RSC Advances



REVIEW

View Article Online
View Journal | View Issue



Cite this: RSC Adv., 2021, 11, 17936

In search of therapeutic candidates for HIV/AIDS: rational approaches, design strategies, structure—activity relationship and mechanistic insights

The HIV/AIDS pandemic is a serious threat to the health and development of mankind, which has affected about 37.9 million people worldwide. The increasing negative health, economic and social impacts of this disease have led to the search for new therapeutic candidates for the mitigation of AIDS/HIV. However, to date, there is still no treatment that can cure this disease. Furthermore, the clinically available drugs have numerous severe side effects. Hence, the synthesis of novel agents from natural leads is one of the rational approaches to obtain new drugs in modern medicinal chemistry. This review article is an effort to summarize recent developments with regards to the discovery of novel analogs with promising biological potential against HIV/AIDS. Herein, we also aim to discuss prospective directions on the progress of more credible and specific analogues. Besides presenting design strategies, the present communication also highlights the structure—activity relationship together with the structural features of the most promising molecules, their IC₅₀ values, mechanistic insights and some interesting key findings revealed during their biological evaluation. The interactions with the amino acid residues of the enzymes responsible for HIV-1 inhibition are also discussed. This collection will be of great interest for researchers working in this area.

Received 19th December 2020 Accepted 19th April 2021

DOI: 10.1039/d0ra10655k

rsc.li/rsc-advances

Introduction

The human immunodeficiency virus (HIV), which causes AIDS, is primarily responsible for the most severe public health challenges. However, there is a global promise to impede new HIV cases and ensure that everyone with HIV has access to HIV treatment. According to the worldwide statistics from UNAIDS, it was estimated that there were 37.9 million people suffering with HIV/AIDS in 2018. Clinically, more than thirty drugs targeting different steps of the viral life cycle have been approved to alleviate AIDS/HIV. 2,3 Unfortunately, the use of drug cocktails

is limited due to their severe noxious side effects and speedy emergence of resistant viral strains. Hence, new natural products can be considered as novel leads for the development of effective and selective potential therapeutic agents for AIDS. Thus, new anti-HIV agents that are less toxic and more effective in targeting HIV reservoirs in the body are still needed.⁴⁻⁷

Traditionally, in the continuing search for natural products, the pedigrees of diverse medicinal agents are considered. Natural products play an important role in drug discovery and chemical biology. S-13 In drug discovery, numerous heterocycles such as pyrans, flavones, coumarins, pyrimidones, thiazoles, xanthenes, imidazoles, pyrazoles, isoxazolines and oxazolidines have been considered for the development of potential novel lead molecules. Typically, they are scaffolds that need to be decorated with selected substituents to exert the desired biological actions. These heterocycles have been used to construct diverse therapeutic drug candidates having an ample range of biological activities, viz, anticancer, anti-inflammatory, antimicrobial, antiviral, anti-HIV and anti-TB. 17-23

Herein, we present a comprehensive summary of some recent advancements in the field of anti-AIDS by prominent scientists, researchers and scholars globally. Besides presenting the design strategies, this article also highlights the structure-activity relationship, IC_{50} values, and mechanistic insights revealed during the biological evaluation of compounds against HIV together with interesting key findings. The interactions

[&]quot;Sri Sai College of Pharmacy, Manawala, Amritsar-143001, Punjab, India. E-mail: dineshkumargndu@gmail.com; Tel: +91-9988902489

^bDepartment of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala. India

Indian Institute of Integrative Medicine (CSIR-IIIM), Canal Road, Jammu 180001, India

^dDepartment of Chemistry, Faculty of Science, University of Buea, P. O. Box 63, Buea, Cameroon. E-mail: fidele.ntie-kang@ubuea.cm; Tel: +237 685625811

^cDepartment of Pharmaceutical Chemistry, Sri Sai College of Pharmacy, Badhani, Pathankot-145001, Punjab, India

Institute for Pharmacy, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 3, 06120 Halle (Saale), Germany. E-mail: ntiekfidele@gmail.com; fidele.ntie-kang@pharmazie-uni-halle.de; Tel: +49 3455525043

^{*}Institute of Botany, Technical University of Dresden, Zellescher Weg 20b, 01062 Dresden, Germany. E-mail: fidele.ntie-kang@tu-dresden.de

Review RSC Advances

with the amino acid residues of enzymes responsible for HIV-1 inhibition are also discussed diagrammatically.

To the best of our knowledge, this is the first comprehensive review of the recent advancements in the field of anti-HIV agents in the literature during the last decade.

The present assemblage will be of great interest to the scientific community to accelerate their further research for the development of novel heterocyclic compounds having potential against AIDS/HIV, thus helping them to adopt a focused and speedy target-oriented drug design. To present the rational approaches, we tried to classify the strategies based on the core functionalities of the chemical motifs. The classification is as follows:

- (1) Andrographolide-based analogs
- (2) Azaindole-based analogs
- (3) Artemisinin-based analogs
- (4) Maslinic acid-based analogs
- (5) Calanolide-based analogs
- (6) Labdane-based analogs
- (7) Gomisin-G-based analogs
- (8) Quinoline-based analogs
- (9) 4-Hydroxypyrone-based analogs
- (10) Ingenol-based analogs
- (11) Lavendustin B-based analogs
- (12) 3,7-Dihydroxytropolone-based analogs
- (13) P1/P1'-substituted cyclic urea-based analogs



Dr Dinesh Kumar graduated in Pharmacy in 2005 from Punjab Technical University and achieved 4th position in the University. In 2008 he obtained his Master's Degree in Pharmaceutical Chemistry from the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar, Punjab, India. He received his PhD in Pharmaceutical Sciences from Guru Nanak Dev University, Amritsar, where

he worked on the Syntheses and Evaluation of Chalconoid Hybrids of Oxa, Aza and Thio Compounds as Potent Anti-proliferative Agents. In 2014, he joined the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar as an Assistant Professor. Currently, he is working as the Director-Cum_Principal in the Department of Pharmaceutical Science, Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India. He has more than 12 years of research experience in pharmaceutical field including academic, research and teaching. His research is focused on the synthesis and evaluation of novel heterocycles and their application in medicinal chemistry. He is also an editorial board member and reviewer of many reputed international and national journals. He has attended many national and international conferences. He has published his research in journals of international repute.

2. Rational approaches/design strategies

2.1. Andrographolide-based analogs

Andrographolide (1, Fig. 1a) is a diterpenoid lactone-based compound obtained from the plant *Andrographis paniculata* with potent anti-HIV activity. ^{24–26} Andrographolide can also be used for the mitigation and management of several diseases including hepatitis, cancer, meningitis, hepatotoxicity, diabetes and other inflammatory disorders. ^{27–32} 3-Nitrobenzylidene, 2′6′-dichloro-nicotinoyl ester-type derivatives, 14-deoxy-11,12-didehydroandrographolide and 12-hydroxy-14-deoxy-13,14-dehydroandrographolide analogs of andrographolide have shown potent activity against the HIV virus. The diterpene



Mrs Pooja Sharma graduated in Pharmacy from Punjab Technical University in 2005 and obtained her Master's Degree in the field of Pharmacognosy (Phytochemistry) in 2008 from the Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar. She achieved 2nd position in the University in her Master's programme. She is pursuing her PhD in the Department of Pharmaceutical Sciences and Drug

Research, Punjabi University, Patiala. She also worked in the Council of Scientific & Industrial Research (CSIR) Laboratory of India at Jammu on the phytochemical investigation and standardization of natural products. Then she joined the Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India as an Assistant Professor. Currently, she is working as the Head of Department at Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India. She has more than 12 years of research experience in the pharmaceutical field including academic, research and teaching. She is also a member of many pharmaceutical associations and societies. Her area of research is focused on the extraction and isolation of phytoconstituents of pharmaceutical interest.



Ms. Sabu graduated with her BSc from Govt. College Dharamshala in 2016. In 2018, she obtained an MSc in Zoology from Himachal Pradesh University, Shimla. Currently, she is pursuing her PhD in Life Science, in Cancer Pharmacology Division from Indian Institute of Integrative Medicine, Jammu, India. She has attended many national and international conferences.

RSC Advances Review

lactone andrographolide 1 (IC₅₀ (μ M) = 0.59) shown in Fig. 1a possesses HIV-1 fusion inhibition properties and was evaluated *in vitro* using AZT (azidothymidine, also known as zidovudine) as a positive control.^{33–35}

Reddy *et al.* reported the synthesis of andrographolide-based derivatives using different aromatic aldehydes together with Amberlyst-15 to obtain 3-nitrobenzylidene derivatives, which include 4'-hydroxyphenyl 2 (IC₅₀ (μ M) = 2.10), 3',4'-methylenedioxy-phenyl 3 (IC₅₀ (μ M) = 2.75), 2',4'-dihydroxyphenyl 4 (IC₅₀ (μ M) = 1.09), 4'-chlorophenyl 5 (IC₅₀ (μ M) = 9.94), 4'-hydroxy-3'-methoxy-phenyl 6 (IC₅₀ (μ M) = 6.09) and 3'-nitro-phenyl 7 (IC₅₀ (μ M) = 0.51), as depicted in Fig. 1a. Upon treatment with acid chlorides, as presented in Fig. 1b, andrographolide afforded the andrographolide-substituted derivatives 2',6'-dichloronicotinoyl 8 (IC₅₀ (μ M) = 0.83 and 2'-hydroxybenzoyl 9 (IC₅₀ (μ M) = 84.24). Further, upon treatment with *p*-toluene sulfonyl isocyanate, another derivative of *p*-toluene sulfonyl amino carbonyl andrographolide, 10 (IC₅₀ (μ M) = 2.08), was obtained, as depicted in Fig. 1c.³⁶



Ms. Ramandeep Kaur graduated with a degree in Pharmacy in the first division from Sri Sai College of Pharmacy, Manawala, Amritsar, Punjab, India, affiliated with Punjab Technical University. Currently, she is working as a Pharmacy Officer at the Department of Health and Family Welfare, Punjab, India. She has attended many national and international conferences.



Dr Maloba M. M. Lobe studied Chemistry at the University of Buea, where she obtained her BSc (2011), M.Sc. (2015) and PhD (2021) under the guidance of Prof. Simon M. N. Efange. Her research interest focuses on the design, synthesis and biological evaluation of novel small molecules against cancer and neglected tropical diseases. She was an Adolphe Monkedje Fellow 2016/2017 and received an award

from the BMBF /DLR-DAAD Project (2018): Partnerships for Sustainable Solutions with Sub-Saharan Africa at TU Dortmund, where she obtained training on Natural Products: Chromatography, Spectroscopy and Biological Aspects. She is currently working on the development of novel spirooxindoles as potential pharmacologically active agents for the treatment of diseases, including cancer, malaria and tuberculosis, which has earned two original publications and two patents for her research group.

2.2. Azaindole analogs/derivatives

The compound 1-(4-benzoylpiperazin-1-yl)-2-(4,7-dimethoxy-1H-pyrrolo[2,3-c]pyridin-3-yl)ethane-1,2-dione **16** was synthesized from azaindole.³⁷⁻⁴⁰ This derivative is considered to act on the HIV gp120 and inhibit the attachment of the viral glycoprotein with the CD₄ molecule in the host cell, which is an essential step for viral entry.⁴¹⁻⁴³ The synthesis of a potent azaindole-based derivative utilizing 5-bromo-2-chloro-3-



Dr Girish Kumar Gupta graduated in pharmacy in 2006 from Guru Jambheshwar University of Science and Technology, Hisar, India. In 2009 he obtained his Master's Degree in Pharmaceutical Chemistry from the University Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana, India. Currently working as a Professor of Pharmaceutical Chemistry in Sri Sai of College of Pharmacy,

Badhani, Pathankot, India. He has more than 12 years of research experience in the pharmaceutical field including academic and industrial research and teaching. He has over 80 publications in the field of heterocyclic chemistry in peer-reviewed high-impact journals. He is also a member of many pharmaceutical associations and societies. Moreover, he is also serving as the Director Research and Development at Sri Sai Group of Institutes, Pathankot, Punjab, India. He is also an editorial board member, editor, guest editor and reviewer of many reputed international and national journals. His area of research encompasses drug design, molecular modelling, and green synthesis related to nitrogen-containing heterocycles.



