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Discovery of a new HIV-1 inhibitor scaffold and synthesis of potential prodrugs of indazoles

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ABSTRACT

A new oxazole scaffold showing great promise in HIV-1 inhibition has been discovered by cell-based screening of an in-house library and scaffold modification. Follow-up SAR study focusing on the 5-aryl substituent of the oxazole core has identified **4k** (EC_{50} = 0.42 μM, TI = 50) as a potent inhibitor. However, the analogues suffered from poor aqueous solubility. To address this issue, we have developed broadly applicable potential prodrugs of indazoles. Among them, *N*-acyloxymethyl analogue **11b** displayed promising results (i.e., increased aqueous solubility and susceptibility to enzymatic hydrolysis). Further studies are warranted to fully evaluate the analogues as the potential prodrugs with improved physiochemical and PK properties

The HIV life cycle encompasses a variety of steps (e.g., attachment to the host cell, viral entry, proviral integration, gene expression to viral budding) and many stages in the life cycle have already been exploited in the search for better HIV inhibitors, resulting in the discovery of ~30 approved drugs for the treatment of this pandemic disease.[1] However, there is still an urgent need for new HIV drug discovery with novel modes of action due to the rapid emergence of drug resistance in HIV patients.[2]

With an aim to find a new chemical scaffold with HIV-1 inhibitory activity, we screened an in-house library consisting of small molecular weight (MW <500) compounds using an MT4 cell-based assay. An MT4 cytoprotection assay has the advantage of detecting compounds inhibiting all stages of HIV life cycles; this provides greater possibilities in identifying a novel chemical structure with a unique mechanism of action. Recently, such traditional cellular phenotypic screening approaches are gaining increased attention for drug discovery due to the advantage in discovering first-in class drugs as compared to target-based screening.[3] Furthermore, recent advances in chemical proteomic technology now enable faster, more efficient target identification after phenotypic screening.[4]

After screening of the library using the MT4 cytoprotection assay, we identified compounds **1**–**3** which have relatively good lead-like[5] characteristics (MW ⩽400, rings ⩽4, hydrogen-bond donors ⩽5, hydrogen-bond acceptors ⩽9, and log*P* 1.9–5.5), exhibited some cytoprotective effect (EC_{50} of 6–13 μM, MT4 cells) and can serve as a starting point for chemical modifications (Fig. 1). Structurally, compounds **1**–**3** have similar pharmacophore features. Each compound commonly contains an aminoindazole ring and an aryl ring, but its structure differs in core (piperidine, quinazoline, and urea for **1**, **2**, and **3**, respectively).

Initial screening results indicated that the modification of the core structure could be an effective lead optimization approach and this consideration prompted us to investigate a scaffold morphing strategy.[6] Consequently, oxazole **4a** was designed based on the structure of urea **3**, synthesized, and evaluated (Scheme 1). To our delight, oxazole **4a** exhibited improved potency and a wider therapeutic index (EC_{50} = 2 μM, TI >45). Encouraged by this result, we initiated a SAR study around this scaffold to find more potent and non-toxic HIV-1 inhibitors that can ultimately be used to identify the molecular target and understand the mechanism of HIV-1 inhibition.

Herein we report the synthesis and SAR study of the oxazole scaffold as well as the design and synthesis of potential prodrugs of indazoles that were developed in an effort to improve the aqueous solubility of the analogues.

A representative example depicted in Scheme 2 is the synthesis of analogue **4d**. We used an iminophosphorane-mediated cyclization for the 2-aminooxazole ring formation.[7] Isothiocyanate **6** was conveniently prepared by treatment of aminoimidazole **5** with

Abbreviations: CDKs, cyclin-dependent kinases; CKII, casein kinase 2; DMAP, dimethylaminopyridine; EDCI, *N*-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; LIMK, LIM kinases; PK, pharmacokinetics; TFA, trifluoroacetic acid.

