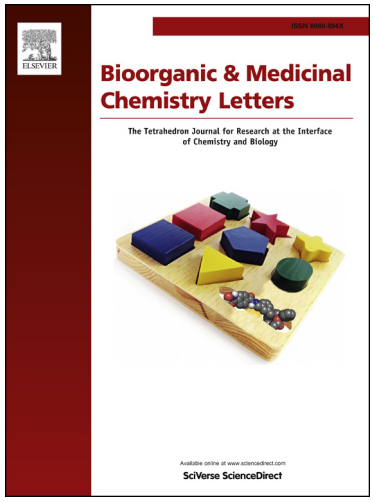


# Analogues of Boswellic acids as inhibitors of pro-inflammatory cytokines TNF-α and IL-6

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# Analogues of Boswellic acids as inhibitors of pro-inflammatory cytokines TNF-α and IL-6

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**Keywords**. β-Boswellic acid, anti-inflammatory, Cytokine, TNF-α, IL-6.

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**Abstract:** A library of boswellic acid analogues were synthesized and tested for their anti-inflammatory potential on key inflammatory mediators, TNF-α and IL-6. The study led to the identification of lead compounds showing significant inhibition of the cytokines, TNF-α and IL-6 both *in vitro* and *in vivo*.

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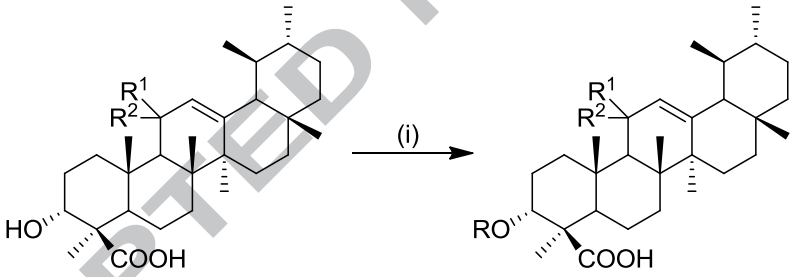
Boswellic acids (BAs) are pentacyclic triterpenoids comprising essentially of β-boswellic acid (BA, **1**) as the main triterpenic acid along with 11-keto-β-boswellic acid (KBA, **2**) and corresponding acetates *i.e.*, acetyl β-boswellic acid (ABA, **3**) and acetyl 11-keto-β-boswellic acid (AKBA, **4**),[1] derived from *Boswellia serrata*.[2] Gum resin of *B. serrata* has been the major target for the anti-inflammatory drug development in recent past[3] and its has been widely used in Ayurvedic preparations since antiquity for the treatment of inflammation[4,5]and arthritis.[6,7,8,9,10,11] Also their activities against other inflammatory conditions like ulcerative colitis,[12] chronic colitis,[13] and asthma[14]are well documented. Besides they have attracted considerable attention for their activity against cancer and ability to induce apoptosis.[15,16] They have been reported to inhibit growth and induce apoptosis in brain tumors,[17] malignant glioma cells,[18] colon cancer cells[19] and leukemic cells.[20]

As pointed out in the press release of Nobel Prize Assembly, Barry J. Marshall and J. Robin Warren, that many diseases in humans such as Crohn's disease, ulcerative colitis, rheumatoid arthritis and atherosclerosis are associated with chronic inflammation[21,22] and because of the fact

boswellic acids are known anti-inflammatory agent, we envisaged revisiting certain derivatives of boswellic acids synthesized by us, which in past have shown anti-cancer activity.[23,24] Thus, in our continuous effort to develop bioactive leads based on the natural products[25] including BAs,[26] we wish to report acyl analogues of BAs including their epimers as well as 4-amino analogues as inhibitors of pro-inflammatory cytokines through *in vitro* and *in vivo* expression of TNF-α, and IL-6.

