NF-κB: The Inducible Factors of HIV-1 Transcription and their Inhibitors

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Abstract: NF-kappaB (NF-κB), the transcription factors of HIV-1, play an important role in triggering HIV transcription. The inhibition of NF-κB activation and their signaling pathway offers a potential anti-HIV therapy strategy. This review reports the mode of action of NF-κB in triggering HIV-1 transcription and the status of the inhibitors.

Key Words :AIDS, HIV-1, NF-κB, transcription , inhibitor, LTR, IκB, IKK.

1. INTRODUCTION

Human immunodeficiency virus type 1 (HIV-1) is the causal agent of acquired immunodeficiency syndrome (AIDS). Many HIV-1 inhibitors have been investigated, such as viral binding inhibitors, virus cell fusion/uncoating inhibitors, reverse transcriptase inhibitors, integrase inhibitors, gene expression inhibitors, protease inhibitors and glucosidase inhibitors [1]. Most of these inhibitors have shown problems, such as low oral bioavailability, poor specificity, and failures due to resistance mutations. The nuclear factor kappa B (NF-κB) family of transcription factors have been demonstrated to be an essential regulator in HIV-1 gene expression and transcription [2]. Targeting NF-κB evades the problem of resistance because it is a normal part of the T-cell and is not subject to mutation. Thus HIV will not become resistant to the effects of NF-κB inhibitors [3]. NF-κB is the major inducible regulatory element involved in the long terminal repeat (LTR) transactivation and HIV-1 replication in CD4 lymphocytes [4]. This review focuses on the NF-κB as a potential target for the development of antiviral strategies against HIV-1 and presents the mode of action of NF-κB in the transcription of HIV-1 and the status of the current inhibitors of NF-κB.

2. THE STRUCTURE OF NF-κB

2.1. The NF-κB/Rel Family

NF-κB is an inducible transcription factor of the Rel family, the NF-κB/Rel family being composed of p65 (RelA), RelB, c-Rel, p50 (NF-κB1,its precursor p105), and p52 (NF-κB2, its precursor p100). NF-κB/Rel proteins exist in the form of homodimers or heterodimers. The complexes of p50/p65, p50/c-rel, p65/p65, and p65/c-rel are all transcriptionally active, while p50/p50 and p52/ p52 are transcriptionally repressive. The heterodimer of p50 and p65, which is the first described NF-κB molecule, is the most abundant form of NF-κB and most widely studied. Structurally, all NF-κB /Rel proteins share a highly conserved NH_2-terminal Rel homology domain (RHD). The RHD contains a phosphorylation site for Protein Kinase A(PKA). Phosphorylation of this site has been consided to be essential for nuclear localization of NF-κB. Close to the C-terminal end of the RHD lies the Nuclear Localization Signal (NLS), which is essential for the transport of active NF-κB complex into the nucleus (Fig. (**1**)) [5-8].

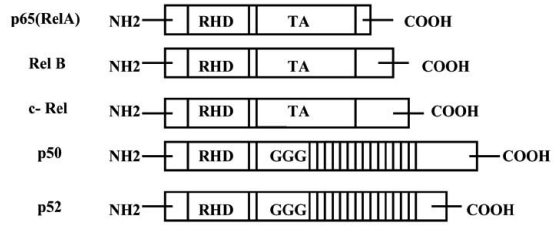

Fig. (1). Schematic representation of the NF-κB/Rel proteins family.

2.2. THE IκB FAMILY AND THE IκB KINASE

NF-κB is retained in the cytoplasm as an inactive complex in association with the inhibitory kappa B (IκB)proteins [9]. There are some known members of the IκB family: IκBα, IκBβ, IκBε, IκBγ and Bcl-3, as well as the precursor proteins p105 and p100 [10]. IκBα is the most extensively studied of the IκB proteins. Many active agents, including cytokines, viruses, and double-stranded RNAs, stimulate the activity of IκBα. Upon stimulation, IκB is phosphorylated by the IκB kinase(IKK). This modification triggers the ubiquitination of IκB. IκB is recognized and degraded by the 26S proteasome [11-13]. The IKK complex (700–900 kDa) is formed by three subunits: two catalytic subunits, the kinases IKK-α(IKK-1) and IKK-β(IKK-2) and a regulatory subunit, the NEMO protein(IKK-γ, or IKKAP) [14]. The kinase sub-units have homology within their functional domains. They both have a kinase, leucine zipper and a helix-loop-helix domain. In the heterodimeric state, the leucine zipper motifs allow formation of both homo- and heterodimers [15]. IKK rapidly phosphorylates IκBα at its two NH_2-terminal serine residues (Ser32 and Ser36). IκBα is rapidly phosphorylated and degraded, resulting in the release of NF-κB .Once released, NF-κB is able to activate target genes until

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new IκBα is synthesized [16]. Therefore, NF-κB can activate transcription of viral genes, including retroviral genes, and plays a major role in the activation of the HIV-1 provirus by external activating agents.

3. FUNCTION AND REGLULATION OF NF-κB IN INDUCING HIV TRANSCRIPTION

3.1. NF-κB-Dependent HIV-1 LTR Activity

The LTR region of the HIV-1 is divided into three regions: U3, R and U5. Meanwhile the three regions contain four functional domains: the transactivating region (TAR), the basal or core promoter, the enhancer region, and the regulatory elements. The TAR is found within the R region, the other functional domains are located within the U3 region [17].

