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Synthesis and HIV-1 Integrase Inhibitory Activities of Catechol and Bis-Catechol Derivatives

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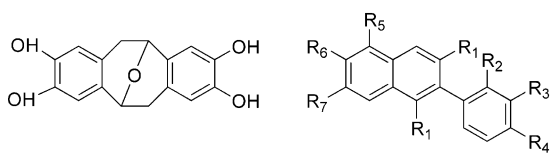
Abstract—Fourteen catechol and bis-catechol derivatives have been synthesised and tested for their HIV-1 inhibitory activities. The six more active molecules have been tested for their antiviral activity and cytotoxicity. We have found that bis-catechols **1** and **2** are the most active HIV-1 integrase inhibitor whereas the best antiviral compound is **4**.

Human Immunodeficiency Virus (HIV) is the causative agent of acquired immune deficiency syndrome (AIDS), thus warranting the interest for the search for new powerful inhibitors of the virus replication. The latter depends on the molecular engine consisting of three viral enzymes, the reverse transcriptase, the protease and the integrase (IN). Inhibitors of reverse transcriptase and protease have been extremely useful for treating HIV-infected people, particularly when used in combination.[1,2] Despite the fact that combination antiretroviral therapy has made it possible to suppress the replication of HIV-1 in infected persons to such an extent that the virus becomes undetectable in the plasma for more than two years, the virus persists in cellular reservoirs, which remain to be clearly identified. This means that HIV-1 infection cannot be eradicated with current treatments.[3,4] It is therefore important to search for new agents that could block the virus at other steps of its replication cycle, which are not affected by current treatments. HIV integrase (IN) is one such promising target because integration is an essential step in retroviral replication cycle.[5,6]

Systematic screening of potential inhibitors has been undertaken using mostly purified integrase-based assays. One of the most important class of IN inhibitor includes hydroxylated aromatic compounds such as aurintricarboxylic acids,[7] bis-catechols,[8–12] CAPE,[13,14] styrylquinoline derivatives[15–17] and lamellarins.[18] Structure–activity base correlations identified the catechol structure as a possible pharmacophore. For reasons that are still not well understood, most of the catechol-containing inhibitors display a toxic effect on cell culture whereas numerous natural polyphenols are not toxic.

In this study, our goal was to test new rigid and semi-rigid catechols and bis-catechols as IN inhibitors and find new motifs that can substitute for catechol.

The three bis-catechols **1**–**3** (Scheme 1) were obtained as previously described by us.[19–21] Compounds **4**–**14**[22] (Scheme 1) were synthesised by a cross-condensation procedure using an equimolecular mixture of 3,4-dimethoxyphenylacetone and another arylacetone treated with boron tribromide. Using this procedure compounds **5** and **6**, **7** and **8**, **9** and **10** and **11** and **12** were obtained



1 **2-14**

Scheme 1.

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from 3,4-dimethoxyphenylacetone and phenylacetone, 4-methylphenylacetone, 2-fluorophenylacetone and 4-fluorophenylacetone, respectively. In each case, **3** and the dimer[21] obtained from two molecules of the other arylacetone were isolated. Each isomer can be separated and purified by repeated liquid chromatographies. The yields in pure products are generally lower than 5%. When the aromatic ring of the other arylacetone was substituted by a electron-withdrawing group, such as trifluoromethyl group, the cross-condensation afforded selectively in low yields the 2,3-dihydroxynaphthalenic isomer **4**, **13** and **14**.

