known to present antiviral activity.[16] Compounds **1b–d** and **5c** were evaluated ex vivo for their antiviral activity against HIV-1 replication in CEM cells (Table 2). They were tested for their ability to lower the viral charge in culture supernatants. CEM cells were infected with HIV-1 and subsequently treated with increasing concentra-

Table 1
HIV-1 IN inhibitory potencies of compounds **1a–n**



1a-c **1d-n**

Compound	R_1	R_2	R_3	R_4	IC_{50}[a] in μM
1a	H	OH	OH	H	2.1[10]
1b	OH	OH	H	H	1.00 ± 0.03
1c	H	OH	OH	OH	0.50 ± 0.1
5c					0.85 ± 0.53 (overall) 0.45 ± 0.07 (3′-P) 0.17 ± 0.14 (ST)
1d	H	OH	OH	H	2.2 ± 0.2
1e	H	H	H	H	6.0 ± 2.6
1f	OH	H	H	H	10.0 ± 4.24
1g	H	OH	H	H	4.8 ± 0.14
1h	H	H	OH	H	8.1 ± 3.1
1i	CF_3	H	H	H	6.0 ± 0.54
1j	H	CF_3	H	H	10.0 ± 0.24
1k	H	H	CF_3	H	10.0 ± 0.31
1l	F	H	H	H	7.3 ± 0.1
1m	H	F	H	H	9.6 ± 0.13
1n	H	H	F	H	8.0 ± 0.1

[a] Concentration giving 50% inhibition of the integrase overall activity.

tions of drugs. The amount of virus was assayed by β-galactosidase assay, with HeLaCD4-β-gal cells as reporting cells. Toxicity was estimated by MTT transformation assay. No activity (>100 μM) against the HIV-1 replication or cytotoxicity (>100 μM) was found for **1b**. Compound **1d** was found to be slightly active (EC_{50} = 40 μM, CC_{50} >100 μM). In deep contrast with **1a–b** and **1d**, **1c** was found to be very toxic. This could be related to its unstability. However the isolated air-oxidized dimeric compound **5c** revealed a good antiviral activity with an EC_{50} of about 1.15 μM and a low toxicity CC_{50} of 85 μM giving a therapeutic index of 74. So we may assume that compound **1c** gives other toxic oxidized (or non-oxidized) compounds during the cellular assays. The antiviral activity of **5c** was also evaluated in the HIV-1 infection of MT-4 cells. The toxicity of **5c** was slightly lower (75.6 μM) than in the HeLaCD4-β-gal cellular test but its antiviral activity slightly decreased (3.9 μM) and the therapeutic index dropped to 19.

3. Conclusion

In this paper we report the anti-integrase activities of 14 2-phenylnaphthalenediols and triols. We demonstrated the instability of compound **1c** which readily undergoes air oxidation over a few days and the remarkable antiviral properties of the resulting *o*-naphthoquinone **5c** that exists (partially) as a radical. A minor biradical has also been characterized. It is a new example of the redox instability of some polyphenols. However, in this particular case, the final dimer was found to be less toxic than the initial polyphenol **1c**. The various oxidation processes are probably responsible for the toxicity of **1c** via formation of semiquinonic radicals. Compound **5c** presents remarkable antiviral activity (compared to other polyphenols) and is amongst the most active antiviral polyphenol reported to date.

Table 2
Antiviral activities of compounds **1b–c** and **5c** compared to L-chicoric acid

Compound	Cell lines	CC_{50}[a] (μM)	EC_{50}[b] (μM)	Ti[c]
Chicoric acid	MT-4	115 ± 21[15]	12.7 ± 8.5[15]	9
1a	HeLa (P4)	51[10]	9.9[10]	5
1b	HeLa (P4)	>100	>100	
1c	MT-4	1	>1	
1d	HeLa (P4)	>100	40	
5c	HeLa (P4)	85 ± 15	1.15 ± 0.85	74
5c	MT-4	75.6 ± 5.5	3.9 ± 0.5	19

[a] Cytotoxic concentration 50%.
[b] Effective concentration 50%.
[c] Therapeutic index = CC_{50}/EC_{50}.

4. Experimental

4.1. Chemistry

All solvents were of commercial quality used from freshly opened containers and were dried and purified by conventional methods. Reagents were purchased from Aldrich-chimie (St Quentin-Fallavier, France). Mps were determined on a Reichert Thermopan apparatus, equipped with a microscope and are uncorrected. NMR spectra were obtained on an AC 300 Bruker spectrometer in the appropriate deuterated solvent with TMS as internal reference (^{1}H 300 MHz, ^{13}C 75 MHz). Mass spectra were recorded on a Thermo-Finnigan PolarisQ mass spectrometer (70 eV, Electronic Impact) or on a Voyager DE STR mass spectrometer (Applied Biosystems) (MALDI-TOF). Elemental analyses were performed by CNRS laboratories (Vernaison).

4.2. Demethylation using boron tribromide—General procedure

To a solution of the methylated compound in dichloromethane (1 mmol in 20 mL) boron tribromide (1 M in dichloromethane, (x +1) mmol, x corresponds to the number of methoxy group) was added dropwise. The mixture was stirred at room temperature for 1 h. The synthesis of **1c** requires 10 equiv of BBr_3 and 48 h at reflux.

4.3. Purification—General procedure

Twenty milliliters of distilled water was slowly added and after stirring for additional 15 min, the precipitate was filtered, washed with water then with dichloromethane, and dried over P_2O_5. Crystallization from acetone gave pure compounds.

4.3.1. 6-(2,3-Dihydroxyphenyl)naphthalene-1,2-diol 1b

Light brown solid; yield = 54%; mp = 107–109 °C; ^{1}H NMR (acetone-d_6): 6.81 (t, 1H, $^3J_{H5'-H4'} = {}^3J_{H5'-H6'}$ = 7.2 Hz, $H_{5'}$); 6.86 (dd, 1H, $^3J_{H4'-H5'}$ = 7.2 Hz, $^4J_{H4'-H6'}$ = 2.0 Hz, $H_{4'}$); 6.91 (dd, 1H, $^3J_{H6'-H5'}$ = 7.2 Hz, $^3J_{H6'-H4'}$ = 2.0 Hz, $H_{6'}$); 7.19 (d, 1H, $^3J_{H3-H4}$ = 8.7 Hz, H_3); 7.34 (d, 1H, $^3J_{H4-H3}$ = 8.7 Hz, H_4); 7.66 (dd, 1H, $^3J_{H7-H8}$ = 8.7 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.92 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.12 (d, 1H, $^3J_{H8-H7}$ = 8.7 Hz, H_8); ^{13}C NMR (acetone-d_6): 114.8 (CH); 118.8 (CH); 120.5 (CH); 120.6 (CH); 121.2 (CH); 122.4 (CH); 125.4 (C); 127.2 (C); 127.6 (CH); 128.4 (CH); 129.7 (C); 134.3 (C); 138.8 (C); 140.7 (C); 143.5 (C); 146.1 (C); MS (EI): m/z (%) = 268 ([M$^+$], 10); 238 (100); 221 (38); 95 (34); 84 (47); 83 (70); 59 (52); Elemental Anal. Calcd C, 71.64; H, 4.51. Found: C, 71.31; H, 4.68.

