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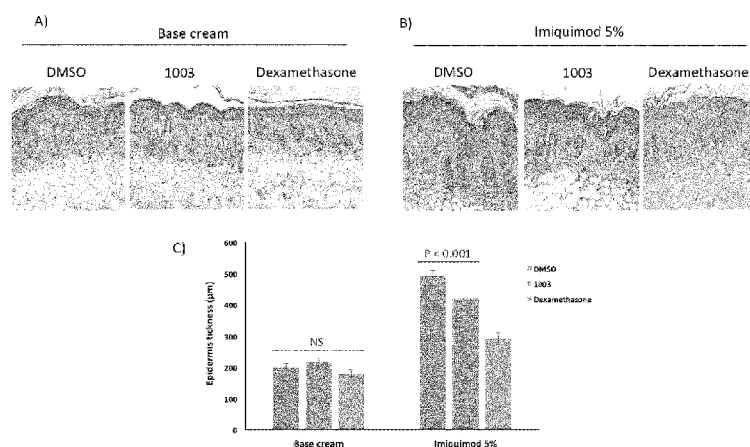
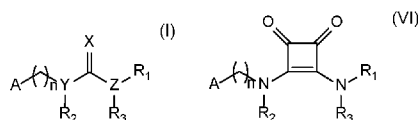


FIG. 2

(57) Abstract: Novel urea, thiourea and squaramide compounds and bioisosteres thereof of formulas (I) and (VI) and the use thereof for treating, attenuating, inhibiting or preventing inflammation and inflammation-related pathologies are described herein.

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TITLE

NOVEL UREA COMPOUNDS AND BIOISOSTERES THEREOF AND THEIR USE FOR TREATING INFLAMMATION AND INFLAMMATION-RELATED PATHOLOGIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application 62/519,281, filed June 14, 2018. The contents of the referenced application are incorporated into the present application by reference.

FIELD

[0002] The present disclosure broadly relates to novel urea compounds and bioisosteres thereof. More specifically, but not exclusively, the present disclosure relates to novel urea compounds, and bioisosteres thereof and pharmaceutical compositions comprising such compounds for treating, attenuating, inhibiting or preventing inflammation and inflammation-related pathologies. Yet more specifically, but not exclusively, the present disclosure relates to novel urea compounds, and bioisosteres thereof and pharmaceutical compositions comprising such compounds for treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. The present disclosure also relates to intermediates and processes useful in the synthesis of the urea compounds and bioisosteres thereof.

BACKGROUND

[0003] Phenyl-3-(2-chloroethyl)ureas (CEUs) were developed as soft alkylating agents covalently binding to a number of intracellular proteins. To this end, two prototypical CEUs, namely 3-(2-chloroethyl)-1-*p*-(*tert*-butyl)phenyl]urea (*t*BCEU) [1] and 1-(2-chloroethyl)-3-(*p*-cyclohexylphenyl)urea (*c*HCEU) [2, 3] (**FIG. 1**) were shown to exhibit potent antiproliferative activity on numerous cancer cell lines [4, 5] as well as cancer cell lines having developed mechanisms of chemoresistance [6, 7]. On one hand, the study of the mechanism of action of *t*BCEU evidenced a unique acylation of Glu198 within the colchicine-binding site on β -tubulin

[8] that lead to microtubule depolymerization, cytoskeleton disruption and anoikis of cancer cells [9]. On the other hand, *c*HCEU acylates prohibitin-1 on Asp40 and thioredoxin-1 on an identified amino acid residue, abrogating the translocation of both proteins from the cytosol to the nucleus [3]. Moreover, *t*BCEU and *c*HCEU were shown to exhibit a strong impact on cell cycle progression, arresting cancer cells in the G2/M and G0-G1 phase, respectively. The alkylating properties of CEUs such as *t*BCEU are due to the presence of a chlorine atom; its absence abrogates the electrophilic properties and the antiproliferative activity of the ethylurea counterparts (e.g. *t*BEU).

[0004] The mechanism of action responsible for the antiproliferative activity of the CEUs has been further investigated and the involvement of the ASK1-P38 signaling pathway in the triggering of cell anoikis was evidenced [10]. Interestingly, a strong link has been established between the P38 signaling pathway and various diseases, notably cancer, inflammation, rheumatoid arthritis and Alzheimer's disease, which depend on the production of cytokines such as IL-6 [11-16]. The inhibition of the synthesis or the release of IL-6 and other pro-inflammatory cytokines (TNF α , IL-1 and IL-2) was previously reported as a potential therapeutic approach for the treatment of diseases associated with inappropriate inflammatory responses [17].

[0005] Psoriasis is an inflammatory cutaneous disease that affects 2 to 3% of the world population, both men and women [18]. Several forms of psoriasis have been identified, but the most common form (90% of all cases) is psoriasis vulgaris also called plaques psoriasis [19]. This type of psoriasis is characterised by the presence of whitish and reddish scaly plaques especially on elbows, knees and scalp [20]. The plaques are the result of a hyperproliferation of keratinocytes and, together with their abnormal differentiation, cause a thickening of the epidermis (acanthosis) [21]. The poor epidermal differentiation induces retention of keratinocytes nuclei in the *stratum corneum* (parakeratosis), in addition to many modifications in protein expression such as involucrin, filaggrin, keratins and loricrin [22-24]. Plaques psoriasis is also characterized by an infiltration of leucocytes in skin and by an increase of angiogenesis producing tortuous, dilated and more permeable capillaries [25-26]. The symptoms of this pathology can be controlled by several treatments; however, no cure is yet available.

SUMMARY

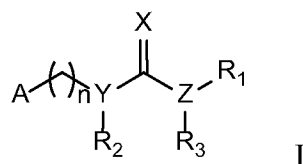
[0006] The present disclosure broadly relates to novel urea, thiourea and squaramide compounds and bioisosteres thereof. In an aspect, the present disclosure relates to novel urea, thioureas and squaramide compounds, and bioisosteres thereof and pharmaceutical compositions comprising such compounds for treating, attenuating, inhibiting or preventing inflammation and inflammation-related pathologies. In a further aspect, the present disclosure relates to novel urea, thioureas and squaramide compounds, and bioisosteres thereof and pharmaceutical compositions comprising such compounds for treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. The present disclosure also relates to intermediates and processes useful in the synthesis of the urea, thioureas and squaramide compounds and bioisosteres thereof.

[0007] In an aspect, the present disclosure relates to urea compounds and bioisosteres thereof and to their use for treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies.

[0008] In an aspect, the present disclosure relates to urea compounds and bioisosteres thereof and to their use for treating, attenuating, inhibiting and/or preventing conditions associated with the expression of IL-6.

[0009] In an aspect, the present disclosure relates to substituted phenyl cycloalkylureas and to their use for treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies. In an embodiment, the present disclosure relates to substituted phenyl cycloalkylureas and to their use for treating, attenuating, inhibiting and/or preventing conditions associated with the expression of IL-6. In a further embodiment, the present disclosure relates to pharmaceutical compositions comprising one or more substituted phenyl cycloalkylureas and to their use for treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. In a further embodiment, the present disclosure relates to intermediates and processes for the synthesis of substituted phenyl cycloalkylureas.

[0010] In an embodiment, the present disclosure relates to a compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

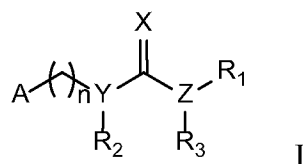
each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0011] In an embodiment, the present disclosure relates to a compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

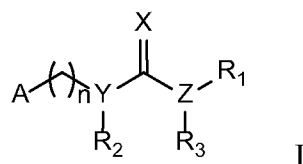
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0012] In an embodiment, the present disclosure relates to a compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

wherein

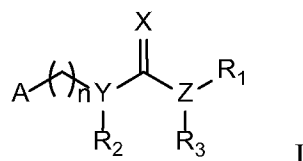
when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0013] In an embodiment, the present disclosure relates to a method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof,

the method comprising administering a therapeutically effective amount of a compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl,

(C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁-C₁₅)alkyl, -O-(C₂-C₁₅) alkenyl, -O-(C₂-C₁₅) alkynyl, -S-(C₁-C₁₅)alkyl, -S-(C₂-C₁₅)alkenyl, -S-(C₂-C₁₅)alkynyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

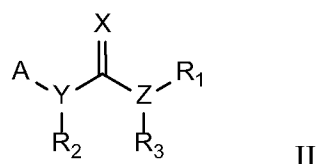
or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0014] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier.

[0015] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula I and a pharmaceutically acceptable carrier.

[0016] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula I and a pharmaceutically acceptable carrier.

[0017] In an embodiment, the present disclosure relates to a compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -

CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

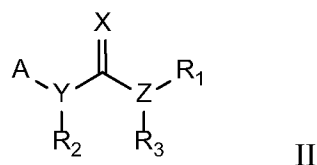
each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0018] In an embodiment, the present disclosure relates to a compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

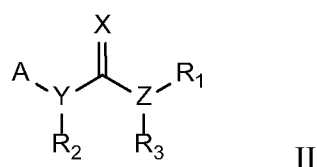
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0019] In an embodiment, the present disclosure relates to a compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

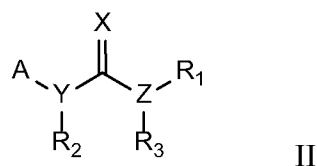
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0020] In an embodiment, the present disclosure relates to a method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -

CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

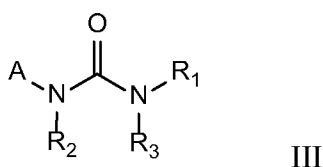
or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0021] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula II and a pharmaceutically acceptable carrier.

[0022] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula II and a pharmaceutically acceptable carrier.

[0023] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula II and a pharmaceutically acceptable carrier.

[0024] In an embodiment, the present disclosure relates to a compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -

NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋

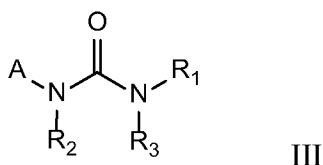
C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0025] In an embodiment, the present disclosure relates to a compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋

₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, (C₂-C₁₅)alkenyl, (C₂-C₁₅)alkynyl, -O-(C₁-C₁₅)alkyl, -O-(C₂-C₁₅) alkenyl, -O-(C₂-C₁₅) alkynyl, -S-(C₁-C₁₅)alkyl, -S-(C₂-C₁₅)alkenyl, -S-(C₂-C₁₅)alkynyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

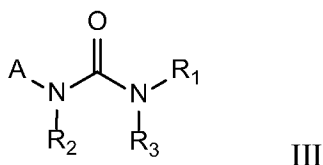
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0026] In an embodiment, the present disclosure relates to a compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -

C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

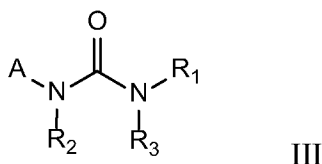
each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0027] In an embodiment, the present disclosure relates to a method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof,

the method comprising administering a therapeutically effective amount of a compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -

CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

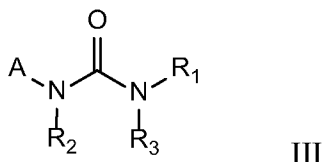
or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0028] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0029] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0030] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0031] In an embodiment, the present disclosure relates to a compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

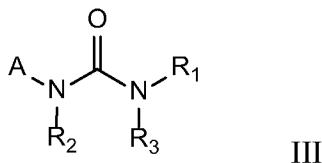
A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁₋₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0032] In an embodiment, the present disclosure relates to a compound of Formula IV:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

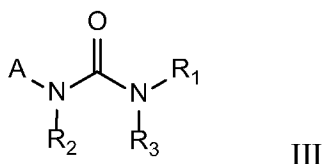
wherein:

each R is independently selected from -H, (C₁₋₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0033] In an embodiment, the present disclosure relates to a compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

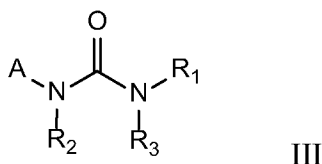
each R is independently selected from -H, (C₁₋₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

[0034] In an embodiment, the present disclosure relates to a method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof,

the method comprising administering a therapeutically effective amount of a compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁₋₁₀)alkyl,

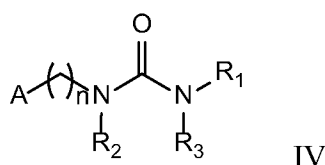
or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0035] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0036] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0037] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula III and a pharmaceutically acceptable carrier.

[0038] In an embodiment, the present disclosure relates to a compound of Formula IV:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

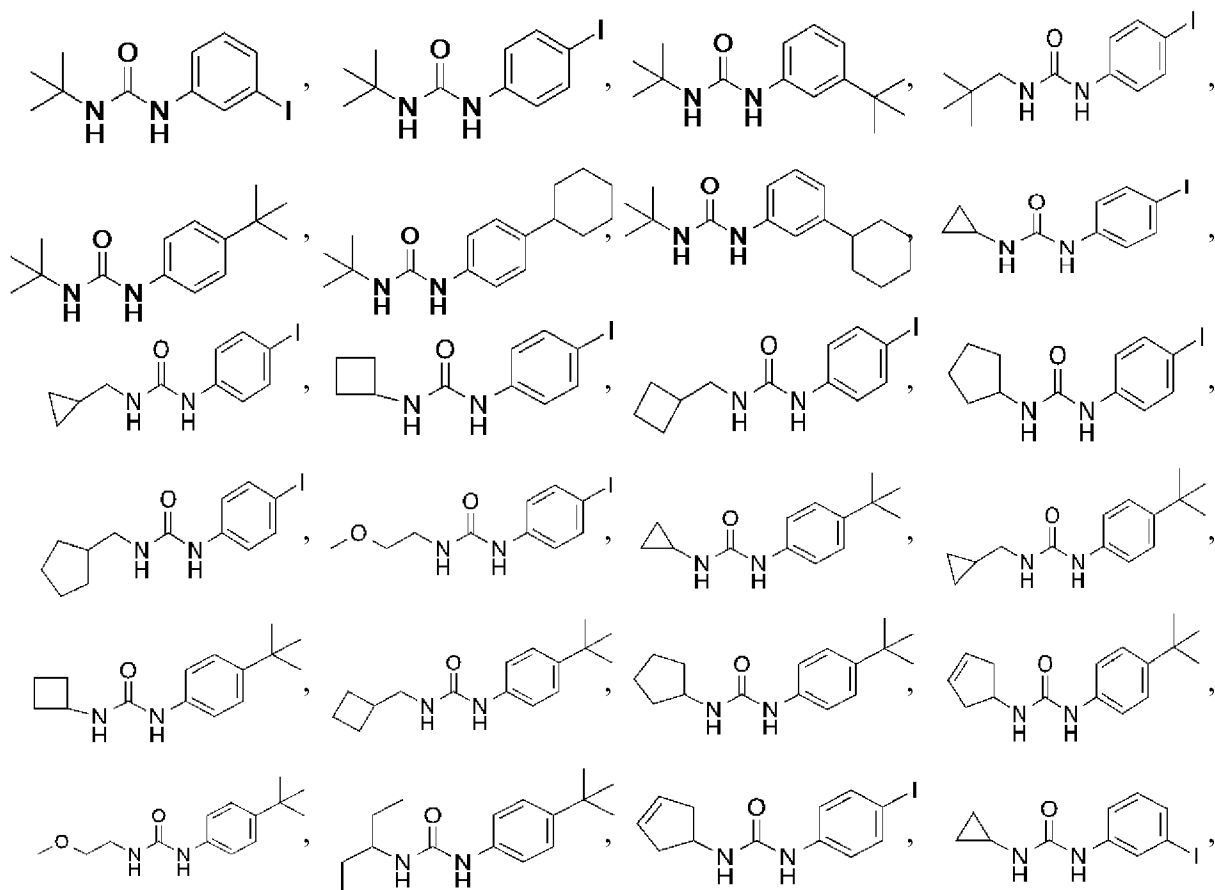
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

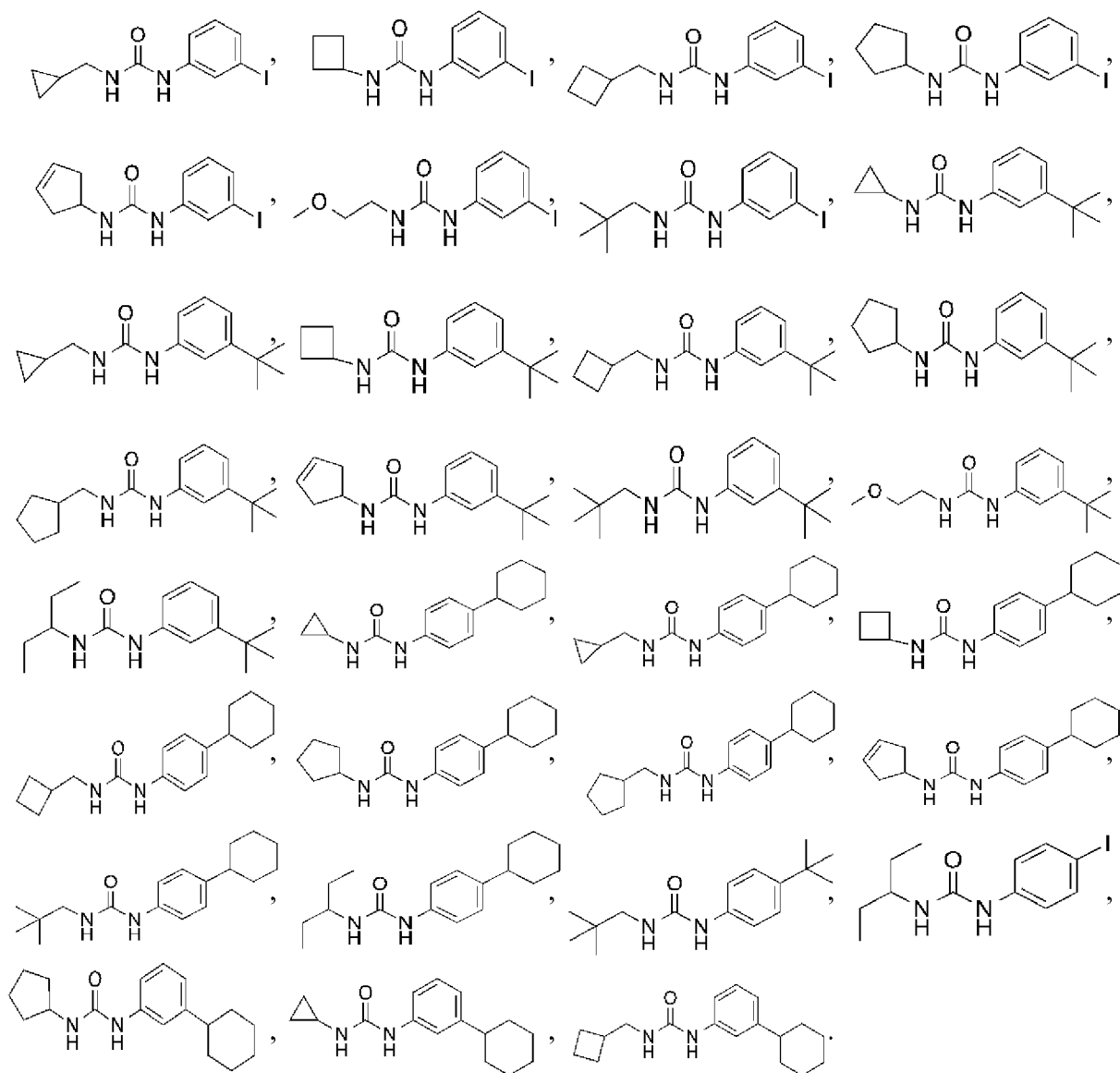
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0039] In an embodiment, the present disclosure relates to a compound of Formula IV including:



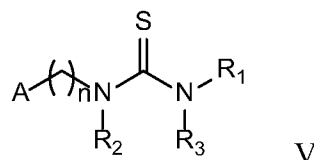


[0040] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula IV and a pharmaceutically acceptable carrier.

[0041] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula IV and a pharmaceutically acceptable carrier.

[0042] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula IV and a pharmaceutically acceptable carrier.