Each new compound was screened for inhibitory activity against HIV-1 IN in both Mg^{2+}-dependant 3′-end-processing and strand-transfer reactions. Since there are no significant differences between the two reactions, we present in Table 1 the inhibitory activity in 3′-processing reaction. These compounds can be roughly classified as active (**1**–**4**, **13**–**14**) and inactive (**5**–**12**). The active series was constituted by the three bis-catechols **1**–**3** and the three 2-(trifluoromethylphenyl)-1,3-dimethylnaphthalene-6,7-diols **4**, **13** and **14**. Micromolar activities were obtained with bis-catechols **1** and **2**, whereas **3**, **4**, **13** and **14** are 10-fold less active. Three dimensional structures of **1**–**3** have been previously reported.[23] Compound **1** presents a folded-rigid structure with an angle of about 90–100° between the two catechol motifs whereas **2** and **3** present a semi-rigid structure where the naphthyl and phenyl rings show an angle of about 40 and 80°, respectively. The tested compounds present the general structural features common to many HIV integrase inhibitors, that is two aryl units, one of which contains the 1,2-dihydroxy pattern, separated by an appropriate linker segment. The other one generally contains at least one hydroxy group. Numerous bis-catechols have been previously tested[8,12] and the best results are obtained when the two catechol rings are not conjugated (linked by one or more sp^3 carbon atom) and presents an angle close to 90° between the two aromatic rings. It is the case for **1** that is the most active in this study. Conversely, numerous bis-catechols where the two aromatic units are conjugated were found to be active.[15–17] It seems that a strong twist between the conjugated rings lower the HIV-1 IN activity (**2** vs **3**). More originally are the comparable activities of **3** and **4**, **13** and **14**. It seems that the 3,4-dihydroxyphenyl group may be replaced by a trifluoromethylphenyl group whatever the position of the trifluoromethyl group on the aromatic ring. The inactive series (**5**–**12**) also revealed some interesting information. It may be divided into two sub-groups: the fairly active molecules (**5**, **7**, **11** and **8**) and the totally inactive ones (**6**, **9**, **10** and **12**). From this sub-division, it appears that the 2,3-dihydroxynaphthyl moiety was found in the less inactive molecules. This is not unexpected since 2,3-dihydroxynaphthalene is known to bind more readily divalent cations than catechol.[24]

Table 1. HIV-1 IN inhibitory potencies of compounds **1**–**14**

Compd	R1	R2	R3	R4	R5	R6	R7	IC_{50} (μM)
1								1.3
2	H	H	OH	OH	H	OH	OH	2.1
3	CH_3	H	OH	OH	H	OH	OH	23
4	CH_3	H	CF_3	H	H	OH	OH	13
5	CH_3	H	H	H	H	OH	OH	76
6	CH_3	H	OH	OH	H	H	H	500
7	CH_3	H	H	CH_3	H	OH	OH	84
8	CH_3	H	OH	OH	H	H	CH_3	157
9	CH_3	F	H	H	H	OH	OH	500
10	CH_3	H	OH	OH	F	H	H	500
11	CH_3	H	H	F	H	OH	OH	138
12	CH_3	H	OH	OH	H	H	F	500
13	CH_3	CF_3	H	H	H	OH	OH	22
14	CH_3	H	H	CF_3	H	OH	OH	21

Compounds **1**–**3**, **13**–**14** were evaluated for their antiviral activities against HIV-1 replication in CEM cells. They were tested for their ability to lower the viral charge in culture supernatants. CEM cells were infected with HIV-1 for 2 h and subsequently treated with increasing drug concentrations. Antiviral effect was estimated three days after infection. Viral load was determined by an infectivity assay on Hela-$CD4^+$-βGal reporter cells. Cytotoxicity was estimated by a cell viability MTT assay. Results are listed in Table 2.

The present molecules exhibited a weak to relatively high toxicity (TC_{50} between 13.6 and 72.6 μM) and a moderate antiviral activity (IC_{50} between 5.7 and 10.5 μM) except for **1** which is poorly active but non-toxic ($TC_{50} > 100$ μM). The best results were obtained with **4** that is the most active and the least toxic molecule presented here with a therapeutic index of about 12.7.

In conclusion, amongst fourteen easily available polyphenols, we have found two active molecules against purified HIV-1 IN. We are currently studying the docking of the rigid molecule **1** to the HIV-1 IN catalytic core. Compounds **1** and **2** will be also tested against a preintegration complex (PIC)-mediated strand transfer assay which constitutes a more relevant assay of anti-integrase compounds in vivo.[25,26] It is now well known that a catechol function is not sufficient to afford HIV-1 integrase inhibitor. The model proposed by Burke et al.[13] involves another ancillary aromatic unit that possess substituent able to form hydrogen bond (generally as a 4-hydroxy substitution).[17] Trifluoromethyl group may be useful to maintain the HIV-1 integrase inhibitor activity (whatever its position on the aromatic ring), increase the antiviral activity and decrease the toxicity (in position 3). Some other compounds that possess the rigid structure of **1** are actually synthesised as well as the three 2-(trifluoromethylphenyl)naphthalene-6,7-diols.