4.3.2. 7-(3,4,5-Trihydroxyphenyl)naphthalene-1,2,3-triol 1c

Gray solid; yield = 75%; mp >250 °C; ^{1}H NMR (DMSO-d_6): 6.77 (s, 2H, $H_{2',6'}$); 6.80 (s, 1H, H_4); 7.40 (dd, 1H, $^3J_{H6-H5}$ = 8.55 Hz, $^4J_{H6-H8}$ = 1.95 Hz, H_6); 7.51 (d, 1H, $^3J_{H5-H6}$ = 8.55 Hz, H_5); 8.10 (d, 1H, $^4J_{H8-H6}$ = 1.95 Hz, H_8); ^{13}C NMR (DMSO-d_6): 100.8 (CH); 105.3 (2 CH); 117.2 (CH); 121.0 (C); 122.1 (CH); 126.0 (CH); 126.9 (C); 131.5 (C); 132.2 (C); 132.5 (C); 133.7 (C); 138.8 (C); 146.5 (2 C); 147.3 (C); MS (MALDI-TOF): m/z (%) = 301 ([M$^+$+H], 16); 300 ([M$^+$], 100); 299 (10); Elemental Anal. Calcd C, 64.00; H, 4.03. Found: C, 63.69; H 4.24.

4.3.3. 4-(2,6-Dihydroxy-4-(6,7,8-trihydroxynaphthalene-2-yl)-phenoxy)-7-(3,4,5-trihydroxyphenyl) naphthalene-1,2,3-triol 5c

^{1}H NMR (DMSO-d_6): 6.65 (s, 2H, $H_{2',6'}$); 6.71 (s, 1H, H_4); 6.74 (s, 2H, $H_{2',6'}$); 7.33 (d, 1H, $^3J_{H5-H6}$ = 8.2 Hz, H_5); 7.69 (dd, 1H, $^3J_{H6-H5}$ = 8.2 Hz, $^4J_{H6-H8}$ = 2.1 Hz, H_6); 7.74 (d, 1H, $^3J_{H5-H6}$ = 7.9 Hz, H_5); 7.99 (dd, 1H, $^3J_{H6-H5}$ = 7.9 Hz, $^4J_{H6-H8}$ = 1.8 Hz, H_6); 8.09 (d, 1H, $^4J_{H8-H6}$ = 2.1 Hz, H_8); 8.16 (d, 1H, $^4J_{H6-H8}$ = 1.8 Hz, H_6); ^{13}C NMR (DMSO-d_6): 105.5 (2 CH); 105.6 (2 CH); 122.1; 124.4; 126.3; 128.1; 128.3; 130.1; 130.5; 131.3; 132.1; 132.2; 133.1; 134.3; 134.5; 139.3; 139.8; 140.5; 140.8; 142.2; 143.3; 145.3; 146.6 (2C); 146.8 (2C); 164.9; 166.7; 180.5; 188.7; MS (EI): m/z (%) = 314 (72); 286 (100); 151 (95); Elemental Anal. Calcd for $C_{32}H_{20}O_{12}$: C, 64.44; H, 3.38. Found: C, 64.77; H, 3.02.

4.3.4. 6-Bromo-1,2-dimethoxynaphthalene 6 was obtained according to published procedure[11] as beige solid, mp = 50–52 °C (lit.[12] 51–53 °C)

^{1}H NMR ($CDCl_3$): 3.99 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 7.31 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.51 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.53 (dd, 1H, $^3J_{H7-H8}$ = 9.0 Hz, $^4J_{H7-H5}$ = 2.0 Hz, H_7); 7.94 (d, 1H, $^4J_{H5-H7}$ = 2.0 Hz, H_5); 8.00 (d, 1H, $^3J_{H8-H7}$ = 9.0 Hz, H_8); ^{13}C NMR($CDCl_3$): 56.8 (CH_3); 61.2 (CH_3); 116.2 (CH); 117.9 (C); 123.2 (CH); 123.3 (CH); 127.5 (C); 129.4 (CH); 129.5 (CH); 130.6 (C); 143.0 (C); 148.6 (C).

4.4. Preparation of 4d–n

A mixture of 6-bromo-1,2-dimethoxynaphthalene **6** (2 mmol 534 mg), the convenient arylboronic acid (2 mmol), tetrakistriphenylphosphine palladium(0) (70 mg) in benzene (2 mL) and an 2 M aqueous solution of potassium carbonate (2 mL) was refluxed for 3 h. The mixture was cooled to room temperature and chloroform (8 mL) and saturated aqueous solution of sodium hydrogenocarbonate (8 mL) were added. The aqueous layer was separated and extracted twice with chloroform (10 mL). The organic layers were grouped, washed with saturated aqueous solution of sodium hydrogenocarbonate (10 mL). The organic layer was dried over sodium sulfate and evaporated to give a residue.

Compounds **4d–h** were crystallized from acetone. In the cases of **4i–n**, the residue was dissolved in petroleum ether (200 mL for 500 mg of residue) and filtered. After evaporation to dryness, crystallization in a minimum of petroleum ether gave pure **4i–n**. In the cases of **4i–k**, the residue was chromatographed on silica column (eluent: dichloromethane) and crystallized from petroleum ether.

4.4.1. 6-(3,4-Dimethoxyphenyl)-1,2-dimethoxynaphthalene 4d

White powder; yield = 30%; mp = 129–130 °C; ^{1}H NMR ($CDCl_3$): 3.93 (s, 3H, OCH_3); 3.98 (s, 3H, OCH_3); 3.99 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 6.96 (d, 1H, $^3J_{H5'-H6'}$ = 8.1 Hz, $H_{5'}$); 7.23 (s, 1H, $H_{2'}$); 7.24 (d, 1H, $^3J_{H6'-H5'}$ = 8.1 Hz, $H_{6'}$); 7.30 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.63 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.71 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.9 Hz, H_7); 7.92 (d, 1H, $^4J_{H5-H7}$ = 1.9 Hz, H_5); 8.17 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.0 (2 × CH_3); 56.9 (CH_3); 61.2 (CH_3); 110.5 (CH); 111.6 (CH); 115.7 (CH); 119.6 (CH); 121.9 (CH); 124.4 (CH); 125.0 (CH); 125.8 (CH); 128.0 (C); 130.0 (C); 134.1 (C); 136.6 (C); 142.9 (C); 148.3 (C); 148.6 (C); 149.2 (C); MS (MALDI-TOF): m/z (%) = 325 (32); 324 ([M$^+$], 100); Elemental Anal. Calcd C, 74.06; H, 6.21. Found: C, 74.24; H, 6.32.

4.4.2. 6-Phenyl-1,2-dimethoxynaphthalene 4e

Gray powder; yield = 37%; mp = 114–115 °C (lit.[12] 114–115 °C); ^{1}H NMR ($CDCl_3$): 4.02 (s, 3H, OCH_3); 4.04 (s, 3H, OCH_3); 7.33 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.38 (tt, 1H, $^3J_{H4'-H3',5'}$ = 7.5 Hz, $^4J_{H4'-H2',6'}$ = 1.3 Hz, $H_{4'}$); 7.49 (m, 2H, $H_{3',5'}$); 7.67 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.72 (m, 2H, $H_{2',6'}$); 7.75 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 8.00 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.21 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.9 (CH_3); 61.2 (CH_3); 115.7 (CH); 122.0 (CH); 124.5 (CH); 125.6 (CH); 125.9 (CH); 127.2 (CH); 127.3 (2 × CH); 128.2 (C); 128.8 (2 × CH); 130.0 (C); 136.8 (C); 141.1 (C); 142.9 (C); 148.5 (C).