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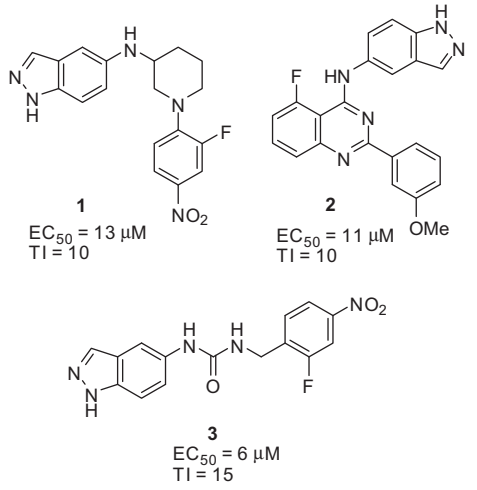
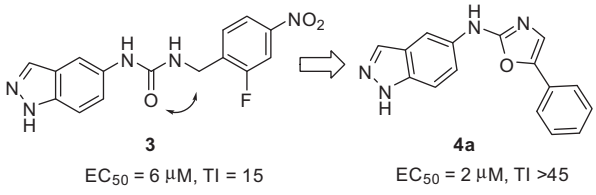


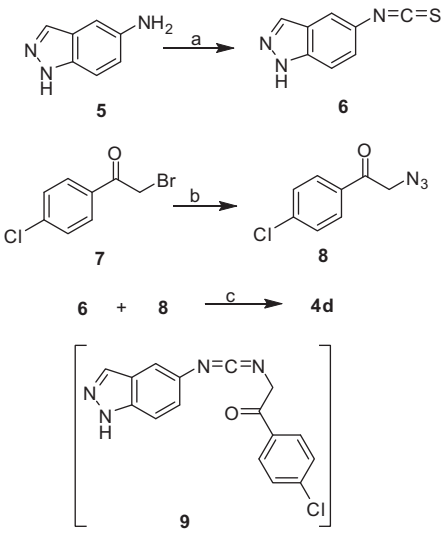
Figure 1. Hits identified through the MT4-cell cytoprotection assay.



Scheme 1. Core modification.

1,1′-thiocarbonyldi-2(*H*)-pyridone or thiocarbodiimidazole. Acyl bromide **7** was easily converted into acyl azide **8** by use of NaN_3. The synthesis of oxazole **4d** was achieved in good yield (85%) via intermediate **9** by heating a mixture of **6** and **7** in the presence of PPh_3. This protecting-group-free two-step procedure allowed for the rapid generation of related analogues.

The Topliss approach has been known as a popular tool in lead optimization for identifying optimal substituents. The approach involves systematic changes in electronic, steric and hydrophobic properties of substituents, and is particularly useful in cases where no structural information about the biological target is available.[8] In our initial study, a similar strategy was used to examine the effect of the substituents (Cl and OMe) on the 5-phenyl moiety in **4a** on the potency. Thus, *ortho*-, *meta*-, and *para*-subsituted phenyl analogues **4b**–**4k** were prepared. As summarized in Table 1, these analogues had markedly different potency. For chloro substituted phenyl analogues **4b**–**d**, the order of potency was *para*->*ortho*- >>*meta*-chlorophenyl analogues (EC_{50} = 3, 9, 54 μM, **4d**, **4b** and **4c**, respectively). The *para*-chlorophenyl analogue **4d** showed a similar potency to parent **4a** but exhibited significantly improved metabolic stability (%$R_{40\ min}$ = 83 for **4d** and **9** for **4a**, mouse liver microsome). These results clearly indicated that the *para*-position of the phenyl moiety is a major metabolic site. The opposite SAR trend was observed for methoxyphenyl analogues **4e**–**g**; *meta*-methoxyphenyl analogue **4f** showed anti-HIV-1 activity (EC_{50} = 2 μM) similar to that of **4a**,**d** whereas *ortho*- and *para*-methoxyphenyl analogues **4e**,**g** lacked the potency (EC_{50} = 100 μM). It was expected that combination of the favorable 4-chloro and 3-methoxy substituents might act synergistically for the in vitro anti-HIV-1 activity. Although the combination of the substitutents did not induce a significant synergistic effect, 4-chloro-3-methoxyphenyl analogue 4i exhibited comparable or slightly better potency (EC_{50} = 1.5 μM) to analogues **4d**,**f**. Interestingly, 3,4-dimethoxyphenyl analogue **4k** (EC_{50} = 0.42 μM, TI = 50)



Scheme 2. Reagents and conditions: (a) 1,1′-thiocarbonyldi-2(1*H*)-pyridone (or thiocarbodiimidazole), CH_2Cl_2, rt, 2 h, 64%; (b) NaN_3, acetone/water, 50 °C, 0.5 h, 92%; (c) PPh_3, dioxane, 90 °C, 0.5 h, 85%.

