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Synthesis of lantadene analogs with marked in vitro inhibition of lung adenocarcinoma and TNF-α induced nuclear factor-kappa B (NF-κB) activation

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ABSTRACT

The new series of pentacyclic triterpenoids reduced lantadene A (**3**), B (**4**), and 22β-hydroxy-3-oxo-olean-12-en-28-oic acid (**5**) analogs were synthesized and tested in vitro for their NF-κB and IKKβ inhibitory potencies and cytotoxicity against A549 lung cancer cells. The lead analog (**11**) showed sub-micromolar activity against TNF-α induced activation of NF-κB and exhibited inhibition of IKKβ in a single-digit micromolar dose. At the same time, **11** showed promising cytotoxicity against A549 lung cancer cells with IC_{50} of 0.98 μM. The Western blot analysis further showed that the suppression of NF-κB activity by the lead analog **11** was due to the inhibition of IκBα degradation, a natural inhibitor of NF-κB. The physicochemical evaluation demonstrated that the lead analog **11** was stable in the simulated gastric fluid of pH 2, while hydrolyzed at a relatively higher rate in the human blood plasma to release the active parent moieties. Molecular docking analysis showed that **11** was hydrogen bonded with the Arg-31 and Gln-110 residues of the IKKβ.

Lung cancer ranks as the first malignant tumor killer worldwide.[1,2] The treatment options include chemotherapy and radiation therapy as well as the combination of both the therapies, as an effort to reduce the tumor mass and halt the disease progression. However, the success rate of these therapies is low and the prognosis of the patients is usually very poor.[3] At the molecular level, it has been established fact that nuclear factor-kappa B (NF-κB) is constitutively activated in a variety of solid tumors, including lung cancer. The tumor samples obtained from lung cancer patients showed high levels of NF-κB activation in both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), and is significantly associated with disease advancement in metastatic stages and poor prognosis in lung cancer patients.[4] Besides this, the NF-κB is constitutively activated in a variety of other cancers, and both chemotherapeutics and radiation therapy induce NF-κB activation in cancer cells, which contributes towards resistance to these therapies.[5] Thus, it is assumed that blockage of NF-κB will increase the efficacy of anticancer therapeutics. Therefore, the development of NF-κB inhibitors can be of prime importance not only in developing new therapeutics for lung cancer but also to improve therapeutics indices of known cytotoxic drugs.

In the last few years, pentacyclic triterpenoids lantadene A (**1**) and B (**2**) isolated from the leaves of weed *Lantana camara* L. (Verbenaceae) have attracted a lot of interest because of their anticancer properties.[6–10] These compounds along with reduced lantadene A (**3**), reduced lantadene B (**4**), and 22β-hydroxy-3-oxo-olean-12-en-28-oic acid (**5**) showed potent cytotoxic effects in antitumor screening launched by the National Cancer Institute, USA[11] and were found to be potent inhibitors of NF-κB.[6,7,12] Recently, we reported the synthesis of C-3, C-17, and C-22 analogs of lantadenes with marked inhibition of lung adenocarcinoma and NF-κB.[13–15] The promising results obtained with a diverse but limited series of target compounds prompted us to further explore the new analogs of lantadenes. The new C-3 and C-22 analog series were synthesized and evaluated for their in vitro anticancer activity and inhibition of tumor necrosis factor-alpha-induced (TNF-α-induced) NF-κB activation in the lung adenocarcinoma cell line A549. The most active analogs were evaluated in vitro for their inhibitory potency against the recombinant inhibitor of nuclear factor-kappa B kinase β (IKKβ) in a non-radioisotope Kinase-Glo Luminescent Kinase assays, while the lead analog was further

