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Invited review

A review on recent developments of indole-containing antiviral agents

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ABSTRACT

Indole represents one of the most important privileged scaffolds in drug discovery. Indole derivatives have the unique property of mimicking the structure of peptides and to bind reversibly to enzymes, which provide tremendous opportunities to discover novel drugs with different modes of action. There are seven indole-containing commercial drugs in the Top-200 Best Selling Drugs by US Retail Sales in 2012. There are also an amazing number of approved indole-containing drugs in the market as well as compounds currently going through different clinical phases or registration statuses. This review focused on the recent development of indole derivatives as antiviral agents with the following objectives: 1) To present one of the most comprehensive listings of indole antiviral agents, drugs on market or compounds in clinical trials; 2) To focus on recent developments of indole compounds (including natural products) and their antiviral activities, summarize the structure property, hoping to inspire new and even more creative approaches; 3) To offer perspectives on how indole scaffolds as a privileged structure might be exploited in the future.

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1. Introduction

Indole derivatives occur widely in natural products, existing in different kinds of plants, animals and marine organisms [1]. The indole core is a near-ubiquitous component of biologically active natural products. For example, indole-3-acetic acid (IAA) **1** (Fig. 1), one of the most common naturally-occurrings, is a plant hormone of the auxin class [2]; tryptophan **2**, an essential amino acid, participates in many essential biological processes [3]; serotonin or 5-hydroxytryptamine (5-HT) **3**, biochemically derived from tryptophan, is a neurotransmitter and is found in all bilateral animals [4]; melatonin **4**, is a hormone found in animals, plants, and microbes, in which animals use the variation in duration of melatonin production each day as a seasonal clock [5]. The indole core is also well known as one of the most important scaffolds for drug discovery, and it has been a major focus of research for generations [6]. Biological studies of indole-3-carbinol (I3C) **5**, and 3,3′-diindolylmethane (DIM) **6**, also a natural product derived from the digestion of I3C which is found at relatively high levels in cruciferous vegetables such as broccoli, Brussels sprouts, cabbage and kale, have been the subjects of on-going research due to their interesting anticarcinogenic, antioxidant, and antiatherogenic effects [7–10]; Ajmalicine **7** (also known as δ-yohimbine or raubasine), an indole alkaloid found naturally in various plants, is an antihypertensive drug used in the treatment of high blood pressure [11]. It acts as a α_1-adrenergic receptor antagonist with preferential actions over α_2-adrenergic receptors, underlying its hypotensive rather than hypertensive effects [12]. Reserpine **8**, an indole alkaloid, is used to treat high blood pressure and severe agitation in patients with mental disorders [13]. Vinblastine **9**, is used to treat several types of cancer, including Hodgkin's disease, Kaposi's sarcoma, non-Hodgkin's lymphoma, and cancer of the breast or testicles [14].

Indole represents one of the most important structural motifs in drug discovery, and it is described as one of the “privileged scaffolds”, a term first introduced by Evans and co-workers to define scaffolds which are capable of serving as ligand for a diverse array of receptors [15–17]. Indole derivatives have the unique property of mimicking the structure of peptides and to bind reversibly to enzymes [18–21], which provide tremendous opportunities to discover novel drugs with different modes of action. There are seven indole-containing commercial drugs in the Top-200 Best Selling Drugs by US Retail Sales in 2012 [22]. This is highlighted by Cialis, an approved drug for the treatment of men's erectile dysfunction (ED), the signs and symptoms of benign prostatic

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List of abbreviations

IAA	indole-3-acetic acid
5-HT	5-hydroxytryptamine
I3C	indole-3-carbinol
DIM	3,3′-diindolylmethane
WHO	world health organization
ED	erectile dysfunction
OD	once-daily
BPH	benign prostatic hyperplasia
HIV	human immunodeficiency virus
HCV	hepatitis C virus
HSV	herpes simplex virus
VSV	vesivular stomatitis virus
H1N1	influenza virus A
CV	cyanovinyl
IE	immediate-early
SARS	severe acute respiratory syndrome
RSV	Respiratory Syncytial Virus
HAART	highly active antiretroviral therapy
MERS	middle east respiratory syndrome
EVD	ebola virus disease
EFVR	efavirenz-resistant
HDAC	histone deacetylase
ADME	absorption, distribution, metabolism, and excretion
RBV	ribavirin
SVR	sustained viral response
NHR	N-terminal heptad repeat
DKA	diketo acid
RT	reverse transcriptase
RTIs	reverse-transcriptase inhibitors
NNRTIs	non-nucleoside reverse transcriptase inhibitors
IAS	indolylarylsulfone
INIs	integrase inhibitors
PPIs	protein–protein interactions
BVDV	Bovine viral diarrhea virus
HRV	Human rhinovirus
FDV	Fosdevirine

hyperplasia (BPH), and both ED and the signs and symptoms of BPH [23,24]. There are also an amazing number of approved indole-containing drugs in the market as well as compounds currently going through different clinical phases or registration statuses.

Viral diseases are extremely widespread infections. Some familiar viral diseases include common cold, influenza, chickenpox, herpes, gastroenteritis (stomach flu), human immunodeficiency virus (HIV/AIDS), hepatitis. Viral diseases can lead to serious, and potentially life-threatening complications, it is estimated that viral infections are responsible for more than 60% of the illnesses occurring in developed countries. In 2003, the severe acute respiratory syndrome (SARS) epidemic originated from southern China took the lives of nearly 800 people worldwide. Middle East Respiratory Syndrome (MERS) is a viral respiratory illness first reported in Saudi Arabia in 2012. It is caused by a corona virus called MERS-CoV. As of June, 2014, the World Health Organization (WHO) reported 699 cases of human infection with MERS, including at least 209 deaths. The most recent outbreak of Ebola virus disease (EVD) in West Africa in 2014 since its first appearance in 1976 has prompted WHO to declare international public health emergency. As of October, 2014, WHO reported that the current outbreak of Ebola has infected more than 7470 people and killed more than 3431 (Updated October 3, 2014). Antiviral drugs play an important role in fast-spreading epidemics; however almost all antivirals are

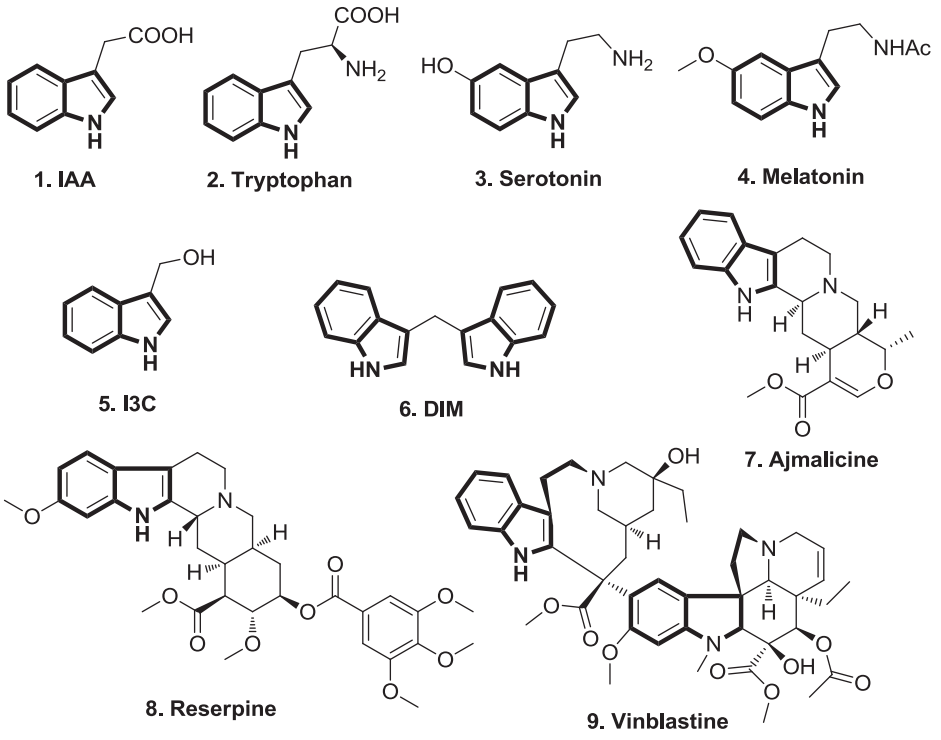

Fig. 1. Structures of indole-containing natural products and drugs.

subject to drug resistance as the pathogens mutate over time, becoming less susceptible to the treatment. Despite recent approvals of new antivirals in HIV and HCV therapeutic areas, there remain important unmet medical needs to improve upon the current therapy as well as those there exists no treatment.

Owing to the vast number of indole-containing molecules in the literature, this review focused primarily on antiviral agents, as limited reports were found in this area [25,26]. This review serves as a comprehensive overview of currently published indole antiviral agents with the following objectives: 1) To present one of the most comprehensive listings of indole antiviral agents, drugs on market or compounds in clinical trials; 2) To focus on recent developments of indole compounds (including natural products) and their antiviral activities, summarize the structure property, hoping to inspire new and even more creative approaches; 3) To offer perspectives on how indole scaffolds as a privileged structure might be exploited in the future.

2. Indole antiviral agents: drugs on market or compounds in clinical trials

Indole scaffold is widely used in antiviral research. Examples of marketed indole-containing antiviral drugs include Arbidol and Delavirdine. Meanwhile, a number of indole derivatives are actively undergoing different phases of clinical evaluation, such as Atevirdine, GSK2248761 (IDX-12899), Golotimod, Panobinostat (LBH589), BILB 1941, BMS-791325, MK-8742 and Enfuvirtide (Fig. 2).

Arbidol **10** (Umifenovir, Fig. 2) represents one of the most highly functionalized indole-containing drugs. Arbidol is a Russian developed broad spectrum antiviral which was widely used in Russia and China since 1990s. It is used for the treatment and prophylactic prevention of influenza A and B virus, respiratory syncytial virus, and SARS. It is Arbidol demonstrated both immunomodulating and anti-influenza effects, specifically against influenza groups A and B, and SARS [27,28]. It prevents contact and entry of the virus into cells by inhibiting the fusion of viral lipid membranes with cell membranes. It has an interferon-inducing action, stimulates humoral and cell-mediated immunity, helps the phagocytic action of macrophages, and heightens the body's ability to fight infection [28]. It decreases the frequency of complications associated with viral infections, and lessens the effects of chronic bacterial illnesses. In additional, arbidol also showed *in vitro* and *in vivo* activities against a panel of human respiratory viruses including influenza A virus (FLU-A, A/PR/8/34H1N1), Respiratory Syncytial Virus (RSV), Human rhinovirus (HRV) 14, coxsackie virus B3 (CVB3), adenovirus type 7 (AdV-7) and HCV [29–31].

