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

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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.

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1. Introduction

The human immunodeficiency virus (HIV), which causes AIDS, is primarily responsible for the most severe public health challenges.¹ 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.^{8–13} In drug discovery, numerous heterocycles such as pyrans, flavones, coumarins, pyrimidones, thiazoles, xanthenes, imidazoles, pyrazoles, isoxazolines and oxazolindines have been considered for the development of potential novel lead molecules.^{14–16} 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, IC₅₀ values, and mechanistic insights revealed during the biological evaluation of compounds against HIV together with interesting key findings. The interactions

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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-Hydroxypyrrone-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

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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



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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.



lactone andrographolide **1** (IC_{50} (μM) = 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** (IC_{50} (μM) = 2.10), 3',4'-methylenedioxy-phenyl **3** (IC_{50} (μM) = 2.75), 2',4'-dihydroxy-phenyl **4** (IC_{50} (μM) = 1.09), 4'-chlorophenyl **5** (IC_{50} (μM) = 9.94), 4'-hydroxy-3'-methoxy-phenyl **6** (IC_{50} (μM) = 6.09) and 3'-nitro-phenyl **7** (IC_{50} (μM) = 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** (IC_{50} (μM) = 0.83 and 2'-hydroxybenzoyl **9** (IC_{50} (μM) = 84.24). Further, upon treatment with *p*-toluene sulfonyl isocyanate, another derivative of *p*-toluene sulfonyl amino carbonyl andrographolide, **10** (IC_{50} (μM) = 2.08), was obtained, as depicted in Fig. 1c.³⁶



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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. Efang. 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-1*H*-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-



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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.



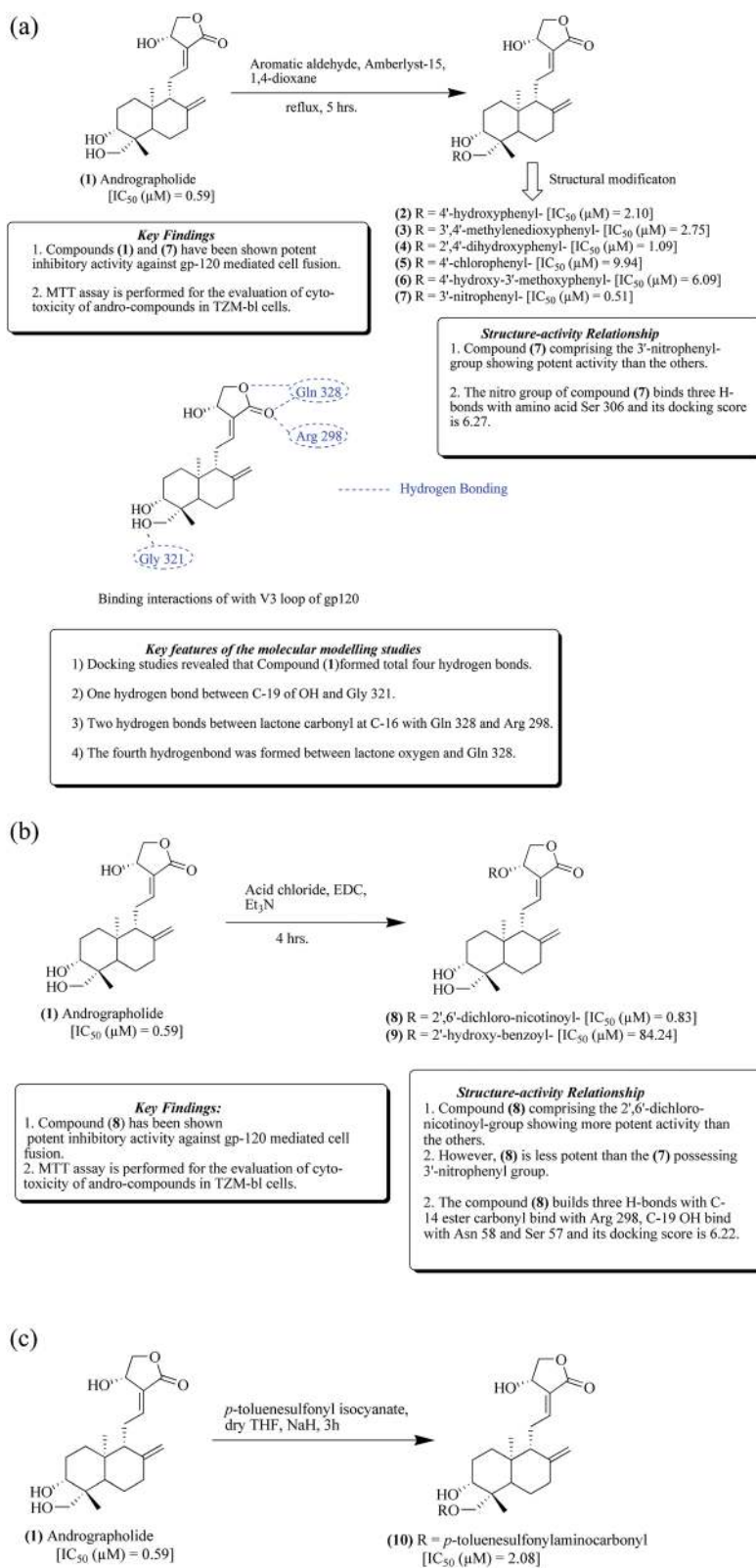


Fig. 1 (a) Andrographolide-based (1–7) analogs. (b) Andrographolide analogs (8 and 9). (c) Structure of andrographolide-based analog (10).

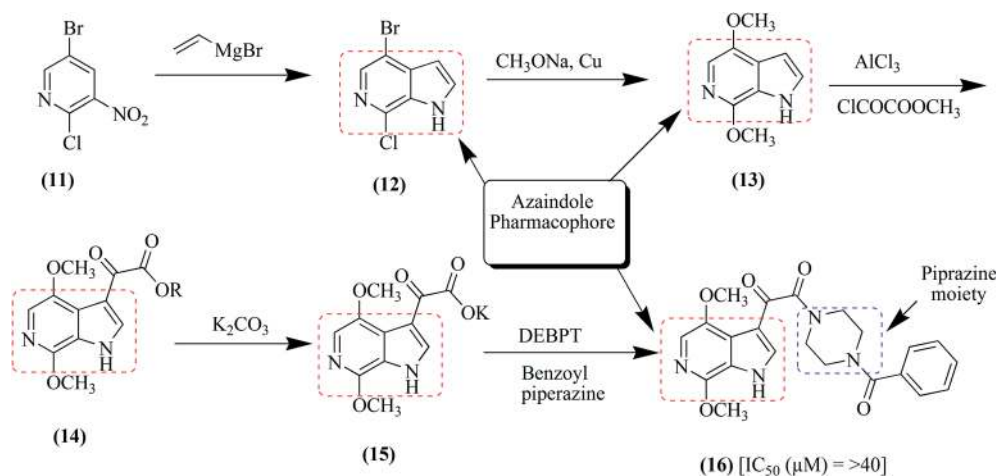


nitropyridine **11** as the starting material is shown in Fig. 2. The reactant **11** was treated with vinyl magnesium bromide at very low temperature to give another compound, 4-bromo-7-chloro-6-azaindole **12** in 35% yield.⁴⁴

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.^{45,46} 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 IC_{50} value of $\geq 40 \mu M$.^{47,48} 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.³⁷

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 chloroquine-resistant and chloroquine-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}



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 permeability 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.



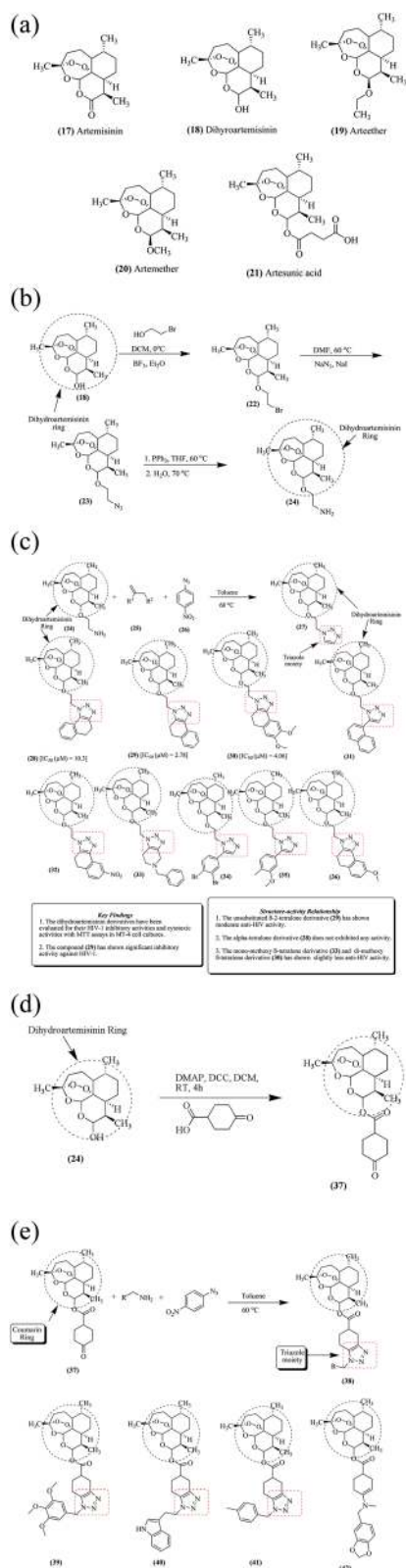


Fig. 3 (a) Artemisinin analogs 17 to 21. (b) Synthetic route for the preparation of artemisinin analogs. (c) Artemisinin derivatives together with their SARs and key features. (d) Synthesis of a ketone precursor from dihydroartemisinin. (e) Triazole-based dihydroartemisinin ketone precursor analogs (38–42).

