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Regioselective Suzuki-Miyaura Reactions of 4,7-Dichloro-*N*-methylisatin. Synthesis, Anti-HIV Activity and Modeling Study

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Abstract. Suzuki-Miyaura reactions of 4,7-dichloro-*N*-methylisatin provide a convenient access to arylated methylisatins. The reactions proceed with excellent site-selectivity in favour of position 4, due to electronic reasons. All the new compounds were evaluated *in vitro* for their antiviral activity against the replication of HIV-1 and HIV-2 in MT4 cells using a MTT assay. 4-(4-Acetylphenyl)-7-chloro-1-methylindoline-2,3-dione (**8l**), containing an acetyl group located at carbon C(4) of the isatin backbone, showed an IC_{50} value of >3.47 μM against HIV-2 with a therapeutic index (SI) of 4. This means that **8l** was cytotoxic to MT-4 cells at a CC_{50} value of 13.43 μM; also 4,7-dichloro-1-methylindoline-2,3-dione (**5**), 7-chloro-4-(4-chlorophenyl)-1-methylindoline-2,3-dione (**8c**), 7-chloro-4-(4-ethoxyphenyl)-1-methylindoline-2,3-dione (**8g**) and 7-chloro-1-methyl-4-(4-vinylphenyl)indoline-2,3-dione (**8m**) were cytotoxic to MT-4 cells within a 2.21-3.11 μM concentration range. In a docking study, **8l** interacted with several amino acids in the reverse transcriptase (RT) binding site of HIV-2.

Key words. Suzuki-Miyaura cross coupling reaction, Isatin, NNRTIs, Anti-HIV activity, Modeling study

Introduction

Isatin derivatives (1*H*-indole-2,3-diones) show diverse biological activities,[1] such as antibacterial,[2] antifugal,[3] antiinflammatory[4] and anticonvulsant activity.[5] A variety of substituted isatin derivatives have been synthesized to date. The possibility of isatin to be attacked by nucleophiles at carbon C-3 allowed for the synthesis of a large number of 3-substituted isatins. This is also reflected by numerous biologically active 3-substituted indolin-2-ones that have been reported in the literature.[6-8] Most recently, Grewal and coworkers[9] have extensively studied the synthesis and biological screening of isatin derivatives. Furthermore, isatin derivatives have received considerable attention, due to their potent anticancer activities.[10-12] Meanwhile, Liu and colleagues[13] identified a class of isatin *O*-acyl oximes that selectively inhibit neuronal ubiquitin *C*-terminal hydrolase (UCH-L1) in a H1299 lung cancer cell line, which is proposed to be linked to tumor progression upon upregulation. Lee *et al*.[14] reported a novel indirubin analog, indirubin-5-nitro-3′-monoxime (**1**) which inhibited cell proliferation against various human cancer cells, meanwhile sunitinib malate (Sutent®) (**2**) had been approved by FDA for the treatment of advanced renal carcinoma,[15] and gastrointestinal stromal tumors.[16] Vine *et al.*[17] have reported that the introduction of electron withdrawing groups at the benzene ring of isatin are generally found to induce cancer cell death *via* apoptosis.

Owing to the broad spectrum of chemotherapeutic properties of isatin derivatives, several researchers[18-24] have found that such derivatives are ideal drugs for AIDS treatment, because they suppress HIV replication. Examples of such isatin derivatives are 3-[(4-amino-5(3,4,5-trimethoxybenzyl)pyrimidin-2-yl)imino)-5-bromo-1-(morpholinomethyl)indolin-2-one (**3**) and its *N*-acetyl derivative.[25] Furthermore, several isatin derivatives showed remarkable anti-HIV activity, like sulfonamide-benzene derivatives and Schiff and Mannich bases of isatin.[26-28] We report herein a convenient approach to arylated isatins by what are, to the best of our knowledge, the first Suzuki–Miyaura cross-coupling reactions of 4,7-dichloro-1-methylindoline-2,3-dione. The reactions proceed with very good regioselectivity in favor of position 4, due to electronic reasons. Besides, the new arylated isatin derivatives were evaluated for their anti-HIV activity. In addition, the molecular modeling structure was studied.

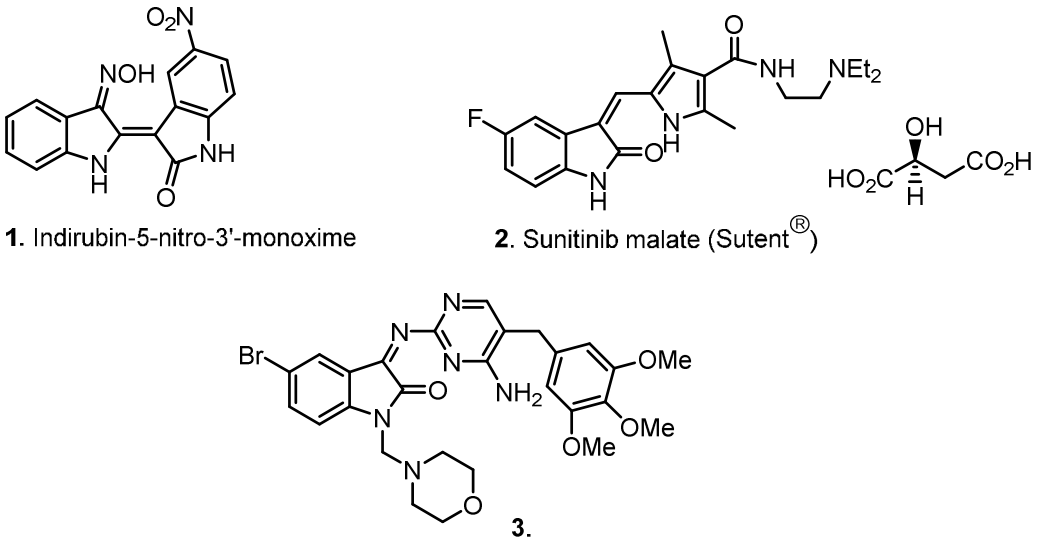
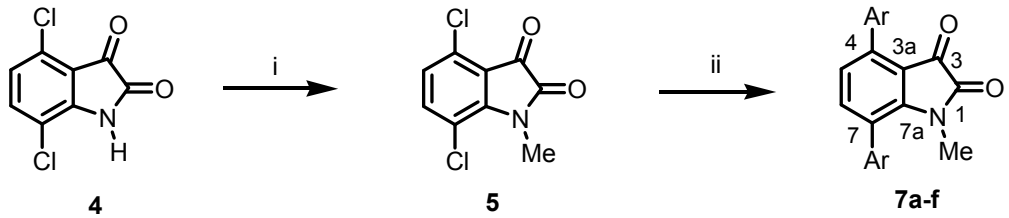


Figure 1. Some potentially active isatin derivatives

Results and Discussion

Chemistry. Commercially available 4,7-dichloroisatin (**4**) was converted, by a known procedure, to *N*-methyl-4,7-dichloroisatin (**5**) in 90% yield by using methyl iodid, DMF as a solvent and K_2CO_3 as the base (Scheme 1).[29] Treatment of **5** with arylboronic acids **6a-f** (2.0 equiv.), applying a Suzuki-Miyaura reaction, afforded *N*-methyl-4,7-diarylisatins **7a-f** in 52-82% yield (Scheme 1). Both electron-poor and electron-rich arylboronic acids could be successfully employed. The best yields were obtained by using $Pd(PPh_3)_4$ (6 mol-%) as the catalyst and K_3PO_4 (3.0 equiv) as the base in dioxane at 120 °C for 8 h.



Scheme 1. *Reagent and conditions*: (i) 1) K_2CO_3 (1.2 equiv.), DMF (1 mL per 0.1 mmol of isatin) 1 h, 4 to 20 °C; 2) CH_3I (1.1 equiv.), KI (cat., 0.2 equiv.), 80 °C, 5 h; (ii) $ArB(OH)_2$ (**6a-f**) (2.0 equiv.), K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%), 1,4-dioxane, 120 °C, 8 h.

Table 1. Synthesis of **7a-f**.

