ACS Medicinal Chemistry Letters

Letter

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ACS Med. Chem. Lett., **Just Accepted Manuscript** • DOI: 10.1021/acsmedchemlett.9b00433 • Publication Date (Web): 27 Feb 2020

Discovery of *N*-Cyano-Sulfoximineurea Derivatives as Potent and Orally Bioavailable NLRP3 Inflammasome Inhibitors

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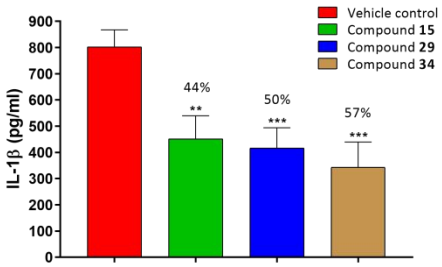
KEYWORDS: NLRP3, NLRP3 inflammasome, Interleukin-1β (IL-1β), Inflammation, Sulfonylurea, N-cyano sulfoximineurea derivatives.

ABSTRACT: NLRP3 inflammasome mediated release of interleukin-1β (IL-1β) has been implicated in various diseases. In this study, rationally designed mimics of sulfonylurea moiety were investigated as NLRP3 inhibitors. Our results culminated into discovery of series of unprecedented *N*-cyano sulfoximineurea derivatives as potent NLRP3 inflammasome inhibitors. Compound **15** (IC_{50} = 7 nM) and analogs were found to be highly potent and selective NLRP3 inflammasome inhibitor with good pharmacokinetic profile. These effects translate *in vivo*, as **15**, **29** and **34** significantly inhibit NLRP3 dependent IL-1β secretion in mice.



Inflammasomes are multi-protein complexes formed by innate immune sensors, including nucleotide oligomerization domain (NOD)-like receptor protein (NLR) family members NLRP1, NLRP3, and NLRC4, along with other non-NLR receptors, such as AIM2 and IFI16.[1] NLRP3 inflammasome activation is dependent on two successive signals. The first step comprises a initiating signal (priming) in which many danger associated molecular patterns (DAMPs) and pathogen associated molecular patterns (PAMPs) are recognized by TLRs, which in turn up-regulates transcription of inflammasome-related components, including inactive NLRP3, proIL-1β, and proIL- 18.[2,3] In the second step of inflammasome activation, the oligomerization of NLRP3 and subsequent assembly of NLRP3, ASC, and procaspase-1 results in formation of a complex. This triggers the transformation of procaspase-1 to caspase-1, leading to the release of active pro-inflammatory cytokines IL-1β and IL-18.[4]

The NLRP3 inflammasome is the most well understood and widely studied owing to its role in host defense and innate immunity.[5] The NLRP3 inflammasome is key component of the inflammatory response. The inappropriate activation of NLRP3 is implicated in a wide range of diseases including rare periodic fever syndrome, CAPS, TRAPS and variety of human complex diseases such as multiple sclerosis, atherosclerosis, alzheimer's disease, diabetes, asthma, gouty arthritis, inflammatory bowel disease (IBD), juvenile arthritis, neurodegenerative and autoimmune diseases.[6,7] Hence, the NLPR3 inflammasome might be a potential target for the treatment of these complex diseases.[8,9]

Additionally, advantage of blocking NLRP3 over simply using an immunosuppressant is that it targets this inflammatory response while leaving the rest of the immune system to operate as normal.[10] Therefore, NLRP3 is emerging as a promising target to develop novel and specific compounds for treatment of anti-inflammatory and autoimmune diseases.[11] Current treatments for these diseases include biologic drugs that target IL-1β, such as anakinra, canakinumab, and rilonacept.[12] However, they also have major limitations such as inconvenient treatment routes and high cost. Hence, an oral small molecule inhibitor of NLRP3 is desirable. This has attracted a great deal of attention in the pharmaceutical industry and in academia.[13-15]

Several structurally diverse small molecule modulators of NLRP3 have been described (Figure 1). MCC950 is reported to be a small molecule inhibitor of NLRP3 inflammasome with an early promise for treatment of inflammatory diseases.[16] In addition, novel boron compound (NBC-6),[17] sulfonamide (JC-171)[18] and compounds like CY09[14] and OLT1177[19] have also been reported as NLRP3 inflammasome inhibitors. Oridonin[20] and Tranilast[21] have recently also been reported to block the NLRP3 inflammasome pathways.

