Available online at www.sciencedirect.com
ScienceDirect
European Journal of Medicinal Chemistry 42 (2007) 1159–1168
EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY
http://www.elsevier.com/locate/ejmech

Mini-review

# Development of integrase inhibitors for treatment of AIDS: An overview

Sonal Dubey*, Y.D. Satyanarayana, Harshita Lavania

*K.L.E.S. College of Pharmacy, Rajajinagar II Block, Bangalore 560010, Karnataka, India*

Received 5 August 2006; received in revised form 18 January 2007; accepted 19 January 2007
Available online 30 January 2007

**Abstract**

HIV-1 integrase (IN) is an essential enzyme for retroviral replication. It is involved in the integration of HIV DNA into host chromosomal DNA. The unique properties of IN makes it an ideal target for drug design. First, there appears to have no functional equivalent in human cells and the reactions catalyzed by IN are unique. Second, IN is absolutely required for viral replication and mutations in a number of key residues block the viral replication. Third, IN has been validated as a legitimate target and the results from the molecules like S-1360, JKT-303 which are under phase II/III clinical trials suggest synergistic effect with reverse transcriptase (RT) and protease (PR) inhibitors. During the past 10 years a plethora of inhibitors have been identified and some were shown to be selective against IN and block viral replication. The classes under which inhibitors of integrase can be classified are catechol-containing hydroxylated aromatics, diketoacid-containing aromatics, quninolines and others (non-catechol containing). In the present article we review all the recent small molecules reported to inhibit recombinant HIV-1 IN under these heads. It seems likely that the efficient use of HIV IN as target for rational design can give potent anti-HIV agents, which can be used alone or in combination regimens with other classes of anti-HIV drugs.


*Keywords:* HIV-1; AIDS; Integrase inhibitors; Catechol; Diketoacids; Quinoline; Non-catechol

## 1. Introduction

Human immunodeficiency virus type-1 (HIV-1) is the etiologic agent of AIDS in humans [1,2]. HIV-1 establishes a persistent infection in human hosts, with the depletion of $CD4^+$ lymphocytes, the major target cells of viral infection in vivo, eventually resulting in defective cellular immunity [3]. Considerable progress has been made in the treatment of patients infected with HIV. Combination regime that includes potent reverse transcriptase and protease inhibitors is in clinical practice [4]. Drugs approved so far include nucleoside (NRTIs) and non-nucleoside RT inhibitors (NNRTIs) [5–7], such as AZT (**1**), ddI, $d_4T$, nevirapine, delavirdine, and efavirenz, and protease inhibitors (PRIs) [8] such as saquinavir, indinavir, ritonavir, nelfinavir, amprenavir and lopinavir.

Highly active antiretroviral therapy (HAART) is a combination regimen which includes two or more classes of anti-HIV drugs given together to have synergistic effect. It is of great benefit for most patients, with reduction of HIV RNA in the plasma of infected individuals to undetectable levels, and can rescue $CD4^+$ cell counts with significant benefit for HIV-seropositive patients and prolonged survival. Unfortunately, long-term therapeutic success may be jeopardized by the toxicity, complicated dosing schedules, considerable side effects making long-term compliance with drug regime difficult for most patients and emergence of drug-resistant virus strains [9,10]. Therefore, it remains essential to develop drugs targeted at alternative steps of viral replication cycle. The integration of retro-transcribed viral DNA into the host chromosome is an essential step in the replication cycle of retrovirus. After integration the proviral DNA is replicated and

* Corresponding author. Tel.: +91 9880985847; fax: +91 8023425373.
*E-mail address:* drsonaldubey@gmail.com (S. Dubey).

0223-5234/$ - see front matter © 2007 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2007.01.024

genetically transmitted as part of cellular genome. Thus, integration defines a point of no return in the life cycle of HIV. The integrase of HIV is an attractive target for selective antiviral therapy since there is no known functional homologue in human cells [11,12].

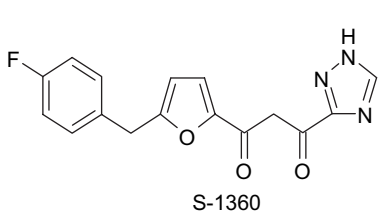
### 1.1. HIV-1 integrase

HIV-1 integration encompasses a series of molecular events that follows the completion of reserve transcription in the cytoplasm of the infected cell and that ends with the initiation of the transcription from the proviral DNA. IN protein carries out the initial DNA breaking and joining reactions responsible for the attachment of HIV cDNA to host DNA i.e. 3′-processing and strand transfer. Prior to integration two nucleotides are removed from each 3′-end in the linear cDNA precursor (terminal cleavage). This reaction may be important to the virus by preparing a defined substrate for subsequent reaction steps because RT often adds mono template bases to the 3′-ends of unintegrated cDNA. The recessed 3′-ends are then joined to protruding 5′-ends of breaks made in the target DNA (strand transfer). The remaining DNA strands are then attached, probably by the action of host DNA repair enzymes, to complete the formation of an integrated provirus [13–18]. Thus, retrovirus integration requires at least two viral components, the retroviral enzyme integrase, and *cis*-acting sequences at the retroviral DNA termini U3 and U5 ends of the long terminal repeats. Since HIV, like other retrovirus cannot replicate without integration into the host chromosome, integrase has been considered as attractive therapeutic target [12].

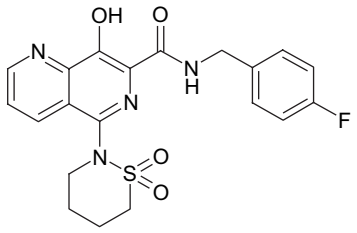
The HIV-1 integrase, produced in an *Escherichia coli* expression system, can carry out both 3′-processsing and strand transfer in vitro in the presence of di-cations such as $Mg^{2+}$and $Mn^{2+}$ [13].

The HIV-1 integrase is a 32 kDa protein, composed of 288 amino acids that can be separated in three domains, the N-terminal domain, catalytic core domain and C-terminal domain which all fold independently. The N-terminal domain and DD(35)E motif in the catalytic core are the highly conserved portions of the integrase. The C-terminal domain shows the least sequence conservation. Not the entire protein but only its core is required for the disintegration step, showing that it contains the enzyme active site. Site-directed mutagenesis experiments showed that catalytic activity is abolished by the substitution of any of the three absolutely conserved carboxylate residues, two aspartic residues, D-64 and D116, and a glutamic residues, E152 (the so-called, DD-35E motif) [12,19–22].

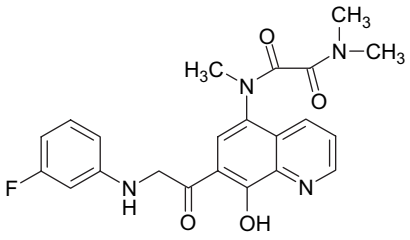
About a decade of research in the field of HIV-1 IN inhibitors has yielded five drugs in clinical trials [23,24]: S-1360 (**1**) is a diketo derivative designed by Shionogi-GSK companies; L-870810 (**2**) and L-870812 (**3**) 8-hydroxynaphthyridines and MK-0518 (**4**) designed by Merck Research Lab.; and JKT-303 (**5**) designed by Japan Tobacco and developed by Gilead.