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-(10 β -dihydro artemisinoxy)ethyl azide **23** in 95% yield. The resultant compound **23** was finally converted into an amine precursor 2-(10 β -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 α -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



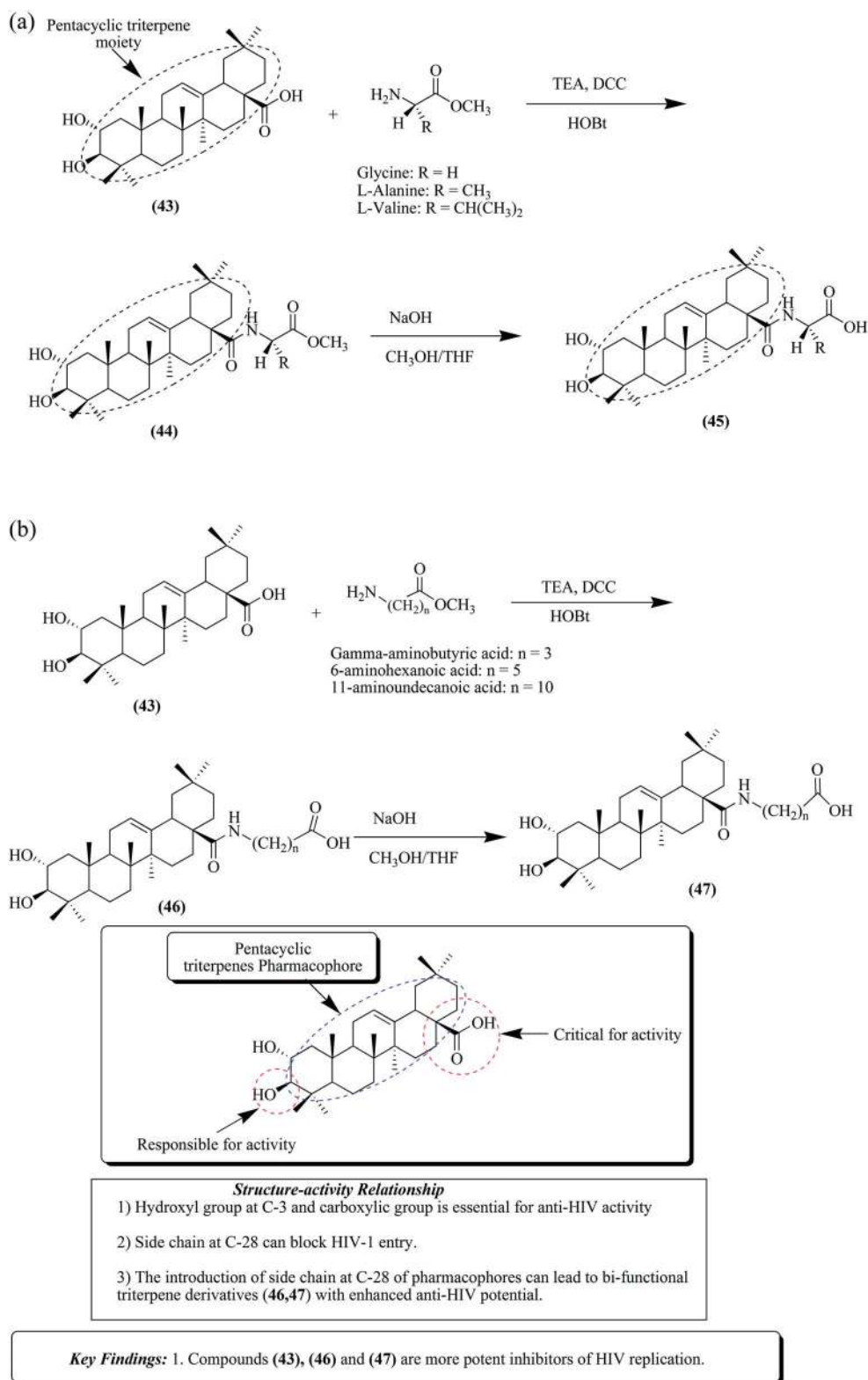
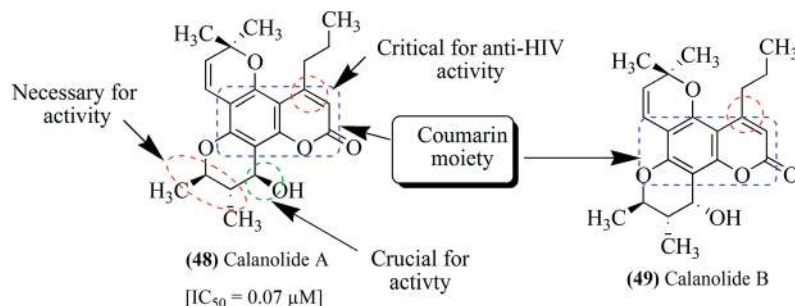


Fig. 4 (a) Synthesis of maslinic acid derivatives from α -amino acids. (b) Synthesis of maslinic acid analogs from ω -amino acids.





Structure-activity Relationship

- 1) Introduction of bulky substituents is essential at C-4 position to enhance 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 responsible for activity.
- 4) Stereochemistry of hydroxyl group at C-12 is also crucial for the activity.
- 5) Compound (48) shows significant anti-HIV activity 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 μ M and 22 μ M, 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 μ M and 12 μ M, 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 μ 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 μ M and 20 μ M, respectively.

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

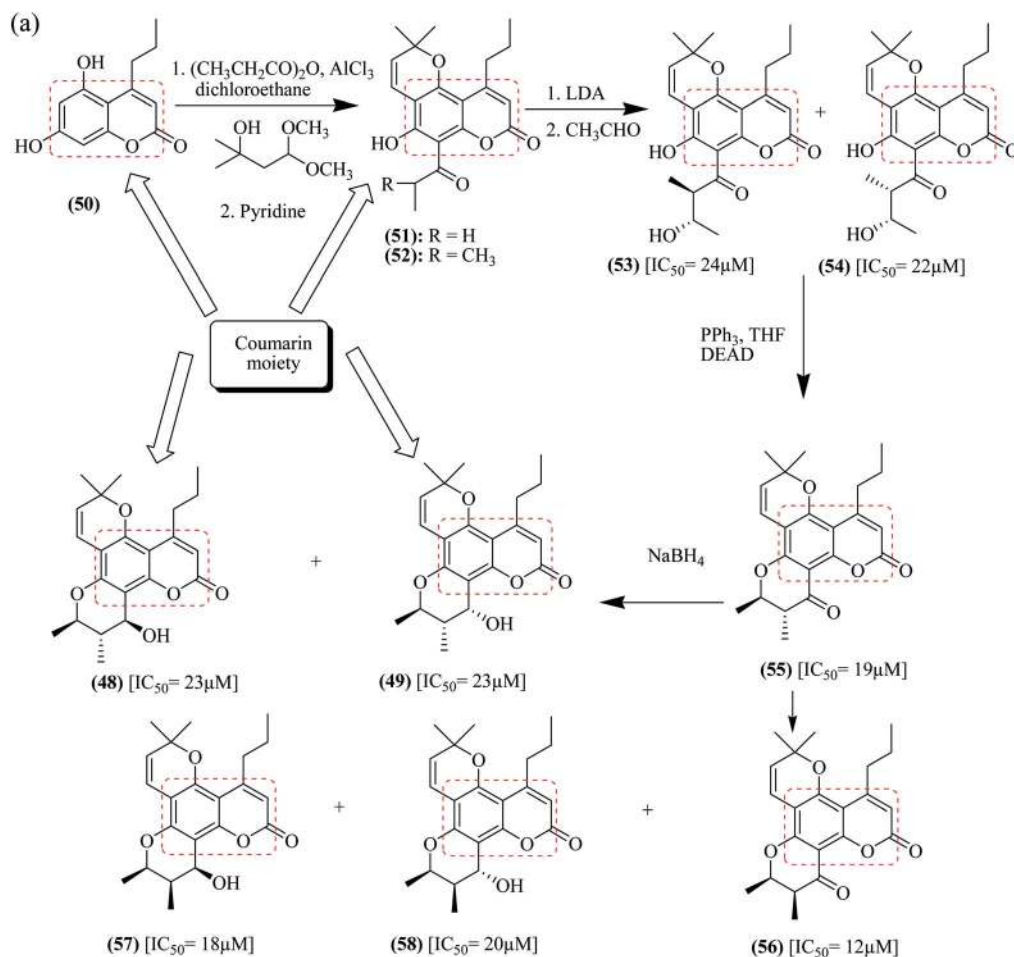
Zembower *et al.* reported a simple and direct modification of ring C of calanolides, which produced potent analogues, as depicted in Fig. 6b. Intermediate compound 51 underwent alkylation in the presence of iodo ethane to produce ketone intermediate 59 ($IC_{50} = 6.6 \mu$ M). This intermediate was 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.⁸² 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 µM, but the compound (58) shows weak anti-viral activity.

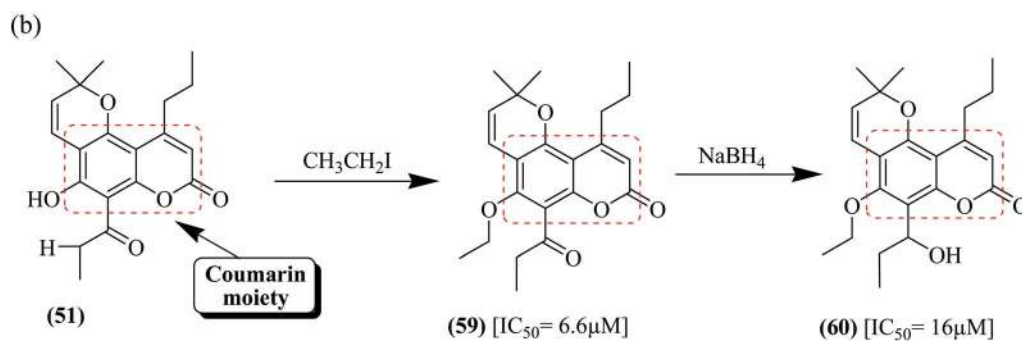


Fig. 6 (a) Synthesis of racemic calanolide A together with important key findings. (b) Synthesis of calanolide A analogs.