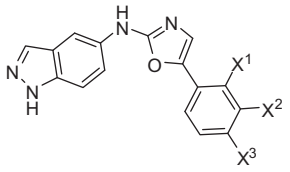
was found to be the most potent compound in this series. Methylenedioxyphenyl analogue **4h** maintained potency (EC_{50} = 2.7 μM) and 3,4-dichlorophenyl analogue **4j** resulted in a big loss in potency (EC_{50} = 35 μM). This brief SAR study revealed that anti-HIV-1 activity was quite sensitive to the substituents and their positions on the 5-aryl ring; the electron-donating methoxy group at 3-position and electron withdrawing chloro group at 4-position were tolerant. The potency of dimethoxyphenyl analogue **4k** could also be fine-tuned by modifying the alkoxy group.

Having identified leads showing good HIV-1 inhibitory activity, we decided to evaluate the PK properties of the analogues. Early PK studies guide decision making in drug discovery process and help reduce the attrition rate in drug development.[9] Initially, compound **4d** was selected for this study because it had reasonable HIV-1 inhibitory potency (EC_{50} = 3.0 μM), good lead like properties (MW = 310, log*P* = 3.3) along with an excellent metabolic stability (%$R_{40\ min}$ = 83, mouse liver microsome). However, the poor aqueous solubility of 4d (0.2 μM at pH 7.4 in phosphate buffer) was a major hurdle for preclinical PK evaluation and these analogues in general suffered from poor solubility properties.

To address this issue, we envisaged a prodrug approach. The indazole nitrogen of **4d**, rather than 2-amino group of the oxazole core, was considered to be a preferred site for attachment of a prodrug moiety because of easy chemical modifications and a stronger acidity of the N–H group that increases the self cleavage rate of a double prodrug.[10] There are relatively few precedents in the literature for prodrugs of indazoles. One is a tetrahydropyridinyl moiety.[11] The mechanism of cleavage of the tetrahydropyridinyl promoiety was proposed to partially mimic bioactivaton pathway that is catalyzed by monoamine oxidase B (MAO-B). Phosphate prodrugs[12] of indoles were also used to overcome formulation problems (e.g., phosphate prodrugs of PD154075[10], a highly potent and selective NK1 receptor antagonist). Inspired by many prodrug strategies designed for amines[13], we designed three types of potential prodrugs of indazoles: (a) double prodrugs containing *N*-acyloxymethyl group as a promoiety, (b) N-mannich bases, (c) *N*-acyl prodrugs (Scheme 3). In the following section, the synthesis and preliminary evaluation of the potential prodrugs are described.

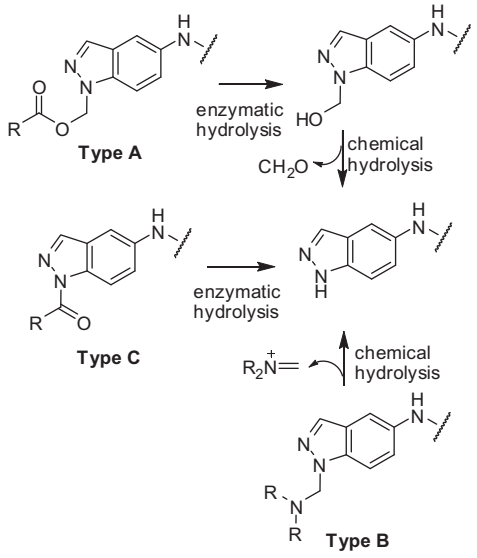
Type A prodrugs are designed to form double prodrug systems that utilize *N*-acyloxymethyl or *N*-alkoxycarbonyloxymethyl

Table 1
EC_{50} data for **4a**–**k** in MT4-cell cytoprotection assay



Compd	X^1	X^2, X^3	MT4 cells EC_{50}[a] (μM)	MT4 cells TC_{50}[b] (μM)	TI[c]
4a	H	H, H	2	>90	>45
4b	Cl	H, H	9	>100	>11
4c	H	Cl, H	54	>100	>1.9
4d	H	H, Cl	3	>90	>30
4e	OMe	H, H	100	>100	>1
4f	H	OMe, H	2	>90	>45
4g	H	H, OMe	100	>100	>1
4h	H	$-OCH_2O-$	2.7	83	31
4i	H	OMe, Cl	1.5	80	53
4j	H	Cl, Cl	35	>100	>2.9
4k	H	OMe, OMe	0.42	21	50