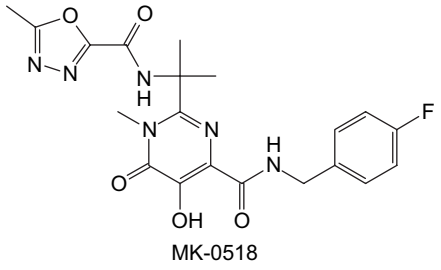

**1**



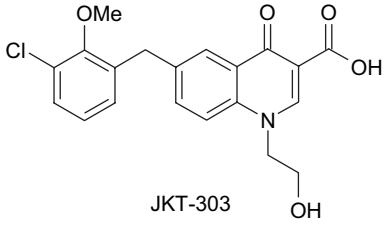

**2**




**3**




**4**



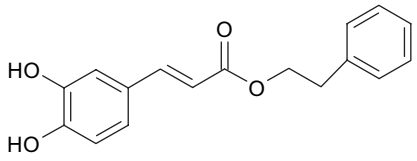

**5**

A large number of molecules have been designed, synthesized and evaluated for their anti-integrase activity with the help of systematic screening using mostly purified IN-based assays. From such screens several IN inhibitor classes have been identified. Present article reviews these potential IN inhibitors and classify them into various chemical classes along with their anti-IN activity.

### 1.2. Catechol derivatives

Catechol containing bis-aryl moieties is a significant structural component in many potent HIV integrase inhibitors. These

compounds contain two aryl units, of which at least one contains 1,2-dihydroxy substitution, separated by a linker. By systemic screening using purified IN-based assays, several IN inhibitors classes have been identified, which include hydroxylated aromatic compounds such as aurintricarboxylic acids [25], bis-catechols [26], caffeic acid phenethyl ester (**6**, CAPE) [27], flavones and flavonoids [28], curcumin [29,30], tyrphostins [31], lignanolides [32], coumarin derivatives [33], cosalanes [34], hydrazide derivatives [35], despide and despidones [36], strylquinoline derivatives [37] and lamellarins [38].



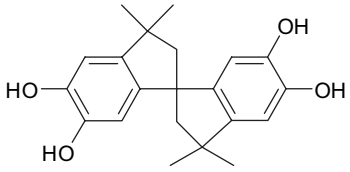

CAPE

**6**

Although such catechol analogues exhibit good inhibition against isolated HIV IN, often corresponding protective effects in HIV-infected cells are not observed due to the dose limiting toxicities in in vitro assays. Thus, development of IN inhibitors either lacking the catechol moiety or modifications which overcome its toxic properties lead to the development of dicaffeoyl quinic acids (DCQAs) and related compounds, L-chicoric acid (**7**, dicaffeoyl tartaric acid). These compounds have multiple caffeoyl groups attached to the carboxylic acid-containing frame and they not only inhibit HIV-1 replication but also inhibit integration in biochemical assays and blocks HIV replication in cell culture. The compounds that have been reported to date as DCQA derivatives include 3,5-DCQA, 1-methoxy oxalyl-3,5-DCQA (**8**, 1-MO-3,5-DCQA), 1,5-DCQA (**9**), and 4,5-DCQA (**10**) [39–41].

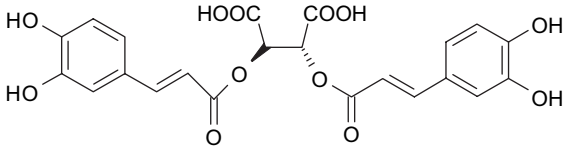
L-Chicoric acid [42] is structurally reminiscent of curcumin [29], 3,5-dicaffeoyl quinic acid [43], rosmarinic acid [30] and dicaffeoyl tartaric acid (DCTAs) [44]. The HIV envelope (gp160) consists of the gp120 surface and gp41 transmembrane glycoproteins. gp120 initiates binding between the virion and cell surface CD4 molecule and triggers fusion between the viral envelope and the host cell membrane allowing infection to proceed [45,46]. L-Chicoric acid owes its anti-HIV activity in cell culture not only to HIV-1 replication inhibition but it is also a potent HIV-1 integrase inhibition [47].

In another study to overcome the toxic effects of catechols on cell culture [39,48–53], which might be related to the cross reactivity of metal requiring enzymes or covalent protein modification, a new class of HIV-1 integrase-3,3,3′,3′-tetramethyl-1,1-spiro bis(indan)-5,5′6,6′-tetrol (TMS) and 3,3,3′3′-tetramethyl-1,1′-spiro(indan)-5,5,6,6′-tetrol (**11**) were synthesized. These catechol isosteres inhibited the IN enzyme in vitro [54].

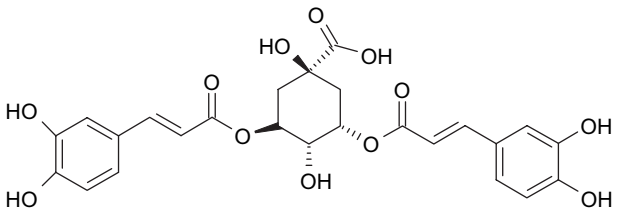



**11**

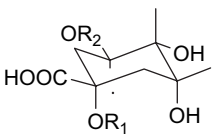
The search of new, potent and selective inhibitors of HIV-1 integrase inhibitors lead to the synthesis of 5,6-dihydroxyindole-2-carboxylic acid (DHICA, **12**) and a series of benzyl or phenylethylamine substituted derivatives and dimmers of DHICA. These compounds were designed as conformationally constrained analogues of CAPE. Seven compounds inhibited catalytic activities of purified IN with $IC_{50}$ values below 10 μM [55].

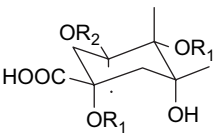


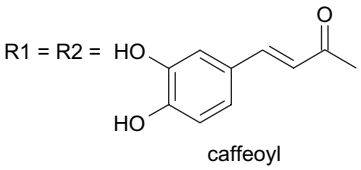

**7**




**8**

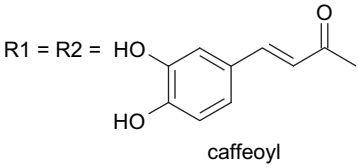


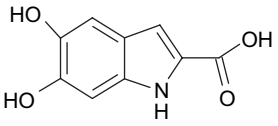

caffeoyl

**9**



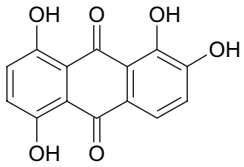

caffeoyl

**10**

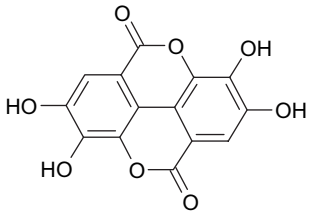


**12**

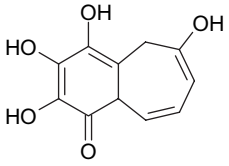
Even though much of the work in IN inhibition has been done on benzene ring with *ortho*-dihydroxyls (catechol), some work has also been done on polyhydroxylated aromatic compounds like quinalizarin (**13**, polyhydroxylated anthraquinones). A series of newer polyhydroxylated anthraquinones and related quinones have been synthesized which yielded new inhibitors of IN. The important ones being ellagic acids (**14**, $IC_{50} = 5.1$ μM) and purpurogallin (**15**, $IC_{50} = 2.1$ μM) [53].