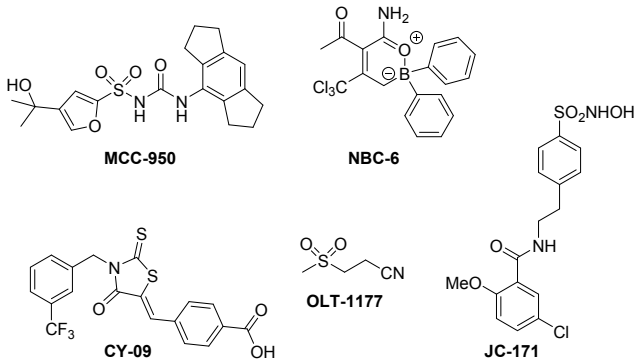


Figure 1. Selected known NLRP3 Inflammasome Inhibitors.

This communication describes the discovery of a series of unprecedented *N*-cyano sulfoximineurea derivatives as highly potent, orally bioavailable, and selective NLRP3 inflammasome inhibitors. We hypothesized that rationally designed mimics of sulfonylurea moiety in the MCC950 would result in structurally novel NLRP3 inflammasome inhibitors with improved properties (Figure 2). Accordingly, we thus focused our SAR efforts on exploring this region of the molecule.

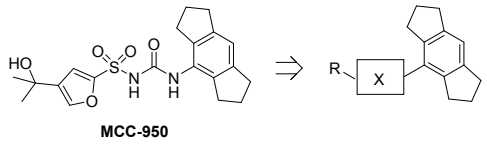
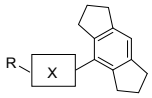
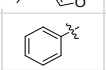
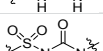
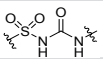
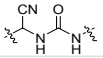
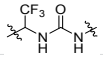
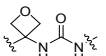
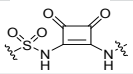
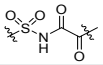
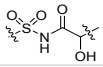
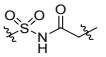
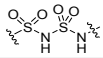
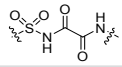
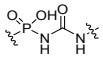
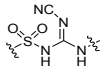
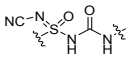
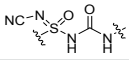
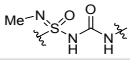
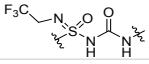
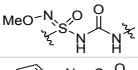
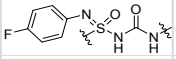


Figure 2. Schematic representation of ligand optimization.

A series of novel compounds have been synthesized by rational and systematic bioisosteric replacement of sulfonylurea (Figure 2). Drug-like properties such as molecular weight (<500) and clog P of these NCEs are generally within acceptable range of oral drugs.[22] The ability of test compounds to inhibit NLRP3 inflammasome was measured in IL-1β assay using THP1 cells.[16] Table 1 describes the structure-activity relationship (SAR) of replacement of sulfonylurea group. The most studied NLRP3 inhibitor, MCC950 (also called CRID3 and CP-456,773) was found to be potent in our hands as well (IC_{50} = 8 nM); and its corresponding phenyl (**2**) and tosyl (**3**) analogues were also potent with IC_{50} of 35 nM and 15 nM respectively. Introduction of cyanomethyl urea or 1-(2,2,2-trifluoroethyl) urea in place of sulfonylurea, (as exemplified by analogs **4** and **5**) resulted in loss of activity with less than 50% inhibition of IL-1β release at 1 μM. Changing the topography by introducing oxetane or squaric acid moiety also resulted in dramatic potency loss (**6** and **7**). Further, various other rationally designed mimics of sulfonylurea moiety like 2-oxo-*N*-(arylsulfonyl)acetamide derivative **8**, corresponding hydroxy derivative **9** and acetamide **10** also lowered the activity. Moreover, sulfonamide derivative **11**, oxalamide derivative **12**, phosphonamidic acid analogue **13**, and cyanoguanidine derivative **14** were also synthesized and explored as NLRP3 inflammasome inhibitors. However, all these performed modulation lowered the activity obtaining less than 50% inhibition of IL-1β release at 1 μM.