4.4.3. 6-(2-Methoxyphenyl)-1,2-dimethoxynaphthalene 4f

Pale yellow powder; yield = 47%; mp = 121–122 °C; ^{1}H NMR ($CDCl_3$): 3.86 (s, 3H, OCH_3); 4.03 (s, 3H, OCH_3); 4.05 (s, 3H, OCH_3); 7.05 (dd, 1H, $^3J_{H3'-H4'}$ = 8.1 Hz, $^4J_{H3'-H5'}$ = 1.0 Hz, $H_{3'}$); 7.10 (td, 1H, $^3J_{H5'-H6'}$ = $^3J_{H5'-H4'}$ = 7.6 Hz, $^4J_{H5'-H3'}$ = 1.0 Hz, $H_{5'}$); 7.32 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.38 (ddd, 1H, $^3J_{H4'-H3'}$ = 8.1 Hz, $^3J_{H4'-H5'}$ = 7.6 Hz, $^4J_{H4'-H6'}$ = 1.7 Hz, $H_{4'}$); 7.45 (dd, 1H, $^3J_{H6'-H5'}$ = 7.6 Hz, $^4J_{H6'-H4'}$ = 1.7 Hz, $H_{6'}$); 7.66 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.73 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.94 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.18 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 55.6 (CH_3); 57.0 (CH_3); 61.2 (CH_3); 111.3 (CH); 115.3 (CH); 120.8 (CH); 121.0 (CH); 124.5 (CH); 127.9 (CH); 128.1 (C); 128.4 (CH); 128.7 (CH); 129.8 (C); 130.7 (C); 131.1 (CH); 134.5 (C); 143.0 (C); 148.4 (C); 156.6 (C); MS (MALDI-TOF): m/z (%) = 295 (23); 294 ([M$^+$], 100); Elemental Anal. Calcd C, 77.53; H, 6.16. Found: C, 77.27; H, 6.15.

4.4.4. 6-(3-Methoxyphenyl)-1,2-dimethoxynaphthalene 4g

White powder; yield = 56%; mp = 107–108 °C; ^{1}H NMR ($CDCl_3$): 3.91 (s, 3H, OCH_3); 4.03 (s, 3H, OCH_3); 4.05 (s, 3H, OCH_3); 6.94 (ddd, 1H, $^3J_{H4'-H5'}$ = 8.0 Hz, $^4J_{H4'-H2'}$ = 2.0 Hz, $^4J_{H4'-H6'}$ = 0.9 Hz, $H_{4'}$); 7.27 (d, 1H, $^4J_{H2'-H4'}$ = 2.0 Hz, $H_{2'}$); 7.32 (dd, 1H, $^3J_{H6'-H5'}$ = 7.8 Hz, $^4J_{H6'-H4'}$ = 0.9 Hz, $H_{6'}$); 7.34 (d, 1H, $^3J_{H3-H4}$ = 8.9 Hz, H_3); 7.41 (dd, 1H, $^3J_{H5'-H4'}$ = 8.0 Hz, $^3J_{H5'-H6'}$ = 7.8 Hz, $H_{5'}$); 7.68 (d, 1H, $^3J_{H4-H3}$ = 8.9 Hz, H_4); 7.76 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.8 Hz, H_7); 8.00 (d, 1H, $^4J_{H5-H7}$ = 1.8 Hz, H_5); 8.21 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 55.4 (CH_3); 57.0 (CH_3). 61.3 (CH_3); 112.7 (CH); 113.1 (CH); 115.8 (CH); 119.9 (CH); 122.1 (CH); 124.6 (CH); 125.7 (CH); 126.0 (CH); 128.4 (C); 129.9 (CH); 130.0 (C); 136.8 (C); 142.8 (C); 143.0 (C); 148.6 (C); 160.1 (C); MS (EI): m/z (%) = 295 (21); 294 (100); 279 (42); 251 (36); 236 (36); Elemental Anal. Calcd C, 77.53; H, 6.16. Found: C, 77.65; H, 6.21.

4.4.5. 6-(4-Methoxyphenyl)-1,2-dimethoxynaphthalene 4h

Gray powder; yield = 72%; mp = 148–149 °C; ^{1}H NMR ($CDCl_3$): 3.89 (s, 3H, OCH_3); 4.03 (s, 3H, OCH_3); 4.05 (s, 3H, OCH_3); 7.04 (d, 2H, $^3J_{H3',5'-H2',6'}$ = 8.8 Hz, $H_{3',5'}$); 7.32 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.65 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.67 (d, 2H, $^3J_{H2',6'-H3',5'}$ = 8.8 Hz, $H_{2',6'}$); 7.74 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.95 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.20 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 55.4 (CH_3); 56.9 (CH_3); 61.2 (CH_3); 114.3 (2 × CH); 115.7 (CH); 121.9 (CH); 124.4 (CH); 124.8 (CH); 125.7 (CH); 127.9 (C); 128.3 (2 × CH); 130.1 (C); 133.6 (C); 136.4 (C); 142.9 (C); 148.2 (C); 159.1 (C); MS (MALDI-TOF): m/z (%) = 296 (20); 295 (73); 294 ([M$^+$], 100); Elemental Anal. Calcd C, 77.53; H, 6.16. Found: C, 77.30; H, 6.11.

4.4.6. 1,2-Dimethoxy-6-(2-trifluoromethylphenyl)naphthalene 4i

White powder; yield = 58%; mp = 86–87 °C; ^{1}H NMR ($CDCl_3$): 4.01 (s, 3H, OCH_3); 4.03 (s, 3H, OCH_3); 7.33 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.40 (d, 1H, ^3J = 7.6 Hz, $H_{3'}$ or $H_{6'}$); 7.45 (br d, 1H, $^3J_{H7-H8}$ = 8.5 Hz, H_7); 7.48 (t, ^3J = 7.6 Hz, $H_{4'}$ or $H_{5'}$); 7.58 (t, ^3J = 7.6 Hz, $H_{4'}$or $H_{5'}$); 7.62 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.72 (br s, 1H, H_5); 7.78 (d, 1H, ^3J = 7.6 Hz, $H_{3'}$ or $H_{6'}$); 8.14 (d, 1H, $^3J_{H8-H7}$ = 8.5 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.9 (s, CH_3); 61.2 (s, CH_3); 115.8 (s, CH); 120.9 (s, CH); 124.3 (q, CF_3, $^1J_{C-F}$ = 272.2 Hz); 124.5 (s, CH); 126.1 (q, CH, $^3J_{C-F}$ = 5.4 Hz); 127.4 (s, CH); 127.5 (q, CH, $^4J_{C-F}$ = 1.7 Hz); 127.7 (q, CH, $^4J_{C-F}$ = 1.7 Hz); 128.3 (s, C); 128.6

(q, C, $^2J_{C-F}$ = 29.8 Hz); 129.1 (s, C); 131.4 (s, CH); 132.4 (s, CH); 135.7 (s, C); 141.4 (q, C, $^3J_{C-F}$ = 1.7 Hz); 143.0 (s, C); 148.7 (s, C); MS (EI): *m*/*z* (%) = 333 (20); 332 ([M$^+$], 98); 317 (49); 289 (28); 250 (21); 249 (100); Elemental Anal. Calcd C, 68.67; H, 4.55; F, 17.15. Found: C, 68.88; H, 4.49; F, 17.33.