Our efforts initiated with the synthesis of 3-acyl derivatives of BAs and their epimers by following previously reported procedure.[23] Treatment of BA with corresponding anhydrides *i.e.*, acetic, propanoic, butyric and hexanoic anhydrides in presence of dimethyl amino pyridine (DMAP) as a catalyst in dry DCM produce 3-*O*-α-acetyl-β-boswellic acid (**3**), 3-*O*-α-propionyl-β-boswellic acid (**5**) and 3-*O*-α-butyryl-β-boswellic acid (**7**) and 3-*O*-α-hexanoyl-β-boswellic acid (**9**)respectively in almost quantitative yields. Likewise3-*O*-α-acetyl-11-keto-β-boswellic acid (**4**), 3-*O*-α-propionyl-11-keto-β-boswellic acid (**6**), 3-*O*-α-butyryl-11-keto-β-boswellic acid (**8**) and 3-*O*-α- hexanoyl-11-keto-β-boswellic acid (**10**) were also prepared in similar yields (95%) (Scheme-1).



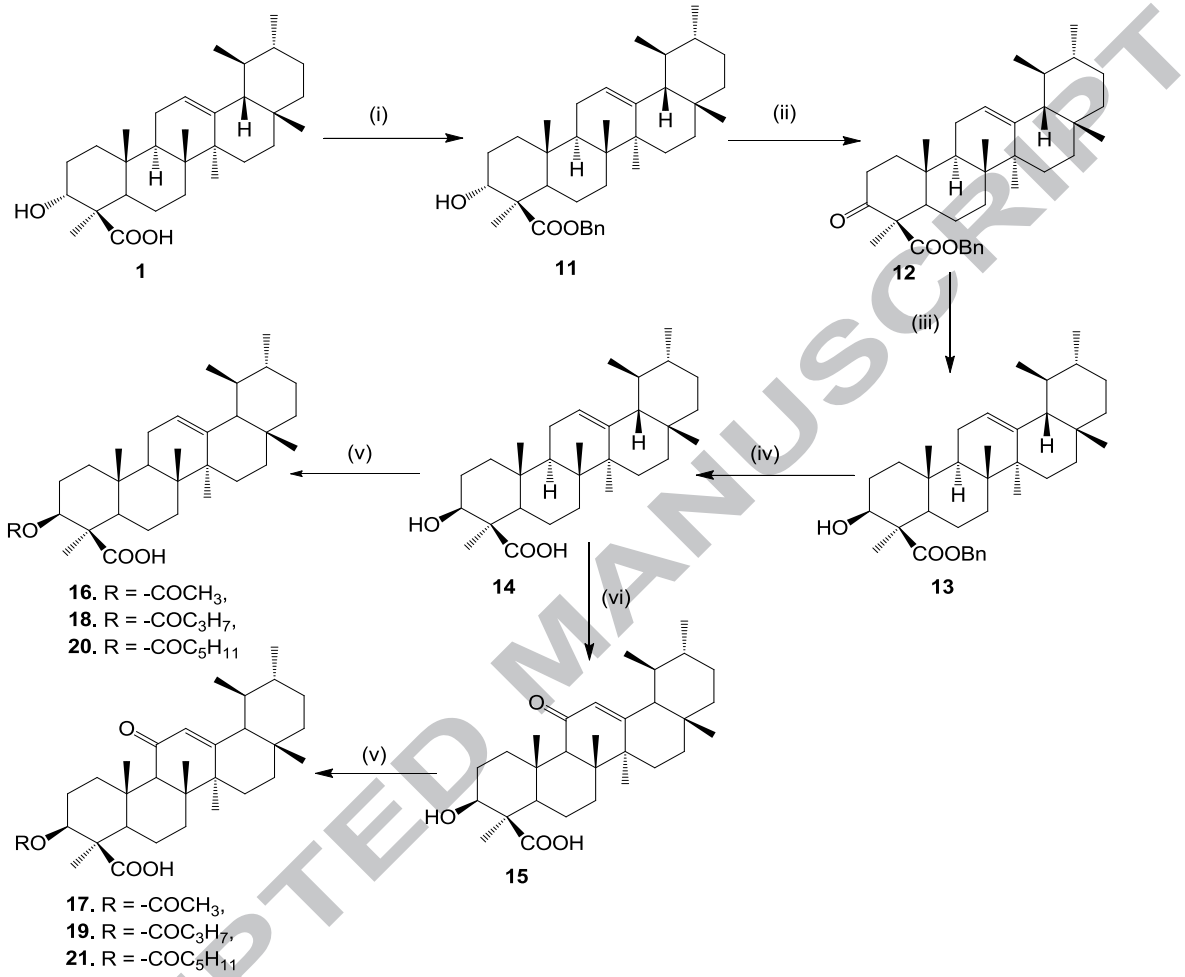

**1.** $R^1 = R^2 = H$
**2.** $R^1 + R^2 = O$

**3.** R = $-COCH_3$, $R^1=R^2= H$
**4.** R = $-COCH_3$, $R^1+R^2 = O$
**5.** R = $-COC_2H_5$, $R^1=R^2= H$
**6.** R = $-COC_2H_5$, $R^1+R^2 = O$
**7.** R = $-COC_3H_7$, $R^1=R^2= H$
**8.** R = $-COC_3H_7$, $R^1+R^2 = O$
**9.** R = $-COC_5H_{11}$, $R^1=R^2= H$
**10.** R = $-COC_5H_{11}$, $R^1+R^2 = O$

**Scheme-1.** Reagents and conditions: (i) $R_2O$, DMAP, DCM (95%).

For the synthesis of 3-*epi* BAs, BA/KBA in DMF was treated with $K_2CO_3$. After stirring it for 30 minutes, benzyl bromide was added at 0°C and further kept it on stirring for 12 h to afford benzyl-3-α-hydroxyurs-12-en-24-oate (**11**) in 95% yield. The ester was oxidized with PCC in DCM to convert it to corresponding 3-keto derivatives *i.e.