6,7	Ar	**7** (%) [a]
a	3,5-MeC_6H_3	61
b	4-$(MeO)C_6H_4$	82
c	4-ClC_6H_4	52
d	4-MeC_6H_4	58
e	4-EtC_6H_4	65
f	4-FC_6H_4	72

[a] Yields of isolated products

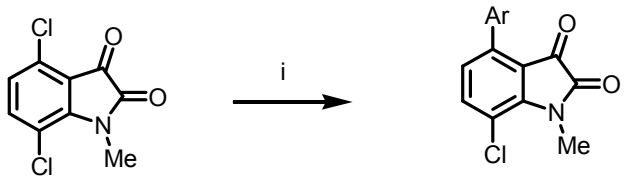
An optimization of the synthesis of **7b** was carried out by using various reaction conditions, such as K_2CO_3, KF and NEt_3 as bases, various solvents, like toluene, DMF and THF, and $Pb(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ as catalysts (Table 2). The use of standard conditions, K_3PO_4 (3.0 equiv.), $Pd(PPh_3)_4$ (6 mol-%) in dioxane at 120 ^oC for 8 h proved to give the best yields of **7b** (82%).

Table 2. Optimization of the synthesis of **7b**

Entry	Base	Solvent	*T* (^oC)	Catalyts	*t* [h)]	Yield (%)[a]
1	K_3PO_4	Toluene	100	$Pd(OAc)_2$	8	25
2	K_2CO_3	DMF	130	$Pd(PPh_3)_4$	9	38
3	KF	Dioxane	80	$Pd(OAc)_2$	10	47
4	NEt_3	THF	65	$Pd(PPh_3)_2Cl_2$	7	34
5	K_3PO_4	Dioxane	120	$Pd(PPh_3)_4$	8	82
6	K_2CO_3	Toluene	90	$Pd(OAc)_2$	10	25

[a] Yields of isolated yields

The Suzuki-Miyaura reaction of **5** with arylboronic acids **6** (1.0 equiv.) afforded the 7-chloro-4-aryl-isatins **8a-d,f-m** in 49-87% yields and with very good site-selectivity (Scheme 2). The best conditions, avoiding double-coupling, require the use of 1.2 equiv. of the arylboronic acid at 70 ^oC instead of 120 °C (reaction time 6 h). Both electron-poor and electron-rich arylboronic acids were successfully used.



5 **8a-d,f-m**

Scheme 2. *Reagents and conditions*: (i) **5** (1.0 equiv), $ArB(OH)_2$, **6a-d,f-m** (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), dioxane, 70 °C, 6 h

Table 3. Synthesis of **8a-d,f-m**

6,8	Ar	**8** (%) [a]
a	3,5-$(Me)_2C_6H_3$	63
b	4-$(MeO)C_6H_4$	83
c	4-ClC_6H_4	52
d	4-MeC_6H_4	79
f	4-FC_6H_4	87
g	4-$(EtO)C_6H_4$	85
h	4-*i*ProC_6H_4	73
i	4-*t*BuC_6H_4	78
j	3-MeC_6H_4	51
k	3,5-$(MeO)_2C_6H_3$	87
l	4-$(Acetyl)C_6H_4$	53
m	4-$(Vinyl)C_6H_4$	49

[a] Yields of isolated products

The structures of the newly prepared compounds were confirmed by their IR, ^1H, ^{13}C NMR and mass spectra, where **7a-f**, **8-a-m** and **9a-c** exhibited additional signals for the protons of the newly introduced aromatic ring.The aromatic protons have been assigned (*cf.* Experimental Section). In the ^{13}C NMR spectra, the carbonyl carbon atom at C-2 of the isatin ring resonated at δ 158.4-168.3 ppm, while the lower field resonances at δ 178.2-181.9 ppm were assigned to the carbonyl carbon atoms at C-3 of isatin moiety. C-5 of the isatin ring were observed at δ 124.1-127.4 ppm, while the resonances at δ 144.4-148.3 ppm were assigned to C-7a of the fused nucleus. In addition, the NMe group appeared at δ 28.6-33.7 ppm. Compound **8b** was selected for further study *via* the HMBC[30] and NOESY[31] NMR spectroscopic measurements. The

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gradient-selected HMBC spectrum of **8b** showed a $^{3}J_{C,H}$ heteronuclear correlation of C-4 of isatin ring (δ_C 133.9 ppm) to the H-2' proton (δ_H 7.32 ppm) of the aromatic moiety at C-4 of isatin. The ^{1}H, ^{1}H NOESY spectrum was characterized by two correlations: one indicated by correlation of protons of methoxy group at δ_H 3.72 ppm with H-5' of the same aromatic ring at δ_H 6.87 ppm, while the other one was observed between the H-6' of the aromatic ring at δ_H 7.32 ppm with H-5 of the isatin ring at δ_H 6.87 ppm (Figure 2).

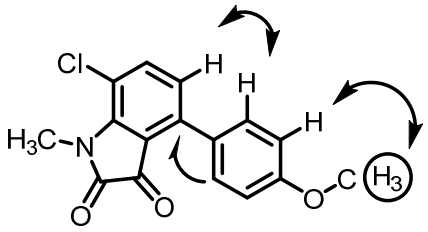


Figure 2. $J_{C,H}$ Correlations in the HMBC (single head arrow) and NOESY (double head arrow) of **8b**.

The structures of **8b** and **8d** were independently confirmed by X-ray crystal structure analyses (Figures 3 and 4 and Experiental section).

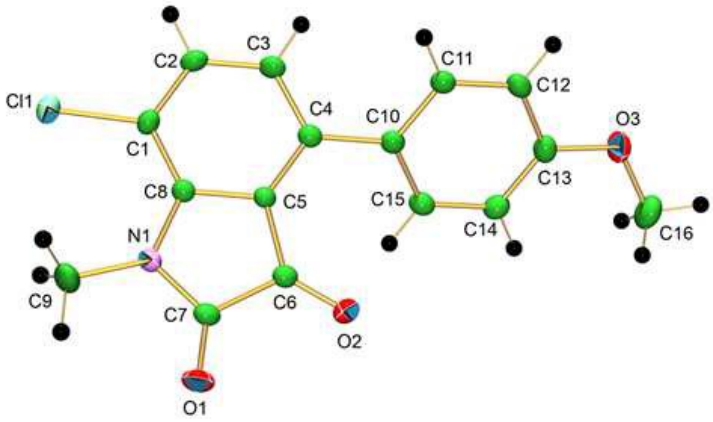


Figure 3. Molecular structure of 7-chloro-4-(4-methoxyphenyl)-1-methylindoline-2,3-dione (**8b**) in the crystal. Displacement ellipsoids are drawn at 50% probability level.

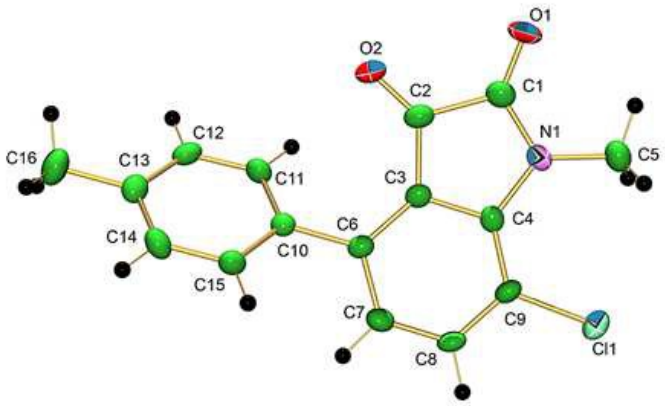
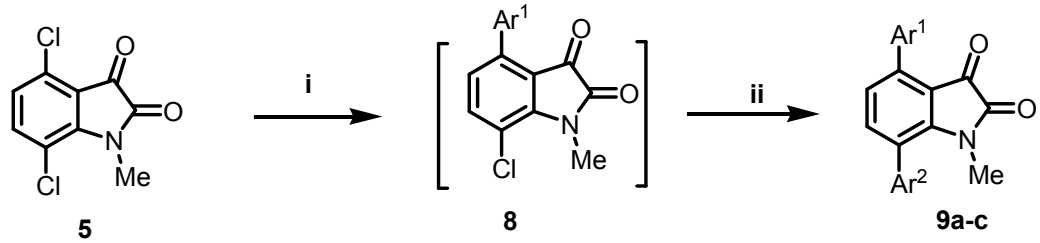


Figure 4. Molecular structure of **7**-chloro-1-methyl-4-(*p*-tolyl)indoline-2,3-dione (**8d**) in the crystal. Displacement ellipsoids are drawn at 50% probability level.

It was interesting for us to study the regioselectivity of the Suzuki-Miyaura reaction of the dichloroisatin moiety, as this substrate contains two different electron deficient centers (C-4 and C-7). Thus, the one-pot Suzuki-Miyaura reaction of **5** with two different arylboronic acids **6** (sequential addition of 1.2 equiv. of each boronic acid) afforded the *N*-methyl-4,7-diarylisatins **6a-d** in 73-81% yields (Scheme 3). The reactions were carried out at 70 °C in the first step (to avoid double coupling), followed by 120 °C in the second step (Scheme 3).