Table 1. Core modification on the sulfonylurea moiety: *In vitro* activity of MCC950 (**1**) and **2-20**.[a]



Compound	R	X	IL-1β (IC_{50})	CLogP[b]
1 (MCC950)			8 ± 0.7 nM	3.27
2			35 ± 3.2 nM	3.52
3			15 ± 2.1 nM	3.93
4			>1 μM	3.53
5			>1 μM	5.25
6			>1 μM	4.39
7			>1 μM	2.31
8			>1 μM	2.94
9			>1 μM	2.23
10			>1 μM	4.14
11			>1 μM	4.34
12			>1 μM	3.78
13			>1 μM	3.44
14			>1 μM	3.35
15			6.8 ± 0.5 nM	2.45
16			21.0 ± 4.0 nM	2.15
17			>1 μM	3.33
18			>1 μM	4.52
19			>1 μM	3.33
20			>1 μM	5.15
21			>1 μM	3.79
22			>1 μM	2.5
23			>1 μM	3.82
24			>1 μM	3.18

[a]IC_{50} values given are expressed as mean ± SEM of three independent experiments. [b]Calculated from Schrödinger Release 2018-3**:** QikProp, Schrödinger, LLC, New York, NY, 2018.

These results indicate that any modification of the sulfonylurea motif in **4**-**14** resulted in complete loss of IL-1β inhibition, showing the critical importance of the sulfonylurea hydrogen bond acceptor-donor pattern. Nevertheless, to our delight, *N*-cyano sulfoximineurea analogue **15** was found to be highly potent (IC_{50} = 7 nM), equipotent to MCC950. In addition, *N*-cyano sulfoximineurea derivative **16** was also found to be active (IC_{50} = 21 nM). Sulfoximine moiety, the monoaza analogues of sulfones, are stable pharmacophore which offers a rich and versatile tool in medicinal chemistry.[23] This prompted us to explore additional *N*-substituted sulfoximineurea analogues. However, introduction of alkyl, methoxy, aryl, heteroaryl, amide, ester or acyl group at sulfoximine nitrogen proved to be detrimental to activity (**17** - **24**). Overviews of all the compounds that have been synthesized and tested for IL-1β activity are listed in Table 1.

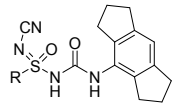
Notably, **15** and **16** were highly selective against TNF-α (IC_{50} >10 μM). The production of TNF-α was not affected by **15** even at high concentration (refer supporting information), indicating its selective effect on the NLRP3 inflammasome. Moreover, **15** blocked the recruitment of ASC during NLRP3 activation, thus providing further evidence to the mechanistic hypothesis of our novel *N*-cyano sulfoximineurea derivatives as NLRP3 inflammasome inhibitors. Furthermore, this compound had no effect on the AIM2 inflammasome, demonstrating specificity for NLRP3 inflammasome. The results obtained suggested that incorporation of the *N*-cyano sulfoximineurea motif may open up new directions for further SAR development. Accordingly, we focused our investigation on this region of the molecule, and thus, in our optimization campaign, series of novel substituted sulfoximineurea derivatives were synthesized and evaluated as NLRP3 inflammasome inhibitors.

Scheme 1. Synthesis of Compound **15**. *Reagents and conditions*: (a) 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (**27**), n-BuLi, dry THF, -78 °C to r.t., 4 h (70%); (b) cyanamide, MeCN, *t*-BuOK, NCS, r.t, 5 h (22%).

An efficient synthesis allowed rapid access to **15** as outlined in Scheme 1. The key intermediate **25** was obtained from commercially available *p*-tosyl chloride using known procedure.[24] The another key intermediate, tricyclic amine (1,2,3,5,6,7-hexahydro-s-indacen-4-amine) (**26**), and its corresponding isocyanate **27**, was synthesized via reported protocol on multi gram scale.[25] The coupling of sulfinimide **25** with 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (**27**) provided sulfinylurea **28** in high yields, using modified reaction conditions reported by Toth et. al.[26] Synthesis of *N*-substituted sulfoximines using alkylamines[27] and cyanamide[28,29] are reported in literature. However, there are no reports for the synthesis of *N*-cyano sulfoximineurea *albeit* synthesis of sulfinylurea followed by chlorination/amination to afford *N*-alkyl sulfoximineurea are documented in literature.[26] Sulfinylurea **28** was converted to *N*-cyano sulfoximineurea derivative **15** using cyanamide with NCS as oxidant and potassium *tert*-butoxide as base in a acetonitrile mixture.

Following the same reaction sequence with various sulfinimides resulted in test compounds **16** and **29 – 34** in good yield and high chemical purity. Synthesis of **2-24** is described in the supporting information.