Fidele Ntie-Kang heads the Molecular Simulations Laboratory, Chemistry Department, University of Buea. He studied Chemistry at the University of Douala (Cameroon) from 1999 to 2005, leading to Bachelor's and Master's Degrees. His PhD from the University of Douala (Cameroon) was based on molecular modeling of anti-tubercular drug targets to design novel inhibitors, followed by a Habilitation in

Pharmaceutical Chemistry from Martin-Luther University Halle-Wittenberg (Germany) under the supervision of Prof. Wolfgang Sippl. His current focus is the discovery of bioactive natural products from African flora by the use of virtual screening followed by in vitro assays. A major contribution of his research team has been the development of the African natural products database.

Binding interactions of with V3 loop of gp120

- Key features of the molecular modelling studies
 1) Docking studies revealed that Compound (1) formed total four hydrogen bonds.
- 2) One hydrogen bond between C-19 of OH and Gly 321.
- 3) Two hydrogen bonds between lactone carbonyl at C-16 with Gln 328 and Arg 298.
- 4) The fourth hydrogenbond was formed between lactone oxygen and Gln 328.

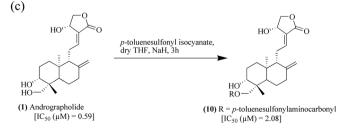


Fig. 1 (a) Andrographolide-based (1–7) analogs. (b) Andrographolide analogs (8 and 9). (c) Structure of andrographolide-based analog (10).

RSC Advances Review

nitropyridine **11** as the starting material is shown in Fig. 2. The reactant **11** was treated with vinyl magnesium bromide at very low temperature to give another compound, 4-bromo-7-chloro-6-azaindole **12** in 35% yield.⁴⁴

This intermediate is then catalyzed by copper metal, causing the replacement of bromide and chloride with sodium or potassium methoxide to give 4,7-dimethoxy-6-azaindole 13 in 75% yield. The latter compound was then treated with methyl chloro oxoacetate in the presence of aluminium chloride to produce ester 14. Further, this ester was hydrolyzed in the presence of aqueous methanolic potassium carbonate and converted into acid salt 15. The resulting acid salt underwent treatment with *N*-benzoyl piperazine in the presence of DEBPT, which is known as 3-(diethoxy-phosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one, to afford the desired compound 16, with an IC₅₀ value of = \geq 40 μ M. These data reveal a safety profile consistent with exploring (16) in phase 1 clinical studies in normal healthy volunteers and proof-of-concept studies in HIV 1-infected subjects.

2.3. Artemisinin analogs

Artemisinin 17 is a 1,2,4-trioxane sesquiterpene compound obtained from the plant Artemisia annua. 49-51 Artemisinin 17 is significantly used towards chloroquinine-resistant and chloroquinine-sensitive strains of Plasmodium falciparum. However, its efficacy is limited because of its poor solubility.52,53 Dihydroartemisinin 18 is also produced from artemisinin via the reduction of its carbonyl group. Other potential reported derivatives of artemisinin are arteether 19, artemether 20 and artesunic acid 21. Artemisinin derivatives exhibit highly potent actions against malaria and cancer.54 Dihydroartemisinin 18 has attracted considerable interest because of its therapeutic activity, and being a versatile precursor, is also used for the synthesis of other artemisinin derivatives. Different analogs of dihydroartemisinin have been used in the treatment of bacterial, viral and autoimmune disorders, as depicted in Fig. 3a.55-62

Br
$$MgBr$$
 $MgBr$ CH_3ONa, Cu OCH_3 $AlCl_3$ $CICOCOOCH_3$ OCH_3 OCH_3

Structure-activity Relationship

- 1) Substitute at C-4 and C-7, pattern associated with improved antiviral activity.
- 2) The electron withdrawing properties of a methoxy group adjacent to the N atom of pyridine increased acidity of the conjugate acid of 2-methoxypyridine.
- 3) Introduction of 4-methoxy group increases the basicity of pyridine as a result of this reduced basicity of the 6-aza nitrogen atom, and thus enhanced the potential for oxidative metabolism to the N-oxide and help to mitigate the potential for inhibition of CYP 450 enzymes.
- 4) The methoxy group at C-4 and C-7 also increase solubility and membrane permeablity and hence enhance antiviral activity

Key Findings

- 1. Compound (16) has shown potent inhibition of CYP450 enzymes.
- 2. The active compound (16) is evaluated for its anti-HIV activity by a pseudotype assay using the CCR5-dependent JRFL HIV-1 strain.
- 3. Addition of nitrogen atoms results in novel compounds having different action profile than the parent compound.
- 4. Clinical studies with (16) have validated HIV-1 attachment inhibition as a potential approach to the control of HIV-1 infection in vivo.

Fig. 2 Synthesis of azaindole derivatives together with important key findings.

(a) (e)

Fig. 3 (a) Artemisinin analogs 17 to 21. (b) Synthetic route for the preparation of artemisinin analogs. (c) Artemisinin derivatives together with their SARs and key features. (d) Synthesis of a ketone precursor from dihydroartemisinin. (e) Triazole-based dihydroartemisinin ketone precursor analogs (38–42).

Among the numerous derivatives from dihydroartemisinin 18, an amine precursor was synthesized and evaluated for its anti-HIV activity, as shown in Fig. 3b. Dihydroartemisinin 18 was reacted with 2-bromoethanol in the presence of catalysts, ethoxy ethane and boron trifluoride to convert it into 10-bromo ethoxy dihydroartemisinin 22. Compound 22 was then treated with sodium azide at 60 °C to form 2-(10β-dihydro artemisinoxy)ethyl azide 23 in 95% yield. The resultant compound 23 was finally converted into an amine precursor 2-(10β-dihydro artemisinoxy)ethyl amine 24 in 74% yield. From amine precursor 24, various potent derivatives have been synthesized and evaluated for their anti-HIV potential.49,63

The amino precursor 24 was further treated with $\alpha\text{-}tetralone 25$ and 4-nitrophenyl azide 26 in the presence of toluene at 60 °C to yield another compound, 27, as depicted in Fig. 3c. Various dihydroartemisinin derivatives (28–36) have been synthesized and evaluated for their anti-HIV potential. It was found that compounds 28 and 29 exhibited significant activity with IC $_{50}$ values of 2.78 μM and 4.06 μM against HIV-1, respectively.

Ketone precursor 37 was also synthesized from dihydroartemisinin 24, as depicted in Fig. 3d. Treatment of 24 with cyclohexanone-4-carboxylic acid in the presence of DCC (N,N'-dicyclohexylcarbodiimide) and DMAP (4-dimethyl amino pyridine) for 4 h led to the formation of compound 37.⁴⁹

Ketone derivative 37 of dihydroartemisinin was further reacted with several benzylamines to obtain active triazoles (38–42) with significant activity, as shown in Fig. 3e.⁴⁹

2.4. Maslinic acid analogs

Maslinic acid 43 is an oleanene triterpenoid isolated from the *Geum japonicum* plant and evaluated for its anti-HIV potential. 64,65 It is considered to inhibit the protease of HIV-1. Maslinic acid and its analogs also exhibited an array of therapeutic activities such as anti-tumor, antioxidant and antiviral. 66,67 Maslinic acid 43 is generally condensed with α -amino acids (L-valine, glycine and L-alanine) and ω -amino acids (11-amino-undecanoic acid, γ -amino butyric acid and 6-amino hexanoic acid), as presented in Fig. 4a and b, respectively.

The condensation of maslinic acid **43**, with amino acids is accomplished in the presence of reagents like HOBt (N-hydroxy benzotriazole), TEA (triethylamine), DCM (dichloromethane) and DCC (N,N'-dicyclohexylcarbodiimide) at room temperature. Hence, different derivatives **44** and **46** were obtained using this approach. The resultant compounds upon saponification at room temperature in the presence of methanol, sodium hydroxide and THF yielded carboxylic acid derivatives **45** and **47** with 80% and 95% yield, respectively.⁶⁴

Parra *et al.* reported that maslinic acid derivatives **45** and **47** exhibited potent inhibition of HIV replication and also found to induce apoptosis in HIV cells.⁶⁴

2.5. Calanolides analogs

Calanolide A 48 and calanolide B 49 (Fig. 5) are two enantiomers isolated from the *Calophyllum lanigerum* plant and reported to

Structure-activity Relationship
1) Hydroxyl group at C-3 and carboxylic group is essential for anti-HIV activity

2) Side chain at C-28 can block HIV-1 entry.

Responsible for activity

triterpenes Pharmacophore

HO

3) The introduction of side chain at C-28 of pharmacophores can lead to bi-functional triterpene derivatives (46,47) with enhanced anti-HIV potential.

Key Findings: 1. Compounds (43), (46) and (47) are more potent inhibitors of HIV replication.

Fig. 4 (a) Synthesis of maslinic acid derivatives from α -amino acids. (b) Synthesis of maslinic acid analogs from ω -amino acids.

Critical for activity

Necessary for activity H_3C CH_3 CH_3

Structure-activity Relationship

activty

- 1) Introduction of bulky substituents is essential at C-4 position to enhace anti- HIV activity.
- 2) Trans orientation of C-10 and C-11 methyl groups is required for the significant activity
- 3) A hydrogen bond acceptor at C-12 is also resposible for activity.

 $[IC_{50} = 0.07 \mu M]$

- 4) Stereochemistry of hydroxyl group at C-12 is also crucial for the activity.
- 5) Compound (48) shows significant anti-HIV activty as compare to compound (49).
- 6) Various studies also reveal that only (+)-calanolide A derivatives are accounted for significant anti-HIV potential.

Fig. 5 Structures of calanolide A and calanolide B.

have potent inhibitory activity against the reverse transcriptase enzyme of HIV-1.68-76 Several important racemic modifications were prepared from calanolides to achieve the desired objectives. Also, numerous synthetic derivatives of (+)-calanolide A and (-)-calanolide A have been prepared and evaluated for their activity. The anti-HIV activity has been attributed to (+)-calanolide A. Moreover, (+)-calanolide A has already been subjected to *in vivo* studies and up to phase II clinical trials in healthy, HIV-negative subjects. ^{13,68,69}

The synthesis utilizing coumarin compound **50** as a starting material is depicted in Fig. 6a. Compound **50** undergoes acetylation with propionic anhydride in the presence of aluminium chloride to produce an 8-propionyl derivative, which on further treatment with 1,1-dimethoxy-3-methylbutan-3-ol results in the formation of intermediate compounds **51** and **52**.^{77,78}

The latter compound was de-protonated by reacting it with LDA (lithium diisopropylamide) and acetaldehyde to produce a combination of erythro-aldol compound 53 and threo-aldol compound 54 with IC $_{50}$ values of 24 μM and 22 μM , respectively. Further cyclization of compounds 53 or 54 was carried out to develop *trans*-ketone 55 and *cis*-ketone 56 with IC $_{50}$ values of 19 μM and 12 μM , respectively. Compound 55 upon reduction with sodium borohydride in ethanol results in the formation of a combination of compounds calanolide A 48 and calanolide B 49 with almost equal IC $_{50}$ values of 23 $\mu M.^{68,79}$ Compound 49 is a racemic calanolide, which was resolved by HPLC to produce (+)-calanolide A and (–)-calanolide A. Compound 56 was reduced in the presence of sodium borohydride to produce a combination of compounds 57 and 58 with IC $_{50}$ values of 18 μM and 20 μM , respectively.

Compound 57 is a racemic calanolide C, which was separated *via* column chromatography. ^{68,80,81}

(49) Calanolide B

Zembower *et al.* reported a simple and direct modification of ring C of calanolides, which produced potent analogues, as depicted in Fig. 6b. Intermediate compound **51** underwent alkylation in the presence of iodo ethane to produce ketone intermediate **59** (IC $_{50} = 6.6 \mu M$). This intermediate was further reduced by sodium borohydride to afford compound **60** (IC $_{50} = 16 \mu M$). Compounds **53–55** exhibited significant anti-viral activity against HIV-1.⁶⁸

2.6. Labdane analogs

Numerous labdane **61**, analogs with different moieties such as hydroquinone, *o*-quinol and catechol have been synthesized and evaluated for their anti-HIV potential.⁸² Many natural terpenoidal compounds possessing catechol and *o*-quinol moieties also exhibit a broad spectrum of activity. The compound eremophilane, **62**, is a sesquiterpenoid-based analog.^{83–86} Other compounds with *o*-keto-*enol* moieties are considered to act against the integrase enzyme of HIV, and thus exhibit anti-HIV activity. Cytosporic acid, **63**, a fungal metabolite obtained from *Cytospora* sp., has shown inhibitory action towards HIV integrase.^{87,88} The quassinoid compound (**64**, Fig. 7) also exhibited many other therapeutic properties, *viz*, malaria, HIV, inflammation, allergies and tumors.⁸⁶

Labdane-based analogues having an o-quinol moiety are generally synthesized from compound 65 via Diels-Alder reaction with myrcene 66 and ocimene 70, respectively. Compound 65 treated with myrcene 66, as presented in Fig. 8, results in the formation of compound 67, a major

- Key Findings:

 1. The derivatives are evaluated with CEM-SS cytoprotection assay for their anti-HIV activity.
- 2. The aldol addition products (53) and (54) and the *trans* ketone compound (55) have shown cytoprotective activity against HIV-1 cytopathicity.
- 3. Compound (57) does not show any activity even at a conc. of $100~\mu M$, but the compound (58) shows weak anti-viral activity.