*,benzyl-3-oxours-12-en-24-oate (**12**) in 85% yield. The 3-keto derivative was then reduced by $NaBH_4$ in methanol to produce benzyl-3-β-hydroxyurs-12-en-24-oate (**13**) having (*S*) or β-configuration at C-3. The debenzylation of

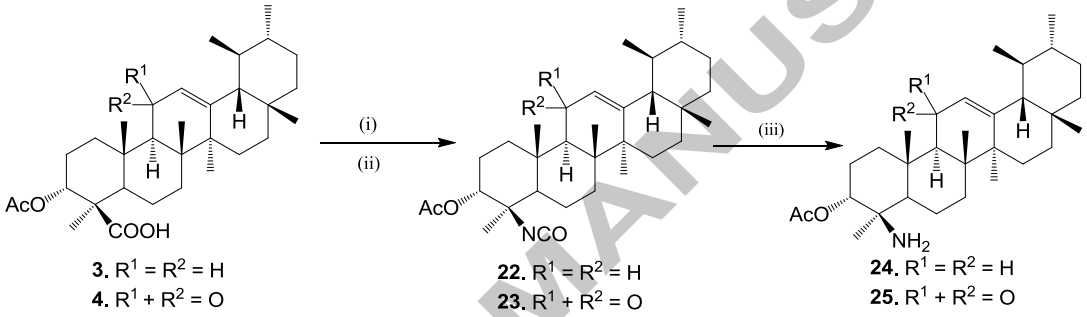
ester was brought about by hydrogenation using Pd/C as catalyst in EtOH: EtOAc (1:1) to afford 3-*epi*-β-boswellic acid (**14**) in 90% yields. To obtain 3-*epi*-11-keto-β-boswellic acid (**15**) half portion of **14** was oxidized with $CrO_3$ in 80% yields




**Scheme-2.** Reagents and conditions: (i) $K_2CO_3$, BnBr, DMF (95%) (ii) PCC, DCM, rt (80%) (iii) $NaBH_4$, MeOH, rt (90%) (iv) $H_2$, Pd/C, EtOH: EtOAc (1:1) (v) $R_2O$, DMAP, DCM (95%) (vi) $CrO_3$, AcOH.

The 3-*O*-acyl analogues of 3-*epi*-β-boswellic acid (**14**) and 3-*epi*-11-keto-β-boswellic acid (**15**) were similarly prepared using alkyl anhydrides in dry DCM using DMAP as a catalyst to obtain 3-*O*-β-acetyl-boswellic acid (**16**), 3-*O*-β-butyryl-β-boswellic acid (**18**) and 3-*O*-β-hexanoyl-β-boswellic acid (**20**) respectively. Similarly, 3-*O*-β-acetyl-11-keto-β-boswellic acid (**17**), 3-*O*-β-butyryl-11-keto-β-boswellic acid (**19**) and 3-*O*-hexanoyl-11-β-keto-boswellic acid (**21**) were prepared in almost quantitative yields (Scheme-2).

