Bioorganic & Medicinal Chemistry Letters 22 (2012) 7309–7313

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

6,7-Dihydroxy-1-oxoisoindoline-4-sulfonamide-containing HIV-1 integrase inhibitors

Xue Zhi Zhao [a,*], Kasthuraiah Maddali [b], Steven J. Smith [c], Mathieu Métifiot [b], Barry C. Johnson [c], Christophe Marchand [b], Stephen H. Hughes [c], Yves Pommier [b], Terrence R. Burke Jr. [a,*]

[a] Chemical Biology Laboratory, Frederick National Laboratory for Cancer Research, National Institutes of Health, Frederick, MD 21702, United States
[b] Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States
[c] HIV Drug Resistance Program, Frederick National Laboratory for Cancer Research, National Institutes of Health, Frederick, MD 21702, United States

ARTICLE INFO

Article history:
Available online 27 October 2012

Keywords:
HIV-1 integrase
Inhibit
Raltegravir
Sulfonamide

ABSTRACT

Although an extensive body of scientific and patent literature exists describing the development of HIV-1 integrase (IN) inhibitors, Merck's raltegravir and Gilead's elvitegravir remain the only IN inhibitors FDA-approved for the treatment of AIDS. The emergence of raltegravir-resistant strains of HIV-1 containing mutated forms of IN underlies the need for continued efforts to enhance the efficacy of IN inhibitors against resistant mutants. We have previously described bicyclic 6,7-dihydroxyoxoisoindolin-1-ones that show good IN inhibitory potency. This report describes the effects of introducing substituents into the 4- and 5-positions of the parent 6,7-dihydroxyoxoisoindolin-1-one platform. We have developed several sulfonamide-containing analogs that enhance potency in cell-based HIV assays by more than two orders-of-magnitude and we describe several compounds that are more potent than raltegravir against the clinically relevant Y143R IN mutant.

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Integrase (IN) is an HIV-1 encoded polynucleotidyl transferase that inserts viral cDNA into the host genome through a process involving two sequential enzymatic steps, termed 3′-processing (3′-P) and strand transfer (ST).[1] Integration is required for viral replication and IN is a validated antiviral target for the treatment of AIDS.[2,3] There is an extensive body of scientific and patent literature describing the development of IN inhibitors.[4,5] Raltegravir (**1**) is the first IN inhibitor FDA-approved for the treatment of HIV/AIDS (Fig. 1).[6] Raltegravir binds at the interface of the macromolecular complex formed by IN and the viral DNA substrate, blocking the active site and preventing the insertion of the viral DNA into the host genome.[7] Because it more potently blocks the second enzymatic step, it is referred to as an IN strand transfer inhibitor, or INSTI. All anti-HIV drugs select for resistant strains of the virus and raltegravir is no exception. Because there are clinical strains of HIV-1 that exhibit reduced sensitivity to raltegravir,[8] 'second-generation' inhibitors are being developed to treat patients failing raltegravir-based treatment.[9] However, in in vitro experiments exposure to such compounds selected IN mutants showing reduced susceptability,[10,11] suggesting that additional work needs to be done to understand the underlying mechanisms of resistance, and to develop new compounds that will be more effective against resistant strains.

Raltegravir shares with other well-described INSTIs, the ability to chelate two catalytic divalent metal ions (Mn^{2+} or Mg^{2+}) through a triad arrangement of heteroatoms (Fig. 1). We have previously described structurally simple bicyclic 6,7-dihydroxyoxoisoindolin-1-one-based IN inhibitors (**2**) that show good potency and strand transfer selectivity in vitro in the presence of Mg^{2+} cofactor.[12] Our earlier reports focused primarily on the arylamide 'right side' of the molecules.[13,14] This paper describes the effects of substitutions at the two free aryl positions on the 'left side' of the molecule (Fig. 1). In designing new analogs we were guided by the fact that Merck's bicylic second-generation inhibitor MK-0536 (**3**)[15,16] has carboxamido and isopropyl substituents at what would be equivalent to positions 4 and 5 of our 1-oxoisoindoline ring system (Fig. 1). We applied a variation of this theme to the dihydroxyoxoisoindoline nucleus by placing several different alkyl groups at the 5-position (**4**) and employing sulfonamido rather than carboxamido functionality at the 4-position (**5**, Fig. 1).