In the enhancer region of the HIV LTR lie two adjacent NF-κB binding sites (-109 to -79), which play a central role in mediating inducible HIV gene expression. In latently HIV-1-infected cells, activation of NF-κB could trigger the transcription of HIV-1 genes, resulting in an explosive increase in HIV replication. These NF-κB responsive elements are major elements in triggering HIV LTR-transcription. Therefore, the deletion of the NF-κB sites in the LTR and the expression of NF-κB inhibitors strongly impair HIV-1 replication [18, 19]. The HIV protease-mediated cleavage of caspase 8 is necessary for optimal HIV-1 LTR activation, and the HIV-1 protease specific cleavage fragment Casp8p41 is sufficient to initiate NF-κB-dependent HIV-1 LTR activity, as well as HIV-1 replication [20].

3.2. NF-κB Signaling Pathways

The activation and subsequent binding of NF-κB to the enhancer region in the LTR of HIV-1 are essential in the regulation of the HIV-1 gene expression. Two major signaling pathways, the classical (canonical) and alternative (non-canonical) pathways (Fig. (**2**)) play a central role in HIV-1 LTR-driven transcription [21]. In the classical pathway, NF-κB exists in the form of the heterodimer of p50/p65 in unstimulated cells. NF-κB is retained in the cytoplasm as an inactive complex in association with the IκB proteins. The classical pathway is activated by tumor necrosis factor (TNF)–α and interleukin1β(IL-1β), viral and bacterial antigens, and stress-inducing agents. IκBα is phosphorylated at two N-terminal serine residues, leading to the translocation of NF-κB p50/p65 heterodimers to the nucleus [22]. In this pathway, the phosphorylation of IκB is mainly mediated by IKK-β. On the other hand, the alternative pathway is activated by different stimuli, such as lymphotoxin-β (LTβ), B cell activating factor(BAFF), and CD40 ligand. The phosphorylation of IκB is mainly mediated by IKK-α and leads to selective activation of p52/RelB heterodimers [23,24].

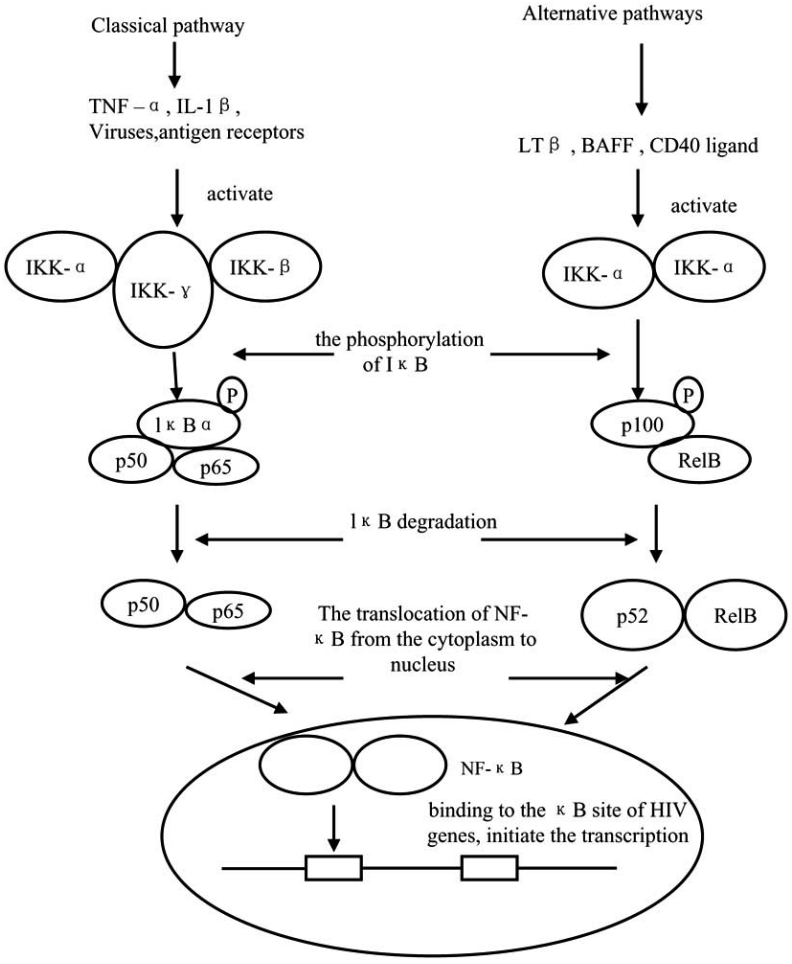


Fig. (2). NF-κB signaling pathways.

3.3. The Mode of Action of NF-κB in the Transcription of HIV-1 (Fig. (3))

In the classical signaling pathway, in the cytoplasm, PKA is involved in the IκB-NF-κB complex . IκB keeps PKA inactivated by masking the catalytic center. In resting cells, PKA is composed of two catalytic subunits and a homodimer of two regulatory subunits that can dissociate upon activation by camp [25]. Upon stimulation, IκBα is phosphorylated and degraded by the IKK. Ubiquitination and degradation of IκBα by the 26S proteasome complex activates PKA. PKA phosphorylates the NF-κB p65 subunit at Serine 276 [26]. Upon release of IκBα, the NLS on the p65 subunit becomes unmasked, which allows for a rapid translocation of NF-κB from cytoplasm to the nucleus [27].