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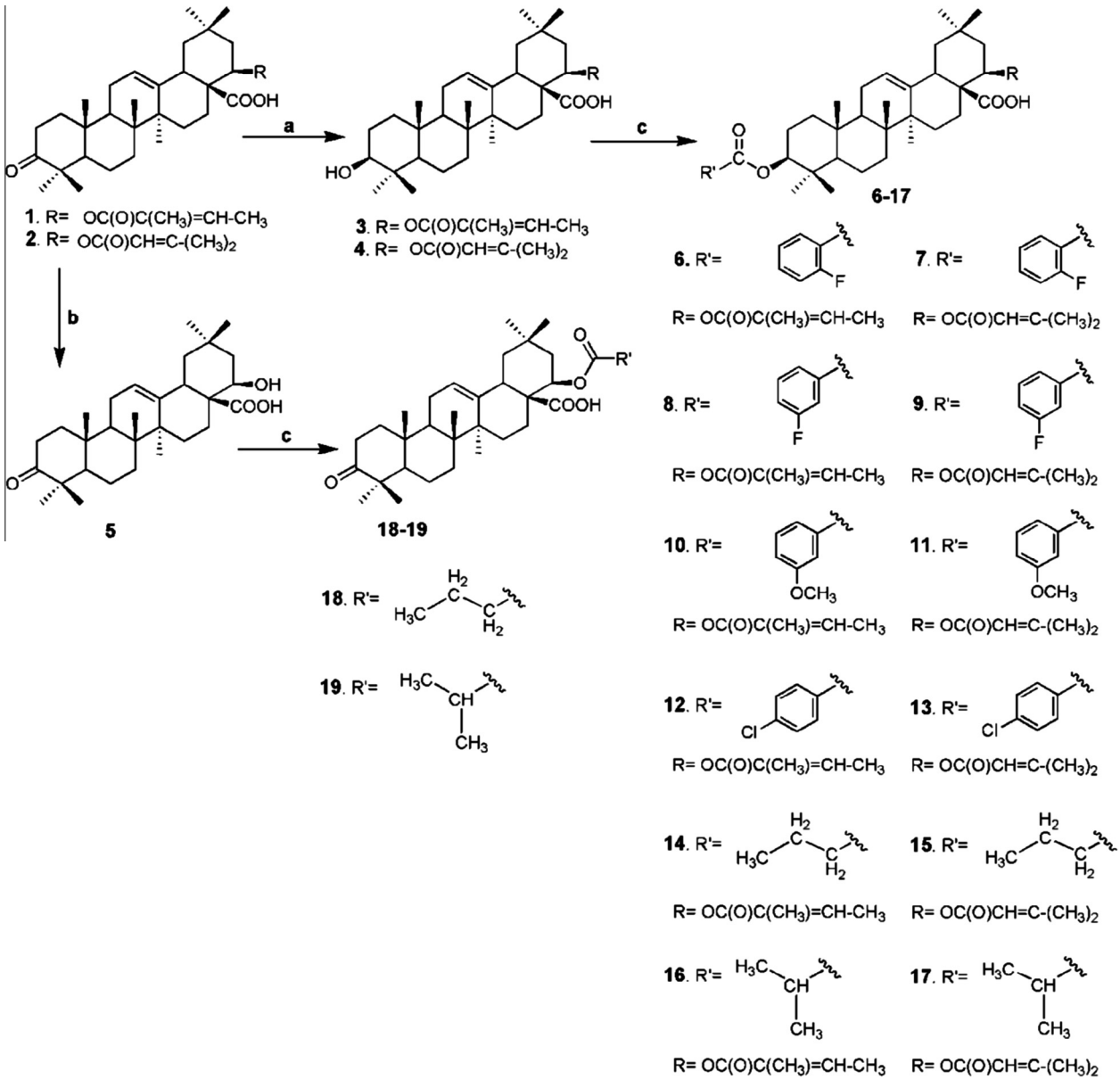
studied for its effect on IκBα protein by employing the Western blot technique. The most active ester analogs were also studied for their stability in the acidic pH and hydrolysis in the human blood plasma. The lead analog was further docked with the crystal structure of IKKβ to predict the possible binding mode of the analog.

Continuing our research interests in lantadene analogs as anticancer agents, we have synthesized a new series of C-3 and C-22 analogs. The sequence of steps involved in the synthesis of compounds is summarized in Scheme 1. The lantadene A (**1**) and B (**2**) are pentacyclic triterpenoids of oleanane series and were isolated from the leaves of weed *Lantana camara* Linn. The isolated compounds **1** and **2** differ only in the arrangement of atoms at the C-22 ester side chain with *E* conformation is present in the **1**, while the side chain of compound **2** possesses *Z* conformation. The isolated compounds **1** and **2** were selectively reduced into the corresponding compounds **3** and **4** in 87.60–89.88% yield, using sodium borohydride as a reducing agent and methanol (MeOH): tetrahydrofuran (THF) mixture as the solvent. The compound **5** was synthesized in 76.47% yield by alkali hydrolysis of **1** and **2** using 10% ethanolic potassium hydroxide. For the synthesis of compounds **6**–**13**, the acidic group of aromatic acids was first converted into the anhydride group by the reaction of an acid with acetyl chloride in the presence of pyridine in dichloromethane (DCM) (Supplementary data: Scheme S1). The aromatic acids were refluxed with an equimolar amount of acetyl chloride to afford solid to semisolid anhydride products of respective acids, which were used in the next step without further purification. In the concluding step of the synthesis of compounds **6**–**19**, appropriate anhydrides were refluxed with compounds **3**, **4**, and **5** in pyridine in the presence of 4-dimethylamino pyridine (4-DMAP) to afford the crude products, which were chromatographed over silica gel (100–200 mesh) and eluted with varying ratios of hexane and ethyl acetate to yield the final purified products (**6**–**19**).