Table 2. Antiviral activity and cytotoxicity

Compd	IC_{50} (μM)	TC_{50} (μM)
1	98	N.R.
2	9.9	51
3	8.7	33
4	5.7	72.6
13	10.3	13.6
14	10.5	19

N.R., not reached.

Acknowledgements

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22. General procedure: BBr_3 (1 M in CH_2Cl_2, 25 mL, 25 mmol) was added dropwise to a solution of 3,4-dimethoxyphenylacetone (2.5 mmol) and arylacetone (2.5 mmol) in CH_2Cl_2 (25 mL) at room temperature. The mixture was stirred for 1 h, then water (40 mL) was added dropwise. The aqueous layer was extracted twice with ethyl acetate (20 mL). The organic layer was dried ($MgSO_4$), the solvent evaporated and the residue was purified by repeated column chromatographies.

4: 5,7-Dimethyl-6-(3-trifluoromethylphenyl)naphthalene-2,3-diol: brown oil, ^{1}H NMR ($CDCl_3$): δ 2.06 (d, 3H, ^4J = 0.95 Hz), 2.22 (s, 3H), 7.20 (s, 1H), 7.30–7.40 (m, 2H), 7.42 (s, 1H), 7.47 (m, 1H), 7.56 (t, 1H, ^3J = 7.65 Hz, ^3J = 7.30 Hz), 7.61–7.68 (m, 1H), ^{13}C NMR ($CDCl_3$): δ 16.8 (q), 21.8 (q), 107.7 (d), 110.2 (d), 123.6 (d, $^3J_{CF}$ = 4 Hz), 124.5 (s, $^1J_{CF}$ = 272 Hz), 124.7 (d), 126.4 (d, $^3J_{CF}$ = 4 Hz), 127.3 (s), 128.9 (s), 129.3 (d, $^4J_{CF}$ = 2 Hz), 129.7 (s, $^2J_{CF}$ = 31 Hz), 131.1 (d), 132.1 (s), 133.1 (s), 137 (s), 142.8 (s), 143.9 (s), 144.2 (s), IEMS (60 eV): 332 ($M^{+\bullet}$, 100%), 317 (15%), 316 (9%), 282 (9%), 247 (12%), 149 (11%), 123 (11%), 101 (11%).

5: 5,7-Dimethyl-6-phenylnaphthalene-2,3-diol: brown solid: mp 75–77 °C, ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H), 2.24 (s, 3H), 6.13 (se, 1H), 6.17 (se, 1H), 7.15 (d, 1H, ^5J = 1.45 Hz), 7.17 (s, 1H), 7.19 (d, 1H, ^5J = 1.45 Hz), 7.40–7.49 (m, 5H), ^{13}C NMR ($CDCl_3$): δ 16.7 (q), 21.7 (q), 107.7 (d), 110.1 (d), 124.3 (d), 126.6 (d), 127.3 (s), 128.3 (d), 129 (s), 129.5 (d), 129.9 (s), 132.7 (s), 138.7 (s), 141.9 (s), 143.7 (s), 143.9 (s), IEMS (60 eV): 264 ($M^{+\bullet}$, 100%), 249 (16%), 231 (8%), 203 (7%), 202 (9%), 101 (12%).