Delavirdine **11** (Rescriptor, Fig. 2) is a first generation non-nucleoside reverse transcriptase inhibitor (NNRTI) marketed by ViiV Healthcare. It was approved by FDA in 1997 for the treatment

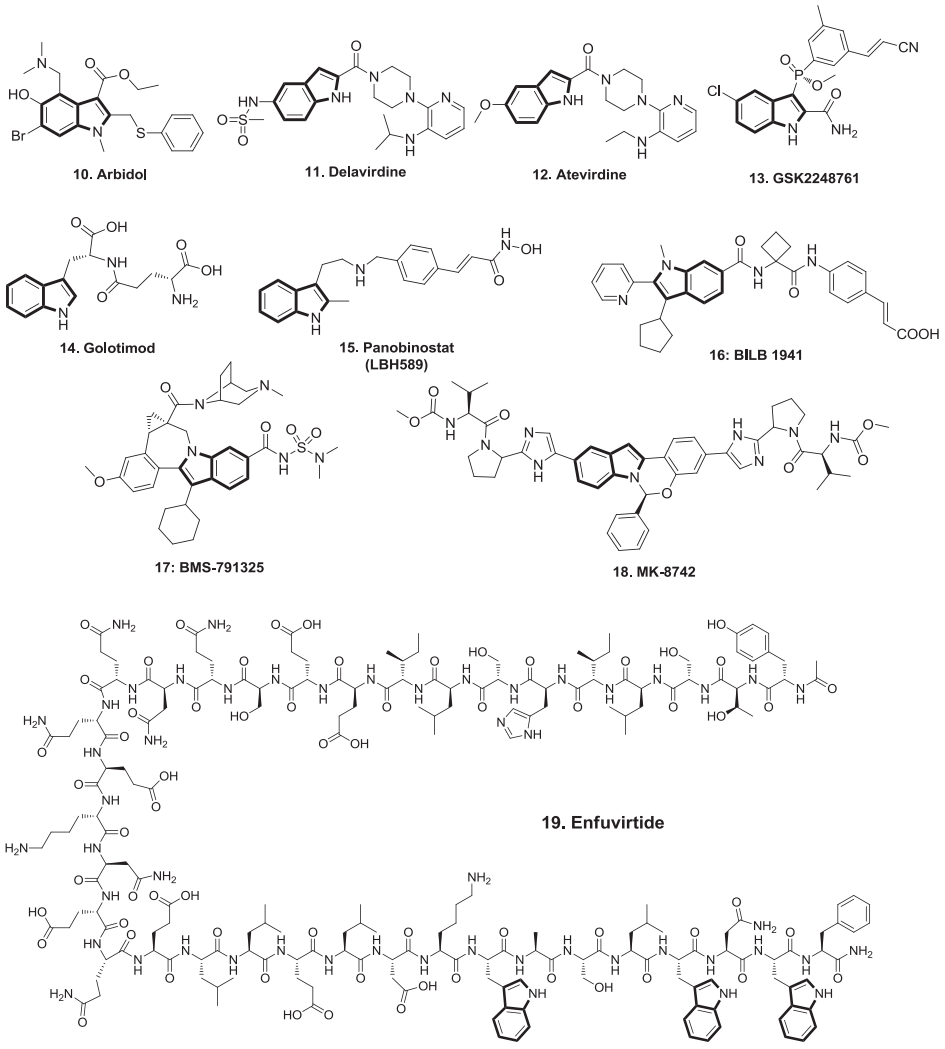

Fig. 2. Structures of indole-containing commercial and on-study antiviral drugs.

of human immunodeficiency virus type 1 (HIV-1). It is used as part of highly active antiretroviral therapy (HAART) [32]. Since then, better NNRTI such as efavirenz, and second generation NNRTIs such as etravirine and rilpivirine have been approved (http://aidsinfo.nih.gov/education-materials/fact-sheets/21/58/fda-approved-hiv-medicines). Delavirdine inhibits the CYP3A4-mediated metabolism of HIV protease inhibitors and thereby increases systemic exposure to protease inhibitors. The ability of delavirdine to enhance the pharmacokinetic profiles of protease inhibitors may permit the use of simplified administration regimens [33].

Atevirdine **12** (U-87201E, Fig. 2) is a new non-nucleoside (heteroarylpiperazine) reverse transcriptase inhibitor that has been studied for the treatment of HIV [34]. Atevirdine mesylate has been shown to have significant anti-HIV RT activity *in vitro*, it inhibits HIV-1 replication in infected peripheral blood leukocyte cultures at a 50% inhibitory concentration of 1 nM and a concentration which is cytotoxic to 50% of cells of 100 μM and also inhibits completely the formation of syncytia in human T-cell leukemia virus type III-infected MT-2 cells at 2 μM. Phase I study of atevirdine alone failed to demonstrate significant antiretroviral activity [35].

GSK2248761 (Fosdevirine, FDV, formerly IDX-12899) **13** (Fig. 2) is a novel, potent, selective, an once-daily (OD), next-generation nonnucleoside reverse-transcriptase inhibitor (NNRTI) with low nanomolar activity *in vitro* [36,37]. GSK2248761 shows good activity against a broad range of HIV-1 strains, including efavirenz-resistant (EFVR) clinical isolates [38,39]. GSK2248761 at 100–800 mg OD for 7 days was well tolerated, demonstrated potent antiviral activity in treatment-naive HIV-infected subjects, and had favorable PK and resistance profiles. The development of GSK2248761A was placed on clinical hold by the US Food and Drug Administration pending further evaluation of 5 reports of seizures in other studies of GSK2248761 in treatment-experienced patients [40].

Golotimod **14** (SCV-07, Fig. 2), an orally bioavailable synthetic peptide containing the amino acids D-glutamine and L-tryptophan connected by a gamma-glutamyl linkage with potential immunostimulating, antimicrobial and antineoplastic activities [41]. In 2010, SciClone Pharmaceuticals Inc. reported the results of phase 2b clinical trial of SCV-07 for the treatment of hepatitis C (HCV). The study evaluated the safety and immunomodulatory effects of SCV-07 as a monotherapy and in combination with ribavirin in relapsed HCV patients. The clinical data demonstrated SCV-07 to be safe and well-tolerated at both administered doses. Results showed a clear biological signal from SCV-07 but did not meet the study's primary efficacy endpoint of a 2 log reduction in viral load from baseline level. A phase 2 study is still on-going with SCV-07 in attenuating oral mucositis in subjects with head and neck cancer; however, no further study is listed for HCV [42].

Panobinostat (LBH589) **15** (Fig. 2) is an experimental drug developed by Novartis as a non-selective histone deacetylase inhibitor (HDAC inhibitor) for treatment of Multiple Myeloma (Phase III) and Acute Myeloid Leukemia (Phase II). The various HDAC inhibitors displayed significant potency differences in stimulating HIV-1 expression from the latently infected cell lines, and panobinostat was significantly more potent than all other HDAC inhibitors and induced virus production even at the very low concentration range (8–31 nM), proof was obtained that panobinostat induce virus production in latently infected primary cells at therapeutic concentrations, and it is currently being used in a Phase I/II clinical trial that aims at curing AIDS in patients on highly active antiretroviral therapy (HAART). In this technique, panobinostat is used to drive the HIV DNA out of the patient's DNA, in the expectation that the patient's immune system in combination with HAART will destroy it, this is the first proof of a viral "kick" leading to consistent plasma release of viral particles [43,44].

BILB-1941 **16** (Fig. 2), the first thumb pocket 1 NS5B inhibitor that demonstrated antiviral activity in patients chronically infected with genotype 1 HCV. Based on the discovery of allosteric (thumb pocket 1) non-nucleoside inhibitors of HCV NS5B polymerase that inhibit replication in replicon systems, and the identification of a metabolic liability common to many previously reported inhibitors in this series, a sparse matrix of indole-based inhibitors were generated that provided a collection of inhibitors satisfying potency criteria and displaying improved *in vitro* ADME profiles, and compound **16** provided the most optimal balance between antiviral potency and a consistent cross-species PK profile, it was selected for development followed by a clinical study in HCV-infected patients [45].

BMS-791325 **17** (Fig. 2), a cyclopropyl-fused indolobenzazepine HCV NS5B RNA-dependent polymerase inhibitor, it inhibited cellar replication of HCV subgenomic replicons representing genotypes 1a and 1b at EC_{50} of 3 nM and 6 nM, respectively, it also exhibited notably enhanced pharmacokinetic profiles with improved solubility and membrane permeability, it was found to perform distinguishing antiviral, safety, and pharmacokinetic properties that resulted in its selection for clinical evaluation, Phase III studies are currently ongoing [46].

MK-8742 **18** (Fig. 2), a tetracyclic indole-based NS5A inhibitor, which is currently in phase 2b clinical trials as part of an all-oral, interferon-free regimen for the treatment of HCV infection [47]. As NS5A protein plays a critical role in the replication of HCV and its inhibitors have shown impressive *in vitro* potency profiles in HCV replicon assays, making NS5A inhibitors attractive components for inclusion in all oral combination regimens. MK-8742, is a second generation NS5A inhibitor. In combination with MK-5172, an NS3/4A protease inhibitor, this candidate drug exhibited improvements in the genetic barrier while maintaining potency, yielding amazing results in terms of efficacy (90–100%), tolerability and safety, Phase II clinical trials are underway. In an interim analysis of treatment-naïve, non-cirrhotic patients administered a 12-week regimen of MK-5172/MK-8742, with and without ribavirin (RBV), a sustained viral response (SVR) was observed in 98 percent (42/43) of patients administered MK-5172/MK-8742 alone and 94 percent (75/80) in those administered MK-5172/MK-8742 plus RBV. This kind of interferon-free therapies is expected to lead the HCV treatment if the high cost is overcome [48,49].

Enfuvirtide (T-20; brand name: Fuzeon) **19** (Fig. 2), the peptide anti-HIV drug targeting gp41N-terminal heptad repeat (NHR), was approved by the U.S. FDA in 2003 as the first HIV fusion/entry inhibitor for treatment of HIV/AIDS patients who fail to respond to the current antiretroviral drugs. However, because T20 lacks the pocket-binding domain, it exhibits low anti-HIV-1 activity and short half-life [50].

TMC647055 **25** (Fig. 3), a nonzwitterionic 17-membered macrocyclic indole, has yielded potent and selective finger-loop inhibitors of the hepatitis C virus (HCV) NS5B polymerase [51]. Lead optimization from **20** to **25** in conjunction with *in vivo* evaluation in rats identified this compound showing nanomolar potency (EC_{50} = 77 nM) in HCV replicon cells, limited toxicity and off–target activities, and encouraging preclinical pharmacokinetic profiles characterized by high liver distribution, and it is currently being evaluated in phase II clinical trials in combination with simeprevir [52].

3. Discovery of novel indole derivatives and their antiviral activity

The general idea of modern antiviral drug design is to identify viral proteins, or parts of proteins, that can be disabled. Generally speaking, these "targets" should be as unlike any proteins or parts

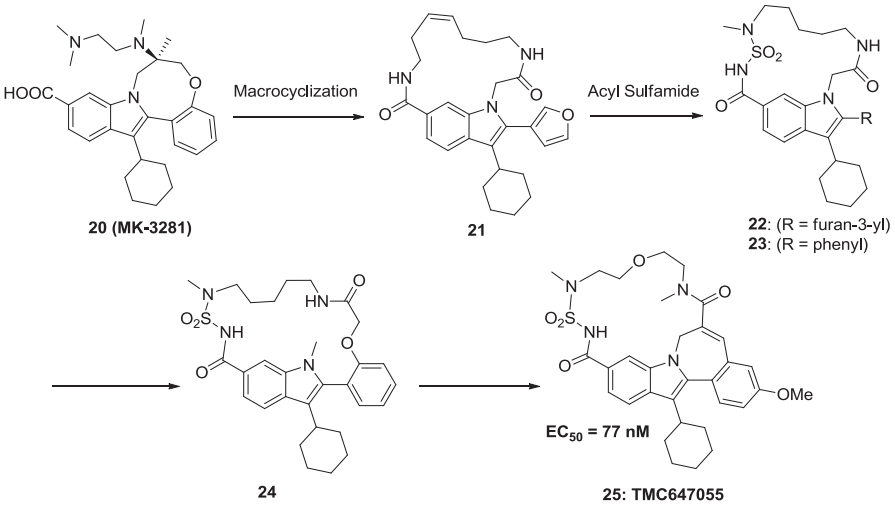

Fig. 3. Optimization route of macrocyclic indole from MK-3281 to TMC647055.

of proteins in humans as possible, to reduce the likelihood of side effects. The targets should also be common across many strains of a virus, or even among different species of virus in the same family, that means a single drug will have broad effectiveness. Once targets are identified, candidate drugs can be selected, either from drugs already known to have appropriate effects, or by actually designing the candidate at the molecular level with a computer-aided design program.

3.1. Indole derivatives as entry and fusion inhibitor

As mentioned in the introduction, Arbidol acts as an inhibitor of virus entry and membrane fusion, and it is a broad-spectrum antiviral agent that inhibits acute and chronic HCV infection. Using Arbidol as a lead compound, Grazia Sellitto and co-workers reported the synthesis and evaluation of a series of ethyl 1*H*-indole-3-carboxylate derivatives **26**–**29** (Fig. 4) [28]. Compounds **26**, **27** and **28** exhibited strong anti-HCV effects, while compound **27**, **28** and **29** showed higher selectivity indices of inhibition on entry and replication. Of all the synthetic initial hits, compound **28** was the most potent candidate. This revealed that the elimination of the phenylsulfonyl moiety preserved the anti-HCV activity, and the removal of the 6-bromo and 5-hydroxy groups from the indole ring of Arbidol did not have an influence on its anti-HCV efficacy. This implies that the indole core rather than these groups might be the antiviral pharmacophore.