Table 2. Modifications on left-hand side of *N*-cyano-sulfoximineurea derivatives: *In vitro* activity and Pharmacokinetics properties[a] of **15**, **29-34**.



Compound	R	IL-1β IC_{50} (nM)	AUC (μg.h/mL)[b]	$t_{½}$ (h)[b]	% F	CLogP[c]
15		6.8 ± 0.5	4.2	2.91	56	2.45
29		5.3 ± 0.2	3.2	2.38	59	2.61
30		34.0 ± 3.5	0.8	1.03	27	1.33
31		11.7 ± 0.3	1.2	1.13	40	1.37
32		110 ± 7	NC	NC	NC	1.18
33		36.3 ± 3.3	1.28	1.66	24	1.19
34		23.0 ± 2.7	8.2	5.2	97	1.48

[a]Compounds dosed 1 mg/kg iv and 3 mg/kg po. [b]po. Mouse PK data is mean data because of composite study design, n = 3/time point. Formulation: PO, 1% Tween 80 + 99% (0.5%) methyl cellulose in water; IV, 5% NMP + 5% solutol + 90% normal saline. [c]Calculated from Schrödinger Release 2018-3: QikProp, Schrödinger, LLC, New York, NY, 2018. NC: Not calculated.

Extensive SAR work on the left-hand side aryl ring fragment was also pursued.[30] Key examples selected from a large set of modifications are presented in Table 2. Notably, the fluorinated compound **29** displayed excellent potency (IC_{50} = 5.3 nM) as well as good pharmacokinetic properties with AUC = 3.2 μg.h/mL at 3 mg/kg, and mice oral bioavailability of 59%. Additional modifications on the left-hand side aryl ring, such as addition of electron-withdrawing groups (**30** and **31**), were made to potentially improve the pharmacokinetic profile. The 4-cyano analogue **30** displayed IL-1β inhibition IC_{50} of 34 nM. However, pharmacokinetic profile of this compound was comparatively inferior (AUC = 0.8 μg.h/mL at 3 mg/kg, $t_{1/2}$= 1 h, mice oral bioavailability 27%). The 3-cyano analogue **31** displayed IC_{50} of 12 nM, with similar pharmacokinetic profile (AUC = 1.2 μg.h/mL at 3 mg/kg, mice oral bioavailability 40%). Next, in a quest to explore heteroaryl analogues, the pyridyl compounds were investigated. The 4-pyridyl analogue **32** was found to be relatively less potent (IC_{50} = 112 nM). The regioisomer, 3-pyridyl compound **33** helped to regain *in vitro* potency but was accompanied by loss of plasma levels and bioavailability. *In vitro* potency was further improved for 2-pyridyl compound **34** (IC_{50} = 23 nM). In addition, the PK properties of **34** were also dramatically improved, with AUC = 8.2 μg.h/mL at 3 mg/kg, $t_{1/2}$= 5.2 h and mice oral bioavailability of 97%, perhaps due to good solubility. It's noteworthy to mention that all these compounds (**15**, **16** and **29-34**) were highly selective against TNF-α (IC_{50} >10 μM). In particular, **34** show a high oral bioavailability along with a long half-life, and represent an improvement in PK properties with respect to regioisomers **32** and **33**. This, combined with the potency of the compound, suggests potential for therapeutic efficacy in *in vivo* models.

Next, having identified compounds with high potency and good pharmacokinetic profile, effect of the lead compounds **15**, **29** and **34**, on the NLRP3 dependent release of IL-1β was evaluated in acute *in vivo* LPS+ATP challenged model in female C57BL/6 mice.[31] A single oral administration of test compounds at 10 mg/kg dose decreases the IL-1β levels by 44%, 50% and 57% respectively w.r.t. vehicle control (Figure 3), indicating that even at this low dose, **15**, **29** and **34** markedly reduced the IL-1β compared to the control.

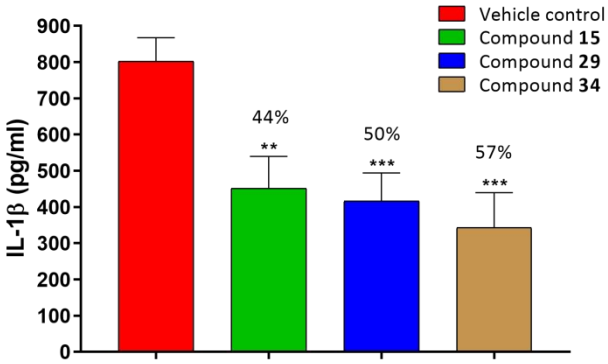


Figure 3. *In vivo* IL-1β inhibition of compounds **15**, **29** and **34** in C57 mice. (n = 6 animals/group; female C57 mice; po 10 mg/kg; formulation, 1% Tween 80 and 99% methyl cellulose (0.5%); ***P < 0.001 versus control, **P < 0.01 versus control; error bar indicates SEM).