In the nucleus, the phosphorylated p65 recruits the transcriptional coactivators histone acetyltransferase p300/CBP to the NF-κB -bound promoter [28]. N-terminal of p65 specifically binds the C-terminal of A-kinase interacting-protein 1 (AKIP1). AKIP1 enhances the transcriptional activity by maintaining the nuclear localization of p65. Meanwhile AKIP1 enhances the Ser276 phosphorylation of p65 by recruiting PKA without changing the substrate specificity [29]. Once in the nucleus, the disulphide bond of the cysteine 62 on the p50 subunit of the NF-κB p50/p65 heterodimers is reduced by a cellular reducing catalyst thioredoxin(TRX). This selective reduction of the oxidized p50 subunit is mediated by the nuclear signaling protein redox factor-1 (Ref-1) and TRX. The reduced p50/p65 heterodimers displace the repressive p50-HDAC1 complexes which bound to κB sites

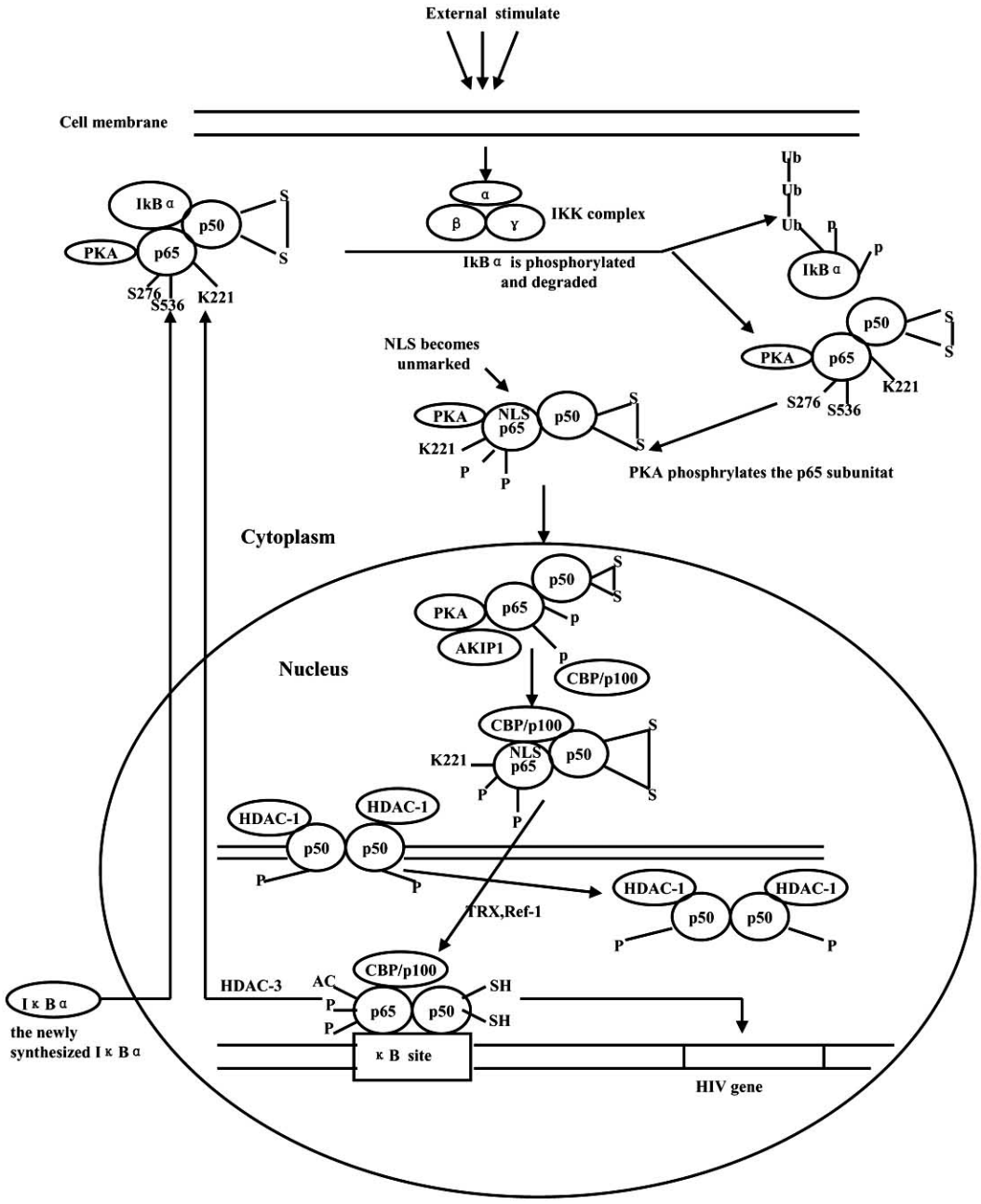


Fig. (3). The mode of action of NF-κB in the transcription of HIV-1.

of the HIV-1 LTR under basal conditions [30]. Then NF-κB p50/p65 heterodimers bind to the enhancer region in the LTR of HIV-1 and initiate HIV-1 transcription.