Scheme 3. *Reagents and Conditions*: (i) **5** (1.0 equiv), $Ar^1B(OH)_2$, **6m,k,d** (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), dioxane, 70 °C, 6 h; (ii) $Ar^2B(OH)_2$, **6d,b** (1.2 equiv.), K_3PO_4 (1.5 equiv.), $Pd(PPh_3)_4$ (3 mol-%), 1,4-dioxane, 120 °C, 6 h.

Table 4. Synthesis of **9a-c**.

6	**9**	Ar^1	Ar^2	**9** (%)[a]
i,d	**a**	4-*t*BuC_6H_4	4-MeC_6H_4	57

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k,b	**b**	3,5-$(MeO)_2C_6H_3$	4-$(MeO)C_6H_4$	70
d,b	**c**	4-MeC_6H_4	4-$(MeO)C_6H_4$	68

[a] Yields of isolated products

The results shown above (Scheme 3) reveal that the chlorine residue at C-4 of the isatin ring has been initially replaced by the aryl group, while the second replacement took place in the second stage (Figure 5). The result can be explained by the fact that position 4, located next to the carbonyl group, is more electron deficient than position 7. In addition, the selectivity might be explained by complexation of the catalyst by the carbonyl group (catalyst-directing effect).

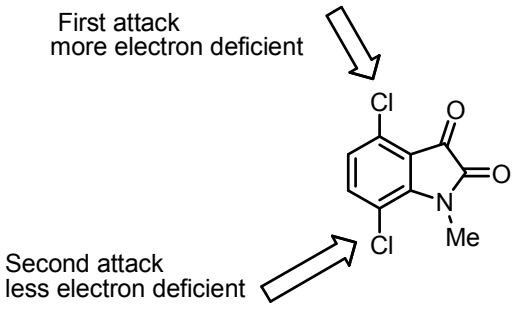

Figure 5. Possible explanation for the reaction

***In vitro* Anti-HIVAssay.** Compounds **5**, **7a-f**, **8a-d**, **8f-m** and **9a-c**, were tested for their in vitro anti-HIV-1 (strain III_B) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells, using MTT method.[32] The results are summarized in Table 5, in which the data for azidothymidine (AZT)[33] and lamivudine (3TC)[34] were included for comparison purposes. Compound **8l** was found to be the only compound from the series inhibiting HIV-2 replication in cell culture at a concentration of 100 μM. Compound **8l** showed an IC_{50} value of > 3.47 μM and a CC_{50} value of 13.43 μM, resulting in a selectivity index (SI) of 4, meanwhile no antiretroviral activity was observed (SI < 1) against HIV-1. However, the activity of the compound is much lower than those of the corresponding reference compounds, AZT, and 3TC. Derivatives **5**, **8c**, **8g** and **8m** demonstrated low CC_{50} values of > 2.21 μM, > 2.24 μM, 3.11 μM and 2.24 μM, respectively, but with a selectivity index (SI) < 1 in comparison to the other analogues. This suggests that these compounds might be used as lead for the development of anticancer drugs.

Appropriate reference compounds are always included in the experiments assessing the anti-HIV activity of new compounds. Our choice for AZT and 3TC as reference compounds is based on the fact that NRTIs are equipotent against HIV-1 and HIV-2.

Our data demonstrated that compound **8l** is not active against HIV-1, but has an activity to HIV-2, in contrast to what was observed in the NNRTIs assay.[35] However, the above data suggested that the halo group binding the benzene ring of isatin backbone (*e.g.*: **8**) considerably increase the anti-HIV activity, meanwhile substitution of the benzene ring of isatin by an arylketo group, as present in **8l**, would enhance such inhibition for HIV, in comparison to the effectiveness of other functional groups. In conclusion, the activity of **8l** against HIV-2 may be considered as an important lead for the development of a more potent and selective molecules which could be used in combination with other drugs to treat individuals infected with HIV-2.

Table 5. *In-vitro* anti-HIV-1[a] and HIV-2[b] of new *N*-methylisatin derivatives.

Entry	HIV-1 (III_B) av. IC_{50} (μM)[c]	HIV-1 (III_B) av. IC_{50} (μM)[c]	av. CC_{50} (μM)[d]	SI[e] (III_B)	SI[e] (ROD)	SD
5	> 2.21	> 2.21	2.21	< 1	< 1	0.33
7a	> 61.75	> 61.75	61.75	< 1	< 1	4.20
7b	> 35.28	> 35.28	35.28	< 1	< 1	18.77
7c	> 10.92	> 10.92	10.92	< 1	< 1	2.42
7d	> 12.30	> 12.30	12.30	< 1	< 1	0.89
7e	> 4.88	> 4.88	4.88	< 1	< 1	3.66
7f	> 12.75	> 12.75	12.75	< 1	< 1	0.65
8a	> 30.35	> 30.35	30.35	< 1	< 1	14.48
8b	> 125.0	> 125.0	125.0	< 1	< 1	-
8c	> 2.24	> 2.24	2.24	< 1	< 1	0.36
8d	> 15.12	> 15.12	15.12	< 1	< 1	0.93
8f	> 10.85	> 10.85	10.85	< 1	< 1	3.91
8g	> 3.11	> 3.11	3.11	< 1	< 1	0.50
8i	> 9.96	> 9.96	9.96	< 1	< 1	2.85
8j	> 12.93	> 12.93	12.93	< 1	< 1	1.16
8k	> 68.33	> 68.33	68.33	< 1	< 1	3.69
8l	> 13.43	> 13.43	13.43	< 1	4	1.06

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8m	> 2.24	> 2.24	2.24	< 1	< 1	0.34
9a	> 33.16	> 33.16	33.16	< 1	< 1	21.22
9b	> 42.13	> 42.13	42.13	< 1	< 1	17.64
9c	> 12.28	> 12.28	12.28	< 1	< 1	0.89
AZT	0.0019	0.0018	> 25	>13144	>14245	
3TC	0.51	2.02	> 20	> 39	> 10	

[a] Anti-HIV-1 activity measured with strain III_B; [b] anti-HIV-2 activity measured with strain ROD; [c] compound concentration required to achieve 50 % protection of MT-4 cells from the HIV-1 and HIV-2 induced cytopathogenic effect; [d] average CC_{50}: compound concentration that reduces the viability of mock-infected MT-4 cells by 50 %; [e] SI: selectivity index (CC_{50}/IC_{50}). Measurements were done in duplicate. Data represent mean values ± standard deviations for at least two separate experiments. The value >XXX means that no IC_{50} value was reached at concentrations as high as the measured CC_{50} value for a specific compound.

Molecular modeling analysis. Our molecular docking analysis of the new analogs is based on the modeling studies which were performed to understand the binding mode of these analogs with the HIV-2 RT binding pocket (NIBP) (PDB code: 1MU2[36]). The molecular docking was performed using SYBYL-X 1.1, and the results were visualized with PYMOL.[37] HIV-2 reverse transcriptase (RT) demonstrates an intrinsic resistance to non-nucleoside RT inhibitors (NNRTIs), one of two classes of anti-AIDS drugs that target the viral RT, however, HIV-2 RT has a similar overall fold to HIV-1 RT but has structural differences within the "NNRTI pocket" at both conserved and nonconserved residues.[36] Compound **8l** has been selected for the docking modeling study, since it showed the lowest binding energy score (-9.2 kcal/mol) (Fig. 6). As shown in Figure 6, the isatin backbone is located in the middle of the binding pocket, anchoring the two carbonyl groups at C-2 and C-3 in a favourable position for hydrogen bonding with the Lys102 and Thr107 of the reverse transcriptase (RT) enzyme, respectively. Further, the amino acids in the binding pocket of RT enzyme are mainly lipophilic with aromatic residues.[36] Therefore, not only hydrogen bonding but hydrophobic interactions also play vital role in deciding anti-HIV activity.[38] The aromatic ring (PhCOMe) of **8l** fitted into an aromatic rich subpocket surrounded by the aromatic side chain of Tyr188. Detailed analysis of the binding mode showed that the aromatic ring of PhCOMe group pointed toward the aromatic ring of Tyr188 residue apparently developing π-π stacking interactions, where the electrostatic interaction is stabilized by these stacking type interactions. Overall, the combination of

hydrophobic interaction and hydrogen bondings appears to govern the binding of **8l** with HIV-2 RT.