Fig. 6 (a) Synthesis of racemic calanolide A together with important key findings. (b) Synthesis of calanolide A analogs.

Review RSC Advances

Fig. 7 Chemical structures of labdane analogs (61-64)

para adduct. It was then subjected to treatment with selenium dioxide and *tert*-butyl peroxide to produce compounds **68** and **69**. Similarly compound **65** upon treatment with ocimene **70** resulted in the formation of compounds **71–74**, as depicted in Fig. 9. Furthermore, a Diels–Alder reaction was carried out by treatment of compound **75** with both myrcene **66** and ocimene **70** to give *para* adduct **76** and *ortho* adduct **77**, respectively, as presented in Fig. 10. In another step, compound **78** was treated with both myrcene **66** and ocimene **70**, resulting in the formation of *ortho* adduct **79** and *para* adduct **80**, respectively. The resultants were evaluated against HIV and it was found that compounds **71**, **76**, **77** and **80** together with raltegravir as a positive control at 50 μM showed IC₅₀ values of 5.0 μM, 12.3 μM, 4.6 μM, 12.4 μM and 0.5 μM for the inhibition of HIV-1, respectively, as depicted in Fig. 11.82

2.7. Gomisin-G-based analogs

Gomisin-G **81** and some related lignans have been isolated from the ethanolic extract of *Kadsura interior* stems, exhibiting anti-

HIV activity.⁸⁹ Several other important natural lignans such as gomisin-A **82**, schisantherin-B **83**, deoxyschizandrin **84**, schizandrin A **85** and schizandrin B **86**, as depicted in Fig. 12a, also exhibited significant anti-HIV activity.⁹⁰⁻⁹⁶ From these natural compounds, various synthetic biphenyl compounds (**87-96**) have been designed by introducing different substitutions on the phenyl ring (Fig. 12b).⁹⁶

Chen *et al.* reported the synthesis of 5,5'-dimethoxy-3,4,3',4'-bis-methylene-dioxy-2,2-dimethoxy carbonyl biphenyl **94** and 2,2'-dimethoxy-3,4,3',4'-bis-methylene-dioxy-5,5'-dimethoxy carbonyl biphenyl **96**, which have reported to exhibit anti-HIV activity.⁸⁹ In Fig. 12c, the esterification of 2,3,4-trihydroxybenzoic acid **97** in the presence of methanol results in the formation of methyl 2,3,4-trihydroxybenzoate **98**. This compound **98** was subjected to treatment with dimethyl sulphate in the presence of sodium borate to produce methyl-2,3-dihydroxy-4-methoxybenzoate **99**. The resultant intermediate **99** was further subjected to treatment in the presence of dichloromethane, potassium carbonate and DMF (*N*,*N*-

COOCH₃

$$Ag_2O, \text{ toluene:}$$

$$0 \text{ °C for 3h,}$$

$$RT \text{ for 20h}$$

$$(65)$$

$$(66)$$

$$(67) [IC_{50} = 170.7 \pm 58.0 \text{ } \mu\text{M}]$$

$$(68) R = -\text{CH}_2\text{OH}$$

$$[IC_{50} = 284.6 \pm 147.0 \text{ } \mu\text{M}]$$

$$(69) R = -\text{CHO}$$

$$[IC_{50} = 171.5 \pm 67.0 \text{ } \mu\text{M}]$$

Key Findings

- 1. All the compounds have been evaulated in vitro by using MTT assay on TZM-bl cells for their cytotoxicity.
- 2. Further, the compounds have been tested by using receptor-gene based cell assay system for their *in vitro* inhibitory activity against HIV-1 infection.
- 3. Compound (67) has shown inhibition of HIV-1 integrase enzyme.
- 4. Compounds (67-69) have shown IC_{50} values of more than 200 μM

Structure-activity Relationship

- Compound (67) binds through two H-bonds with the integrase CCD, but not through active site residues, hence it shows less anti-HIVactivity.
- The structural modifications of compound (67) by Se₂O oxidation causes decrease in the activity as compare to the compound (67) itself.
- 3. The docking score of compounds (67), (68) and (69) are given as 3.32, 3.89 and 3.97 respectively.

Fig. 8 Synthesis of labdane analogs via Diels-Alder reaction (67-69).

2. Compounds (71-74) have shown inhibitory activity against the HIV-1 integrase enzyme.

- Structure-activity Relationship

 1. Compound (71) with o-quinol moiety exhibits significant anti-HIV activity.
- 2. In the compound (71), the acyl protection of hydroxyl (OH) group of o-quinol diminishs the activity completely.
- 3. The docking score of compounds (71), (72), (73) and (74) is given as 5.36, 4.28, 4.33 and 4.68 respectively.

Fig. 9 Labdane analogs by Diels-Alder reaction (71-74).

dimethylformamide), resulting in the formation of methyl-2,3-methylene-dioxy-4-methoxybenzoate **100** in 91% yield. The latter compound then underwent bromination with dioxane dibromide or with dry bromine in trichloromethane to yield methyl-2,3-methylene-dioxy-4-methoxy-5-bromo-benzoate **102** in 80% yield. A small amount of diphenyl compound **96** could be obtained from compound **102** by reacting it with active copper powder *via* Ullmann reaction. To obtain a good yield of compound **96**, compound **100** was iodinated with silver trifluoro acetate, giving a poor yield of halogenated precursor **101**. The nitration of compound **100** was carried out with conc.

HNO₃ in acetic anhydride, leading to the formation of compounds **103** and **104**. These two compounds were then reduced by Pd–C hydrogenation to produce amino acid derivatives **107** and **105**, respectively. Furthermore, compound **105** underwent diazotization with sodium nitrite in the presence of sulphuric acid to produce a diazonium salt, which underwent treatment with KI and copper to form iodo derivative **106**. The resulting compound subsequently underwent Ullmann reaction to give biphenyl derivative **94**. Compound **94** was further subjected to treatment with bromine and trichloro methane to yield another derivative **95**. Compound **94** can also be directly

(77) $[IC_{50} = 4.6 \pm 1.0 \mu M]$

Review

HO OH ACN, diisopropyl ether HO OH O'C for 1h OH OH O'C for 1h

(75)

Key Findings

- 1. Compounds (76) and (77) have shown potent inhibition of HIV-1 integrase enzyme.
- 2. Compound (77) has shown IC $_{50}$ value of 4.6 μ M and the compound (76) has shown the IC $_{50}$ value of 12.3 μ M evaluated by using MTT assay.

Structure-activity Relationship

- The compound (77) binds through two H-bonds with the active site residues of amino acids Gln 148.
 Hence, it shows more activity than the compound (67).
- 2. The compound (77) is the most potent because it binds through two H-bonds with the active site residues of amino acid Gln 148 and get completely accommodated within the IN CCD.
- 3. The docking score of compounds (76) and (77) is given as 4.77 and 5.01 respectively.

Fig. 10 Labdane analogs by Diels-Alder reaction (76-77).

(76) $[IC_{50} = 12.3 \pm 4.0 \mu M]$

synthesized from compound **105** by diazotization reaction in the presence of alkaline medium. Simultaneously, compound **96** can also be formed directly from compound **107** *via* similar types of reaction conditions. The IC $_{50}$ value of compounds **87**, **88** and **90–92** is > 100 μ g mL $^{-1}$ towards HIV-1 inhibition, while compound **96** shows significant HIV-1 inhibition with an IC $_{50}$ value of 1.8 μ g mL $^{-1}$.89

2.8. Quinoline-based analogs

Chemical scaffolds containing the quinoline pharmacophore exhibit an wide range of biological activities such as anti-HIV, anti-bacterial, anti-inflammatory, anti-fungal, immunosuppressive and anti-tumor activities.⁹⁷⁻¹⁰⁴ 8-Hydroxyquinolines

and 2-styrylquinolines are the two major categories among them that have been evaluated and considered to act on the integrase enzyme of HIV-1.¹⁰⁵⁻¹⁰⁷ Some natural quinolines such as, γ-fagarine **108** and haplopine **109** were extracted from the roots and barks of the *Zanthoxylum ailanthoides* plant and found to exert their anti-HIV actions through the inhibition of HIV replication.¹⁰⁸ Various quinoline derivatives (**110–116**) have been synthesized with amide and styryl linkers and evaluated for inhibition of HIV-1 together with the positive control azidothymidine (AZT), as depicted in Fig. 13.⁹⁷

Quinoline derivatives have been synthesized *via* two approaches, as depicted in Fig. 14. In the first step, the acetylation of aniline 117 by treatment with acetic anhydride

Open Access Article. Published on 18 May 2021. Downloaded on 12/4/2025 5:28:26 PM

RSC Advances Review

Key Findings

- 1. Compound (80) has shown potent inhibition of HIV-1 integrase enzyme.
- 2. The compound (80) has shown IC₅₀ value of 12.4 μ M evaluated by using MTT assay

Structure-activity Relationship

- 1. Compounds (76), (77) and (80) have shown effective hydrogen-bonding interactions with the active site of IN CCD.
- 2. The compound (79) binds through only one H-bond with C=O of CYS63, that is not an active site residue. Hence, it is inactive against HIV-1 integrase.
- 3. The ocimene side chain at C-5 of ortho adducts (71), (77) and (80) enhances the anti-HIV activity compared to the myrcene side chain of para adducts (67), (76) and (79).
- 4. The catechol moiety of compounds (76) and (77) is more superior than the hydroquinone moiety of compounds (79) and (80)

Fig. 11 Synthesis of labdane analogues by Diels-Alder reaction (80) and their SAR features.

at 40 °C for 10 min resulted in the formation of acetanilide 118 in 88% yield. Acetanilide was further refluxed with phosphoryl chloride in DMF at 80 °C for 8 h, which resulted the formation of another intermediate, 2-chloro-quinoline-3-carbaldehyde 119 using Vilsmeier–Haack reaction in 65% yield. From 2-chloro-quinoline-3-carbaldehyde 120, many 2,3-disubstituted quinoline derivative (121–127) were obtained in >60% yield using substituted anilines at 75 °C for 7 h.

Conversely, C-2-substituted 8-methoxyquinoline derivatives have been synthesized, as presented Fig. 15a, b, and c(i and ii). Compound o-anisidine 128 was used as the starting material and refluxed with 6 M HCl, toluene and crotonaldehyde at 110 °C for 3 h, resulting in the formation of intermediate 8-methoxy-2-quinaldine 129 in 61% yield via a modified Skraup synthesis. The resulting compound 129 was further treated with selenium dioxide and anhydrous 1,4-dioxane at 110 °C for 2 h to form 8-methoxyquinoline-2-carbaldehyde 130 in 81% yield. Compound 130 was reacted with pyridine and malonic acid at 70 °C for 2 h, giving compound (E)-3-(8methoxyquinolin-2-yl) acrylic acid 133 in 65% total yield. Subsequently, compound 133 was reacted with substituted anilines in the presence of HOBt (hydroxylbenzotriazole), DMF and molecular nitrogen at 40 °C for 12 h to produce several α,β-unsaturated amide derivatives (134-139) in 60-70% yield. In another route, compound 130 was treated with acyl hydrazines in ethanol at 80 °C for 3 h, yielding 8-methoxyquinoline-2-carbaldehyde acyl hydrazine 131, which was then converted into compound, 132. The resulting hydrazines when treated with molecular iodine and potassium carbonate at 110 °C for 6-10 h produced 1,3,4-oxadiazole derivatives (140-157) in 70-90% in yield, as depicted in

Fig. 15a, b, and c(i and ii) together with the important key findings.⁹⁷

2.9. 4-Hydroxypyrone analogs

The 4-hydroxypyrone class of compounds was found to prevent HIV-1 replication by inhibiting the protease enzyme of this virus. The compound 4-hydroxycoumarin, **158**, has been identified for its significant protease inhibition property. $^{109-112}$ It was also found that compound **159** showed effective inhibition of the HIV-1 protease enzyme. 112 4-Hydroxy-3-thio-substituted pyran-2-one derivative **160** was also found to be potent. 113 Substitution on C-3 of compound 5,6-dihydro-4-hydroxy-pyran-2-one with a thio substituent resulted in the formation of a new derivative, **161**, which was evaluated and found to possess potent HIV protease inhibitory actions. Another compound, **162**, was screened and displayed potent anti-HIV activity with an EC $_{50}$ value of 1.7 μM , as represented in Fig. 16.