The synthesized compounds were evaluated for their potential to inhibit TNF-α-induced NF-κB activation in lung adenocarcinoma



Scheme 1. Synthesis of lantadene analogs **3**–**19**. Reagents and conditions: (a) $NaBH_4$, MeOH-THF, stir 7 h; (b) 10% ethanolic KOH, reflux 6 h; (c) R′-CO-O-CO-CH_3 (**6**–**13**)/R′-CO-O-CO-R′ (**14**–**19**), 4-DMAP, pyridine, reflux 92–95 °C, 10–14 h.

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cell line A549. The human lung adenocarcinoma A549 cell line, transiently co-transfected with NF-κB-luc was used to monitor the effects of lantadene analogs on TNF-α-induced NF-κB activation. The compounds (**1**–**19**) were evaluated in a dose-dependent manner to determine the concentration needed to inhibit 50% of TNF-α-induced NF-κB activation (IC_{50}). The parent compounds **1**–**4** showed inhibition of TNF-α-induced NF-κB activation in the range of 1.56–0.98 μM. The reduction of a C-3 keto group of compounds **1** and **2** into the C-3 hydroxyl group of compounds **3** and **4** led to an increase in the activity, whereas hydrolysis of a C-22 ester side chain of compound **1** and **2** into the compound **5** led to a decrease in the activity. It was observed that the C-22 ester side chain played a critical role in the inhibition of TNF-α-induced NF-κB activation in lung adenocarcinoma cell line A549. The hydrolysis of the C-22 ester functionality in lantadenes led to a significant reduction in activity, supporting the notion that the mechanism of inhibition is likely through a covalent Michael addition of nucleophiles (such as SH from cysteine) from protein candidate(s) to lantadenes.[13] The introduction of 3-methoxybenzoyloxy and 4-chlorobenzoyloxy functionality at C-3 position of compound **4** led to an increase in the activity, whereas the 2- and 3-flurobenzoyloxy functionalities at C-3 position decreased the activity, significantly. The alkyl and branched chain esters at C-3 position of **3** and **4** were found to be the least active. The results of inhibition of TNF-α-induced NF-κB activation in A549 lung adenocarcinoma cell line by compounds **1**–**19** are shown in Table 1.

The NF-κB activation pathway in most of the cells involves dimers composed of p50 and p65 or c-Rel and is often activated by microbial infections, pro-inflammatory growth factors and cytokines, including TNF-α.[16] The TNF-α engagement induces trimerization of TNF-α receptor 1 (TNFR1) and recruitment of multiple adaptor proteins and kinases, resulting in the activation of IKKβ, causing phosphorylation or degradation of inhibitor of NF-κB proteins (IκB proteins), which releases NF-κB from the cytoplasm to the nucleus, where it carry out transcription of proteins responsible for proliferation and differentiation of cancer cells.[17] As compounds **11** and **13** showed the potent NF-κB inhibition; therefore, we further evaluated the effect of parent compounds **3** and **4** and their analogs **11** and **13** against upstream kinase IKKβ that has been reported to activate the NF-κB pathway. The compounds were evaluated in vitro for their inhibitory potential against the recombinant IKKβ in a non-radioisotope Kinase-Glo Luminescent Kinase Assays (Promega, USA). It was found that **11** and **13** remarkably inhibited IKKβ with IC_{50}s of 1.36 and 1.54 μM, respectively (Table 2).