Synthesis of derivatives of compound 4 modified at the 5-position employed methodologies similar to those used to prepare the unsubstituted congeners.[12–14] Substituents that would ultimately occupy the 5-position of the 6,7-dihydroxyoxoisoindolines final products were derived from appropriately substituted methyl dimethoxybenzyl ethers (**6**, Scheme 1). Methyl-substituted **6b**

* Corresponding authors. Tel.: +1 301 846 5906; fax: +1 301 846 6033 (T.R.B.); tel.: +1 301 846 5907; fax: +1 301 846 6033 (X.Z.Z.).
E-mail addresses: xuezhi.zhao@nih.gov (X.Z. Zhao), burkete@helix.nih.gov (T.R. Burke).

0960-894X/$ - see front matter Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.bmcl.2012.10.088

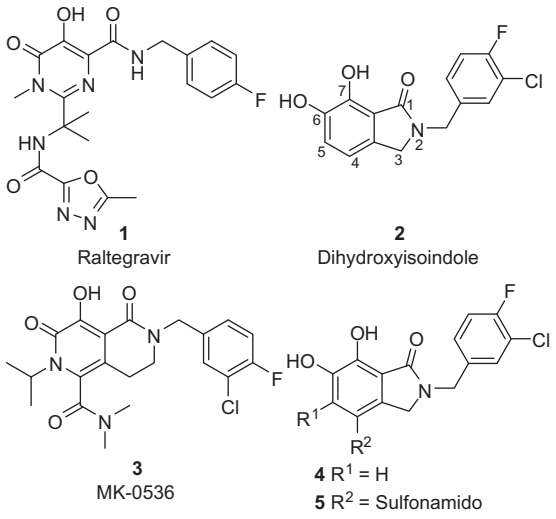
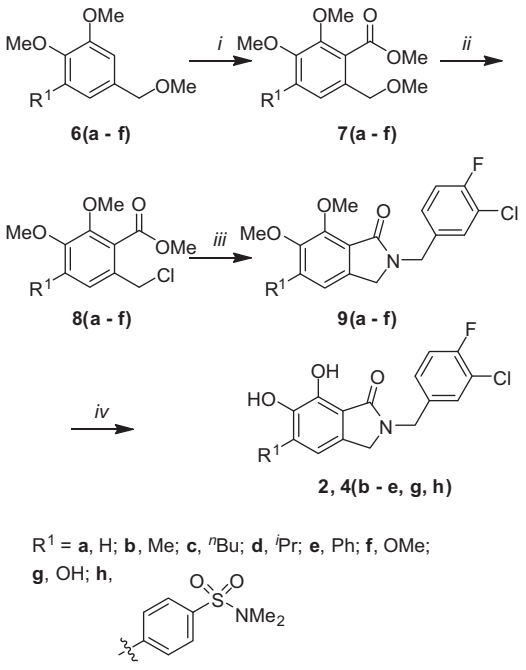


Figure 1. Structures of IN inhibitors discussed in the text.



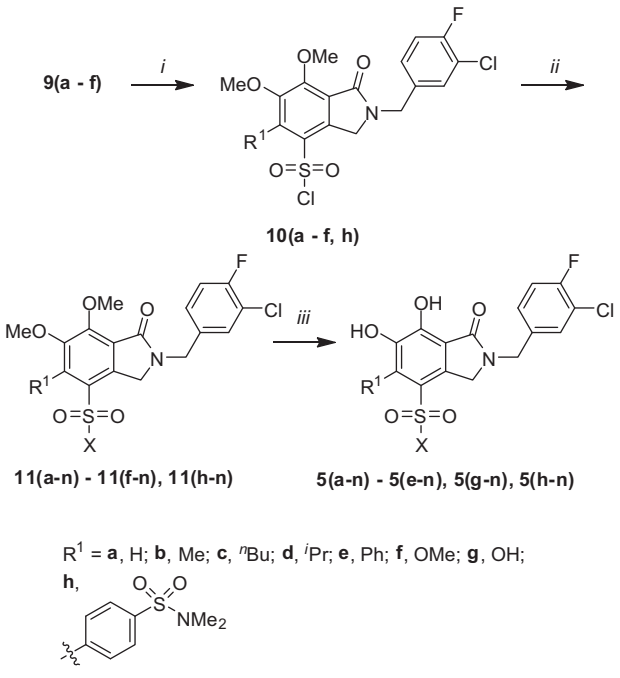
Scheme 1. Reagents and conditions: (i) ^{n}BuLi, $ClCO_2Me$; (ii) AcCl, $ZnCl_2$, Et_2O; (iii) 3-chloro-4-fluoro-benzylamine, Et_3N, CH_3CN; (iv) BBr_3, CH_2Cl_2.