BMS-378806 (**32**) is reported as a prototype of novel HIV attachment inhibitors that block the gp120 and CD4 interaction, the first step of HIV-1 entry into cells (Fig. 5). The initial screen hit was an indole analog **30**, which interferes with the interaction of the HIV surface protein gp120 with the host cell receptor CD4, and the 4-fluoro derivative **31** exhibited markedly enhanced potency and was bioavailable in the rat, dog, and cynomolgus monkey when administered orally as a solution formulation. However, aqueous suspensions of **31** were poorly bioavailable, indicative of dissolution-limited absorption. The 7-azaindole derivative **32**, **BMS-**378806, exhibited improved pharmaceutical properties while retaining the HIV-1 inhibitory profile of compound **31** [53–55].

Seung Joo Cho and coworkers employed *in silico* methods such as molecular docking, MD simulations and three-dimensional quantitative structure-activity relationship (3D-QSAR), to guide the molecular design of new indole derivatives (Fig. 6). A data set of 68 indole-based inhibitors along with their biological activities was collected from the literatures [56–58]. In this approach, lowest energy conformation of the most potent compound **34** derived from systematic conformational search was considered as template for sketching the rest of the molecules. This study can also contribute to the better understanding of binding pose between these inhibitors and gp120 glycoprotein, and provide structural information affecting activity of these inhibitors and improve the understanding of ligand–receptor interactions, resulting in some useful and rational suggestions for further design of novel inhibitors for HIV/AIDS therapy [59].

As virus-cell fusion is the primary means by which the human immunodeficiency virus-1 (HIV) delivers its genetic material into the human T-cell host, fusion is mediated in large part by the viral glycoprotein 41 (gp41), and the hydrophobic pocket in the HIV-1 gp41 N-terminal heptad repeat (NHR) domain plays an important role in viral fusion and entry into the host cell, and serves as an attractive target for development of HIV-1 fusion/entry inhibitors. Robert C. Rizzo and co-workers reviewed current approaches to study the interactions between inhibitors and gp41, putting an emphasis on atomic-level computer modeling methods (Fig. 7). Compounds **35**–**38**, having anti-fusion activity, were reported to interact in a specific manner with the binding site formed by the most conserved residues [50,60]. For example, compound **35**, discovered by virtual screening as a fusion inhibitor targeting gp41 [61], had high geometric overlap between its carboxylic acid and

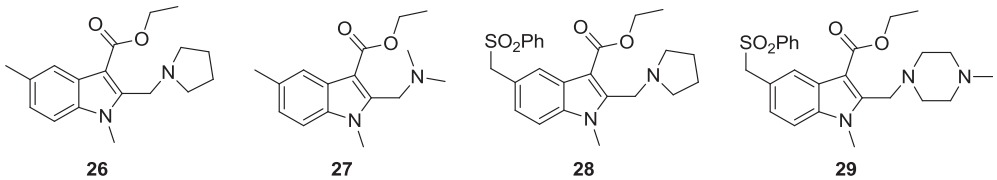

Fig. 4. Structures of Arbidol derivatives.

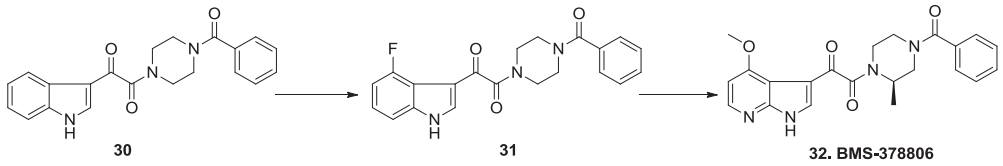

Fig. 5. Optimization route for BMS-378806.

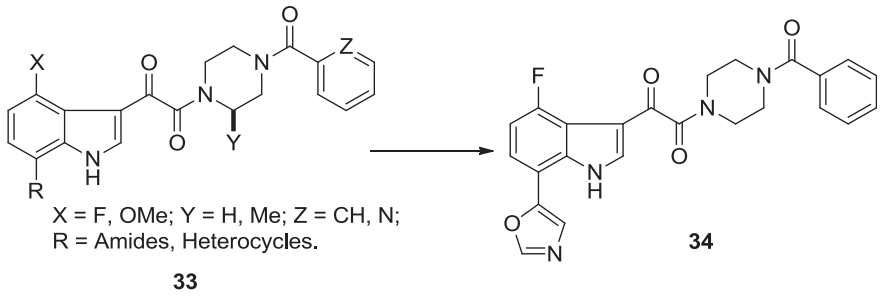

Fig. 6. Indole-containing inhibitors employed in 3D QSAR study.

the position of Asp121 inside the binding pocket. Compound **36**, discovered by a structure-based approach, exhibited inhibition constant of 2.1 μM and IC_{50} of 1.1 μM for cell–cell fusion inhibition [61]. **37** with a long hydrophobic interface showed submicromolar binding, fusion inhibition and blocking viral replication. The molecular simulations showed that **37** was able to adopt a structure mimicking the hydrophobic contacts of the D-peptide PIE7 [62]. **38** exhibited effective activity against HIV-1 Env-mediated cell–cell fusion with IC_{50} value of 1.3 μM, and bound in the hydrophobic pocket of gp41 to make a favorable interaction with Lys574 [63].

3.2. Indoles as reverse transcriptase inhibitors

Reverse-transcriptase inhibitors (RTIs) are a class of antiretroviral drugs used to treat HIV infection or AIDS, and in some cases hepatitis B. RTIs inhibit the activity of reverse transcriptase, a viral DNA polymerase that is required for replication of HIV and other retroviruses. What's summarized below is the recent progress of discovery and design of indole derivatives as RTIs.

3.2.1. Indolylarylsulfones (IAS) as reverse transcriptase inhibitors

Compound **39** (L-737,126) (Fig. 8), an indolylarylsulfone (IAS) derivative endowed with high selectivity and potency against HIV-1 WT and Y181C mutant, developed by Merck in 1992 as a novel inhibitor of HIV reverse transcriptase. It is useful in the prevention or treatment of HIV infection and AIDS [64,65]. The following development of indolylarylsulfones (IASs) NNRTIs was based on L-737,126 as the reference compound, there are mainly four structural modification sites, including the benzene group of SO_2Ph, the sulfonyl, the amide and the substituent(s) of indole ring.

Romano Silvestri et al. [66] reported a series of indolylarylsulfone derivative **40**–**44** (Fig. 8) as analogues of L-737,126. These compounds were obtained by introducing two methyl groups at positions 3 and 5 of the benzenesulfonyl moiety **40**–**41** and coupling the glycinamide/alaninamide units to its carboxyamide function **42**–**44**. The cell-based assays showed that these compounds exhibited higher potency against HIV-1 wild type and NNRTI-resistant mutants than the parent indole derivative **39**.

Based on the previous work, Giuseppe La Regina and coworkers synthesized a series of novel IAS derivatives bearing nitrogen-containing substituents at the indole-2-carboxamide linked through a CH_2/CH_2CH_2 spacer (Fig. 9) [67]. Most of these IASs **46** were proved to be potent inhibitors of the HIV-1 WT (NL4–3 strain) in MT-4 cells at low nanomolar concentrations and weakly cytotoxic. Several compounds were also identified as potent inhibitors of the mutant HIV-1 strains.

Zhijian Zhao and coworkers from Merck reported the design, synthesis, and biological evaluation of novel 3-indole sulfonamides as potent NNRTIs with balanced profiles against common HIV RT mutants K103N and Y181C (Fig. 10) [68]. Introduction of a pyrrolidine sulfonamide at the 3-position of the indole ring of lead compound **39** led to analog **47** with excellent wild-type HIV RT potency and comparatively weak K103N and Y181C RT activities. Compounds **48**–**50** with variation in the indole 2-substituent

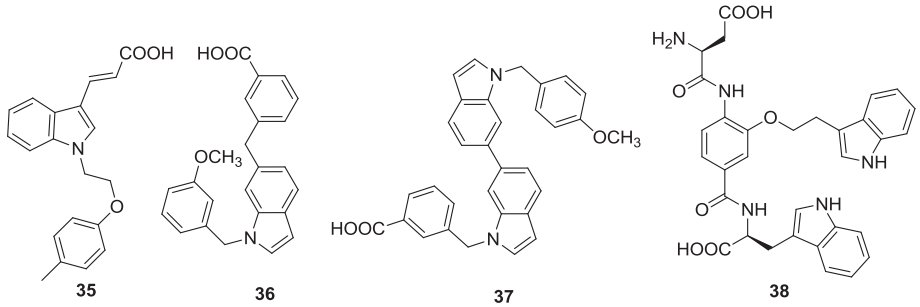

Fig. 7. Indole-containing structures with gp41-binding activity.

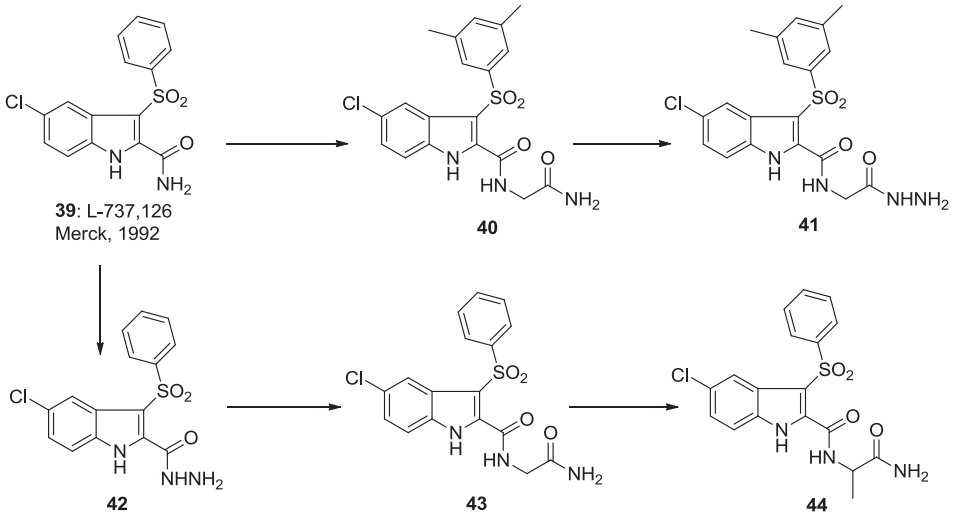

Fig. 8. Optimization route of Sulfonylindolecarboxamide as NNRTI.

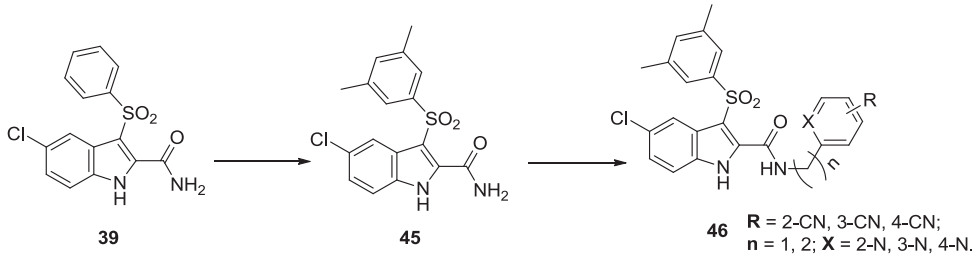

Fig. 9. Optimization route of novel IAS derivatives as NNRTIs.

showed improved activities against wild-type and some mutants, such as K103N and Y181C.

Rino Ragno and his coworkers performed 3D-QSAR and docking simulations to design and synthesize a series of novel derivatives of **39**. N-(2-hydroxyethyl)carboxamide **51** [69] or substituted N′-carboxyhydrazide derivatives **52** [70] showed high activity against the K103N RT mutant virus (Fig. 11). Meanwhile, the 5-chloro-4-fluoro derivative **53** and 4,5-difluoro derivative **54** turned out to be potent inhibitors of HIV-1 WT and the NNRTI-resistant Y181C RT and K103N–Y181C RT HIV-1 strains. In particular, compound **54** was exceptionally potent against RT WT and RTs carrying the K103N, Y181I, L100I mutations.