6: 2-(3,4-Dihydroxyphenyl)-1,3-dimethylnaphthalene: brown solid: mp 92–94 °C, ^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3H), 2.40 (s, 3H), 5.70 (se, 2H), 6.62 (dd, 1H, ^3J = 8.10 Hz, ^4J = 1.75 Hz), 6.71 (d, 1H, ^4J = 1.75 Hz), 6.96 (d, 1H, ^3J = 8.10 Hz), 7.47 (m, 2H), 7.59 (s, 1H), 7.80 (m, 1H), 8.01 (m, 1H), ^{13}C NMR ($CDCl_3$): δ 16.5 (q), 21.9 (q), 115.5 (d), 116.6 (d), 122.2 (d), 124.5 (d), 125.2 (d), 125.5 (d), 125.8 (d), 127.7 (d), 131.3 (s), 131.8 (s), 132.9 (s), 134.8 (s), 134.9 (s), 139.8 (s), 142.3 (s), 143.5 (s), IEMS (60 eV): 264 ($M^{+\bullet}$, 100%), 231 (14%), 203 (10%), 202 (15%), 193 (10%), 151 (14%), 108 (11%), 101 (16%).

7: 6-(4-Methylphenyl)-5,7-dimethylnaphthalene-2,3-diol: brown solid: mp 103–105 °C, ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.14 (s, 3H), 2.42 (s, 3H), 4.35 (se, 2H), 6.99 (d, 2H, ^3J = 8.30 Hz), 7.06 (s, 1H), 7.15 (d, 2H, ^3J = 8.30 Hz), 7.24 (s, 1H), 1.30 (s, 1H), ^{13}C NMR ($CDCl_3$): δ 16.8 (q), 21.3 (q), 21.9 (q), 107.8 (d), 110.3 (d), 124.3 (d), 127.4 (s), 129 (d), 129.5 (d), 130.1 (2s), 132.9 (s), 136.1 (s), 138.6 (s), 138.9 (s), 143.7 (s), 143.8 (s), IEMS (60 eV): 278 ($M^{+\bullet}$, 100%), 263 (17%), 248 (8%), 247 (7%), 245 (7%), 202 (6%), 139 (7%), 108 (7%), 107 (7%), 101 (9%).

8: 2-(3,4-Dihydroxyphenyl)-1,3,7-trimethylnaphthalene: brown solid: mp 66–68 °C, ^{1}H NMR ($CDCl_3$): δ 2.15 (d, 3H, ^4J = 0.95 Hz), 2.37 (s, 3H), 2.55 (s, 3H), 5.66 (se, 2H), 6.61 (dd, 1H, ^3J = 7.95 Hz, ^4J = 1.90 Hz), 6.70 (d, 1H, ^4J = 1.90 Hz), 6.95 (d, 1H, ^3J = 7.95 Hz), 7.31 (dd, 1H, ^3J = 8.30 Hz, ^4J = 1.60 Hz), 7.53 (s, 1H), 7.69 (d, 1H, ^3J = 8.30 Hz), 7.77 (se, 1H), ^{13}C NMR ($CDCl_3$): δ 16.5 (q), 21.8 (q), 22.1 (q), 115.4 (d), 116.6 (d), 122.1 (d), 123.6 (d), 125.5 (d), 127.6 (d), 127.7 (d), 131.07 (s), 131.13 (s), 131.4 (s), 133.9 (s), 134.7 (s), 134.8 (s), 139.9 (s), 142.4 (s), 143.6 (s), IEMS (60 eV): 278 ($M^{+\bullet}$, 100%), 263 (8%), 245 (13%), 207 (8%), 202 (8%), 115 (8%), 108 (10%), 107 (9%), 101 (11%).

9: 6-(2-Fluorophenyl)-5,7-dimethylnaphthalene-2,3-diol: brown oil: ^{1}H NMR ($CDCl_3$): δ 2.12 (s, 3H), 2.29 (s, 3H), 5.78 (se, 2H), 7.12–7.23 (m, 4H), 7.32–7.45 (m, 3H), ^{13}C NMR ($CDCl_3$): δ 16.7 (q), 21.3 (q), 108.4 (d), 110.8 (d), 116.4 (d, $^2J_{CF}$ = 22.30 Hz), 124.9 (d, $^3J_{CF}$ = 3.70 Hz), 125.3 (d), 128 (s), 129.7 (s, $^2J_{CF}$ = 17.90 Hz), 129.8 (d, $^3J_{CF}$ = 7.80 Hz), 130.3 (s), 131.8 (d, $^4J_{CF}$ = 0.75 Hz), 132.7 (s), 132.8 (s, $^3J_{CF}$ = 3.70 Hz), 133.5 (s), 144.8 (s), 145.2 (s), 160.9 (s, $^1J_{CF}$ = 243.80 Hz), IEMS (60 eV): 282 ($M^{+\bullet}$, 100%), 267 (19%), 220 (8%), 110 (10%).