4.4.7. 1,2-Dimethoxy-6-(3-trifluoromethylphenyl)naphthalene 4j

Cream powder; yield = 85%; mp = 65–67 °C; ^{1}H NMR ($CDCl_3$): 4.02 (s, 3H, OCH_3); 4.06 (s, 3H, OCH_3); 7.34 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.58 (d, 1H, $^3J_{H4'-H5'}$ = 7.6 Hz, $H_{4'}$); 7.62 (t, 1H, $^3J_{H5'-H4'}$ = $^3J_{H5'-H6'}$ = 7.6 Hz, $H_{5'}$); 7.67 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.73 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.9 Hz, H_7); 7.86 (d, 1H, $^3J_{H6'-H5'}$ = 7.6 Hz, $H_{6'}$); 7.99 (br s, 1H); 7.99 (d, 1H, $^4J_{H5-H7}$ = 1.9 Hz, H_5); 8.24 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.8 (s, CH_3); 61.2 (s, CH_3); 115.8 (s, CH); 122.4 (s, CH); 123.8 (q, CH, $^3J_{C-F}$ = 3.9 Hz); 123.9 (q, CH, $^3J_{C-F}$ = 3.9 Hz); 124.3 (q, CF_3, $^1J_{C-F}$ = 272.2 Hz); 124.7 (s, CH); 125.4 (s, CH); 126.0 (s, CH); 128.6 (s, C); 129.3 (s, CH); 129.8 (s, C); 130.5 (s, CH); 131.2 (q, C, $^2J_{C-F}$ = 32.3 Hz); 135.2 (s, C); 141.9 (s, C); 142.9 (s, C); 148.8 (s, C); MS (EI): *m*/*z* (%) = 332 ([M$^+$], 100); 317 (43); 289 (42); 274 (22); 269 (31); 249 (27); Elemental Anal. Calcd C, 68.67; H, 4.55; F, 17.15. Found: C, 68.48; H, 4.64; F, 17.27.

4.4.8. 2-Dimethoxy-6-(4-trifluoromethylphenyl)naphthalene 4k

White powder; yield = 55%; mp = 131–132 °C; ^{1}H NMR ($CDCl_3$): 4.02 (s, 3H, OCH_3); 4.04 (s, 3H, OCH_3); 7.34 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.66 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.71 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.71 (d, 2H, $^3J_{H2',6'-H3',5'}$ = 7.9 Hz, $H_{2',6'}$ or $H_{3',5'}$); 7.78 (d, 2H, $^3J_{H2',6'-H3',5'}$ = 7.9 Hz, $H_{2',6'}$ or $H_{3',5'}$); 7.98 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.23 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.8 (s, OCH_3); 61.2 (s, OCH_3); 115.8 (s, CH); 122.3 (s, CH); 124.4 (q, CF_3, $^1J_{C-F}$ = 271.9 Hz); 124.7 (s, CH); 125.4 (s, CH); 125.8 (q, 2 × CH, $^3J_{C-F}$ = 3.7 Hz); 126.1 (s, CH); 127.5 (s, 2 × CH); 128.6 (s, C); 129.1 (q, C, $^2J_{C-F}$ = 32.4 Hz); 129.7 (s, C); 135.2 (s, C); 142.9 (s, C); 144.6 (s, C); 148.9 (s, C); MS (MALDI-TOF): *m*/*z* (%) = 333 (21); 332 ([M$^+$], 100); Elemental Anal. Calcd C, 68.67; H, 4.55; F, 17.15. Found: C, 68.85; H, 4.60; F, 17.02.

4.4.9. 6-(2-Fluorophenyl)-1,2-dimethoxynaphthalene 4l

Beige powder; yield = 54%; mp = 82–84 °C; ^{1}H NMR ($CDCl_3$): 4.01 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 7.18 (ddd, 1H. $^3J_{H3'-F}$ = 10.7 Hz, $^3J_{H3'-H4'}$ = 8.1 Hz, $^4J_{H3'-H5'}$ = 1.5 Hz, $H_{3'}$); 7.24 (td, 1H, $^3J_{H5'-H4'}$ = $^3J_{H5'-H6'}$ = 7.5 Hz, $^4J_{H5'-H3'}$ = 1.5 Hz, $H_{5'}$); 7.30–7.37 (m, 1H, $H_{4'}$); 7.32 (d, 1H, $^3J_{H3-H4}$ = 8.9 Hz, H_3); 7.54 (td, 1H, $^3J_{H6'-H5'}$ = $^4J_{H6'-F}$ = 7.5 Hz, $^4J_{H6'-H4'}$ = 1.9 Hz, $H_{5'}$); 7.65 (d, 1H, $^3J_{H4-H3}$ = 8.9 Hz, H_4); 7.68 (dt, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = $^5J_{H7-F}$ = 1.8 Hz, H_7); 7.96 (br s, 1H, H_5); 8.19 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.9 (s, CH_3); 61.2 (s, CH_3); 115.6 (s, CH); 116.2 (d, CH, $^2J_{C-F}$ = 22.6 Hz); 121.6 (s, CH); 124.5 (d, CH, $^4J_{C-F}$ = 3.7 Hz); 124.7 (s, CH); 127.4 (d, CH, $^4J_{C-F}$ = 3.0 Hz); 128.0 (d, CH, $^4J_{C-F}$ = 3.0 Hz); 128.4 (s, C); 129.0 (d, CH, $^3J_{C-F}$ = 8.6 Hz); 129.1 (d, C, $^2J_{C-F}$ = 13.7 Hz); 129.7 (s, C); 131.0 (d, CH, $^3J_{C-F}$ = 3.0 Hz); 131.5 (d, C, $^3J_{C-F}$ = 1.8 Hz); 142.9 (s, C); 148.8 (s, C); 160.1 (d, C, $^1J_{C-F}$ = 247.8 Hz); MS (MALDI-TOF): *m*/*z* (%) = 283 (50); 282 ([M$^+$], 100); Elemental Anal. Calcd C, 76.58; H, 5.36; F, 6.73. Found: C, 76.39; H, 5.43; F, 6.85.

4.4.10. 6-(3-Fluorophenyl)-1,2-dimethoxynaphthalene 4m

Cream prism; yield = 67%; mp = 95–97 °C; ^{1}H NMR ($CDCl_3$): 4.01 (s, 3H, OCH_3); 4.02 (s, 3H, OCH_3); 7.02–7.08 (m, 1H, $H_{4'}$); 7.33 (d, 1H, $^3J_{H3-H4}$ = 9.0 Hz, H_3); 7.38–7.50 (m, 3H, $H_{2'}$, $H_{5'}$, and $H_{6'}$); 7.66 (d, 1H, $^3J_{H4-H3}$ = 9.0 Hz, H_4); 7.70 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.96 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.19 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.8 (s, CH_3); 61.1 (s, CH_3); 113.9 (d, CH, $^2J_{C-F}$ = 21.4 Hz); 114.0 (d, CH, $^2J_{C-F}$ = 22.0 Hz); 115.7 (s, CH); 122.1 (s, CH); 122.8 (s, CH); 124.6 (s, CH); 125.4 (s, CH); 125.7 (s, CH); 128.4 (s, C); 129.7 (s, C); 130.2 (d, CH, $^3J_{C-F}$ = 8.6 Hz); 135.4 (s, C); 142.8 (s, C); 143.4 (d, C, $^3J_{C-F}$ = 7.3 Hz); 148.6 (s, C); 163.2 (d, C, $^1J_{C-F}$ = 245.4 Hz); MS (EI): *m*/*z* (%) = 283 (25); 282 ([M$^+$], 100); 267 (52); 239 (69); 224 (36); 196 (36); Elemental Anal. Calcd C, 76.58; H, 5.36; F, 6.73. Found: C, 76.35; H, 5.47; F, 6.52.