[0043] In an embodiment, the present disclosure relates to a compound of Formula V:



wherein:

A is an arene;

R₁ is a (C₁₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-; -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-; -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-

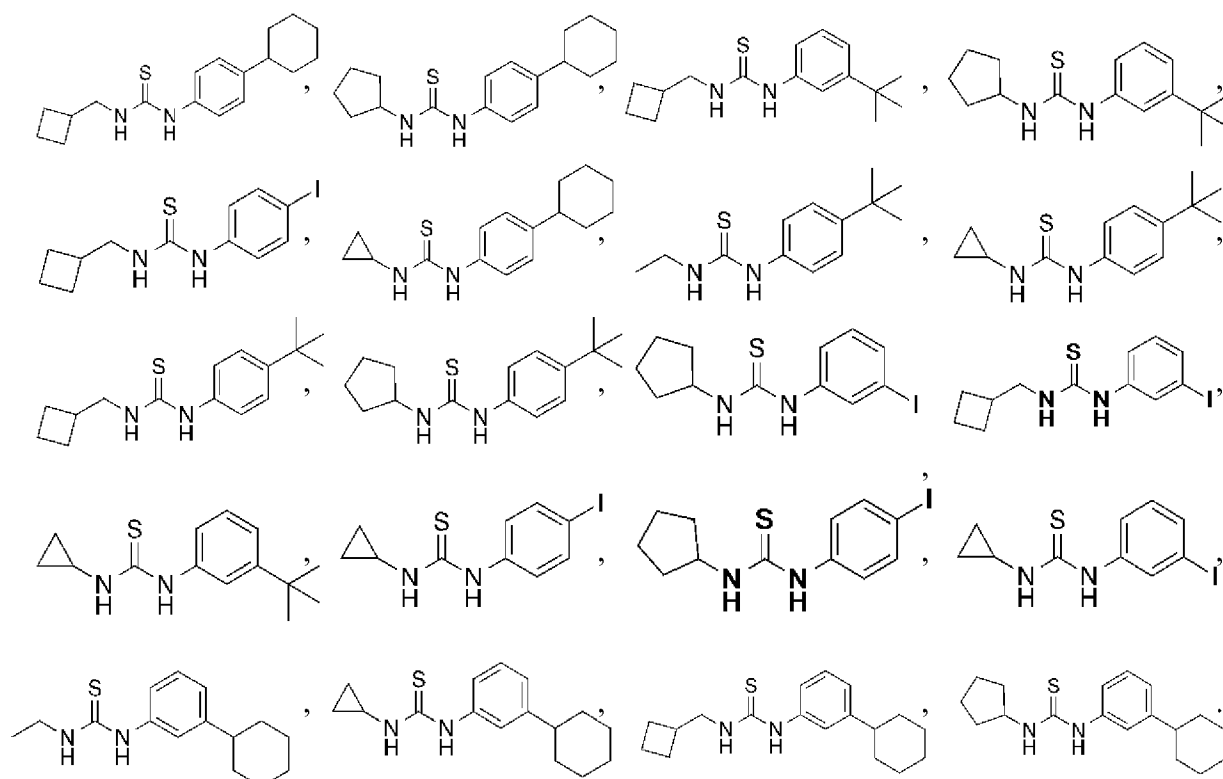
(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0044] In an embodiment, the present disclosure relates to a compound of Formula V including:

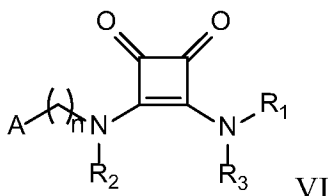


[0045] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula V and a pharmaceutically acceptable carrier.

[0046] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula V and a pharmaceutically acceptable carrier.

[0047] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula V and a pharmaceutically acceptable carrier.

[0048] In an embodiment, the present disclosure relates to a compound of Formula VI:



wherein:

A is an arene;

R₁ is a (C₁₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-; -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-; -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

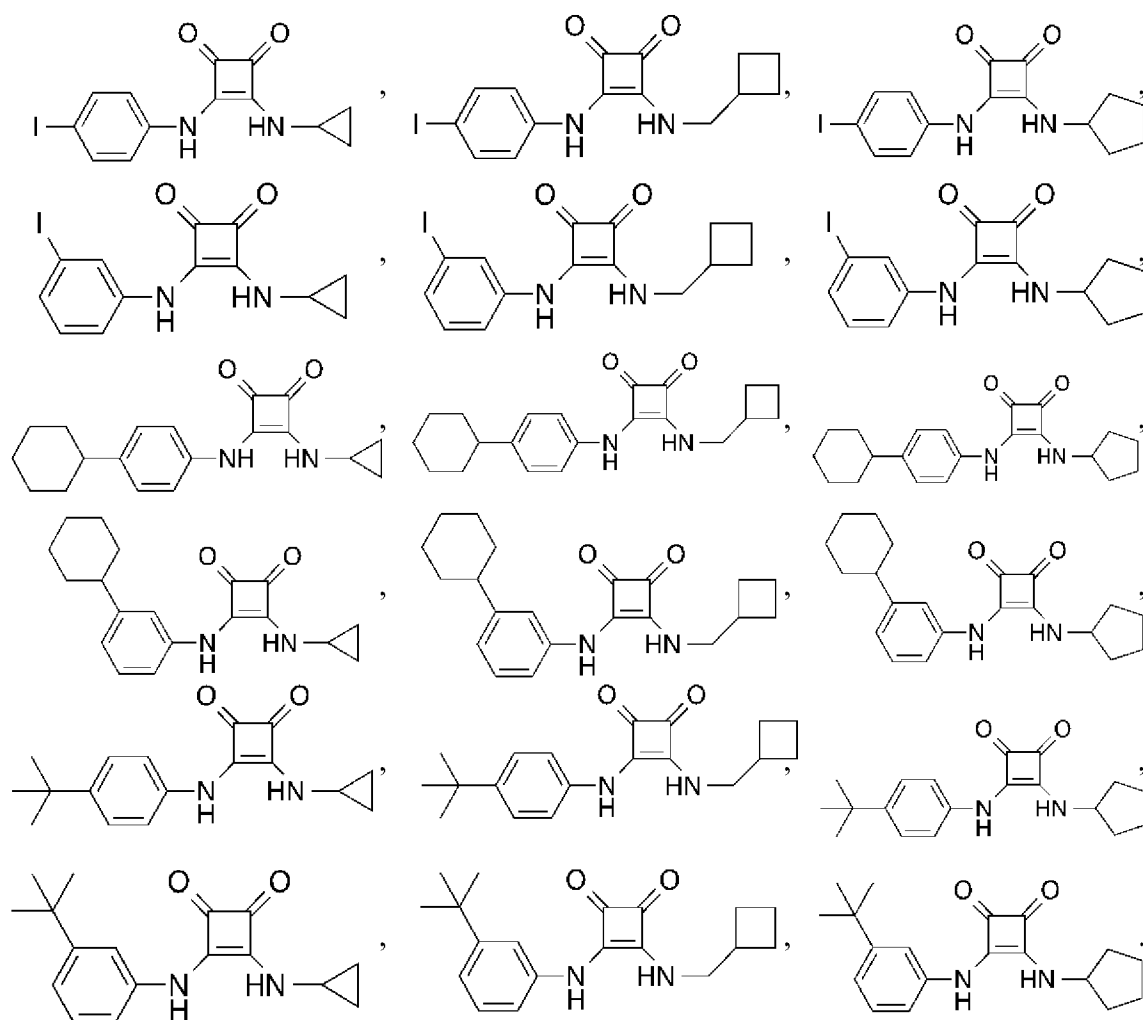
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

[0049] In an embodiment, the present disclosure relates to a compound of Formula VI including:



[0050] In an embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of Formula VI and a pharmaceutically acceptable carrier.

[0051] In an embodiment, the present disclosure relates to a medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound of Formula VI and a pharmaceutically acceptable carrier.

[0052] In an embodiment, the present disclosure relates to a medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound of Formula VI and a pharmaceutically acceptable carrier.

[0053] The foregoing and other advantages and features of the present disclosure will become more apparent upon reading of the following non-restrictive description of illustrative embodiments thereof, given by way of example only with reference to the accompanying drawings/figures.

BRIEF DESCRIPTION OF THE DRAWINGS/FIGURES

[0054] In the appended drawings/figures:

[0055] **FIG. 1** is an illustration of the molecular structures of *t*BCEU and *c*HCEU respectively.

[0056] **FIG. 2** is an illustration of the effect of compound **20** (**Table 4**) on the thickness of the epidermis in a mouse model of psoriasis; **A**) H&E staining of skin sections from mice topically treated for 6 days with base cream or **B**) imiquimod (5%) to induce psoriasis-like symptoms. The mice either received DMSO as a negative control, dexamethasone as a positive control or compound **20**. The epidermis thickness was measured on 8 mice per condition (**C**).

DETAILED DESCRIPTION**[0057] Glossary**

[0058] In order to provide a clear and consistent understanding of the terms used in the present disclosure, a number of definitions are provided below. Moreover, unless defined otherwise, all technical and scientific terms as used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this specification pertains.

[0059] The word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one", but it is also consistent with the meaning of "one or more", "at least one", and "one or more than one" unless the content clearly dictates otherwise. Similarly, the word "another" may mean at least a second or more unless the content clearly dictates otherwise.

[0060] As used in this specification and claim(s), the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "include" and "includes") or "containing" (and any form of containing, such as "contain" and "contains"), are inclusive or open-ended and do not exclude additional, unrecited elements or process steps.

[0061] As used in this specification and claim(s), the word "consisting" and its derivatives, are intended to be close ended terms that specify the presence of stated features, elements, components, groups, integers, and/or steps, and also exclude the presence of other unstated features, elements, components, groups, integers and/or steps.

[0062] The term "consisting essentially of", as used herein, is intended to specify the presence of the stated features, elements, components, groups, integers, and/or steps as well as those that do not materially affect the basic and novel characteristic(s) of these features, elements, components, groups, integers, and/or steps.

[0063] The terms "about", "substantially" and "approximately" as used herein mean a reasonable amount of deviation of the modified term such that the end result is not significantly

changed. These terms of degree should be construed as including a deviation of at least $\pm 1\%$ of the modified term if this deviation would not negate the meaning of the word it modifies.

[0064] The term "suitable" as used herein means that the selection of the particular compound or conditions would depend on the specific synthetic manipulation to be performed, and the identity of the molecule(s) to be transformed, but the selection would be well within the skill of a person trained in the art. All process/method steps described herein are to be conducted under conditions sufficient to provide the product shown. A person skilled in the art would understand that all reaction conditions, including, for example, reaction solvent, reaction time, reaction temperature, reaction pressure, reactant ratio and whether or not the reaction should be performed under an anhydrous or inert atmosphere, can be varied to optimize the yield of the desired product and it is within their skill to do so.

[0065] The expression "proceed to a sufficient extent" as used herein with reference to the reactions or process steps disclosed herein means that the reactions or process steps proceed to an extent that conversion of the starting material or substrate to product is maximized. Conversion may be maximized when greater than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99% of the starting material or substrate is converted to product.

[0066] The term "substituted" as used herein, means that a hydrogen radical of the designated moiety is replaced with the radical of a specified substituent, provided that the substitution results in a stable or chemically feasible compound. Non-limiting examples of substituents include halogen (F, Cl, Br, or I) for example F, hydroxyl, thiol, alkylthiol, alkoxy, amino, amido, carboxyl, alkyl, cycloalkyl, arene, heteroarene and cyano.

[0067] As used herein, the term "alkyl" can be straight-chain or branched. This also applies if they carry substituents or occur as substituents on other residues, for example in alkoxy residues, alkoxycarbonyl residues or arylalkyl residues. Substituted alkyl residues can be substituted in any suitable position. Examples of alkyl residues containing from 1 to 15 carbon atoms are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl and pentadecyl, the *n*-isomers of all these residues, isopropyl,

isobutyl, isopentyl, neopentyl, isohexyl, isodecyl, 3-methylpentyl, 2,3,4-trimethylhexyl, *sec*-butyl, *tert*-butyl, or *tert*-pentyl. A specific group of alkyl residues is formed by the residues methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl and *tert*-butyl.

[0068] As used herein, the term “lower alkyl” can be straight-chain or branched. This also applies if they carry substituents or occur as substituents on other residues, for example in alkoxy residues, alkoxycarbonyl residues or arylalkyl residues. Substituted alkyl residues can be substituted in any suitable position. Examples of lower alkyl residues containing from 1 to 6 carbon atoms are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, pentyl, isopentyl, neopentyl, and hexyl.

[0069] As used herein, the term “cycloalkyl” is understood as being a carbon-based ring system, non-limiting examples of which include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

[0070] As used herein, the term “cycloalkenyl” is understood as being a carbon-based ring system containing a carbon-carbon double bond, non-limiting examples of which include, cyclobutenyl, cyclopentenyl and cyclohexenyl.

[0071] As used herein, the term “alkycycloalkyl” is understood as being a cycloalkyl group attached to the parent molecular group through an alkylene group.

[0072] The terms “alkoxy” or “alkyloxy,” as used interchangeably herein, represent an alkyl group attached to the parent molecular group through an oxygen atom.

[0073] The term “alkylsulfinyl” as used herein, represents an alkyl group attached to the parent molecular group through an S(O) group.

[0074] The term “alkylsulfonyl,” as used herein, represents an alkyl group attached to the parent molecular group through a S(O)₂ group.

[0075] The term “alkylthio” as used herein, represents an alkyl group attached to the parent molecular group through a sulfur atom.

[0076] The term “alkenyl,” as used herein, represents monovalent straight or branched chain groups of, unless otherwise specified, from 2 to 15 carbons, such as, for example, 2 to 6 carbon atoms or 2 to 4 carbon atoms, containing one or more carbon-carbon double bonds and is exemplified by ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like and may be optionally substituted with one, or more substituents.

[0077] The term “alkynyl” as used herein, represents monovalent straight or branched chain groups of from 2 to 15 carbon atoms comprising a carbon-carbon triple bond and is exemplified by ethynyl, 1-propynyl, and the like and may be optionally substituted with one or more substituents.

[0078] The term “carbonyl” as used herein, represents a C(O) group, which can also be represented as C=O.

[0079] The terms “carboxy” or “carboxyl,” as used interchangeably herein, represents a CO₂H group.

[0080] As used herein, the term "arene" is understood as being an aromatic substituent which is a single ring or multiple rings fused together and which is optionally substituted. When formed of multiple rings, at least one of the constituent rings is aromatic. In an embodiment, arene substituents include phenyl, naphthyl, indane, and fluorene groups.

[0081] The term "heteroarene" as used herein embraces fully unsaturated or aromatic heterocyclo groups. The heteroarene groups are either monocyclic, bicyclic, tricyclic or quadracyclic, provided they have a suitable number of atoms, for example from 3 to 30 atoms, and are stable. A bicyclic, tricyclic or quadracyclic heteroaryl group is fused, bridged and/or simply linked via a single bond. Examples of heteroarene groups include unsaturated 3 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (*e.g.*, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (*e.g.* 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.; unsaturated condensed heterocyclo groups containing 1 to 5 nitrogen, oxygen and/or sulfur atoms including, for example, indolyl, isoindolyl, indolizinyl,

benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (*e.g.*, tetrazolo[1,5-b]pyridazinyl, etc.), etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, including, for example, pyranyl, furyl, etc.; unsaturated 3 to 6-membered heteromonocyclic groups containing a sulfur or a selenium atom, including for example, thienyl, selenophen-yl, etc.; unsaturated 3- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, including, for example, oxazolyl, isoxazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.; unsaturated condensed heterocyclo groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (*e.g.* benzoxazolyl, benzoxadiazolyl, etc.); unsaturated 3 to 6-membered heteromonocyclic: groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, including, for example, thiazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.) etc.; unsaturated condensed heterocyclo groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (*e.g.*, benzothiazolyl, benzothiadiazolyl, etc.), unsaturated linked 5 or 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and/or 1 to 3 nitrogen atoms, including, for example, bithienyl and trithienyl and the like. The term also embraces groups where heterocyclo groups are fused with aryl groups. Examples of such fused bicyclic groups include benzofuran, benzothiophene, benzopyran, and the like.

[0082] The term “pharmaceutically acceptable salt,” as used herein, refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. The salts can be prepared *in situ* during the final isolation of the compounds, or separately by reacting the free base or acid function with a suitable organic acid or base, respectively. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate,

oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group (or other acidic moiety) with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of pharmaceutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine and piperazine.

[0083] The term “derivative” as used herein, is understood as being a substance which comprises the same basic carbon skeleton and carbon functionality in its structure as a given compound, but can also bear one or more substituents or rings.

[0084] The term “analogue” as used herein, is understood as being a substance similar in structure to another compound but differing in some slight structural detail.

[0085] As used herein, the term "bioisostere" shall refer to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. Such an exchange is termed a "bioisosteric replacement" and is useful to create a new compound with similar biological properties to the parent compound. Bioisosteric replacement generally enhances desired biological or physical properties of a compound without making significant changes in chemical structure. For example, the replacement of a hydrogen atom with a fluorine atom at a site of metabolic oxidation in a drug candidate may prevent such metabolism from taking place. Because the fluorine atom is similar in size to the hydrogen atom the overall topology of the molecule is not significantly affected, leaving the desired biological activity

unaffected. However, with a blocked pathway for metabolism, the drug candidate may have a longer half-life. Another example is aromatic rings, a phenyl -C₆H₅ ring can often be replaced by a different aromatic ring such as thiophene or naphthalene which may improve efficacy or change binding specificity of a respective bioisostere.

[0086] In an aspect, the present disclosure broadly relates to novel urea compounds and bioisosteres thereof and to their use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies. In an embodiment, the present disclosure relates to novel urea compounds and bioisosteres thereof and to their use in treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. In an embodiment, the present disclosure relates to compounds of Formulas I-VI and to their use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies. In an embodiment, the present disclosure relates to compounds of Formulas I-VI and to their use in treating, attenuating, inhibiting and/or preventing conditions associated with the expression of IL-6. In a further embodiment, the present disclosure relates to pharmaceutical compositions comprising one or more compounds of Formulas I-VI and to their use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies. In a further embodiment, the present disclosure relates to pharmaceutical compositions comprising one or more compounds of Formulas I-VI and to their use in treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. In a further embodiment, the present disclosure relates to pharmaceutical compositions comprising one or more substituted phenyl cycloalkylureas and to their use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies. In a further embodiment, the present disclosure relates to pharmaceutical compositions comprising one or more substituted phenyl cycloalkylureas and to their use in treating, attenuating, inhibiting or preventing conditions associated with the expression of IL-6. In a further embodiment, the present disclosure relates to intermediates and processes for the synthesis of compounds of Formulas I-VI.

[0087] In an embodiment of the present disclosure, the compounds of Formulas I-VI can be used to treat, attenuate, inhibit and/or prevent conditions associated with the expression of IL-6 in

a patient in need of such therapy. The compounds of Formulas I-VI can be used alone or they can be used as part of a multi-drug regimen in combination with known therapeutics.

[0088] In an embodiment of the present disclosure, the compounds of Formulas I-VI comprise pharmaceutically acceptable solvates thereof. Many of the compounds of Formulas I-VI can combine with solvents such as water, methanol, ethanol and acetonitrile to form pharmaceutically acceptable solvates such as the corresponding hydrate, methanolate, ethanolate and acetonitrilate.

[0089] In an aspect, the present disclosure relates to pharmaceutical compositions comprising one or more compounds of Formulas I-VI and a pharmaceutically acceptable carrier, diluent, or excipient. The pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients.

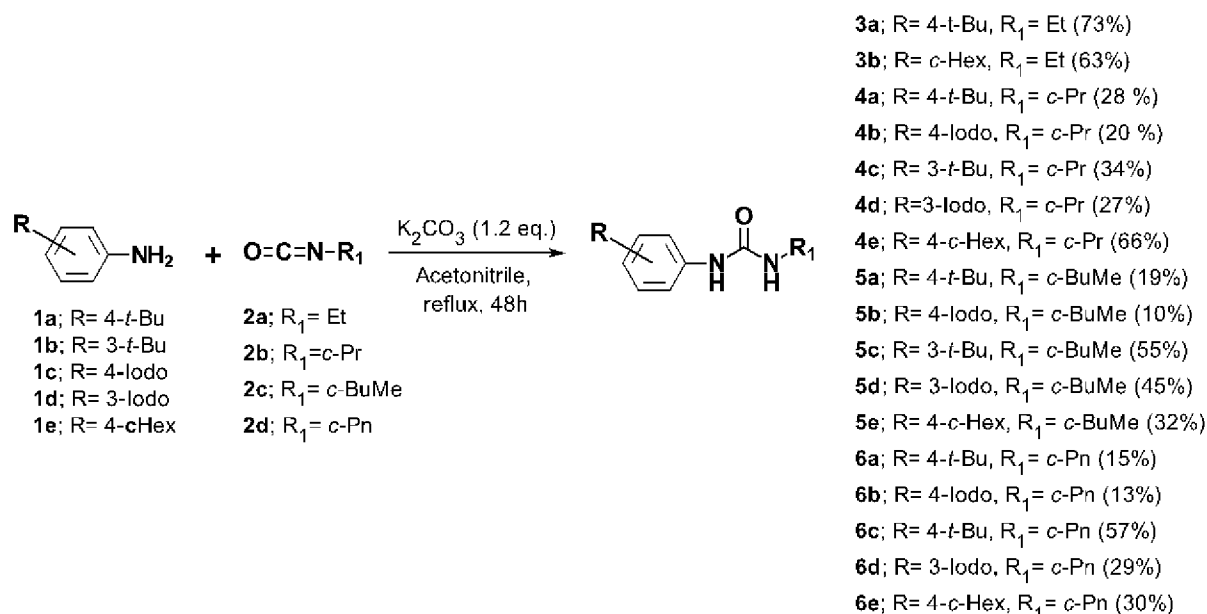
[0090] In an embodiment of the present disclosure, the compounds of Formulas I-VI or pharmaceutical compositions comprising the compounds of Formulas I-VI may be administered topically or percutaneously in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. In the usual course of therapy, the compounds of Formulas I-VI are incorporated into an acceptable vehicle to form a composition for administration to the affected area, such as hydrophobic or hydrophilic creams or lotions, or into a form suitable for percutaneous administration.