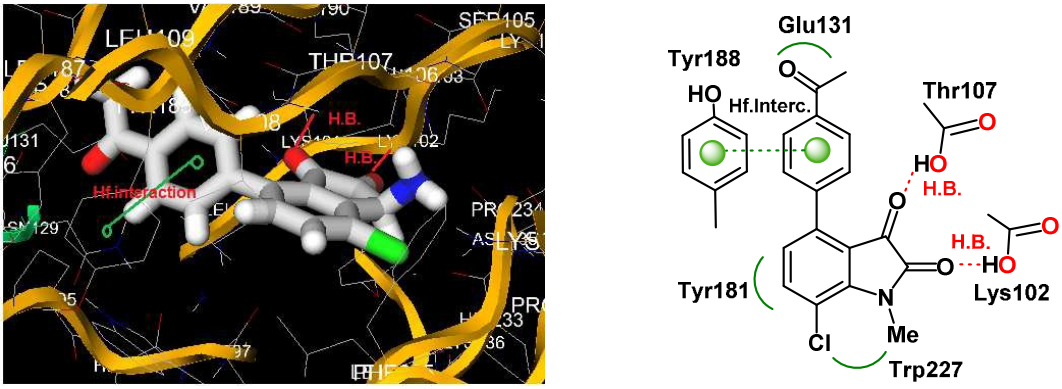

Figure. 6. Docked conformation of **8l** showing two hydrogen bonds: Thr107 with oxygen atom at C-3 of isatin ring and Lys102 with oxygen atom at C-2 of the same ring. In addition, a hydrophobic interaction was observed between the phenyl group of acetophenone moiety at C-4 of isatin backbone and Tyr188 of reverse transcriptase (RT) enzyme residues of HIV-2.

Experimental Section

Melting points are uncorrected and were measured on a Büchi melting point apparatus B-545 (BÜCHI Labortechnik AG, Switzerland). NMR data were obtained at 400 and 600 MHz (^{1}H) as well as 100 MHz and 150.91 MHz (^{13}C) spectrometers (Avance III, Bruker, Germany) with TMS as internal standard and on δ scale in ppm. Heteronuclear assignments were verified by HMQC and NOESY NMR experiments. Microanalytical data were obtained with a Vario, Elemental apparatus (Shimadzu, Japan). Mass spectra were recorded on 70 eV EI and FAB MAT 8200 spectrometers (Finnigana MAT, USA). Silica gel (0.040-0.063 mm) used for column chromatography and analytical silica gel TLC plates 60 F254 were purchased from Merck. In a number of cases, the solvent heptane (mixture of isomers) could not be completely removed. The corresponding signals were marked in the copies of NMR spectra.

4,7-Dichloro-1-methylindoline-2,3-dione (5)

Isatin **4** (216 mg, 1.00 mmol) was taken up in anhydrous DMF (1 mL per 0.1 mmol isatin) and cooled on ice with stirring. Solid K_2CO_3 (166 mg, 1.2 mmol) was added in one portion, and the dark colored suspension was brought to room temperature and stirred for a further 1 h. The

appropriate MeI (156 mg, 1.1 mmol) and KI (33.2 mg, 0.20 mmol) were added, and the reaction material had been consumed (TLC). The reaction mixture was poured into 0.5 M HCl (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with brine and dried (Mg_2SO_4) and filtered. The filtrate was evaporated, and the crude product was purified on a flash column chromatography using CH_2Cl_2 as eluent to give **5** as an orange solid (195 mg, 90 %); mp 173-175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 3H, CH_3), 6.95 (d, J = 8.8 Hz, 1H, ArH), 7.37 (d, J = 8.8 Hz, 1H, ArH). ^{13}C-NMR (75.4 MHz, $CDCl_3$): δ 29.8 (NCH_3), 115.7, 116.6 ($C_{arom.}$), 126.6 (C-4), 132.8 (C-6), 140.3 (C-5), 147.7 (C-7a), 157.7 (C_2=O), 179.3 (C_3=O). IR (KBr, cm^{-1}): v 3450, 3075, 3063, 2952, 2921, 2851, 1788 (w), 1728, 1584 (s), 1584, 1494 (w). GC-MS (EI, 70 eV): m/z (%) 227/229 ([M]$^+$, 2x[^{35}Cl] ,100), 203 (21), 201 (21), 200 (10), 174 (78), 160 (12), 158 (16), 151 (12), 111 (17). HRMS (EI, 70 eV): calcd for $C_9H_5{}^{35}Cl_2NO_2$ ([M]$^+$): 228.96973, found 228.96932.

General procedure for the preparation of biaryl-*N*-methylisatin analogues (7a-f)

To a suspension of **5** (70 mg, 0.304 mmol), dioxane (3 mL), $Pd(PPh_3)_4$ (11 mg, 6 mol -%, 0.0092 mmol), and arylboronic acid (0.669 mmol) was added K_3PO_4 (98 mg, 0.46 mmol) in dioxane (3 mL). The mixture was heated at 120 ^{o}C under Argon atmosphere in a pressure tube for 8 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc / heptane).

4,7-Bis(3,5-dimethylphenyl)-1-methylindoline-2,3-dione (7a)

From 3,5-dimethylphenylboronic acid **6a** (100 mg). Yield: 78 mg (69 %); as a red solid; mp 164-166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 12H, 4xCH_3), 3.20 (s, 3H, CH_3), 6.70 (d, J = 8.6 Hz, 2H, ArH), 6.97 (d, J = 8.3 Hz, 2H, ArH), 7.16-7.19 (m, 4H, ArH), 7.57 (t, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 21.3 (4xCH_3), 33.7 (NCH_3), 125.7 (C-5), 126.7, 129.7 130.8, 131.8, 137.5, 139.2, 143.3, 145.0 ($C_{arom.}$), 147.6 (C-7a), 147.8, 152.2, 157.3, 157.5, 158.2 *C*-OMe, 166.4 (C_2=O), 180.9 (C_3=O). IR (KBr, cm^{-1}): *v* 3075, 2953, 2919, 2852 (w), 1742, 1723 (s), 1605, 1585, 1564, 1499 (m). GC-MS (EI, 70 eV): m/z (%) 369 ([M]$^+$, 100), 344 (23), 332 (11), 220 (16), 163 (10), 120 (10). HRMS (EI, 70 eV) calcd for $C_{25}H_{23}NO_2$ ([M]$^+$): 369.17288, found: 369.17233.

4,7-Bis(4-methoxyphenyl)-1-methylindoline-2,3-dione (7b)

From 4-methoxyphenylboronic acid **6b** (102 mg). Yield: 93 mg (82 %) as a red solid; mp 220-222 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (s, 6H, 2xOCH_3), 3.79 (s, 3H, CH_3), 6.73 (dd, J = 8.3, 2.4 Hz, 2H, ArH), 6.97 (d, *J* = 8.0 Hz, 2H, ArH), 7.16-7.19 (m, 4H, ArH), 7.55 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 33.7 (NCH_3), 38.1 (2xOMe), 119.3 ($C_{arom.}$-3' + $C_{arom.}$-5'), 125.1 (C-5), 128.6, 128.9, 129.6, 130.6, 130.8, 132.4, 132.4 ($C_{arom.}$), 134.9 (C-7), 144.3 (C-7a), 146.5 (2x*C*-OMe), 160.6 (C_2=O), 181.2 (C_3=O). IR (KBr, cm^{-1}): *v* 3074, 2952, 2918, 2851 (w), 1743, 1724 (m), 1605, 1586, 1564, 1497, 1488 (s). GC-MS (EI, 70 eV): m/z (%) 373 ($[M]^+$,100), 364 (23), 365 (11), 310 (16), 311 (32), 210 (34), 174 (10), 134 (23). HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_4$ ($[M]^+$): 373.13141, found: 373.13100.

4,7-Bis(4-chlorophenyl)-1-methylindoline-2,3-dione (7c)

From 4-chlorophenylboronic acid **6c** (105 mg). Yield: 60 mg (52 %) as a red solid; mp 231-232 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.20 (s, 3H, CH_3), 6.81 (d, *J* = 8.2 Hz, 2H, ArH), 7.10 (d, *J* = 8.1 Hz, 2H, ArH), 7.22-7.26 (m, 4H, ArH), 7.10 (t, *J* = 7.8 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 33.0 (NCH_3), 124.5 (C-5), 127.2, 128.4, 129.2, 130.9, 132.5, 134.9 ($C_{arom.}$), 140.7 ($C_{arom.}$-1'), 146.6 (C-7a), 156.4 (C_2=O), 180.9 (C_3=O). IR (KBr, cm^{-1}): *v* 3074, 2952, 2919, 2851 (w), 1743, 1724 (s), 1605, 1586, 1565, 1499 (m). GC-MS (EI, 70 eV): m/z (%) 381 ($[M]^+$, 2x[^{35}Cl],100), 352 (23), 252 (11), 250 (16). HRMS (EI, 70 eV) calcd for $C_{21}H_{13}{}^{35}Cl_2NO_2$ ($[M]^+$): 381.03233, found: 381.03211.