4.4.11. 6-(4-Fluorophenyl)-1,2-dimethoxynaphthalene 4n

White powder; yield = 78%; mp = 118–119 °C; ^{1}H NMR ($CDCl_3$): 4.02 (s, 3H, OCH_3); 4.04 (s, 3H, OCH_3); 7.17 (t, 2H, $^3J_{H3',5'-H2',6'}$ = $^3J_{H3',5'-F}$ = 8.6 Hz, $H_{3',5'}$); 7.33 (d, 1H, $^3J_{H3-H4}$ = 8.9 Hz, H_3); 7.65 (d, 1H, $^3J_{H4-H3}$ = 8.9 Hz, H_4); 7.66 (d, 2H, $^3J_{H2',6'-H3',5'}$ = 8.6 Hz, $H_{2',6'}$); 7.69 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.93 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.20 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR ($CDCl_3$): 56.9 (s, CH_3); 61.2 (s, CH_3); 115.7 (d, 2 × CH, $^2J_{C-F}$ = 21.4 Hz); 115.8 (s, CH); 122.1 (s, CH); 124.5 (s, CH); 125.4 (s, CH); 125.7 (s, CH); 128.1 (s, C); 128.8 (d, 2 × CH, $^3J_{C-F}$ = 7.9 Hz); 129.9 (s, C); 135.8 (s, C); 137.2 (d, C, $^4J_{C-F}$ = 3.0 Hz); 142.9 (s, C); 148.5 (s, C); 162.4 (d, C, $^1J_{C-F}$ = 246.0 Hz); MS (MALDI-TOF): *m*/*z* (%) = 283 (42); 282 ([M$^+$], 100); Elemental Anal. Calcd C, 76.58; H, 5.36; F, 6.73. Found: C, 76.72; H, 5.39; F, 6.59.

Compounds **1d–n** were obtained using the same procedure of compounds **1b–c**. Compounds **1i–n** were isolated in the dichloromethane layer. After evaporation, they were crystallized in a minimum of dichloromethane.

4.4.12. 6-(3,4-Dihydroxyphenyl)naphthalene-1,2-diol 1d

Brown powder; yield = 95%; mp >250 °C; ^{1}H NMR (acetone-d_6): 6.83 (d, 1H, $^3J_{H5'-H6'}$ = 8.2 Hz, $H_{5'}$); 7.11 (dd, 1H, $^3J_{H6'-H5'}$ = 8.2 Hz, $^4J_{H6'-H2'}$ = 2.2 Hz, $H_{6'}$); 7.20 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.25 (d, 1H, $^4J_{H2'-H6'}$ = 2.2 Hz, $H_{2'}$); 7.36 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.64 (dd, 1H, $^3J_{H7-H8}$ = 8.7 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.89 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.03 (br s, 4H, 4 × OH); 8.14 (d, 1H, $^3J_{H8-H7}$ = 8.7 Hz, H_8); ^{13}C NMR (acetone-d_6): 114.8 (CH); 116.6 (CH); 119.1 (CH); 119.3 (CH); 120.5 (CH); 122.2 (CH); 125.0 (CH); 125.1 (CH); 125.3 (C); 130.5 (C); 134.1 (C); 136.5 (C); 138.7 (C); 140.5 (C); 145.5 (C); 146.2 (C); MS (EI): *m*/*z* (%) = 268 ([M$^+$], 24); 238 (56); 165 (29); 119 (37); 105 (100); 91 (63); 77 (72); 67 (59); Elemental Anal. Calcd C, 71.64; H, 4.51. Found: C, 71.42; H, 4.63.

4.4.13. 6-Phenylnaphthalene-1,2-diol 1e

Light brown powder; yield = 65%; mp = 178–180 °C (dec); ^{1}H NMR (acetone-d_6): 7.24 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.35 (tt, 1H, $^3J_{H4'-H3',5'}$ = 7.3 Hz, $^4J_{H4'-H2',6'}$ = 1.3 Hz, $H_{4'}$); 7.42 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.48 (m, 2H, $H_{3',5'}$); 7.73 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.9 Hz, H_7); 7.76 (m, 2H, $H_{2',6'}$); 8.02 (d, 1H, $^4J_{H5-H7}$ = 1.9 Hz, H_5); 8.22 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); ^{13}C NMR (acetone-d_6): 119.2 (CH); 120.7 (CH); 122.4 (CH); 125.0 (CH); 125.7 (C); 126.1 (CH); 127.7 (2 × CH); 127.8 (CH); 129.7 (2 × CH); 130.4 (C); 136.3 (C); 138.7 (C); 140.8 (C); 141.9 (C); MS (MALDI-TOF): *m*/*z* (%) = 238 (25); 237 (58); 236 ([M$^+$], 100); 235 (40); Elemental Anal. Calcd C, 81.34; H, 5.12. Found: C, 81.18; H, 5.21.

4.4.14. 6-(2-Hydroxyphenyl)naphthalene-1,2-diol 1f

Dark brown powder; yield = 47%; mp = 168 °C (dec); ^{1}H NMR (acetone-d_6): 6.76–6.88 (m, 2H, $H_{3'}$ and $H_{5'}$); 7.04–7.36 (m, 3H, H_3, H_4 and $H_{6'}$); 7.57–7.78 (m, 2H, H_7 and $H_{4'}$); 7.93 (br s, 1H, OH); 8.11–8.24 (m, 2H, H_5 and H_8); 8.53 (br s, 2H, 2 × OH); ^{13}C NMR (acetone-d_6): 116.9 (CH); 119.1 (CH); 120.7 (CH); 122.2 (CH); 122.3 (CH); 124.9 (CH); 125.8 (C); 126.0 (CH); 129.0 (C); 129.1 (CH); 129.2 (CH); 130.4 (C); 136.5 (C); 138.8 (C); 140.7 (C); 154.6 (C); MS (MALDI-TOF): *m*/*z* (%) = 253 (38); 252 ([M$^+$], 100); Elemental Anal. Calcd C, 76.18; H, 4.79. Found: C, 76.49; H, 4.96.

4.4.15. 6-(3-Hydroxyphenyl)naphthalene-1,2-diol 1g

Light brown powder; yield = 75%; mp = 186–187 °C (dec); ^{1}H NMR (acetone-d_6): 6.85 (ddd, 1H, $^3J_{H4'-H5'}$ = 7.9 Hz,

$^4J_{H4'-H2'}$ = 2.4 Hz, $^4J_{H4'-H6'}$ = 1.2 Hz, $H_{4'}$); 7.22–7.33 (m, 4H, $H_{2'}$ and $H_{6'}$ and H_3 and $H_{5'}$); 7.41 (d, 1H, $^3J_{H4-H3}$ = 8.5 Hz, H_4); 7.70 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.84 (br s, 1H, OH); 7.99 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.20 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.40 (br s, 2H, 2 × OH); ^{13}C NMR (acetone-d_6): 114.6 (CH); 114.9 (CH); 119.0 (CH); 119.2 (CH); 120.7 (CH); 122.3 (CH); 125.0 (CH); 125.7 (C); 126.1 (CH); 130.4 (C); 130.7 (CH); 136.4 (C); 138.8 (C); 140.8 (C); 143.5 (C); 158.7 (C); MS (EI): *m*/*z* (%) = 253 (42); 252 ([M$^+$], 100); 251 (21); Elemental Anal. Calcd C, 76.18; H, 4.79. Found: C, 75.97; H, 4.87.