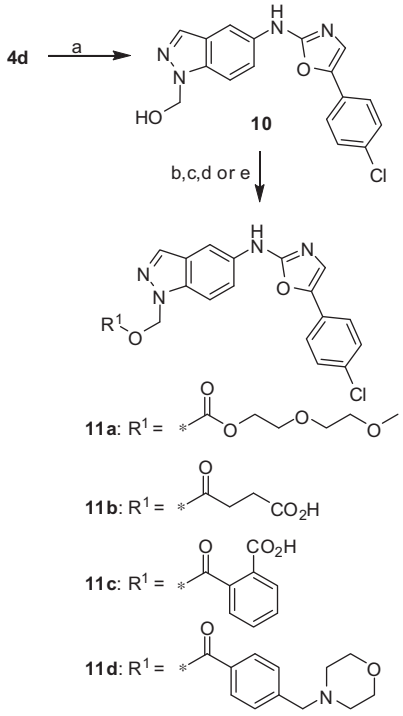
The data are an average of two experiments; the standard deviations are normally less than 20%.
[a] EC_{50}: 50% effective concentration.
[b] TC_{50}: 50% toxic concentration.
[c] Therapeutic index: TC_{50}/EC_{50}.



Scheme 3. Design of potential prodrugs of indazoles.

groups as a promoiety where the hydroxymethyl group acts as a self-cleavable second linker. The bioconversion of these prodrugs is generally initiated by enzymatic hydrolysis or intramolecular activation by carboxylate nucleophiles (for **11b**,**c**) and the newly revealed *N*-hydroxymethyl intermediates rapidly release the parent drugs and formaldehyde (Schemes 3 and 4).

The synthesis of type A compounds **11a**–**d** began with N-hydroxymethylation of indazole moiety of **4d** with formaldehyde (37% in water) that proceeded in good yield to form 10 under acidic or basic conditions (Scheme 4).[14] The primary hydroxyl group of 10 was then acylated to afford potential prodrugs **11a**–**d**. Compound **11a** bearing a ethylene glylcol promoiety was prepared by reaction of **10** with carbonic acid, 2,5-dioxo-1-pyrrolidinyl 2-(2-methoxyethoxy)ethyl ester in the presence of DMAP in pyridine. Under



Scheme 4. Reagents and conditions: (a) CH_2O (37% in water), NaOH, EtOH, 80%; (b) carbonic acid, 2,5-dioxo-1-pyrrolidinyl 2-(2-methoxyethoxy)ethyl ester, DMAP, pyridine, rt, 65% for **11a**; (c) succinic anhydride, DAMP, pyridine, rt, 81% for **11b**; (d) phthalic anhydride, DMAP, pyridine, rt, 47% for **11c**; (e) 4-(4-morpholinomethyl)benzoic acid, EDCI, DMAP, CH_2Cl_2, 42% for **11d**.

the identical condition, the acylation reactions with succinic anhydride and phthalic anhydride yielded **11b** and **11c**, respectively. EDCI-mediated coupling reaction of **10** with 4-(4-morpholinylmethyl)benzoic acid provided **11d**.

We also designed double prodrug **15** that consists of a phosphate group and an aminocarbonyloxymethyl linker (Scheme 5). The initial synthetic plan for **15** involved a functionalization of the primary hydroxyl group in compound **10**. This approach, however, proved to be unsuccessful. In the second approach, 5-nitroindazole (**12**) was used as the starting material. After N-hydroxymethylation of **12** with formaldehyde, the resulting hydroxyl moiety was converted to a reactive carbonate by reacting with *p*-nitrophenylchloroformate. The reactive carbonate intermediate formed was then reacted with 2-aminoethanol to provide carbamate **13**. The hydroxyl group of **13** was phosphorylated using di-*t*-butyl *N*,*N*-diisopropylphosphoramidite with subsequent hydrogen peroxide oxidation of the phosphite intermediate. After reduction of 5-nitro group of the indazole moiety, the resultant aniline compound was transformed to isothiocyanate **14**. Oxazole **15** was obtained in good yield from acyl azide **8** and **14** under the identical condition as described above for synthesis of **4d**. Unfortunately, deprotection of *t*-butyl group of **15** under standard TFA conditions resulted in the formation of parent **4d**, suggesting the poor stability of the promoiety under acidic conditions and the need of different protecting groups. In spite of the failure in the final deprotection step, this synthetic route will be amenable to the synthesis of diverse phosphate prodrugs[12] such as prodrug **15** bearing different protecting groups (e.g., R^2 = benzyl or acyloxymethyl ester).