1-Methyl-4,7-(di-*p*-tolyl)indoline-2,3-dione (7d)

From 4-methylphenylboronic acid **6d** (91 mg). Yield: 62 mg (58 %) as a red solid; mp154-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 6H, 2xCH_3), 3.19 (s, 3H, CH_3), 6.73 (d, *J* = 8.3 Hz, 2H, ArH), 6.99 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (t, *J* = 7.8 Hz, 4H, ArH), 7.57 (t, *J* = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 26.8 (2xCH_3), 33.7 (NCH_3), 120.0 ($C_{arom.}$), 125.7 (C-5), 129.7, 131.8, 137.5, 139.2 ($C_{arom.}$), 143.3 ($C_{arom.}$-1'), 147.6 (C-7a), 165.4 (C_2=O), 181.9 (C_3=O). IR (KBr, cm^{-1}): *v* 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): m/z (%) 341 ($[M]^+$, 100), 244 (23), 232 (11), 210 (16), 164 (10). HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_2$ ($[M]^+$): 341.14158, found: 341.14124.

4,7-Bis(4-ethylphenyl)-1-methylindoline-2,3-dione (7e)

From 4-ethylphenylboronic acid **6e** (100 mg). Yield: 73 mg (65 %) as a red solid; mp 123-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (m, 6H, 2xCH_3), 2.22 (m, 4H, 2xCH_2), 3.19 (s, 3H, CH_3), 6.73 (dd, *J* = 8.3, 2.4 Hz, 2H, ArH), 6.99 (d, *J* = 8.0 Hz, 2H, ArH), 7.16 (d, *J* = 7.8 Hz, 4H,

ArH), 7.57 (t, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 20.8 (2xCH_2*CH_3*), 24.6 (2x*CH_2*CH_3), 33.7 (NCH_3), 124.8 (C-5), 125.0, 128.7, 128.8, 129.6, 130.7, 130.9, 132.4, 132.5, 134.9 ($C_{arom.}$), 144.1 (2x*$C_{arom.}$*-Et), 146.6 (C-7a), 160.4 (C_2=O), 180.2 (C_3=O). IR (KBr, cm^{-1}): ν 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): m/z (%) 369 ($[M]^+$, 100), 344 (23), 332 (11), 210 (16), 164 (10), 154 (23). HRMS (EI, 70 eV) calcd for $C_{25}H_{23}NO_2$ ($[M]^+$): 369.17288, found: 369.17255.

4,7-Bis(4-fluorophenyl)-1-methylindoline-2,3-dione (7f)

From 4-fluorophenylboronic acid **6f** (94 mg). Yield: 76 mg (72 %) as a red solid; mp 190-192 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.10 (s, 3H, CH_3), 6.75-6.79 (m, 2H, ArH), 6.94-7.05 (m, 4H, ArH), 7.31 (t, J = 8.2 Hz, 2H, ArH), 7.46-7.50 (m, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 29.6 (NCH_3), 100.6 (d, $J_{3',F}$ = 26.4 Hz, $C_{arom.}$-3'), 100.7 (d, $J_{3'',F}$ = 22.6 Hz, $C_{arom.}$-3''), 100.8 (d, $J_{5',F}$ = 20.6 Hz, $C_{arom.}$-5'), 110.9 (d, $J_{5'',F}$ = 30.6 Hz, $C_{arom.}$-5''), 115.2 (q, $J_{3',F}$ = 32.2 Hz, $C_{arom.}$-3'), 115.5 (q, $J_{3'',F}$ = 28.0 Hz, $C_{arom.}$-3''), 124.4 (C-5), 125.7, 128.9 ($C_{arom.}$), 130.2 (q, $J_{4',F}$ = 280.1 Hz, , $C_{arom.}$-4'), 130.9 (q, $J_{4'',F}$ = 280 Hz, $C_{arom.}$-4''), 146.2 (C-7a), 160.3 (C_2=O), 180.1 (C_3=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -114.4, -112.0. IR (KBr, cm^{-1}): ν 3273, 3065, 2957, 2922, 2851 (w), 1782 (s), 1727, 1716, 1687, 1603, 1580 (w). GC-MS (EI, 70 eV): m/z (%) 394 ($[M]^+$, 100), 370 (17), 369 (30), 265 (10), 255 (23), 188 (34), 165 (12). HRMS (EI, 70 eV) calcd for $C_{21}H_{13}F_2NO_2$ $[M]^+$: 349.09144; found: 349.09100.

General procedure for the preparation compounds (8a-d,f-m)

To a dioxane suspension (3 mL) of **5** (70 mg, 0.304 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.005 mmol), and arylboronic acid (0.365 mmol) was added K_3PO_4 (49 mg, 0.23 mmol). The mixture was heated at 70 °C under Argon atmosphere in a pressure tube for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc / heptane).

7-Chloro-4-(3,5-dimethylphenyl)-1-methylindoline-2,3-dione (8a)

From 3,5-dimethylphenylboronic acid **6a** (53 mg). Yield: 77 mg (85 %) as a red solid; mp 124-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 6H, 2xCH_3), 3.59 (s, 3H, CH_3), 6.87 (d, J = 8.4 Hz, 1H, ArH), 7.01 (d, J = 8.7 Hz, 3H, ArH), 7.41 (d, J = 8.3 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.2 (2xCH_3), 28.9 (NCH_3), 125.5 (C-5), 125.9, 130.0, 134.0, 136.8, 138.5 ($C_{arom.}$), 141.5, 142.3 ($C_{arom.}$-3' + $C_{arom.}$-5'), 146.1 (C-7a), 157.2 (C_2=O), 180.0 (C_3=O). IR (KBr,

cm^{-1}): *v* 3446, 3073, 3047, 3032, 2950, 2922, 2853 (w), 1727 (s), 1637 (w), 1585, 1581, 1557 (w). GC-MS (EI, 70 eV): m/z (%) 299 ($[M]^+$, [^{35}Cl], 100), 272 (12), 255 (23), 250 (30), 246 (11), 244 (16), 228 (15), 222 (18), 221 (25), 199 (17). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{35}ClNO_2$ ($[M]^+$): 299.07131; found: 299.07122.

7-Chloro-4-(4-methoxyphenyl)-1-methylindoline-2,3-dione (8b)

From 4-methoxyphenylboronic acid **6b** (54 mg). Yield: 78 mg (85 %) as a red solid; mp 114-115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 6.87 (dd, *J* = 4.3, 8.7 Hz, 3H, ArH), 7.32 (d, *J* = 8.6 Hz, 2H, ArH), 7.40 (d, *J* = 8.2 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 28.9 (NCH_3), 54.5 (OCH_3), 112.7 ($C_{arom.}$-3' + $C_{arom.}$-5'), 126.3 (C-5), 127.0, 129.4, 128.6 ($C_{arom.}$), 133.9 (C-4), 138.5 (C-6), 146.2 (C-7a), 157.4 (C_2=O), 159.5 (*C*-OMe), 180.5 (C_3=O). IR (KBr, cm^{-1}): *v* 3068, 3044, 3019, 2999, 2956, 2845 (w), 1741, 1728, 1605, 1591, 1561 (m). GC-MS (EI, 70 eV): m/z (%) 303 ($[M]^+$, [^{37}Cl], 34), 301 ($[M]^+$, [^{35}Cl], 100), 275 (12), 273 (33), 272 (15), 245 (13), 244 (17), 242 (37), 238 (11), 230 (21), 210 (46), 173 (12), 167 (16). HRMS (EI, 70 eV), calcd for $C_{16}H_{12}{}^{37}ClNO_3$ ($[M]^+$): 303.04783; found: 303.04707; calcd for $C_{16}H_{12}{}^{35}ClNO_3$ ($[M]^+$): 301.04983; found: 301.05002.

7-Chloro-4-(4-chlorophenyl)-1-methylindoline-2,3-dione (8c)

From 4-chlorophenylboronic acid **6c** (56 mg). Yield: 79 mg (87 %) as a red solid; mp 183-184 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.14 (s, 3H, CH_3), 6.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.28-7.34 (m, 4H, ArH), 7.47 (d, *J* = 8.7 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 30.0 (NCH_3), 125.2 (C-5), 127.7, 128.9, 132.2, 138.3, ($C_{arom.}$), 146.2 (C-7a), 160.5 (C_2=O), 179.0 (C_3=O). IR (KBr, cm^{-1}): *v* 3077, 2952, 2921, 2852 (w), 1730, 1580, 1558 (s), 1610 (w). GC-MS (EI, 70 eV): m/z (%) 305 ($[M]^+$, 2x[^{35}Cl], 97), 279 (13), 259 (16), 277 (25), 250 (10), 249 (12), 248 (14), 242 (38), 216 (14), 164 (32). HRMS (EI, 70 eV): calcd for 287.05245 ; $C_{15}H_9{}^{35}Cl_2NO_2$ ($[M]^+$): 305.00103; found: 305.00144.