**13**



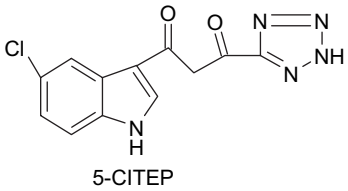
**14**



**15**

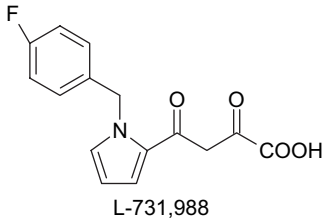
## 2. Diketo derivatives

A series of diketo derivatives were found to inhibit HIV-1 integrase activity. CITEP (**16**, 1-(5-chloroindol-3-yl)-3-hydroxy-3-(2*H*-tetrazol-5-yl)-propenone) was reported by Goldgur et al. in 1999. They had reported the structure of the HIV-1 integrase catalytic domain complexed with 5-CITEP. In the structure 5-CITEP seems to mimic the DNA substrate/integrase interaction lying in the middle of the active site of enzyme subunit A between the three catalytic acidic residues, Asp-64, Asp116 and Glu-152, without displacing the bound magnesium ion [56]. Hazuda et al. [57] reported L-731988 (**17**) in 2000, in this the tetrazole ring of CITEP is replaced isosterically with carboxylic acid; and the keto–enol is tautomeric with the diketo functionality. Approximately 600 nM L-731988 inhibited the replication of 12 HIV type-1 isolates from multiple clades, including primary isolates and cloned viruses. It was reported to be a selective inhibitor of the strand transfer process and prevents proviral DNA integration thereby preventing the HIV-1 replication in the cell culture. Replacing the central pyrrole ring with a series of aromatic systems having various substitution patterns provided optimum relative orientation of the benzyl and diketoacid side chain. The most active compounds from this series inhibit replication of HIV-1 in cell culture at $IC_{95}$ 0.10–0.62 μM. The results showed a 100-fold improvement in the potency of **18** as compared to the lead compound **17** [61]. Another compound L-708906 (**19**) [53] inhibited the replication of HIV-1 (50% inhibitory concentration, 0.2 μM) at 3′-end-processing. It also inhibits DNA strand transfer at $IC_{50}$ of 3.5 μM along with another compound P13 having the value 15.1 μM [12,58,59].



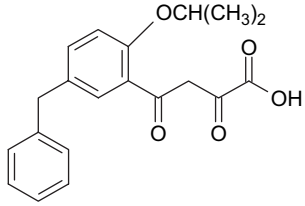
5-CITEP

**16**

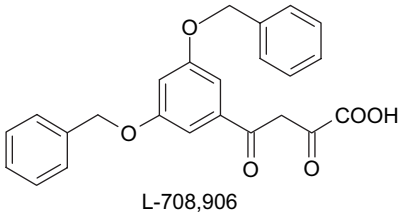


L-731,988

**17**



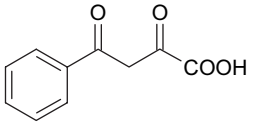
**18**



L-708,906

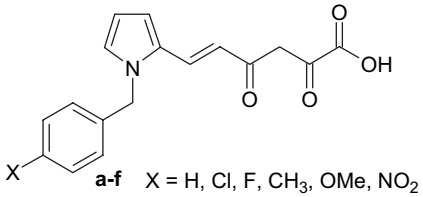
**19**

The 4-phenyl-4-oxo-2-hydroxybuten-2-oic acid (benzoylpyruvic acid (BPA, **20**) the pharmacophore of HIV-1 integrase inhibitors, was screened for inhibitory activity against HIV-1 IN in both $Mg^{2+}$ dependent 3′-end-processing and strand transfer reactions. These results reconfirmed the metal-dependent IN inhibition of DKAs [60].



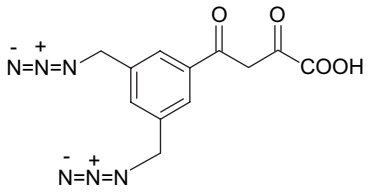

**20**

More recently, compounds containing distinct dioxobutanoic acid moiety have been identified as potent and specific inhibitors of HIV-1 multiplication targeting the integration process [61]. The anti-IN activity was also retained when (i) the terminus carboxylic function was masked by a tetrazole ring [51] and (ii) the dioxobutanoic group was shortened into oxopropanoic moiety [62]. Attempts have also been made to check the effect of lengthening of dioxobutanoic group, e.g. series of 6-aryl-2,4-dioxo-5-hexanoic acids were synthesized (**21a–f**). Compound **21a** showed potent antiretroviral activity ($EC_{50} = 1.5$ μM) and significant inhibition against IN (strand transfer: $IC_{50} = 7.9$ μM; 3′-processing: $IC_{50} = 7.0$ μM) [63].

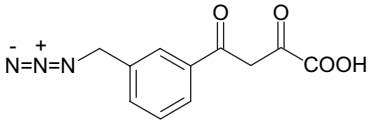



**21**

Certain other azido-containing β-DKA derivatives have also been reported. Both these compounds (**22** and **23**) inhibited the HIV-1 infection in 293T, CFM-SS and $H_9$ cells [64].



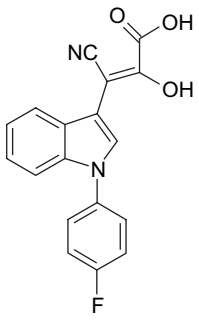

**22**



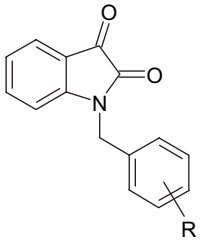

**23**

β-Diketoacid derivatives were independently discovered by scientists from Shionogi & Co. [56,65] and Merck as selective IN inhibitors [57]. Several potent analogs were identified, of which, S-1360 (**1**) is undergoing phase II clinical trials with HIV-infected subjects. It inhibits HIV-1 replication in cell culture with $IC_{95}$ value of 12 000 nm [23,57,66].

Sechi et al. have done a 3D computational search on NCI database to identify the possible bioisosteres. Several structural platforms with potential as HIV-1 IN inhibitors were selected and their pharmacophoric fragments were incorporated into aromatic or heteroaromatic frameworks to give eight general structures. The target compounds were synthesized and evaluated, compound **24** showed good activity for strand transfer with $IC_{50}$ value of 10 μM [67]. In another study by different group, different sets of indole DKA derivatives were synthesized. These compounds (**25**) inhibited 3′-processising or strand transfer activities of IN showing $IC_{50} \leq 25$ μM [68].