4.4.16. 6-(4-Hydroxyphenyl)naphthalene-1,2-diol 1h

Brown powder; yield = 91%; mp >250 °C (dec); ^{1}H NMR (acetone-d_6): 6.96 (d, 2H, $^3J_{H3',5'-H2',6'}$ = 8.5 Hz, $H_{3',5'}$); 7.21 (d, 1H, $^3J_{H3-H4}$ = 8.5 Hz, H_3); 7.37 (d, 1H, $^3J_{H4-H3}$ = 8.5 Hz, H_4); 7.62 (d, 2H, $^3J_{H2',6'-H3',5'}$ = 8.5 Hz, $H_{2',6'}$); 7.68 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.80 (s, 1H, OH); 7.93 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.17 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.34 (s, 1H, OH); 8.46 (s, 1H, OH); ^{13}C NMR (acetone-d_6): 116.5 (2 × CH); 119.1 (CH); 120.5 (CH); 122.2 (CH); 124.9 (CH); 125.0 (CH); 125.2 (C); 128.8 (2 × CH); 130.5 (C); 133.2 (C); 136.3 (C); 138.8 (C); 140.4 (C); 157.7 (C); MS (EI): *m*/*z* (%) = 252 ([M$^+$]. 5); 250 (7); 223 (19); 222 (100); 194 (18); 165 (20); Elemental Anal. Calcd C, 76.18; H, 4.79. Found: C, 76.04; H, 4.90.

4.4.17. 6-(2-Trifluoromethylphenyl)naphthalene-1,2-diol 1i

Brown powder; yield = 85%; mp = 110 °C (dec); ^{1}H NMR (acetone-d_6): 7.24 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.31 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.32 (dm, 1H, $^3J_{H7-H8}$ = 8.8 Hz, H_7); 7.45 (dm, 1H, $^3J_{H6'-H5'}$ = 6.9 Hz, $H_{6'}$); 7.59 (ddm, 1H, $^3J_{H4'-H5'}$ = 8.1 Hz, $^3J_{H4'-H3'}$ = 7.8 Hz, $H_{4'}$); 7.63 (m, 1H, H_5); 7.70 (ddm, 1H, $^3J_{H5'-H4'}$ = 8.1 Hz, $^3J_{H5'-H6'}$ = 6.9 Hz, $H_{5'}$); 7.80 (dm, $^3J_{H3'-H4'}$ = 7.8 Hz, $H_{3'}$); 7.90 (br s, 1H, OH); 8.11 (d, 1H. $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.47 (br s, 1H, OH); MS (MALDI-TOF): *m*/*z* (%) = 305 (42); 304 ([M$^+$]. 100); 303 (33); Elemental Anal. Calcd C, 67.11; H, 3.64; F, 18.73. Found: C, 67.45; H, 3.78; F, 18.49. Since **1i** rapidly degraded in acetone solution the ^{13}C NMR spectra cannot be recorded.

4.4.18. 6-(3-Trifluoromethylphenyl)naphthalene-1,2-diol 1j

Gray powder; yield = 90%; mp = 154–157 °C; ^{1}H NMR (acetone-d_6): 7.29 (d, 1H, $^3J_{H3-H4}$ = 8.7 Hz, H_3); 7.46 (d, 1H, $^3J_{H4-H3}$ = 8.7 Hz, H_4); 7.67–7.69 (m, 2H, $H_{5'}$ and $H_{6'}$); 7.78 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.9 Hz, H_7); 7.94 (br s, 1H, OH); 8.03 (m, 1H. $H_{4'}$); 8.08 (br s, 1H, $H_{2'}$); 8.16 (d, 1H, $^4J_{H5-H7}$ = 1.9 Hz, H_5); 8.27 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.53 (br s, 1H, OH); ^{13}C NMR (acetone-d_6): 119.4 (s, CH); 121.0 (s, CH); 122.7 (s, CH); 124.2 (q, CH, $^3J_{C-F}$ = 3.7 Hz); 124.3 (q, CH, $^3J_{C-F}$ = 3.7 Hz); 124.7 (s, CH); 125.4 (q, CF_3, $^1J_{C-F}$ = 271.6 Hz); 126.0 (s, C); 126.8 (s, CH); 130.3 (s, C); 130.6 (s, CH); 131.5 (s, CH); 131.5 (q, C, $^2J_{C-F}$ = 31.7 Hz); 134.6 (s, C); 138.8 (s, C); 141.3 (s, C); 143.0 (s, C); MS (MALDI-TOF): *m*/*z* (%) = 305 (33); 304 ([M$^+$]. 100); 303 (19); Elemental Anal. Calcd C, 67.11; H, 3.64; F, 18.73. Found: C, 67.32; H, 3.71; F, 18.54.

4.4.19. 6-(4-Trifluoromethylphenyl)naphthalene-1,2-diol 1k

Green powder; yield = 94%; mp = 114–117 °C (dec); ^{1}H NMR (acetone-d_6): 7.28 (d, 1H, $^3J_{H3-H4}$ = 8.7 Hz, H_3); 7.45 (d, 1H, $^3J_{H4-H3}$ = 8.7 Hz, H_4); 7.73 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.95 Hz, H_7); 7.80 (d, 2H, $^3J_{H3',5'-H2',6'}$ = 8.8 Hz, $H_{3',5'}$ or $H_{2',6'}$); 7.94 (br s, 1H, OH); 7.97 (d, 2H, $^3J_{H3',5'-H2',6'}$ = 8.8 Hz, $H_{3',5'}$ or $H_{2',6'}$); 8.12 (d, 1H, $^4J_{H5-H7}$ = 1.95 Hz, H_5); 8.26 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.54 (br s, 1H, OH); ^{13}C NMR (acetone-d_6): 119.3 (s, CH); 121.0 (s, CH); 122.7 (s, CH); 124.7 (s, CH); 125.5 (q, CF_3, $^1J_{C-F}$ = 271.0 Hz); 126.0 (s, C); 126.5 (q, CH, $^3J_{C-F}$ = 3.7 Hz); 126.9 (s, CH); 128.2 (s, CH); 129.1 (q, C, $^2J_{C-F}$ = 32.3 Hz); 130.2 (s, C); 134.6 (s, C); 138.7 (s, C); 141.2 (s, C); 145.8 (s, C); MS (MALDI-TOF): *m*/*z* (%) = 305 (50); 304 ([M$^+$], 100); 303 (51); Elemental Anal. Calcd C, 67.11; H, 3.64; F, 18.73. Found: C, 67.02; H, 3.75; F, 18.82.