10: 2-(3,4-Dihydroxyphenyl)-5-fluoro-1,3-dimethylnaphthalene: brown oil: ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 2.38 (s, 3H), 6.56 (dd, 1H, ^3J = 7.95 Hz, ^4J = 1.90 Hz), 6.72 (d, 1H, ^4J = 1.90 Hz), 6.98 (d, 1H, ^3J = 7.95 Hz), 7.11 (dd, 1H, ^3J = 7.60 Hz, $^3J_{HF}$ = 9.85 Hz), 7.37 (ddd, 1H, ^3J = 8.60 Hz, ^3J = 7.60 Hz, $^4J_{HF}$ = 5.70 Hz), 7.76 (de, 1H, ^3J = 8.60 Hz), 7.83 (se, 1H), ^{13}C NMR ($CDCl_3$): δ 16.8 (q), 22.1 (q), 109 (d, $^2J_{CF}$ = 19.70 Hz), 115.4 (d), 116 (d), 117.8 (d, $^3J_{CF}$ = 5.90 Hz), 120.3 (d, $^4J_{CF}$ = 3.90 Hz), 121.9 (d), 123 (s, $^2J_{CF}$ = 15.75 Hz), 124 (s, $^4J_{CF}$ = 3.40 Hz), 124.6 (d, $^3J_{CF}$ = 8.90 Hz), 127.7 (s, $^3J_{CF}$ = 7.90 Hz), 127.9 (s), 134.2 (s), 140.7 (s), 142.4 (s), 143.5 (s), 158.7 (s, $^1J_{CF}$ = 250.50 Hz), IEMS (60 eV): 282 ($M^{+\bullet}$, 34%), 101 (15%), 86 (100%), 58 (30%).

11: 6-(4-Fluorophenyl)-5,7-dimethylnaphthalene-2,3-diol: brown solid: mp = 68–70°C, ^{1}H NMR ($CDCl_3$): δ 2.08 (d, 3H, ^4J = 0.65 Hz), 2.24 (s, 3H), 7.11 (s, 2H), 7.15 (s, 2H), 7.17 (se, 1H), 7.37 (se, 1H), 7.40 (se, 1H), ^{13}C NMR ($CDCl_3$): δ 16.3 (q), 21.1 (q), 107.4 (d), 109.9 (d), 115.1 (d, $^2J_{CF}$ = 21 Hz), 124.3 (d), 127.2 (s), 130.7 (d, $^3J_{CF}$ = 6.30 Hz), 129.4 (s), 130.1 (s), 132.5 (s), 137.2 (s, $^4J_{CF}$ = 3 Hz), 137.6 (s), 144 (s), 144.2 (s), 161.6 (s, $^1J_{CF}$ = 244.90 Hz), IEMS (60 eV): 282 ($M^{+\bullet}$, 100%), 267 (16%), 249 (8%), 221 (7%), 220 (11%), 110 (12%).