7-Chloro-1-methyl-4-(*p*-tolyl)indoline-2,3-dione (8d)

From 4-methylphenylboronic acid **6d** (48.5 mg). Yield: 74 mg (85 %) as a red solid; mp 141-142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 6.82 (d, *J* = 8.4 Hz, 1H, ArH), 7.09 (d, *J* = 8.2 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH), 7.38 (d, *J* = 8.0 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.3 ($C_{arom.}$-*Me*), 28.8 (NCH_3), 125.2 (C-5), 127.7, 127.9, 131.2, 138.4, 138.6 ($C_{arom.}$), 146.8 (C-7a), 157.5 (C_2=O), 180.0 (C_3=O). IR (KBr, cm^{-1}): *v* 3469, 3451, 3089, 3068, 3043, 3026, 3003, 2952, 2919, 2854 (w), 1731 (s), 1610 (w), 1589, 1580,

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1559 (w). GC-MS (EI, 70 eV): m/z (%) 287 ([M]$^+$, [^{37}Cl], 35), 285 ([M]$^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}{}^{37}ClNO_2$ ([M]$^+$): 287.05271; found: 287.05245; calcd for $C_{16}H_{12}{}^{35}ClNO_2$ ([M]$^+$): 285.05566; found: 285.05522.

7-Chloro-4-(4-fluorophenyl)-1-methylindoline-2,3-dione(8f).

From 4-flourophenylboronic acid **6f** (50 mg). Yield: 75 mg, (85 %) as a red solid; mp 202-203 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (s, 3H, CH_3), 6.90 (d, J = 8.9 Hz, 1H, ArH),7.05 (t, *J* = 8.3 Hz, 2H, ArH), 7.33-7.35 (m, 2H, ArH), 7.45 (d, *J* = 8.5 Hz, 1H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 28.9 (NCH_3), 114.2 (d, $J_{3',5',F}$ = 21.6 Hz, $C_{arom.}$-3' + $C_{arom.}$-5'), 115.3 (d, *J* = 8.2 Hz, $C_{arom.}$-2' + $C_{arom.}$-6' + C-5), 125.2 (C-5), 125.6 (C-Cl), 129.8 (C-4 + C-3a), 138.7 (C-6), 139.9 (d, $J_{1',F}$ = 3.3 Hz, $C_{arom.}$-1'), 147.1 (C-7a), 157.1 (q, $J_{4',F}$ = 245 Hz, $C_{arom.}$-4'), 164.0 (C_2=O), 180.1 (C_3=O). ^{19}F NMR (282 MHz, $CDCl_3$): δ -111.5. IR (KBr, cm^{-1}): *v* 3458, 3081, 2956, 2916, 2849 (w), 1736, 1727 (s), 1637 (w), 1596, 1569 (M). GC-MS (EI, 70 eV): m/z (%) 291 ([M]$^+$, [^{37}Cl], 22), 289 ([M]$^+$, [^{35}Cl], 62), 261 (23), 260 (10), 233 (13), 232 (20), 199 (15), 182 (13). HRMS (EI, 70 eV): calcd for $C_{15}H_9{}^{35}ClFNO_2$ ([M]$^+$): 289.03004; found: 289.03004; calcd for $C_{15}H_9{}^{37}ClFNO_2$ ([M]$^+$): 291.02709; found: 291.02803.

7-Chloro-4-(4-ethoxyphenyl)-1-methylindoline-2,3-dione (8g).

From 4-ethoxyphenylboronic acid **6g** (59 mg). Yield: 81 mg (84 %) as a red solid; mp 94-95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, *J* = 8.0 Hz, 3H, CH_3), 3.18 (s, 3H, CH_3), 3.32 (q, *J* = 6.5, 2.8 Hz 2H, CH_2), 7.28 (t, *J* = 8.0 Hz, 3H, ArH), 7.36-7.38 (m, 3H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 13.9 (CH_2CH_3), 28.8 (NCH_3), 62.9 (CH_2CH_3), 113.1 ($C_{arom.}$-3' + $C_{arom.}$-5'), 126.5 (C-5), 127.0, 127.4, 127.5, 131.9, 132.2, 134.4, 131.2 ($C_{arom.}$), 146.8 (C-7a), 157.5 (C_2=O + $C_{arom.}$-OEt), 180.0 (C_3=O). IR (KBr, cm^{-1}): *v* 3056, 3021, 2972, 2962, 2923, 2898, 2852 (w), 1726 (s), 1608, 1581, 1559,1514, 1501 (w). GC-MS (EI, 70 eV): m/z (%) 317 ([M]$^+$, [^{37}Cl], 34), 315 ([M]$^+$, [^{35}Cl], 100), 287 (21), 259 (27), 258 (21), 242 (23), 230 (20), 224 (20), 196 (67). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{37}ClNO_3$ ([M]$^+$): 317.06327; found: 317.06310; calcd for $C_{17}H_{14}{}^{35}ClNO_3$ ([M]$^+$): 315.06622; found: 315.06644.

7-Chloro-4-(4-isopropoxyphenyl)-1-methylindoline-2,3-dione(8h)

From 4-isopropylphenylboronic acid **6h** (58 mg). Yield: 85 mg (84 %) as a red solid; mp 83-85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.4 Hz, 6H, 2xCH_3), 3.32 (s, 3H, CH_3), 3.61-3.65 (m, 1H, CH), 6.80 (d, *J* = 8.2 Hz, 1H, ArH), 6.91 (d, *J* = 8.5 Hz, 2H, ArH), 7.29-7.35 (m, 3H,

ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 21.0 (2xCH_3), 28.9 (NCH_3), 68.9 (OCH), 114.3, 115.3 ($C_{arom.}$-3' + $C_{arom.}$-5'), 125.9 (C-5), 126.3, 138.5, 139.5, 141.0 ($C_{arom.}$), 146.6 (C-7a), 156.5 ($C_{arom.}$-O^{i}Pr)), 159.5 (C_2=O), 178.2 (C_3=O). IR (KBr, cm^{-1}): *v* 3444, 3062, 3022, 2978, 2951, 2945 (w), 1728, 1579 (s), 1563, 1514, 1479 (m). GC-MS (EI, 70 eV): m/z (%) = 331 ([M]$^+$, [^{37}Cl], 24), 329 ([M]$^+$, [^{35}Cl], 100), 289 (23), 288 (14), 287 (77), 245 (13), 261 (23), 260 (18), 259 (74), 258 (22), 242 (24), 197 (14). HRMS (EI, 70 eV), calcd for $C_{18}H_{16}{}^{37}ClNO_3$ ([M]$^+$): 331.07895; found: 331.07837; calcd for $C_{18}H_{16}{}^{35}ClNO_3$ ([M]$^+$): 329.08116; found: 329.08132.

4-(4-*Tert*-butylphenyl)-7-chloro-1-methylindoline-2,3-dione (8i)

From *tert*-butylphenylboronic acid **6m** (63 mg). Yield: 84 mg (84 %) as a red solid; mp 104-105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.53 (s, 9H, 3xCH_3), 2.34 (s, 3H, CH_3), 6.81 (d, *J* = 8.6 Hz, 2H, ArH), 7.02 (d, *J* = 8.0 Hz, 2H, ArH), 7.18 (d, *J* = 8.0 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 19.3 (C*(Me)$_3$*), 28.6 (NMe), 35.8 (*C*(Me)$_3$), 125.2 (C-5), 127.9, 131.2, 138.4 ($C_{arom.}$), 141.1 ($C_{arom.}$-1'), 146.1 ($C_{arom.}$-4'), 146.8 (C-7a), 157.5 (C_2=O), 180.0 (C_3=O). IR (KBr, cm^{-1}): *v* 3469, 3451, 3089, 3068, 3043, 3026, 3003, 2952, 2919, 2854 (w), 1731 (s), 1610 (w), 1589, 1580, 1559 (w). GC-MS (EI, 70 eV): m/z (%) 327 ([M]$^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{19}H_{18}{}^{35}ClNO_2$ ([M]$^+$): 327.10261; found: 327.1024.