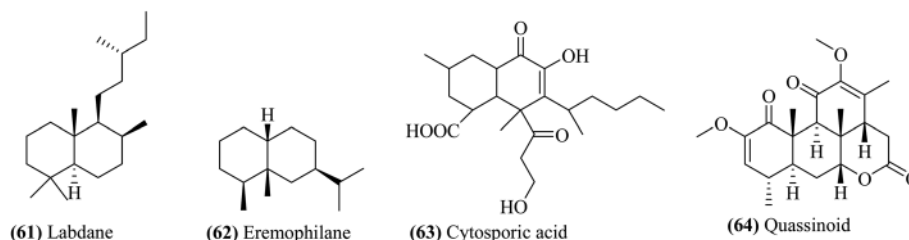


Fig. 7 Chemical structures of labdane analogs (61–64).

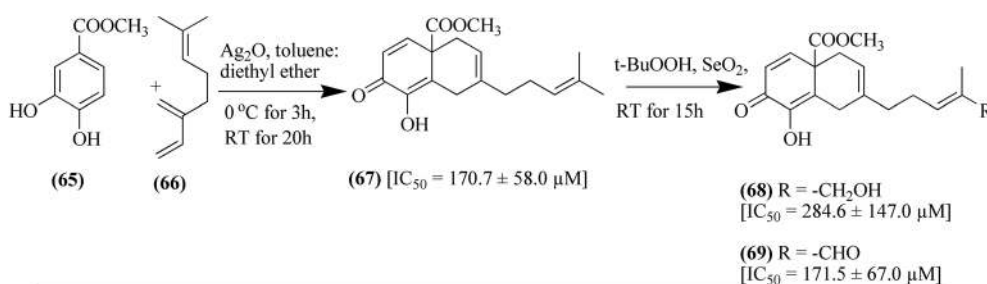
para adduct. It was then subjected to treatment with selenium dioxide and *tert*-butyl peroxide to produce compounds **68** and **69**. Similarly compound **65** upon treatment with ocimene **70** resulted in the formation of compounds **71–74**, as depicted in Fig. 9. Furthermore, a Diels–Alder reaction 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 IC_{50} 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*-



Key Findings

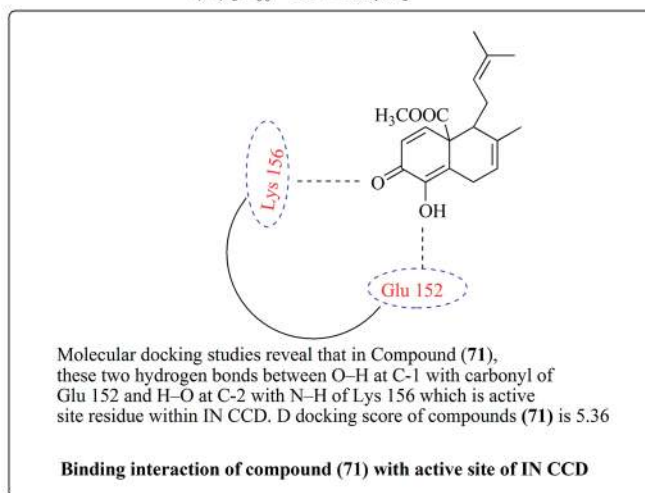
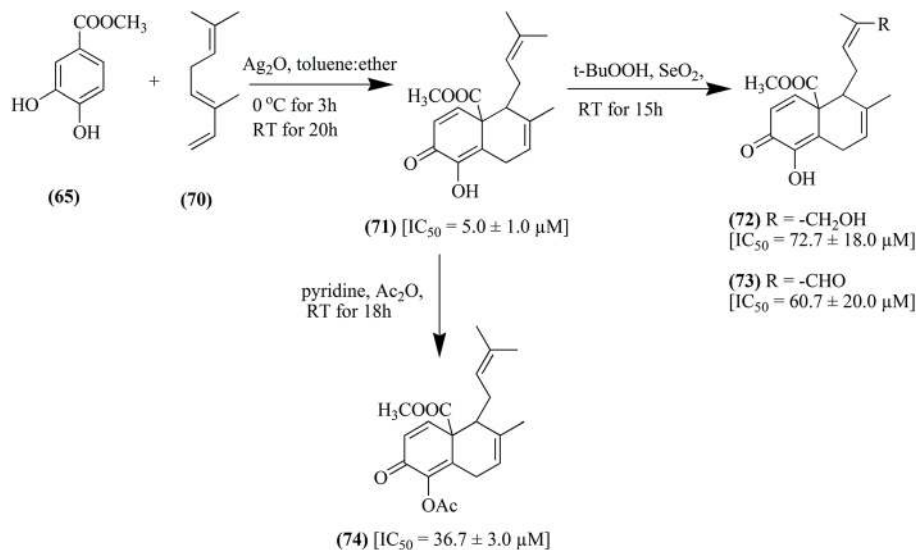
- All the compounds have been evaluated *in vitro* by using MTT assay on TZM-bl cells for their cytotoxicity.
- Further, the compounds have been tested by using receptor-gene based cell assay system for their *in vitro* inhibitory activity against HIV-1 infection.
- Compound (**67**) has shown inhibition of HIV-1 integrase enzyme.
- 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-HIV activity.
- The structural modifications of compound (**67**) by Se_2O oxidation causes decrease in the activity as compare to the compound (**67**) itself.
- 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).





Key Findings

1. Compounds (72-74) have been evaluated by using MTT assay.
2. Compounds (71-74) have shown inhibitory activity against the HIV-1 integrase enzyme.

Structure-activity Relationship

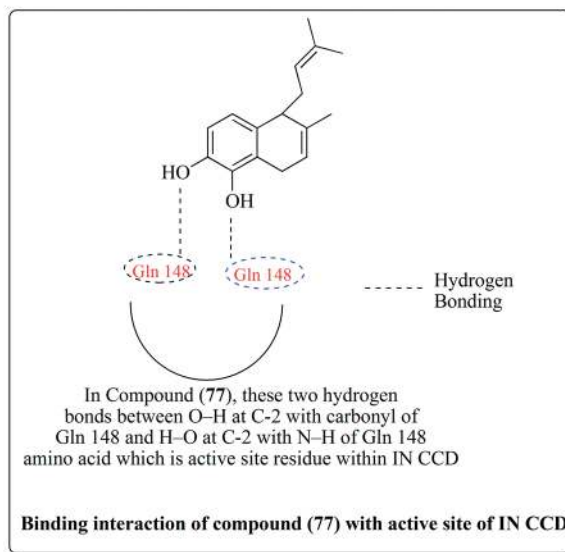
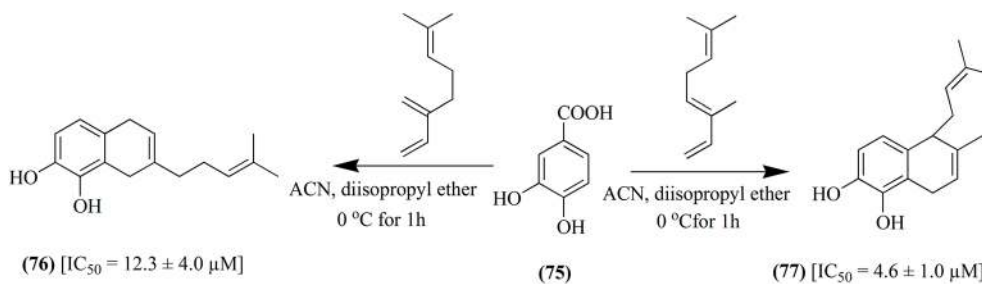
1. Compound (71) with o-quinol moiety exhibits significant anti-HIV activity.
2. In the compound (71), the acyl protection of hydroxyl (OH) group of o-quinol diminishes the activity completely.
3. The docking score of compounds (71), (72), (73) and (74) is given as 5.36, 4.28, 4.33 and 4.68 respectively.

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.

HNO_3 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



**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 μM and the compound (76) has shown the IC_{50} value of 12.3 μM evaluated by using MTT assay.

Structure-activity Relationship

1. 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).

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 $> 100 \mu g mL^{-1}$ towards HIV-1 inhibition, while compound 96 shows significant HIV-1 inhibition with an IC_{50} value of $1.8 \mu g mL^{-1}$.⁸⁹

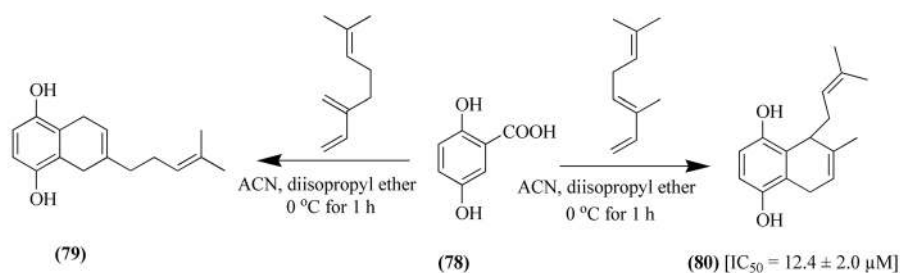
2.8. Quinoline-based analogs

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





Key Findings

1. Compound (80) has shown potent inhibition of HIV-1 integrase enzyme.
2. The compound (80) has shown IC_{50} value of 12.4 μM 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-quinoline **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-(8-methoxyquinolin-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-Hydroxypyrene analogs

The 4-hydroxypyrene 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-hydroxypyrene derivatives has been described into two steps. In first approach (Fig. 17), the dihydro pyrene 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-bromo-dihydro-pyrene was carried out with NBS (*N*-bromosuccinimide), and then the bromide atom was displaced by a suitable thiophenol substituent in the presence of thiophenol,