[0091] In general, the route of administration of the compounds of Formulas I-VI is topical (including administration to the skin and scalp), or percutaneously. Topical administration is usually the most effective for the treatment of psoriasis where such direct application is practical. Shampoo formulations can be advantageous for treating psoriasis of the scalp. The present disclosure contemplates the administration of one or more compounds of Formulas I-VI either alone or in combination with other therapeutics.

[0092] The dosage to be administered is not subject to defined limits, but it will usually be an effective amount. It will usually be an amount sufficient to achieve a desired pharmacological and physiological effect. The pharmaceutical compositions of the present disclosure comprise a

pharmaceutically effective amount of at least one compound of Formulas I-VI or pharmaceutically acceptable salt thereof as described herein and one or more pharmaceutically acceptable carriers, excipients or diluents. In an embodiment of the present disclosure, the pharmaceutical compositions contain from about 0.1% to about 99% by weight of a compound of Formulas I-VI or pharmaceutically acceptable salt thereof as disclosed herein. In a further embodiment of the present disclosure, the pharmaceutical compositions contain from about 10% to about 60% by weight of a compound of Formulas I-VI or pharmaceutically acceptable salt thereof as disclosed herein. Physicians will determine the most-suitable dosage of the compounds of Formulas I-VI or pharmaceutically acceptable salts thereof.

[0093] Previous work by Applicant on the ASK1-p38 downstream pathway suggested that CEUs could possibly impact the expression of IL-6. Knowing that minor structural modifications/substitutions, notably on the phenyl ring and/or on the R₁ part of the compounds of the present disclosure, may greatly impact the biological properties of the compounds, initial experiments were conducted using *t*BCEU and *c*HCEU. In an embodiment of the present disclosure, the effect of *t*BCEU and *c*HCEU on the expression of IL-6 by HaCaT cells, a human aneuploid immortal keratinocyte cell line treated with IL-17 and TNF α , confirmed a significant decrease on the expression of IL-6. In order to further assess the activity of this class of compounds, a series of novel substituted phenyl cycloalkylureas (**4a-6e**), in accordance with various embodiments of the present disclosure, were prepared. A general procedure for the synthesis of various substituted phenyl cycloalkylureas in accordance with an embodiment of the present disclosure, is illustrated in **Scheme 1**. Compounds **4a-6e** were prepared in low to good yields (10-66%) by nucleophilic addition of anilines **1a-1e** to the cycloalkylisocyanates **2a-2d**.



Scheme 1

[0094] The effect of compounds **3a-b**, **4a-e**, **5a-e** and **6a-e** on the expression of IL-6 was subsequently assessed using the HaCaT spontaneously transformed aneuploid immortal keratinocyte cell line, stimulated by the addition of IL-17A and TNF α in the culture medium (**Table 1**). Curcumin and ibuprofen were used as known IL-6 expression inhibitors. DMSO was used for solubilizing the drugs. The *in vitro* inhibitory data revealed that substituted phenyl cycloalkylureas **3b**, **4b-e**, **5b**, **5c**, **5e** and **6e** at 10 μ M had a significant inhibitory effect on IL-6 expression in HaCaT cells stimulated with IL-17A and TNF α . Indeed, the inhibitory effect of these molecules was at least equivalent to that of curcumin [27] and ibuprofen, both recognized as anti-inflammatory drugs [28]. The inhibitory effect of the substituted phenyl cycloalkylureas in accordance with an embodiment of the present disclosure on proinflammatory cytokines was also found at the mRNA level. Indeed, the mRNAs of the cytokines IL-6 and TNF- α as well as the mRNA of the chemokine IL-8 were lowered in TNF- α /IL-17A-stimulated HaCaT cells. Similar results were obtained in THP-1 cells stimulated with LPS where treatments with CHEU and **4e** diminished the mRNA levels of the cytokines IL-1B, IL-6 and TNF- α in addition to the mRNA levels of the chemokine IL-8. It is surmised that the anti-inflammatory mechanism of

action of the compounds of the present disclosure is likely mediated, at least in part, by modulating the phosphorylation state of the MAP kinase p38. The level of phospho-p38 (p-p38) is rapidly increased (approx. 15 min.) following stimulation of HaCaT cells with the cytokines TNF- α and IL-17A. Addition of a compound in accordance with an embodiment of the present disclosure, prior to stimulation with the aforementioned cytokines, decreases the level of p-p38 at 30-60 minutes post-stimulation. This diminution in p-p38 levels destabilizes the mRNAs of pro-inflammatory cytokines, non-limiting examples of which include TNF- α and IL-6. Moreover, it is surmised that the effect of the compounds of the present disclosure on p-p38 is potentially mediated by the activation of the phosphatase named DUSP1.

[0095] **Table 1:** Effect on IL-6 expression for 10 μ M solutions of *t*BCEU, *c*HCEU, compounds **3a-b**, **4a-e**, **5a-e**, **6a-e**, curcumin and ibuprofen.

Expression of IL-6 ^a (pg/mL)			Expression of IL-6 ^a (pg/mL)		
Compound	HaCaT	Adjust Pvalue	Compound	HaCaT	Adjust Pvalue
<i>t</i> BCEU	130.6 $\pm$ 15.6	>0.9999	5d	90.2 $\pm$ 11.1	>0.9999
3a	81.9 $\pm$ 10.8	0.5465	5e	64.1 $\pm$ 5.4	0.0528
<i>c</i> HCEU	46.8 $\pm$ 8.5	0.0001	6a	127.5 $\pm$ 17.3	>0.9999
3b	36.2 $\pm$ 7.4	<0.0001	6b	65.1 $\pm$ 7.6	0.0382
4a	91.9 $\pm$ 7.6	>0.9999	6c	74.6 $\pm$ 6.7	0.3709
4b	47.9 $\pm$ 4.5	0.0003	6d	89.8 $\pm$ 9.0	>0.9999
4c	50.4 $\pm$ 2.6	0.0009	6e	50.3 $\pm$ 4.7	0.0024
4d	57.3 $\pm$ 4.4	0.0086	IL-17α/ TNFα	177.9 $\pm$ 20.3	
4e	29.2 $\pm$ 3.5	<0.0001	DMSO	29.2 $\pm$ 7.1	<0.0001
5a	70.6 $\pm$ 7.6	0.1507	Curcumin	62.8 $\pm$ 12.0	0.0064
5b	33.9 $\pm$ 4.3	0.0001	Ibuprofen	120.3 $\pm$ 18.6	>0.9999
5c	47.5 $\pm$ 3.3	0.0003			

^aValues are means of five separate experiments conducted in duplicate

[0096] The antiproliferative activity of compounds **3a-b**, **4a-e**, **5a-e** and **6a-e** was subsequently evaluated using the human HT-29 colon adenocarcinoma and the A549 adenocarcinoma alveolar epithelial cancer cell lines, the HaCaT spontaneously transformed aneuploid immortal keratinocyte cell line and the HDFn neonatal dermal fibroblast cell line

(Table 2). Cell growth inhibition was assessed according to the NCI/NIH Developmental Therapeutics Program [29]. Furthermore, compounds **3a-b**, **4a-e**, **5a-e** and **6a-e** showed low to very low antiproliferative activity on the cancer and primary cell lines tested. Interestingly, these molecules were shown to exhibit lower antiproliferative activity than curcumin.

[0097] **Table 2:** Antiproliferative activity of *t*BCEU, *c*HCEU and compounds **3a-6e** on the HT-29, HaCaT, HDFn and A549 cell lines.

Compound	Antiproliferative activity (GI ₅₀ , μ M) ^a			
	HT-29	HaCaT	HDFn	A549
<i>t</i> BCEU	6.5	12	11	6.9
3a	75	>100	60	69
<i>c</i> HCEU	15	27	11	12
3b	23	>100	92	54
4a	85	>100	55	>100
4b	82	>100	95	>100
4c	>100	>100	>100	>100
4d	>100	>100	79	84
4e	54	74	40	48
5a	21	35	8.2	>100
5b	29	62	74	27
5c	43	39	21	37
5d	25	31	15	25
5e	>100	>100	>100	>100
6a	>100	>100	>100	83
6b	9.7	>100	>100	62
6c	27	>100	84	34
6d	30	49	23	30
6e	13	82	56	11
Curcumin	4.2	7.0	7.6	9.9
Ibuprofen	>100	>100	>100	>100

^aValues are means of two separate experiments conducted in triplicate and the deviation from the mean is <10%

[0098] The effect of compounds **3a-b**, **4e**, **5b-c**, **6a** and **6e** on cell cycle progression was subsequently assessed using a flow cytometer in accordance with established experimental

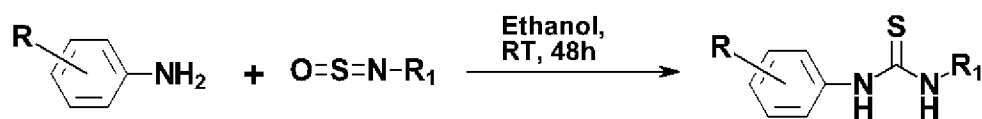
protocols [30-32] to evaluate any potential drug toxicity at specific phases of the cell cycle (Table 3). Compounds **3a-b**, **4e**, **5b-c**, **6a** and **6e** did not affect the cell cycle progression whereas curcumin is clearly arresting the cell cycle progression in the G2-M phase similarly to tBCEU which are both known to act as an antimicrotubule agents.

[0099] **Table 3:** Effect of compounds **3a-b**, **4e**, **5b-c**, **6a** and **6e** on cell cycle progression.

Compound	Cell cycle progression ^a		
	G ₀ -G ₁	S	G ₂ -M
3a	44	25.1	31
3b	46.9	25.3	27.8
4e	47.7	24.2	28.1
5b	45	25.6	29.4
5c	46.1	23.5	30.4
6a	48	25.1	25.8
6e	50.1	24.7	25.2
DMSO	45.7	24.8	29.5
Curcumin	14.8	8.1	77.1
Ibuprofen	57.9	25.6	16.3
tBCEU	57.3	26.8	15.6
tBEU	55.5	25.3	19.1
cHCEU	56.5	24.4	19.1

^aValues are the means of two separate experiments conducted in triplicate and the deviation from the mean value is <10% (Cell cycle analysis performed using HaCaT cells)

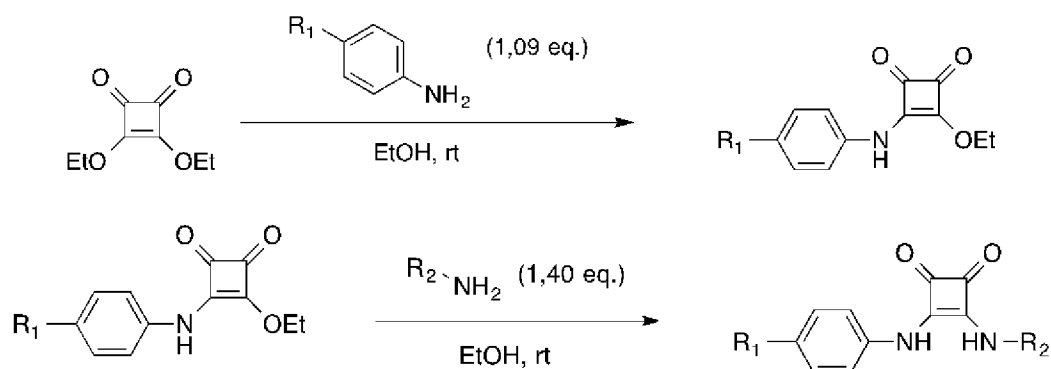
[00100] A general procedure for the synthesis of various substituted phenyl alkylthioureas in accordance with an embodiment of the present disclosure, is illustrated in **Scheme 2**. The compounds were prepared in low to good yields by nucleophilic addition of anilines to alkylisothiocyanates.



Scheme 2

[00101] Desired substituted anilines (50mg, 1.0 eq.) were dissolved in acetonitrile (6 ml) followed by the addition of K_2CO_3 (1.2 eq.) and an isothiocyanate (1.2 eq.). The resulting reaction mixture was stirred for 48 h under reflux. The reaction mixture was subsequently evaporated to dryness under reduced pressure and the residue purified by flash chromatography on silica gel. Alternatively, desired substituted anilines (50mg, 1.0 eq.) were dissolved in ethanol (2 ml) followed by the addition of an isothiocyanate (1.2 eq.). The resulting reaction mixture was stirred for 48 h at room temperature. The reaction mixture was subsequently evaporated to dryness under reduced pressure and the residue purified by flash chromatography on silica gel.

[00102] A general procedure for the synthesis of various substituted phenyl alkyl squaramides in accordance with an embodiment of the present disclosure, is illustrated in **Scheme 3**. The compounds were prepared in low to good yields by the addition of anilines to dialkoxysquarate.

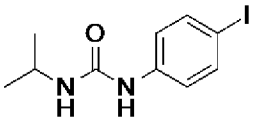
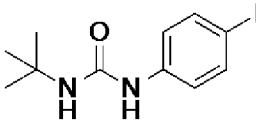
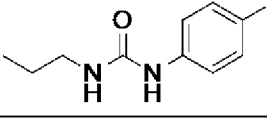
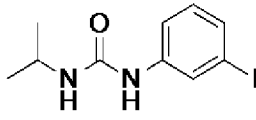
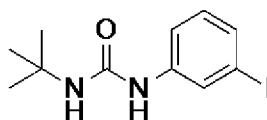
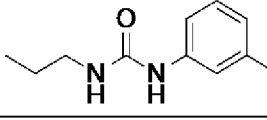
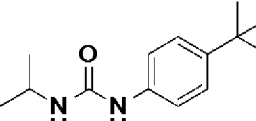
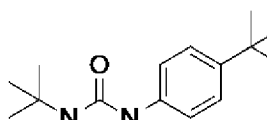


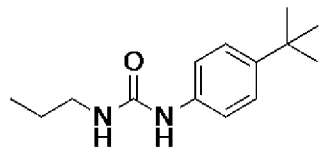
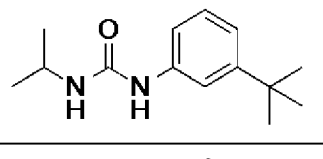
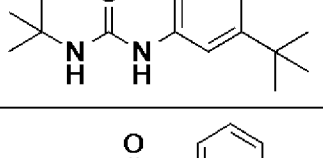
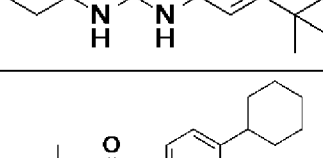
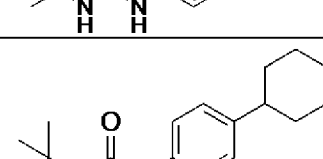
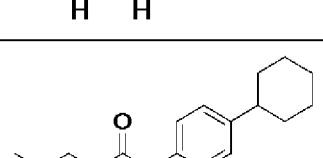
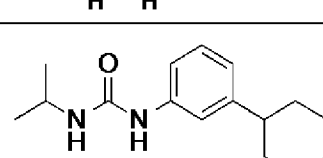
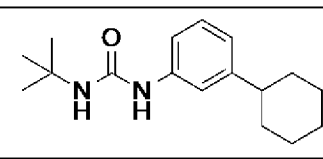
Scheme 3

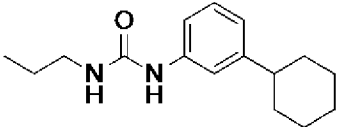
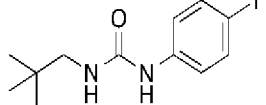
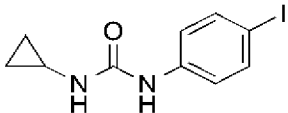
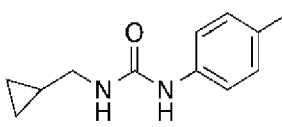
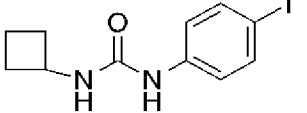
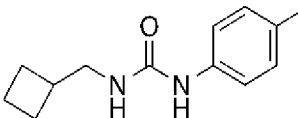
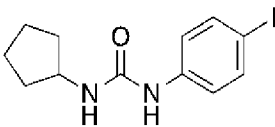
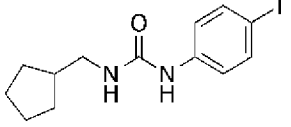
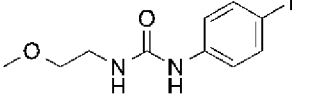
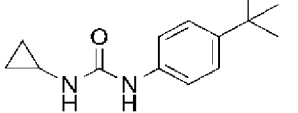
[00103] To a solution of the desired aniline (200mg, 1.0 eq.) in EtOH (2.5 mL) at rt was added dropwise diethoxysquarate (1.09 eq.). The solution was first stirred at 0°C for 2 hours, then at rt for 48h and finally cooled down again to 0°C. The reaction mixture was evaporated to dryness under reduced pressure and the residue purified by flash chromatography on silica gel using hexanes/ethyl acetate (80/20) yielding the desired amino alkoxy squarate. The amino alkoxy squarate (40 mg, 1 eq.) was subsequently dissolved in EtOH (2 mL) at rt followed by the addition of an amine (1.4 eq.). The resulting mixture was stirred for 48h at room temperature and then filtered. The solid residue was washed with a mixture of cold EtOH/MeOH (1/1) to afford the desired squaramide without further purification.

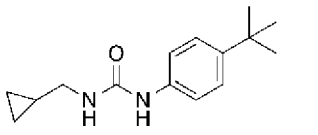
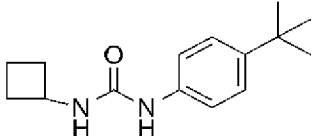
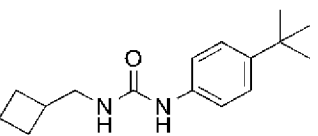
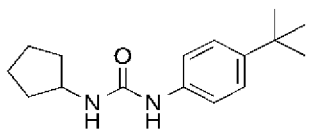
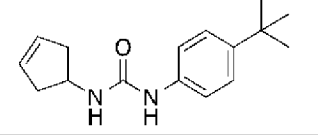
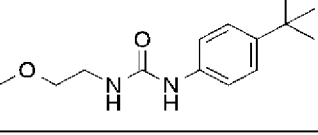
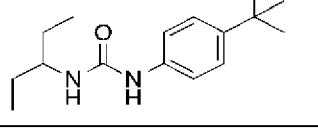
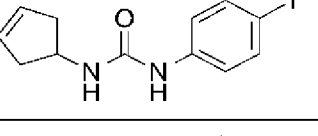
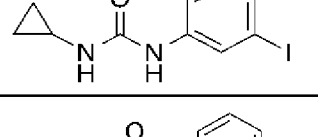
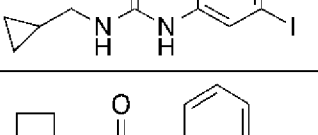
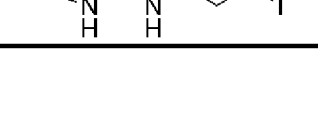
[00104] A representative number of substituted phenyl alkylureas, substituted phenyl alkylthioureas and substituted phenyl alkyl squaramides in accordance with various embodiments of the present disclosure are illustrated in **Table 4**.