The synthesis of 4-hydroxypyrone derivatives has been described into two steps. In first approach (Fig. 17), the dihydro pyrone derivatives **163–170** were synthesized using different ketones. The ketones were treated with sodium hydride and butyl lithium in dry THF followed by the addition of ketone at 0 °C. Cyclization was achieved using sodium hydroxide and methanol, resulting in the formation of the substituted derivative in 50–65% yield.

Subsequently, the preparation of the compound 3-bromodihyropyrone was carried out with NBS (*N*-bromosuccinimide), and then the bromide atom was displaced by a suitable thiophenol substituent in the presence of thiophenol,

Review RSC Advances

Fig. 12 (a) Chemical structures of natural lignans. (b) Structures of synthetic biphenyl compounds (87 to 96). (c) Synthesis of anti-HIV biphenyl derivatives.

dichloromethane and piperidine. Molecular modelling studies revealed that the naphthyl group at C-6 can possibly occupy the S2 pocket of the HIV protease and improve the anti-HIV potential, as depicted in Fig. 17. In the other step, a synthetic pathway has been described for the synthesis of the desired ketone derivatives 171–175, as depicted in Fig. 18.¹⁰⁹

2.10. Ingenol-based analogs

Ingenol **176**, is a diterpene compound isolated from plant genus *Euphorbia*. It is extracted from various species of *Euphorbia* like *Euphorbia ingens*, *Euphorbia esula*, *Euphorbia sikkimensis*, *Euphorbia fischeriana* and *Euphorbia tirucalli*. The isolated compounds from these species have been used for the treatment and management of various diseases such as cancer and keratosis. The synthetic modification of natural ingenol compounds has led to the formation of novel derivatives that are active against HIV-1. The modification of ingenol compound **176** at C-3 of its core ring with some significant ester chains led to the production of novel compounds such as ingenol-3-transcinnamate (ING-A) **177**, ingenol-3-hexanoate (ING-B) **178** and ingenol-3-dodecanoate (ING-C) **179**, as depicted in Fig. 19. 114

2.11. Lavendustin B-based analogs

Lavendustin-B **180** is a natural product that has been identified as an allosteric inhibition inducer of the HIV-1 integrase enzyme. ¹²³ Integration is an important step for HIV replication, through which the viral genome gets inserted into the host genome for transcription of new viral proteins. ¹²⁴⁻¹³³ Several other allosteric integrase inhibitors have been evolved, which act on the LEDGF/p75 binding site and inhibit the process of integration. ¹³⁴⁻¹³⁸ Agharbaoui *et al.* reported the synthesis and evaluation of lavendustin-B and its derivatives. The structures of a few of the most potent molecules (**181–190**) having potential against HIV-1 are depicted in Fig. 20.

As shown in Fig. 21, 2-hydroxy-5-nitrobenzoic acid, 191 was reduced with zinc dust in the presence of conc. HCl and subjected to refluxing for 4 h at 0-5 °C to produce 5-amino-2hydroxy-benzoic acid 192. Compound 192 underwent esterification by treating with methanol in the presence of sulphuric acid to form 5-amino-2-hydroxybenzoate 193. Intermediate compound 193 formed in the previous step was treated with different substituted benzaldehydes in the presence of NaCNBH3 (sodium cyanoborohydride), affording methyl-5-(benzylamino)-2-hydroxybenzoates 194-199. These intermediates 194-199 were further subjected to treatment with dimethyl formamide together with sodium hydride and benzyl bromide under an argon atmosphere, resulting in 5-(dibenzyl amino)-2hydroxybenzoates 200-205. In the last step, the desired lavendustin B derivatives 181-183, 185, 186, and 188 were formed by treating compounds 200-205 with sodium hydroxide and methanol.123 The anti-HIV potential of all the lavendustin B derivatives was evaluated for their inhibitory activity against IN-LEDGF/p75 binding using HTRF (homogeneous time-resolved fluorescence)-based assays. Lavendustin-B compounds 181 and 182 displayed IC₅₀ values of 94.07 μ M, 8.75

Quinoline moiety (108) Gama-fagarine (109) Haplopine Amide linker OH OH OH R (110) R = H,
$$[IC_{50} = 2.4 \, \mu\text{M}]$$
 (111) R = OH, $[IC_{50} = 0.3 \, \mu\text{M}]$ (112) R = OCH₃, $[IC_{50} = 0.7 \, \mu\text{M}]$ (114) R = OCH₃, $[IC_{50} = 6.5 \, \mu\text{M}]$ (115) R = H, $[IC_{50} \, \text{HIV-1}_{VB59} \, \text{(R5)} = 3.99 \, \mu\text{M}]$ (116) R = CI, $[IC_{50} \, \text{HIV-1}_{VB59} \, \text{(R5)} = 3.99 \, \mu\text{M}]$ (116) R = CI, $[IC_{50} \, \text{HIV-1}_{VB59} \, \text{(R5)} = 0.33 \, \mu\text{M}]$ $[IC_{50} \, \text{HIV-1}_{UG070} \, \text{(X4)} = 3.99 \, \mu\text{M}]$ (116) R = CI, $[IC_{50} \, \text{HIV-1}_{UG070} \, \text{(X4)} = 0.61 \, \mu\text{M}]$

Fig. 13 Quinoline analogs (108-116) possessing amide and styryl linkers with anti-HIV potential.

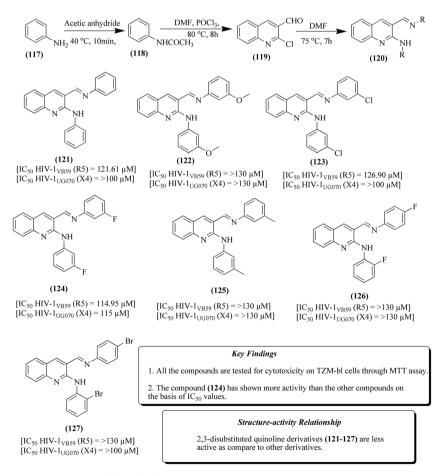
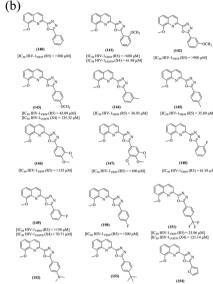
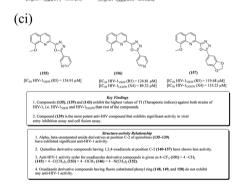


Fig. 14 2,3-Disubstituted quinoline derivatives (121–127).

a) μ M and 3.28 μ M against IN-LEDGF/p75 binding, respectively. The most potent compound 182 together with its docking features are also presented in Fig. 21. 123

(34) Oct III Concent (Applied Part | Applied Part





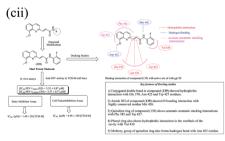


Fig. 15 (a) Synthesis of 2-substituted quinoline derivatives together with the structures of the most potent compounds (135–139). (b) 2-Substituted quinoline derivatives (140–154). (c(i)) 2-Substituted quinoline derivatives (155–157) together with their SAR and important key features. (c(ii)) 2-Substituted quinoline derivatives together with their important docking features.

2.12. 3,7-Dihydroxytropolone-based analogs

3,7-Dihydroxytropolones are oxygenated troponoid compounds, which have been used as potential agents against several human disorders including viral infections. Thy 7-Hydroxytropolones (α -HTs) **206** are troponoid compounds containing three oxygen atoms, whereas 3,7-dihydroxytropolones **207** are troponoid compounds containing four oxygen atoms, as shown in Fig. 22. 140,141

The synthesis of various 3,7-dihydroxytropolone derivatives has been described using the following approaches. Fig. 23 demonstrates that in the first approach, D-(+)-galactose **208** was utilized as a substrate for the synthesis of new 7-hydroxytropolone and 3,7-dihydroxytropolone derivatives. ^{139,142} In another approach, kojic acid **209** was used as a starting material for the synthesis of two types of hydroxytropolone derivatives. ¹³⁹

The cyclo addition of kojic acid with (oxido)pyrylium triflate salt 210a and iodo alkynes 211 and 212 resulted in the formation of iodo bicycles 213a/213b, respectively. These iodo bicycles were further subjected to methanolysis in the presence of DMAP (4-dimethylaminopyridine) to form methoxy bicycles 214a and 214b, respectively. The resultant iodo bicycles were subsequently treated with various reagents to afford compounds 215a and 215b and 216a and 216b. Compound 213b was treated with DMAP in the presence of CDCl₃ (deuterated chloroform) to obtain compound 217 and further treatment of compound 213b with potassium carbonate and methanol yielded another compound, 218, as depicted in Fig. 24. Furthermore, compound 213b was treated with MsOH (methane sulfonic acid) to produce (oxido)pyrylium dimer compound 219a, as presented in Fig. 25.

As shown in Fig. 26, the methyl ester of compound 215a when treated with hydrobromic acid in the presence of acetic acid yielded 3,7-dihydroxytropolone 216c at 120 °C.139 Puberulonic acid 222 and puberulic acid 224 are two important 3,7dihydrotropolones obtained from the Penicillium puberulum fungus. 143 These two compounds are considered to be very similar to stipitatonic acid 221 and stipitatic acid 223, which are derivatives of 6-hydroxytropolone compounds. 144,145 Also, lactone stipitalide 220 was used for the synthesis of stipitatonic acid 221, which was further utilized for the synthesis of stipitatic acid 223, as depicted in Fig. 27. Puberulonic acid 222 and puberulic acid 224 can also be synthesized from 3,7-dihyroxytropolone. Also, compound 216d has been utilized for the biosynthesis of different 3,7-dihydroxytropolones. Fig. 28 also demonstrates another strategy for the synthesis of compound 216d.139

In a different approach, compounds 213b/213c were synthesized from compound, 210b together with the compound 219b, which was formed using TEA (triethyl amine) and dichloromethane. Subsequently, methoxy tropolone compound 215c was formed, and then converted into compound 216d

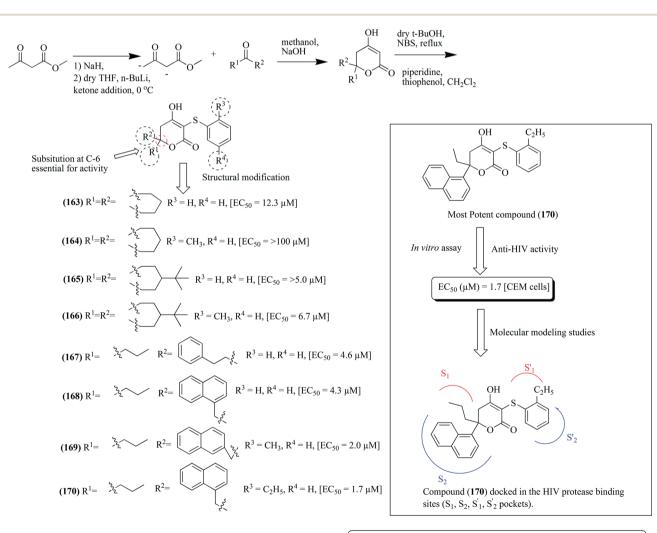
(162)

 $[IC_{50} = 1.7 \mu M]$

Fig. 16 4-Hydroxypyrone HIV protease inhibitors (158–162).

(161)

 $[IC_{50} = 1.1 \text{ nM}]$



Key Findings

The anti-HIV activities of all the derivatives have been evaluated by using SIV-infected CEM cells.

Structure-activity Relationship

- 4-Hydroxypyrones having a spirocycle at position C-6 show some inhibitory activity towards HIV protease enzyme.
- $2. \ \mbox{Compounds}$ that have six-membered ring have been shown greater potency.

Fig. 17 Structures of potent 4-hydroxypyrone derivatives (163-170) together with important key findings and their SAR features.

Review **RSC Advances**

OH
$$\frac{DMF, SOCl_2}{EtoAc}$$

R

(171)

 R^1

CI

(172)

 $-78 \, ^{\circ}C$

R

(174)

Li + CuI $\frac{dry \text{ ether.}}{-40 \, ^{\circ}C}$

CuLi

(173)

OH acetone, K₂CO₃

(175)

Fig. 18 Synthesis of ketone derivatives.