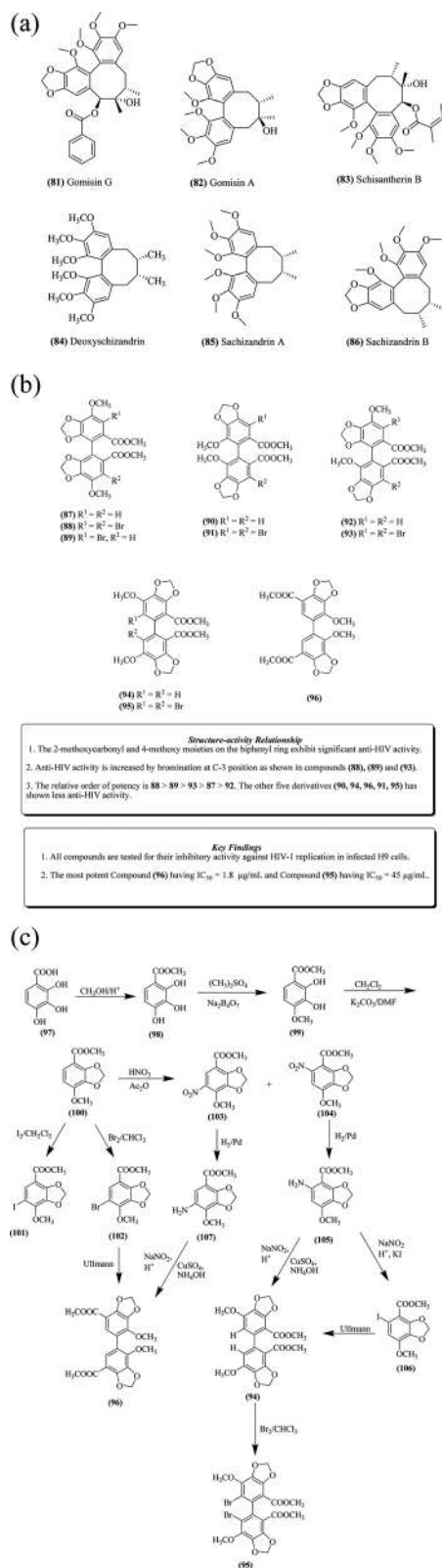


Fig. 12 (a) Chemical structures of natural lignans. (b) Structures of synthetic biphenyl compounds (87 to 96). (c) Synthesis of anti-HIV biphenyl derivatives.

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*.^{114–119} The isolated compounds from these species have been used for the treatment and management of various diseases such as cancer and keratosis.^{120–122} 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-*trans*-cinnamate (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-2-hydroxybenzoic 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)-2-hydroxybenzoates 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 180 and compounds 181 and 182 displayed IC₅₀ values of 94.07 μM, 8.75



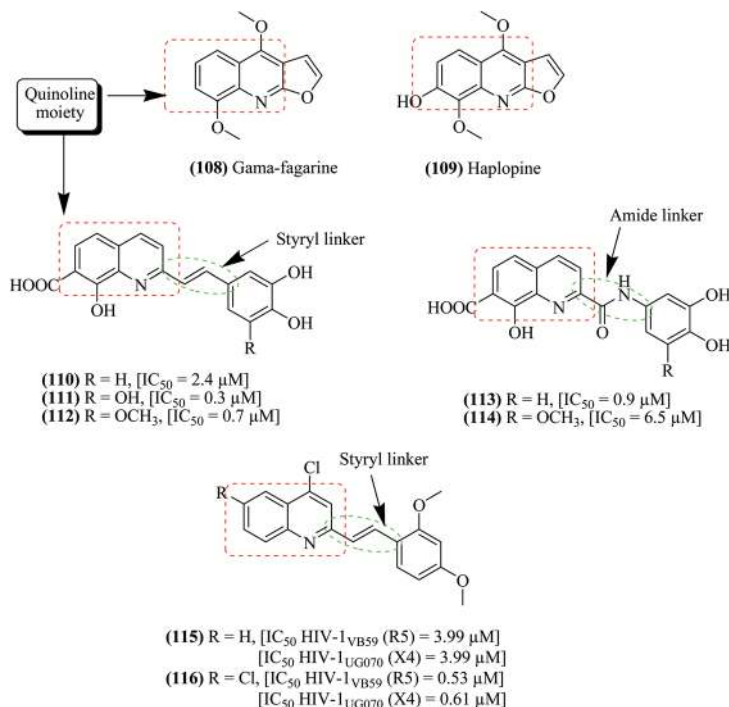


Fig. 13 Quinoline analogs (108–116) possessing amide and styryl linkers with anti-HIV potential.

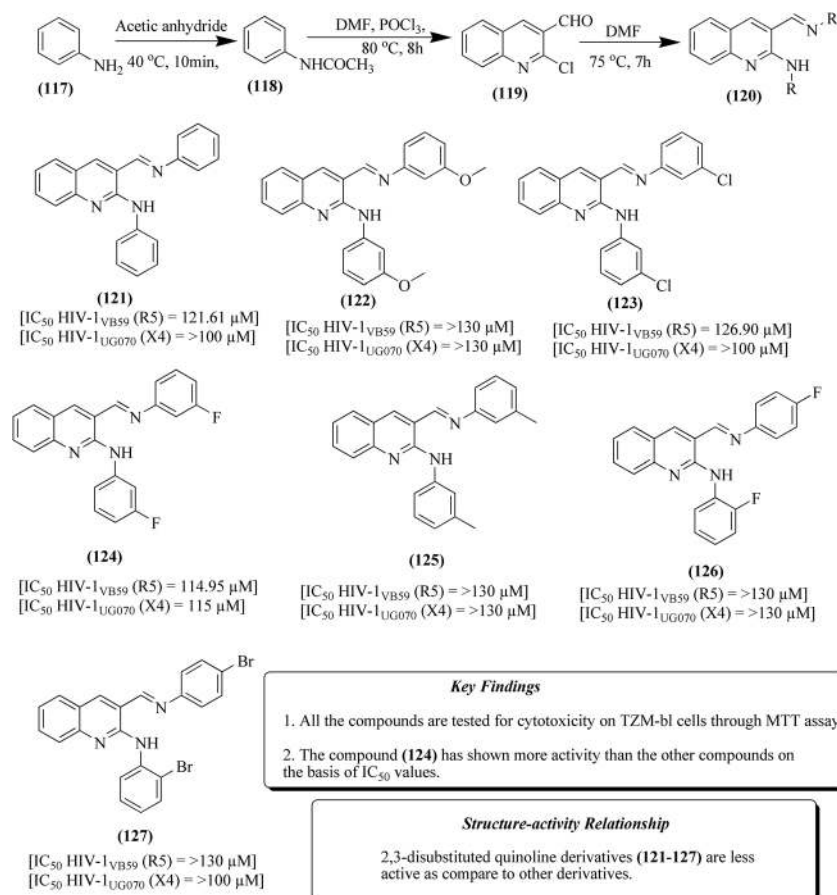


Fig. 14 2,3-Disubstituted quinoline derivatives (121–127).



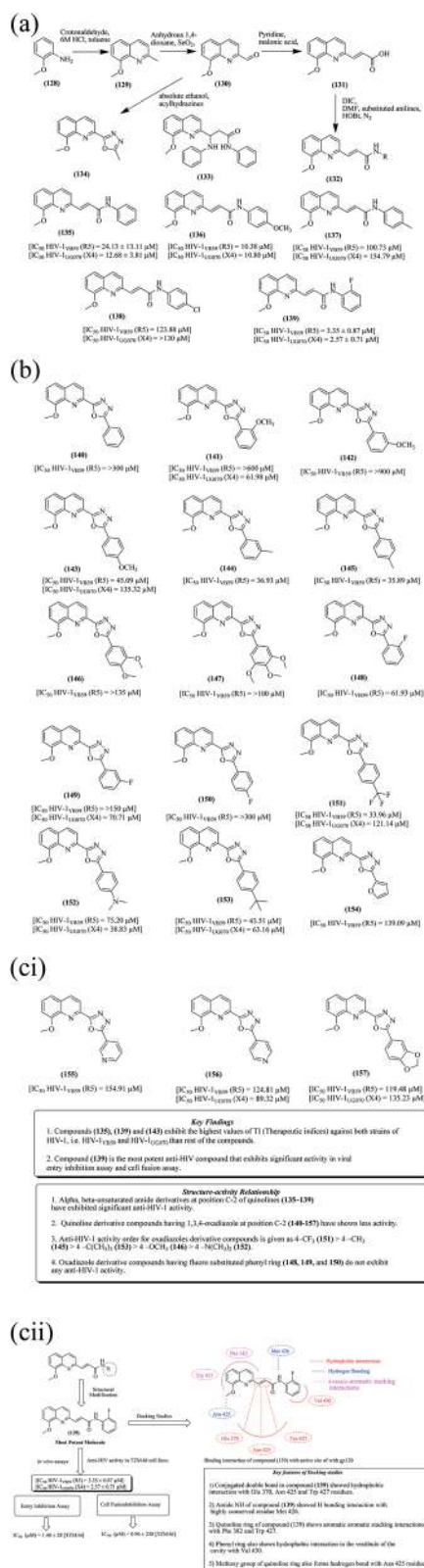


Fig. 15 (a) Synthesis of 2-substituted quinoline derivatives together with the structures of the most potent compounds (**135**–**139**). (b) 2-Substituted quinoline derivatives (**140**–**154**). (c(i)) 2-Substituted quinoline derivatives (**155**–**157**) together with their SAR and important key features.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

μM and $3.28 \mu\text{M}$ against IN-LEDGF/p75 binding, respectively. The most potent compound **182** together with its docking features are also presented in Fig. 21.¹²³

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.¹³⁹ 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 CDCl_3 (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 3,7-dihydroxytropolones obtained from the *Penicillium puberulum* fungus.¹⁴³ These two compounds are considered to be very similar to stipitatic acid **221** and stipitonic acid **223**, which are derivatives of 6-hydroxytropolone compounds.^{144,145} Also, lactone stipitalide **220** was used for the synthesis of stipitatic acid **221**, which was further utilized for the synthesis of stipitonic acid **223**, as depicted in Fig. 27. Puberulonic acid **222** and puberulic acid **224** can also be synthesized from 3,7-dihydroxytropolone. 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**