As reported earlier,[24] to synthesize 4-amino analogues of BAs, ABA (**3**)/AKBA (**4**) was subjected to Curtius reaction involving firstly refluxing of **3**/**4** with $SOCl_2$ in dry benzene to prepare corresponding acid chlorides. The excess of $SOCl_2$ was distilled out under reduced pressure followed by *in situ* reaction with $NaN_3$ in dry acetone to produce corresponding isocyanates, 3-α-acetoxy-4-isocyanato-24-norurs-12-ene (**22**) and 3-α-acetoxy-4-isocyanato-11-oxo-24-norurs-12-ene (**23**) in 90% yield. Then TFA: $H_2O$ (2:1, 10 ml) was added and the reaction mixture was kept on stirring at room temperature for 3 h. After that, solution was neutralized and the product (**24)** and **(25)** was extracted with DCM and was then purified by column chromatography (Scheme-3).




**Scheme-3.** Reagents and conditions: (i) $SOCl_2$, benzene, reflux (ii) $NaN_3$, acetone, reflux (90%) (iii) TFA: $H_2O$ (2:1) stirring, rt (80%).

The release of pro-inflammatory cytokines is an important mechanism by which the immune cells regulate the inflammatory responses and contribute to various inflammatory and autoimmune disorders. All the synthesized compounds were analyzed for their ability to decrease lipopolysaccharide (LPS) induced tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) production in human peripheral blood mononuclear cells (PBMCs).[27] Co-incubation of boswellic acid analogues with LPS at 5 h showed a considerable inhibition of TNF-α and IL-6 at 10 µM, when compared to LPS-induced control cells and rolipram standard (Table 1).

**Table.1** *In vitro* TNF-α and IL-6 expression

| **Compound** | **Conc. (µM)** | **% TNF-α inhibition** | **% IL-6 inhibition** |
|---|---|---|---|
| **1** | 10 | 44.5±3.7 | 48.6±3.0 |
| **2** | 10 | 56.3±9.4 | 59.6±1.2 |

| | | | |
|---|---|---|---|
| **3** | 10 | 43.83±1.9 | ND |
| **4** | 10 | 55.03±1.47 | 53.93±1.2 |
| **5** | 10 | 40±3.36 | 43.5±2.05 |
| **6** | 10 | 38.9±0.89 | 36.6±1.6 |
| **7** | 10 | 41.4±1.13 | 34.83±1.5 |
| **8** | 10 | 34.1±2.5 | 22.5±2.6 |
| **9** | 10 | 72.33±4.36 | 50.5±1.9 |
| **10** | 10 | 18.28±2.19 | 13.8±1.4 |
| **14** | 10 | 41.37±6.96 | 42.3±1.7 |
| **15** | 10 | 53.47±9.06 | 49.6±1.7 |
| **16** | 10 | 57.93±2.16 | 51.1±0.8 |
| **17** | 10 | 39.6±2.61 | 44.7±1.1 |
| **18** | 10 | 68.93±4.47 | 39.5±2.2 |
| **19** | 10 | 44.17±2.8 | 52.3±1.8 |
| **20** | 10 | 42.53±1.84 | 53.43±1.4 |
| **21** | 10 | 44.67±1.47 | 64.03±2.8 |
| **22** | 10 | 40.63±2.92 | ND |
| **23** | 10 | 40.57±2.44 | 69.8±1.5 |
| **24** | 10 | 68.33±5.16 | 63.3±1.2 |
| **25** | 10 | 78.93±1.44 | 58.4±1.3 |
| **Rolipram** | 10 | 34.6±2.54 | 26.2±1.73 |

Compounds having % inhibition >50 are considered as active compounds.[28,29] Results are summarized in table for both % of cytokine inhibition and expressed as the mean ± SEM.