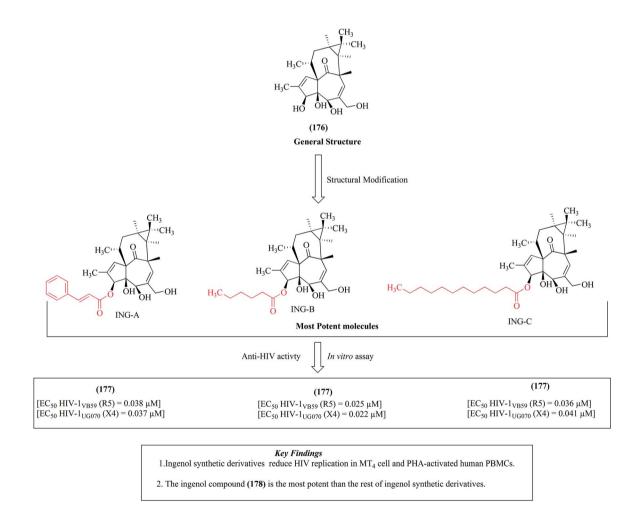


Fig. 19 Structures of the most potent ingenol derivatives (176 to 179).

through various reaction steps such as acetolysis, lactonization and demethylation. The 3,7-dihydroxytropolone compounds 216a and 216b displayed IC₅₀ values of 1.5 μM and 1.1 μM , respectively, against HIV-RT, as depicted in Fig. 28.139

2.13. P1/P1'-substituted cyclic urea-based analogs

P1/P1'-substituted cyclic urea-based compounds have been reported to exhibit potent activity against the protease enzyme of HIV-1.146 In recent years, several compounds have **RSC Advances** Review

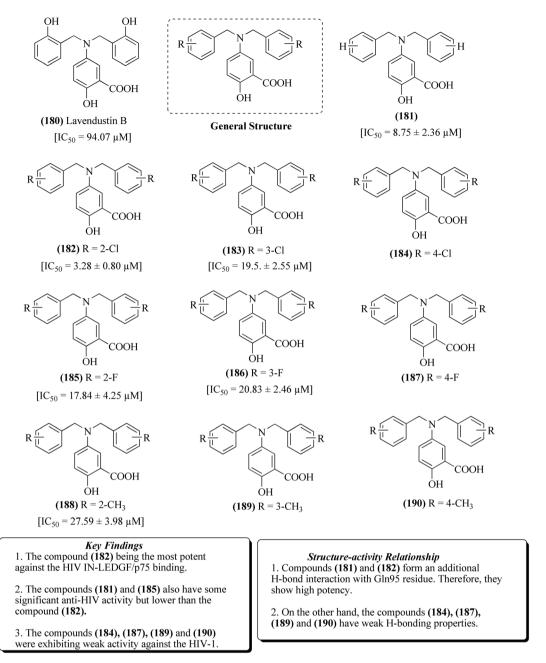


Fig. 20 Lavendustin-B and its derivatives together with their SAR and key features.

been identified that act as protease inhibitors and exhibit potent anti-viral activities. 147,148 However, it has been established that the modification at P1/P1' binding is necessary to enhance the potency of protease inhibitors as potential agents.149 It has been shown that the potency has about an 8-15 fold enhancement by introducing 4-(3-hydroxypropyl) at the P1' phenyl ring.

The introduction of a new (hydroxyl ethyl) urea isosterebased protease inhibitor permits deviations of the P1 substituent. 150 DMP 323 225 is a 7-membered cyclic urea-based HIV-1 protease inhibitor, which showed poor binding affinity towards the protease enzyme of HIV-1.151 Oppositely, the DMP

450 226 molecule exhibited good pharmacokinetic properties together with significant inhibition and recently completed phase I clinical trials, as depicted in Fig. 29.152

There are three different strategies adopted for the synthesis of P1/P1'-substituted cyclic ureas. DMP 323 225 has been synthesized from amino acids. 153 The commercially available N-Cbz-D-alanine 227 upon treatment with NMM (N-methylmorpholine) and N,O-dimethoxy hydroxyl amine resulted in the formation of amide compound 228, as presented in (Fig. 30). Subsequent reduction with LAH (lithium aluminium hydride) yielded an amino aldehyde in 96% yield. The formed amino aldehyde was further added to a slurry of [V₂Cl₃(THF)₆]₂ [Zn₂Cl₆]

CHO COOCH: COOH cone HCl Methanol, HoSO4 COOH Methanol, AcOH, 40 °C, RT 0-5 °C, reflux 0 °C, 80 °C, (191)(192)(193) 24 hrs COOCH₂ COOCH₂ NaOH, methanol, THF, 60 °C, 24hrs Compound (181-183,185,186,187) (194,200,181), R = HSodium hydride, argon. (195,201,182), R = 2-C1DMF, 3h, RT (196,202,183), R = 3-Cl (194-199) (197,203,185), R = 2-F(200-205)(198,204,186), R = 3-F (199,205,188), R = 2-CH₂ (184), R = 4-Cl, (187), R= 4-F. (189), R = 3-CH₃ (190), R = 4-CH₃Compound 194,200,181), R = H Strutural (195,201,182), R = 2-C1modification (196,202,183), R = 3-Cl (197.203.185) R = 2-F (198,204,186), R = 3-F $(199,205,188), R = 2-CH_3$ (184), R = 4-Cl. (187), R = 4-F 189), R = 3-CH₂ (190), R = 4-CH ÓН (182)General Structure (Most Potent Molecule) (Trp 131) (Gln 168) 1) HIV-1 inhibition activity Ala 169 In vitro Assavs 2) Homogeneoustime-resolved fluorescence (HTRF)-based assays Ala 128 $IC_{50} (\mu M) = 25.62 \pm 1.88 [TZM-bl cells]$ IC_{50} (μ M) = 3.78 ± 0.35 [LEDGF/p75 dependent IN Activity] COOH $IC_{50} (\mu M) = 3.28 \pm 0.80 [IN-LEDGF/p75 binding]$ ÓН His 171 (Thr 174) -- H Bonding (Gln 95) Hydrophobic interactions Binding Interation of Compound (182) with binding pocket of HIV-1 IN. Key Findings . All the derivatives have been evaluated by using homogeneous Structure Activity Relationship 1. The synthetic modification of lavendustin B with 2-Cl group exhibits time-resolved fluorescence (HTRF)-based assays for their inhibitory activity on the IN-LEDGF/p75 binding. highly potent activity as in the compound (182).

Fig. 21 Structures of lavendustin B analogs together with their docking features.



2. The compound (182) has been reported to be the most potent compound.

3. Compound (182) acts by inhibiting both LEDGF/p75 dependent and

independent activities of integrase enzyme.

Fig. 22 Hydroxylated tropolones

in the presence of dichloromethane to produce compound 229 in 66% yield.

Compound **229** was treated with 2-(trimethylsilyl) ethoxy methyl chloride (SEM-Cl) to yield ether compound **230** in 87% yield. Subsequent reactions of compound **230** in the presence of catalytic Pd(OH)₂ and CDI (1,1-carbonyldiimidazole) produced urea-based scaffold **231** in 81% yield. *N*-alkylation of the urea in the presence of benzyl bromide and NaH afforded the P2/P2′ substituent-based analogs. Acid-catalysed cyclization of the

latter in methanol resulted in the target cyclic urea-based compound 232 in 54% yield.^{146,154}

2. The modification at the positions C-3 or C-4 with different functional

groups exhibits weaker activity as in the compounds (184), (187), (189) and (190).

In the second approach, L-tartaric acid is used as the starting material for the synthesis of P1/P1'-substituted cyclic ureas. (–)-Dimethyl 2,3-O-isopropylidene-_L-tartrate 233 was treated with trimethyl aluminium and N,O-dimethyl hydroxylamine hydrochloride to afford a new bis-Weinreb amide compound 234. It was further treated with p-isopropyl benzyl magnesium chloride in THF to form diketone scaffold 235 in 95% yield. The E:Z oxime isomer 236 was obtained together with the E:Z isomer by reacting compound 235 with hydroxylamine hydrochloride. The resulting oxime mixture was further reduced with diisobutyl aluminium hydride (DIBAL) in the presence of toluene to produce a di-amine compound, 237. Di-amine 237 was subsequently reacted with 1,1'carbonyl-diimidazole to produce imidazolide

Fig. 23 Synthesis of tropolone derivatives through p-(+)-galactose route and through kojic acid route.

Fig. 24 3,7-Dihydroxytropolone and tropolone derivatives.

Conversion of oxabicyclic intermediates into (oxido)pyrylium dimer compound (219a)

Fig. 26 Acid-mediated hydrolysis and decarboxylation of compound (215a).

(220) Stipitalide,
$$X = H$$
 (216d), $X = OH$ (221) Stipitatonic acid, $X = H$ (222) Puberulonic acid, $X = OH$ (224) Puberulic acid, $X = OH$

Fig. 27 Synthesis of compounds (221–224) from stipitalide and other 3,7-DHTs.

intermediate, which was further cyclized in the presence of tetrachloroethane to produce cyclic urea-based compound 238 in 62% yield. Compound 238 further underwent alkylation in the presence of benzyl bromide and potassium tertbutoxide. The resultant compound was treated with HCl and

methanol, yielding the target urea-based compound 239 in 67% yield, as presented in Fig. 31.146,155,156

In the third strategy, lactone 240 was reduced with lithium borohydride in the presence of methanol to form a crude Lmannitol. The reaction of the latter with 2,2-dimethoxypropane

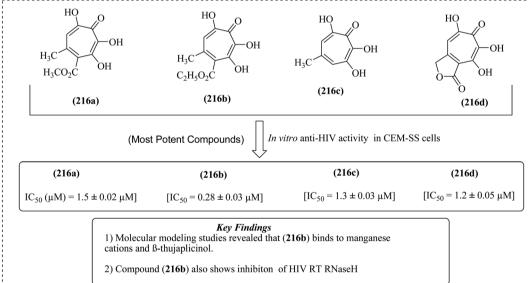


Fig. 28 Synthesis of 3,7-dihydroxytropolone analogs together with important key findings of the potent compounds.

and hydrochloric acid in acetone resulted in the formation of a new compound triacetonide **241** in 80% yield. Further treatment with acetic acid yielded a tetraol intermediate in 80% yield. This tetraol intermediate was subsequently reacted with triphenyl phosphine and diethyl azo dicarboxylate (DEAD) in the presence of toluene for the production of volatile diepoxide **242** in 80% yield. Diepoxide **242** was reacted in the presence of butyl lithium and $4\text{-CH}_3\text{SC}_6\text{H}_4\text{Br}$ to obtain diol compound **243**.

The reaction of diol compound 243 in the presence of DEAD, triphenyl phosphine and diphenyl phosphorazidate resulted in the formation of diazide scaffold 244 together with significant amounts of monoazide compound 245. The diazide compound was further reduced using LAH to form a diamine, which was further cyclized to form urea-based compound 246. The cyclic urea-based compound 246 was alkylated in the presence of benzyl bromide and potassium *tert*-butoxide. In the last step,

Key Findings

- 1) DMP 450 (226), has recently completed phase I trials.
- 2) It also showed an improved pharmacokinetic profile in humans.

Fig. 29 Chemical structures of P1/P1'-substituted cyclic urea compounds.

$$\begin{array}{c} \text{i-BuOCOCCI,} \\ \text{CH}_2\text{Cl}_2 \\ \text{NMM} \\ \text{(227)} \\ \\ \text{(228)} \\ \\ \text{CbzHN} \\ \text{NHCbz} \\ \text{NHCbz} \\ \text{NHCbz} \\ \text{NHCbz} \\ \text{NHCbz} \\ \text{Ch}_2\text{Cl}_2 \\ \text{NMM} \\ \text{H}_3\text{C} \\ \text{OOH} \\ \text{OCH}_3 \\ \text{CH}_2\text{Cl}_2 \\ \text{VCI}_3(\text{THF})_3, \\ \text{Zn-CU} \\ \text{(229)} \\ \\ \text{(229)} \\ \\ \text{(229)} \\ \\ \text{CbzHN} \\ \text{NHCbz} \\ \text{ethanol,} \\ \text{cyclohexane} \\ \text{H}_3\text{C} \\ \text{OSEM} \\ \text{SEMO} \\ \text{OSEM} \\ \text{SEMO} \\ \text{OSEM} \\ \text{(231)} \\ \\ \text{(231)} \\ \\ \text{(232)} \\ \\ \text{[IC}_{90} = >10,000 \text{ nM]} \\ \\ \text{(232)} \\ \\ \text{(233)} \\ \\ \text{(234)} \\ \\ \text{(235)} \\ \\ \text{(236)} \\ \\ \text{(236)} \\ \\ \text{(236)} \\ \\ \text{(237)} \\ \\ \text{(237)} \\ \\ \text{(237)} \\ \\ \text{(238)} \\ \\ \text{(238)} \\ \\ \text{(238)} \\ \\ \text{(231)} \\ \\ \text{(231)} \\ \\ \text{(231)} \\ \\ \text{(231)} \\ \\ \text{(232)} \\ \\ \text{(232)} \\ \\ \text{(232)} \\ \\ \text{(232)} \\ \\ \text{(233)} \\ \\ \text{(234)} \\ \\ \text{(235)} \\ \\ \text{(236)} \\ \\ \text{(236)} \\ \\ \text{(236)} \\ \\ \text{(237)} \\ \\ \text{(237)} \\ \\ \text{(237)} \\ \\ \text{(238)} \\ \\ \text{(238)$$

SEM = 2-(Trimethylsilyl)ethoxymethyl

Fig. 30 Synthesis of P1/P1'-substituted cyclic ureas.