In order to terminate the NF-κB transcriptional response, HDAC-3 deacetylates the p65 subunit of the NF-κB p50/p65 heterodimer. The newly synthesized IκBα enters the nucleus and binds to the deacetylated p65. Then NF-κB p50/p65 heterodimers are removed from the viral promoter to the cytoplasm, leading to the termination of the NF-κB -dependent transcription [31]. In fact, HIV LTR-driven transactivation and HIV replication can be blocked by IκBα over-expression. The balance between NF-κB and IκBα at the nuclear level would be a key mechanism involved in both the maintenance of HIV latency and the induction of low level HIV replication [32].

4. NF-κB TARGETED HIV INHIBITORS

Several compounds were reported to suppress HIV-1 gene expression and replication through the inhibition of NF-κB activation. The inhibitors studied against NF-κB into five categories: (1) antioxidants, against oxidative stress conditions, which aid in NF-κB activation, (2) PKC inhibitors, (3) IκB phosphorylation and degradation inhibitors, (4) direct inhibitors of NF-κB, which do not allow DNA binding, (5) mechanism-unidentified inhibitor.

Antioxidants

NF-κB activation is stimulated by a pro-oxidative cell status. Antioxidants inhibitors have been shown to inhibit NF-κB activation by acting as general free-radical scavengers [33]. N-acetylcysteine (NAC) (Fig. (**4**)), which is bioavailable from the diet, is a sulfhydryl-containing compound. Structurally, the biological activity of NAC is attributed to its sulfhydryl group. And its acetyl substituted amino group affords it protection against oxidative and metabolic processes. Another antioxidant studied in the context of NF-κB is pyrrolidine dithiocarbamate (PDTC) (Fig. (**4**)), which is a dithioic acid. PDTC has been reported to be a potent inhibitor of NF-κB activation *via* suppression of TNF-α related activation pathways. Various antioxidants, such as α-lipoic acid, oltipraz, α-tocopherol (vitamin E), and butylated hydroxyanisole (BHA) (Fig. (**4**)) were also found to inhibit HIV-1 LTR-directed gene expression and to suppress viral replication [34]. Although these antioxidants hold potential as general inhibitors of ractive oxygen species (ROS) related NF-κB activation, the selectivity of these antioxidants for the NF-κB system is still a main challenge.

PKC Inhibitors

NF-κB is present in most cells as an inactive complex that is activated by diverse agents such as cytokines TNF-α and interleukin- 1 (IL-1), porbol 12-myristate 13-acetate (PMA). The mechanism of inhibitory action of protein kinase C (PKC) inhibitors on virus replication and NF-κB-induced transactivation of HIV-1 gene expression has been elucidated as due to blocking PKC-dependent PMA- or TNF-α-induced activation of NF-κB [35].

Gö 6976 (Fig. (**4**)), a synthetic inhibitor of PKC, structurally belongs to the nonglycosidic indolocarbazole, which inhibits induction of HIV-1 from the latent/ low- level-producing proviral state in vitro without the development of resistance [36].

Pentoxifylline (PTX) [1-(5'-oxohexyl)-3,7-dimethylxanthine] (Fig. (**4**)) could down regulate HIV-1 gene expression and viral replication with little toxicity to the cells. The mechanism of inhibitory action of PTX on virus replication and NF-κB-induced transactivation of HIV-1 gene expression has been elucidated as being due to inhibiting PKC-catalyzed activation of NF-κB [37].

The combined use of anti-Tat sFv intrabodies and the two NF-κB inhibitors Gö 6976 and PTX resulted in more durable inhibition of HIV-1 replication than was detected with the NF-κB inhibitors alone or with the anti-Tat sFv intrabodies alone. Such combination may enhance the efficacy and reduce the toxic effect of individual molecules. They may also minimize or retard the emergence of drug-resistant escape variants of HIV-1 [38].

IκB Phosphorylation and Degradation Inhibitors

NF-κB is retained in the cytoplasm as an inactive complex in association with the IκB proteins. The phosphorylation and degradation of IκB is necessary to make NF-κB free and move to the nucleus. IκB is phosphorylated by the IKK. Some inhibitors were also found to suppress IκB phosphorylation and degradation through the inhibition of IKK activity and IκB activity [39-42].

ACHP(2-amino-6-(2-(cyclopropylmethoxy)-6-hydroxyphenyl)-4-(piperidin-4-yl)nicotinonitrile) (Fig. (**4**)) was developed and evaluated as a potent and specific inhibitor for IKK-α and IKK-β [39]. This compound can inhibit HIV-1 replication in OM10.1cells latently infected with HIV. EC_{50} was approximately $0.56\mu mol \cdot L^{-1}$ and CC_{50} was approximately $15\mu mol \cdot L^{-1}$. ACHP acts as a potent suppressor of TNF–α induced HIV replication in latently infected cells, which is mediated through suppression of IKK activity. This compound and its derivatives appear to be feasible candidates for novel anti-HIV therapy, but ACHP is not potent in actively replicating cells and might cause aberrant regulation of inflammatory cytokines. Therefore, further studies are needed to evaluate its feasibility as a potential drug for eventual anti-HIV therapy.

Herpes simplex virus type 1 (HSV-1) infection could induce IKK-mediated NF-κB activation and enhance HIV-1 expression and replication in human T cells. NF-κB activities are induced by HSV-1 infection in human T cells. The block of IKK function can inhibit HIV-1 LTR expression in transient transfection assays, as well as in preventing HSV-1-induced HIV-1 replication in chronically infected T cells [40]. The cyclopentenone prostaglandin A1 (PGA1) (Fig. (**4**)) is a potent inhibitor of IKKβ. Research indicates that PGA1 or prostanoid-derived molecules could be good candidates as potent inhibitors of HSV-1-induced HIV-1 reactivation, and suitable for use in combination with conventional anti-herpetic agents in HIV-infected individuals.