Various Mannich-base prodrugs (type B) have been developed to increase the aqueous solubility or the stability of the parent molecule (e.g., rolitetracycline and hetacillin).[13] In this study, Mannich-base prodrugs **16a**–**c** were designed and synthesized using a standard Mannich reaction condition (Scheme 6).

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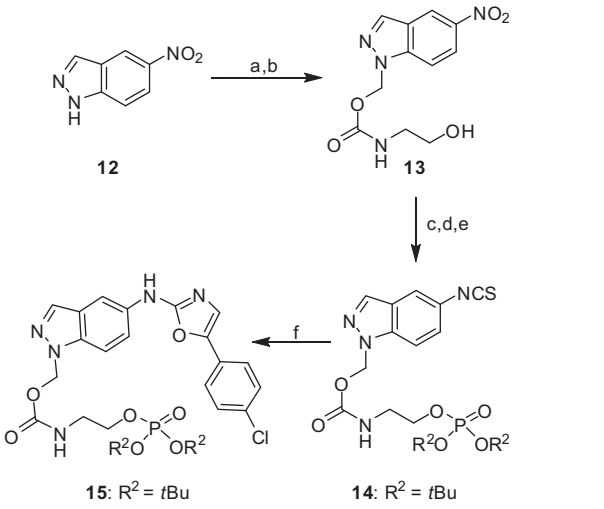
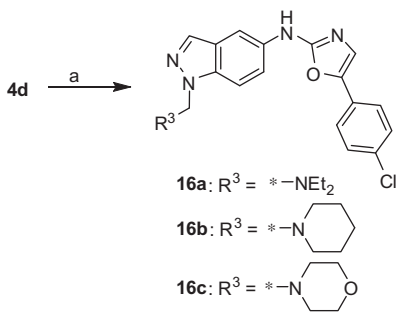


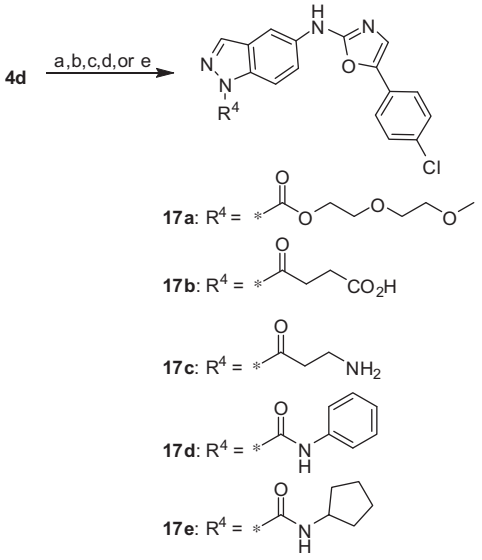
Scheme 5. Reagents and conditions: (a) CH_2O (37% in water), NaOH, EtOH, 84%; (b) *p*-nitrophenylchloroformate, NEt_3, CH_2Cl_2, 0 °C to rt, then 2-aminoethanol, rt, 45%; (c) di-*t*-butyl *N*,*N*-diisopropylphosphoramidite, 1*H*-tetrazole, H_2O_2 (30% wt/wt in water), CH_2Cl_2, 68%; (d) H_2 (1 atm), Pd/C (10% w/w), EtOAc, 93%; (e) 1,1′-thiocarbonyl-2(*H*)-pyridone, CH_2Cl_2, 86%; (f) PPh_3, 8, dioxane, 78%.

The synthesis of *N*-acyl prodrugs (type C) is shown in Scheme 7. Although several successful *N*-acyl prodrugs are in clinical use, their utility in prodrug design has been limited due to the relatively high enzymatic stability in vivo.[13] Acylation of **4d** with appropriate succinimidyl carbonate, succinimidyl ester, or anhydride in the presence of DMAP in pyridine proceeded to give prodrugs **17a**–**c**. In addition, potential urea prodrugs **17d**–**e** were also prepared by treatment of **4d** with cyclopentyl isocyanate or phenyl isocyanate.