In conclusion, through systematic exploration of rationally designed mimics of sulfonylurea moiety, we have identified a novel series of *N*-cyano sulfoximineurea derivatives as potent and selective NLRP3 inflammasome inhibitors. The *in vitro* inhibition potency of *N*-cyano sulfoximineurea analogue **15**, on IL-1β release by LPS/ATP stimulation was found to be similar to the reference compound MCC950, thus indicating that structural modifications at the sulfonylurea moiety can be tolerated. Further **15**, **29** and **34** exhibited significant IL-1β lowering efficacy in animal models with desired pharmacokinetic profile. These data also warrant further investigation of **15** and analogues for treatment of chronic inflammatory diseases mediated *via* NLRP3 inflammasome. These NLRP3 inflammasome inhibitors with novel chemical structure having high potency and desired PK/PD profile would be helpful in further investigations as potential clinical candidates.

ASSOCIATED CONTENT

Supporting information

Supporting information file with experimental procedures and analytical data. Spectral data file. This material is available free of charge via the Internet at http://pubs.acs.org.

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Conflict of interest: Authors declare no conflict of interest.

Funding Sources: No external funding.

Notes

ZRC Communication No. 595.

ACKNOWLEDGMENT

Authors thank Mr. Jeevan Kumar for LogP calculations using QikProp, Schrödinger Software.

ABBREVIATIONS

NLRP3, NOD-like receptor family, pyrin domain-containing protein 3; ASC, apoptosis-associated speck-like protein containing a CARD; AIM2, absent in melanoma 2; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern; TLR, Toll-like receptor; IFI16, Gamma-interferon-inducible protein 16; IL-1R, Interleukin-1 receptor; LPS, Lipopolysaccharide; ATP, adenosine triphosphate; CAPS, cryopyrin associated periodic syndromes; TRAPS, Tumor necrosis factor receptor-associated periodic syndrome; NCE, New Chemical Entity; NMP, *N*-Methyl-2-Pyrrolidone; NCS, *N*-Chlorosuccinimide; PK/PD, Pharmacokinetic/pharmacodynamics; TNF-α, Tumour Necrosis Factor alpha.

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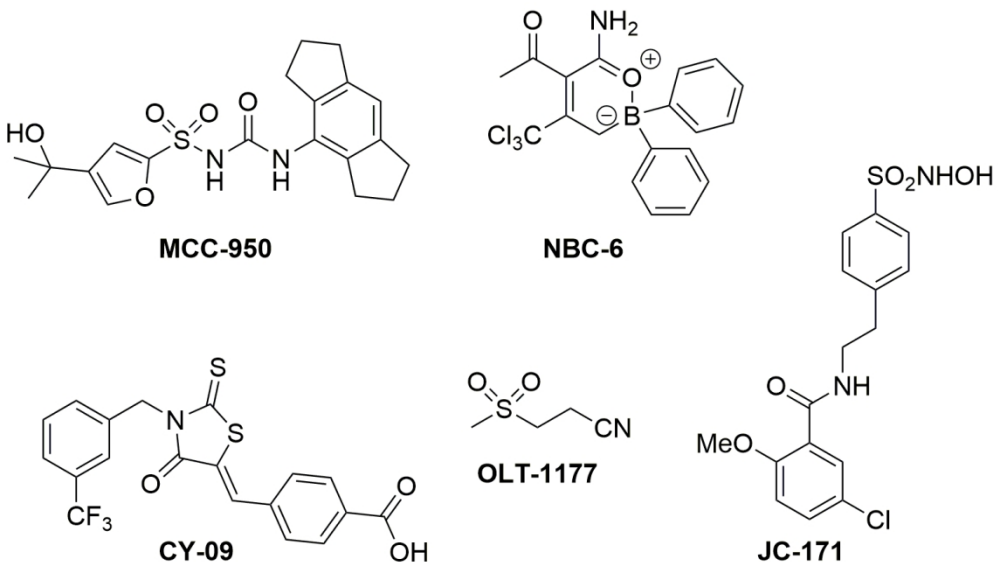

Figure 1. Selected known NLRP3 Inflammasome Inhibitors.