7-Chloro-1-methyl-4-(*m*-tolyl)indoline-2,3-dione (8j)

From 4-isopropylphenylboronic acid **6j** (58 mg). Yield: 74 mg (85 %) as a red solid; mp 124-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 6.87 (d, *J* = 8.4 Hz, 1H, ArH), 7.12-7.23 (m, 4H, ArH), 7.41 (d, *J* = 8.3 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 20.3 (Me), 28.9 (NCH_3), 124.8 (C-5), 125.9, 127.1, 128.4, 129.0, 134.0, 136.9 ($C_{arom.}$), 140.1 ($C_{arom.}$-1'), 141.2 ($C_{arom.}$-3'), 146.1 (C-7a), 157.2 (C_2=O), 180.0 (C_3=O). IR (KBr, cm^{-1}): *v* 3447, 3074, 3048, 3033, 2952, 2921, 2854 (w), 1728 (s), 1637 (w), 1588, 1581, 1558 (w). GC-MS (EI, 70 eV): m/z (%) 287 ([M]$^+$, [^{37}Cl], 35), 285 ([M]$^+$, [^{35}Cl], 97), 270 (13), 259 (10), 257 (33), 256 (23), 244 (16), 229 (15), 228 (18), 227 (14), 195 (16). HRMS (EI, 70 eV) calcd for $C_{16}H_{12}{}^{37}ClNO_2$ ([M]$^+$): 287.05271; found: 287.05245; calcd for $C_{16}H_{12}{}^{35}ClNO_2$ ([M]$^+$): 285.05566; found: 285.05522.

7-Chloro-4-(3,5-dimethoxyphenyl)-1-methylindoline-2,3-dione(8k).

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From 3,5-dimethoxyphenylboronic acid **6k** (65 mg). Yield: 86 mg (85 %) as a red solid; mp 124-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (3H, CH_3), 3.72 (6H, 2xOCH_3), 6.43-6.49 (m, 3H, ArH), 6.92 (d, *J* = 8.7 Hz, 1H, ArH), 7.42 (d, *J* = 8.4 Hz, 1H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 30.0 (NCH_3), 55.5 (2xOCH_3), 101.6 ($C_{arom.}$-4'), 106.9 ($C_{arom.}$-3' + $C_{arom.}$-5'), 126.8 (C-5), 128.0, 129.5, 134.4, 134.6, 135.0, 137.0 ($C_{arom.}$), 141.3 ($C_{arom.}$-1'), 147.3 (C-7a), 158.5 (C_2=O), 160.5 (2x*C*-OMe), 179.2 ((C_3=O). IR (KBr, cm^{-1}): *v* 3455, 3094, 3077, 3053, 3011, 2947, 2841 (w), 1731 (s), 1695, 1684, 1652, 1646, 1635, 1601(w). GC-MS (EI, 70 eV): m/z (%) 331 ([M]$^+$, [^{35}Cl], 100), 316 (13), 303 (11), 302 (21), 288 (11), 252 (16), 245 (10). HRMS (EI, 70 eV) calcd for $C_{17}H_{14}{}^{35}ClNO_4$ ([M]$^+$): 331.06114; found: 331.06122.

4-(4-Acetylphenyl)-7-chloro-1-methylindoline-2,3-dione (8l)

From 4-acetylphenylboronic acid **6l** (58 mg). Yield: 81 mg (85 %) as a red solid; mp 124-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.52 (s, 3H, $COCH_3$), 3.56 (s, 3H, CH_3), 6.95 (d, *J* = 8.4 Hz, 1H, ArH), 7.49 (t, *J* = 8.7 Hz, 3H, ArH), 7.93 (d, *J* = 8.8 Hz, 2H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 26.7 (CO*CH*$_3$), 30.7 (NCH_3), 127.4 (C-5), 128.1, 128.3, 129.1 130.8, 133.2 ($C_{arom.}$), 137.4 ($C_{arom.}$-4'), 139.9 ($C_{arom.}$-1'), 146.9 (C-7a), 158.5 (C_2=O), 181.1 (C_3=O), 197.5 (*CO*Me). IR (KBr, cm^{-1}): *v* 3072, 3058, 3006, 2958, 2921, 2850 (w), 1731, 1681, 1583, 1556 (s). GC-MS (EI, 70 eV): m/z (%) 315 ([M]$^+$, [^{37}Cl], 30), 313 ([M]$^+$, [^{35}Cl], 88), 298 (28), 285 (11), 272 (33), 271 (16), 244 (14), 242 (40), 214 (13), 207 (11), 180 (36), 164 (22), 150 (25). HRMS (EI, 70 eV), calcd for $C_{17}H_{12}{}^{37}ClNO_3$ ([M]$^+$): 315.04707; found: 315.04762; calcd for $C_{17}H_{12}{}^{35}ClNO_3$ ([M]$^+$): 313.05002; found: 313.04983.

7-Chloro-1-methyl-4-(4-vinylphenyl)indoline-2,3-dione (8m)

From 4-vinylphenylboronic acid **6i** (53 mg). Yield: 77 mg (86 %) as a red solid; mp 124-125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.56 (3H, CH_3), 5.09 (d, *J* = 1.8 Hz, 1H, CH), 5.76 (d, *J* = 1.9 Hz, 1H, CH), 6.67 (q, *J* = 7.1, 2.2 Hz, 1H, CH), 6.91 (d, *J* = 8.9 Hz, 2H, ArH), 7.33-7.42 (m, H, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 29.9 (NCH_3), 115.1 (*CH*$_2$=CH), 126.1 (C-5), 126.3, 126.9, 129.2, 134.5 ($C_{arom.}$), 136.2 (CH_2=*CH*), 139.8 ($C_{arom.}$-4'), 140.4 ($C_{arom.}$-1'), 141.7 (C-7a), 158.3 (C_2=O), 180.1 (C_3=O). IR (KBr, cm^{-1}): *v* 3449, 3067, 2944, 2922, 2851 (w), 1734 (s), 1627 (w), 1581 (s), 1554, 1478, 1458, 1438 (w). GC-MS (EI, 70 eV): m/z (%) 299 ([M]$^+$, [^{37}Cl], 34), 297 ([M]$^+$, [^{35}Cl], 100), 271 (14), 270 (17), 269 (42), 268 (30), 252 (16), 242 (21), 240 (40), 239 (11), 234 (18). HRMS (EI, 70 eV), calcd for $C_{17}H_{12}{}^{37}ClNO_2$ ([M]$^+$): 299.05216; found: 299.05303; calcd for $C_{17}H_{12}{}^{35}ClNO_2$ ([M]$^+$): 297.05511; found: 297.0545.

General procedure for the preparation of compounds (9a-c)

To a dioxane suspension (3 mL) of **5** (70 mg, 0.304 mmol), $Pd(PPh_3)_4$ (5 mg, 3 mol -%, 0.005 mmol), and arylboronic acid $Ar^1B(OH)_2$ **6m,k,d** (0.365 mmol) was added K_3PO_4 (49 mg, 0.230 mmol). The mixture was heated at 70 °C under Argon atmosphere for 6 h. The mixture was cooled to 20 °C. arylboronic acid $Ar^2B(OH)_2$ **6d,b** (0.365 mmol) was added K_3PO_4 (49 mg, 0.230 mmol). The mixture was heated at 120 °C under Argon atmosphere in a pressure tube for 6 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (silica gel, EtOAc / heptane).

4-(4-*Tert*-butylphenyl)-1-methyl-7-*p*-tolylindoline-2,3-dione (9a)

From *tert*-butylphenylboronic acid **6m** (65 mg), 4-methylphenylboronic acid **6d** (50 mg). Yield: 85 mg (73 %) as a red solid; mp 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 9H, 3xCH_3), 2.31 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 6.71 (d, J = 8.4 Hz, 2H, ArH), 6.66 (d, J = 8.1 Hz, 2H, ArH), 7.11 (t, J = 7.3 Hz, 4H, ArH), 7.57 (d, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 19.1 (3xCH_3), 20.2 ($C_{arom.}$-*CH_3*), 33.7 (NCH_3 + *C*(Me)$_3$), 124.1 (C-5), 124.5, 124.7, 127.7, 127.9, 128.5, 132.0, 133.4, 137.2, 139.6, 141.2 ($C_{arom.}$), 148.3 (C-7a), 158.3 (C_2=O), 181.9 (C_3=O). IR (KBr, cm^{-1}): *v* 3074, 2952, 2918, 2851 (w), 1743, 1724 (s), 1605, 1586, 1564, 1497 (m). GC-MS (EI, 70 eV): m/z (%) 383 ([M]$^+$, 100), 369 (27), 368 (94), 340 (18), 327 (22), 326 (30), 313 (12), 312 (43), 310 (10), 299 (10), 296 (11), 284 (10), 283 (12), 282(10), 141 (22). HRMS (EI, 70 eV) calcd for $C_{26}H_{25}NO_2$ ([M]$^+$): 383.18853, found: 383.18788.