was obtained from vanillin using 4-hydroxy-3-methoxy-5-methylbenzaldehyde[17] as an intermediate (see Supplementary Scheme S1). The *n*-butyl-substituted compound (**6c**) was obtained serendipitously in an attempt to prepare the isopropyl congener (**6d**). The synthesis started from 5-bromovanillin and there was an unintended introduction of the *n*-butyl group when *n*-butyl lithium was used for metalation of the aryl bromide of intermediate 1-bromo-2,3-dimethoxy-5-(methoxymethyl)benzene (see Supplementary Scheme S2). The desired isopropyl containing analog (**6d**) was synthesized through the known 5-bromo-1-isopropyl-2,3-dimethoxybenzene[18] (see Supplementary Scheme S3). The phenyl-substituted compound **6e** was obtained through a route involving Suzuki coupling of phenylboronic acid with the above-mentioned 1-bromo-2,3-dimethoxy-5-(methoxymethyl)benzene (see Supplementary Scheme S4). Finally, the trimethoxyphenyl-containing analog **6f** was obtained from commercially-available (3,4,5-trimethoxyphenyl)methanol by methylation using iodomethane and sodium hydride (see Supplementary Scheme S5).

Treatment of the benzyl methyl ethers **6**(**a**–**f**) with *n*-butyl lithium followed by methyl chloroformate provided the corresponding methyl esters **7**(**a**–**f**) (Scheme 1). Transformation to the benzyl chlorides **8**(**a**–**f**) was then accomplished using acetyl chloride in the presence of a catalytic amount of zinc chloride. Subsequent ring closure to the isoindolin-1-ones **9**(**a**–**f**) was achieved by coupling with 3-chloro-4-fluorobenzylamine. The final 5-substituted 6,7-dihydroxyisoindolin-1-ones **2, 4**(**b**–**e**, **g**, **h**) were obtained by demethylation using boron tribromide in dichloromethane (Scheme 1).

Introduction of sulfonyl functionality at the indolin-1-one 4-position was achieved by reacting the methyl ether-protected intermediates **9**(**a**–**f**) with chlorosulfonic acid gave the sulfonyl chlorides **10**(**a**–**f**, **h**) (Scheme 2). Further treatment with a variety of primary and secondary amines yielded the corresponding sulfonamides **11**(**a**–**n**)–**11**(**f**–**n**) and **11**(**h**–**n**), where 'n' designates variation in the sulfonamido group. Finally, deprotection of the methyl ethers was accomplished by cleavage with boron tribromide in dichloromethane to produce the final products **5**(**a**–**n**)–**5**(**e**–**n**), **5**(**g**–**n**) and **5**(**h**–**n**) (Scheme 2).

Our previous structural studies on 6,7-dihydroxyoxoisoindolin-1-one-based IN inhibitors (**2**) were limited to analogs that were unsubstituted at the 4- and 5-positions.[12–14] An important objective of our current work was to explore the effects of incorporating functionalities at the 5-position of the isoindolinone ring system (compounds **4**). MK-0536 (**3**) is one example of a diverse range of IN inhibitors that have substituents in this region.[5] We were also interested in determining the effects of placing sulfonamido groups at the 4-position. Highly potent IN inhibitors have been reported that have sulfonamide groups located in this region. However, in almost all cases the sulfonamides are either in 'reversed' orientations, having the amine rather than the sulfur attached to the metal-chelating aryl ring (for example[19,20]), or the sulfonamide is attached indirectly through intervening structures (for exam-



Scheme 2. Reagents and conditions: (i) $ClSO_3H$; (ii) R^2R^3NH, Et_3N, CH_2Cl_2; (iii) BBr_3, CH_2Cl_2.