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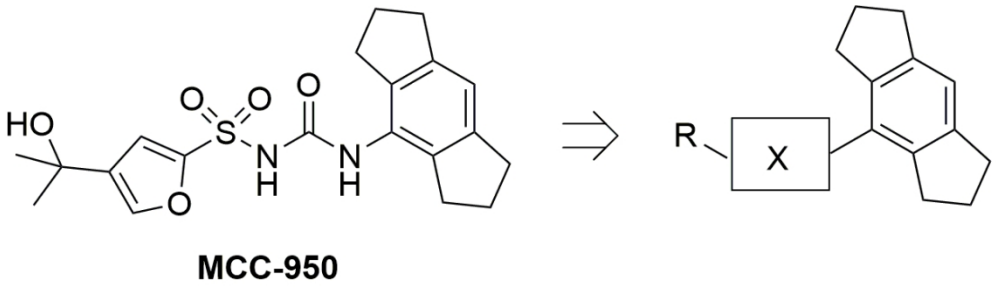

Figure 2. Schematic representation of ligand optimization.

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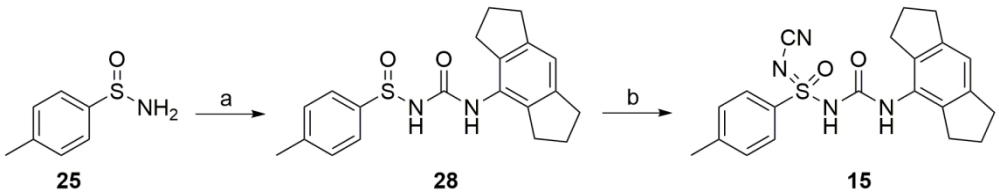

Scheme 1. Synthesis of Compound 15. Reagents and conditions: (a) 4-isocyanato-1,2,3,5,6,7-hexahydro-s-indacene (27), n-BuLi, dry THF, -78 °C to r.t., 4 h (70%); (b) cyanamide, MeCN, t-BuOK, NCS, r.t, 5 h (22%).

157x31mm (300 x 300 DPI)

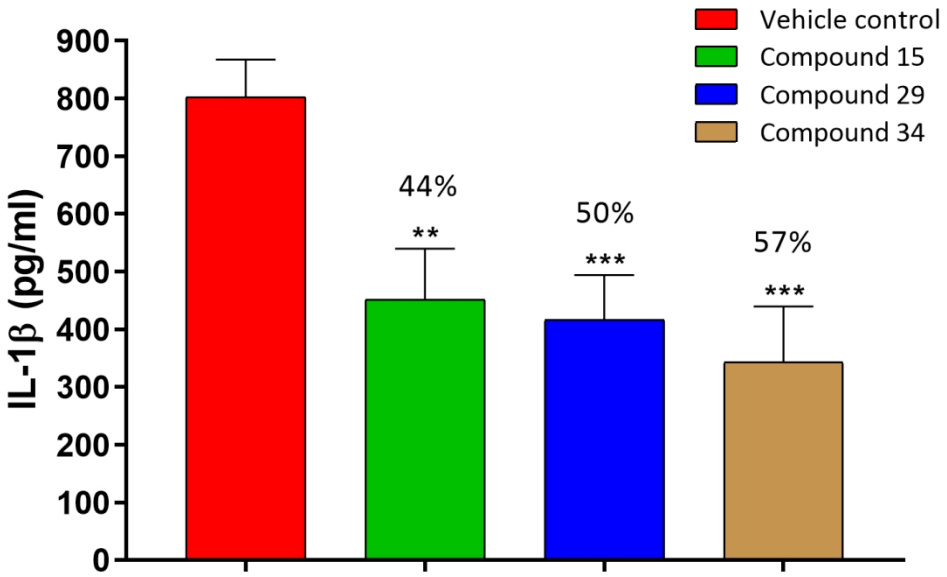

Figure 3. In vivo IL-1β inhibition of compounds 15, 29 and 34 in C57 mice. (n = 6 animals/group; female C57 mice; po 10 mg/kg; formulation, 1% Tween 80 and 99% methyl cellulose (0.5%); ***P < 0.001 versus control, **P < 0.01 versus control; error bar indicates SEM).

130x81mm (300 x 300 DPI)