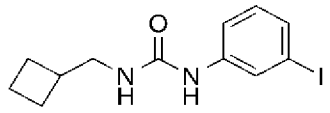
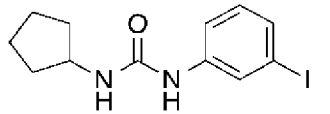
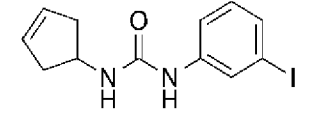
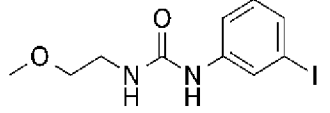
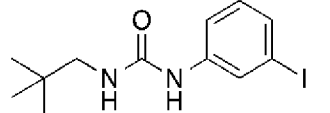
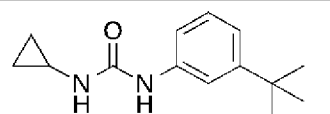
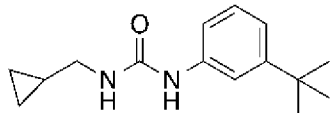
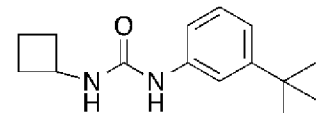
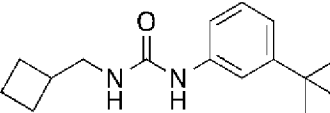
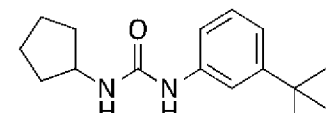
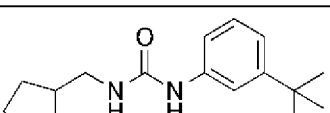
[00105] **Table 4:** Selected substituted phenyl alkylureas, substituted phenyl alkylthioureas and substituted phenyl alkyl squaramides

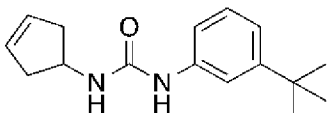
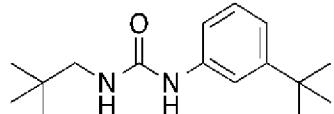
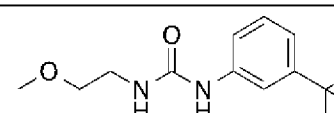
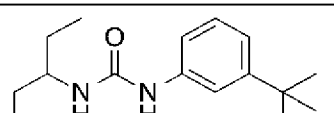
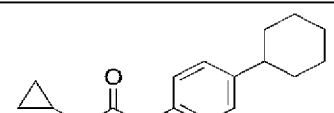
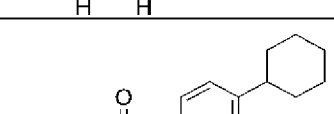
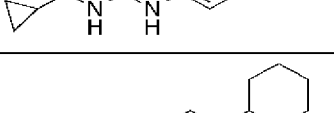
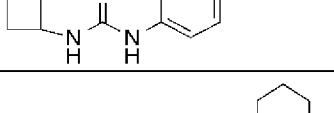
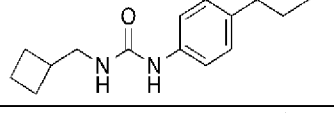
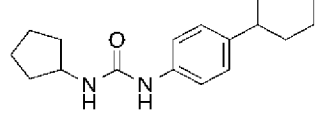
Compound	Structure	Appearance	Yield (%)	Melting Point (°C)	Exact Mass
1		White solid	100	Decomposition 237-249	304.01
2		White Solid	44	179-199	318.02
3		White Solid	61	197-199	304.01
4		White Solid	97	153-156	304.01
5		White Solid	83	189-193	318.02
6		White Solid	100	132-136	304.01
7		White Solid	90	152-155	234.17
8		White Solid	78	167-174	248.19

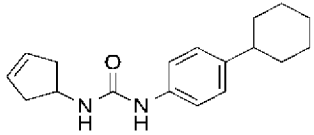
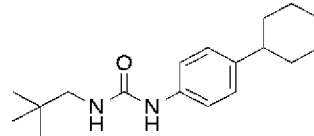
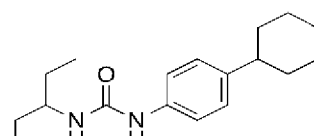
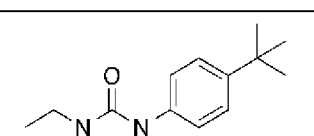
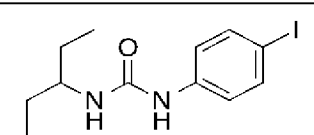
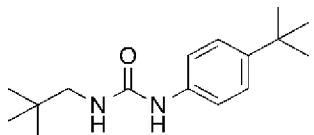
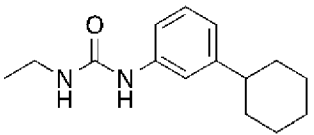
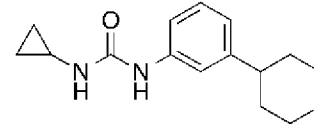
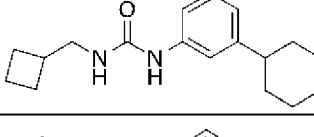
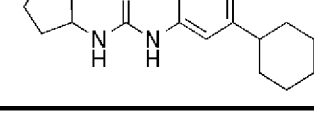
9		White Solid	100	147-151	234.17
10		White Solid	81	146-149	234.17
11		Light brown solid	70	161-170	248.19
12		Light brown solid	88	138-141	235.17
13		White Solid	80	163-170	260.19
14		White Solid	77	182-189	274.20
15		White Solid	100	166-168	260.19
16		White Solid	86	178-181	260.19
17		White Solid	54	195-203	274.20

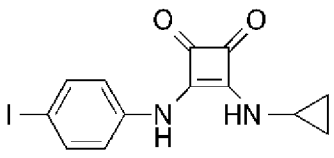
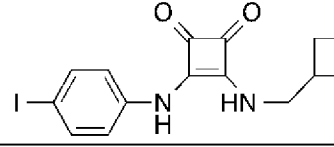
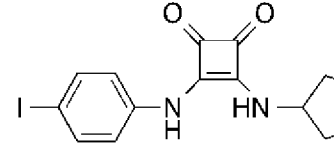
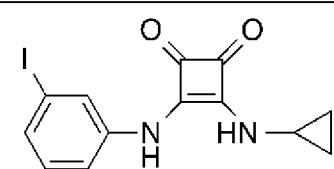
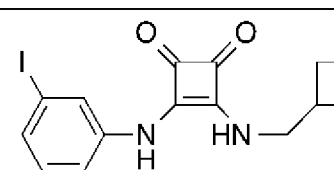
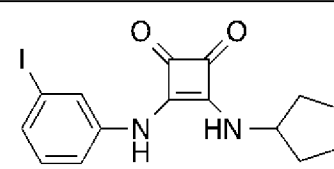
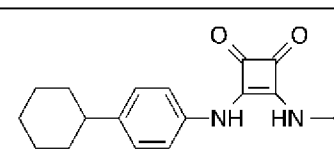
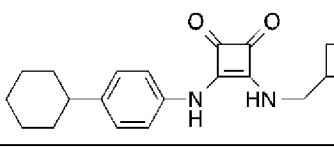
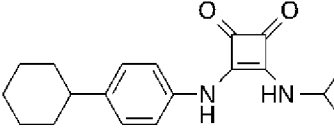
18		White Solid	91	131-134	260.19
19		Sticky Solid	11.3		332.04
20		White Solid	19.6	216-218	301.99
21		White Solid	26	192-194	316.01
22		White Solid	12.5	208-210	316.01
23		White Solid	10	159-160	330.02
24		White Solid	13.4	188-191	330.02
25		White Solid	9.5	158-161	344.04
26		White Solid	19.7	141-143	320.00
27		Light yellow solid	27.7	138-139	232.16

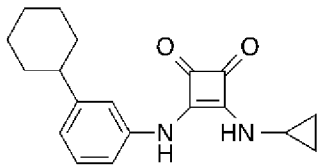
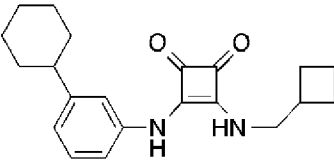
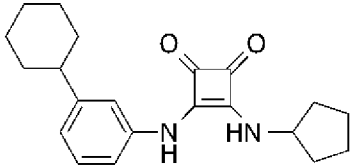
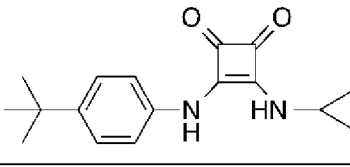
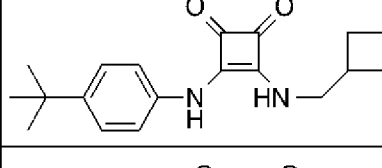
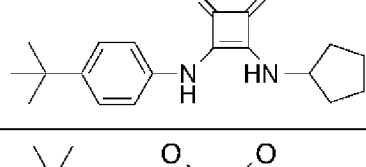
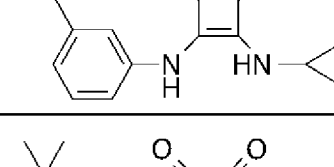
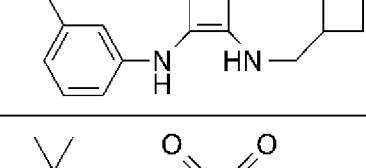
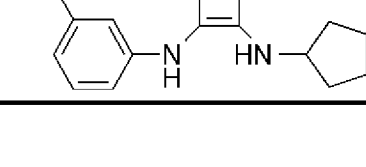
28		White solid	16.5	168-170	246.17
29		White solid	28.9	189-190	246.17
30		White solid	19.1	179-184	260.19
31		White solid	30.0	218-223	260.19
32		White solid	34.1	189-191	258.17
33		Light yellow solid	29.2	122-124	250.17
34		White solid	20.6	119-121	262.20
35		White solid	15	201-202	328.01
36		White solid	27.2	153-154	301.99
37		White solid	15.2	139-140	316.01
38		White solid	15.6	178-180	316.01

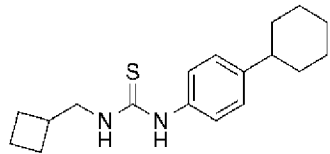
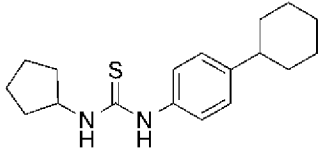
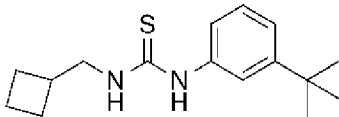
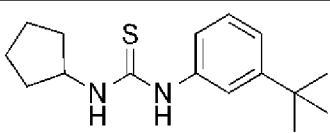
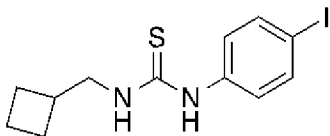
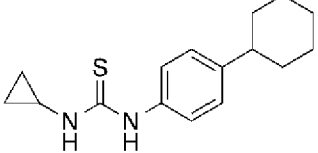
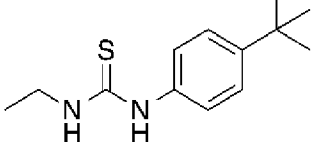
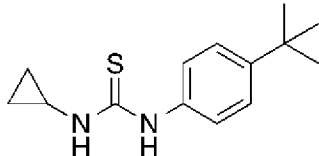
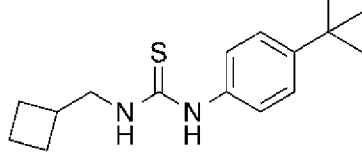
39		White solid	45.3	138-140	330.02
40		White solid	15.8	142-143	330.02
41		Light brown solid	29.2	151-153	328.01
42		Light yellow solid	16.3	99-101	320.00
43		White solid	45.3	114-115	332.04
44		White solid	34.2	169-171	232.16
45		White solid	43.5	165-166	246.17
46		White solid	56.9	165-166	246.17
47		White solid	54.9	126-127	260.19
48		White solid	57.3	152-154	260.19
49		White solid	53.1	113-114	274.20

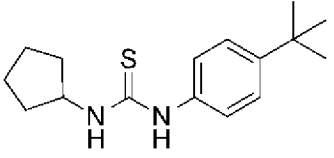
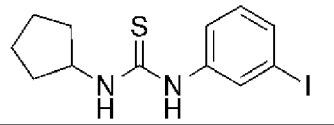
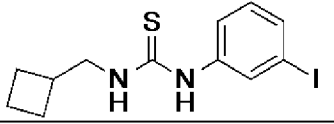
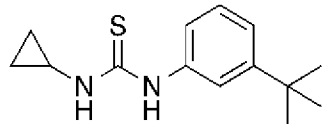
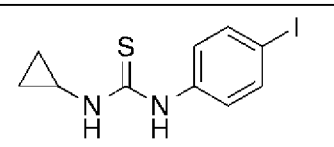
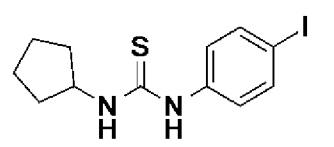
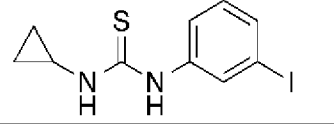
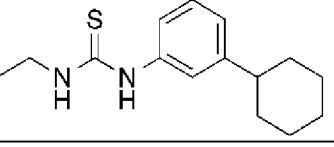
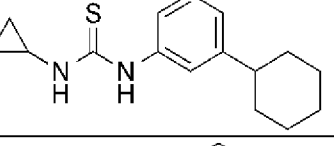
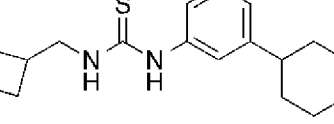
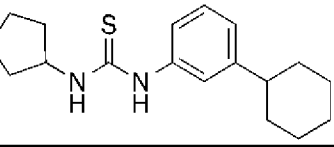
50		White solid	33.6	135-137	258.17
51		White solid	26.4	145-147	262.20
52		White solid	60.9	119-120	250.17
53		White solid	11.4	159-161	262.20
54		White solid	66.2	173-176	258.17
55		White solid	72.0	178-181	272.19
56		White solid	11.0	137-139	272.19
57		White solid	32.1	172-173	286.20
58		White solid	29.8	197-199	286.20
59		White solid	13.5	142-144	300.22

60		White solid	41.1	167-169	284.19
61		White solid	20.8	167-169	282.22
62		White solid	13.5	174-176	282.22
63		White solid	73.0	136-139	220.16
64		White solid	8.0	174-176	332.04
65		White solid	51.9	185-187	262.20
66		White solid	64.0	141-144	246.17
67		White solid	100.0	138-144	258.17
68		White solid	89.0	115-120	286.20
69		White solid	54.0	132-137	286.20

70		Light yellow solid	75.3	Decomposition 269-278	353.99
71		White solid	89.8	Decomposition 274-294	382.02
72		Light yellow solid	90.4	Decomposition 260-268	382.02
73		Light brown solid	52.6	Decomposition 233-276	353.99
74		Light yellow solid	55.5	Decomposition 231-277	382.02
75		Light yellow solid	80.1	Decomposition 230-274	382.02
76		Light brown solid	99.0	Decomposition 232-247	310.17
77		White solid	82.3	Decomposition 285-316	338.20
78		White solid	85.4	Decomposition 268-329	338.20

79		Light brown solid			310.17
80		White solid			338.20
81		White solid			338.20
82		White solid	75.0	Decomposition 186-258	284.15
83		Yellow solid	71.1	Decomposition 263-319	312.18
84		White solid	80.7	Decomposition 261-308	312.18
85		White solid	67.8	Decomposition 171-239	284.15
86		White solid	53.8	Decomposition 234-241	312.18
87		White solid	48.8	Decomposition 239-247	312.18

88		Light brown solid	71.6	144-152	302.18
89		White solid	100.0	146-152	302.18
90		White solid	57.0	105-111	276.17
91		White solid	21.0	170-180	276.17
92		White solid	18.0	98-108	346.00
93		Light yellow solid	53.0	157-165	274.15
94		Light yellow solid	74.0	109-115	236.13
95		White solid	100.0	119-143	248.13
96		Light brown solid	25.8	129-146	276.17

97		White solid	73.2	142-154	276.17
98		White solid	21.4	136-147	346.0
99		White solid	20.0	136-147	346.0
100		White solid	78.0	125-140	248.13
101		Yellow solid	67.0	166-180	317.97
102		Light brown solid	22.0	154-162	346.0
103		White solid	55.0	142-152	317.97
104		Sticky pale yellow oil	30.0		262.15
105		Light yellow solid	100.0	122-128	274.15
106		Light yellow solid	51.0	102-110	302.18
107		White solid	62.0	129-142	302.18

[00106] **Table 5:** Effect on IL-6 expression and antiproliferative activity of compounds **1-18** (Table 4) on the HaCaT, HT-29, A549 and HDFn cell lines.

Compound	HaCaT (IC ₅₀)	HT-29 (IC ₅₀)	A549 (IC ₅₀)	HDFn (IC ₅₀)	Reduction IL-6 (%)
1	91,9	54,8	81,9	83,6	-6.9
2	44,7	32,9	37,1	27,1	-14.6
3	94,9	51,9	82,7	81,3	16.2
4	94,5	>100	80,3	59,1	1.7
5	>100	81,3	61,8	17,4	54.5
6	99,7	87,9	80,0	44,2	57.2
7	>100	74,2	83,2	57,4	13.6
8	55,0	35,6	34,2	14,5	-10.6
9	>100	54,9	67,1	10,5	20.0
10	>100	85,2	96,8	92,4	35.3
11	46,5	34,9	36,7	13,1	-41.6
12	>100	>100	>100	81,5	-9.6
13	>100	56,9	60,8	59,1	51.3
14	35,4	25,5	18,5	17,2	28.5
15	>100	>100	>100	59,1	33.4
16	>100	>100	>100	30,5	26.1
17	87,9	58,3	44,1	16,3	52.4
18	32,0	24,1	21,0	23,0	70.4
Dexamethasone					68.3
DMSO					
DMSO + Cytokines					
Ibuprofen					62.1

[00107] **Table 6:** Effect on IL-6 expression and antiproliferative activity of compounds **20, 23-24, 27, 30-31, 36, 39, 40, 44, 47-48, 54, 57-58, 63 and 66-69** (Table 4) on the HaCaT, HT-29, A549 and HDFn cell lines.

Compound	HaCaT (IC₅₀)	HT-29 (IC₅₀)	A549 (IC₅₀)	HDFn (IC₅₀)	Reduction IL-6 (%)
20	100	82	100	95	73.1
23	62	29	27	74	81.0
24	100	9,7	62	100	63.4
27	100	85	100	55	48.4
30	35	21	100	8,2	60.3
31	100	100	83	100	28.4
36	100	100	84	79	67.8
39	31	25	25	15	49.3
40	49	30	30	23	49.6
44	100	100	100	100	71.7
47	39	43	37	21	73.3
48	100	27	34	84	58.1
54	74	54	48	40	83.6
57	100	100	100	100	64.0
58	82	13	11	56	71.7
63	100	75	69	60	54.0
66	37	31	58	31	39.7
67	17	26	37	25	44.1
68	3.7	5.6	8.0	12	44.9
69	4.0	8.9	12	7.6	41.3
IL-17α/ TNFα					
DMSO					
Curcumin					64.6
Ibuprofen					32.6
Dexamethasone (1μM)					45.3

[00108] **Table 7:** Effect on IL-6 expression and antiproliferative activity of compounds **70-87** (Table 4) on the HaCaT, HT-29, A549 and HDFn cell lines.

Compound	HaCaT (IC ₅₀)	HT-29 (IC ₅₀)	A549 (IC ₅₀)	HDFn (IC ₅₀)	Reduction IL-6 (%)
70	>100	>100	>100	>100	0.9
71	>100	>100	>100	>100	-1.4
72	10,6	10,0	8,0	6,9	50.0
73	37,7	39,8	26,8	19,6	-3.2
74	10,9	15,0	8,3	4,1	-54.2
75	11,8	15,2	9,0	4,6	-19.3
76	>100	>100	74,0	>100	-18.7
77	>100	>100	89,6	>100	-19.7
78	>100	>100	96,1	>100	-14.3
79	11,0	7,9	8,0	4,3	6.7
80	6,0	4,5	4,2	1,9	11.8
81	5,6	4,3	3,7	1,9	-34.2
82	47,9	18,7	17,9	13,2	10.4
83	>100	>100	>100	>100	-9.5
84	>100	>100	15,1	>100	12.1
85	81,4	64,1	40,8	57,3	41.7
86	56,1	14,8	13,7	3,8	-103.7
87	5,5	4,3	4,0	2,8	-58.6
Dexamethasone					68.3
DMSO					
DMSO + Cytokines					
Ibuprofen					62.1

[00109] **Table 8:** Effect on IL-6 expression and antiproliferative activity of compounds **20**, **23-24**, **27**, **30-31**, **36**, **39**, **40**, **44**, **47-48**, **54**, **57-58**, **63** and **66-69** (**Table 4**) on the HaCaT, HT-29, A549 and HDFn cell lines.

Compound	HaCaT (IC ₅₀)	HT-29 (IC ₅₀)	A549 (IC ₅₀)	HDFn (IC ₅₀)	Reduction IL-6 (%)
88	32,5	20,4	15,3	15,7	1.8
89	34,9	21,6	20	14,6	4.8
90	34,3	20,2	17,5	18,2	-27.9
91	31,8	21	19,4	16,3	-12.0
92	48,2	27,2	26,2	24,2	9.6
93	84,7	30,8	20,8	84	22.1
94	>100	92	71,1	94	-18.2
95	94,5	64,4	57,9	60	-28.5
96	>100	44	23,3	>100	6.8
97	40	28,8	26,2	22,6	8.6
98	32,8	23,4	21,9	16,4	36.8
99	35,5	27	26,2	19,4	49.2
100	>100	75,7	70	>100	46.5
101	>100	63,3	65,1	>100	23.8
102	39,1	25,1	25,3	18,6	45.5
103	>100	>100	>100	>100	9.6
104	19,3	17,9	22,4	12,9	15.2
105	16,3	12,7	15,9	14,7	44.1
106	14,9	13,2	17	4,9	48.4
107	7,9	5,7	6,2	3,8	42.9
Curcumin					32.3
Dexamethasone (1μM)					54.5
DMSO					
DMSO + Cytokines					

Ibuprofen			51.0
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[00110] IL-6 Evaluation

[00111] HaCaT cells (1×10^5) were suspended in DMEM culture media (500 μ L) and incubated for 24 h in 24-well microtiter plates at 37°C in a moisture-saturated atmosphere containing 5% CO₂. Compounds were solubilized in DMSO and diluted in fresh DMEM. The compound (500 μ L) was then added to the cell medium to obtain a final concentration of 10 μ L/well and the cells incubated over a period of 1 hour. In the meantime, IL-17 α (200 ng/mL) and TNF α (20 ng/mL) (PeproTech, Rocky Hill, NJ) were added to the drug solution in DMEM. Following the initial incubation of the cells, the culture medium was aspirated from each well and the IL-17 α + TNF α + compound solution was added to each well for incubation (6 hours). The culture media was then removed and transferred to a clean tube (1.5 mL) at -80°C until the ELISA test was performed. The presence of IL-6 in the cell media was determined using an IL-6 human DuoSet ELISA kit (Fisher Scientific, Ottawa, On.) according to the manufacturer's instructions. Standards and samples were prepared and assessed in duplicate. Two separate replicates were performed for each sample. The absorbance was measured at 450 nm and 540 nm using a TECAN infinite M1000 plate reader.