4-(3,5-Dimethoxyphenyl)-7-(4-methoxyphenyl)-1-methylindoline-2,3-dione (9b)

From 3,5-dimethoxyphenylboronic acid **6k** (65 mg), 4-methoxyphenylboronic acid **6b** (54 mg). Yield: 89 mg (73 %) as a red solid; mp 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.59 (s, 9H, 3xOCH_3), 6.70 (d, J = 8.4 Hz, 2H, ArH), 7.12 (t, J = 7.3 Hz, 5H, ArH), 7.55 (d, J = 8.3 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 29.2 (NCH_3), 33.7 (3xOCH_3), 124.1 (C-5), 124.5, 124.7, 127.7, 127.9, 128.5, 132.0, 133.4, 137.2, 139.6, 140.1, 141.2 ($C_{arom.}$), 147.8 (C-7a), 148.3, 151.1, 152.3 (3x*C*OMe), 168.3 (C_2=O), 180.9 (C_3=O). IR (KBr, cm^{-1}): *v* 3070, 2951, 2917, 2851 (w), 1747, 1723 (s), 1604, 1585, 1564, 1497 (m). GC-MS (EI, 70 eV): m/z (%) 403 ([M]$^+$, 100), 379 (27), 378 (94), 350 (18), 337 (22), 323 (12), 322 (43), 320 (10), 289 (10), 286 (11), 284 (13), 283 (12), 282(10), 141 (22). HRMS (EI, 70 eV) calcd for $C_{24}H_{21}NO_5$ ([M]$^+$): 403.14197, found: 403.14145.

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7-(4-Methoxyphenyl)-1-methyl-4-*p*-tolylindoline-2,3-dione (9c)

From 4-methylphenylboronic acid **6d** (50 mg), 4-methoxyphenylboronic acid **6b** (54 mg). Yield: 79 mg (73 %); mp 172-174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.54 (s, 3H, OCH_3), 6.71 (d, J = 8.1 Hz, 2H, ArH), 6.64 (d, J = 8.6 Hz, 2H, ArH), 7.11-7.15 (m,4H, ArH), 7.50 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR (75.46 MHz, $CDCl_3$): δ 20.2 ($C_{arom.}$-CH_3), 33.7 (NMe), 54.2 (OMe), 124.1 (C-5), 124.5, 124.7, 127.7, 127.9, 128.5, 132.0, 133.4, 137.2, 139.6, 141.2 ($C_{arom.}$), 147.8 (C-7a), (C), 158.3 (C_2=O), 181.9 (C_3=O). IR (KBr, cm^{-1}): v 3174, 2952, 2818, 2751 (w), 1843, 1824 (s), 1705, 1686, 1564, 1497 (m). GC-MS (EI, 70 eV): m/z (%) 357 ($[M]^+$, 100), 349 (27), 348 (94), 340 (18), 326 (30), 310 (17), 283 (13), 280 (10), 145 (22). HRMS (EI, 70 eV) calcd for $C_{23}H_{19}NO_3$ ($[M]^+$): 357.13649, found: 357.13623.

Crystal structure data (**8b**) $C_{16}H_{12}ClNO_3$, M_r = 301.72, red plates, crystal dimensions = 0.30 × 0.19 × 0.17 mm^3, orthorhombic, space group *Pbca*, a =7.3328 (3), b = 9.2003 (4), c = 19.7779 (8) Å, Z = 4, $D_{calcd.}$ = 1.38 mg cm^{-3}, μ(MoK$_\alpha$) = 0.1 mm^{-1}, F(000)=1.760 e, T = 173(2) K. MoK$_\alpha$ radiation, λ = 0.71073 Å, 56177 collected refls. (*hkl*- 21/20, ± 16, ± 27), 5261 unique refls. (R_{int} = 0.062), 290 refined parameters, $R1/wR2$ = 0.0771/0.1363 (all data), GOF = 1.023, $\Delta\rho_{fin}$ (max/min) = 0.33/- 0.23 e $Å^{-3}$.

Crystal structure data (**8d**) $C_{16}H_{12}ClNO_2$, M_r =285.72, red plates, crystal dimensions = 0.99 x 0.03 x 0.03 mm^3, orthorhombic, space group *Pbca*, a = 3.8951 (6), b = 24.185 (3), c = 13.5874 (17) Å, Z = 4, $D_{calcd.}$ = 1.38 g cm^{-3}, μ(MoKα) = 0.1 mm^{-1}, F(000)=1.760 e, T = 173(2) K. MoK$_\alpha$ radiation, λ = 0.71073 Å, 56177 collected refls. (*hkl*- 21/20, ± 16, ± 27), 5261 unique refls. (R_{int} = 0.062), 290 refined parameters, R1/$wR2$ = 0.0771/0.1363 (all data), GOF = 1.023, $\Delta\rho_{fin}$ (max/min) = 0.36/-0.39 e $Å^{-3}$

CCDC 1410098 contains the supplementary crystallographic data for this paper. These data can be obtained freeof charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif.

Crystal structure data (**8d**) $C_{16}H_{12}ClNO_2$, M_r =285.72, red plates, crystal dimensions = 0.99 x 0.03 x 0.03 mm^3, orthorhombic, space group *Pbca*, a = 3.8951 (6), b = 24.185 (3), c = 13.5874 (17) Å, Z = 4, $D_{calcd.}$ = 1.38 g cm^{-3}, μ(MoKα) = 0.1 mm^{-1}, F(000)=1.760 e, T = 173(2) K. MoK$_\alpha$ radiation, λ = 0.71073 Å, 56177 collected refls. (*hkl*- 21/20, ± 16, ± 27), 5261 unique refls. (R_{int} = 0.062), 290 refined parameters, R1/$wR2$ = 0.0771/0.1363 (all data), GOF = 1.023, $\Delta\rho_{fin}$ (max/min) = 0.36/-0.39 e $Å^{-3}$.

CCDC 1410099 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centrevia www.ccdc.cam.ac.uk/data request/cif.[38]

In vitro HIV assay

Evaluation of the antiviral activity of compounds **5**, **7a-f**, **8a-d**, **8f-m** and **9a-c** against the HIV-1 strain (III_B) and the HIV-2 strain (ROD) in MT-4 cells was performed using an MTT assay as described previously.[32] In brief, stock solutions (10 times final concentration) of test compounds were added in 25-µl volumes to two series of triplicate wells to allow simultaneous evaluation of their effects on mock and HIVinfected cells at the beginning of each experiment. Stock solutions of the compounds were made in DMSO (10 mg /ml) as described in ref. 32. Serial 5-fold dilutions of test compounds were made directly in flat-bottomed 96-well microtiter trays using a Biomek 3000 robot (Beckman instruments). Untreated control, HIV and mock-infected cell samples, were included for each sample. HIV-1 (III_B)[39] or HIV-2 (ROD)[40] stock (50 µL) at 100-300 CCID50 (50 % cell culture infectious dose) or culture medium was added to either of the infected or mock-infected wells of the microtiter tray. Mock-infected cells were used to evaluate the effect of test compound on uninfected cells in order to assess the cytotoxicity of the test compounds. Exponentially growing MT-4 cells[35] were centrifuged for 5 min at 1000 rpm, and the supernatant was discarded. The MT-4 cells were resuspended at 6×105 cells per ml, and 50-µl volumes were transferred to the microtiter tray wells. Five days after infection, the viability of the mock- and HIV-infected cells was examined spectrophotometrically

Viruses

The origins of virus stocks were as described previously: The HIV-1 (III_B) strain was originally provided by Prof. R.C. Gallo and Dr. M. Popovic (at that time at the NIH, Bethesda, MD, USA);[39] HIV-2 (ROD)[40] was provided by Dr. L. Montagnier and was obtained from the culture supernatant of infected MT-4 cells.

Acknowledgements

Financial support by the DAAD (scholarships for A. M. H.) and by the State of Iraq is gratefully acknowledged.

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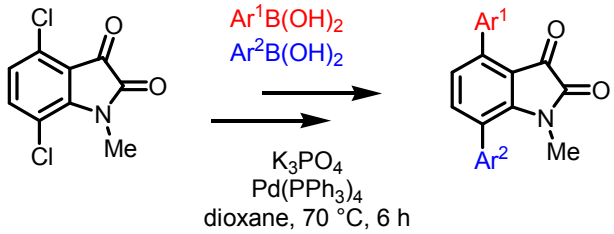

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