New indolylarylsulfone derivatives **55** bearing cyclic substituents at indole-2-carboxamide linked through a methylene/

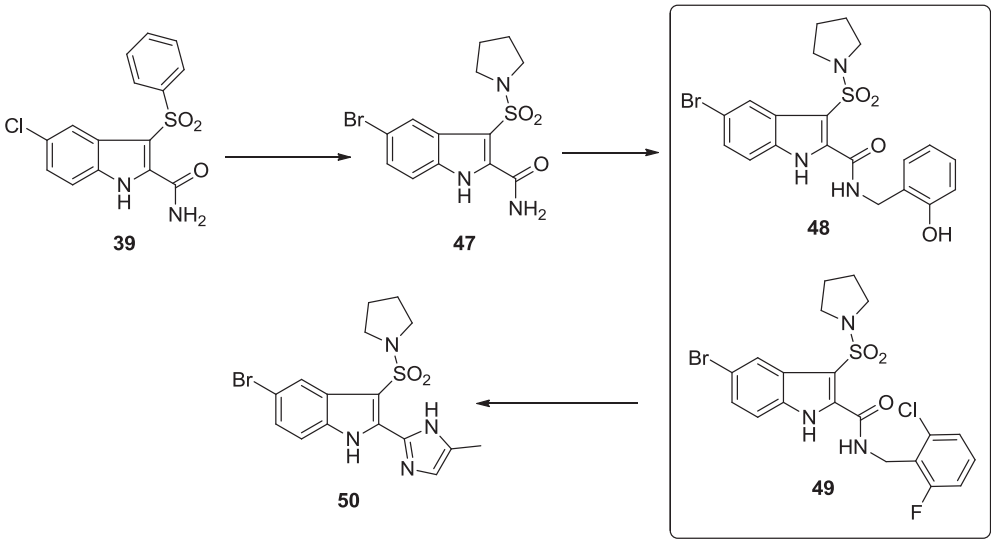

Fig. 10. Optimization route of novel 3-indole sulfonamides as potent NNRTIs.

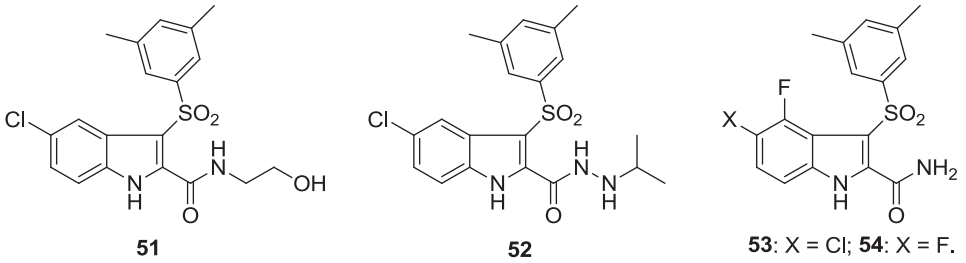

Fig. 11. Structures of indole-containing NNRTIs.

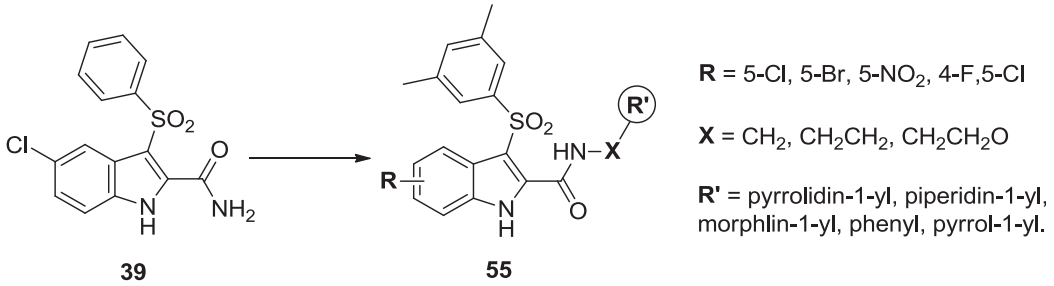

Fig. 12. Optimization route of novel IAS derivatives as NNRTIs.

ethylene spacer were designed and synthesized as novel IAS analogues by Giuseppe La Regina and his coworkers. These compounds were potent inhibitors of the WT HIV-1 replication in CEM and PBMC cells and showed inhibitory concentrations in the low nanomolar range (Fig. 12) [71]. The substituents introduced at positions 4 and 5 of the indole did not show a significant effect on the antiviral activity against the HIV-1 WT. 5-Bromo and 5-nitro-IASs bearing the ethylene linker were less cytostatic than the corresponding 5-chloro and 5-chloro-4-fluoro derivatives. Against the mutant L100I and K103N RT HIV-1 strains in MT-4 cells, some compounds showed antiviral potency superior to that of NVP and EFV. Further molecular docking experiments revealed that the H–bond interaction between the nitrogen atom in the carboxamide chain of IAS and Glu138B played an important role for the binding of these analogues.

Recently, a series of new indolylarylsulfones as HIV-1 NNRTIs were synthesized and evaluated for the unexplored substitutions of the benzyl/phenylethyl group linked at the indole-2-carboxamide (Fig. 13) [72]. Compound **56** exhibited 535-folds, 76-folds and 18-folds higher antiviral activity against the NL4_3 HIV-1 WT strain than the references NVP, EFV and AZT, respectively. In addition, several compounds showed nanomolar potency towards the K103N HIV-1 mutant strain and were superior to EFV, while some derivatives were superior to EFV against the Y181C and L100I HIV-1 mutant strains. Very interestingly, the enantiomers **57** and **58** showed small differences of activity against the NL4-3 HIV-1 strain, but **57** turned out significantly more potent than **58** against the whole panel of mutant HIV-1 strains. The enzymatic results for **57** and **58** were in well agreement with the cellular data. The molecular simulations suggested that the difference in the observed inhibitory activities of these two isomers could be due to a kinetic rather than affinity differences. The results showed compound **57** represents a robust lead compound to develop NNRTIs with improved activity and selectivity against K103N that is the most frequently emerging HIV-1 mutation in EFV-treated patients.

Idenix Pharmaceuticals and Merck & Co. showed a renewed interest in IASs and replaced the 3-arylsulfonyl group by either an arylphosphonyl **59** [73] or a sulfonamide group **60** [68]. Francesco Piscitelli reported new potent indolylarylsulfone (IAS) HIV-1 NNRTIs **61** obtained by coupling natural and unnatural amino acids to the 2-carboxamide and introducing different electron-withdrawing substituents at position 4 and/or 5 of the indole rings (Fig. 14). The new IASs inhibited the HIV-1 replication in human T-lymphocyte (CEM) cells at low/subnanomolar concentration and were weakly cytostatic [74].

Francois-Rene Alexandre and coworkers designed and synthesized a series of 3-phenylphosphinate-2-carboxamide indoles **62** as novel NNRTIs (Fig. 15) [75]. As the substituted bicyclic hydrogen donor scaffold could interact with K101 and F227, and the branching phosphorus tetrahedral linker would direct the

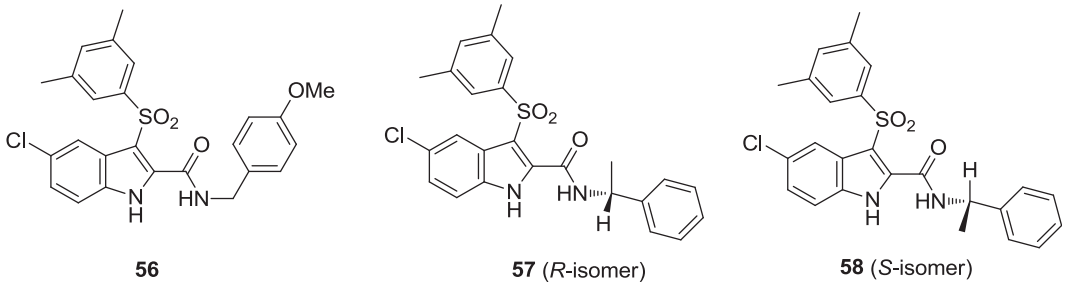

Fig. 13. Chiral IAS derivatives as NNRTIs.

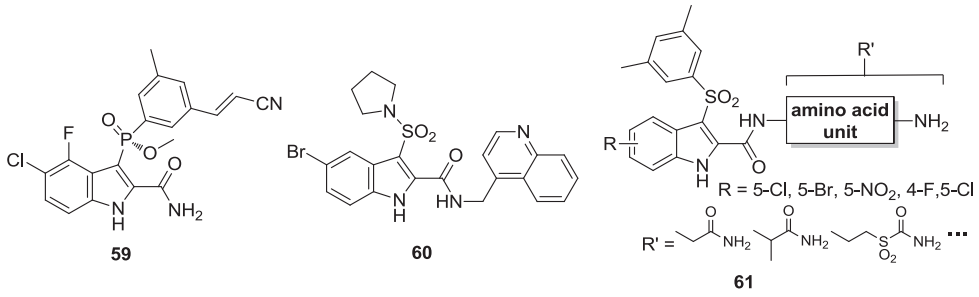

Fig. 14. Novel IAS derivatives as NNRTIs.

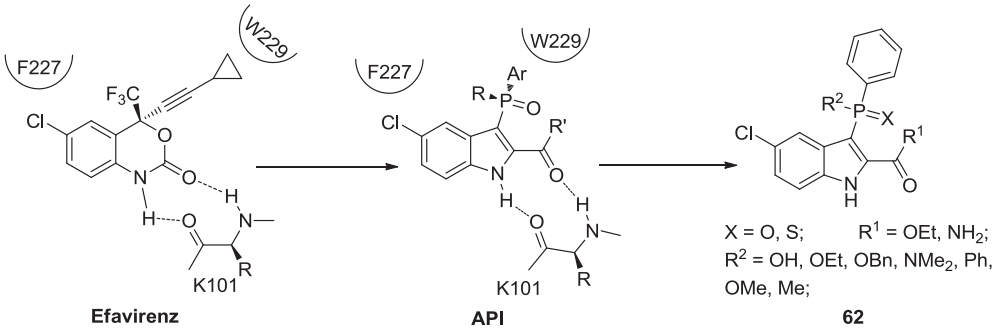

Fig. 15. Optimization and binding of IAS derivatives as NNRTIs.

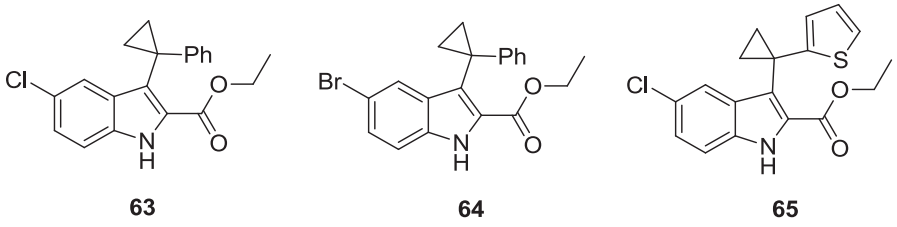

Fig. 16. Cyclopropyl indole derivatives as NNRTIs.

substitution toward the lipophilic W229 region, chemical variation in the phosphorus linker led to the discovery of 3-phenyl-methyl-phosphinate-2-carboxamide, which showed excellent potency against wild-type HIV-1 and K103N and Y181C single mutants in the reverse transcriptase gene. Most importantly, in addition to the potency, the pharmacokinetic, solubility, and metabolic properties of this series compounds were also encouraging.

Utilizing molecular modeling, Mohammad Hassam and co-workers have designed and synthesized a series of novel cyclopropyl indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors [76], and these inhibitors facilitate a double hydrogen bonding interaction to K101 and efficiently occupy the hydrophobic pockets in the regions of Y181/188 and V179. Several of these compounds, such as **63**, **64** and **65** (Fig. 16), inhibited HIV replication as effectively as nevirapine when tested in a phenotypic assay.