4.4.20. 6-(2-Fluorophenyl)naphthalene-1,2-diol 1l

Green powder; yield = 95%; mp = 145–147 °C (dec); ^{1}H NMR (acetone-d_6): 7.22–7.34 (m, 2H, $H_{3'}$ and $H_{5'}$); 7.25 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.37–7.45 (m, 1H, $H_{4'}$); 7.41 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.60–7.65 (m, 2H, H_7 and $H_{6'}$); 7.88 (s, 1H, OH); 7.94 (br s, 1H, H_5); 8.20 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.46 (s, 1H, OH); ^{13}C NMR (acetone-d_6): 116.8 (d, CH, $^2J_{C-F}$ = 22.6 Hz); 119.2 (s, CH); 120.7 (s, CH); 121.9 (s, CH); 125.5 (d, CH, $^4J_{C-F}$ = 3.7 Hz); 125.7 (s, C); 126.6 (d, CH, $^4J_{C-F}$ = 3.0 Hz); 128.6 (d, CH, $^4J_{C-F}$ = 3.0 Hz); 129.8 (d, CH, $^3J_{C-F}$ = 8.6 Hz); 129.9 (d, C, $^2J_{C-F}$ = 13.4 Hz); 130.0 (s, C); 131.2 (d, C, $^3J_{C-F}$ = 1.2 Hz); 131.8 (d, CH, $^3J_{C-F}$ = 3.7 Hz); 138.7 (s, C); 141.0 (s, C); 160.7 (d, C, $^1J_{C-F}$ = 246.0 Hz); MS (ei): *m*/*z* (%) = 255 (24); 254 ([M$^+$], 100); 253 (33); Elemental Anal. Calcd C, 75.58; H, 4.36; F, 7.47. Found: C, 75.25; H, 4.49; F, 7.30.

4.4.21. 6-(3-Fluorophenyl)naphthalene-1,2-diol 1m

Green powder; yield = 90%; mp = 146–148 °C; ^{1}H NMR (acetone-d_6): 7.11 (dddd, 1H, $^3J_{H4'-F}$ = 9.2 Hz, $^3J_{H4'-H5'}$ = 7.8 Hz, $^4J_{H4'-H2'}$ = 2.7 Hz, $^4J_{H4'-H6'}$ = 1.0 Hz, $H_{4'}$); 7.25 (d, 1H, $^3J_{H3-H4}$ = 8.8 Hz, H_3); 7.43 (d, 1H, $^3J_{H4-H3}$ = 8.8 Hz, H_4); 7.47–7.56 (m, 2H, $H_{2'}$ and $H_{5'}$); 7.61 (ddd, 1H, $^3J_{H6'-H5'}$ = 7.8 Hz, $^4J_{H6'-H2'}$ = 1.7 Hz, $^4J_{H6'-H4'}$ = 1.0 Hz, $H_{6'}$); 7.74 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 2.0 Hz, H_7); 7.90 (s, 1H, OH); 8.07 (d, 1H. $^4J_{H5-H7}$ = 2.0 Hz, H_5); 8.22 (d, 1H,$^3J_{H8-H7}$ = 8.8 Hz,H_8); 8.50 (s,1H,OH); ^{13}C NMR (acetone-d_6): 114.2 (d, CH, $^2J_{C-F}$ = 22.0 Hz);114.3 (d, CH, $^2J_{C-F}$ = 21.4 Hz); 119.3 (s, CH); 120.9 (s, CH); 122.5 (s, CH); 123.5 (d, CH, $^4J_{C-F}$ = 3.1 Hz); 124.7 (s, CH); 125.9 (s, C); 126.5 (s, CH); 130.3 (s, C); 131.4 (d, CH, $^3J_{C-F}$ = 8.6 Hz); 134.8 (d, C, $^4J_{C-F}$ = 2.5 Hz); 138.8 (s, C); 141.1 (s, C); 144.5 (d, C, $^3J_{C-F}$ = 7.9 Hz); 164.1 (d, C, $^1J_{C-F}$ = 243.5 Hz); MS (MALDI-TOF): *m*/*z* (%) = 255 (40); 254 ([M$^+$]. 100); 253 (26); Elemental Anal. Calcd C, 75.58; H, 4.36; F, 7.47. Found: C, 75.81; H, 4.28; F, 7.33.

4.4.22. 6-(4-Fluorophenyl)naphthalene-1,2-diol 1n

Green powder; yield = 69%; mp = 161–163 °C (dec); ^{1}H NMR (acetone-d_6): 7.21–7.26 (m, 2H, $H_{3',5'}$); 7.24 (d, 1H, $^3J_{H3-H4}$ = 8.6 Hz, H_3); 7.40 (d, 1H, $^3J_{H4-H3}$ = 8.6 Hz, H_4); 7.69 (dd, 1H, $^3J_{H7-H8}$ = 8.8 Hz, $^4J_{H7-H5}$ = 1.7 Hz, H_7); 7.76–7.81 (m, 2H, $H_{2',6'}$); 7.87 (s, 1H, OH); 7.99 (d, 1H, $^4J_{H5-H7}$ = 1.7 Hz, H_5); 8.20 (d, 1H, $^3J_{H8-H7}$ = 8.8 Hz, H_8); 8.46 (s, 1H, OH); ^{13}C NMR (acetone-d_6): 116.3 (d, 2 × CH, $^2J_{C-F}$ = 21.4 Hz); 119.3 (s, CH); 120.7 (s, CH); 122.5 (s, CH); 124.9 (s, CH); 125.6 (s, C); 126.1 (s, CH); 129.5 (d, 2 × CH, $^3J_{C-F}$ = 8.6 Hz); 130.3 (s, C); 135.2 (s, C); 138.3 (d, C, $^4J_{C-F}$ = 3.0 Hz); 138.8 (s, C); 140.9 (s, C); 163.1 (d, C, $^1J_{C-F}$ = 244.1 Hz); MS (ei): *m*/*z* (%) = 254 ([M$^+$]. 32); 224 (100); 196 (36); Elemental Anal. Calcd C, 75.58; H, 4.36; F, 7.47. Found: C, 75.76; H, 4.30; F, 7.58.

4.5. ESR spectroscopy

The CW X-band ESR measurement were carried out on a Bruker Elexys 580_FT spectrometer at room temperature. The using parameters are 6.34 microwave power and 10 G amplitude modulation. The sample powder was analyzed in a quartz tube inserted in a standard cavity.

4.6. Integrase inhibition

To determine the susceptibility of the HIV-1 integrase enzyme to different compounds, we used an enzyme-linked immunosorbent assay. This assay uses an oligonucleotide substrate in which one oligo (5′-ACTGCTAGAGATTTTCCACACTGACTAAAAGGGTC-3′) is labeled with biotin on the 3′ end and in which the other oligo is labeled with digoxigenin at the 5′ end. For the overall integration assay, the second 5′-digoxigenin-labeled oligo is

5′-GACCCTTTTAGTCAGTGTGGAAAATCTCTAGCA*GT*-3′. The integrase was diluted in 750 mM NaCl, 10 mM Tris (pH 7.6), 10% glycerol, 1 mM β-mercaptoethanol, and 0.1 mg/mL bovine serum albumin. To perform the reaction, 4 μL of diluted integrase (corresponds to a concentration of WT integrase[17] of 1.6 μM) and 4 μL of annealed oligos (7 nM) were added in a final reaction volume of 40 μL containing 10 mM $MgCl_2$, 5 mM DTT, 20 mM HEPES (pH 7.5), 5% PEG, and 15% DMSO. The reaction was carried out for 1 h at 37 °C. These reactions were followed by an immunosorbent assay on avidin-coated plates.[18] 3′-Processing and strand transfer assays were performed according to previously reported methods.[19]