Fig. 31 Synthesis of P1/P1'-substituted cyclic urea derivatives (239).

Fig. 32 Synthesis of P1/P1'-substituted cyclic urea-based derivatives together with important key findings of most potent compounds (248–250).

treatment with HCl afforded the target urea-based compound **247** in 60–70% yield, as presented in Fig. 32 together with the important key findings of the most potent compounds **248–250.** ^{146,157}

Abbreviations

potential.

AIDS

3. Conclusion

Numerous efforts have been made in the recent decades for the synthesis of anti-HIV agents. The literature survey clearly indicated that several chemical entities have been clinically approved and recommended for the management of AIDS. However, there is still great demand to search novel scaffolds because the existing drugs exhibit severe noxious harmful effects. This review article presented some interesting rational approaches behind the design of potential therapeutic candidates employed by researchers, prominent scientists, academicians and scholars globally.

In the present communication, we summarized the design strategies, structure of the most potent molecules, their $\rm IC_{50}$ values, structure–activity relationships, most important key findings, binding interactions with the amino acid residues of the enzymes responsible for HIV 1 inhibition and mechanistic insights into plant-based analogs such as andrographolide, azaindole, artemisinin, maslinic acid, calanolides, labdane, gomisin-G, ingenol, lavendustin-B, dihydroxy tropolone, and cyclic urea-based analogs in the context of their action against HIV/AIDS. The synthesized compounds display modified pharmacological profiles together with increased potency against different strains of HIV-1. The present assemblage can be immensely beneficial for medicinal chemists focusing on the

design of therapeutic candidates having significant anti-HIV

Acquired immunodeficiency syndrome

AZT Azidothymidine
CDI Carbonyl diimidazole
DCC Dicyclohexylcarbodiimide

DCM Dichloromethane

DIBAL Diisobutyl aluminium hydride
DMAP Dimethyl amino pyridine
DMF Dimethylformamide
DNA Deoxyribonucleic acid
HCl Hydrochloric acid

HIV Human immunodeficiency virus

HOBt Hydroxybenzotriazole

HPLC High performance liquid chromatography HTRF Homogeneous time-resolved fluorescence

LAH Lithium aluminium hydride LDA Lithium diisopropyl amide

μM Micromolar

NBS *N*-Bromosuccinimide NMM *N*-Methyl morpholine

SARs Structure activity-relationships

TEA Triethylamine
THF Tetrahydrofuran

UNAIDS Joint United Nations Programme on AIDS/HIV

Author contributions

Review

Conceptualization, G. K. G, F. N. K and D. K.; methodology, R. K., P. S. and D. K.; software, data curation, R. K., P. S., S., F. N. K and D. K.; writing—original draft preparation, D. K., P. S., and R. K., writing—review and editing, R. K., P. S., S., G. K. G, F. N. K, and D. K.; visualization, X. X.; supervision, F. N. K., and D. K.; project administration, F. N. K., G. K. G, and D. K.; funding acquisition, F. N. K. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

F. N. K. acknowledges financial support from the German Academic Exchange Services (DAAD) through the guest professorship program.

References

- B. Salehi, N. V. A. Kumar, B. Sener, M. Sharifi-Rad, M. Kılıç,
 G. B. Mahady, S. Vlaisavljevic, M. Iriti, F. Kobarfard,
 W. N. Setzer, S. A. Ayatollahi, A. Ata and J. Sharifi-Rad, *Int. J. Mol. Sci.*, 2018, 19, 1459.
- C. Reynolds, C. B. de Koning, S. C. Pelly, W. A. L. Otterlo and M. L. Bode, *Chem. Soc. Rev.*, 2012, 41, 4657–4670.
- 3 www.hiv.gov, accessed on 16 December 2020.
- 4 D. Y. Lu, H. Y. Wu, N. S. Yarla, B. Xu, J. Ding and T. R. Lu, *Infect. Disord.: Drug Targets*, 2018, **18**, 15–22.
- 5 M. S. Cohen, Y. Q. Chen, M. McCauley, T. Gamble, M. C. Hosseinipour, N. Kumarasamy, J. G. Hakim, J. Kumwenda, B. Grinsztejn and J. H. Pilotto, N. Engl. J. Med., 2011, 365, 493–505.
- 6 WHO, Bull. W. H. O., 1989, 87, 613-618.
- 7 P. Cos, L. Maes, D. V. Berghe, N. Hermans, L. Pieters and A. Vlietinck, J. Nat. Prod., 2004, 67, 284–293.
- 8 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, 75, 311e335.
- 9 Y. W. Chin, M. J. Balunas, H. B. Chai and A. D. Kinghorn, *AAPS J.*, 2006, **8**, 239–253.
- 10 D. Kumar and S. K. Jain, Curr. Med. Chem., 2016, 23, 4338–4394.
- 11 V. Kumar, K. Kaur, G. K. Gupta and A. K. Sharma, *Eur. J. Med. Chem.*, 2013, **69**, 735–753.
- 12 K. Kaur, V. Kumar, G. K. Gupta and A. K. Sharma, *Eur. J. Med. Chem.*, 2014, 77, 121–133.
- 13 R. Kaur, P. Sharma, G. K. Gupta, F. Ntie-Kang and D. Kumar, *Molecules*, 2020, 25, 2070.
- 14 D. Kumar, P. Sharma, H. Singh, K. Nepali, G. K. Gupta, S. K. Jain and F. Ntie-Kang, RSC Adv., 2017, 7, 36977–36999.
- 15 K. Nepali, S. Sharma, D. Kumar, A. Budiraja and K. L. Dhar, *Recent Pat. Anti-Cancer Drug Discovery*, 2014, **9**, 303–339.
- 16 D. Kumar, K. Nepali, P. M. S. Bedi, S. Kumar, F. Malik and S. Jain, Anti-Cancer Agents Med. Chem., 2015, 15, 793–803.

- 17 D. Kumar, O. Singh, K. Nepali, P. M. S. Bedi, A. Qayum, S. Singh and S. K. Jain, *Anti-Cancer Agents Med. Chem.*, 2016, 16, 881–890.
- 18 D. Kumar, F. Malik, P. M. S. Bedi and S. K. Jain, *Chem. Pharm. Bull.*, 2016, **64**, 399-409.
- 19 D. Kumar, G. Singh, P. Sharma, A. Qayum, G. Mahajan, M. J. Mintoo, S. K. Singh, D. M. Mondhe, P. M. S. Bedi, S. K. Jain and G. K. Gupta, *Anti-Cancer Agents Med. Chem.*, 2018, 18, 57–73.
- 20 D. Kumar, P. Sharma, K. Nepali, G. Mahajan, M. J. Mintoo, A. Singh, G. Singh, D. M. Mondhe, G. Singh, S. K. Jain, G. K. Gupta and F. Ntie-Kang, *Heliyon*, 2018, 4, e00661.
- 21 P. Sharma, R. Sharma, H. S. Rao and D. Kumar, *Int. J. Pharma Sci. Res.*, 2015, **6**, 505–513.
- 22 D. Kumar and P. M. S. Bedi, Indian Drugs, 2009, 46, 675-681.
- 23 T. Kaur, P. Sharma, G. K. Gupta, F. N. Kang and D. Kumar, *Plant Arch.*, 2019, **19**(2), 2168–2176.
- 24 C. Calabrese, S. H. Berman, J. G. Badish, X. Ma, L. Shinto, M. Dorr, K. Well, C. A. Wenner and L. J. Standish, *Phytother. Res.*, 2000, 14, 333–338.
- 25 W. Li, X. Xu, H. Zhang, C. Ma, H. Fong, V. Richard and F. John, *Chem. Pharm. Bull.*, 2007, 55, 455-458.
- 26 R. S. Chang, L. Ding, G. Q. Chen, Q. C. Pan, J. L. Zhao and K. M. Smith, *Proc. Soc. Exp. Biol. Med.*, 1991, 197, 59–66.
- 27 V. Rajpal, *Standardization of Botanicals*, Estern Publishers, New Delhi, 1st edn, 2002, pp. 29–37.
- 28 S. Vetriselvan and U. Subasini, *Asian J. Phytomed. Clin. Res.*, 2013, 1, 57–63.
- 29 R. Kumar, K. Sridevi, N. Kumar, N. Srinivas and S. Rajagopal, *J. Ethnopharmacol.*, 2004, **92**, 291–295.
- 30 S. Jada, G. Subur, C. Matthews, A. Hamzah, N. Lajis and M. Saad, *Phytochemistry*, 2007, **68**, 904–912.
- 31 V. Menon and S. V. Bhat, *Nat. Prod. Commun.*, 2010, 5, 717–720.
- 32 H. W. Xu, F. D. Gui, Z. L. Gai, F. W. Jun and M. L. Hong, *Bioorg. Med. Chem.*, 2007, **15**, 4247–4255.
- 33 V. L. N. Reddy, S. M. Reddy, V. Ravikanth, P. Krishnaiah, T. V. Goud, T. P. Rao, T. S. Ram, R. G. Gonnade, M. Bhadbhade and Y. Venkateswarlu, *Nat. Prod. Res.*, 2005, 19, 223–230.
- 34 B. Wang, L. Ge, W. Huang, H. Zhang, H. Qian, J. Li and Y. Zheng, *Med. Chem.*, 2010, **6**, 252–258.
- 35 B. Wang, J. Li, W. L. Haung, H. B. Zhang, H. Qian and Y. T. Zheng, *Chin. Chem. Lett.*, 2011, 22, 781–784.
- 36 M. M. Uttekar, T. Das, R. S. Pawar, B. Bhandari, V. Menon, Nutan, S. K. Gupta and S. V. Bhat, *Eur. J. Med. Chem.*, 2012, 56, 368–374.
- 37 T. Wang, Z. Yin, Z. Zhang, J. A. Bender, Z. Yang, G. Johnson, Z. Yang, L. M. Zadjura, C. J. D'Arienzo, D. D. G. Parker, C. Gesenberg, G. A. Yamanaka, Y. F. Gong, H. T. Ho, H. Fang, N. Zhou, B. V. McAuliffe, B. J. Eggers, L. N. Fan, B. Sans, I. B. Dicker, Q. Gao, R. J. Colonno, P. F. Lin, N. A. Meanwell and J. F. Kadow, J. Med. Chem., 2009, 52, 7778–7787.
- 38 T. Wang, Z. Zhang, O. B. Wallace, M. Deshpande, H. Fang, Z. Yang, L. M. Zadjura, D. L. Tweedie, S. Huang, F. Zhao, S. Ranadive, B. S. Robinson, Y. F. Gong, K. Ricarrdi,

T. P. Spicer, C. Deminie, R. Rose, H. G. H. Wang, W. S. Blair, P. Y. Shi, P. F. Lin, R. J. Colonno and N. A. Meanwell, *J. Med. Chem.*, 2003, **46**, 4236–4239.