[00112] Antiproliferative Activity

[00113] The antiproliferative activity assay of all compounds was assessed using the procedure recommended by the National Cancer Institute for its drug screening program with minor modifications. Briefly, 96-well microtiter plates were seeded with 75 μ L of a suspension of either HaCaT (5×10^3), HT-29 (3.0×10^3), A549 (3.0×10^3) or HDFn (3×10^3) cells per well in DMEM and incubated for 24 h at 37°C in a moisture-saturated atmosphere containing 5% CO₂. Compounds freshly solubilized in DMSO (40 mM) were diluted in fresh DMEM, and 75 μ L aliquots containing serially diluted concentrations of the compound were added. Final compound concentrations ranged from 100 μ M to 781 nM. DMSO was maintained at a concentration of < 0.5% (v/v) to avoid any related cytotoxicity. Plates were subsequently incubated for 48 h. Cell growth was then stopped by the addition of cold trichloroacetic acid to

the wells (10% w/v, final concentration), followed by a 1 h incubation period at 4°C. The plates were washed 4-times with water. A sulforhodamine B solution (75 µL; 0.1% w/v) in acetic acid (1%) was subsequently added to each well and the plates incubated over a 15 min period while at room temperature. After staining, any unbound dye was removed by washing 4-times with an acetic acid solution (1%). Bound dye was solubilized in 20 mM Tris base and the absorbance was measured at an optimal wavelength (530-568 nm) using a µQuant® Universal microplate spectrophotometer (BioTek, Winooski, VT). The measurements for treated cells were compared with measurements from control cell plates fixed on treatment day and the percentage of cell growth inhibition was calculated for each drug. The experiments were performed at least twice in triplicate. The assays were considered valid when the coefficient of variation for a given set of conditions and within the same experiment was < 10%.

[00114] Cell Cycle Analysis

[00115] HaCaT cells (2.5×10^5) were incubated with compounds **3a-b**, **4e**, **5b-c**, **6a** and **6e** and curcumin (10 µM) over a period of 24 h. The cells were subsequently trypsinized, washed with PBS, resuspended in PBS (250 µL), fixed by the addition of ice-cold EtOH (750 µL) under agitation and stored at -20°C until analysis. Prior to FACS analysis, cells were washed with PBS and resuspended in PBS (500 µL) containing 4',6'-diamidino-2-phenylindole (DAPI) (2 µg/mL). The cell cycle was analyzed using an LSR II flow cytometer (BD Biosciences, Franklin Lakes, NJ).

[00116] Psoriasis (Imiquimod) in Mice

[00117] On day 0, Balb/c mice, aged 7 to 9 weeks, are shaved (3/4 of the back) to clear the base of the neck. On day 1, the mice are topically treated on the shaved area with freshly prepared compound **20** (**Table 4**) at 2.5 mg/mouse in DMSO, dexamethasone at 0.2 mg/mouse in DMSO or with DMSO. After 1 hour, 62.5 mg of Imiquimod 5% (Apo-imiquimod) or base cream (Base Atlas Cream; negative control) is applied on the shaved area of the mice. Two hours later, the mice were treated a second time with compound **20** at 2.5 mg/mouse in DMSO, dexamethasone at 0.2 mg/mouse in DMSO or with DMSO. These treatments were repeated daily for a total of 6

days. The mice were weighed and the treated skin areas analyzed for redness, thickening and peeling (repeated daily). The mice were sacrificed on day 6 and the skin from the treated areas removed, fixed and embedded in paraffin for histological analysis. Organs, such as the liver, the kidneys and the spleen were harvested and fixed for future analysis.

[00118] Candidate compounds of Formula I-VI can be tested *in vitro* and/or *in vivo* to determine their activity in attenuating, inhibiting or preventing conditions associated with the expression of IL-6.

[00119] **EXPERIMENTAL**

[00120] **General:** ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (Bruker, Germany). Chemical shifts (δ) are reported in parts per million (ppm). Melting points were determined using an electrothermal melting point apparatus. HPLC analyses were performed using a Prominence LCMS-2020 system with binary solvent and equipped with an UV/vis photodiode array and an APCI probe (Shimadzu, Columbia, MD). Compounds were eluted within 15 min on an Alltech® Alltima C18 reversed-phase column (5 mm, 250 mm, 4.6 mm) equipped with an Alltech® Alltima C18 pre-column (5 mm, 7.5 mm, 4.6 mm) and a MeOH/H₂O linear gradient of 60:40 at 1.0 mL/min. The purities of the final compounds were >95%. All chemicals were supplied by Sigma-Aldrich Canada (Oakville, Ontario, Canada), VWR International (Mont-Royal, Québec, Canada) or Enamine LLC (Princeton, New Jersey, USA) and used as received unless specified otherwise. Flash column chromatography was performed on silica gel F60, 60 Å, 40-63 μm supplied by Silicycle (Quebec City, Québec, Canada) using a FPX flash purification system (Biotage, Charlottesville, VA) and using solvent mixtures expressed as volume/volume ratios. The progress of the chemical reactions was monitored by TLC using pre-coated silica gel 60 F254 TLC plates (VWR International, Mont-Royal, Québec, Canada). The chromatograms and spots were visualized under UV light at 254 and/or 265 nm.

[00121] A number of non-limiting examples, illustrating the preparation of selected substituted phenyl cycloalkylureas in accordance with the present disclosure, are illustrated in the following section.

[00122] **General procedure for the preparation of *t*BCEU, *c*HCEU, and 3a-b, 4a-e, 5a-e and 6a-e.**

[00123] Anilines **1a-1e** (1.0 eq.) were dissolved in acetonitrile (6 ml) and K₂CO₃ (1.2 eq.) was added to the resulting solution. The proper isocyanate (**2a-2d**; 1.2 eq.) was then added to the solution and the reaction mixture was stirred for 48 h under reflux. The reaction mixture was then evaporated to dryness under reduced pressure and the resulting residue was purified by flash chromatography on silica gel.

[00124] 1-(4-(*t*-Butyl)phenyl)-3-ethylurea (**3a**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 73%; White solid; mp: 136-139°C; ¹H NMR (CDCl₃ and MeOD): δ 7.18-7.08 (m, 4H, Ar), 3.10 (quint, 2H, J=6.6Hz, CH₂), 1.18-1.12 (m, 9H, 3x CH₃), 1.03-0.94 (m, 3H, CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.9, 145.5, 136.4, 125.6, 119.4, 34.5, 34.0, 31.2, 15.1. MS (ES+) found 221.20; C₁₃H₂₀N₂O (M⁺ + H) requires 221.17.

[00125] 1-(4-(*t*-Butyl)phenyl)-3-cyclopropylurea (**4a**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 28%; Light yellow solid; mp: 138-139°C; ¹H NMR (CDCl₃): δ 7.29-7.27 (m, 4H, Ar), 7.21 (s, 1H, NH), 5.42 (s, 1H, NH), 2.62-2.52 (m, 1H, CH), 1.28 (s, 9H, 3x CH₃), 0.76 (d, 2H, J=5.5Hz, 2x CH), 0.57 (s, 2H, 2x CH); ¹³C NMR (CDCl₃): δ 157.4, 146.4, 135.9, 125.9, 120.2, 34.3, 31.4, 22.6, 7.4. MS (ES+) found 233.20; C₁₄H₂₀N₂O (M⁺ + H) requires 233.17.

[00126] 1-Cyclopropyl-3-(4-iodophenyl)urea (**4b**). Flash chromatography (hexanes/ethyl acetate (75:25)) Yield: 20%; White solid; mp: 208-209°C; ¹H NMR (CDCl₃ and MeOD): δ 7.42 (d, 2H, J=8.3Hz, Ar), 7.06 (d, 2H, J=8.3Hz, Ar), 2.44 (apparent non, 1H, CH), 0.65-0.58 (m, 2H, 2x CH), 0.43-0.37 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 157.2, 138.9, 137.5, 120.9, 84.9, 22.1, 6.7. MS (ES+) found 303.00; C₁₀H₁₁IN₂O (M⁺ + H) requires 333.05.

[00127] 1-(3-*t*-Butyl)phenyl)-3-cyclopropylurea (**4c**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 34%; White solid; mp: 169-171°C; ¹H NMR (CDCl₃ and MeOD): δ 7.36-7.34 (m, 1H, Ar), 7.19-7.16 (m, 2H, Ar), 7.07-7.04 (m, 1H, Ar), 2.58-2.52 (m, 1H, CH), 1.27 (s, 9H, 3x CH₃) 0.78-0.72 (m, 2H, 2x CH), 0.58-0.54 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 157.3, 152.2, 138.1, 128.6, 120.5, 117.4, 34.7, 31.2, 22.4, 7.2. MS (ES+) found 233.10; C₁₄H₂₀N₂O (M⁺ + H) requires 233.17.

[00128] 1-Cyclopropyl-3-(3-iodophenyl)urea (**4d**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 27%; White solid; mp: 153-154°C; ¹H NMR (CDCl₃ and MeOD): δ 7.74-7.72 (m, 1H, Ar), 7.30-7.25 (m, 2H, Ar), 6.92 (t, 1H, J=8.0Hz, Ar), 2.54-2.47 (m, 1H, CH), 0.70 (d.d, 2H, J=6.0Hz, 2x CH), 0.51-0.46 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 157.0, 140.1, 131.6, 130.3, 127.8, 118.4, 94.1, 22.3, 7.0. MS (ES+) found 303.00; C₁₀H₁₁IN₂O (M⁺ + H) requires 303.00.

[00129] 1-(4-Cyclohexylphenyl)-3-cyclopropylurea (**4e**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 66%; White solid; mp: 173-176°C; ¹H NMR (CDCl₃ and MeOD): δ 7.21 (d, 2H, J=8.4Hz, Ar), 7.07 (d, 2H, J=8.4Hz, Ar), 2.51 (apparent sept, 1H, CH), 2.44-2.32 (m, 1H, CH), 1.79-1.19 (m, 10H, 5x CH₂), 0.71 (q, 2H, J=6.8Hz, 2x CH), 0.54-0.49 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 157.5, 143.4, 136.1, 127.3, 120.3, 43.9, 34.5, 26.9, 26.1, 22.4, 7.1. MS (ES+) found 259.20; C₁₆H₂₂N₂O (M⁺ + H) requires 259.18.

[00130] 1-(4-(*t*-Butyl)phenyl)-3-(cyclobutylmethyl)urea (**5a**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 19%; White solid; mp: 179-184°C; ¹H NMR (CDCl₃): δ 7.30 (d, 2H, J=8.7Hz, Ar), 7.18 (d, 2H, J=8.7Hz, Ar), 3.23 (d, 2H, J=7.2Hz, CH₂), 2.44 (sept, 1H, J=7.5Hz, CH), 2.06-1.94 (m, 2H, 2x CH), 1.91-1.78 (m, 2H, 2x CH), 1.71-1.60 (m, 2H, CH₂) 1.30-1.27 (m, 9H, 3x CH₃); ¹³C NMR (CDCl₃): δ 156.8, 147.1, 135.5, 126.1, 121.4, 45.6, 35.3, 34.3, 31.3, 25.6, 18.2. MS (ES+) found 261.20; C₁₆H₂₄N₂O (M⁺ + H) requires 261.20.

[00131] 1-(Cyclobutylmethyl)-3-(4-iodophenyl)urea (**5b**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 10%; White solid; mp: 159-160°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.35 (d, 2H, J=8.9Hz, Ar), 7.07 (d, 2H, J=8.9Hz, Ar), 3.08 (d, 2H, J=7.1Hz, CH₂),

2.33 (sept, 1H, $J=7.5\text{Hz}$, CH), 1.85-1.93 (m, 2H, 2x CH), 1.77-1.69 (m, 2H, 2x CH), 1.61-1.53 (m, 2H, CH₂); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 155.9, 140.1, 137.4, 120.2, 83.6, 44.8, 35.4, 25.5, 18.2. MS (ES⁺) found 331.00; C₁₂H₁₅IN₂O (M⁺ + H) requires 331.03.

[00132] 1-(3-(*t*-Butyl)phenyl)-3-(cyclobutylmethyl)urea (**5c**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 55%; White solid; mp: 126-127°C; ¹H NMR (CDCl₃ and MeOD): δ 7.32-7.30 (m, 1H, Ar), 7.18-7.00 (m, 3H, Ar), 3.18 (d, 2H, $J=7.2\text{Hz}$, CH₂), 2.39 (sept, 1H, $J=7.5\text{Hz}$, CH), 2.02-1.92 (m, 2H, 2x CH), 1.88-1.76 (m, 2H, CH₂), 1.68-1.59 (m, 2H, 2x CH), 1.24 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.9, 152.3, 138.6, 128.6, 120.3, 117.5, 117.5, 45.2, 35.3, 34.6, 31.2, 25.5, 18.2. MS (ES⁺) found 261.25; C₁₆H₂₄N₂O (M⁺ + H) requires 261.20.

[00133] 1-(Cyclobutylmethyl)-3-(3-iodophenyl)urea (**5d**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 45%; White solid; mp: 138-140°C; ¹H NMR (CDCl₃ and MeOD): δ 7.66-7.63 (m, 1H, Ar), 7.18-7.11 (m, 2H, Ar), 6.85-6.77 (m, 1H, Ar), 3.09-3.04 (m, 2H, CH₂), 2.38-2.26 (m, 1H, CH), 1.96-1.85 (m, 2H, 2x CH), 1.79-1.68 (m, 2H, 2x CH), 1.61-1.51 (m, 2H, CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 156.2, 140.9, 130.9, 130.2, 127.2, 117.7, 94.0, 44.8, 35.2, 25.3, 18.1. MS (ES⁺) found 331.00; C₁₂H₁₅IN₂O (M⁺ + H) requires 331.03.

[00134] 1-(Cyclobutylmethyl)-3-(4-cyclohexylphenyl)urea (**5e**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 32%; White solid; mp: 172-173°C; ¹H NMR (CDCl₃ and MeOD): δ 7.17(d, 2H, $J=8.4\text{Hz}$, Ar), 7.08 (d, 2H, $J=8.5\text{Hz}$, Ar), 3.20-3.17 (m, 2H, CH₂), 2.46-2.37 (m, 2H, 2x CH), 2.03-1.94 (m, 2H, CH₂), 1.88-1.20 (m, 14H, 7x CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 156.9, 143.2, 136.5, 127.3, 120.6, 45.1, 43.9, 35.4, 34.5, 26.9, 26.1, 25.5, 18.2. MS (ES⁺) found 287.25; C₁₈H₂₆N₂O (M⁺ + H) requires 287.21.

[00135] 1-(4-(*t*-Butyl)phenyl)-3-cyclopentylurea (**6a**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 15%; White solid; mp: 219-221°C; ¹H NMR (CDCl₃ and MeOD): δ 7.21 (d, 2H, $J=9.0\text{Hz}$, Ar), 7.15 (d, 2H, $J=8.9\text{Hz}$, Ar), 3.99 (apparent quint, 1H, $J=6.7\text{Hz}$, CH), 1.93-1.82 (m, 2H, CH₂), 1.64-1.45 (m, 4H, 2x CH₂), 1.37-1.25 (m, 2H, CH₂) 1.21 (s, 9H, 3x CH₃); ¹³C

NMR (CDCl₃ and MeOD): δ 156.5, 145.8, 136.2, 125.8, 119.7, 51.6, 34.1, 33.2, 31.3, 23.5. MS (ES+) found 261.25; C₁₆H₂₄N₂O (M⁺ + H) requires 261.20.

[00136] 1-Cyclopentyl-3-(4-iodophenyl)urea (**6b**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 13%; White solid; mp: 188-191°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.31 (d, 2H, J=8.7Hz, Ar), 7.03 (d, 2H, J=8.8Hz, Ar), 3.93-3.87 (m, 1H, CH), 1.81-1.73 (m, 2H, CH₂), 1.53-1.39 (m, 4H, 2x CH₂), 1.27-1.19 (m, 2H, CH₂); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 155.4, 140.1, 137.3, 120.1, 83.4, 51.3, 33.3, 23.5. MS (ES+) found 331.00; C₁₂H₁₅IN₂O (M⁺ + H) requires 331.03.

[00137] 1-(3-(*t*-Butyl)phenyl)-3-cyclopentylurea (**6c**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 57%; White solid; mp: 152-154°C; ¹H NMR (CDCl₃ and MeOD): δ 7.33-7.31 (m, 1H, Ar), 7.16-7.13 (m, 1H, Ar), 7.09-7.01 (m, 2H, Ar), 4.05 (quint, 1H, J=6.8Hz, CH), 1.96-1.85 (m, 2H, 2x CH), 1.63-1.48 (m, 4H, 2x CH₂), 1.38-1.29 (m, 2H, 2x CH), 1.25 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.3, 152.3, 138.6, 128.6, 120.2, 117.4, 117.3, 51.7, 34.6, 33.3, 31.2, 23.5. MS (ES+) found 261.25; C₁₆H₂₄N₂O (M⁺ + H) requires 261.20.

[00138] 1-Cyclopentyl-3-(3-iodophenyl)urea (**6d**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 16%; White solid; mp: 142-143°C; ¹H NMR (CDCl₃ and MeOD): δ 7.71-7.69 (m, 1H, Ar), 7.28-7.21 (m, 2H, Ar), 6.90 (t, 1H, J=8.0Hz, Ar), 3.99 (apparent quint, 1H, J=6.5Hz, CH), 1.93-1.86 (m, 2H, 2x CH), 1.61-1.52 (m, 4H, 4x CH) 1.37-1.30 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 155.7, 140.8, 131.1, 130.3, 127.4, 117.9, 94.1, 51.5, 33.2, 23.5. MS (ES+) found 331.00; C₁₂H₁₅IN₂O (M⁺ + H) requires 331.03.

[00139] 1-(4-Cyclohexylphenyl)-3-cyclopentylurea (**6e**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 30%; White solid; mp: 197-199°C; ¹H NMR (CDCl₃ and MeOD): δ 7.14 (d, 2H, J=8.5Hz, Ar), 7.05 (d, 2H, J=8.4Hz, Ar), 4.00 (quint, 1H, J=6.6Hz, CH), 2.42-2.32 (m, 1H, CH), 1.95-1.85 (m, 2H, 2x CH), 1.81-1.20 (m, 16H, 2x CH + 7x CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 156.4, 143.1, 136.6, 127.3, 120.3, 51.7, 43.9, 34.5, 33.3, 26.9, 26.1, 23.5. MS (ES+) found 287.20; C₁₈H₂₆N₂O (M⁺ + H) requires 287.21.

[00140] General procedure for the preparation of 7-38.

[00141] Suitable aniline (1.0 eq.) were dissolved in acetonitrile (6 ml) and K₂CO₃ (1.2 eq.) was added to the resulting solution. The proper isocyanate (1.2 eq.) was then added to the solution and the reaction mixture was stirred for 48 h under reflux. The reaction mixture was then evaporated to dryness under reduced pressure and the resulting residue was purified by flash chromatography on silica gel.

[00142] 1-(4-Iodophenyl)-3-neopentylurea **(7)**. Flash chromatography (methylene chloride/hexanes (95:5)) Yield: 11%; Sticky solid; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.45 (d, 2H, J=8.9Hz, Ar), 7.14 (d, 2H, J=8.9Hz, Ar), 2.97 (s, 2H, CH₂), 0.87 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 156.1, 140.0, 137.5, 120.6, 84.0, 51.1, 31.9, 27.2. MS (ES+) found 333.00; C₁₂H₁₇IN₂O (M⁺ + H) requires 333.05.

[00143] 1-(Cyclopropylmethyl)-3-(4-iodophenyl)urea **(8)**. Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 26%; White solid; mp: 192-194°C; ¹H NMR (CDCl₃ and MeOD): δ 7.42 (d, 2H, J=8.6Hz, Ar), 7.07 (d, 2H, J=8.6Hz, Ar), 2.97 (apparent t, 2H, J=7.1Hz, CH₂), 0.93-0.82 (m, 1H, CH), 0.44-0.35 (m, 2H, 2x CH), 0.15-0.06 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 156.1, 139.5, 137.5, 120.6, 84.3, 44.4, 10.9, 3.1. MS (ES+) found 317.00; C₁₁H₁₃IN₂O (M⁺ + H) requires 317.02.

[00144] 1-Cyclobutyl-3-(4-iodophenyl)urea **(9)**. Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 13%; White solid; mp: 208-210°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.35 (d, 2H, J=8.9Hz, Ar), 7.06 (d, 2H, J=8.9Hz, Ar), 4.12 (quint, 1H, J=7.9Hz, CH), 2.23-2.14 (m, 2H, 2x CH), 1.77-1.64 (m, 2H, 2x CH), 1.60-1.50 (m, 2H, CH₂); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 154.7, 139.9, 137.4, 120.3, 83.8, 45.0, 31.6, 14.8. MS (ES+) found 317.00; C₁₁H₁₃IN₂O (M⁺ + H) requires 317.02.