From the results given in Table 1, it is clear that at 10 µM concentrations, the analogues **4**, **9, 15, 16**, **18, 24** and **25** displayed maximum inhibitory effects of 55.03, 72.33, 53.47, 57.93, 68.93, 68.33 and 78.93% respectively, wherein the compounds **9**, **16 18**, **24** and **25** showed TNF-α inhibition better than parent compounds. Among all these compounds **9** and **25** presented significant level of TNF-α inhibition of over 70%. Similarly compounds **4, 9, 16, 19**, **20**, **21**, **23, 24** and **25** suppressed extracellular IL-6 expression level to 53.93, 50.5, 51.1, 52.3, 53.43, 64.03, 69.8, 63.3 and 58.4% respectively at the dose of 10 µM, wherein the compounds **21**, **23, 24** were found to be more potent than parent compounds. The compounds showing more than 50% inhibition of TNF-α and IL-6 expressions are considered to have potent TNF-α and IL-6 inhibitory activity respectively. In structure activity relationship studies, acyl analogues of 11-K-β -BAs with short carbon chain resulted in enhancement of TNF-α activity while higher acyl homologues displayed better TNF-α inhibition in case of β-BAs. Also the epimerisation at 3-OH position resulted in enhancement of TNF-α inhibition in both β-BAs & 11-K-β–BAs. In case of IL-6 supression higher acyl homologues gave better results than lower acyl homologues. Also

the compounds **24** & **25** where the amino group was introduced in place of acid group, resulted in enhancement of anti-inflammatory potential. Further to confirm that the suppressive effect of the active compounds from *in vitro* assay is not because of cytotoxicity, the compounds were tested for their cell viability against normal breast epithelial cell line fR2 at 10µM concentration for 48 h. Among these compounds **4**, **9**, **15**, **16**, **23**, **24** & **25** were found to be non-toxic and compound **21**, **18** & **19** with very low toxicity on normal cell line fR2.

**Table2.** *In vitro* cell viability of lead compounds against fR2

| Compd | 1 | 2 | 4 | 9 | 15 | 16 | 18 | 19 | 20 | 21 | 23 | 24 | 25 | control |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| % viability (50µM) | 73 | 86 | 100 | 89 | 100 | 99 | 83 | 80 | 97 | 85 | 91 | 100 | 97 | 100 |

These compounds were further chosen for *in vivo* evaluation. The objective of *in vivo* study was to determine if the lead compounds identified from *in vitro* studies were able to replicate in animal models. The compounds were evaluated in PBMC cells because this macrophage model produces high concentrations of IL-6 and TNF-α in culture upon activation with LPS,[30] and reduced the need for additional animals required to obtain and use primary cultures. Cytokine levels were also evaluated in mice using LPS as a stimulant. Levels of IL-6 and TNF-α were not detectable in untreated cells and animals which served as control *in vitro* and *in vivo* respectively. *In vivo* results of the compounds listed in table.2.

**Table 3.** Effect of lead compounds on *In vivo* expression of TNF-α and IL-6

| **Compound** | **Conc. (mg /kg)** | **% TNF-α inhibition** | **% IL-6 inhibition** |
|---|---|---|---|
| **1** | 10 | 50.8±7.6 | 53.0±3.9 |
| **2** | 10 | 58.7±5.4 | 61.6±9.4 |
| **4** | 10 | 70.7±0.6 | 54.3±0.8 |
| **9** | 10 | 42.5±2.2 | 57.5±1.6 |
| **15** | 10 | 71.3±.3.7 | 28.9±8.6 |
| **16** | 10 | ND | 19.5 |
| **18** | 10 | 58.7±2.2 | 51.6±4.5 |
| **19** | 10 | 37.8±7.4 | 48.5±9.9 |
| **20** | 10 | 59.3±9.7 | 41.6±4.7 |
| **21** | 10 | 30.7±6.3 | 44.1±5.7 |
| **23** | 10 | 26.4±4.8 | 40.2±8.7 |
| **24** | 10 | 39.5±13.3 | 41.4±8.9 |
| **25** | 10 | 53.3±5.9 | 39.1±4.1 |

| | | | |
|---|---|---|---|
| **Rolipram** | 10 | 48.1±5.7 | 36.9±3.2 |

Compounds having % inhibition >50 are considered as active compounds.[31,32] Results are summarized in table for both % of cytokine inhibition and expressed as the mean ± SEM.