These indazole analogues were briefly evaluated as potential prodrugs with improved aqueous solubility. The preliminary solubility screening showed that analogues **11b** and **11c** exhibited a remarkably improved aqueous solubility (~300-fold) compared to that of the parent compound **4d** (aqueous solubility = 0.2, 60, 66 μM at pH 7.4 in phosphate buffer, **4d**, **11b** and **11c**, respectively). However, no improvement in aqueous solubility was observed in other analogues such as *N*-hydroxymethyl analogue **10**, *N*-alkoxycarbonyloxymethyl analogue **11a**, *N*-acyloxymethyl analogue **11d**, analogue **15** containing a phosphate group and Mannich-base analogues **16a**–**c**. The insufficient aqueous solubility led us to eliminate these analogues from further study. Also, *N*-acyl and *N*-urea analogues **17a**–**e** were not considered suitable as a prodrug due to their well known enzymatic stability. Therefore, analogues **11b**,**c** with adequate aqueous solubility were selected to assess for their ability to undergo conversion to the parent **4d** in vitro. When incubated in phosphate buffered 80% human plasma



Scheme 6. Reagents and conditions: (a) CH_2O (37% in water), diethylamine, piperidine, or morpholine, MeOH, 60 °C, 63–76%.



Scheme 7. Reagents and conditions: (a) carbonic acid, 2,5-dioxo-1-pyrrolidinyl 2-(2-methoxyethoxy)ethyl ester, DMAP, pyridine, rt, 35%; (b) succinic anhydride, DAMP, pyridine, 65 °C, 10 h, 26%; (c) 2,5-dioxopyrrolidin-1-yl 3-(*tert*-butoxycarbonylamino)propanoate, DMAP, pyridine, rt; TFA, CH_2Cl_2, 27% (two-steps), (d) phenyl isocyanate, CH_3CN, 100 °C, 76%; (e) cyclopentyl isocyanate, CH_3CN, 100 °C, 59%.

(pH 7.4) at 37 °C, analogue **11b** underwent enzymatic hydrolysis (~35% remaining of **11b** after 40 min) and the time dependent formation of the parent **4d** was observed whereas analogue **11c** was quite stable and almost no conversion was observed under identical conditions. Analogue **11b** was stable at pH 7.4 in phosphate buffer at 37 °C over 40 min and no significant hydrolysis was observed. The improved aqueous solubility of **11b** and its susceptibility to enzymatic hydrolysis suggested that **11b** could be a promising prodrug and was selected for further evaluation. Potential prodrug **11b** retained the potency of parent **4d** even it had a relatively narrow value of TI (EC_{50} = 2 μM, TI = 15 for **11b**, EC_{50} = 3 μM and TI >30 for **4d**).

Further investigations such as various in vitro HIV assays, kinase profiling and chemical proteomics studies are needed to identify the cellular targets and elucidate the mechanism underlying the anti-HIV activity of the new analogues. A possible mechanism could be an inhibition of protein kinases since the molecules contain motifs common to kinase inhibitors[15] and several kinase inhibitors (e.g., CDKs, CKII, and LIMK inhibitors) have been found to have effective anti-HIV activity.[16] Analogue **17c** particularly attracted our attention because it did not impede HIV inhibitory potency (EC_{50} = 2 μM, TI = 24, **17c**) and contains a primary amine moiety that is required for immobilization of a compound on a solid support. Thus, the immobilized inhibitor can be used in an affinity chromatography based chemical proteomics study for target identification.[4,17]

In summary, new oxazole containing inhibitors of HIV-1 have been discovered through cell-based screening of an in-house library and subsequent scaffold modification. The SAR study focusing on substituent on the 5-aryl moiety of the oxazole core led to the identification of potent inhibitor **4k** (EC_{50} = 0.42 μM, TI = 50, MT4 cells). In an effort to improve the aqueous solubility of the analogues, broadly applicable potential prodrugs of indazoles were designed and synthesized. A preliminary evaluation has shown that *N*-acyloxymethyl analogue **11b** is a promising prodrug of indazoles. Additional studies are needed to evaluate full potential of the prodrug approach and determine cellular targets of these inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2013.03.075.

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