RSC Advances

- 39 P. F. Lin, W. S. Blair, T. Wang, T. P. Spicer, Q. Guo, N. Zhou, Y. F. Gong, H. G. H. Wang, R. Rose, G. Yamanaka, B. Robinson, C. B. Li, R. Fridell, C. Deminie, G. Demers, Z. Yang, L. Zadjura, N. A. Meanwell and R. J. Colonno, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 11013–11018.
- 40 H. T. Ho, L. Fan, B. Nowicka-Sans, B. McAuliffe, C. B. Li, G. Yamanaka, N. Zhou, H. Fang, I. Dicker, R. Dalterio, Y. F. Gong, T. Wang, Z. Yin, Y. Ueda, J. Matiskella, J. F. Kadow, P. Clapham, J. Robinson, R. J. Colonno and P. F. Lin, J. Virol., 2006, 80, 4017–4025.
- 41 N. Madani, A. L. Perdigoto, K. Srinivasan, J. M. Cox, J. J. Chruma, J. LaLonde, M. Head, A. B. Smith and J. G. Sodroski, *J. Virol.*, 2004, 78, 3742–3752.
- 42 Z. Si, N. Madani, J. M. Cox, J. J. Chruma, J. C. Klein, A. Schon, N. Phan, W. Wang, A. C. Biorn, S. Cocklin, I. Chaiken, E. Freire, A. B. Smith and J. G. Sodroski, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, 101, 5036–5041.
- 43 G. Hanna, J. Lalezari, J. Hellinger, D. Wohl, T. Masterson, W. Fiske, J. F. Kadow, P. F. Lin, M. Giordano, R. J. Colonno and D. Grasela, Antiviral Activity, Safety, and Tolerability of a Novel, Oral Small-Molecule HIV-1 Attachment Inhibitor, BMS-488043, in HIV-1-Infected Subjects, San Francisco, CA, 2004.
- 44 Z. Zhang, Z. Yang, N. A. Meanwell, J. F. Kadow and T. Wang, J. Org. Chem., 2002, 67, 2345–2347.
- 45 T. Yamato, C. Hideshima and M. Tashiro, *Chem. Express*, 1990, **5**, 845–848.
- 46 H. Van de Poel, G. Guillaumet and M. C. Viaud-Massuard, *Heterocycles*, 2002, 57, 55–71.
- 47 H. Li, X. Jiang, Y. H. Ye, C. Fan, T. Romoff and M. Goodman, *Org. Lett.*, 1999, **1**, 91–93.
- 48 Z. Zhang, Z. Yang, H. Wong, J. Zhu, N. A. Meanwell, J. F. Kadow and T. Wang, J. Org. Chem., 2002, 67, 6226–6227.
- 49 S. Jana, S. Iram, J. Thomas, M. Q. Hayat, C. Pannecouque and W. Dehaen, *Molecules*, 2017, 22, 303.
- 50 Y. Tu, Nat. Med., 2011, 17, 1217-1220.
- 51 I. S. Lubbe, T. Klimkait and F. V. D. Kooy, *J. Ethnopharmacol.*, 2012, **141**, 854–859.
- 52 D. L. Klayman, Science, 1985, 228, 1049-1055.
- 53 D. Chaturvedi, A. Goswami, P. P. Saikia, N. C. Barua and P. G. Rao, *Chem. Soc. Rev.*, 2010, **39**, 435–454.
- 54 M. Jung, K. Lee, H. Kim and M. Park, *Curr. Med. Chem.*, 2004, 11, 1265–1284.
- 55 J. J. Lu, S. M. Chen, X. W. Zhang, J. Ding and L. H. Meng, Invest. New Drugs, 2011, 29, 1276–1283.
- 56 H. Chen, B. Sun, S. Pan, H. Jiang and X. Sun, *Anticancer Drugs*, 2009, 20, 131–140.
- 57 J. J. Lu, L. H. Meng, Y. J. Cai, Q. Chen, L. J. Tong, L. P. Lin and J. Ding, *Cancer Biol. Ther.*, 2008, 7, 1017–1023.
- 58 Y. Li, J. M. Wu, F. Shan, G. S. Wu, J. Ding, D. Xiao, J. X. Han, G. Atassi, S. Leonce and D. H. Caignard, *Bioorg. Med. Chem.*, 2003, 11, 977–984.

- 59 Z. S. Yang, W. L. Zhou, Y. Sui, J. X. Wang, J. M. Wu, Y. Zhou, Y. Zhang, P. L. He, J. Y. Han and W. Tang, *J. Med. Chem.*, 2005, 48, 4608-4617.
- 60 D. Mu, W. Zhang, D. Chu, T. Liu, Y. Xie, E. Fu and F. Jin, Cancer Chemother. Pharmacol., 2008, 61, 639-645.
- 61 T. Chen, M. Li, R. Zhang and H. Wang, *J. Cell. Mol. Med.*, 2009, 13, 1358–1370.
- 62 C. Wu, J. Liu, X. Pan, W. Xian, B. Li, W. Peng, J. Wang, D. Yang and H. Zhou, *Molecules*, 2013, 18, 6866–6882.
- 63 Y. Liu, Z. Liu, J. Shi, H. Chen, B. Mi, P. Li and P. Gong, Molecules, 2013, 18, 2864–2877.
- 64 A. Parra, F. Rivas, P. L. Lopez, A. G. Granados, A. Martinez, F. Albericio, N. Marquez and E. Munoz, *Bioorg. Med. Chem.*, 2009, 17, 1139–1145.
- 65 H. X. Xu, F. Q. Zeng, M. Wan and K. Y. Sim, *J. Nat. Prod.*, 1996, **59**, 643.
- 66 R. Mukherjee, V. Kumar, S. K. Srivastava, S. K. Agarwal and A. C. Burman, *Anti-Cancer Agents Med. Chem.*, 2006, **6**, 271–279.
- 67 M. P. Montilla, A. Agil, M. C. Navarro, M. I. Jimenez, A. G. Garcia, A. Parra and M. M. Cabo, *Planta Med.*, 2003, 69, 472–474.
- 68 D. E. Zembower, S. Liao, M. T. Flavin, Z. Q. Xu, T. L. Stup, R. W. Buckheit Jr, A. Khilevich, A. A. Mar and A. K. Sheinkman, *J. Med. Chem.*, 1997, 40, 1005–1017.
- 69 T. Creagh, J. L. Ruckle, D. T. Tolbert, J. Giltner, D. A. Eiznhamer, B. Dutta, M. T. Flavin and Z. Q. Xu, Antimicrob. Agents Chemother., 2001, 45, 1379–1386.
- 70 Z. Q. Xu, E. R. Kern, L. Westbrook, L. B. Allen, R. W. Buckheit, C. K. Tseng, T. Jenta and M. T. Flavin, Antiviral Chem. Chemother., 2000, 11, 23–29.
- 71 A. D. Patil, A. J. Freyer, D. S. Eggleston, R. C. Haltwanger, M. F. Bean, P. B. Taylor, M. J. Caranfa, A. L. Breen, H. R. Bartus, R. K. Johnson, R. P. Hertzberg and J. W. Westley, *J. Med. Chem.*, 1993, 36, 4131–4138.
- 72 Y. Kashman, K. R. Gustafson, R. W. Fuller, J. H. Cardellina, J. B. McMahon, M. J. Currens, R. W. Buckheit Jr, S. H. Hughes, G. M. Cragg and M. R. Boyd, *J. Med. Chem.*, 1992, 35, 2735–2743.
- 73 J. H. Cardellina, H. R. Bokesch, T. C. McKee and M. R. Boyd, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 1011–1014.
- 74 M. T. Flavin, J. D. Rizzo, A. Khilevich, A. Kucherenko, A. K. Sheinkman, V. Vilaychack, L. Lin, W. Chen, E. M. Greenwood, T. Pengsuparp, J. M. Pezzuto, S. H. Hughes, T. M. Flavin, M. Cibulski, W. A. Boulanger, R. L. Shone and Z. Q. Xu, J. Med. Chem., 1996, 39, 1303–1313.
- 75 A. Kucherenko, M. T. Flavin, W. A. Boulanger, A. Khilevich, R. L. Shone, J. D. Rizzo, A. K. Sheinkman and Z. Q. Xu, *Tetrahedron Lett.*, 1995, 36, 5475–5478.
- 76 A. Khilevich, J. D. Rizzo, M. T. Flavin, A. K. Sheinkman, A. Mar, A. Kucherenko, C. Yan, S. Dzekhtser, D. Brankovic, L. Lin, J. Liu, T. M. Rizzo and Z. Q. Xu, Synth. Commun., 1996, 20, 3757–3771.
- 77 B. Chenera, M. L. West, J. A. Finkelstein and G. B. Dreyer, *J. Org. Chem.*, 1993, **58**, 5605–5606.

78 A. L. Gemal and J. L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454–5459.

- 79 L. Crombie, R. C. F. Jones and C. J. Palmer, *J. Chem. Soc.*, *Perkin Trans.* 1, 1987, 317–331.
- 80 C. J. Palmer and J. L. Josephs, *J. Chem. Soc., Perkin Trans.* 1, 1995, 3135–3151.
- 81 T. C. McKee, J. H. Cardellina, G. B. Dreyer and M. R. Boyd, *J. Nat. Prod.*, 1995, **58**, 916–920.
- 82 R. Pawar, T. Das, S. Mishra, Nutan, B. Pancholi, S. K. Gupta and S. V. Bhat, *Bioorg. Med. Chem. Lett.*, 2014, 24, 302–307.
- 83 T. Konishi, M. Azuma, R. Itoga, S. Kiyosawa, Y. Fujiwara and Y. Shimada, *Chem. Pharm. Bull.*, 1996, 44, 229–231.
- 84 D. Kenifield, G. Bunkers, G. Strobel and F. Sugawara, In: Ref., 1989, 26, 319–335.
- 85 M. F. Braulio, Nat. Prod. Rep., 2001, 18, 650.
- 86 S. V. Bhat, Life Chem. Rep., 1994, 12, 137.
- 87 D. J. Lee and W. E. Robinson Jr, *Antimicrob. Agents Chemother.*, 2006, **50**, 134–142.
- 88 H. Jayasuriya, Z. Guan, J. D. Polishook, A. W. Dombrowski, P. J. Felock, D. J. Hazuda and S. B. Singh, *J. Nat. Prod.*, 2003, **66**, 551–553.
- 89 D. F. Chen, S. X. Zhang, L. Xie, J. X. Xie, K. Chen, Y. Kashiwada, B. N. Zhou, P. Wang, L. M. Cosentino and K. H. Lee, *Bioorg. Med. Chem.*, 1997, 5, 1715–1723.
- 90 T. Fujihashi, H. Hara, T. Sakata, K. Mori, H. Higuchi, A. Tanaka, H. Kaji and A. Kaji, Antimicrob. Agents Chemother., 1995, 39, 2000–2007.
- 91 X. W. Yang, H. Miyanshiro, M. Hattori, T. Namba, Y. Tezuka, T. Kikuchi, D. F. Chen, G. J. Xu, T. Hori, M. Extine and H. Mizuno, *Chem. Pharm. Bull.*, 1992, **40**, 1510–1516.
- 92 Y. Ikeya, H. Taguchi, I. Yosioka and H. Kobayashi, *Chem. Pharm. Bull.*, 1979, 27, 1583.
- 93 R. S. Coleman and S. R. Gurrala, *Org. Lett.*, 2005, 7, 1849–1852.
- 94 Y. Y. Chen, Z. B. Shu and L. N. Li, *Sci. Sin.*, 1976, **19**, 276–290.
- 95 Y. Ikeya, H. Taguchi and I. Yosioka, *Chem. Pharm. Bull.*, 1982, **30**, 3207.
- 96 J. X. Xie, J. Zhou, C. Z. Zhang, J. H. Yang and J. X. Chen, *Sci. Sin.*, 1983, **26**, 1291.
- 97 P. Shah, D. Naik, N. Jariwala, D. Bhadane, S. Kumar, S. Kulkarni, K. K. Bhutani and I. P. Singh, *Bioorg. Chem.*, 2018, 80, 591-601.
- 98 J. L. McCormick, T. C. Mckee, J. H. Cardellina and M. R. Boyd, J. Nat. Prod., 1996, 59, 469–471.
- 99 C. Benard, F. Zouhiri, M. Normand-Bayle, M. Danet, D. Desmaele, H. Leh, J. F. Mouscadet, G. Mbemba, C. M. Thomas, S. Bonnenfant, M. L. Bret and J. D'Angelo, *Bioorg. Med. Chem. Lett.*, 2004, 14, 2473–2476.
- 100 Q. Q. He, S. X. Gu, J. Liu, H. Q. Wu, X. Zhang, L. M. Yang, Y. T. Zheng and F. E. Chen, *Bioorg. Med. Chem.*, 2011, 19, 5039–5045.
- 101 S. Mahajan, S. Gupta, N. Jariwala, D. Bhadane, K. K. Bhutani, S. Kulkarni and I. P. Singh, *Lett. Drug Des. Discovery*, 2018, **15**, 937–944.