[00145] 1-(Cyclopentylmethyl)-3-(4-iodophenyl)urea **(10)**. Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 10%; White solid; mp: 158-162°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.33 (d, 2H, J=8.9Hz, Ar), 7.05 (d, 2H, J=8.9Hz, Ar), 2.97(d, 2H, J=7.2Hz, CH₂),

1.87 (sept, 1H, $J=7.5\text{Hz}$, CH), 1.64-1.53 (m, 2H, 2x CH), 1.51-1.33 (m, 4H, 4x CH), 1.10-1.00 (m, 2H, 2x CH); ^{13}C NMR (CDCl_3 and DMSO-d_6): δ 155.8, 140.2, 137.3, 120.1, 83.4, 44.5, 40.0, 30.2, 25.1. MS (ES+) found 345.00; $\text{C}_{13}\text{H}_{17}\text{IN}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 345.05.

[00146] 1-(4-Iodophenyl)-3-(2-methoxyethyl)urea (**11**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 20%; White solid; mp: 141-143°C; ^1H NMR (CDCl_3): δ 7.56 (d, 2H, $J=8.5\text{Hz}$, Ar), 7.09 (d, 2H, $J=8.6\text{Hz}$, Ar), 3.55-3.47 (m, 2H, CH_2), 3.46-3.40 (m, 2H, CH_2), 3.38 (s, 3H, CH_3); ^{13}C NMR (CDCl_3): δ 156.0, 138.8, 137.9, 121.8, 85.9, 72.4, 58.8, 40.5. MS (ES+) found 320.95; $\text{C}_{10}\text{H}_{13}\text{IN}_2\text{O}_2$ ($\text{M}^+ + \text{H}$) requires 321.01.

[00147] 1-(4-(*t*-Butyl)phenyl)-3-(cyclopropylmethyl)urea (**12**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 17%; White solid; mp: 168-170°C; ^1H NMR (CDCl_3 and DMSO-d_6): δ 7.21-7.20 (m, 4H, Ar), 3.03 (d, 2H, $J=7.0\text{Hz}$, CH_2), 1.22-1.21 (m, 9H, 3x CH_3), 0.93-0.86 (m, 1H, CH), 0.44-0.36 (m, 2H, 2x CH), 0.15-0.11 (m, 2H, 2x CH); ^{13}C NMR (CDCl_3 and DMSO-d_6): δ 156.4, 145.3, 136.7, 125.7, 119.3, 44.7, 34.1, 31.4, 11.2, 3.3. MS (ES+) found 247.15; $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 247.18.

[00148] 1-(4-(*t*-Butyl)phenyl)-3-cyclobutylurea (**13**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 29%; White solid; mp: 189-190°C; ^1H NMR (CDCl_3 and DMSO-d_6): δ 7.19-7.12 (m, 4H, Ar), 4.23-4.14 (m, 1H, CH), 2.27-2.15 (m, 2H, 2x CH), 1.79-1.65 (m, 2H, 2x CH), 1.61-1.49 (m, 2H, CH_2), 1.21-1.17 (m, 9H, 3x CH_3); ^{13}C NMR (CDCl_3 and DMSO-d_6): δ 155.5, 140.8, 136.8, 125.6, 119.3, 45.2, 34.1, 31.6, 31.4, 14.8. MS (ES+) found 247.15; $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 247.18.

[00149] 1-(4-(*t*-Butyl)phenyl)-3-(2-methoxyethyl)urea (**14**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 29%; Light yellow solid; mp: 122-124°C; ^1H NMR (CDCl_3): δ 7.29 (d, 2H, $J=7.4\text{Hz}$, Ar), 7.21 (d, 2H, $J=7.6\text{Hz}$, Ar), 5.62 (s, 1H, NH), 3.49-3.45 (m, 4H, 2x CH_2), 3.35 (s, 3H, CH_3), 1.29 (s, 9H, 3x CH_3); ^{13}C NMR (CDCl_3): δ 146.6, 136.2, 126.1, 120.8, 72.4, 58.9, 40.3, 34.4, 31.5. MS (ES+) found 251.15; $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_2$ ($\text{M}^+ + \text{H}$) requires 251.18.

[00150] 1-(4-(*t*-Butyl)phenyl)-3-(pentan-3-yl)urea (**15**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 21%; White solid; mp: 119-121°C; ¹H NMR (CDCl₃): δ 7.29 (d, 2H, J=8.6Hz, Ar), 7.20 (d, 2H, J=8.6Hz, Ar), 6.90 (s, 1H, NH), 4.93 (s, 1H, NH), 3.65 (apparent quint, 1H, J=7.9Hz, CH), 1.58-1.45 (m, 2H, 2x CH) 1.41-1.19 (m, 11H, 2x CH + 3x CH₃), 0.89 (t, 6H, J=7.4Hz, 2x CH₃); ¹³C NMR (CDCl₃): δ 156.4, 146.6, 136.2, 126.1, 120.9, 52.9, 34.3, 31.4, 27.8, 10.3. MS (ES+) found 263.25; C₁₆H₂₆N₂O (M⁺ + H) requires 263.21.

[00151] 1-(Cyclopent-3-en-1-yl)-3-(4-iodophenyl)urea (**16**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 15%; White solid; mp: 201-202°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ 7.42 (d, 2H, J=8.8Hz, Ar), 7.05 (d, 2H, J=8.6Hz, Ar), 5.61-5.57 (m, 2H, CH₂), 4.34-4.26 (m, 1H, CH), 2.68-2.59 (m, 2H, 2x CH), 2.13-2.03 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 155.3, 140.1, 137.3, 128.9, 120.0, 83.4, 49.0, 40.3. MS (ES+) found 329.00; C₁₂H₁₃IN₂O (M⁺ + H) requires 329.02.

[00152] 1-(Cyclopropylmethyl)-3-(3-iodophenyl)urea (**17**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 15%; White solid; mp: 139-140°C; ¹H NMR (CDCl₃ and MeOD): δ 7.74-7.67 (m, 1H, Ar), 7.30-7.18 (m, 2H, Ar), 6.93-6.84 (m, 1H, Ar), 3.02-2.93 (m, 2H, CH₂), 0.94-0.82 (m, 2H, 2x CH), 0.16-0.05 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 156.0, 140.7, 130.9, 130.1, 127.2, 117.7, 93.9, 44.3, 10.7, 2.9. MS (ES+) found 317.00; C₁₁H₁₃IN₂O (M⁺ + H) requires 317.02.

[00153] 1-Cyclobutyl-3-(3-iodophenyl)urea (**18**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 16%; White solid; mp: 178-180°C; ¹H NMR (CDCl₃ and MeOD): δ 7.68-7.62 (m, 1H, Ar), 7.22-7.12 (m, 2H, Ar), 6.88-6.79 (m, 1H, Ar), 4.09 (apparent sept, 1H, J=8.3Hz, CH), 2.26-2.11 (m, 2H, 2x CH), 1.78-1.48 (m, 4H, 2x CH + CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 155.1, 140.7, 131.0, 130.2, 127.3, 117.8, 94.0, 44.9, 31.4, 14.8. MS (ES+) found 317.00; C₁₁H₁₃IN₂O (M⁺ + H) requires 317.02.

[00154] 1-(Cyclopent-3-en-1-yl)-3-(3-iodophenyl)urea (**19**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 29%; Light brown solid; mp: 151-153°C; ¹H NMR (CDCl₃ and MeOD): δ 7.69-7.67 (m, 1H, Ar), 7.25-7.21 (m, 2H, Ar), 6.89 (t, 1H, J=8.0Hz, Ar), 4.34

(apparent sept, 1H, $J=4.1$ Hz, CH), 2.68 (dd, 2H, $J=7.7$ Hz, 2x CH), 2.13 (dd, 2H, 2x CH); ^{13}C NMR (CDCl_3 and MeOD): δ 155.7, 140.7, 131.2, 130.3, 128.8, 127.5, 118.0, 94.2, 49.3, 40.3. MS (ES+) found 329.05; $\text{C}_{12}\text{H}_{13}\text{IN}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 329.02.

[00155] 1-(3-Iodophenyl)-3-(2-methoxyethyl)urea (**20**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 16%; Light yellow solid; mp: 99-101°C; ^1H NMR (CDCl_3 and MeOD): δ 7.73 (s, 1H, Ar), 7.30 (d, 2H, $J=7.8$ Hz, Ar), 6.95 (t, 1H, $J=7.7$ Hz, Ar), 3.52-3.36 (m, 4H, 2x CH_2), 3.36 (s, 3H, CH_3); ^{13}C NMR (CDCl_3 and MeOD): δ 156.1, 140.7, 131.2, 130.3, 127.5, 118.0, 94.1, 72.1, 58.7, 39.7. MS (ES+) found 321.00; $\text{C}_{10}\text{H}_{13}\text{IN}_2\text{O}_2$ ($\text{M}^+ + \text{H}$) requires 321.01.

[00156] 1-(3-Iodophenyl)-3-neopentylurea (**21**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 45%; White solid; mp: 114-115°C; ^1H NMR (CDCl_3 and MeOD): δ 7.68-7.66 (m, 1H, Ar), 7.18-7.12 (m, 2H, Ar), 6.85-6.77 (m, 1H, Ar), 2.87-2.85 (m, 2H, CH_2), 0.78-0.76 (m, 9H, 3x CH_3); ^{13}C NMR (CDCl_3 and MeOD): δ 156.4, 141.0, 130.9, 130.2, 127.2, 117.7, 94.0, 50.9, 31.8, 26.9. MS (ES+) found 333.05; $\text{C}_{12}\text{H}_{17}\text{IN}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 333.05.

[00157] 1-(3-(*t*-Butyl)phenyl)-3-(cyclopropylmethyl)urea (**22**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 44%; White solid; mp: 165-166°C; ^1H NMR (CDCl_3 and MeOD): δ 7.33-7.31 (m, 1H, Ar), 7.21-7.15 (m, 1H, Ar), 7.11-7.02 (m, 2H, Ar), 3.05 (d, 2H, CH_2), 1.26 (s, 9H, 3x CH_3) 0.97-0.87 (m, 1H, CH), 0.44-0.41 (m, 2H, 2x CH), 0.16-0.12 (m, 2H, 2x CH); ^{13}C NMR (CDCl_3 and MeOD): δ 156.5, 152.3, 138.5, 128.7, 120.4, 117.7, 117.6, 44.8, 34.6, 31.2, 11.0, 3.1. MS (ES+) found 247.15; $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 247.18.

[00158] 1-(3-(*t*-Butyl)phenyl)-3-cyclobutylurea (**23**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 57%; White solid; mp: 165-166°C; ^1H NMR (CDCl_3 and MeOD): δ 7.34-7.32 (m, 1H, Ar), 7.18-7.08 (m, 2H, Ar), 7.05-7.01 (m, 1H, Ar), 4.23 (quint, 1H, $J=7.5$ Hz, CH), 2.31-2.21 (m, 2H, 2x CH), 1.83-1.69 (m, 2H, 2x CH), 1.64-1.53 (m, 2H, CH_2), 1.25 (s, 9H, 3x CH_3); ^{13}C NMR (CDCl_3 and MeOD): δ 155.7, 152.2, 138.6, 128.6, 120.2, 117.5, 117.4, 45.2, 34.6, 31.4, 31.2, 14.8. MS (ES+) found 247.15; $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$ ($\text{M}^+ + \text{H}$) requires 247.18.

[00159] 1-(3-(*t*-butyl)phenyl)-3-cyclopentylurea (**24**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 57%; White solid; mp: 152-154°C; ¹H NMR (CDCl₃ and MeOD): δ 7.33-7.31 (m, 1H, Ar), 7.16-7.13 (m, 1H, Ar), 7.09-7.01 (m, 2H, Ar), 4.05 (quint, 1H, J=6.8Hz, CH), 1.96-1.85 (m, 2H, 2x CH), 1.63-1.48 (m, 4H, 2x CH₂), 1.38-1.29 (m, 2H, 2x CH), 1.25 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.3, 152.3, 138.6, 128.6, 120.2, 117.4, 117.3, 51.7, 34.6, 33.3, 31.2, 23.5. MS (ES+) found 261.25; C₁₆H₂₄N₂O (M⁺ + H) requires 261.20.

[00160] 1-(3-(*t*-Butyl)phenyl)-3-(cyclopentylmethyl)urea (**25**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 53%; White solid; mp: 113-114°C; ¹H NMR (CDCl₃ and MeOD): δ 7.33-7.31 (m, 1H, Ar), 7.21-7.16 (m, 1H, Ar), 7.10-7.04 (m, 2H, Ar), 3.12 (d, 2H, J=7.3Hz, CH₂), 1.98 (sept, 1H, J=7.7Hz, CH), 1.74-1.64 (m, 2H, 2x CH), 1.62-1.45 (m, 4H, 2x CH₂), 1.26 (s, 9H, 3x CH₃), 1.21-1.09 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 156.7, 152.4, 138.5, 128.7, 120.6, 118.0, 117.9, 45.0, 40.0, 34.7, 31.2, 30.2, 25.2. MS (ES+) found 275.20; C₁₇H₂₆N₂O (M⁺ + H) requires 275.21.

[00161] 1-(3-(*t*-Butyl)phenyl)-3-(cyclopent-3-en-1-yl)urea (**26**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 34%; White solid; mp: 135-137°C; ¹H NMR (CDCl₃): δ 7.32-7.30 (m, 1H, Ar), 7.22-7.17 (m, 1H, Ar), 7.09-7.06 (m, 2H, Ar), 6.94 (s, 1H, NH), 5.66 (s, 2H, 2x CH), 5.44 (d, 1H, J=7.4Hz, NH), 4.52-4.41 (m, 1H, CH), 2.73 (dd, 2H, J=7.6Hz, 2x CH), 2.17 (dd, 2H, J=3.8Hz, 2x CH), 1.27 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃): δ 156.0, 152.5, 138.5, 128.9, 128.9, 120.7, 118.1, 118.0, 49.8, 40.5, 34.7, 31.3. MS (ES+) found 259.10; C₁₆H₂₂N₂O (M⁺ + H) requires 259.18.

[00162] 1-(3-(*t*-Butyl)phenyl)-3-neopentylurea (**27**). Flash chromatography (hexanes/ethyl acetate (90:10)) Yield: 26%; White solid; mp: 145-147°C; ¹H NMR (CDCl₃): δ 7.34-7.31 (m, 1H, Ar), 7.24-7.19 (m, 1H, Ar), 7.12-7.08 (m, 2H, Ar), 7.02 (s, 1H, NH), 5.30 (s, 1H, NH), 3.03 (s, 2H, CH₂), 1.28 (s, 9H, 3x CH₃), 0.88 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃): δ 156.7, 152.6, 138.5, 128.9, 120.9, 118.6, 118.4, 51.4, 34.7, 32.0, 31.3, 27.2. MS (ES+) found 263.20; C₁₆H₂₆N₂O (M⁺ + H) requires 263.21.

[00163] 1-(3-(*t*-Butyl)phenyl)-3-(2-methoxyethyl)urea (**28**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 61%; White solid; mp: 119-120°C; ¹H NMR (CDCl₃ and MeOD): δ 7.33-7.32 (m, 1H, Ar), 7.21-7.16 (m, 1H, Ar), 7.11-7.03 (m, 2H, Ar), 3.47 (t, 2H, J=5.0Hz, CH₂), 3.39 (t, 2H, J=5.0Hz, CH₂), 3.33 (s, 3H, CH₃), 1.27 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.7, 152.3, 138.5, 128.7, 120.4, 117.5, 117.5, 72.1, 58.7, 39.9, 34.7, 31.2. MS (ES+) found 251.15; C₁₄H₂₂N₂O₂ (M⁺ + H) requires 251.18.

[00164] 1-(3-(*t*-Butyl)phenyl)-3-(pentan-3-yl)urea (**29**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 11%; White solid; mp: 159-161°C; ¹H NMR (CDCl₃): δ 7.35-7.34 (m, 1H, Ar), 7.31-7.29 (m, 1H, Ar), 7.19-7.12 (m, 2H, Ar), 6.54 (s, 1H, NH), 4.65 (s, 1H, NH), 3.73 (quint, 1H, J=5.8Hz, CH), 1.64-1.52 (m, 2H, 2x CH), 1.48-1.36 (m, 2H, 2x CH), 1.34 (s, 9H, 3x CH₃), 0.95 (t, 6H, J=7.4Hz, 2x CH₃); ¹³C NMR (CDCl₃): δ 156.0, 152.8, 138.3, 129.1, 121.3, 119.0, 118.9, 52.9, 34.8, 31.3, 27.7, 10.2. MS (ES+) found 263.20; C₁₆H₂₆N₂O (M⁺ + H) requires 263.21.

[00165] 1-(4-Cyclohexylphenyl)-3-(cyclopropylmethyl)urea (**30**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 72%; White solid; mp: 178-181°C; ¹H NMR (CDCl₃ and MeOD): δ 7.12 (d, 2H, J=8.6Hz, Ar), 7.00 (d, 2H, J=8.4Hz, Ar), 2.96 (d, 2H, J=7.0Hz, CH₂), 2.39-2.29 (m, 1H, CH), 1.74-1.12 (m, 10H, 5x CH₂), 0.90-0.81 (m, 1H, CH), 0.41-0.34 (m, 2H, 2x CH), 0.11-0.05 (m, 2H, 2x CH); ¹³C NMR (CDCl₃ and MeOD): δ 156.8, 142.7, 136.6, 127.1, 119.9, 44.5, 43.8, 34.4, 26.8, 26.0, 10.9, 2.9. MS (ES+) found 273.15; C₁₇H₂₄N₂O (M⁺ + H) requires 273.20.

[00166] 1-Cyclobutyl-3-(4-cyclohexylphenyl)urea (**31**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 11%; White solid; mp: 137-139°C; ¹H NMR (CDCl₃ and MeOD): δ 7.16 (d, 2H, J=8.6Hz, Ar), 7.10 (d, 2H, J=8.5Hz, Ar), 6.85 (s, 1H, NH), 4.22 (quint, 1H, J=7.7Hz, CH), 2.34-2.27 (m, 2H, CH₂), 1.81-1.22 (m, 15H, CH + 7x CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 155.7, 146.1, 136.1, 127.5, 121.2, 45.3, 43.9, 34.5, 31.5, 26.9, 26.1, 14.8. MS (ES+) found 273.20; C₁₇H₂₄N₂O (M⁺ + H) requires 273.20.

[00167] 1-(4-Cyclohexylphenyl)-3-(cyclopentylmethyl)urea (**32**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 14%; White solid; mp: 142-144°C; ¹H NMR (CDCl₃ and MeOD): δ 7.16 (apparent s, 4H, Ar), 6.37 (s, 1H, NH), 3.17 (d, 2H, J=7.3Hz, CH₂), 2.51-2.41 (m, 1H, CH), 2.03 (sept, 1H, J=7.7Hz, CH), 1.85-1.25 (m, 18H, 9x CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 156.3, 144.6, 135.9, 127.8, 122.4, 45.4, 44.0, 40.1, 34.5, 30.3, 26.9, 26.2, 25.3. MS (ES+) found 301.20; C₁₉H₂₈N₂O (M⁺ + H) requires 301.23.

[00168] 1-(4-Cyclohexylphenyl)-3-(cyclopent-3-en-1-yl)urea (**33**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 41%; White solid; mp: 167-169°C; ¹H NMR (CDCl₃ and MeOD): δ 7.15 (d, 2H, J=8.4Hz, Ar), 7.05 (d, 2H, J=8.4Hz, Ar), 5.63 (apparent s, 2H, 2x CH), 4.41-4.32 (m, 1H, CH), 2.68 (dd, 2H, J=7.6Hz, 2x CH), 2.43-2.35 (m, 1H, CH), 2.16-2.09 (m, 2H, 2x CH), 1.83-1.15 (m, 10H, 5x CH₂); ¹³C NMR (CDCl₃ and MeOD): δ 156.4, 143.1, 136.5, 128.9, 127.3, 120.3, 49.5, 43.9, 40.3, 34.5, 26.9, 26.1. MS (ES+) found 285.20; C₁₈H₂₄N₂O (M⁺ + H) requires 285.20.

[00169] 1-(4-Cyclohexylphenyl)-3-neopentylurea (**34**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 21%; White solid; mp: 167-169°C; ¹H NMR (CDCl₃ and MeOD): δ 7.18 (d, 2H, J=8.4Hz, Ar), 7.08 (d, 2H, J=8.5Hz, Ar), 2.96 (s, 2H, CH₂), 2.44-2.36 (m, 1H, CH), 1.80-1.16 (m, 10H, 5x CH₂), 0.85 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.9, 143.3, 136.5, 127.4, 120.7, 51.1, 43.9, 34.5, 32.0, 27.1, 26.9, 26.1. MS (ES+) found 289.20; C₁₈H₂₈N₂O (M⁺ + H) requires 289.23.