3.2.2. *Other indole derivatives as reverse transcriptase inhibitor*

Rilpivirine **66,** the most recently FDA-approved NNRTI, has an uncommon structural feature of the cyanovinyl (CV) group. For most medicinal chemists viewing the substructure, concern arises that the CV group may be sufficiently electrophilic to act as a Michael acceptor, leading to potential covalent modification of proteins, nucleic acids, or other biological entities. Although in reality unsaturated nitriles are poor Michael acceptors that require reactive organometallic nucleophiles to undergo conjugate

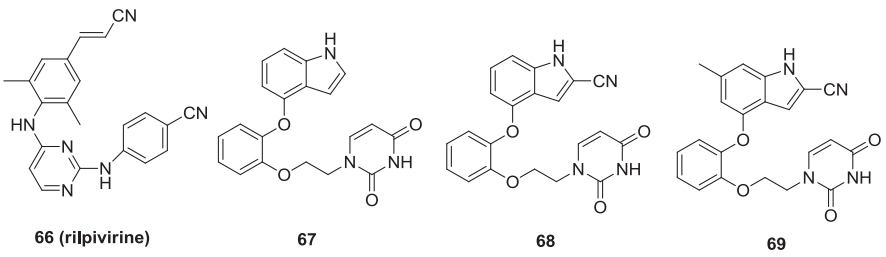

Fig. 17. Cyanovinyl (CV) indole derivatives as NNRTIs.

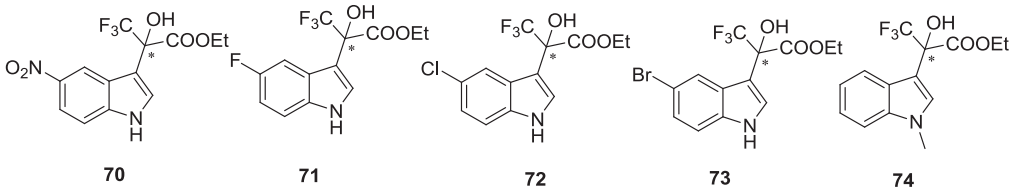

Fig. 18. Chiral indole-based trifluoropropanoates as NNRTIs.

additions, the fact is that almost no approved drugs contain a cyanovinyl group, and lack of precedent is often taken as a warning sign in drug discovery. Keeping these consideration in mind, Won-Gil Lee and coworkers carried out computer simulations to guide the molecular design of bicyclic replacements for the CVP group, which led to the discovery of compounds **67**, **68** and **69** (Fig. 17) [77]. Against the wild-type virus, these three compounds exhibited EC_{50} values of 85 nM, 56 nM and 10 nM, respectively. Unfortunately, these compounds did not showed promising potency towards the mutant strains of HIV-1, including the challenging HIV-1 variant that contains K103N/Y181C double mutation in the RT enzyme.

Hai-Bing Zhou and coworkers described the design, synthesis and biological evaluation of indole-based trifluoropropanoates **70**–**74** as efficient inhibitors of reverse transcriptase (RT) of HIV-1 (Fig. 18). The inhibitory activities of the two enantiomers and the corresponding racemic mixture were compared. Among the non-racemic and racemic compounds, the enantiomer with the *R*-configuration usually showed the lowest EC_{50} value. For example, the R-isomer of compound **70** was identified as the most active candidate when tested in the TZM-bl cells on HIV virus type HIV−1IIIB, with an EC_{50} value of 19 nM, CC_{50} value of 210.697 μM and SI (selectivity index, CC_{50}/EC_{50}) value of 11,089, respectively [78].

Based on butterfly-shaped (Wing 1–Body–Wing 2) pharmacophore requirements, Ashok Penta and coworkers have designed 50 novel 1-phenyl-2,3,4,9 -tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid analogs as HIV-1 NNRTIs [79]. Molecular modeling, Lipinski rule of five parameter and toxicity parameters of designed analogs were employed to predict the rational structures (Fig. 19). Among the designed analogs, **75**, **76** and **77** showed significant binding free energy and predicted inhibitory constant values, they have screened off for next level of study because of their predicted poor pharmacokinetic and toxicity profile.

3.3. Indole derivatives as integrase (IN) inhibitors

Current treatments of HIV/AIDS employ a combination of therapeutic agents that target the viral reverse transcriptase, protease enzymes and viral entry. However, the ability of HIV to rapidly evolve resistance to these agents, together with their significant side effects, requires the development of new antiviral drugs with novel mode of action. Therefore, it is an urgent task to develop novel agents that interfere with alternate stages in the viral life cycle. Integrase catalyzed the integration of the HIV genome into the cellular chromosome, an essential process for HIV replication. Because of no mammalian counterparts, integrase has become an attractive target for antiviral drug design. Furthermore, integrase uses a single active site to accommodate two different configurations of DNA substrates, which may constrain the ability of HIV to develop drug resistance to integrase inhibitors (INI). Discovery of new INI has attracted great interest from the medicinal chemists in recent years.

Hui Xu and coworkers designed and synthesized eight simple N-arylindoles (**78**–**85**) as HIV-1 integrase inhibitors *in vitro* for the first time (Fig. 20) [80,81]. Among these structurally simple compounds, compound **79**, **82** and **84** exhibited the highest potency against anti-HIV-1 integrase with a EC_{50} value of 7.88 mg/mL and a TI value of 24.61.

Diketo acid (DKA) derivatives **86** and **87** were independently discovered by scientists from Shionogi and Merck as a new class of

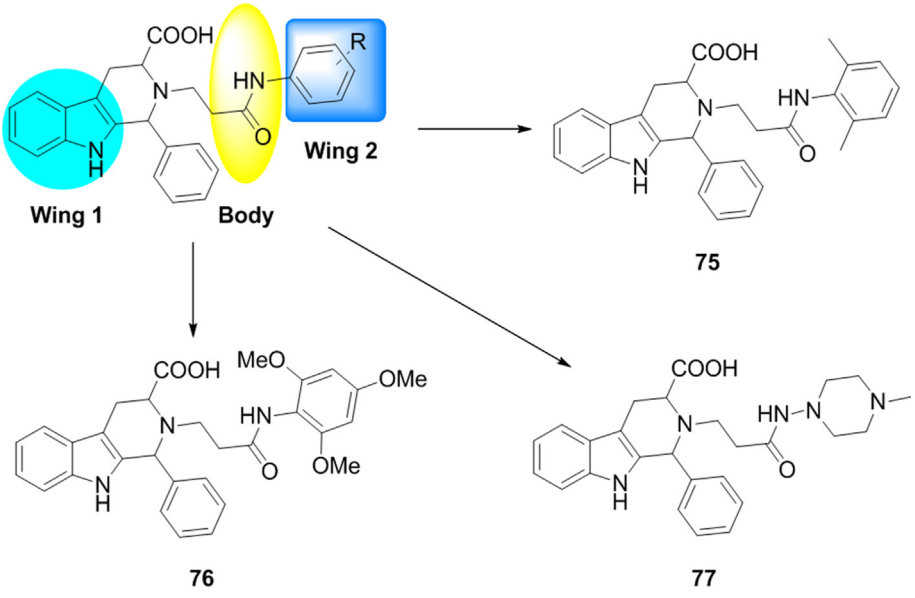

Fig. 19. Butterfly-shaped indole compounds as NNRTIs.

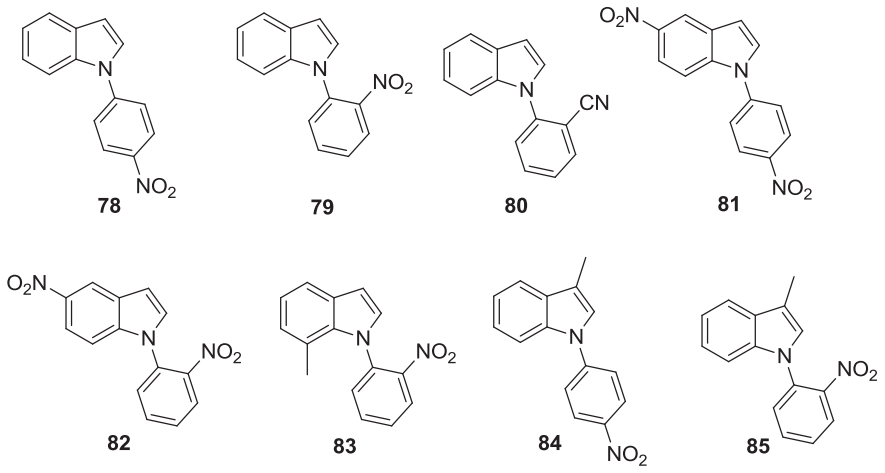

Fig. 20. N-arylindoles as integrase inhibitors.

HIV-1 integrase inhibitors (Fig. 21) [82,83]. In order to establish a coherent structure-activity relationship among the substituted indole nucleus bearing a β-diketo acid moiety, Mario Sechi and coworkers [84] designed a series of substituted indole-based DKA derivatives **88**–**91**, which showed anti-IN activity at low micromolar concentrations with varied selectivity against the strand transfer process. The experimental results have demonstrated that the diketo acid functionality is important for selectivity against strand transfer and that the aromatic ring plays a major role in potency. However, the selectivity for strand transfer is not sufficient for antiviral activity. Although diketo acid-containing compounds represent a novel class of compounds and are considered as a step forward in drug design in targeting IN, many analogues showed significant cytotoxicity and lack of antiviral activity. This work demonstrated once again that the physicochemical properties of a compound could potentially make a major contribution to antiviral activity *in vitro*.

Subsequently, in order to investigate the influence of diketo acid moiety on the biological activity and cytotoxicity, Stefania Ferro and coworkers designed and synthesized a series of novel compounds **92** and its corresponding analogues, 4-[(1-benzyl-1*H*-indol-3-yl)-carbonyl]-3-hydroxyfuran-2(5*H*)-ones **93** (Fig. 22) [85,86], in which 4-carbonyl-3 -hydroxy-furan-2(5*H*)-one moiety was introduced as a suitable replacement for the β-diketo acid motif. Even if the furanone derivatives **93** generally exhibited good potency in a micromolar range, the comparison of these derivatives with their corresponding diketo acids pointed out a diminished potency both in enzymatic and cell assays. These results suggest that the replacement of the β-diketo acid motif negatively influences the *in vitro* biological activity, probably due to a reduced conformational mobility of a closed system with respect to the open form.

Apart from targeting the critical proteins, the manipulation of specific protein–protein interactions (PPIs) involved in the HIV life cycle could potentially result in potent drugs that lack cellular toxicity. For example, the interaction between HIV-1 integrase (IN) and the cellular protein lens epithelium-derived growth factor or transcriptional coactivator p75 (LEDGF/p75) has recently gained attention as a valuable target for a novel antiviral strategy. For example, Chimirri and his coworkers established a structure-based pharmacophore model based on the X-ray crystal structure of HIV-1 IN in complex with LEDGF/p75 IBD [87]. Then, the 3D pharmacophore model was used as a query in a virtual screening approach to filter a library of 3055 small molecules and produced compound **94** as the best hit. After optimization, compounds **95** and **96** (Fig. 22) were obtained. In agreement with the prediction, compound **95** showed a higher potency than **94**, while compound **96** proved to be the most active molecule, providing a valid starting point for the discovery of new and more potent derivatives able to disrupt PPIs between IN and its intracellular cofactor LEDGF/p75.