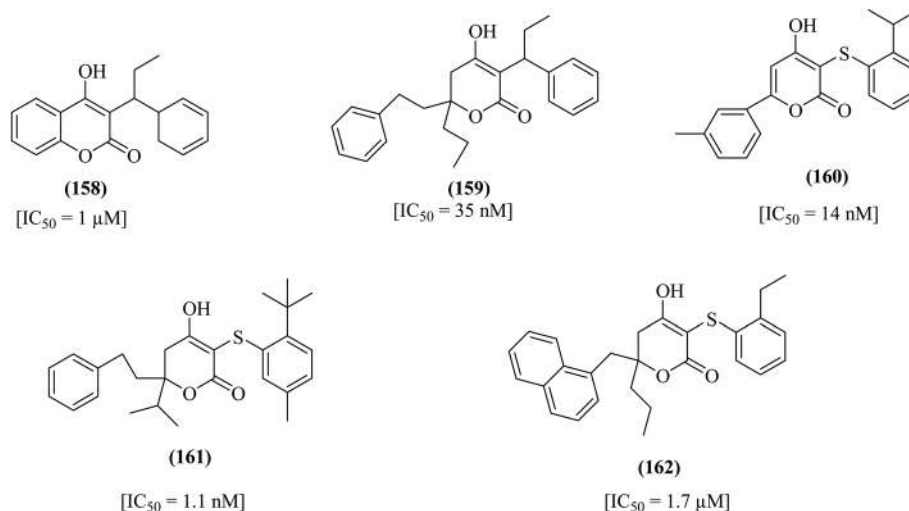
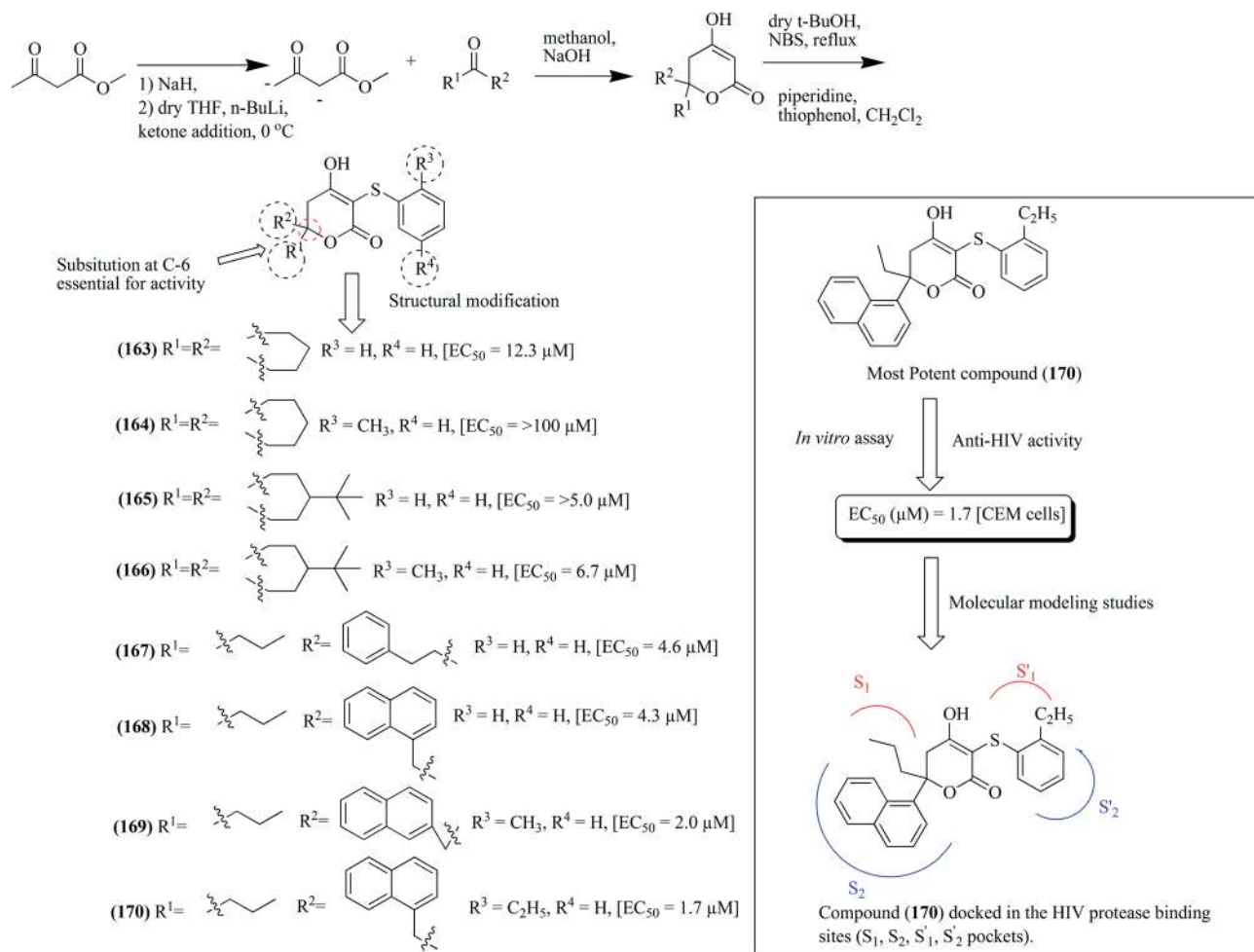


Fig. 16 4-Hydroxypyrrone HIV protease inhibitors (158–162).

**Key Findings**

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

Structure-activity Relationship

1. 4-Hydroxypyrrones having a spirocycle at position C-6 show some inhibitory activity towards HIV protease enzyme.
2. Compounds that have six-membered ring have been shown greater potency.

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



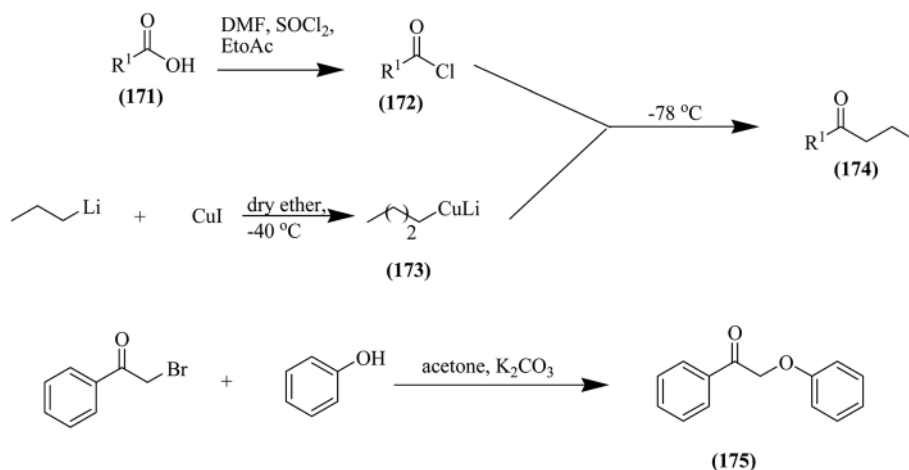


Fig. 18 Synthesis of ketone derivatives.

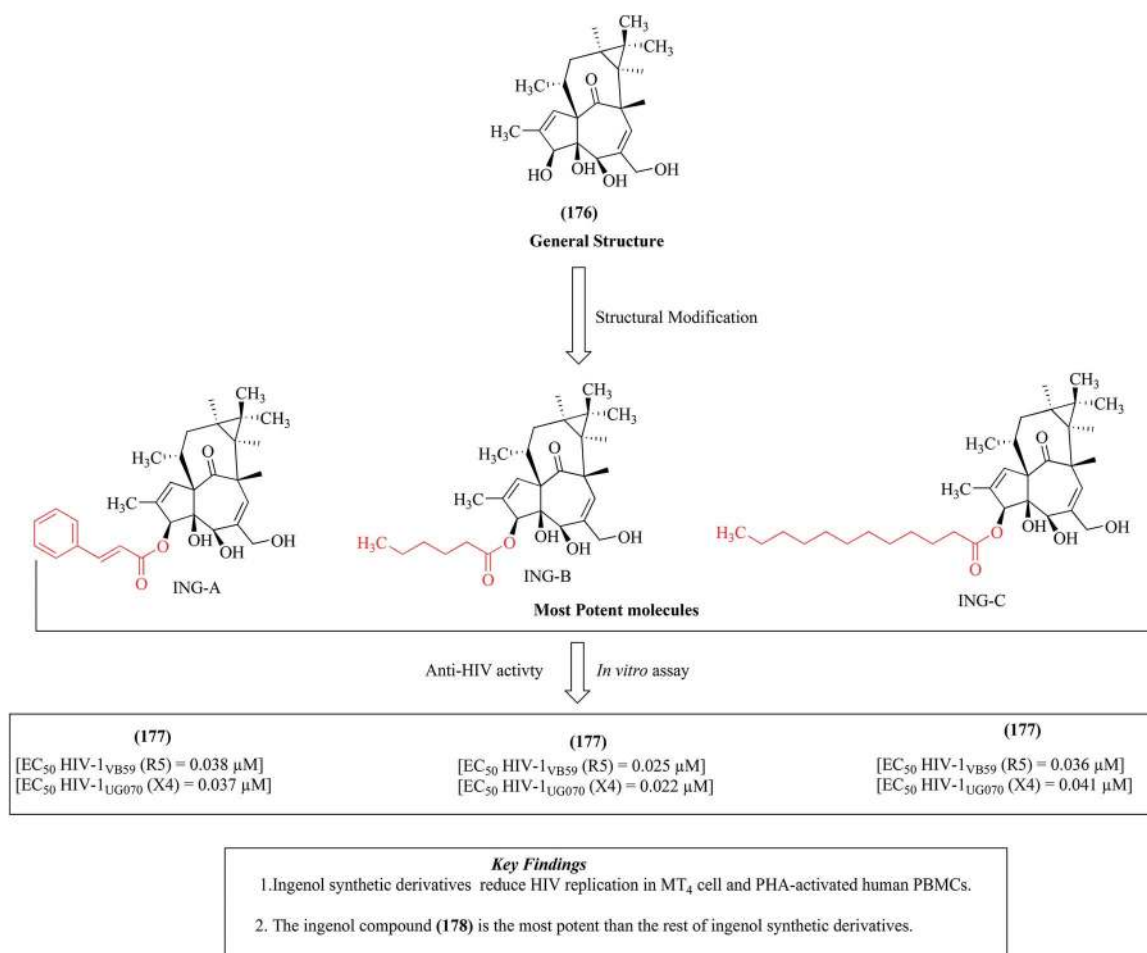


Fig. 19 Structures of the most potent ingenol derivatives (176 to 179).