The NF-κB is a positive mediator of cell growth and proliferation. The mutual interplay between NF-κB and pro-inflammatory cytokines, such as TNF-α has been involved in stimulating cancer cell proliferation, particularly during chronic inflammation of the lungs.[18] Since, the lantadene analogs showed marked inhibition of NF-κB, they were further evaluated for their in vitro cytotoxicity against lung cancer cells A549. The cytotoxicity profile of parent compounds (**1**–**5**) and ester analogs (**6**–**19**) are reported in Table 3. The parent pentacyclic triterpenoids **1**, **2**, **3**, and **4** showed cytotoxicity against A549 lung cancer cells with IC_{50} values of 2.84, 1.19, 0.79, and 0.43 μM, respectively, whereas the compound **5** showed IC_{50} >10 μM. The introduction of 3-methoxybenzoyloxy (**11**) and 4-chlorobenzoyloxy (**13**) groups in compound **4** showed marked cytotoxicity with IC_{50}s of 0.98 and 1.12 μM, respectively (Table 3). From the cytotoxicity profiles of compounds **1**–**19**, it was evident that the removal of the ester side chain at C-22 position led to a decrease in the activity. The strongly electrophilic α,β-unsaturated carbonyl group of the ester side chain seems to play an important role in binding of compounds to the receptor site.

The IκBα is a natural inhibitor of oncogenic protein NF-κB. The activation of NF-κB requires phosphorylation and subsequent degradation of IκBα. The lead lantadene analog **11**, which showed an appreciable degree of inhibition of TNF-α-induced NF-κB activation in the lung adenocarcinoma cell line A549, was chosen for further study. To explore whether the inhibition of TNF-α-induced NF-κB activation was due to the inhibition of IκBα degradation, the cells were treated with various concentrations of compound **11** for 8 h and then exposed to 0.1 nmol TNF-α for 30 min. The cell extracts were then subjected to Western blot analysis for an estimation of IκBα level in the cytoplasm. The results showed that TNF-α induced the IκBα degradation in the control cells, whereas in the cells pretreated with compound **11**, TNF-α failed to induce the degradation of IκBα (Fig. 1A and B).

A successful ester analog should be stable in the acidic pH of the stomach and should be hydrolyzed in the blood plasma to release the active parent moieties. The compounds **11** and **13** that emerged as the most potent ester analogs from the synthesized

Table 2
In vitro IKKβ inhibition by parent compounds (**3** and **4**) and analogs (**11** and **13**)

Compd.	IC_{50} (μM)
3	2.62 ± 0.82
4	4.24 ± 0.94
11	1.36 ± 0.06
13	1.54 ± 0.04

Results are given as the mean of at least three independent experiments with triplicates in each experiment.

Table 1
TNF-α-induced NF-κB activation inhibitory activities of parent compounds (**1**–**5**) and analogs (**6**–**19**)

Compd	IC_{50} (μM)	Compd	IC_{50} (μM)
1	1.06 ± 0.46	**15**	2.82 ± 0.24
2	1.56 ± 0.04	**16**	3.12 ± 0.12
3	0.98 ± 0.02	**17**	>10
4	1.02 ± 0.62	**18**	>10
5	6.42 ± 1.24	**19**	>10
6	1.94 ± 0.24		
7	1.80 ± 0.60		
8	2.32 ± 0.01		
9	2.04 ± 0.02		
10	1.64 ± 0.74		
11	0.74 ± 0.24		
12	0.96 ± 0.36		
13	0.82 ± 0.02		
14	3.12 ± 0.42		

Results are given as the mean of at least three independent experiments with triplicates in each experiment.

Table 3
In vitro cytotoxicity profile of parent compounds (**1**–**5**) and analogs (**6**–**19**) against A549 cell line

Compd	IC_{50} (μM)	Compd	IC_{50} (μM)
1	2.84 ± 0.72	**15**	>10
2	1.19 ± 0.28	**16**	>10
3	0.79 ± 0.01	**17**	2.56 ± 0.36
4	0.43 ± 0.03	**18**	>10
5	>10	**19**	>10
6	2.04 ± 0.04	**Cisplatin**	21.3 ± 3.62
7	1.96 ± 0.24		
8	>10		
9	6.86 ± 1.32		
10	1.84 ± 0.42		
11	0.98 ± 0.08		
12	1.32 ± 0.32		
13	1.12 ± 0.02		
14	>10		

Results are given as the mean of at least three independent experiments with triplicates in each experiment.