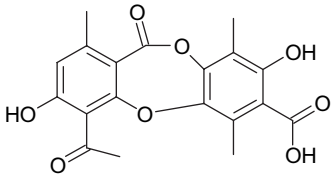



**24**



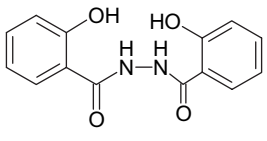

**25**

Some of the other well-known examples of diketo compounds possessing integrase inhibiting properties are granulatine (**26**) [69], salicylhydrazide (**27**) [70,71], and integric acid (**28**) [72].



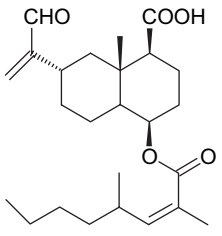

Granulatine

**26**




Salicylhydrazide

**27**




Integric acid

**28**

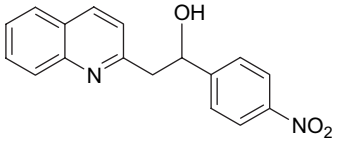
## 3. Quinoline derivatives

2-Alkylquinolines and 2-arylquinolines isolated from plants [73] and prepared by total synthesis [74,75] were found to inhibit the HIV-IN as well as the proliferation of HTLV-1 transformed cell lines. Several 2-substituted quinolines (**29**–**32**) have been synthesized and tested in vitro for HTLV-1 activity [76].

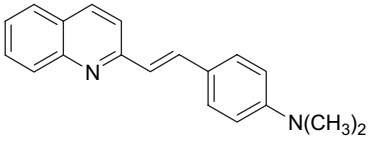
A new series of HIV-1 IN inhibitors (**33**–**36**) were synthesized and tested by both in vitro and ex vivo assays. These inhibitors featured quinoline subunit and ancillary aromatic ring linked by functionalized spacers such as amide, hydrazide, urea and 1-hydroxyprop-1-en-3-one moiety. Among these derivatives the amide group containing derivatives were the most promising ones [77].

Certain styrylquinoline compounds (**37** and **38**) have been shown to be potent HIV-1 IN inhibitors in vitro [78]. These compounds have also displayed an antiviral activity in a de novo infection assay of CEM4 cells, thereby opening an exciting new lead for the design of new anti-HIV drugs. These styrylquinoline derivatives target the integrase core domain since they inhibited the disintegration assay carried out by the active site containing deletion mutation [79].

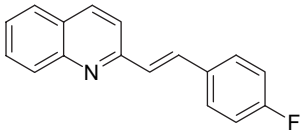
Many polyhydroxylated styrylquinolines **39** and **40** were synthesized and found to be potent HIV-1 IN inhibitors that block the replication of HIV-1 in cell culture at non-toxic concentrations. The SAR of these compounds reveled that for in vitro activity the carboxyl group at C-7, a hydroxyl group at C-8 in the quinoline subunit and an ancillary phenyl ring is required. However, it tolerates deep alterations of this ring. Regarding the ex vivo assay, the structural requirements for activity are more stringent; as in addition to an *o*-hydroxy acid group in the quinoline, the presence of one *ortho* pair of substituents at C-3′ and C-4″, particularly two hydroxyl groups, in the ancillary phenyl ring is imperatively required for inhibitory potency [80].



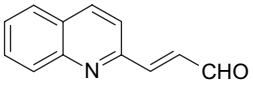

**29**



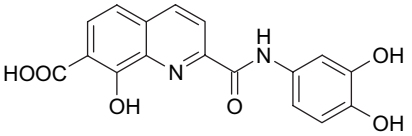

**30**



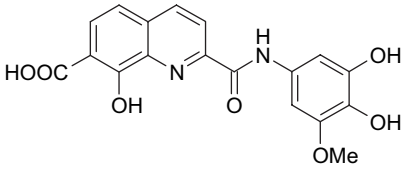

**31**



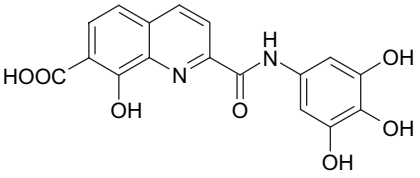

**32**



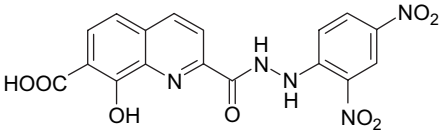

**33**



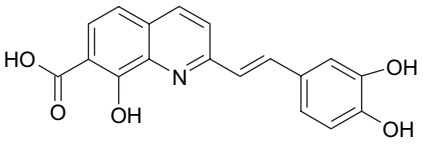

**34**



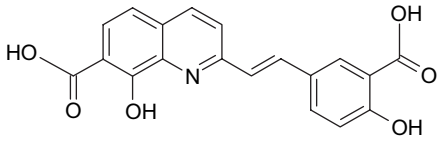

**35**



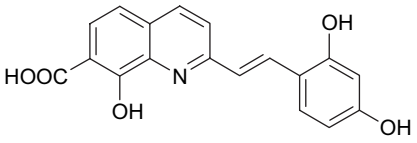

**36**



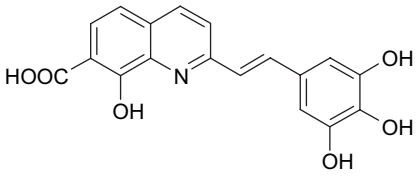

**37**




**38**

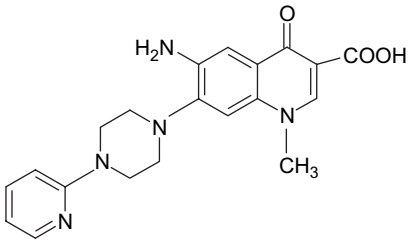


**39**



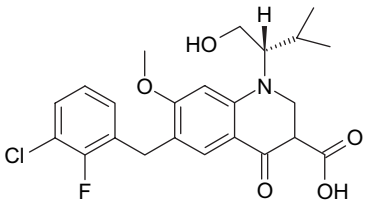
**40**

A 6-amino quinolone derivative, WM5 (**41**), which bears a methyl substituent at the *N*-1 position and 4-(2-pyridyl)-1-piperazine moiety at position 7 of bicyclic quinoline ring system, was previously shown to exhibit potent activity against replication of human immunodeficiency virus type-1 (HIV-1) in the de novo − infected human lymphoblastoid cells [81,82].



**41**

Modification of a quinolone antibiotic produces the novel integrase inhibitor JTK-303 (GS 9137) (**42**) that blocks strand transfer by the viral enzyme. It shares the core structure of quinoline antibiotics, exhibits an $IC_{50}$ of 7.2 nM in the strand transfer assay, and shows an $EC_{50}$ of 0.9 nM in an acute HIV-1 infection assay [83].