Norepinephrine (NE), a catecholamine neurotransmitter, has been reported to inhibit HIV-1 infection [41]. NE increased cytoplasmic levels of IκBα, a natural inhibitor of NF-κB. Those results suggested that NE down- regulates HIV-1 LTR, at least in part, through inhibition of NF-κB

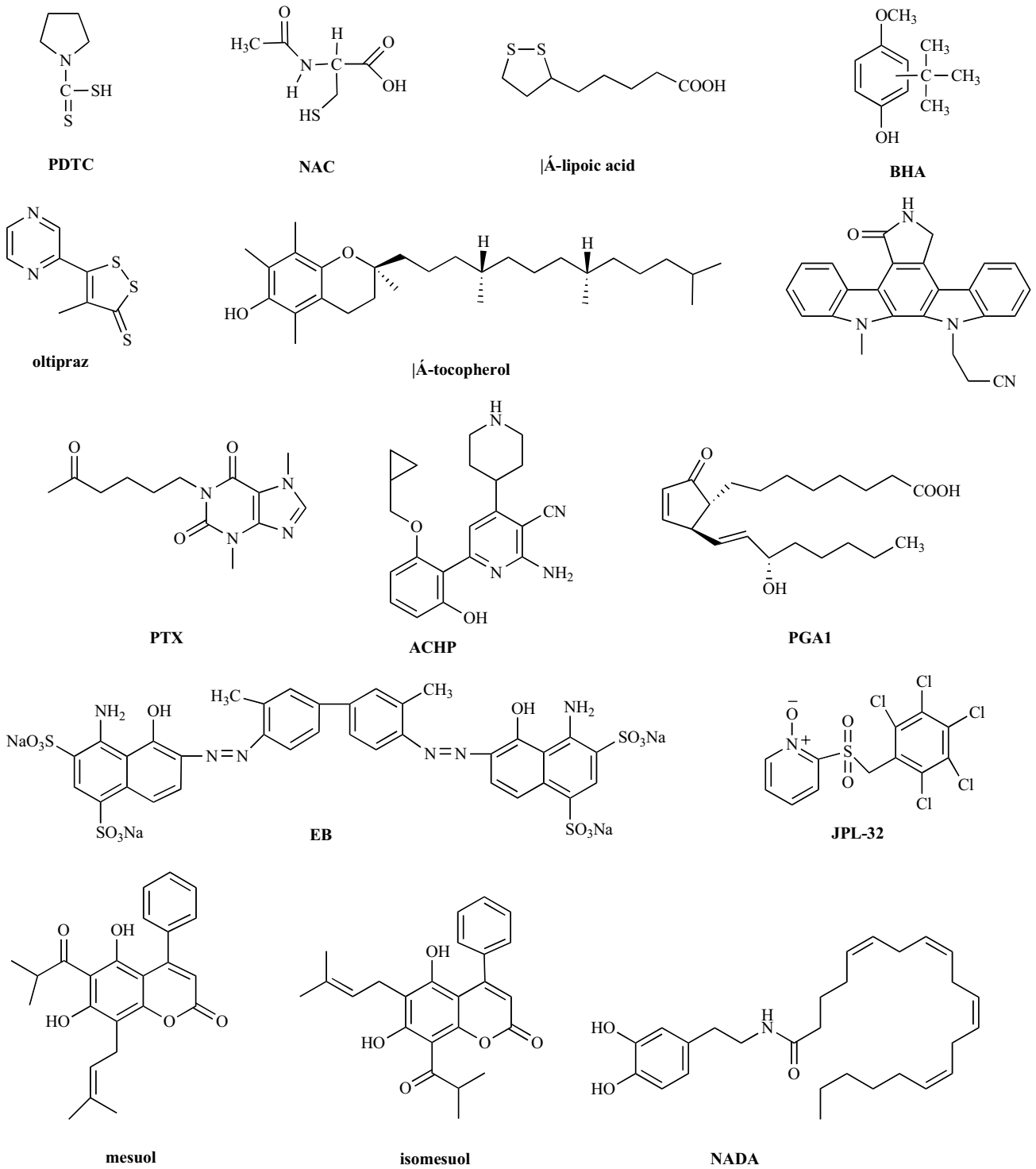


Fig. (4). Chemical structures of NF-κB inhibitors.

activity. NE and other catecholamines apparently mediated quite different effects on NF-κB activity. The reason is unknown. The precise molecular mechanisms remain obscure. Further studies are needed to clarify this issue [41].

Kwon *et al*. [42] examined the effect of tetracycline-inducible expression of transdominant repressors of IκBα (TD-IκBα) on HIV-1 multiplication. TD-IκBα was inducibly expressed as early as 3 h after doxycycline addition. Induced TD-IκBα expression decreased endogenous IκBα expression to undetectable levels and dramatically reduced both NF-κB DNA binding activity and LTR-directed gene activity. TD-IκBα induction altered dramatically de novo HIV-1 infection of Jurkat cells and inhibited HIV-1 multiplication.