After a number of rational modifications both on the indole system and the benzyl moiety, 4-[1-(3,5-dimethylbenzyl)-4-hydroxy-1*H*-indol-3-yl]-2-hydroxy-4-oxobut-2-enoic acid **97** was

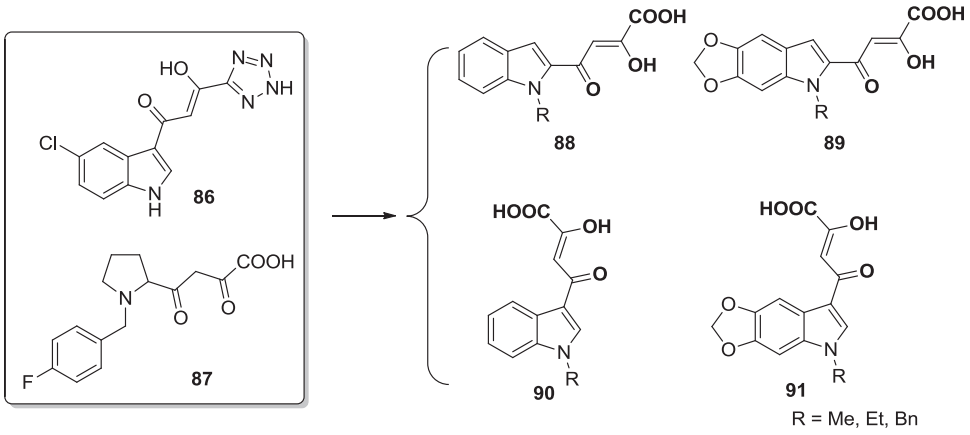

Fig. 21. Diketo acid (DKA) derivatives as integrase inhibitors.

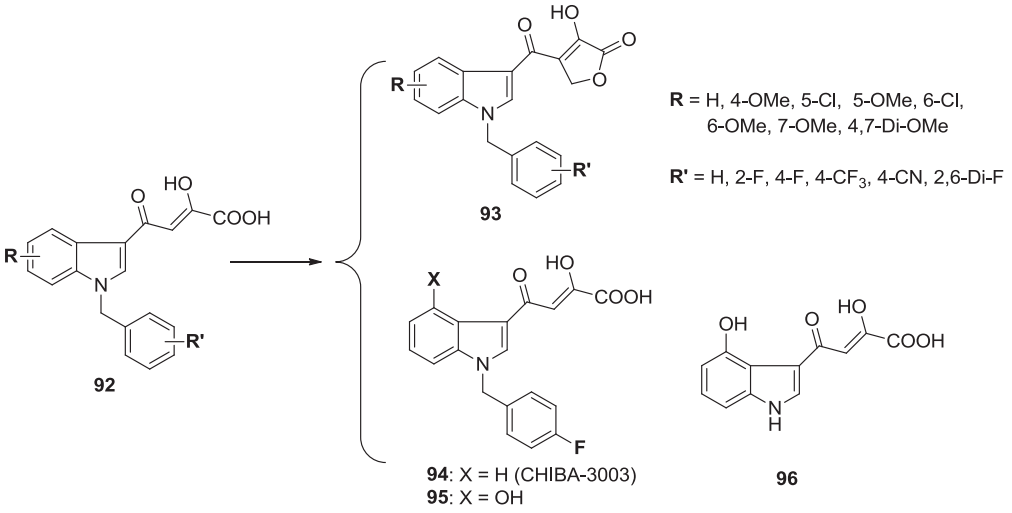

Fig. 22. Optimization of DKA derivatives as integrase inhibitors.

identified as the most potent compound with an IC_{50} value of 3.5 μM (Fig. 23) [88,89]. Methylation of the hydroxyl group afforded the first dual inhibitor of HIV-1 integration process, compound **98**, which inhibits both the IN ST step (IC_{50} = 0.14 μM) and IN-LEDGF/p75 interaction (IC_{50} = 36 μM). Very interestingly, the replacement of the 4-fluorobenzyl portion at N-1 with a 3,5-dimethylbenzyl moiety negatively influenced the inhibition of IN ST step. Compound **99** drastically reduced the ST inhibitory effects with respect to compound **98** (IC_{50} = 5.49 μM versus IC_{50} = 0.14 μM). Moreover, compound **99** showed a poorer anti-HIV activity (EC_{50} = 4.63 μM versus EC_{50} = 0.59 μM) in MT4 cells and cytotoxicity at the same concentrations. The introduction of an additional methoxy group at C-5 or C-7 position increases the IN-inhibitory effects [90]. For example, the disubstituted compound **100** is more potent than the 4-monosubstituted derivative **98**. Moreover, the simultaneous presence of the methoxy substituent at 5 and 7 positions afforded the most potent INSTI of this series, the 4-[1-(4-fluorobenzyl)-5,7-dimethoxy-1*H*-indol-3-yl]-2- hydroxy-4-oxobut-2-enoic acid **101**; it proved to be active at 6 nM concentration that is comparable to raltegravir (7 nM) and better than elvitegravir (15 nM), two HIV integrase inhibitors approved by US FDA in 2007 and 2012, respectively. On the contrary, the introduction of an additional methoxy group at C-6 seems to negatively influence the activity of this class of INSTIs.

Encouraged by these results, with the aim to identify small molecules able to inhibit both the IN strand-transfer step and IN-LEDGF/p75 interaction, Rogolino and coworkers evaluated the potent IN ST inhibitor **98** and two analogues (**102** and **103**) and their magnesium(II) complexes (**104**) for their ability to act as dual inhibitors (Fig. 24) [91]. Both the free ligands (**102** and **103**) are able to inhibit the IN-LEDGF/p75 interaction at mM values, and the metal complexes (**104**) exhibited IN inhibition potency in low nM or μM concentration range. Moreover, these magnesium compounds showed good antiviral activity on infected cells. This is the first data regarding the activity of metal complexes as allosteric inhibitors, and offers a promising approach to prevent viral replication and underlines the possibility to use coordination chemistry to obtain unconventional scaffold to target enzymes.

Based on the previously obtained SAR information and benzyl-indole derivatives (**97**, **98**) as anti-HIV agents, Stefania Ferro and

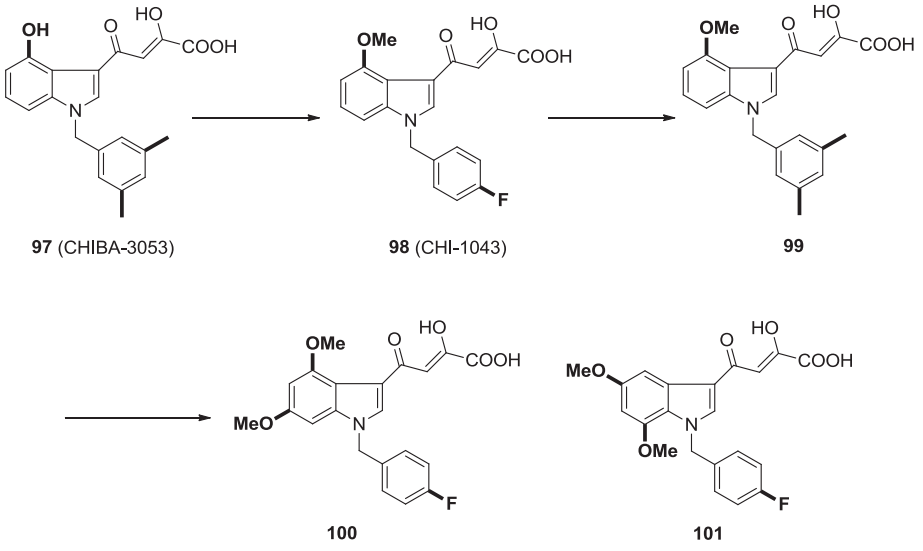

Fig. 23. Rational modifications of DKA derivatives as integrase inhibitors.

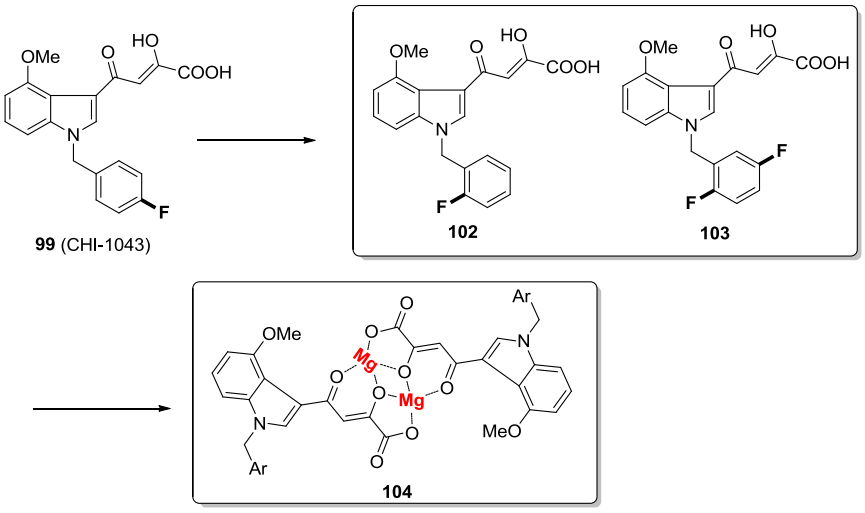

Fig. 24. Magnesium(II) complexes of DKA derivatives as novel integrase inhibitors.

coworkers reported their research on the identification of new dual target small molecules able to target different steps of HIV-1 life cycle (Fig. 25), and obtained two series of novel anti-HIV agents (**105**, **106**), some of which are dual inhibitors of the integration process acting both in the IN strand-transfer step and by disrupting the protein–protein interaction between IN and its cofactor LEDGF/p75, and compound **107** is the most active one [92].

Laura De Luca and coworkers used the fragment hopping approach to design and synthesize novel non-peptidyl compounds (Fig. 26) that mimic the biological function of some IBD residues and in particular the LEDGF hot spot residues Ile365 and Asp366 [93]. However, these newly synthesized compounds generally were not able to produce significant inhibitory effects. The most active molecules were derivatives **109** and **111** with a percentage of inhibition of 34% and 39% at a fixed dose of 100 μM, significantly lower than that of prototype **97**.

3.4. Indole derivatives as protease inhibitors

Protease (PR) inhibitors became available in the 1990s and have proven effective to an important mean to treat viral disease [94], considerable research has been performed to find "protease inhibitors" to attack virus at that phase of its life cycle and led to some FDA-approved protease inhibitors in clinic trail or in development [95]. For example, HIV protease plays a key role in the life cycle of the virus, its inhibition prevents maturation of the viral particles and renders them noninfectious. More than 25 years after its discovery, HIV PR remains one of the primary targets for development of novel HIV treatments. Recently, allosteric regulation of HIV PR activity has been recognized as a novel way to limit the development of drug-resistance. X-ray crystallography experiments showed that two indole-carboxylate small molecules, indole-6-carboxylic acid (**112**) and 3-indolepropionic acid (**113**) (Fig. 27), could be used as fragment-like starting points for the discovery of novel HIV PR inhibitors, although these two fragments did not show significant inhibition of PR up to the concentration of 1 mM. In addition, Lucia Chiummiento and coworkers reported the synthesis and antiviral activity of new non-peptidic heteroaromatic molecules **114**–**116** (Fig. 27) as protease inhibitors. Among them the best one **114** showed a moderate potency ($IC_{50} = 1$ μM), considering the novel skeleton and ease of preparation, this compound represented a reference structure for further modification.

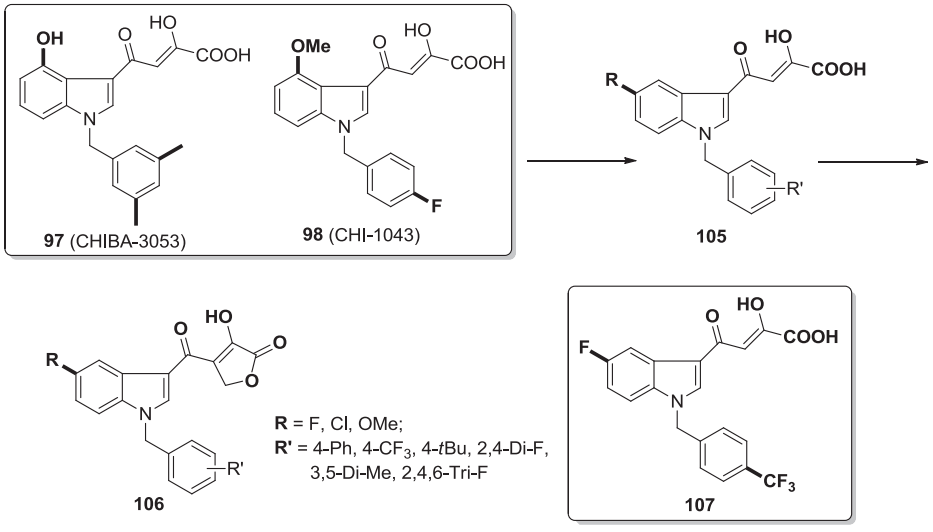

Fig. 25. DKA derivatives as dual integrase inhibitors.