- 102 S. Chen, R. Chen, M. He, R. Pang, Z. Tan and M. Yang, *Bioorg. Med. Chem.*, 2009, 17, 1948–1956.
- 103 R. Musiol, Curr. Pharm. Des., 2013, 19, 1835-1849.
- 104 A. Marella, O. P. Tanwar, R. Saha, M. R. Ali, S. Srivastava, M. Akhter, M. Shaquiquzzaman and M. M. Alam, *Saudi Pharm. J.*, 2013, 21, 1–12.
- 105 M. Billamboz, V. Suchaud, F. Bailly, C. Lion, J. Demeulemeester, C. Calmels, M. L. Andréola, F. Christ, Z. Debyser and P. Cotelle, ACS Med. Chem. Lett., 2013, 4, 606–611.
- 106 E. Serrao, B. Debnath, H. Otake, Y. Kuang, F. Christ, Z. Debyser and N. Neamati, *J. Med. Chem.*, 2013, 56, 2311–2322.
- 107 J. F. Mouscadet and D. Desmaele, *Molecules*, 2010, 15, 3048–3078.
- 108 M. J. Cheng, K. H. Lee, I. L. Tsai and I. S. Chen, *Bioorg. Med. Chem.*, 2005, 13, 5915–5920.
- 109 C. L. Sun, R. F. Pang, H. Zhang and M. Yang, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3257–3262.
- 110 K. R. Romines and R. A. Chrusciel, Curr. Med. Chem., 1995, 2, 825.
- 111 J. V. Prasad, F. E. Boyer, J. M. Domagala, E. L. Ellsworth, C. Gajda, H. W. Hamilton, S. E. Hagen, L. J. Markoski, B. A. Steinbaugh, B. D. Tait, C. Humblet, E. A. Lunney, A. Pavlovsky, J. R. Rubin, D. Ferguson, N. Graham, T. Holler, D. Hupe, C. Nouhan, P. J. Tummino, A. Urumov, E. Zeikus, G. Zeikus, S. J. Gracheck and J. W. Erickson, *Bioorg. Med. Chem.*, 1999, 7, 2775–2800.
- 112 S. Thaisrivongs, D. L. Romero, R. A. Tommasi, M. N. Janakiraman, J. W. Strohbach, S. R. Tuner, C. Biles, R. R. Morge, P. D. Johnson, P. A. Aristoff, P. K. Tomich, J. C. Lynn, M. M. Horng, K. T. Chong, R. R. Hinshaw, W. J. Howe, B. C. Finzel and K. D. Watenpaugh, *J. Med. Chem.*, 1996, 39, 4630–4642.
- 113 H. I. Skulnick, P. D. Johnson, W. J. Howe, P. K. Tomich, K. T. Chong, K. D. Watenpaugh, M. N. Janakiraman, L. A. Dolak, J. P. McGrath and J. C. Lynn, *J. Med. Chem.*, 1995, 38, 4968–4971.
- 114 C. M. Abreu, S. L. Price, E. N. Shirk, R. D. Cunha, L. F. Pianowski, J. E. Clements, A. Tanuri and L. Gama, *PLoS One*, 2014, **9**, e97257.
- 115 C. Jiang, P. Luo, Y. Zhao, J. Hong, S. L. Morris-Natschke, J. Xu, C. H. Chen, K. H. Lee and Q. Gu, *J. Nat. Prod.*, 2016, 79, 578–583.
- 116 M. Zhou, L. Deng and V. Lacoste, *J. Virol.*, 2004, **78**, 13522–13533.
- 117 A. R. Jassbi, Phytochemistry, 2006, 67, 1977-1984.
- 118 P. Hampson, K. Wang and J. M. Lord, *Drugs Future*, 2005, 30, 1003–1005.
- 119 R. Barrero, B. Chapman, Y. Yang, P. Moolhuijzen and G. Keeble-Gagne`re, *BMC Genomics*, 2011, **12**, 600.
- 120 R. Norman, JAMA Dermatol., 2013, 149, 666-670.
- 121 L. Jorgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer and J. Felding, *Science*, 2013, **341**, 878–882.
- 122 M. Nirmala, A. Samundeeswari and P. Sankar, *Res Plant Biol.*, 2011, **1**, 1–14.

RSC Advances

- 124 L. Feng, R. C. Larue, A. Slaughter, J. J. Kessl and M. Kvaratskhelia, *Curr. Top. Microbiol. Immunol.*, 2015, 389, 93–119.
- 125 M. Jaskolski, J. N. Alexandratos, G. Bujacz and A. Wlodawer, *FEBS J.*, 2009, **276**, 2926–2946.
- 126 M. Li, M. Mizuuchi, T. R. Burke Jr and R. Craigie, *EMBO J.*, 2006, 25, 1295–1304.
- 127 A. Engelman and P. Cherepanov, *Nat. Rev. Microbiol.*, 2012, **10**, 279–290.
- 128 M. Llano, D. T. Saenz, A. Meehan, P. Wongthida, M. Peretz, W. H. Walker, W. Teo and E. M. Poeschla, *Science*, 2006, 314, 461–464.
- 129 K. Busschots, J. Vercammen, S. Emiliani, R. Benarous, Y. Engelborghs, F. Christ and Z. Debyser, *J. Biol. Chem.*, 2005, **280**, 17841–17847.
- 130 P. Cherepanov, G. Maertens, P. Proost, B. Devreese, J. V. Beeumen, Y. Engelborghs, E. D. Clercq and Z. Debyser, J. Biol. Chem., 2003, 278, 372–381.
- 131 L. Q. Al-Mawsawi and N. Neamati, *Trends Pharmacol. Sci.*, 2007, **28**, 526–535.
- 132 M. C. Shun, N. K. Raghavendra, N. Vandegraaff, J. E. Daigle, S. Hughes, P. Kellam, P. Cherepanov and A. Engelman, *Genes Dev.*, 2007, **21**, 1767–1778.
- 133 P. Cherepanov, E. Devroe, P. A. Silver and A. Engelman, *J. Biol. Chem.*, 2004, **279**, 48883–48892.
- 134 F. Christ, A. Voet, A. Marchand, S. Nicolet, B. A. Desimmie, D. Marchand, D. Bardiot, N. J. Van der Veken, B. Van Remoortel, S. V. Strelkov, M. D. Maeyer, P. Chaltin and Z. Debyser, *Nat. Chem. Biol.*, 2010, 6, 442–448.
- 135 A. Sharma, A. Slaughter, N. Jena, L. Feng, J. J. Kessl, H. J. Fadel, N. Malani, F. Male, L. Wu, E. Poeschla, F. D. Bushman, J. R. Fuchs and M. Kvaratskhelia, *PLoS Pathog.*, 2014, 10, e1004171.
- 136 L. D. Fader, E. Malenfant, M. Parisien, R. Carson, F. Bilodeau, S. Landry, M. Pesant, C. Brochu, S. Morin, C. Chabot, T. Halmos, Y. Bousquet, M. D. Bailey, S. H. Kawai, R. Coulombe, S. LaPlante, A. Jakalian, P. K. Bhardwaj, D. Wernic, P. Schroeder, M. Amad, P. Edwards, M. Garneau, J. Duan, M. Cordingley, R. Bethell, S. W. Mason, M. Bos, P. Bonneau, M. A. Poupart, A. M. Faucher, B. Simoneau, C. Fenwick, C. Yoakim and Y. Tsantrizos, ACS Med. Chem. Lett., 2014, 5, 422–427.
- 137 N. Van Bel, Y. van der Velden, D. Bonnard, E. L. Rouzic, A. T. Das, R. Benarous and B. Berkhout, *PLoS One*, 2014, **9**, e103552.
- 138 L. D. Luca, F. Morreale, F. Christ, Z. Debyser, S. Ferro and R. Gitto, *Eur. J. Med. Chem.*, 2013, **68**, 405–411.
- 139 D. R. Hirsch, D. V. Schiavone, A. J. Berkowitz, L. A. Morrison, T. Masaoka, J. A. Wilson, E. Lomonosova, H. Zhao, B. S. Patel, S. H. Datla, S. G. Hoft, S. J. Majidi, R. K. Pal, E. Gallicchio, L. Tang, J. E. Tavis, S. F. J. Le Grice, J. A. Beutler and R. P. Murelli, *Org. Biomol. Chem.*, 2018, 16, 62.

- 140 C. Meck, M. P. D'Erasmo, D. R. Hirsch and R. P. Murelli, Med. Chem. Commun., 2014, 5, 842–852.
- 141 S. R. Budihas, I. Gorshkova, S. Gaidamakov, A. Wamiru, M. K. Bona, M. M. A. Parniak, R. J. Crouch, J. B. McMahon, J. A. Beutler and S. F. J. L'Grice, *Nucleic Acids Res.*, 2005, 33, 1249–1256.
- 142 G. Sennari, T. Hirose, M. Iwatsuki, S. Omura and T. Sunazuka, *Chem. Commun.*, 2014, **50**, 8715–8718.
- 143 L. D. Ferretti and J. H. Richards, Proc. Natl. Acad. Sci. U. S. A., 1960, 46, 1438–1444.
- 144 J. Davison, A. al. Fahad, M. Cai, Z. Song, S. Y. Yehia, C. M. Lazarus, A. M. Bailey, T. J. Simpson and R. J. Cox, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, 7642–7647.
- 145 J. H. Birkinshaw, A. H. Chambers and H. Raistrick, *Biochem. J.*, 1942, **36**, 242–251.
- 146 D. A. Nugiel, K. Jacobs, T. Worley, M. Patel, R. F. Kaltenbach, D. F. Meyer, P. K. Jadhav, G. V. D'Lucca, T. E. Smyser, R. M. Klabe, L. T. Bacheler, M. M. Rayner and S. P. Seitz, *J. Med. Chem.*, 1996, 39, 2156–2169.
- 147 D. D. Ho, A. U. Neumann, A. S. Perelson, W. Chen, J. M. Leonard and M. Markowitz, *Nature*, 1995, 373, 123– 126.
- 148 K. E. B. Parkes, D. J. Bushnell, P. H. Crackett, S. J. Dunsdon, A. C. Freeman, M. P. Gunn, R. A. Hopkins, R. W. Lambert, J. A. Martin, J. H. Merrett, S. Redshaw, W. C. Spurden and G. J. Thomas, J. Org. Chem., 1994, 59, 3656–3664.
- 149 S. Thaisrivongs, Annu. Rep. Med. Chem., 1994, 29, 133-144.
- 150 D. P. Getman, G. A. DeCrescenzo, R. M. Heintz, K. L. Reed, J. J. Talley, M. L. Bryant, M. Clare, K. A. Houseman, J. J. Marr, R. A. Mueller, M. L. Vazquez, H. S. Shieh, W. C. Stallings and R. A. Stegeman, J. Med. Chem., 1993, 36, 288-291.
- C. H. Chang, M. C. Schadt, F. A. Lewandowski, R. DeLoskey,
 J. Duke, J. C. Calabrese, P. Y. S. Lam, P. K. Jadhav,
 C. J. Eyerman, C. N. Hodge and P. C. Weber, *J. Biol. Chem.*, 1998, 273, 12325–12398.
- 152 C. N. Hodge, P. E. Aldrich, L. T. Bacheler, C. H. Chang, C. J. Eyerman, M. Grubb, D. A. Jackson, P. K. Jadhav, B. Korant, P. Y. S. Lam, M. B. Maurin, J. L. Meek, M. J. Otto, M. M. Rayner, T. R. Sharpe, L. Shum, D. L. Winslow and S. EricksonViitanen, *Chem. Biol.*, 1996, 3, 301–314.
- 153 P. Y. S. Lam, Y. Ru, P. K. Jadhav, P. E. Aldrich, G. V. De Lucca, C. J. Eyermann, C. H. Chang, G. Emmett, E. R. Holler, W. F. Daneker, L. Li, P. N. Confalone, R. J. McHugh, Q. Han, R. Li, J. A. Markwalder, S. P. Seitz, T. R. Sharpe, L. T. Bacheler, M. M. Rayner, R. M. Klabe, L. Shum, D. L. Winslow, D. M. Kornhauser, D. A. Jackson, S. Erickson-Viitanen and C. N. Hodge, J. Med. Chem., 1996, 39, 3514–3525.
- 154 A. W. Konradi and S. F. Pederson, *J. Org. Chem.*, 1992, 57, 28–32.
- 155 S. Sasatani, T. Miyazaki, K. Maruoka and H. Yamamoto, *Tetrahedron Lett.*, 1983, 24, 4711–4712.
- 156 J. I. Levin, E. Turos and S. M. Weinreb, *Synth. Commun.*, 1982, **12**, 989–993.
- 157 O. Mitsunobu, Synthesis, 1981, 1-28.