Direct Inhibitors of NF-κB

NF-κB has kappa B binding sites in the HIV-1 LTR. The kappa B binding sites are critical in HIV gene expression . In

the classical pathway, NF-κB exists in the form of the heterodimer of p50/p65 in unstimulated cells. NF-κB p50/p65 heterodimers bind to the enhancer region in the LTR of HIV-1 and initiate HIV-1 transcription. Some inhibitors directly act on the p50 subunit and the p65 subunit of NF-κB, which do not allow NF-κB DNA binding.

Evans Blue (EB) (Fig. (**4**)) has been recognized as an inhibitor of NF-κB -DNA binding [43]. EB docked and energy minimized with the DNA binding region(DBR) of the p50 subunit of NF-κB The DBR for DNA are residues 59–71 of the p50 subunit of NF-κB (starting with 59: Arg, Tyr, Val, Cys, Glu, Gly, Pro, Ser, His, Gly, Gly, Leu, Pro:71). Molecular modeling indicated that EB was subjected to docking onto the p50 protein, with the DBR, defined as the docking site. EB interacts in an energetically and conformationally favorable manner with the DBR, from Cys-62 through His-67. Once EB interacted with the DBR, the DBR of the p50 subunit of NF-κB couldn't bind to the enhancer region in the LTR of HIV-1.EB was found to be inhibiting DNA binding of NF-κB at a low concentration of 100μmol·L^{-1} [43]. EB appears to be a promising lead compound against NF-κB -DNA binding, but EB does not readily enter the cells. Therefore, further studies are needed to address the mode of anti-HIV action of EB.

Pyridine N-oxide derivatives show inhibitory activity on HIV-1 expression. A prototype pyridine N oxide derivative, JPL-32 (Fig. (**4**)), inhibited TNF–α-induced HIV-1 expression in latently HIV-1-infected OM-10.1 and U1 cells [44]. The release and subsequent degradation of IκBα and the nuclear translocation of NF-κB were not affected by JPL-32. JPL-32 inhibits TNF-α induced HIV-1-LTR transcriptional activity by altering the intracellular redox status and interfering with NF-κB binding. JPL-32 directly prevents NF-κB DNA binding by oxidation of the thiol groups on the purified p50 subunit of NF-kB. The oxidative modification of the thiol groups on NF-κB by JPL-32 could be ascribed to the intracellular pro-oxidant effect of JPL-32. Therefore, JPL-32 was able to increase the intracellular glutathione (GSH) levels and to induce apoptosis in a dose-dependent way. EC_{50} was approximately 0.24 μg.ml^{-1}. JPL-32 proved to be an effective inhibitor in acutely and latently HIV-infected cells.

Phosphorylation of p65 is considered to be an important step in the up-regulation of the transcriptional activity of NF-κB, independent of its DNA-binding activity [45]. The binding subunit of pertussis toxin (PTX-B) inhibits phosphorylation and nuclear translocation of the p65 subunit of NF-κB. PTX-B reduces the level of nuclear NF-κB p65 subunit. This