Among eleven analogous of BAs taken for *in vivo* assay, five compounds **4**, **15**, **18**, **20** and **25** displayed more than 50% TNF-α inhibition that is 70.7, 71.3, 58.7, 59.3 and 53.3% respectively wherein compounds **4** and **15** showed TNF-α inhibition more than parent compounds. Also the compounds **4**, **9** and **18** suppress IL-6 at level 54.3, 57.5 and 51.6% respectively, more than standard rolipram. Parent compound **2** found to be most potent inhibitor of IL-6 and its epimer that is compound **15** was found to be the strongest inhibitor of TNF-α. *In vivo* results shows more potency in acid analogues as compared with amino analogues for both cytokines. Our results revealed that in both *in vitro* and *in vivo* experiments TNF-α inhibition is more as compared to IL-6.

In summary a series of 3-acyl analogues including their epimers and 4-amino analogues of BAs was synthesized and evaluated for their activity against pro-inflammatory cytokines TNF-α and IL-6 in LPS stimulated macrophage model. The *in vitro* studies showed seven analogues viz., **4**, **9, 15, 16**, **18, 24** and **25** having significant TNF-α inhibition activity, and eight compounds viz., **4, 9, 16, 19**, **20**, **21**, **23, 24** and **25** showing IL-6 inhibitory activity. Among these, compound **25** is most potent inhibitor of TNF-α & compound **23** is most potent inhibitor of IL-6. The in *vivo* studies showed that compound **15** and parent compound **2** as lead inhibitor of TNF-α and IL-6 respectively. Thus, BAs analogues with interesting structural profiles present an important platform for further development into the products of therapeutic significance.

**Supporting Information:**

Experimental procedures and compound characterization data.

**Author Contributions**

‡These authors contributed equally.

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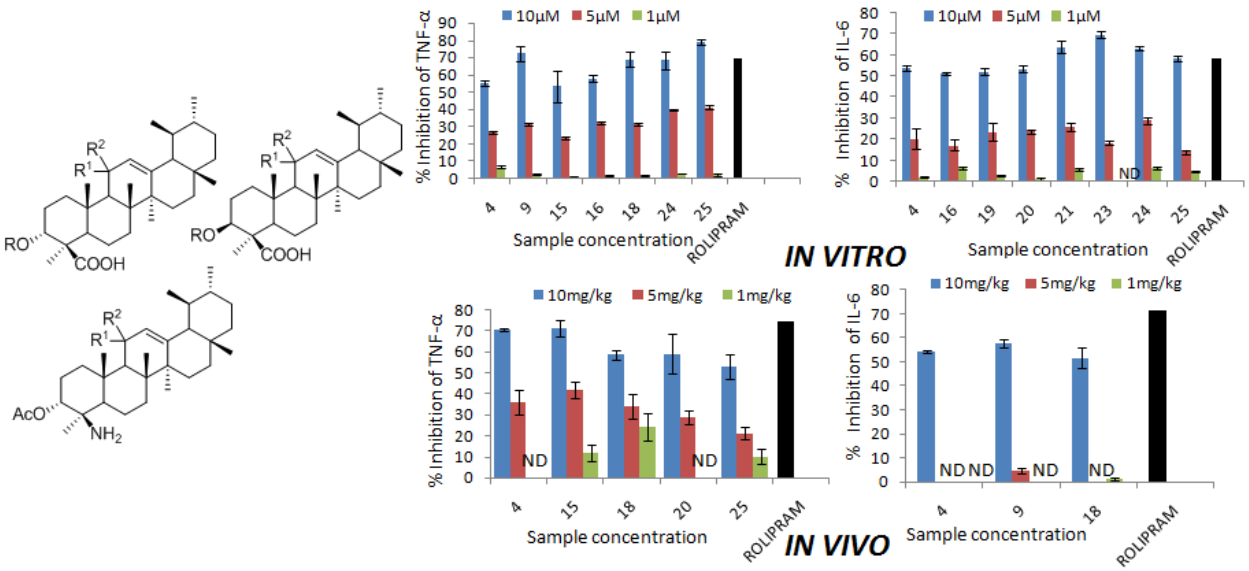
# Graphical Abstract




Boswellic acids analogues were synthesized and evaluated for their anti-inflamattory potential. One of the lead compounds was found to be an inhibitor of TNF-α and IL-6 in both in vivo and in vitro experiments