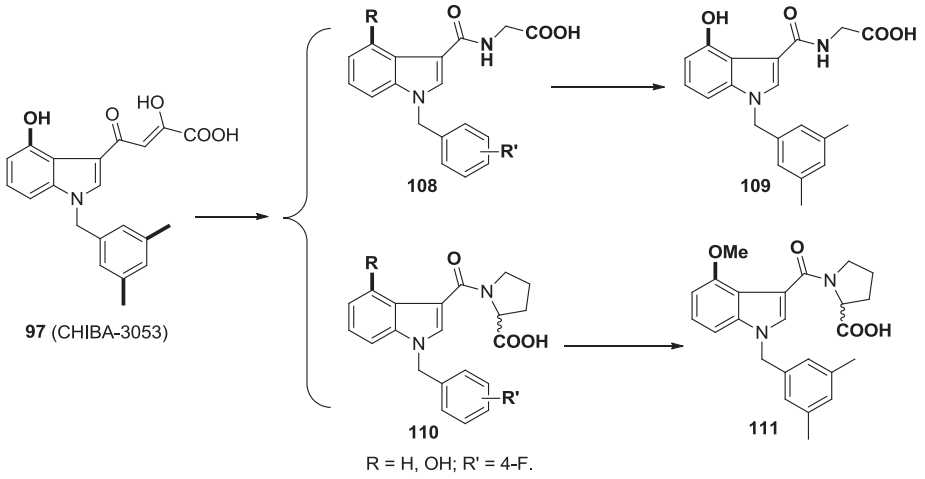

Fig. 26. Non-peptidyl DKA derivatives as integrase inhibitors.

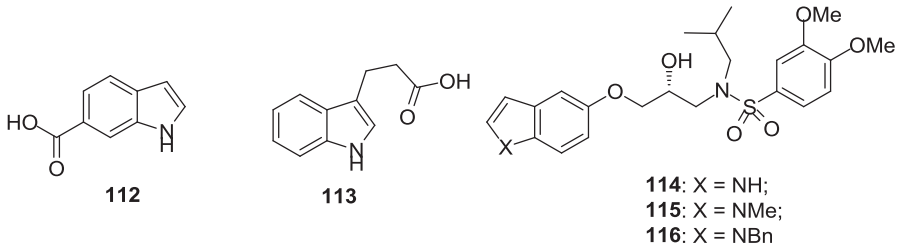

Fig. 27. Indole-carboxylate molecules as Protease (PR) inhibitors.

The hepatitis C virus (HCV) infects approximately 170 million people worldwide. The NS3 protease has been considered as one of the most attractive targets for anti-HCV therapy because it is essential for viral replication and formation of infectious viral particles. Considerable efforts by different research groups have been directed toward development of HCV NS3 protease inhibitors [96]. For example, Nasser S. M. Ismail and coworkers used computational simulations techniques, such as molecular docking and pharmacophore modeling, to design novel indole-based derivatives as HCV NS3 protease inhibitors (Fig. 28). Among the compounds showing significant high simulation docking score and fit values, compounds **117** and **118** were identified as the most potent candidates with IC_{50} values of 15 and 13 μM, respectively [97].

3.5. Indole derivatives as polymerase inhibitors

In addition to NS3, the nonstructural region of the HCV genome encodes several additional enzymes that are believed to play fundamental roles in the viral life cycle. NS5B RNA-dependent RNA polymerase, one of these central enzymes in the viral replication cycle, has emerged as an especially attractive target for drug discovery efforts toward antivirals for HCV and has been described as the most drugable HCV protein. Small molecule inhibitors of this target have received much attention in the recent past as potential therapeutic agents for treatment of HCV infection, including the well-known anti-HCV drug Sovaldi. Recently, Ariamala Gopalsamy and his coworkers designed and synthesized a novel class of HCV NS5B polymerase inhibitors containing 2,3,4,9-tetrahydro-1*H*-carbazole and 1,2,3,4-tetrahydro-cyclopenta[*b*]indole scaffolds based on the lead compound **119** (Fig. 29) [98]. Structure-activity relationships indicated that optimization of the aromatic region showed preference for 5,8-disubstitution pattern in both the scaffolds examined while favoring the *n*-propyl moiety for the C-1 position. 1,2,3,4-Tetrahydro-cyclopenta[*b*]indole scaffold was slightly more potent than the corresponding 2,3,4,9-tetrahydro-1*H*-carbazole. For example, 2,3,4,9-Tetrahydro-1*H*-carbazole **120** and 1,2,3,4-tetrahydro-cyclopenta[*b*]indole **121** displayed IC_{50} values of 3200 nM and 550 nM against HCV NS5B enzyme, respectively.

Steven Harper and coworkers reported a series of 2-(indol-1-yl) acetamides as potent allosteric inhibitors of the HCV NS5B

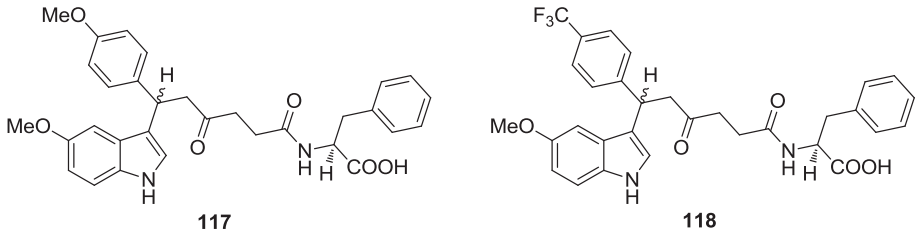

Fig. 28. Novel indole-based derivatives as protease inhibitors.

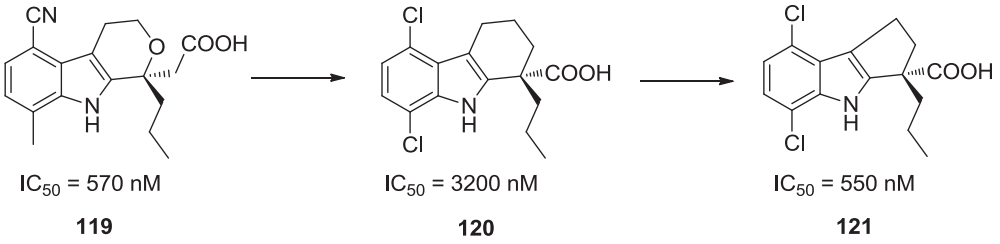

Fig. 29. Compounds with indole scaffolds as polymerase inhibitors.

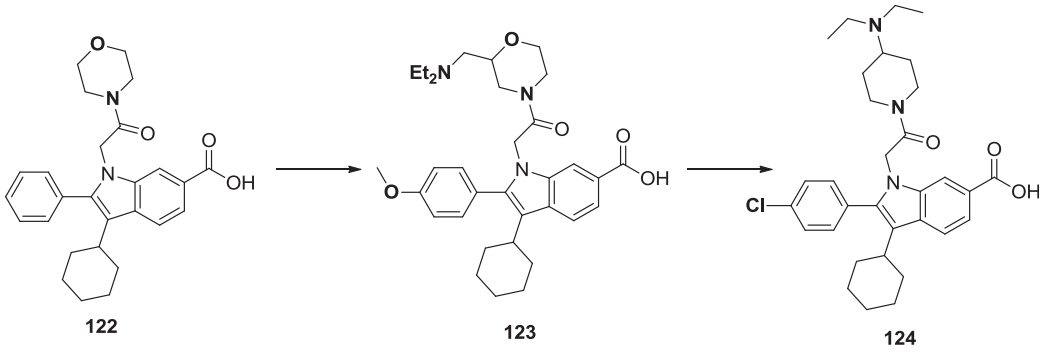

Fig. 30. Indole-*N*-acetamides as polymerase inhibitors.

polymerase enzyme (Fig. 30). Based on the lead structure of indole-*N*-acetamide **122**, that are potent inhibitors of the NS5B enzyme and show promising activity in the replicon assay, a library-based approach toward exploration with the intracellular activity improvement was established, some derivatives (**123**–**124**) showed strong potency in the cell-based assay under routine conditions and in the presence of a high concentration of human serum, especially compound **124**, it showed encouraging PK properties in both rat and dog and is clean in an extensive panel of counter screening assays [99].

3.6. Indole-based natural products and their antiviral activity

During the past fifty years, natural products have served as a major source of drugs, about fifty percent of today's commercial drugs are derived from natural product. While, there are only few drugs available currently for the cure of viral diseases, including acyclovir which is modeled on a natural product parent. In order to discover novel antiviral natural products with new mode of action, many research efforts have been devoted for the discovery of new antiviral natural products, the following focus on the indole natural products and their antiviral activities, summarize the structure property, hoping to inspire new and even more creative approaches.

Sattazolin (**125**) (Fig. 31) is an indole acyloin natural product [100], it is reported to exhibit potent antiviral activity with an ID_{50} of 1.5 μg/mL against herpes simplex virus type 1 (HSV1) and type 2 (HSV2) [101]. Drymaritin (**126**), a novel indole alkaloid isolated from *Drymaria diandra*, is reported to exhibit anti-HIV effects in H9 lymphocytes with an EC_{50} value of 0.699 μg/mL and a TI of 20.6 [102]. Caulerpin (**127**) was isolated from the green alga *Caulerpa racemosa*, collected on vertical rock walls in São Pedro and São Paulo Archipelago, it is reported the antiviral activity against Bovine viral diarrhea virus (BVDV) replication, also suggest that it might be relevant to evaluate antiviral activity against HCV due to their similar characteristics [103].

Minghua Chen and coworkers reported the isolation of seventeen new indole alkaloids and fourteen known analogues from an aqueous extract of the root of *Isatis indigotica* (Fig. 32), and compounds **128**–**130** and arvelexin (**131**) show antiviral activity against the influenza virus A/Hanfang/359/95 (H3N2), with IC_{50} values of 3.70–12.35 μM [104].

Paromita Bag and coworkers reported the isolation of an indole alkaloid 7-methoxy-1-methyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole **132** (Harmaline, HM) from an ethnomedicinal herb *Ophiorrhiza nicobarica*, and it demonstrated a potent anti-HSV-1 activity against both wild type and clinical isolates of HSV-1 (Fig. 33). It is reported that this indole alkaloid **132** interferes with the viral immediate-early (IE) transcriptional events, and significantly reduces virus

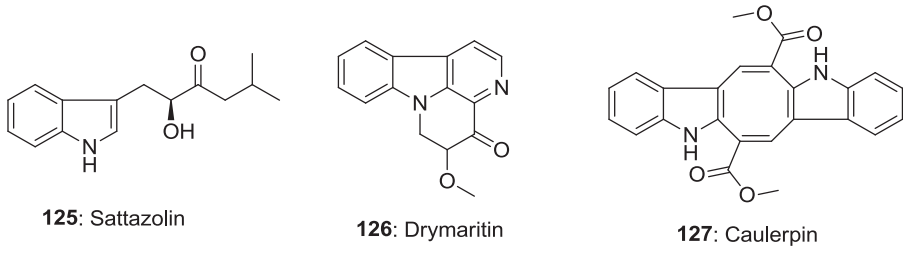

Fig. 31. Structures of antiviral Sattazolin, Drymaritin and Caulerpin.

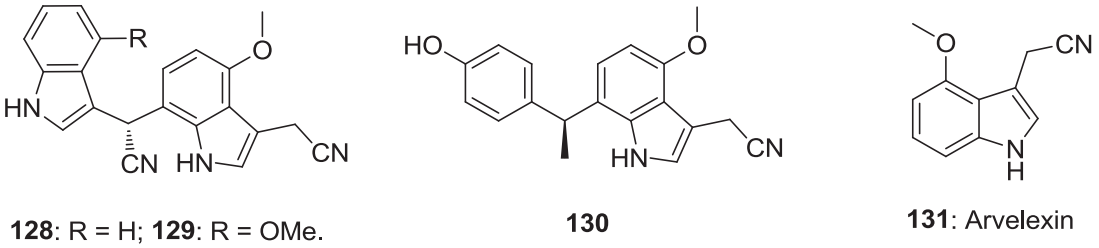

Fig. 32. Structures of antiviral indole alkaloids from root of *Isatis indigotica*.