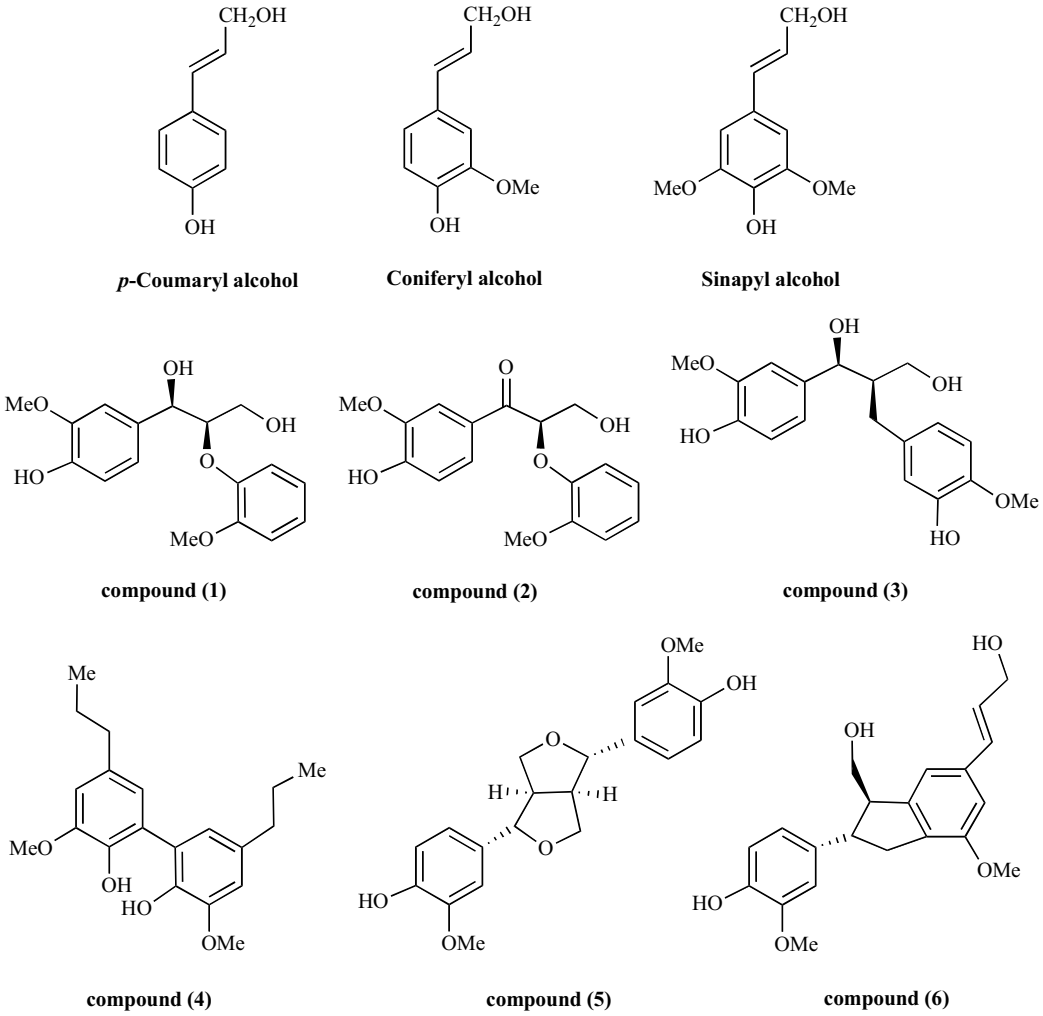


Fig. (5). Structures of lignin monomer and lignin model compounds.

effect mediates the decrease of p65 steady-state levels and suppression of HIV-1 LTR-driven transcription inhibitory activity by PTX-B. The inhibitory effect of PTX-B is independent of IκB. Future studies will further investigate the molecular mechanisms underlying the observed inhibitory activity of PTX-B on NF-κB p65 phosphorylation at the nuclear level [46].

Marquez *et al*. [47] reported that mesuol and isomesuol (Fig. (**4**)), two 4-phenyl coumarins, isolated from the tree *Marila pluricostata*, suppressed HIV-1 replication in Jurkat T cells. Mesuol inhibits TNF–α-induced HIV-1 LTR transcriptional activity by targeting the NF-κB pathway. Mesuol inhibits the phosphorylation and the transcriptional activity of the p65 subunit of NF-κB in TNF–α-stimulated cells. IC_{50} was approximately ranging from 2 to 2.5μmol·L^{-1} and reaching a complete inhibition at 15μmol·L^{-1}. Plant-derived antiviral compounds interfering with HIV-1 LTR promoter regulatory proteins are unlikely to generate drug-resistant HIV strains.Thus 4-phenyl-coumarins might have a potential therapeutic role in the management of AIDS most probably in combination with conventional anti-HIV therapy in HIV-infected individuals.

N-arachidonoyldopamine(NADA) (Fig. (**4**)) showed inhibitory activity in HIV-1 replication assays [48]. NADA counteracted the TNF–α mediated transactivation capacity of the p65 subunit of NF-κB, but NADA did not affect the physical association of p65 subunit to the HIV-1-LTR promoter. NADA inhibited the transcriptional activity of p65 by specifically phosphorylating the p65 subunit at the Ser536. This finding provides new mechanistic insights into the biological activities of NADA and highlights the potential of lipid mediators in the management of AIDS.

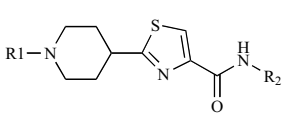
Mechanism-Unidentified Inhibitor

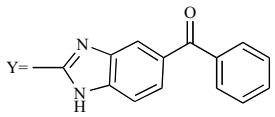
Fraction of small molecular mass in High-boiling solvent (HBS) lignin (less than 0.5 kDa) had stronger inhibitory effects than large molecular mass (more than 1.3 kDa). Lignin is a polyphenolic material arising from oxidative polymerization of three phenylpropanoid monomers, *p*-coumaryl, coniferyl, and sinapyl alcohols (Fig. (**5**)). The structural elements comprising lignin are linked by various species of carbon-carbon and ether bonds. Among six lignin dimer-like compounds, compound 6 containing β-5 structure has more strong inhibitory activity than compounds 1, 2, 3, 4 and 5, which contain β-1, β-O-4, 5-5, or β–β structures (Fig. (**5**)). These results suggested that small molecules of lignin inhibit HIV-1 replication through suppression of HIV-1 transcription from LTR including activation of NF-κB and inhibitory effect is attributed to low molecular weight lignin [49]. Low molecular weight lignin may be considered a new lead compound for an NF-κB-targeted AIDS therapy.

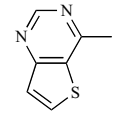
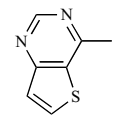
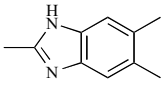
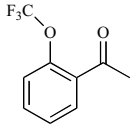
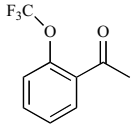
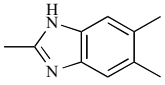
The piperidinyl-thiazole scaffold was explored by medicinal chemistry [50]. Synthesis the analogs modified at the N- and C-terminal of the molecule. QSAR model was used to guide the optimization of the compounds. Selection of building blocks with respect to availability and predicted NF-κB activity resulted in a series of compounds, which is depicted in Table **1**. On the average the substitution of the amino-benzimidazole by a phenylketo residue resulted in a substantial improvement.