through various reaction steps such as acetylation, lactonization and demethylation. The 3,7-dihydroxytropolone compounds **216a** and **216b** displayed IC₅₀ values of 1.5 μ M and 1.1 μ M, 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



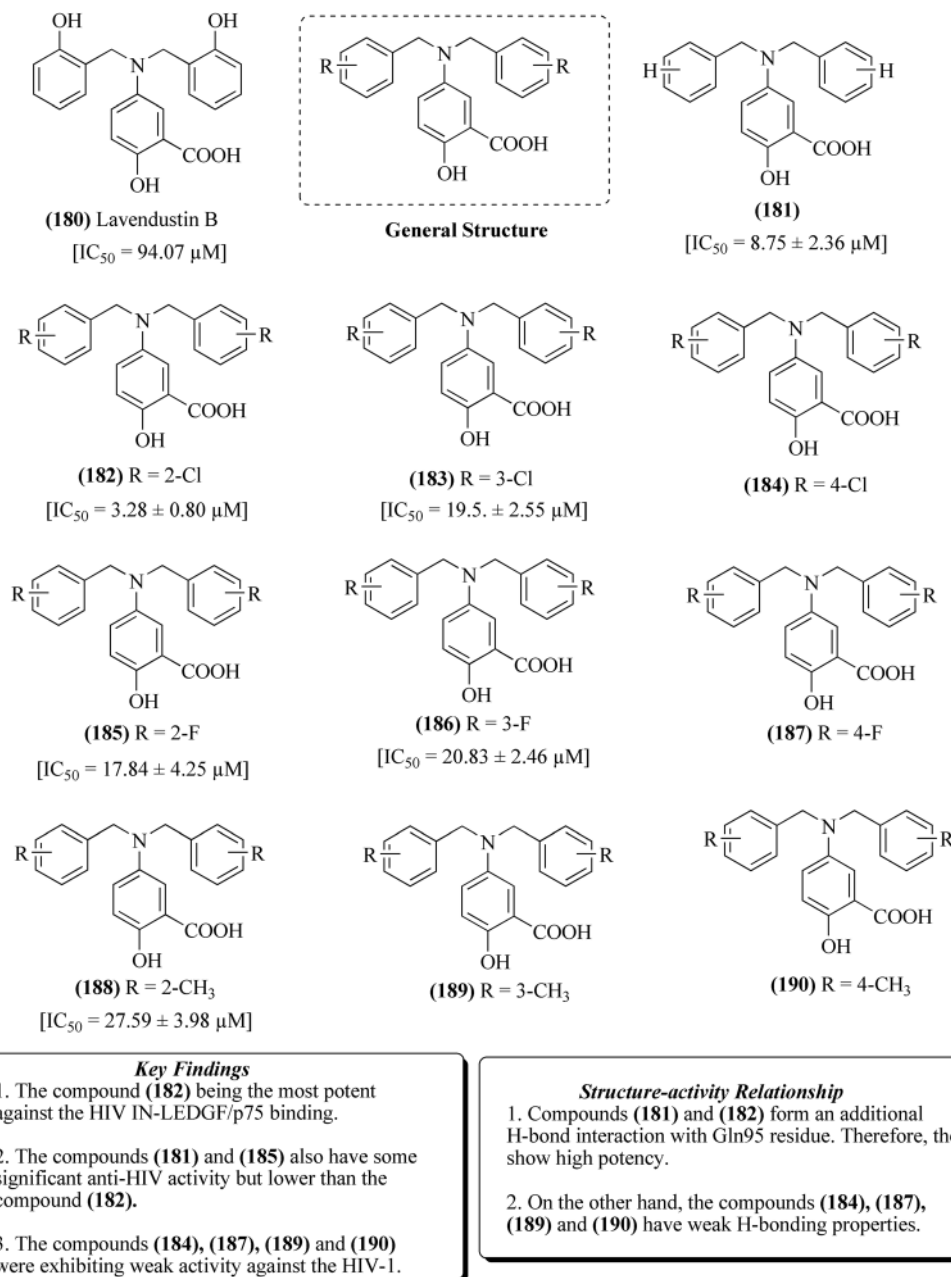


Fig. 20 Lavendustin-B and its derivatives together with their SAR and key features.

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 isostere-based 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]



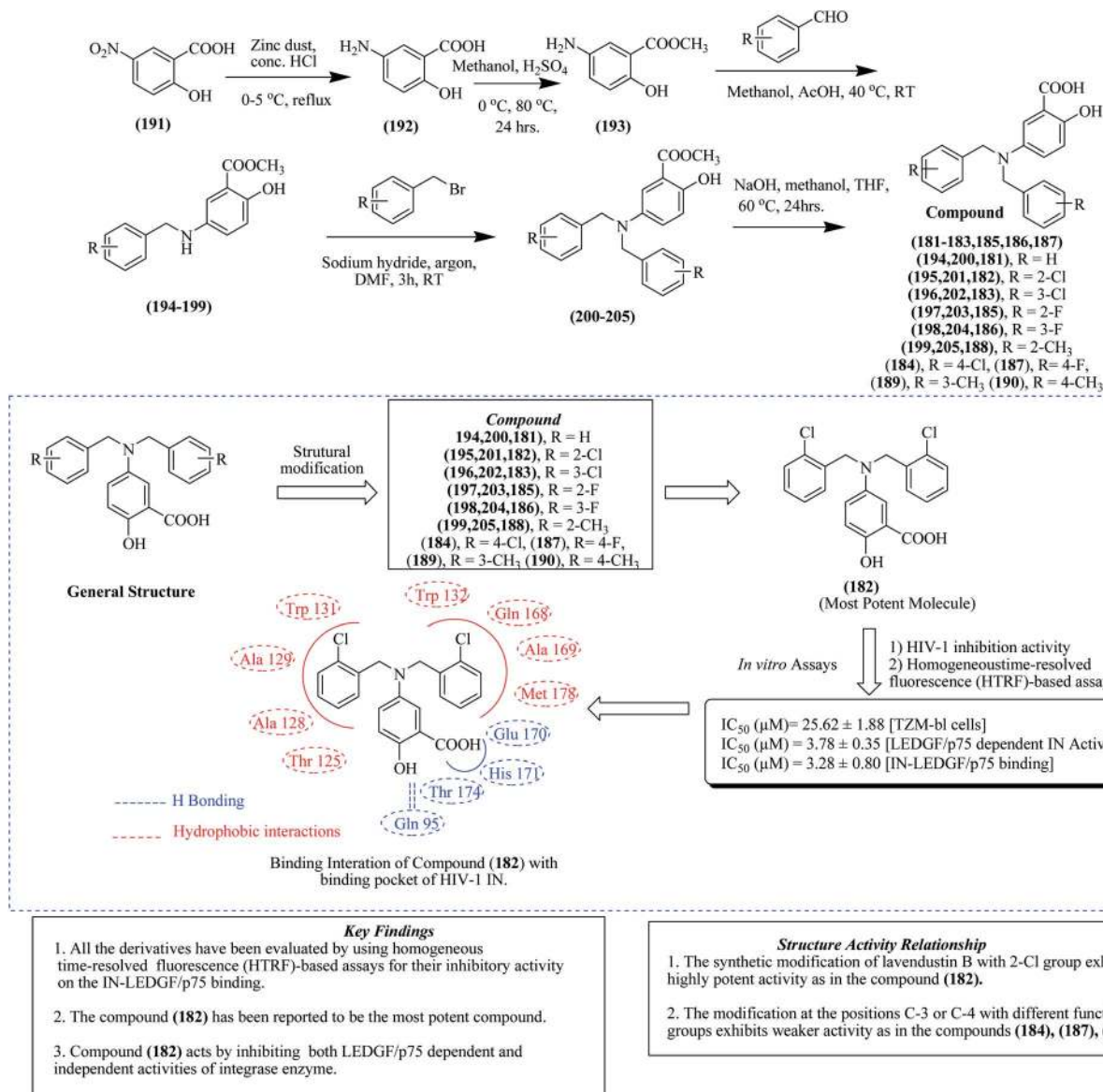


Fig. 21 Structures of lavendustin B analogs together with their docking features.

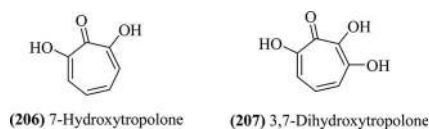


Fig. 22 Hydroxylated tropolones.