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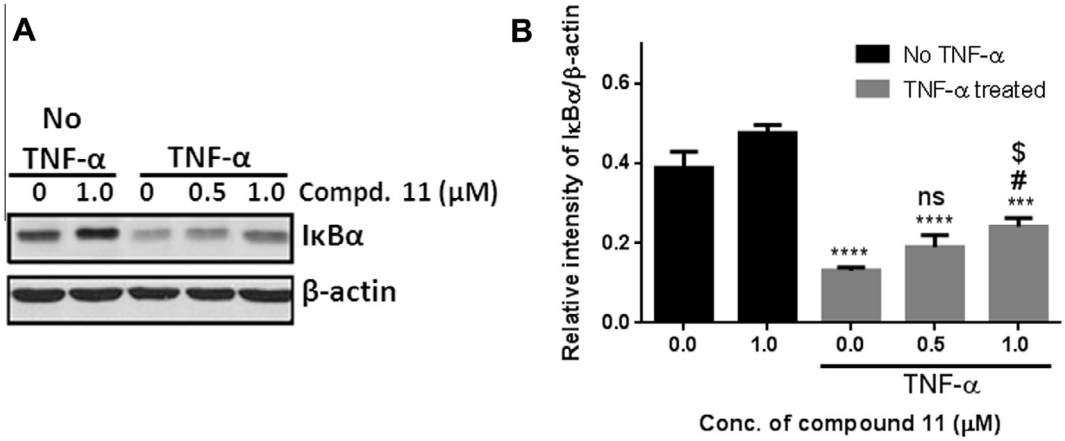

Figure 1. The effect of the lead compound **11** on TNF-α-induced IκBα degradation. The TNF-α-induced and IKK mediated IκBα degradation leads to an activation of NF-κB, which then transmigrates into nucleus, where it binds with the DNA and carry out transcription of proteins responsible for oncogenesis. (A) Western blot analysis describing the effect of compound **11** on TNF-α-induced IκBα degradation. The protein bands obtained in the Western blot indicate that compound **11** was able to suppress the degradation of IκBα, which subsequently decreased the activity of NF-κB. (B) The densitometry analysis of the Western blots shows the relative intensity of IkBα/β-actin. The results shown are the mean ± SD of three separate experiments. A P value <0.05 was considered significant. $^{****}P < 0.0001$, 0 TNF-α-treated versus 0; $^{****}P < 0.0001$, 0.5 TNF-α-treated versus 0; $^{ns}P > 0.05$ or not significant, 0.5 TNF-α-treated versus 0 TNF-α-treated; $^{***}P < 0.001$, 1.0 TNF-α-treated versus 0; $^{\#}P < 0.0001$, 1.0 TNF-α-treated versus 1.0; $^{\$}P < 0.01$, 1.0 TNF-α-treated versus 0 TNF-α-treated.

series were further explored for their stabilities in the chemical/acidic and enzymatic media. For chemical stability studies, the ester analogs **11** and **13** were exposed to the simulated gastric fluid of pH 2 for 0, 2, 5, 8, and 12 h. Results of HPLC analysis of ester analogs exposed to the simulated gastric fluid of pH 2 showed that only 0.0%, 6.96%, 11.80%, 16.68%, and 22.75% of **11** and 0.0%, 7.84%, 13.48%, 19.72%, and 27.18% of **13** were hydrolyzed after the exposure time of 0, 2, 5, 8, and 12 h, respectively (Table 4). It can be inferred from the results of chemical hydrolysis studies that the ester analog **11** showed slightly higher resistance towards hydrolysis in comparison with the **13** and both of them survived the gastric pH conditions. To study plasma hydrolysis or susceptibility of ester analogs **11** and **13** towards human plasma esterases, they were exposed to 80% human plasma for 0, 15, 30, 60, and 120 min and extent of hydrolysis was monitored by HPLC. On exposure to human plasma, the ester analogs **11** and **13** were hydrolyzed at a noticeably higher rate than the rate of their hydrolysis observed in the simulated gastric fluid. A level of ester analogs hydrolyzed was found to be 0.0%, 29.62%, 46.76%, 53.30%, and 64.68% of **11** and 0.0%, 29.76%, 47.82%, 55.70%, and 67.73% of **13** after the exposure time of 0, 15, 30, 60, and 120 min, respectively (Table 5). The ester analog **11** showed a slightly lesser degree of hydrolysis than its counterpart **13**. HPLC results indicated that the ester analogs **11** and **13** underwent rapid hydrolysis in human blood plasma to liberate the parent drug molecules, to reach the site of action, while in the simulated gastric fluid of pH 2, they survived the stomach pH conditions. The analog **11** was hydrolyzed to a comparatively lesser extent than **13** due to the bearing of an electron releasing methoxy group that decreased the electrophilicity of the C-3 ester carbonyl carbon, whereas the analog **13** possessed the electron withdrawing chloro group. Additionally, the chloro substitution in **13** was present at the *para*-position, while methoxy substitution in **11** was present at the *meta*-position that further shielded the C-3 ester carbonyl carbon from the nucleophilic attack with a greater capacity than that of the *para*-substitution of **13**.