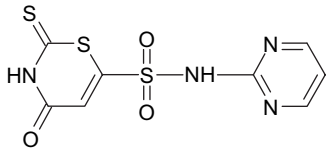
**42**

## 4. Miscellaneous compounds

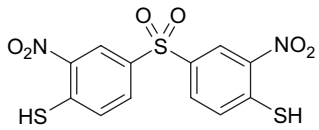
As opposed to the catechol containing compounds, non-catechol containing and/or other miscellaneous structures are excellent leads to develop a selective potent IN inhibitors, for they possess considerably less cytotoxicity.

Several sulfonamides (**43**), diaryl sulfones (**44**), and aromatic disulfides (**45**) were found to inhibit IN function at low micromolar concentrations. However, only the 2-mercaptobenzenesulfonamide (**46**) and to a lesser extent the naphthalene disulfonate exhibited antiviral activity [84].

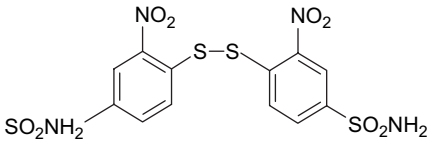
A series of thiazolothiazepines were prepared and tested against purified human immunodeficiency virus type-1 integrase (HIV-1) and viral replication. Compounds **47**, **48** and **49** which showed antiviral activity were selective inhibitors for IN, but were found to be almost inactive in cell culture. These compounds inhibited IN even when $Mn^{2+}$ or $Mg^{2+}$ was used as cofactor suggesting that these compounds differ from hydroxylated aromatics and perhaps act at different site of integrase [85].



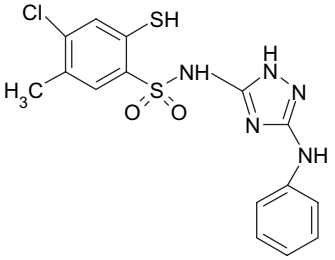
**43**



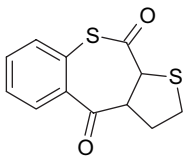
**44**



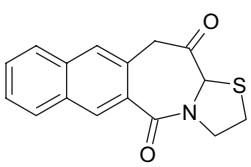
**45**



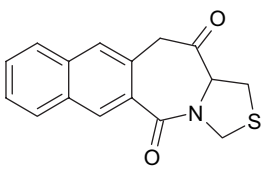
**46**



**47**

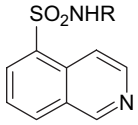


**48**

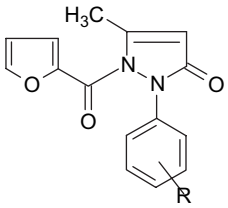


**49**

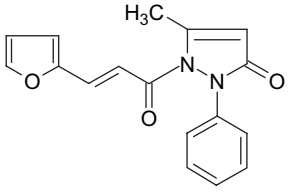
The SAR of the existing active compounds was developed by Makhija et al. [68], and a de novo drug design program, Leap Frog was used to design novel inhibitors on HIV-1 IN and their binding energy were calculated. The compounds showing improved binding energies were synthesized and tested in vitro inhibition of 3′-processing and 3′-strand transfer activities in HIV-1 IN. Four different series of compounds were synthesized: isoquinoline sulfonamides (**50**), furoyl pyrazolones (**51**, **52**), *N*-substituted indole-2,3-dione (**26**, isatins) and 2-phenylmethanesulfonyl-benzothiazoles (**53**).



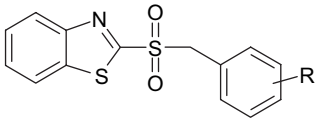

**50**




**51**




**52**

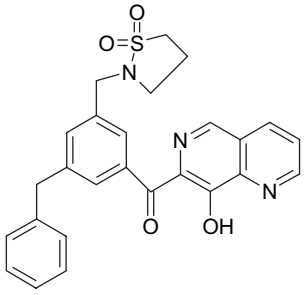



**53**

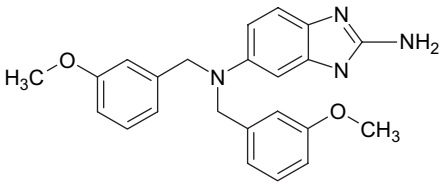
On the basis of SAR from the 1,3-diketoacid HIV IN inhibitors the following assumptions regarding their biological activity can be made: the 1,3-diketo moiety enolizes at the α-position and the resultant conjugated *Z*-4-oxo-2-hydroxy-2-butenoic acid side chain is coplanar with the central benzene ring. It was hypothesized that similar arrangements of key hydroxyl group can be achieved in 1,2-catechol nucleus by incorporating a heteroatom bridge to maintain coplanarity of the two phenyl rings. In one such study by Zhuang et al., 8-hydroxy-[1,6]-naphthyridines were synthesized and evaluated for HIV-1 IN inhibitory activity. In this series the compound **54** inhibited the strand transfer of the integration process catalyzed by IN with $IC_{50}$ of 10 μM [86]. One of the most potent compounds in this series is L-870810 (**2**) which inhibits HIV-1 replication in cell culture with $IC_{95}$ value of 100 nm [60,66]. Guare et al. [87] synthesized a series of 5-amino derivatives of 8-hydroxyl-[1,6]-naphthyridine-7-carboxamide exhibiting submicromolar potency against replication of HIV-1 in cell culture. One of these analogs L-870812 (**3**) displayed excellent pharmacokinetic properties. This compound was demonstrated to be efficacious against replication of simian-human immunodeficiency virus (SHIV). Both of these compounds **2** and **3** are currently undergoing clinical trials. This work by Merck research Lab. has lead to the discovery of 8-hydroxy-[1,6]-naphthyridines as a suitable replacement for 1,3-diketo moiety as HIV IN inhibitor.

Another very potent compound developed by Merck is MK-0518 (**4**), which is 5-hydroxy-1-methyl-2-{1-methyl-1-[(5-methyl-[1,3,4]-oxadiazole-2-carbonyl)-amino]-ethyl}-6-oxo-1,6-dihydro-pyrimidine-4-carboxylic acid 4-fluoro-benzylamide, with 2–7 nM strand transfer integrase inhibition potency. This compound is active orally and is currently under phase-III of clinical trials [88,89].

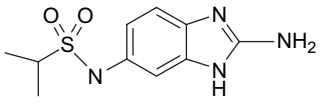
There are certain 2-benzimidazole derivatives and naphthamidines, both substituted at C-6 positions have been synthesized and evaluated. Compounds **55**, **56** and **57**, **58** have shown $IC_{50}$ value for integrase strand transfer activity of 1.8, 2.6, 3.4 and 2.1 μM, respectively [90].