[00170] 1-(4-Cyclohexylphenyl)-3-(pentan-3-yl)urea (**35**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 14%; White solid; mp: 174-176°C; ¹H NMR (CDCl₃ and MeOD): δ 7.17 (d, 2H, J=8.4Hz, Ar), 7.10 (d, 2H, J=8.5Hz, Ar), 3.59 (quint, 1H, J=5.6Hz, CH), 2.46-2.36 (m, 1H, CH), 1.86-1.22 (m, 14H, 7x CH₂), 0.87 (t, 6H, 2x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 156.5, 143.6, 136.4, 127.5, 121.1, 52.6, 43.9, 34.5, 27.7, 26.9, 26.1, 10.2. MS (ES+) found 289.15; C₁₈H₂₈N₂O (M⁺ + H) requires 289.23.

[00171] 1-(4-Iodophenyl)-3-(pentan-3-yl)urea (**36**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 8%; White solid; mp: 174-176°C; ¹H NMR (CDCl₃ and MeOD): δ 7.49

(d, 2H, J=8.7Hz, Ar), 7.10 (d, 2H, J=8.8Hz, Ar), 3.60-3.52 (m, 1H, CH), 1.55-1.40 (m, 2H, 2x CH), 1.34-1.23 (m, 2H, 2x CH), 0.86 (t, 6H, J=7.4Hz, 2x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 155.9, 139.5, 137.7, 120.9, 84.7, 52.4, 27.6, 10.1. MS (ES+) found 333.00; C₁₂H₁₇IN₂O (M⁺ + H) requires 333.05.

[00172] 1-(4-(*t*-Butyl)phenyl)-3-neopentylurea (**37**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 52%; White solid; mp: 185-187°C; ¹H NMR (CDCl₃ and MeOD): δ 7.74 (s, 1H, NH), 7.25-7.15 (apparent s, 4H, Ar), 5.77 (s, 1H, NH), 2.95 (s, 2H, CH₂), 1.23 (s, 9H, 3x CH₃), 0.83 (s, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and MeOD): δ 157.1, 145.5, 136.6, 125.7, 119.7, 119.5, 51.1, 34.2, 32.0, 31.4, 27.1. MS (ES+) found 263.20; C₁₆H₂₆N₂O (M⁺ + H) requires 263.21.

[00173] 1-(4-(*t*-Butyl)phenyl)-3-(cyclopent-3-en-1-yl)urea (**38**). Flash chromatography (hexanes/ethyl acetate (80:20)) Yield: 34%; White solid; mp: 179-184°C; ¹H NMR (CDCl₃ and DMSO-d₆): δ), 7.75 (s, 1H, NH), 7.14-7.02 (m, 4H, Ar), 3.93-3.85 (m, 1H, CH), 1.80-1.70 (m, 2H, CH₂), 1.53-1.34 (m, 4H, 2x CH₂), 1.25-1.15 (m, 2H, CH₂), 1.11-1.07 (m, 9H, 3x CH₃); ¹³C NMR (CDCl₃ and DMSO-d₆): δ 155.8, 144.2, 137.4, 125.4, 118.2, 51.3, 33.9, 33.3, 31.3, 23.4. MS (ES+) found 259.20; C₁₆H₂₄N₂O (M⁺ + H) requires 259.18.

[00174] While the present disclosure has been described with reference to specific examples, it is to be understood that the disclosure is not limited to the disclosed examples. To the contrary, the disclosure is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

[00175] All publications, patents and patent applications cited in the present disclosure are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

References

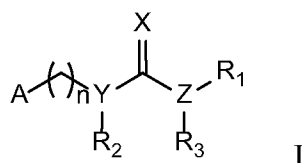
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CLAIMS:

1. A compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

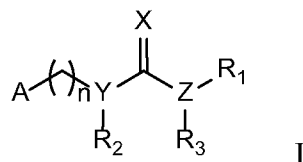
each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

2. A compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR,

-NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

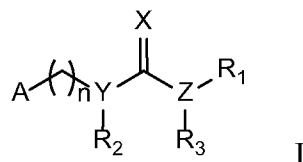
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

3. A compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR,

-NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

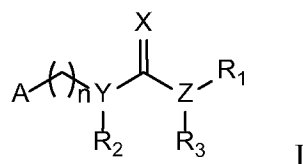
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

4. A method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula I:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

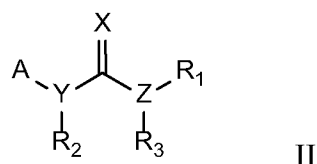
each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

5. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.
6. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.
7. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in any one of claims 1 to 3, and a pharmaceutically acceptable carrier.
8. A compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -

CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -

CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

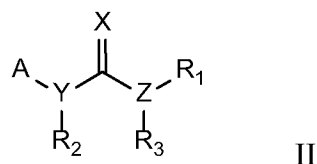
each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

9. A compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -

CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -

CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

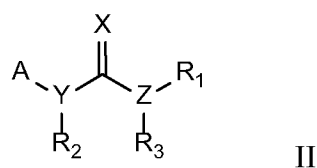
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

10. A compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -

C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅) alkenyl, -O-(C₂₋₁₅) alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -

CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

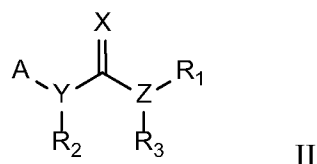
wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

11. A method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula II:



wherein:

A is an arene or a heteroarene;

Y is N, O or S;

Z is N, O or S;

X is O, S or N=CN;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -

O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, (C₂-C₁₅)alkenyl, (C₂-C₁₅)alkynyl, -O-(C₁-C₁₅)alkyl, -O-(C₂-C₁₅) alkenyl, -O-(C₂-C₁₅) alkynyl, -S-(C₁-C₁₅)alkyl, -S-(C₂-C₁₅)alkenyl, -S-(C₂-C₁₅)alkynyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -

C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein

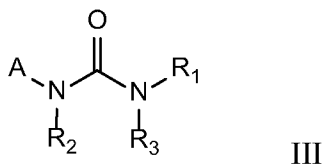
each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

wherein

when Y and/or Z are O or S, R₂ and/or R₃ are absent;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

12. A pharmaceutical composition comprising a compound as defined in any one of claims 8 to 10, and a pharmaceutically acceptable carrier.
13. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in any one of claims 8 to 10, and a pharmaceutically acceptable carrier.
14. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in any one of claims 8 to 10, and a pharmaceutically acceptable carrier.
15. A compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-

C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

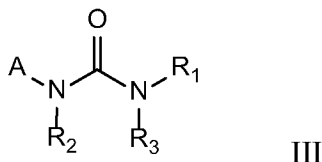
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, (C₂-C₁₅)alkenyl, (C₂-C₁₅)alkynyl, -O-(C₁-C₁₅)alkyl, -O-(C₂-C₁₅) alkenyl, -O-(C₂-C₁₅) alkynyl, -S-(C₁-C₁₅)alkyl, -S-(C₂-C₁₅)alkenyl, -S-(C₂-C₁₅)alkynyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

16. A compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -

C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -

CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

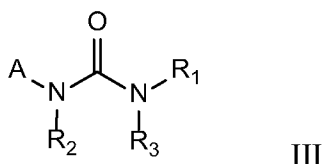
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

17. A compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄-

₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, (C₂-C₁₅)alkenyl, (C₂-C₁₅)alkynyl, -O-(C₁-C₁₅)alkyl, -O-(C₂-C₁₅)alkenyl, -O-(C₂-C₁₅)alkynyl, -S-(C₁-C₁₅)alkyl, -S-(C₂-C₁₅)alkenyl, -S-(C₂-C₁₅)alkynyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

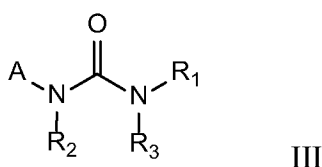
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₃-C₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

18. A method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula III:



wherein:

A is an arene or a heteroarene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -

CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; (C₆₋₁₈)aryl; or (C₆₋₁₈)aryl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

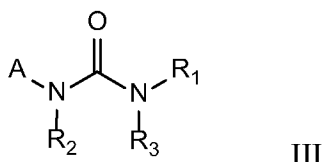
A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, (C₂₋₁₅)alkenyl, (C₂₋₁₅)alkynyl, -O-(C₁₋₁₅)alkyl, -O-(C₂₋₁₅)alkenyl, -O-(C₂₋₁₅)alkynyl, -S-(C₁₋₁₅)alkyl, -S-(C₂₋₁₅)alkenyl, -S-(C₂₋₁₅)alkynyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -NO₂, -CN, -C(O)R, -C(S)R, -C(O)OR, -C(S)OR, -SC(S)R, -OC(S)R, -C(O)NRR, -C(S)NRR, -C(O)NR(OR), -C(S)NR(OR), -C(O)NR(SR), -C(S)NR(SR), -CH(CN)₂, -CH[C(O)R]₂, -CH[C(S)R]₂, -CH[C(O)OR]₂, -CH[C(S)OR]₂, -CH[C(O)SR]₂, -CH[C(S)SR]₂, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁₋₁₀)alkyl, (C₂₋₁₀)alkenyl, (C₂₋₁₀)alkynyl, (C₃₋₈)cycloalkyl, aryl or substituted aryl;

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

19. A pharmaceutical composition comprising a compound as defined in any one of claims 15 to 17, and a pharmaceutically acceptable carrier.
20. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in any one of claims 15 to 17, and a pharmaceutically acceptable carrier.
21. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in any one of claims 15 to 17, and a pharmaceutically acceptable carrier.
22. A compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

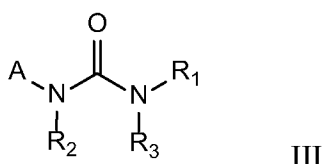
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

23. A compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-

(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

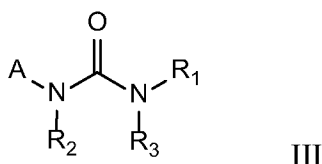
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as an anti-proliferative agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

24. A compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-

(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

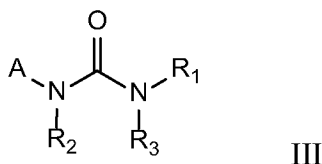
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof;

for use as a therapeutic agent in the attenuation, inhibition, or prevention of conditions associated with IL-6 expression.

25. A method for treating, attenuating, inhibiting, or preventing a condition associated with IL-6 expression in a subject in need thereof, the method comprising administering a therapeutically effective amount of a compound of Formula III:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; or (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

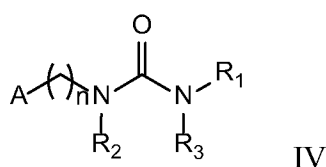
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

26. A pharmaceutical composition comprising a compound as defined in any one of claims 22 to 24, and a pharmaceutically acceptable carrier.
27. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in any one of claims 22 to 24, and a pharmaceutically acceptable carrier.
28. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in any one of claims 22 to 24, and a pharmaceutically acceptable carrier.
29. A compound of Formula IV:



wherein:

A is an arene;

R₁ is a (C₄₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, ROR-, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl,

(C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-; -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, -S-(C₁₋₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

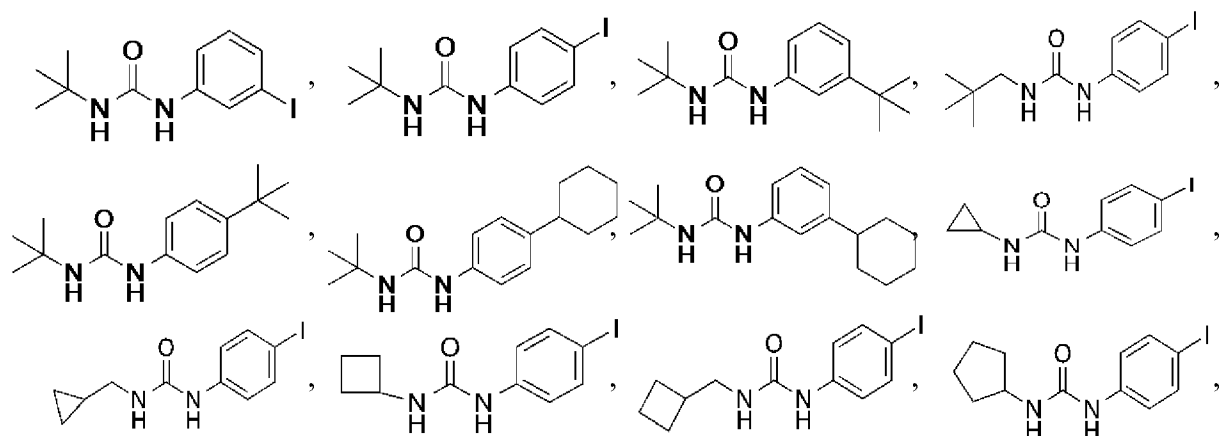
A is optionally substituted with one or more substituents selected from the group of (C₁₋₁₅)alkyl, -O-(C₁₋₁₅)alkyl, -S-(C₁₋₁₅)alkyl, (C₃₋₈)cycloalkyl, -O-(C₃₋₈)cycloalkyl, -S-(C₃₋₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

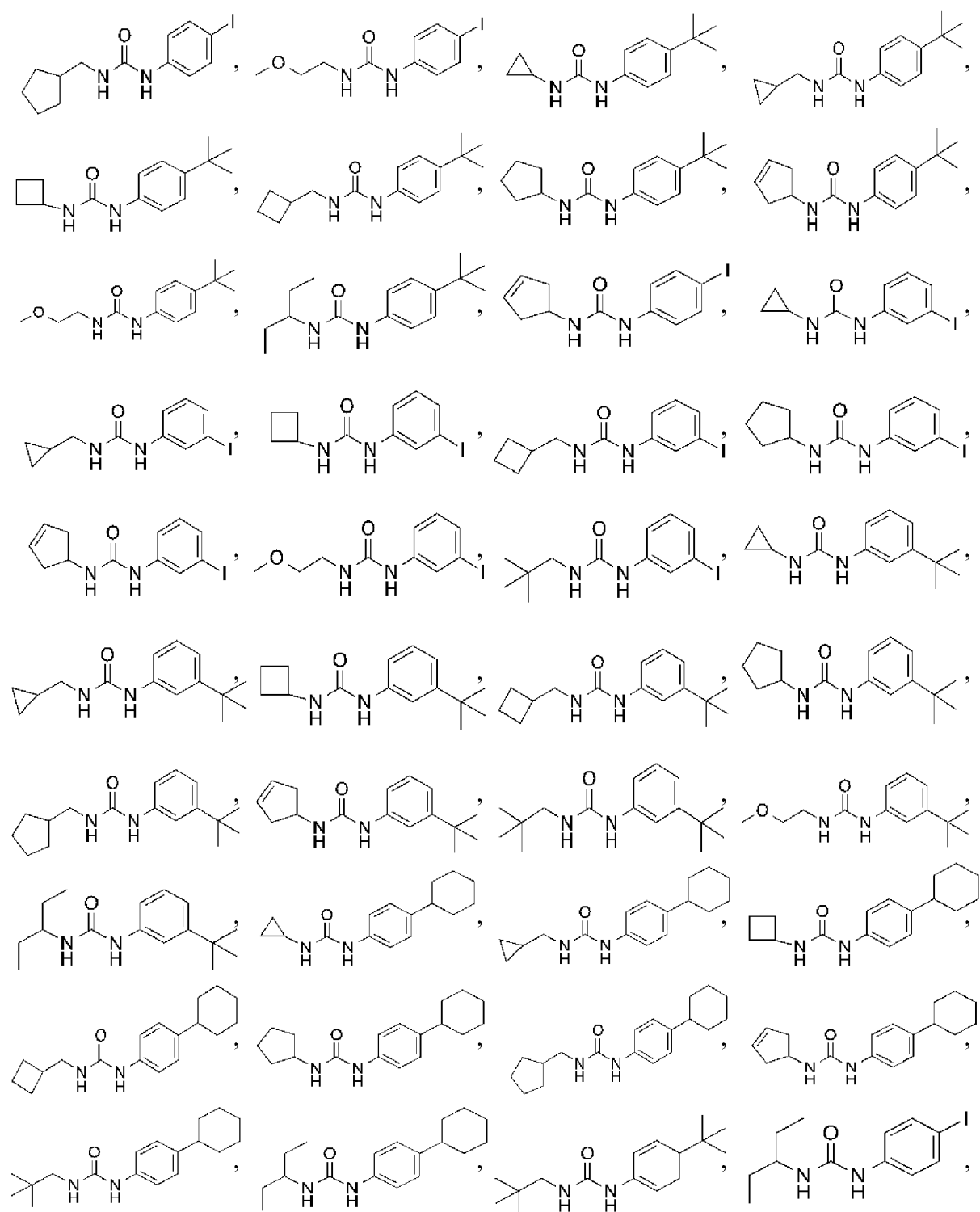
wherein:

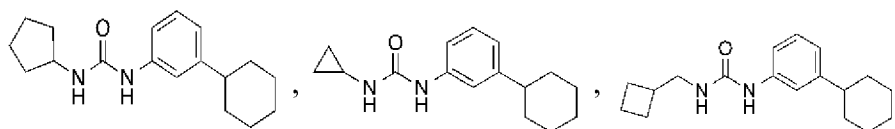
each R is independently selected from -H, (C₁₋₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

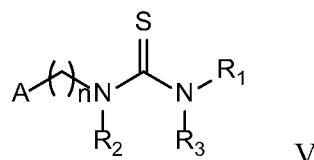
30. The compound of claim **29**, including:







31. A pharmaceutical composition comprising a compound as defined in claim 29 or 30, and a pharmaceutically acceptable carrier.
32. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in claim 29 or 30, and a pharmaceutically acceptable carrier.
33. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in claim 29 or 30, and a pharmaceutically acceptable carrier.
34. A compound of Formula V:



wherein:

A is an arene;

R₁ is a (C₁₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋

₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

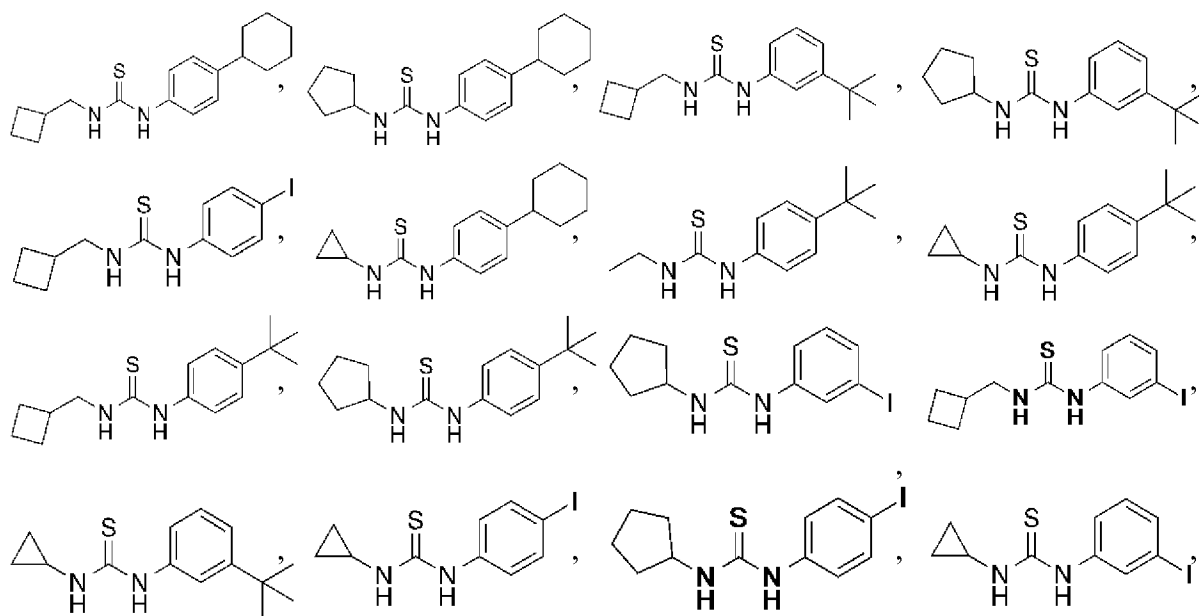
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

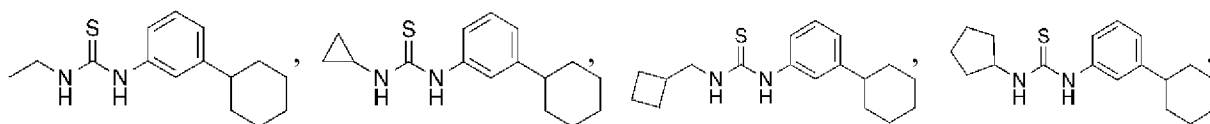
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

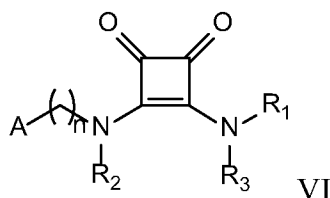
or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

35. The compound of claim 34, including:





36. A pharmaceutical composition comprising a compound as defined in claim 34 or 35, and a pharmaceutically acceptable carrier.
37. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in claim 34 or 35, and a pharmaceutically acceptable carrier.
38. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in claim 34 or 35, and a pharmaceutically acceptable carrier.
39. A compound of Formula VI:



wherein:

A is an arene;

R₁ is a (C₁₋₁₅)alkyl; (C₄₋₁₅)-branched alkyl; (C₃₋₈)cycloalkyl; alk(C₃₋₈)cycloalkyl, (C₃₋₈)cycloalkenyl, alk(C₃₋₈)cycloalkenyl, (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR; or (C₃₋₈)cycloalkenyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁₋₁₀)alkyl, ROR-, -S-(C₁₋₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -S(O)-R, -S(O)OR, and -S(O)NRR;

R₂ and R₃ are independently hydrogen, (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, (C₃₋₈)cycloalkyl; (C₃₋₈)cycloalkyl having at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋

₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR; or

R₂ and R₃ are linked together to form a nitrogen containing ring system, wherein the nitrogen containing ring system is optionally substituted by at least one substituent selected from (C₁₋₁₀)alkyl, (C₄₋₁₀)branched alkyl, -O-(C₁-C₁₀)alkyl, -S-(C₁-C₁₀)alkyl, -NRR, CN, -C(O)R, -C(O)OR, -C(O)NRR, -S(O)-R, -S(O)OR, and -S(O)NRR;

n is 0, 1 or 2;

wherein:

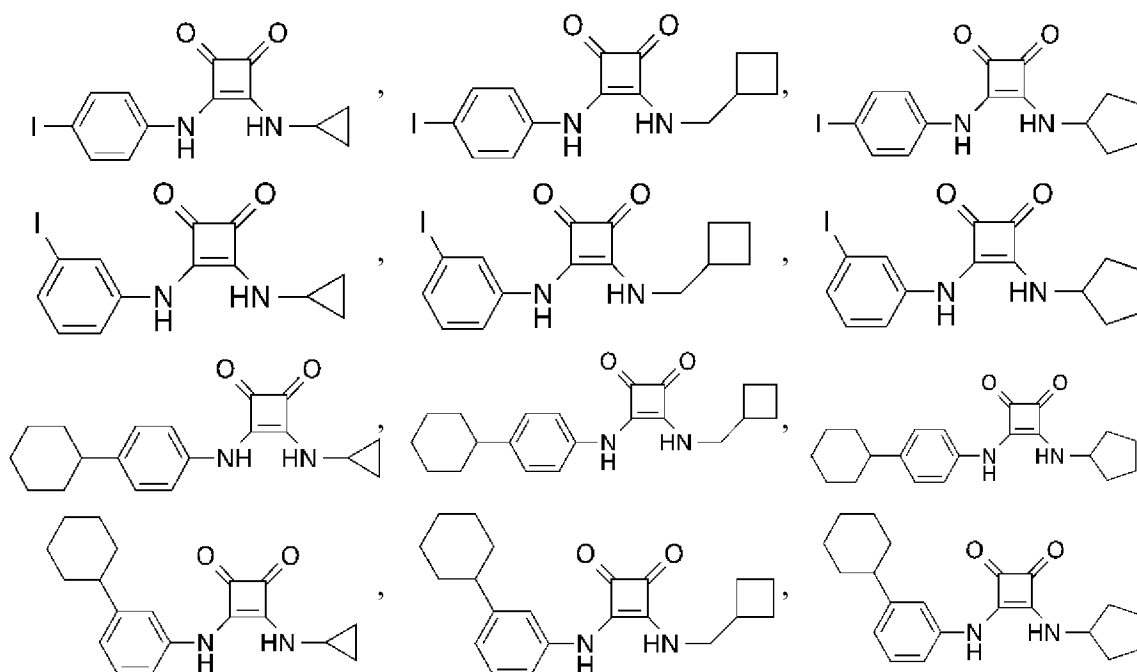
A is optionally substituted with one or more substituents selected from the group of (C₁-C₁₅)alkyl, -O-(C₁-C₁₅)alkyl, -S-(C₁-C₁₅)alkyl, (C₃-C₈)cycloalkyl, -O-(C₃-C₈)cycloalkyl, -S-(C₃-C₈)cycloalkyl, -halo, -NRR, -CN, -C(O)R, -C(O)OR, -C(O)NRR, -NRC(O)R, -NRC(O)OR, -S(O)-R, -S(O)OR, and -S(O)NRR;

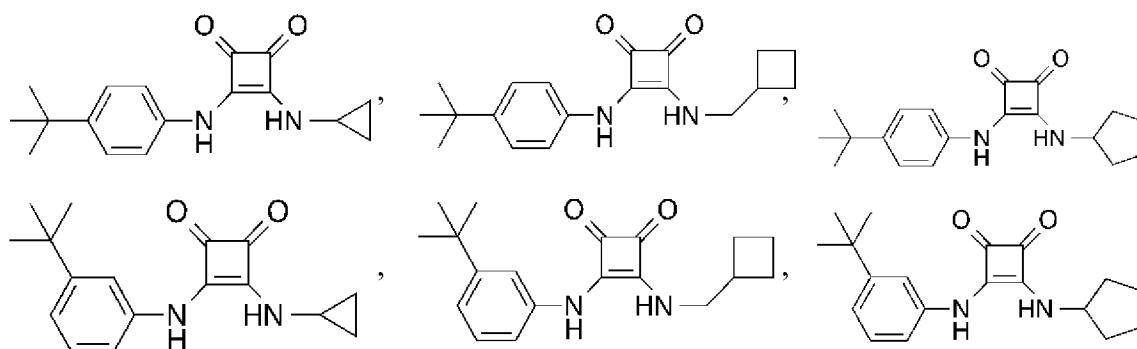
wherein:

each R is independently selected from -H, (C₁-C₁₀)alkyl,

or a pharmaceutically acceptable salt, a prodrug, a tautomer or a solvate thereof.

40. The compound of claim 39, including:





41. A pharmaceutical composition comprising a compound as defined in claim 39 or 40, and a pharmaceutically acceptable carrier.
42. A medicament for use in treating, attenuating, inhibiting and/or preventing inflammation and inflammation-related pathologies, the medicament comprising a compound as defined in claim 39 or 40, and a pharmaceutically acceptable carrier.
43. A medicament for use in treating a condition associated with IL-6 expression, the medicament comprising a compound as defined in claim 39 or 40, and a pharmaceutically acceptable carrier.

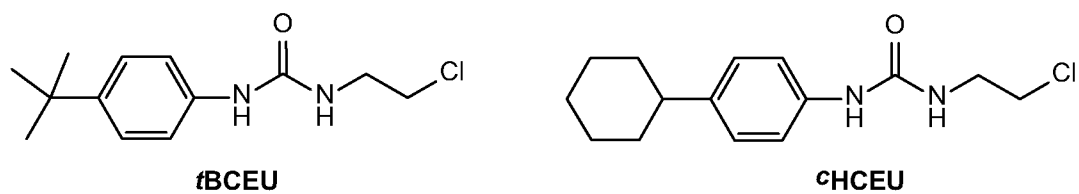


FIG. 1 [PRIOR ART]

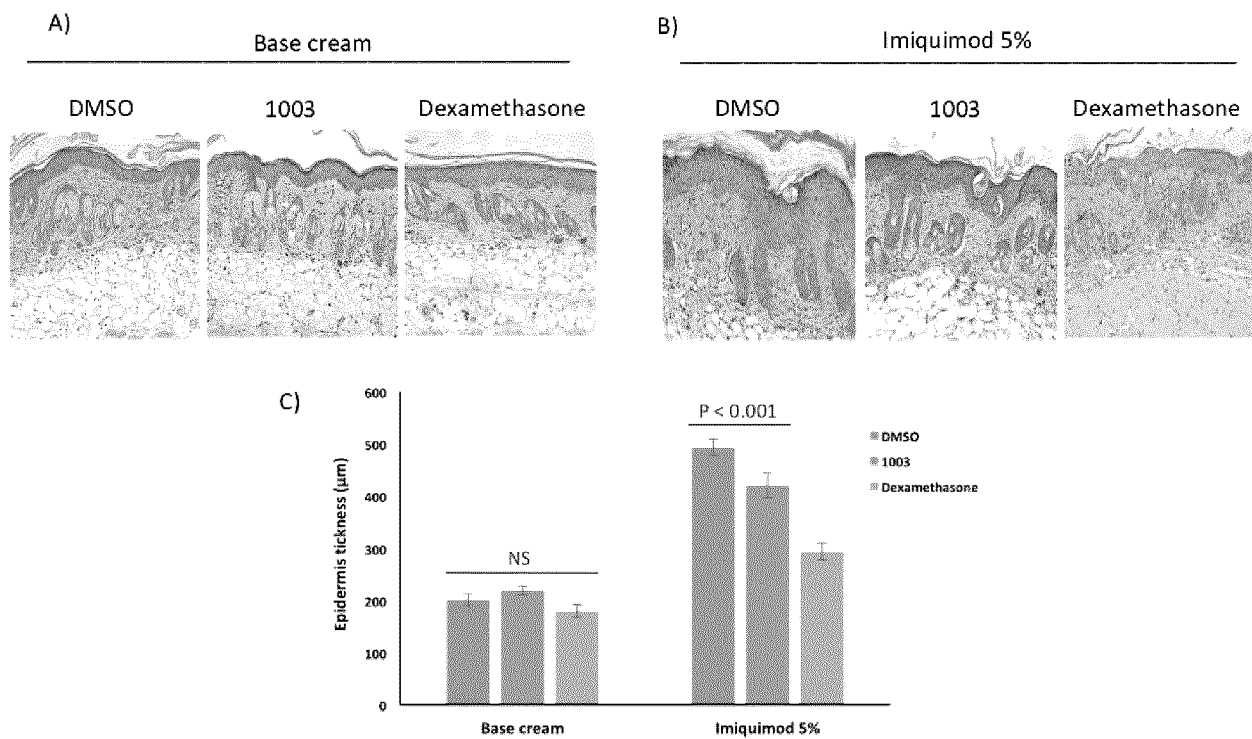


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050721

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07C 275/30** (2006.01), **A61K 31/136** (2006.01), **A61K 31/17** (2006.01), **A61P 29/00** (2006.01),
C07C 225/22 (2006.01), **C07C 275/28** (2006.01), **C07C 335/16** (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: **C07C 275/30** (2006.01), **A61K 31/136** (2006.01), **A61K 31/17** (2006.01), **A61P 29/00** (2006.01),
C07C 225/22 (2006.01), **C07C 275/28** (2006.01), **C07C 335/16** (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

STN Structure Search

Questel: (rene, and gaudreault and urea; rousseau and jean and urea; stephane and gobeil and urea; rousseau and gaudreault and gobeil)

Google: (urea based antiinflammatory)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US20090068699 A1 (SCHILLING, S. et al.) 12 March 2009 (12-03-2009) *see [00249]-[00266]*	1-38
X	WO2014022287 A1 (YIN, H. et al.) 06 February 2014 (06-02-2014) *whole document, in particular Figure 7A*	1-38
X	FLIRI, A. F. et al. Drug effects viewed from a signal transduction network perspective. <i>J. Med. Chem.</i> 2009, 52 (24) 8038-8046. *whole document; CAS 60560-33-0 and CAS 139051-78-8*	1-21

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* "A" "E" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier application or patent but published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	"T" "X" "Y" "&"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
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Date of the actual completion of the international search
02 August 2018 (02-08-2018)

Date of mailing of the international search report
05 September 2018 (05-09-2018)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 819-953-2476

Authorized officer

Karla Randell (819) 635-5133

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050721

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2004063181 A1 (STAVESKI, M.M. et al.) 29 July 2004 (29-07-2004) *whole document*	1-33
X	AU2009221793 B2 (XIA, Y. et al.) 11 September 2009 (11-09-2009) *whole document, D184, D185, D186, D187, D188, D189*	1-33
X	AU2005292152 A1 (FALSEY, J.R. et al.) 13 April 2006 (13-04-2006) *compounds 875-1048*	1-33
X	WO2004014387 A1 (SIMIANER, S. et al.) 19 February 2004 (19-02-2004) *whole document*	1-21
X	WO2016023014 A2 (SHAMJI, A. et al.) 11 February 2016 (11-02-2016) *whole document*	1-33
X	WO2010025043 A1 (WANG, Y.-X. et al.) 04 March 2010 (04-03-2010) *Table 2*	1-33
X	US20040102636 A1 (MILLER, S. et al.) 27 May 2004 (27-05-2004) *whole document*	1-33
X	WO9923091 A1 (REGAN, J. R. et al.) 14 May 1999 (14-05-1999) *Table 1*	1-38
X	LIU, J.-Y. et al. Substituted phenyl groups improve the pharmacokinetic profile and anti-inflammatory effect of urea-based soluble epoxide hydrolase inhibitors in murine models. <i>Eur. J. Pharm. Sci.</i> 2013, 48(4-5), 619-627.	1-38
X	CAS Registry Numbers: 1909234-63-4 12 May 2016 1905824-68-1 08 May 2016 1904711-27-8 06 May 2016 1775894-93-3 08 June 2015 1710417-20-1 22 May 2015 1603132-26-8 12 May 2014 1592909-02-8 29 April 2014 1491204-38-6 09 December 2013 1249766-38-8 31 October 2010 1249723-02-1 31 October 2010 1248898-29-4 01 November 2010 1223517-76-7 14 May 2010 1223311-61-2 14 May 2010 1223196-98-2 14 May 2010 1216808-02-4 05 April 2010 1215482-02-2 01 April 2010 1210140-69-4 16 March 2010 1208456-32-9 10 March 2010 1022099-14-4 23 May 2008 345973-07-1 16 July 2001 197456-33-0 18 November 1997 102-07-8 15 November 1984	1, 8, 15, 22, 29, 30
X	CAS Registry Numbers: 1715585-16-2 29 May 2015 1602073-70-0 11 May 2014 1597802-20-4 06 May 2014 1013308-97-8 10 April 2008 897509-09-0 31 July 2006 680181-69-5 06 May 2004 39964-27-7 16 November 1984	1, 8, 34, 35

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050721**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 1-29, 31-34, 36-38
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The search of the prior art has been limited to a generalization of formulas that have been exemplified, Y is N, Z is N, X is O, S and N-CN. No search has been carried out for the compounds wherein R2 and R3 are taken together. These limitations still resulted in an extremely large number of documents. A selection of the documents is presented herein.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1-38 are directed to compounds of formulas I-V, encompassing urea, thiourea and guanidine derivatives, their uses and pharmaceutical compositions; and
Group B - Claims 39-43 are directed to compounds of formula VI, their uses and pharmaceutical compositions.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.: 1-38

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2018/050721

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
US2009068699A1	12 March 2009 (12-03-2009)	US2009068699A1 US8338120B2 CA2524009C CA2542419C CA2554809C CA2679446C EP1620082B1 EP1620082B9 EP1620091B1 EP1622870A2 EP1675578B1 EP1675578B9 EP1713780B1 EP1961416B1 EP2206496B1 EP2289498A1 EP2481408A2 US7304086B2 US7371871B2 US7381537B2 US7462599B2 US7655684B2 US7732162B2 US7897633B2 US8470781B2 US8685664B2 US8809010B2 US2004229848A1 US2012184518A1 WO2004098591A2 WO2004098625A2 WO2004099134A2 WO2005039548A2 WO2005075436A2 WO2008104580A1	12 March 2009 (12-03-2009) 25 December 2012 (25-12-2012) 29 April 2014 (29-04-2014) 04 June 2013 (04-06-2013) 29 April 2014 (29-04-2014) 17 May 2016 (17-05-2016) 21 April 2010 (21-04-2010) 25 August 2010 (25-08-2010) 31 March 2010 (31-03-2010) 08 February 2006 (08-02-2006) 22 May 2013 (22-05-2013) 25 June 2014 (25-06-2014) 18 January 2012 (18-01-2012) 23 January 2013 (23-01-2013) 17 September 2014 (17-09-2014) 02 March 2011 (02-03-2011) 01 August 2012 (01-08-2012) 04 December 2007 (04-12-2007) 13 May 2008 (13-05-2008) 03 June 2008 (03-06-2008) 09 December 2008 (09-12-2008) 02 February 2010 (02-02-2010) 08 June 2010 (08-06-2010) 01 March 2011 (01-03-2011) 25 June 2013 (25-06-2013) 01 April 2014 (01-04-2014) 19 August 2014 (19-08-2014) 18 November 2004 (18-11-2004) 19 July 2012 (19-07-2012) 18 November 2004 (18-11-2004) 18 November 2004 (18-11-2004) 18 November 2004 (18-11-2004) 06 May 2005 (06-05-2005) 18 August 2005 (18-08-2005) 04 September 2008 (04-09-2008)
WO2014022287A1	06 February 2014 (06-02-2014)	WO2014022287A1 EP2879669A1 EP2879669A4 US2015251987A1 US9517993B2	06 February 2014 (06-02-2014) 10 June 2015 (10-06-2015) 13 April 2016 (13-04-2016) 10 September 2015 (10-09-2015) 13 December 2016 (13-12-2016)
WO2004063181A1	29 July 2004 (29-07-2004)	WO2004063181A1 AU2003303678A1 US2004180871A1 US7186725B2	29 July 2004 (29-07-2004) 10 August 2004 (10-08-2004) 16 September 2004 (16-09-2004) 06 March 2007 (06-03-2007)

Continued on extra sheet

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050721

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
AU2009221793A1	11 September 2009 (11-09-2009)	AU2009221793A1 AU2009221793B2 CA2718170A1 EP2187893A2 EP2564857B1 EP3246034A1 US8039450B2 US8461135B2 US8461336B2 US9012431B2 US9416146B2 US2016318955A1 WO2009111676A2 WO2009111676A8 WO2010028005A1	11 September 2009 (11-09-2009) 19 February 2015 (19-02-2015) 11 September 2009 (11-09-2009) 26 May 2010 (26-05-2010) 03 May 2017 (03-05-2017) 22 November 2017 (22-11-2017) 18 October 2011 (18-10-2011) 11 June 2013 (11-06-2013) 11 June 2013 (11-06-2013) 21 April 2015 (21-04-2015) 16 August 2016 (16-08-2016) 03 November 2016 (03-11-2016) 11 September 2009 (11-09-2009) 30 September 2010 (30-09-2010) 11 March 2010 (11-03-2010)
AU2005292152A1	13 April 2006 (13-04-2006)	AU2005292152A1 AU2005292152B2 CA2582029A1 CA2582029C EP1836174A2 EP1836174B1 ES2405783T3 JP2008515812A JP5134368B2 MX2007003784A US2007054916A1 WO2006039718A2 WO2006039718A3	13 April 2006 (13-04-2006) 12 August 2010 (12-08-2010) 13 April 2006 (13-04-2006) 06 December 2011 (06-12-2011) 26 September 2007 (26-09-2007) 27 February 2013 (27-02-2013) 03 June 2013 (03-06-2013) 15 May 2008 (15-05-2008) 30 January 2013 (30-01-2013) 24 April 2007 (24-04-2007) 08 March 2007 (08-03-2007) 13 April 2006 (13-04-2006) 13 July 2006 (13-07-2006)
WO2004014387A1	19 February 2004 (19-02-2004)	WO2004014387A1 AU2003256410A1 AU2003256410A8 CA2497448A1 EP1530477A1 JP2006501218A US2004110755A1 US2007099832A1	19 February 2004 (19-02-2004) 25 February 2004 (25-02-2004) 25 February 2004 (25-02-2004) 19 February 2004 (19-02-2004) 18 May 2005 (18-05-2005) 12 January 2006 (12-01-2006) 10 June 2004 (10-06-2004) 03 May 2007 (03-05-2007)
WO2016023014A2	11 February 2016 (11-02-2016)	WO2016023014A2 WO2016023014A3 AU2015300782A1 CA2955082A1 EP3177295A2 EP3177295A4 US2017224700A1	11 February 2016 (11-02-2016) 11 August 2016 (11-08-2016) 02 February 2017 (02-02-2017) 11 February 2016 (11-02-2016) 14 June 2017 (14-06-2017) 13 June 2018 (13-06-2018) 10 August 2017 (10-08-2017)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA2018/050721

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
WO2010025043A1	04 March 2010 (04-03-2010)	WO2010025043A1 AR073233A1 TW201010994A US2010063583A1	04 March 2010 (04-03-2010) 20 October 2010 (20-10-2010) 16 March 2010 (16-03-2010) 11 March 2010 (11-03-2010)
US2004102636A1	27 May 2004 (27-05-2004)	US2004102636A1 US7517880B2 US2009093526A1 US2012270878A1	27 May 2004 (27-05-2004) 14 April 2009 (14-04-2009) 09 April 2009 (09-04-2009) 25 October 2012 (25-10-2012)
WO9923091A1	14 May 1999 (14-05-1999)	WO9923091A1 AU1367599A CA2308428A1 EP1028953A1 EP1473292A1 JP2001521934A US6080763A US6228881B1 US2001039290A1 US6432995B2	14 May 1999 (14-05-1999) 24 May 1999 (24-05-1999) 14 May 1999 (14-05-1999) 23 August 2000 (23-08-2000) 03 November 2004 (03-11-2004) 13 November 2001 (13-11-2001) 27 June 2000 (27-06-2000) 08 May 2001 (08-05-2001) 08 November 2001 (08-11-2001) 13 August 2002 (13-08-2002)