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}

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 an imidazolide

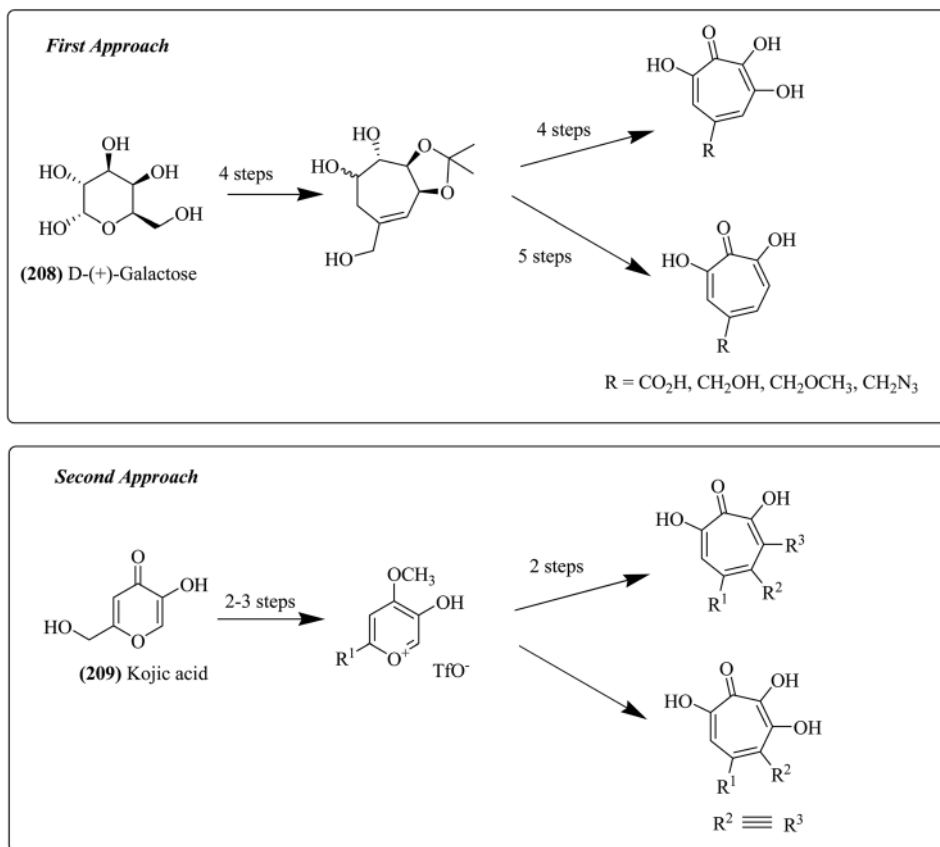


Fig. 23 Synthesis of tropolone derivatives through D-(+)-galactose route and through kojic acid route.

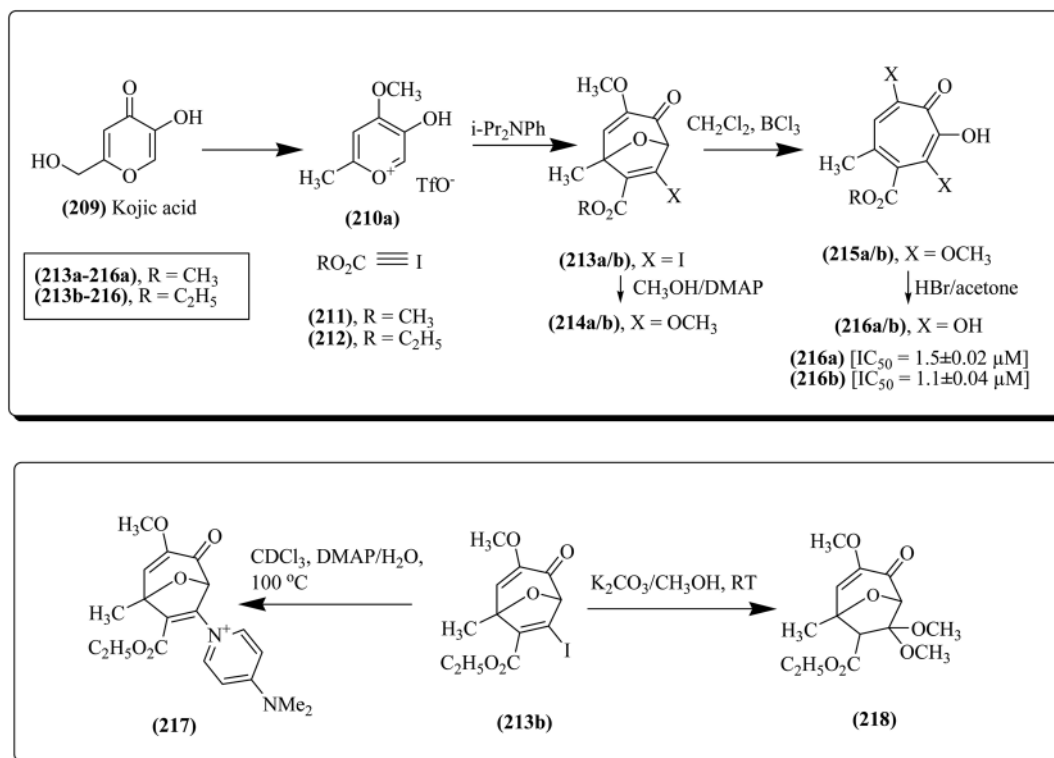


Fig. 24 3,7-Dihydroxytropolone and tropolone derivatives.



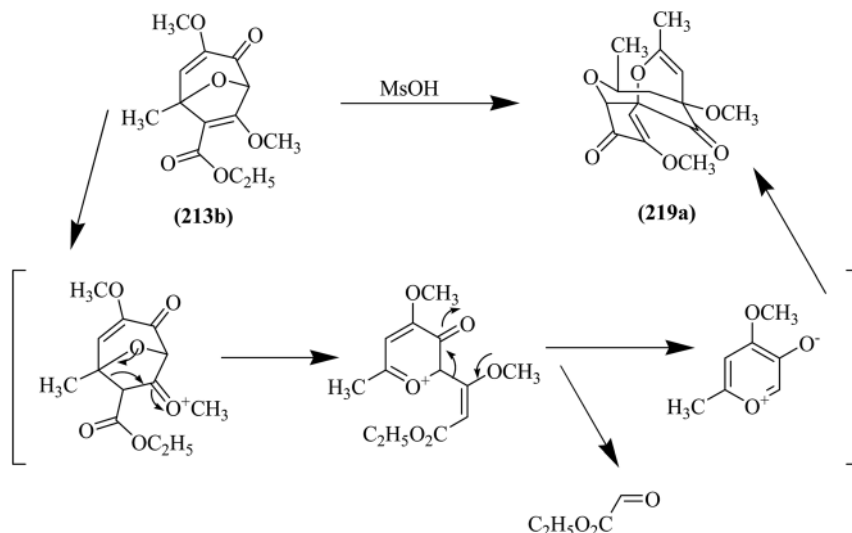
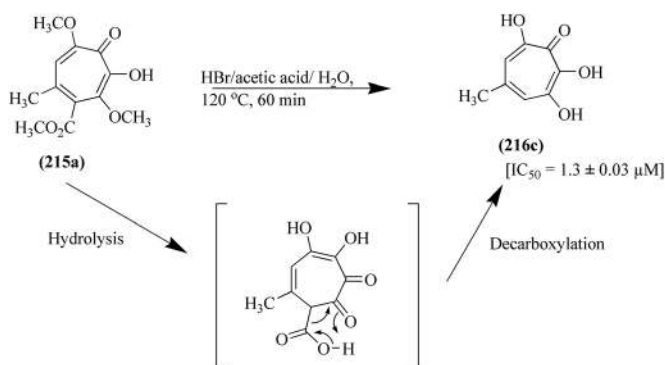


Fig. 25 Conversion of oxabicyclic intermediates into (oxido)pyrylium dimer compound (219a).



Key Findings

1. Cytotoxicity of the 3,7-dihydroxytropolone derivatives has been evaluated on the host CEM-SS cells.
2. The compounds (215a) and (216a-216d) have been evaluated for their activity against the HIV-1 RT. The compounds (216a-216d) have shown significant anti-HIV activity while the compound (215a) is less active.

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

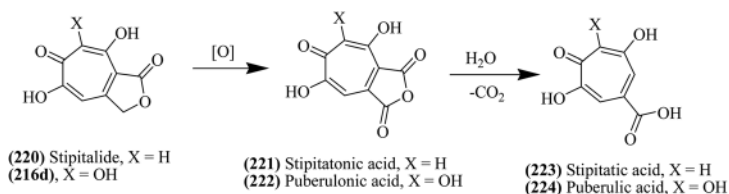


Fig. 27 Synthesis of compounds (221–224) from stipitalide and other 3,7-DHTs.

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 *tert*-butoxide. 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 *l*-mannitol. The reaction of the latter with 2,2-dimethoxypropane