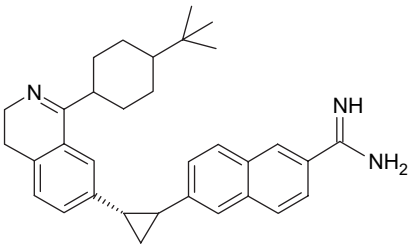

**54**



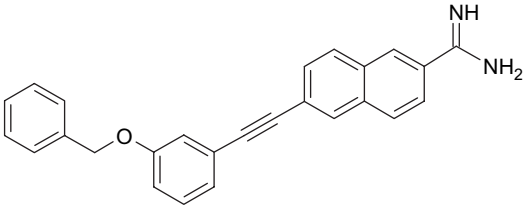

**55**




**56**




**57**




**58**

## 5. Oligonucleotides

6-Oxocytidine containing-oligonucleotide was found to be efficient inhibitors of integrase in vitro. The inhibitory effect is sequence-specific and strictly requires the presence of the 6-oxocytidine base. It is due to the impairment of the integrase binding to its substrate and does not involve an auto-structure of the oligonucleotides.

G-quartets are oligonucleotides that can form a highly stable intramolecular four-stranded DNA structure containing two sacked guanosine quartets (G-quartets) [91].

## 6. Conclusion

Remarkable progress has been made since HIV integrase was recognized as a rational therapeutic target for treating HIV infection and preventing AIDS. It took almost 12 years to develop clinically usable inhibitors of integrase. But the discovery of novel inhibitors and optimization of lead compounds remains hampered by the lack of atomic structures that reveal the atomic interactions between integrase and its DNA substrates (viral and target DNA) or the atomic structure of the complete enzyme with its three domains.

Off late DKAs and 8-hydroxy-[1,6]-naphthyridines have emerged as significant classes of IN inhibitors. The results of the clinical trials with the strand transfer inhibitors are eagerly awaited, and will affect the future development of integrase inhibitors for the prophylaxis and treatment of AIDS.

## References


[1] F. Barre-Sinoussi, J.C. Chermann, M.T. Nugeyre, S. Chamaret, J. Gruest, C. Dauget, C. Axler-Bin, F. Vezinet-Brun, C. Rouzioux, W. Rozenbaum, L. Montagnier, Science 220 (1983) 868–871.

[2] R.C. Gallo, S.Z. Salahuddin, M. Popovic, G.M. Shearer, M. Kalpana, B.F. Haynes, T.J. Palker, R. Redfield, J. Oleske, B. Safai, G. White, P. Foster, P.D. Markham, Science 224 (1984) 500–503.

[3] A. Fauci, A. Macher, D. Longo, H.C. Lane, A. Rook, H. Masur, E. Gelmann, Ann. Intern. Med. 100 (1984) 92–106.

[4] F.J. Palella Jr., K.M. Delaney, A.C. Moorman, M.O. Loveless, J. Fuhrer, G.A. Satten, D.J. Aschman, S.D. Holmberg, J. Med. Chem. 338 (1998) 853–860.

[5] A.S. Mehanna, in: A. Burger, D.J. Abraham, J. Andrako, J.H. Block, R.T. Borchardt, A. Abraham (Eds.), Rationale of Design of Anti-HIV Drugs, sixth ed., Burger's Medicinal Chemistry and Drug Discovery, vol. 5, John Wiley and Sons, Inc., New Jersey, 2003, pp. 4574–4584.

[6] O.S. Pedersen, E.B. Pedersen, Antivir. Chem. Chemother. 10 (1999) 285–314.

[7] E. De Clercq, J. Med. Chem. 38 (1995) 2491–2517.

[8] J.P. Vacca, J.H. Condra, Drug Discov. Today 2 (1997) 261–267.

[9] M.S. Hirsch, B. Conway, R.T. D'Aquila, V.A. Johanson, F. Brun-Vezinet, B. Clotet, L.M. Demeter, S.M. Hammer, D.M. Jacobsen, D.R. Kuritzkes, C. Loveday, J.W. Mellors, S. Vella, D.D. Richman, JAMA 279 (1998) 1984–1991.

[10] C. Parolin, B. Gatto, C.D. Vecchio, T. Pecere, E. Tramontano, V. Cecchetti, A. Fravolini, S. Masiero, M. Palumbo, G. Palu, Antimicrob. Agents Chemother. 47 (2003) 889–896.

[11] R.L. LaFemina, C.L. Schneider, H.L. Robbins, P.L. Callahan, K. LeGrow, E. Roth, W.A. Schleif, E.A. Emini, J. Virol. 66 (1992) 7414–7419.

[12] Z. Debyser, P. Cherepanov, B.V. Maele, E. De Clercq, M. Witvrouw, Antivir. Chem. Chemother. 13 (2002) 1–15.

[13] F.D. Bushman, R. Craige, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 1339–1343.

[14] M. Sechi, M. Derudas, R. Dallocchio, A. Dessi, A. Bacchi, L. Sannia, F. Carta, M. Palomba, O. Ragab, C. Chan, R. Shoemaker, S. Sei, R. Dayam, N. Neamati, J. Med. Chem. 47 (2004) 5298–5310.

[15] E. Asante-Appiah, A.M. Skalka, Adv. Virus Res. 52 (1999) 351–369.

[16] H. Sakai, M. Kawamura, J. Sakuragi, S. Sakurgi, R. Shibata, A. Ishimoto, N. Ono, S. Ueda, A. Adachi, J. Virol. 7 (1993) 1169–1174.

[17] B. Taddeo, W.A. Haseltine, C.M. Farnet, J. Virol. 68 (1994) 8401–8405.

[18] A. Engleman, G. Englund, J.M. Orenstein, M.A. Martin, R. Craige, J. Virol. 69 (1995) 2729–2736.

[19] J. Kulkosky, K.S. Jones, R.A. Katz, J.P. Mack, A.M. Skalka, Mol. Cell. Biol. 12 (1992) 2331–2338.

[20] E. Khan, J.P. Mack, R.A. Katz, J. Kulkosky, A.M. Skalka, Nucleic Acids Res. 19 (1991) 851–860.

[21] P.M. Cannon, E.D. Byles, S.M. Kingsman, A.J. Kingsman, J. Virol. 70 (1996) 651–657.

[22] R. Craigie, J. Biol. Chem. 276 (2001) 23213–23216.

[23] A.A. Johanson, C. Marchand, Y. Pommier, Curr. Top. Med. Chem. 4 (2004) 671–686.

[24] N. Neamati, Expert Opin. Ther. Pat. 12 (2002) 709–724.

[25] M. Cushman, P. Sherman, Biochem. Biophys. Res. Commun. 185 (1992) 85–90.

[26] R.L. Lafemina, P.L. Graham, K. Legrow, J.C. Hastings, A. Wolfe, S.D. Youg, E.A. Emini, D.J. Hazuda, Antimicrob. Agents Chemother. 39 (1995) 320–324.

[27] A. Mazumder, S. Wang, N. Neamati, M. Nicklaus, S. Sunder, J. Chen, G. Milne, W.G. Rice, T.R. Burke, Y. Pommier, J. Med. Chem. 39 (1996) 2472–2481.

[28] M.R. Fesen, Y. Pommier, F. Leteurtre, S. Hirogouchi, J. Yung, K.W. Kohn, Biochem. Pharmacol. 48 (1994) 595–608.