Table 4
Chemical stability of the most potent ester analogs (**11** and **13**) in simulated gastric fluid of pH 2

Time (h)	% Ester analog remaining unhydrolyzed in simulated gastric fluid	
	Compd **11**	Compd **13**
0	100	100
2	93.04	92.16
5	88.20	86.52
8	83.32	80.28
12	77.25	72.82

Table 5
Metabolic stability of the most potent ester analogs (**11** and **13**) in 80% human plasma

Time (min)	% Ester analog remaining unhydrolyzed in 80% human plasma	
	Compd **11**	Compd **13**
0	100	100
15	70.38	70.24
30	53.24	52.18
60	46.70	44.30
120	35.32	32.27

The IKKβ protein is made up of 8 chains and 676 amino acid residues. The kinase domain of human IKKβ is consisting of 15–312 residues. In order to rationalize the biological activity of the lead analog **11** and to further predict the possible interactions that might take place between the analog **11** and IKKβ, it was docked into the active site of IKKβ. Results of molecular docking studies indicated that the analog **11** showed estimated free energy of binding of −5.15 kcal/mol towards IKKβ, while final intermolecular energy of **11** was found to be −7.24 kcal/mol. The detailed stereoview of the complex formed by docking of the analog **11** into the active site of target protein IKKβ is presented in Figure 2A and B. The closer inspection of the docked complex indicated that three oxygen atoms of the 3-methoxybenzoyloxy, 22β-ester side chain, and 28-carboxylic acid group of **11** participated in hydrogen bond formations with the IKKβ. The methoxy oxygen was hydrogen bonded with the amino group hydrogen of Gln-110 (H_3C—O. . .H—N, 2.5 Å). The oxygen atoms of the 22β-ester side chain and the 28-carboxylic acid group were hydrogen bonded with the amino group hydrogens of Arg-31. The 22β-ester oxygen was 2.2 Å away from Arg-31 (O═C—O. . .H—N, 2.2 Å), while the 28-carboxylic oxygen was placed at 2.3 Å distance from the Arg-31 (O═C—O. . .H—N, 2.3 Å), which resulted in the generation of third hydrogen bond between **11** and IKKβ. As we know that hydrogen bond is formed between two electronegative atoms, where one atom has a lone pair of electrons and another has acidic proton. Molecular docking analysis showed that the 22β-ester side chain