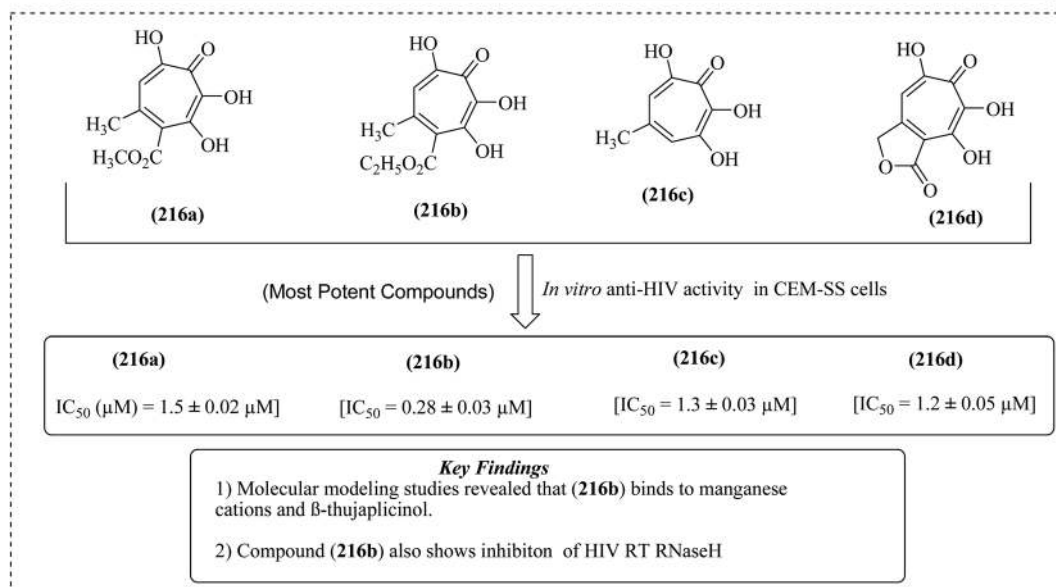
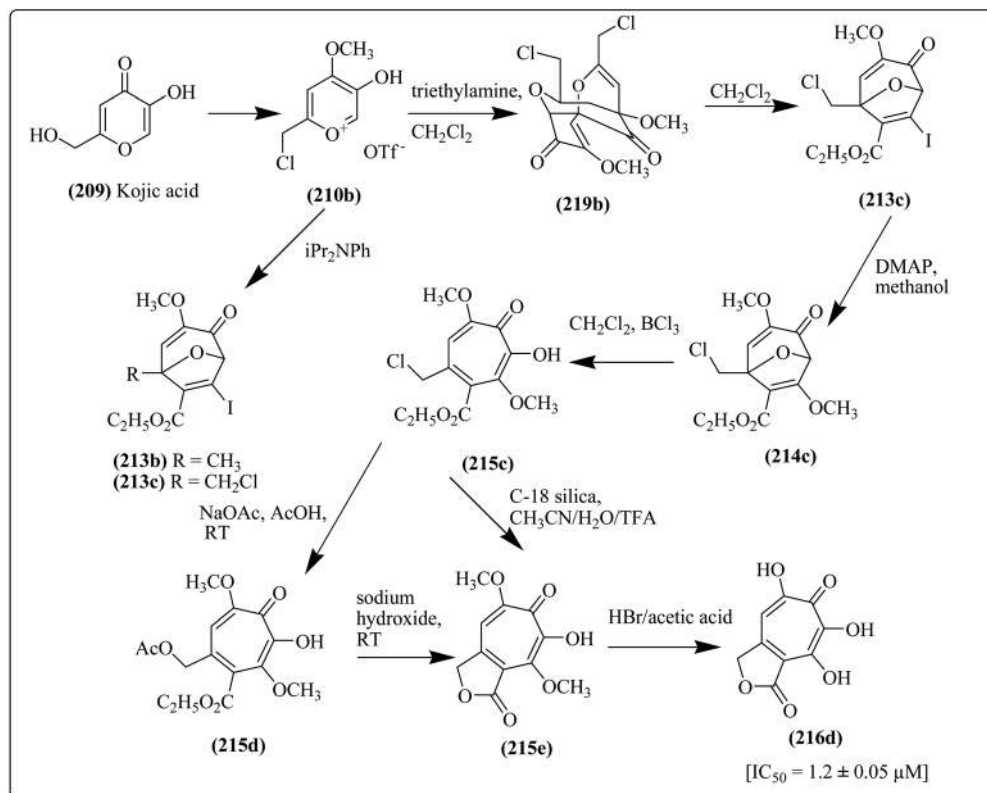
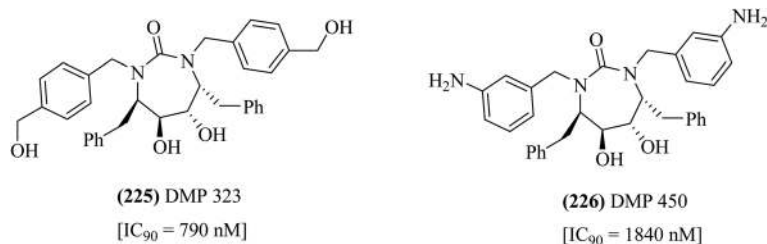


Fig. 28 Synthesis of 3,7-dihydroxytropolone analogs together with important key findings of the potent compounds.

and hydrochloric acid in acetone resulted in the formation of a new compound triacetone 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-CH₃SC₆H₄Br 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.

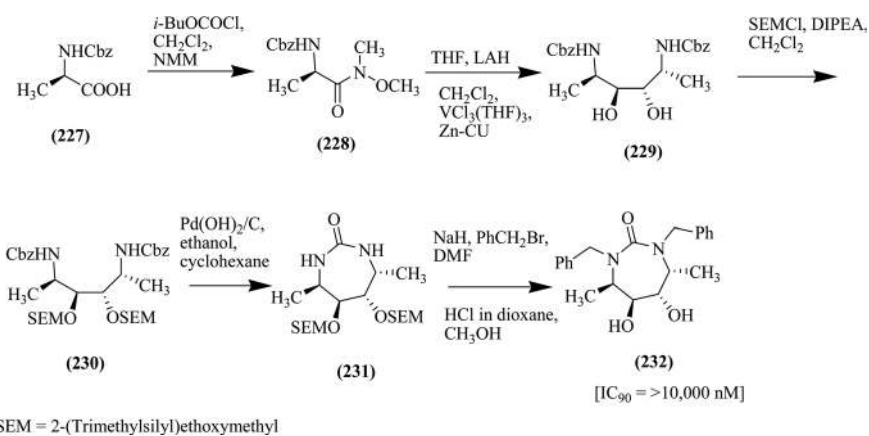


Fig. 30 Synthesis of P1/P1'-substituted cyclic ureas.

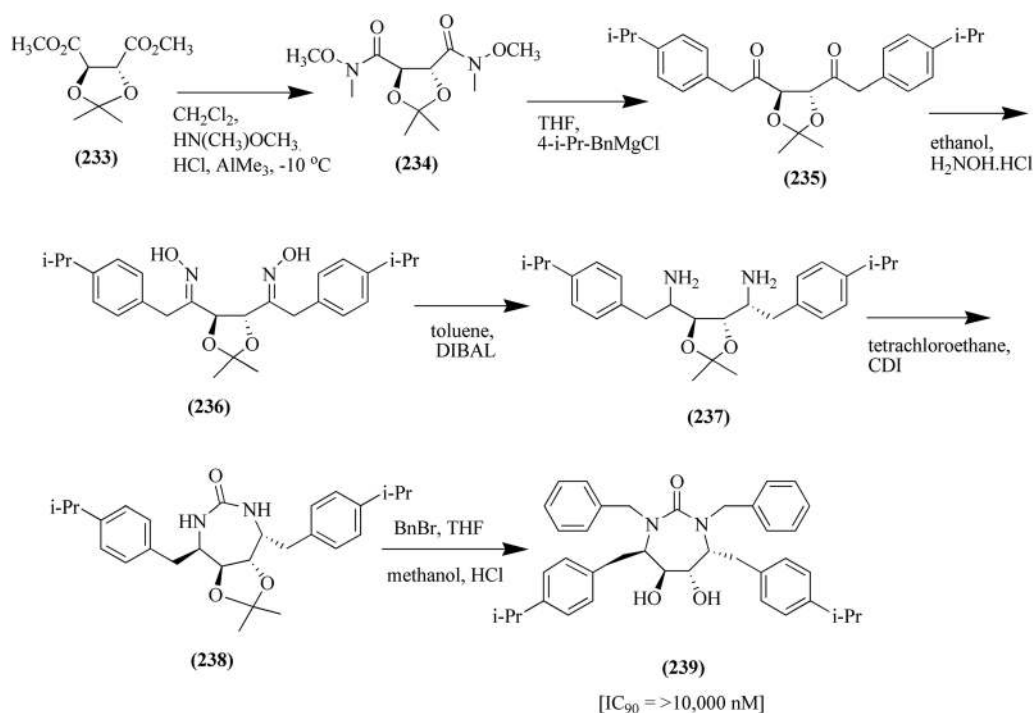


Fig. 31 Synthesis of P1/P1'-substituted cyclic urea derivatives (239).



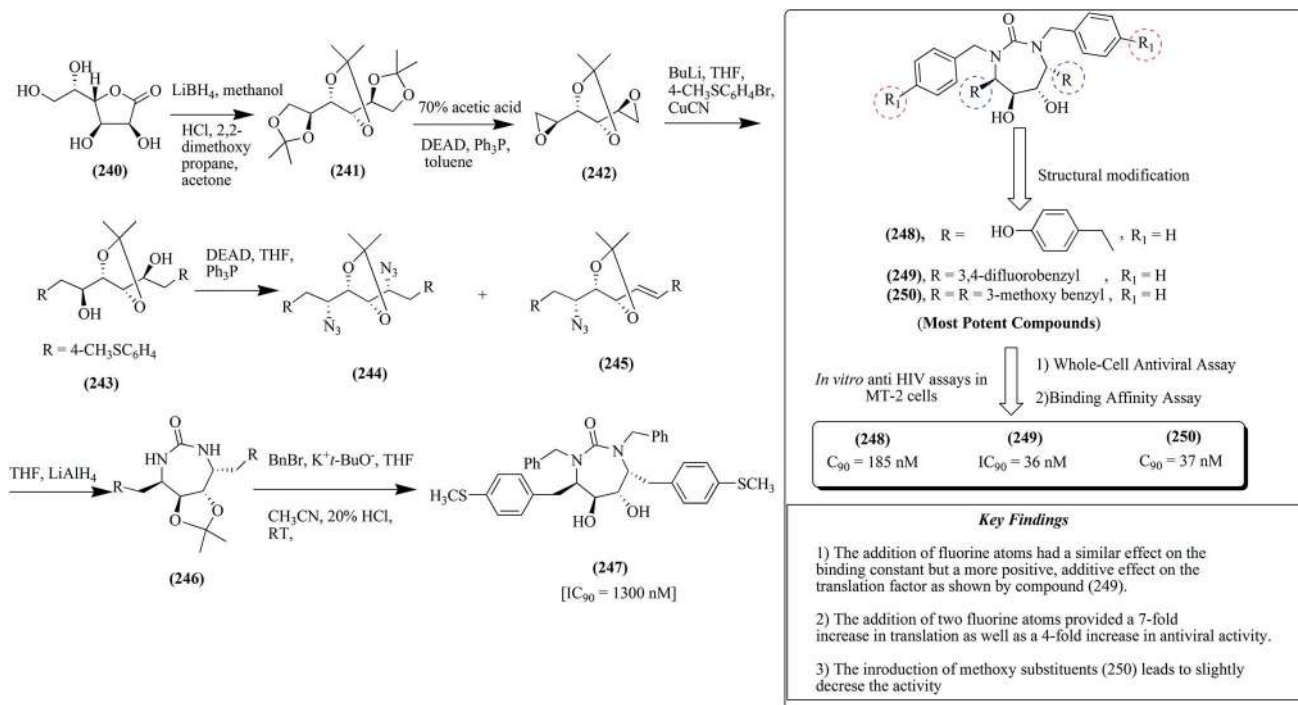


Fig. 32 Synthesis of P1/P1'-substituted cyclic urea-based derivatives together with important key findings of most potent compounds (248–250).

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}

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 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 potential.

Abbreviations

AIDS	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

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.

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