Stilbene-related heterocyclic compounds including benzalphthalide, phthalazinone, imidazoindole and pyrimidoi-

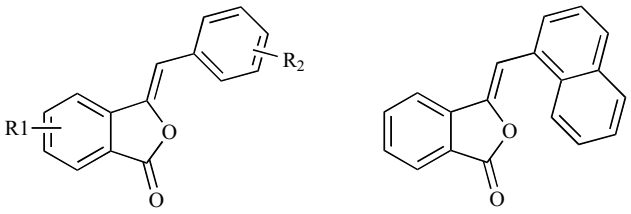
Table 1. Amino-Benzimidazole Analogs





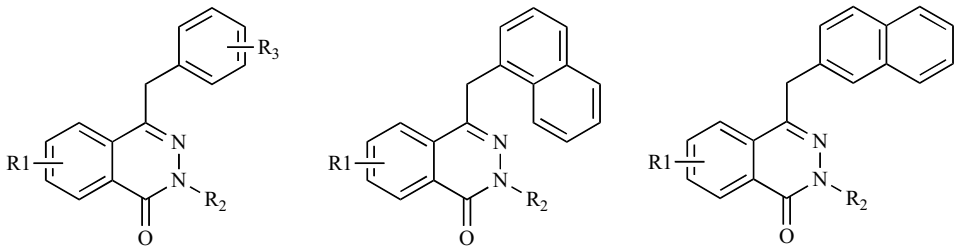
R1	R2	NF-κB EC_{50} (μM)
	Y	0.2
		0.3
	Y	0.8
		3.0

benzalphthalides



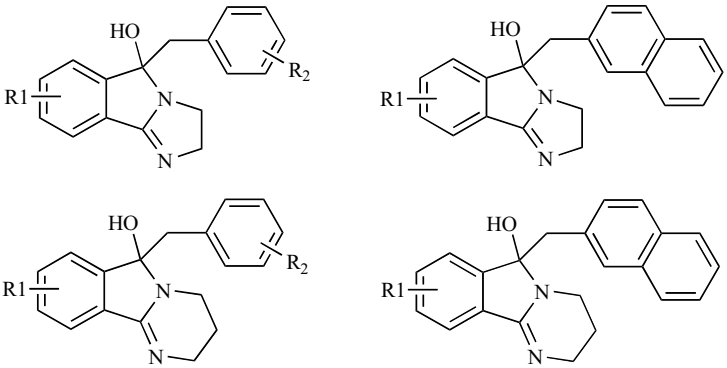
R_1=H,4-NO_2,5,6-Cl_2 R_2=H,2-Cl,4-Cl,4-OCH_3

phthalazinones



R_1=H,6(7)-CH_3,6,7-Cl_2 R_2=H,Allyl,n-Bu,t-Bu,Ph,4-BrPh,4-NO_2Ph R_3=H,4-Cl,2,4- Cl_2

imidazoisoindoles and pyrimidoisoindoles



R_1=H,7(8)-CH_3,7,8-Cl_2 R_2= 4-Cl,2,4-Cl_2,4-OCH_3,2-Naphthyl

Fig. (6). Chemical structures of stilbene-related heterocyclic compounds.

soindole derivatives (Fig. (**6**)) are tested for their anti-HIV activity [51]. Results among benzalphthalides showed activity, but only one was interesting. Imidazoisoindoles and pyrimidoisoindoles were also effective against HIV replication , acting through Tat, NF-κB inhibition or both, but most probably their activity correlates with their cytotoxicity. On the other hand, benzylphthalazinones were less cytotoxic than the isoindole derivatives .

CONCLUSION

As an essential regulator in HIV-1 gene expression and transcription, NF-κB plays an important role in triggering HIV transcription. Any intervention with the NF-κB signaling pathways can arrest HIV-1 transcriptional process. The toxicity and drug resistance of traditional HIV-1 reverse transcriptase and protease inhibitors result in their failure in clinical trials. Targeting NF-κB evades the problem of resistance because it is a normal part of the T-cell and is not subject to mutation. In this view of point, NF-κB seems to be a good candidate as a target for inhibition of HIV-1 replication and NF-κB inhibitors may become a new therapeutic modality onto add to current anti-HIV chemotherapy.

ABBREVIATIONS

NF-κB	=	Nuclear factor kappa B
AIDS	=	Acquired immunodeficiency syndrome
HIV-1	=	Human immunodeficiency virus type 1
LTR	=	Long terminal repeat
RHD	=	Rel homology domain
PKA	=	Protein kinase A
NLS	=	Nuclear Localization Signal

IκB	=	Inhibitory kappa B
IKK	=	IκB kinase
TAR	=	Transactivating region
TNF	=	Tumor necrosis factor
IL-1β	=	Interleukin1β
LTβ	=	Lymphotoxin-β
BAFF	=	B cell activating factor
AKIP1	=	A-kinase interacting-protein 1
TRX	=	Thioredoxin
Ref-1	=	Redox factor-1
NAC	=	N-acetylcysteine
PDTC	=	Pyrrolidine dithiocarbamate
BHA	=	Butylated hydroxyanisole
ROS	=	Ractive oxygen species
IL-1	=	Interleukin- 1
PMA	=	Phorbol 12-myristate 13-acetate
PKC	=	Protein kinase C
PTX	=	Pentoxifylline
HSV-1	=	Herpes simplex virus type 1
PGA1	=	Prostaglandin A1
NE	=	Norepinephrine
TD-IκBα	=	Transdominant repressors of IκBα
EB	=	Evans Blue
DBR	=	DNA binding region
GSH	=	Glutathione
PTX-B	=	The binding subunit of pertussis toxin
NADA	=	N-arachidonoyldopamine
HBS	=	High-boiling solvent

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