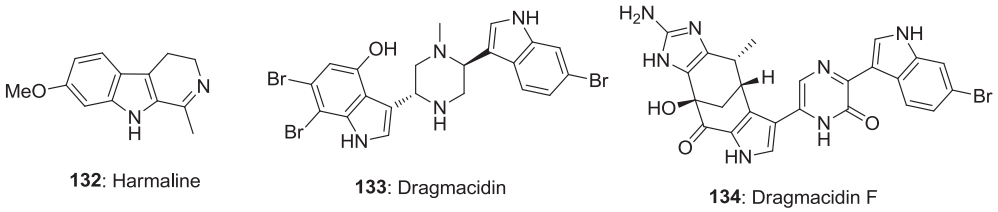

Fig. 33. Structures of antiviral Harmaline, Dragmacidin and Dragmacidin F.

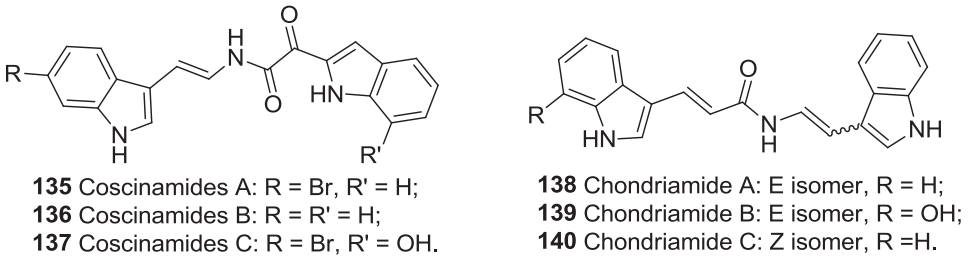

Fig. 34. Structures of antiviral Coscinamides and Chlondriamides.

yield in mice at well-tolerated dose. Because IE complex is a critical component of herpes virus reactivation mechanism, **132** may help to prevent both the multiplication and reactivation of HSV, and provide an interesting molecular target for the development of better HSV therapy [105,106].

The bioactive marine natural products dragmacidins **133**–**134** (Fig. 33), obtained by an exhaustive set of protocols from a marine sponge of the genus *Halicortex*, also reported to display modest antiviral activity [107], and compound **134**, dragmacidin F, containing an unprecedented carbon skeleton that is very likely derived from cyclization of a partially oxidized form of dragmacidin series derivatives, it showed *in vitro* antiviral activity against HSV-1 (EC_{50} = 95.8 μM) and HIV-1 (EC_{50} = 0.91 μM) [108].

The bisindole alkaloids are a class of marine natural products that show unique promise in the development of new drug leads (Fig. 34) [109]. Coscinamides **135**–**137**, which contains unusual 2-ketoenamide functionality, showed partial cytoprotection activity against HIV in the NCI assay. Chondriamides **138**–**140** are indolic enamides and show antiviral activity against HSV II with IC_{50} values of about 1 μM [110].

Cheng-Jian Tan and coworkers reported the isolation, structural elucidation, and anti-HIV-1 activity of three novel indole alkaloids trigonoliimines A-C (**141**–**143**) (Fig. 35) with unprecedented polycyclic skeletons. They were isolated from the extract of the leaves of *Trigonostemon. lii* Y. T. Chang. The anti-HIV-1 activity of compound **141** and **142** was tested by a microtiter syncytium formation infectivity assay with Zidovudine (EC_{50} = 0.02 μM, TI = 59,924) as a positive control. Trigonoliimine A showed modest anti-HIV-1 activity (EC_{50} 0.95 μM, TI = 7.9) [111].

Zhongli Xu and coworkers independently reported the structures of pentacyclic indolocarbazoles from *Streptomyces* spp. (Fig. 36), namely the diastereomers oridamycin (**144**) [112] and xiamycin A (**145**) [113], the xiamycin B (**146**), and the seco-derivative indosespene (**147**) [114], these rare endophyte

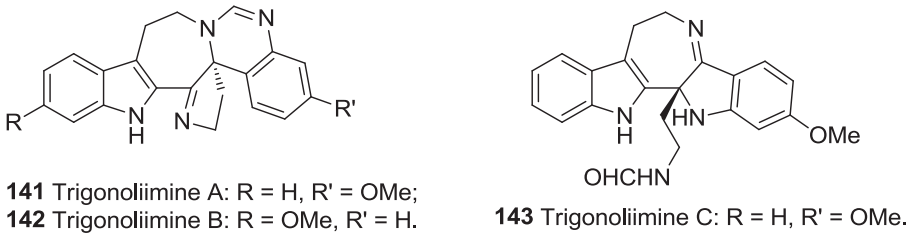

Fig. 35. Structures of antiviral Trigonoliimines.

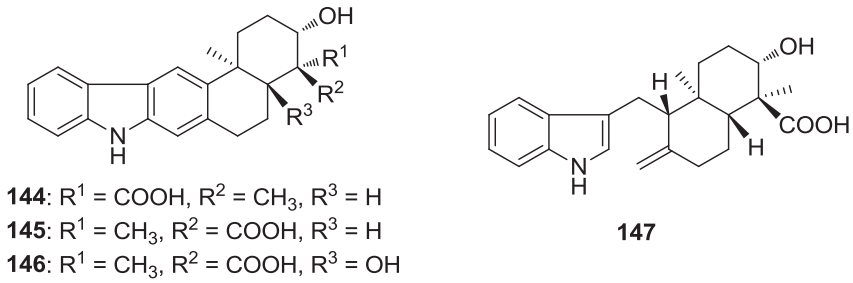

Fig. 36. Structures of antiviral pentacyclic indolocarbazoles.

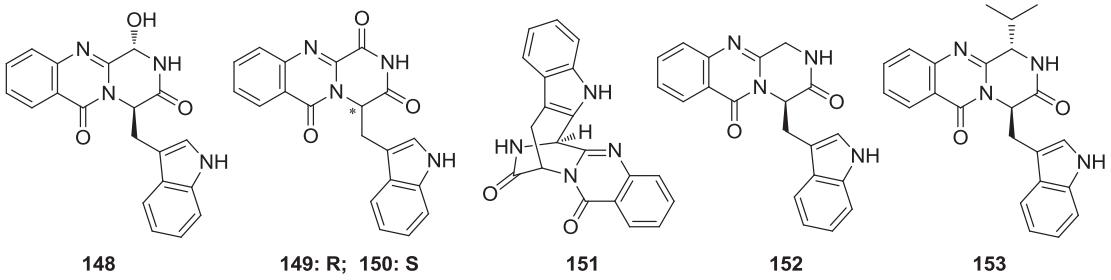

Fig. 37. Structures of antiviral indole alkaloids from *Cladosporium* sp. PJX-41.

metabolites likely play an ecological role in their habitats because their antiviral activity may contribute to the antibiotic reservoir of the mangrove plants [115].

Jixing Peng and coworkers reported the isolation of three new indole alkaloids (**148**–**150**) and three known alkaloids (**151**–**153**) (Fig. 37) from the culture of the mangrove-derived fungus *Cladosporium* sp. PJX-41. All compounds were evaluated for their antiviral activities against influenza virus A (H1N1), and compounds **150** exhibited significant activities (IC_{50} = 85 μM) against H1N1 [116].

Eudistomins are β-carboline derivatives (Fig. 38), isolated from different kinds of ascidians (marine tunicates of the family Ascidiacea), such as *Ritterella sigillinoides, Lissoclinum fragile* or *Pseudodistoma aureum*. In recent investigations, it is reported that eudistomins containing the oxathiazepine ring (**154**–**158**, Eudistomins C, E, F, K, and L) showing the most significant antiviral activity against HSV-1, of which C and E, with a phenolic group were as active as at 0.005–0.01 μg/disk. Eudistomins C and E are also reported to possess the activities against RNA viruses such as Coxsackie A-21 virus, equine rhinovirus and against DNA viruses [117].

What's worth noting is the indole dimer derivatives Topsentin **159** and bromotopsentin **160** (Fig. 38) isolated from the Caribbean deep-sea sponge *Spongosorites ruetzleri*, they exhibited antiviral activities in corona virus A-59, vitro against HSV-1 and Vesivular stomatitis virus (VSV) [117].

Compounds **161** CPI-2081a and **162** CPI-2081b (Fig. 39), isolated from a biologically active culture supernatant of *Streptomyces* sp. NCIM2081 by Sihgh et al. in 2010, as the cysteine protease inhibitor, it is found that nanomolar concentration of compounds CPI-2081a is able to inhibit papain hydrolytic activity, it also showed significantly inhibitory activity of tumor cell migration at sub cytotoxic concentration [118,119].

4. Prospective

It is reported that macrocyclic indole derivatives can demonstrate favorable druglike properties [120,121], including good solubility, increased lipophilicity, enhanced membrane penetration, improved metabolic stability, and good oral bioavailability with desirable pharmacokinetic and pharmacodynamic properties [122,123]. Compound **25** (TMC647055), the 17-membered macrocyclic indole derivative, is currently being evaluated in phase II clinical trials. It may set up a very good example for exploited strategy of indole macrocycle as antiviral agent.

We also notice that, as an important class of marine natural products, bis and trisindole alkaloids show unique promise in the development of new drug leads [110,124,125]. Bis and trisindole may be treated as new drug leads due to their unique structures and functionalities. This area is well worth more scientific attention wherein lies a huge potential for development of new active

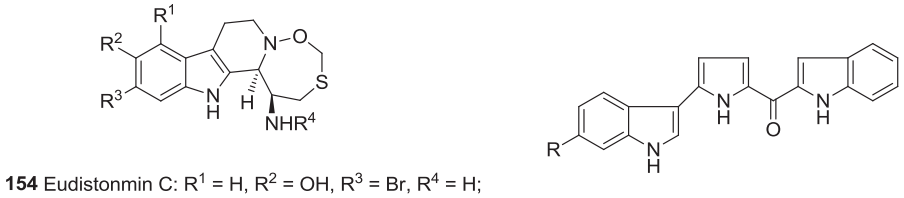

Fig. 38. Structures of antiviral Eudistomins, Topsentin and Bromotopsentin.

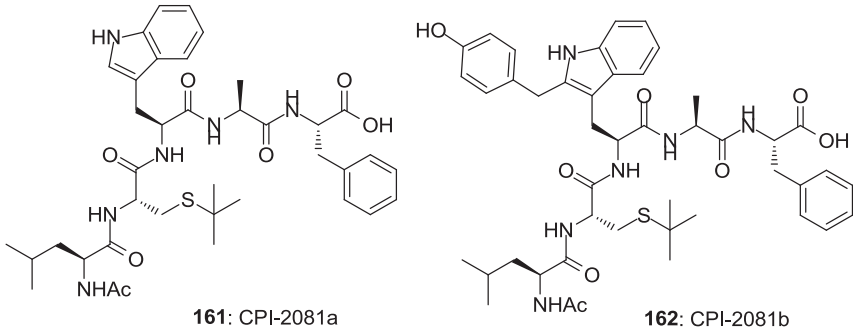

Fig. 39. Structures of CPI-2081a and CPI-2081b.

compounds and exploration of various biological activities, so that they may be useful as novel lead structures in the future.

5. Conclusion

As the most abundant heterocycle in nature, indole is commonly found in biologically active natural products, pharmaceuticals and agrochemicals. There has been an increasing interest in the use of indole derivatives as bioactive molecules against different kinds of diseases. This review updates recent developments and current status of important indole derivatives in the areas of antiviral drug discovery, serves a comprehensive overview on indole antiviral agents being on the market or in clinical trials as well as currently evaluated in experimental studies, focus on recent developments of indole compounds as antiviral agents, and promote the ideas of indole macrocycle and Bis (Tris) indole as novel lead structures might be exploited in the future.

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