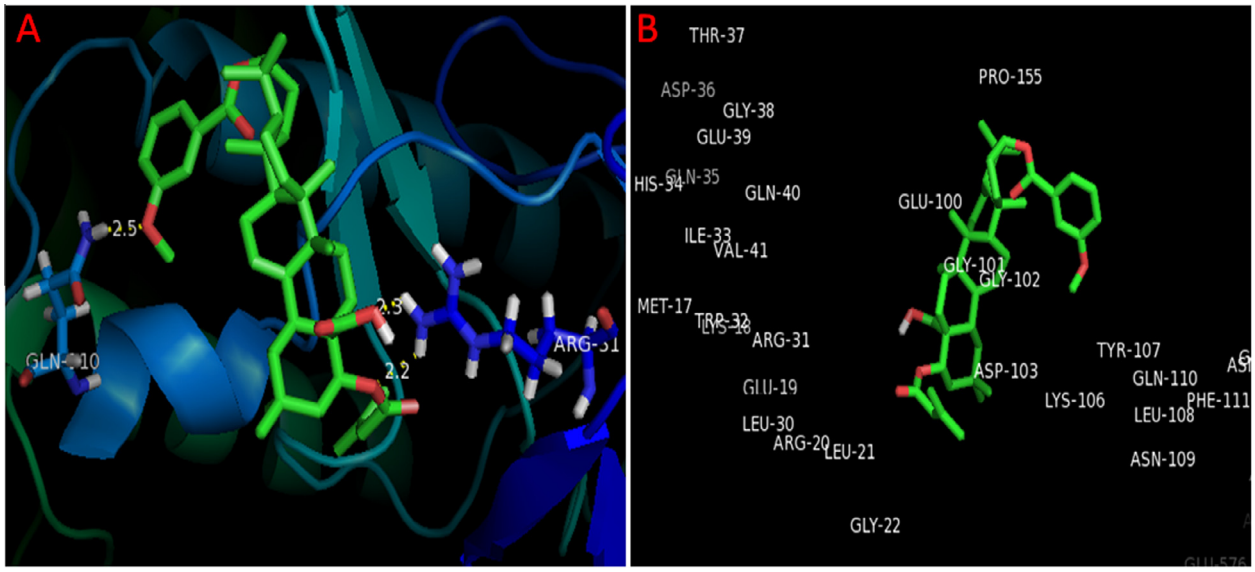

Figure 2. Molecular docking of the lead analog **11** in the active site of IKKβ. (A) Amino acid residues Arg-31 and Gln-110 of IKKβ involved in hydrogen bond interactions with **11** are highlighted. (B) Amino acid residues of IKKβ present in the surroundings of **11** and also involved in hydrogen, hydrophobic, and van der Waals interactions with **11** are highlighted.

along with 28-carboxylic group were crucial for the activity of **11**, wherein electronegative oxygen atoms were involved in hydrogen bond formations with the protons of an electronegative nitrogen of Arg-31. The substitution on benzoyloxy ring with the 3-methoxy group also played a vital part in the potency of analog **11**, as the electron releasing methyl group further increased the electron density on the methoxy oxygen (oxygen of O—CH_3 group) that prompted the oxygen to undergo a hydrogen bond formation with the proton attached to the another electronegative atom, the nitrogen of Gln-110. Taken together, the 3-methoxy group on 3-benzoyloxy ring, 22β-ester side chain, and 28-carboxylic acid group were critical for the IKKβ inhibitory activity of the lead lantadene analog 3β-(3-methoxybenzoyloxy)-22β-senecioyloxy-olean-12-en-28-oic acid (**11**). Apart from hydrogen bondings, the analog **11** was also interacted with the IKKβ through hydrophobic and van der Waals contacts. The hydrophobic interactions are one of the major contributors to the stability of ligand at the binding site of the receptor. An analysis of the docked complex showed that the 22β-ester side chain was positioned deep within the hydrophobic pocket created by Met-17, Leu-21, Leu-30, Ile-33, and Val-41, while the 3-methoxybenzoyloxy scaffold was positioned in the proximity of non-polar residues Leu-108 and Phe-111. The ring A and B of pentacyclic triterpenoid scaffold of the **11** further demonstrated the strong hydrophobic interactions with the Pro-155 residue of the IKKβ. Although, van der Waals interaction is considered as a weak interaction, still sum of a large number of van der Waals interactions may add appreciably to the orientation, stability, and binding of the ligand at the receptor site. Many residues, which took part in such interactions, are also highlighted in Figure 2B.

In conclusion, the C-3 analogs of pentacyclic triterpenoids **3** and **4** showed marked inhibitory potential against TNF-α-induced activation of NF-κB and cytotoxicity against A549 lung cancer cells. The study showed that 3-methoxybenzoyloxy (**11**) and 4-chlorobenzoyloxy (**13**) substituted analogs inhibited kinase activity of IKKβ in a single-digit micromolar concentration, while the lead analog **11** was able to inhibit the degradation of IκBα. The experimental and docking studies revealed that the C-22 ester side chain bearing α,β-unsaturated carbonyl group was critical for the activity. Moreover, ester analogs **11** and **13** showed stability in the acidic pH and were hydrolyzed readily in the human blood plasma to release the two active moieties. The most potent lantadene analogs **11** and **13** are promising anticancer candidates against lung cancer with promising inhibition of IKKβ activity and warranting further investigations.

Acknowledgments

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Supplementary data

Supplementary data (experimental section, FT-IR, NMR, and Mass spectra of all the compounds (**1**–**19**)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.06.068.

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