[29] A. Mazumder, K. Raghavan, J. Weinstein, K.W. Kohn, Y. Pommier, Biochem. Pharmacol. 49 (1995) 1165–1170.

[30] A. Mazumder, N. Neamati, S. Sunder, J. Schulz, H. Pertz, E. Eich, Y. Pommier, J. Med. Chem. 40 (1997) 3057–3063.

[31] A. Mazumder, A. Gazit, A. Levitzki, M. Nicklaus, J. Yung, G. Kohlhagen, Y. Pommier, Biochemistry 34 (1995) 15111–15122.

[32] E. Eich, H. Pertz, M. Kaloga, J. Schulz, M.R. Fesen, A. Mazumder, Y. Pommier, J. Med. Chem. 39 (1996) 86–95.

[33] H. Zhao, N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, G.W.A. Milne, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 40 (1997) 242–249.

[34] M. Cushman, W.M. Golebiewsky, Y. Pommier, A. Mazumder, D. Reymen, E. De Clercq, L. Graham, W.G. Rice, J. Med. Chem. 38 (1995) 443–452.

[35] H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G.W.A. Milne, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 40 (1997) 937–941.

[36] N. Neamati, H. Hong, A. Mazumder, S. Wang, S. Sunder, M.C. Nicklaus, G.W.A. Milne, Y. Pommier, J. Med. Chem. 40 (1997) 942–951.

[37] K. Melouar, J. Mouscadet, D. Desmaele, F. Subra, H. Leh, D. Savoure, C. Auclair, J. D'Angelo, J. Med. Chem. 41 (1998) 2846–2857.

[38] M.V.R. Reddy, M.R. Rao, D. Rhodes, M. Hansen, K. Rubins, F.D. Bushman, Y. Venkateshwarlu, D.J. Faulkner, J. Med. Chem. 42 (1999) 1901–1907.

[39] W.E. Robinson, M.G. Reinecke, M.S. Abdel, Q. Jia, S.A. Chow, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 6326–6331.

[40] N. Neamati, H.X. Hong, S. Sunder, G.W.A. Milne, Y. Pommier, Mol. Pharmacol. 52 (1997) 1041–1055.

[41] N. Neamati, H.X. Hong, A. Mazumder, S. Wang, S. Sunder, M.C. Nicklaus, G.W.A. Milne, B. Proksa, Y. Pommier, J. Med. Chem. 40 (1997) 942–951.

[42] P.J. King, W.E. Robinson Jr., J. Virol. 72 (1998) 8420–8424.

[43] W.E. Robinsonm Jr., M. Coideiro, S. Abdel-Malek, Q. Jia, S.A. Chow, M.G. Reinecke, W.M. Mitchell, Mol. Pharmacol. 50 (1996) 846–855.

[44] B. McDougall, P.J. King, B.W. Wu, Z. Hostomsky, M.G. Reinecke, W.E. Robinson Jr., Antimicrob. Agents Chemother. 42 (1998) 140–146.