12: 2-(3,4-Dihydroxyphenyl)-7-fluoro-1,3-dimethylnaphthalene: brown solid: mp = 172–174 °C, ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H), 2.33 (s, 3H), 6.60 (dd, 1H, ^3J = 7.90 Hz, ^4J = 1.60 Hz), 6.70 (d, 1H, ^4J = 1.60 Hz), 6.96 (d, 1H, ^3J = 7.90 Hz), 7.23 (td, 1H, ^3J = 8.90 Hz, $^3J_{HF}$ = 8.90 Hz, ^4J = 2.50 Hz), 7.56 (s, 1H), 7.59 (dd, 1H, $^3J_{HF}$ = 7.60 Hz, ^4J = 2.50 Hz), 7.76 (dd, 1H, ^3J = 8.90 Hz, $^4J_{HF}$ = 5.70 Hz), ^{13}C NMR ($CDCl_3$): δ 16.7 (q), 21.9 (q), 108.7 (d, $^2J_{CF}$ = 21.60 Hz), 116 (d, $^2J_{CF}$ = 25.60 Hz), 116.4 (d), 117.4 (d), 121.6 (d), 126.6 (s, $^4J_{CF}$ = 1.50 Hz), 131.1 (s), 131.3 (d, $^5J_{CF}$ = 1 Hz), 132.1 (s, $^3J_{CF}$ = 5.40 Hz), 133.5 (d, $^3J_{CF}$ = 8.40 Hz), 134.5 (s), 135.3 (s, $^4J_{CF}$ = 2.50 Hz), 142.7 (s), 145.3 (s), 146.4 (s), 161.8 (s, $^1J_{CF}$ = 242.20 Hz), IEMS (60 eV): 282 ($M^{+\bullet}$, 100%), 267 (7%), 249 (17%), 221 (11%), 220 (20%), 211 (14%), 110 (16%).

13: 5,7-Dimethyl-6-(2-trifluoromethylphenyl)naphthalene-2,3-diol: brown oil, ^{1}H NMR ($CDCl_3$): δ 2.01 (d, 3H, ^4J = 0.95 Hz), 2.15 (s, 3H), 6.23 (se, 2H), 7.17 (s, 1H), 7.20 (m, 1H), 7.37 (se, 1H), 7.38 (d, 1H, ^4J = 0.95 Hz), 7.45–7.65 (m, 2H), 7.80 (dd, 1H, ^3J = 7.65 Hz, ^4J = 1.60 Hz), ^{13}C NMR ($CDCl_3$): δ 16.9 (q), 21.2 (q), 107.6 (d), 110.1 (d), 123.9 (s, $^1J_{CF}$ = 274 Hz), 124.1 (d), 126.1 (d, $^3J_{CF}$ = 5.45 Hz), 127.4 (s), 128.9 (s, $^2J_{CF}$ = 29.4 Hz), 129.2 (d), 130.4 (d, $^4J_{CF}$ = 1.10 Hz), 131.1 (s), 131.6 (s), 131.7 (d, $^4J_{CF}$ = 1.10 Hz), 132.4 (s, $^4J_{CF}$ = 0.70 Hz), 135.1 (s), 140.7 (s, $^3J_{CF}$ = 2.20 Hz), 143.9 (s), 144.2 (s), IEMS (60 eV): 332 ($M^{+\bullet}$, 100%), 317 (10%), 293 (8%), 248 (9%), 247 (9%), 149 (44%), 101 (10%).

14: 5,7-Dimethyl-6-(4-trifluoromethylphenyl)naphthalene-2,3-diol: brown oil, ^{1}H NMR ($CDCl_3$): δ 2.07 (d, 3H, ^4J = 0.65 Hz), 2.23 (s, 3H), 5.63 (se, 2H), 7.18 (s, 1H), 7.30 (d, 2H, ^3J = 7.95 Hz), 7.39 (se, 1H), 7.41 (s, 1H), 7.71 (d, 2H, ^3J = 7.95 Hz), ^{13}C NMR ($CDCl_3$): δ 16.6 (q), 21.6 (q), 107.6 (d), 110.1 (d), 124.3 (s, $^1J_{CF}$ = 271.8 Hz), 124.5 (d), 125.2 (d, $^3J_{CF}$ = 3.60 Hz), 127.1 (s), 129.1 (s), 129.4 (s, $^2J_{CF}$ = 30.5 Hz), 129.8 (d, $^4J_{CF}$ = 2 Hz), 129.9 (s), 131.8 (s), 137 (s), 143.9 (s), 144.1 (s), 145.7 (s, $^5J_{CF}$ = 1.45 Hz), IEMS (60 eV): 332 ($M^{+\bullet}$, 100%), 317 (18%), 247 (10%), 202 (9%), 159 (14%), 107 (9%), 101 (11%).

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