4.7. In vitro anti-HIV and drug susceptibility assays

4.7.1. Hela-CD4+-ßGal (P4) cells

The lymphocytes cell line CEM4fx was maintained in RPMI-1640 medium supplemented with 10% fetal calf serum. Hela-CD4+-ßGal (P4) cells were grown in DMEM with 10% fetal calf serum and 0.5 mg/mL geneticin. Cell-free viral supernatants were obtained by trans-fection of P4 cells with HIV-1 PLN4-3 genomic clone.[20] CEM4fx cells were plated in triplicate on a 96-well plate (100 μL) and infected with cell-free virus. Viral supernatants were removed 2 h after infection and drugs dissolved in DMSO were added in fresh medium. Infected cells were grown in the presence of drugs for 3 days. Supernatants were then collected at $t = 72$ h and used to infect P4 cells. P4 cultures were incubated for 24 h and subsequently lyzed in a phosphate buffer containing 50 mM 2-mercaptoethanol, 10 mM $MgSO_4$, 25 mM EDTA, 0.125% NP40. 20 μL of lyzate was incubated with 100 μL of CPRG-containing buffer. The red staining intensity was quantified on a multiscan photometer at 570 nm. CEM4fx cell viability was estimated by the MTT (Sigma) assay after 3 days treatment with drugs (20 μL). A solution of (7.5 mg/mL) in phosphate buffer was added to each well of microtiter trays. Plates were further incubated at 37 °C in a CO_2 incubator for 4 h. Solubilization of formazan crystals was achieved by adding 100 mL of 10% SDS, 10 mM HCl. Absorbance was read in a multiscan photometer at 570 nm. Experiments were performed in triplicate and averaged.

4.7.2. Lymphocyte MT-4 cell

The inhibitory effect of antiviral drugs on the HIV-1-induced cytopathic effect (CPE) in human lymphocyte MT-4 cell culture was determined by the MT-4/MTT assay.[21] This assay is based on the reduction of the yellow colored 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) by mitochondrial dehydrogenase of metabolically active cells to a blue formazan derivative, which can be measured spectrophotometrically. The 50% cell culture infective dose ($CCID_{50}$) of the HIV-1 (III_B) strain was determined by titration of the virus stock using MT-4 cells. For the drug susceptibility assays, MT-4 cells were infected with 100−300 $CCID_{50}$ of the virus stock in the presence of fivefold serial dilutions of the antiviral drugs. The concentration of various compounds achieving 50% protection against the CPE of the different HIV strains, which is defined as the EC_{50}, was determined. In parallel, the 50% cytotoxic concentration (CC_{50}) was determined.

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References and notes

1. De Clercq, E. *Int. J. Antimicrob. Agents* **2009**, *33*, 307.
2. Low, A.; Mohri, H.; Markowitz, M. 14th Conference on Retroviruses and Opportunistic Infections Feb 25–28, 2007. Los Angeles, CA.
3. Cooper, D. A.; Steigbigel, R. T.; Gatell, J. M.; Rockstroh, J. K.; Katlama, C.; Yeni, P.; Lazzarin, A.; Clotet, B.; Kumar, P. N.; Eron, J. E.; Schechter, M.; Markowitz, M.; Loutfy, M. R.; Lennox, J. L.; Zhao, J.; Chen, J.; Ryan, D. M.; Rhodes, R. R.; Killar, J. A.; Gilde, L. R.; Strohmaier, K. M.; Meibohm, A. R.; Miller, M. D.; Hazuda, D. J.; Nesly, M. L.; DiNubile, M. J.; Isaacs, R. D.; Tippler, H.; Nguyen, B. Y. *N. Eng. J. Med.* **2008**, *359*, 355.
4. Malet, I.; Delelis, O.; Valantin, M. A.; Montes, B.; Soulie, C.; Wirden, M.; Tchertanov, L.; Peytavin, G.; Reynes, J.; Mouscadet, J. F.; Katlama, C.; Calvez, V.; Marcelin, A. G. *Antimicrob. Agents Chemother.* **2008**, *52*, 1351.
5. Goethals, O.; Clayton, R.; Van Ginderen, M.; Vereycken, I.; Wagemans, E.; Geluykens, P.; Dockx, K.; Strijbos, R.; Smits, V.; Vos, A.; Meersseman, G.; Jochmans, D.; Vermeire, K.; Schols, D.; Hallenberger, S.; Hertogs, K. *J. Virol.* **2008**, *82*, 10366.
6. Kobayashi, M.; Nakahara, K.; Seki, T.; Miki, S.; Kawauchi, S.; Suyuma, A.; Wakasa-Morimoto, C.; Kodama, M.; Endoh, T.; Oosugi, E.; Matsushita, Y.; Murai, H.; Fujishita, T.; Yoshinaga, T.; Garvey, E.; Foster, S.; Underwood, M.; Johns, B.; Sato, A.; Fujiwara, T. *Antiviral Res.* **2008**, *80*, 213.
7. Serrao, E.; Odde, S.; Ramkumar, K.; Neamati, N. *Retrovirology* **2009**, *6*, 25.
8. Cowan, J. A. *The Biological Chemistry of Magnesium*; VCH: New York, 1995. pp 1–23.
9. (a) Maurin, C.; Bailly, F.; Cotelle, P. *Curr. Med. Chem.* **2003**, *10*, 1795; (b) Ramkumar, K.; Serrao, E.; Odde, S.; Neamati, N. *Med. Res. Rev.* **2010** doi:10.1002/med.20194.
10. Dupont, R.; Jeanson, L.; Mouscadet, J.-F.; Cotelle, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3175.
11. Maurin, C.; Bailly, F.; Cotelle, P. *Tetrahedron* **2005**, *61*, 7054.
12. Burke, T. R., Jr.; Lim, B.; Marquez, V. E.; Li, Z. H.; Bolen, J. B.; Stefanova, I.; Horak, I. D. *J. Med. Chem.* **1993**, *36*, 425.
13. Nakashima, H.; Murakami, T.; Yamamoto, N.; Naoe, T.; Kawazoe, Y.; Konno, K.; Sakagami, H. *Chem. Pharm. Bull.* **1992**, *40*, 2102.
14. Cotelle, P.; Vezin, H. *Res. Chem. Intermed.* **2003**, *29*, 365.
15. Pluymers, W.; Neamati, N.; Pannecouque, C.; Fikkert, V.; Marchand, C.; Burke, T. R.; Pommier, Y.; Shols, D.; De Clercq, E.; Debyser, Z.; Witvrouw, M. *Mol. Pharmacol.* **2000**, *58*, 641.
16. Cos, P.; Maes, L.; Vlietinck, A.; Pieters, L. *Planta Med.* **2008**, *74*, 1323.
17. Debyser, Z.; Cherepanov, P.; Pluymers, W.; De Clercq, E. *Methods Mol. Biol.* **2001**, *160*, 139.
18. Hwang, Y.; Rhodes, D.; Bushman, F. *Nucleic Acids Res.* **2000**, *28*, 4884.
19. Busschots, K.; Voet, A.; De Mayer, M.; Rain, J. C.; Emiliani, S.; Benarous, R.; Desender, L.; Debyser, Z.; Christ, F. *J. Mol. Biol.* **2007**, *365*, 1480.
20. Jeanson, L.; Subra, F.; Vaganay, S.; Hervy, M.; Marangoni, E.; Bourhis, J.; Mouscadet, J. F. *Virology* **2002**, *300*, 100.
21. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewijn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309.