[45] W. Pluymers, N. Neamati, C. Pannecouque, V. Fikkert, C. Marchand, T.R. Burke Jr., Y. Pommier, D. Schols, E. De Clercq, Z. Debyser, M. Witvrouw, Mol. Pharmacol. 58 (2000) 641–648.
[46] E. De Clercq, Biochim. Biophys. Acta 1587 (2002) 258–275.
[47] Z. Lin, N. Neamati, H. Zhao, Y. Kiryu, J.A. Turpin, C. Aberham, K. Strebel, K. Kohn, M. Witvrouw, C. Pannecouque, Z. Debsyer, E. De Clercq, W.G. Rice, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 42 (1999) 1401–1414.
[48] C. Farnet, R. Lipford, B. Wang, F.D. Bushman, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 9742–9747.
[49] H. Higuchi, K. Mori, A. Kato, T. Ohkuma, H. Kaji, A. Kaji, Antiviral Res. 15 (1991) 205–216.
[50] R.F. Schinazi, C.K. Chu, J.R. Babu, B.J. Oswald, V. Saalmann, D.L. Cannon, B.F.H. Errikson, M. Nasr, Antiviral Res. 13 (1990) 265–272.
[51] C. Stanwell, B. Ye, S.H. Yuspa, T.R. Burke, Biochem. Pharmacol. 52 (1996) 475–480.
[52] T.R. Burke Jr., M.R. Fesen, A. Mazumdar, J. Wang, A.M. Carothers, D. Grumberger, J. Driscoll, K. Kohn, Y. Pommier, J. Med. Chem. 38 (1995) 4171–4178.
[53] C.M. Farnet, B. Wang, M. Hansen, J.R. Lipford, L. Zalkow, W.E. Robinson Jr., J.S. Siegel, F.D. Bushman, Antimicrob. Agents Chemother. 42 (1998) 2245–2253.
[54] V. Molteni, D. Rhodes, K. Rubins, M. Hansen, F.D. Bushman, J.S. Siegel, J. Med. Chem. 43 (2000) 2031–2039.
[55] M. Sechi, G. Angotzi, R. Dallocchio, A. Dessi, F. Carta, L. Sannia, A. Mariani, S. Fiori, T. Sanchez, L. Movsessian, C. Plasencia, N. Neamati, Antivir. Chem. Chemother. 15 (2004) 67–81.
[56] Y. Goldgur, R. Craigie, G.H. Cohen, T. Fugiwara, T. Yoshinaga, T. Fujishita, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 13040–13043.
[57] D.J. Hazuda, P.J. Felock, M. Witmer, K. Wolfe, J.A. Stillmock, A. Espeseth, L. Gabryelski, W. Scheif, C. Blau, M.D. Miller, Science 287 (2000) 646–650.
[58] Z. Debyser, P. Cherepanov, W. Pluymers, E. De Clercq, Nucleases, in: C.H. Schein (Ed.), Methods in molecular biology, Human Press, Totowa, N.J., 2001, pp. 139–155.
[59] W. Pluymers, G. Pais, B.V. Maele, C. Pannecouque, V. Fikkert, T.R. Burke Jr., E. De Clarke, M. Witvrouw, N. Neamati, Z. Debyser, Antimicrob. Agents Chemother. 46 (2002) 3292–3297.
[60] C. Maurin, F. Bailly, E. Buisine, H. Vezin, G. Mbemba, J.F. Mouscadet, P. Cotelle, J. Med. Chem. 47 (2004) 5583–5586.
[61] J.S. Wai, M.S. Egberston, L.S. Payne, M.W. Fisher, L.O. Tran, J.Y. Melamed, H.M. Langford, J.P. Guare Jr., L. Zhuang, V.E. Grey, J.P. Vacca, M.K. Holloway, A.M. Naylor-Olsen, D.J. Hazuda, P.J. Felock, A.L. Wolfe, L.J. Gabryelski, S.D. Young, J. Med. Chem. 43 (2000) 4923–4926.
[62] T. Kawasuji, T. Yoshinaga. Patent WO 01 17,968. Chem. Abstr. 134 (2001) 2347486m.
[63] R. Costi, R.D. Santo, M. Artico, A. Roux, R. Ragno, S. Massa, E. Tramontano, M. La Colla, R. Loddo, M.E. Marongiu, A. Pani, P. La Colla, Bioorg. Med. Chem. Lett. 14 (2004) 1745–1749.
[64] E.S. Svarovskaia, R. Barr, X. Zhang, G.C. Pais, C. Marchand, Y. Pommier, T.R. Burke Jr., V.K. Pathak, J. Virol. 78 (2004) 3210–3222.
[65] A. Billich, Curr. Opin. Investig. Drugs 4 (2003) 206–209.
[66] C. Maurin, F. Bailly, G. Mbemba, J.F. Mouscadet, P. Cotelle, Bioorg. Med. Chem. 14 (2006) 2978–2984.
[67] M. Sechi, L. Sannia, F. Carta, M. Palomba, R. Dallocchio, A. Dessi, M. Derudas, Z. Zawahir, N. Neamati, Antivir. Chem. Chemother. 16 (2005) 41–61.
[68] M.T. Makhija, R.T. Kasliwal, V.M. Kulkarni, N. Neamati, Bioorg. Med. Chem. 12 (2004) 2317–2333.
[69] N. Neamati, H. Hong, S. Sunder, G.W. Milne, Y. Pommier, Mol. Pharmacol. 52 (1997) 1041–1055.
[70] N. Neamati, H. Hong, J.M. Owen, S. Sunder, H.E. Winslow, J.L. Christensen, H. Zhao, T.R. Burke Jr., G.W. Milne, Y. Pommier, J. Med. Chem. 41 (1998) 3202–3209.
[71] H. Zhao, N. Neamati, S. Sunder, H. Hong, S. Wang, G.W. Milne, Y. Pommier, T.R. Burke Jr., J. Med. Chem. 40 (1997) 937–941.
[72] D. Hazuda, C.U. Blau, P. Felock, J. Hasting, B. Pramanik, A. Wolfe, F. Bushman, C. Farnet, M. Goetz, M. Williams, K. Silverman, R. Lingham, S. Singh, Antivir. Chem. Chemother. 10 (1999) 63–70.
[73] A. Fournet, B. Vagneur, P. Richomme, J. Bruneton, Can. J. Chem. 67 (1989) 2116–2118.
[74] M.A. Fakhfakh, X. Franck, A. Fournet, R. Hocquemiller, B. Figadere, Tetrahedron Lett. 42 (2001) 3847–3850.
[75] M.A. Fakhfakh, X. Franck, R. Hocquemiller, B. Figadere, J. Organomet. Chem. 624 (2001) 131–135.
[76] X. Franck, A. Fournet, E. Prina, R. Mahieux, R. Hocquemiller, B. Figadere, Bioorg. Med. Chem. Lett. 14 (2004) 3635–3638.
[77] C. Benard, F. Zouhiri, D.M. Normand-Bayle, D. Desmaele, H. Leh, J.F. Mouscadet, G. Mbemba, C.M. Thomas, S. Bonnenfant, M. Le Bret, J. D'Angelo, Bioorg. Med. Chem. Lett. 14 (2004) 2473–2476.
[78] K. Mekour, J.F. Mouscadet, D. Desmaele, F. Subra, H. Leh, D. Savoure, C. Auclair, J. d'Angelo, J. Med. Chem. 41 (1998) 2846–2857.
[79] M. Ouali, C. Laboulais, H. Leh, D. Gill, D. Desmaele, K.J. Mekouar, F. Zouhiri, J. d'Angelo, C. Auclair, J.-F. Mouscadet, M. Le Bret, J. Med. Chem. 43 (2000) 1949–1957.
[80] F. Zouhiri, J.F. Mouscadet, K. Mekour, D. Desmaele, D. Savoure, H. Leh, J. Med. Chem. 43 (2000) 1533–1540.
[81] C. Parolin, G. Barbara, C.D. Vecchio, T. Pecere, E. Tramontano, V. Cecchetti, A. Fravolini, S. Masiero, M. Palumbo, G. Palu, Antimicrob. Agents Chemother. 47 (2003) 889–896.
[82] V. Cecchetti, C. Parolin, S. Moro, T. Pecere, E. Filipponi, A. Calistri, O. Tabarrini, B. Gatto, M. Palumbo, A. Fravolini, G. Palu, J. Med. Chem. 43 (2000) 3799–3802.
[83] M. Sato, T. Motomura, H. Aramaki, T. Matsuda, M. Yamshita, Y. Ito, H. Kawakami, Y. Matsuzaki, W. Watanabe, K. Yamataka, S. Ikeda, E. Kodama, M. Matsuoka, H. Shinkai, J. Med. Chem. 49 (2006) 1506–1508.
[84] E. Pomarnacka, A. Kornicka, Farmaco 56 (2001) 571–577.
[85] N. Neamati, J.A. Turpin, H.E. Winslow, J.L. Christensen, K. Williamson, A. Orr, W.A. Rice, Y. Pommier, A. Garofalo, A. Brizzi, G. Campiani, J. Med. Chem. 42 (1999) 3334–3341.
[86] L. Zhuang, J.S. Wai, M.W. Embrey, T.E. Fisher, N.S. Egberston, L.S. Payne, J.P. Guare Jr., J.P. Vacca, D.J. Hazuda, P.J. Felock, A.L. Wolfe, K.A. Stillmock, M.V. Witmer, G. Moyer, W.A. Schleif, L.J. Gabryelski, Y.M. Leonard, J.J. Lynch Jr., S.R. Michelson, S.D. Young, J. Med. Chem. 46 (2003) 453–456.
[87] J. Guare, J.S. Pai, R.P. Gomez, N.J. Anthony, S.M. Jolly, A.R. Cortes, J.P. Vacca, P.J. Felock, K.A. Stillmock, W.A. Schleif, G. Moyer, L.J. Gabryelski, L. Jin, I.W. Chen, D.J. Hazuda, S.D. Young, Bioorg. Med. Chem. Lett. 16 (2006) 2900–2904.
[88] http://aidsinfo.nih.gov/DrugsNew.
[89] M. Markowitz, J.O. Morales-Ramirez, B.Y. Nguyen, C.M. Kovacs, R.T. Steigbigel, D.A. Cooper, R. Liporace, R. Schwartz, R. Isaacs, L.R. Gilde, L. Wenning, J. Zhao, H. Teppler, J. Acquir. Immune Defic. Syndr. 43 (2006) 509–515.
[90] T. Middleton, H.B. Lim, D. Montgomery, T. Rockway, H. Tang, X. Cheng, L. Lu, H. Mo, W.E. Kohlbrenner, A. Molla, W.M. Kati, Antiviral Res. 64 (2004) 35–45.
[91] P. Brodin, M. Pinskaya, U. Parsch, J. Bischerour, H. Leh, E. Romanova, J.W. Engels, M. Gottikh, J.F. Mouscadet, Nucleosides, Nucleotides, Nucleic Acids 20 (2001) 481–486.