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(54) Title: COMPOSITIONS, PROCESS OF PREPARATION OF SAID COMPOSITIONS AND METHOD OF TREATING INFLAMMATORY DISEASES

(57) Abstract: The present disclosure describes a composition and a kit having a plurality of compounds for use in the treatment of inflammatory joint diseases and chronic inflammatory connective tissue diseases, such as Rheumatoid Arthritis (RA). The disclosure also relates to a process of obtaining the composition and the method of treating diseases by administration of the compositions.



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**COMPOSITIONS, PROCESS OF PREPARATION OF SAID
COMPOSITIONS AND METHOD OF TREATING INFLAMMATORY
DISEASES**

CROSS REFERENCE

[0001] This application claims priority to Indian Provisional Patent Application No. 662/CHE/2011, filed on March 14, 2011, which is incorporated by reference herein in its entirety.

INCORPORATION BY REFERENCE

[0002] Every patent, patent application, and non-patent publication recited herein is incorporated by reference in its entirety as if each patent, patent application, and non-patent publication had been incorporated by reference individually.

TECHNICAL FIELD

[0003] Embodiments of the invention disclosed herein describe compositions and kits, each containing compounds for use in the treatment of inflammatory joint diseases and chronic inflammatory connective tissue diseases, such as Rheumatoid Arthritis (RA). The invention also provides processes for obtaining the compositions and methods of treatment by administration of the compositions.

BACKGROUND OF THE DISCLOSURE

[0004] Joint disease includes any of the diseases or injuries that affect human joints. Arthritis is a generic term for inflammatory joint disease. Inflammation of the joints may cause pain, stiffness, swelling, and some redness of the skin about the joint. Inflammation may be of such nature and severity as to destroy the joint cartilage and underlying bone and cause irreparable deformities, also resulting in loss of mobility (ankylosis). Synovitis occurs when the inflammation is restricted to the lining of the joints. Arthralgias, which is pain in the joints, is a key symptom of Rheumatism that refers to all manners of discomfort of the articular apparatus including joints, bursas, ligaments and tendons. Inflammation of spinal joints is called spondylitis. Bursitis is the inflammation of the lubricating sac or bursa over a joint or between tendons and muscles or bones. Rheumatoid arthritis (RA) and juvenile RA (JRA) are the key diseases in this class of inflammatory joint diseases. The allied arthritic diseases also

include psoriatic arthritis, ankylosing spondylitis, infectious arthritis including osteomyelitis, reactive arthritis; intestinal diseases including ulcerative colitis, inflammatory bowel disease (IBD) and the like.

[0005] Connective tissue diseases are those with abnormalities in the collagen containing connective tissues. These are systemic diseases and are also frequently accompanied by joint problems. Systemic lupus erythematosus (SLE) may affect any structure or organ of the body, but has commonality with Rheumatoid arthritis due to the presence of rheumatoid factor. Scleroderma is another collagen disease in which the skin becomes thickened and tight. Rheumatic fever is often classified as a connective tissue disease with transient manifestations of joint issues seen in RA.

[0006] Rheumatoid arthritis (RA) is one of the most common rheumatic diseases. Features of RA are bilateral tender, warm, swollen joints, joint inflammation, fatigue, occasional fever, long-lasting pain and stiffness in the morning. In RA, the immune system attacks cells within the joint capsule leading to an autoimmune inflammation called synovitis.

[0007] In addition to the local inflammation of the joints, patients in such inflammatory diseases exhibit an increased frequency of cardiovascular disease caused by an associated vasculitis [Bacon, P. A. et al.]. The role of endothelial cell dysfunction is established in the cardiovascular mortality of RA patients. [Bacon PA et al., Int. Rev. Immunol. 2002, 21(1): 1-17]. Endothelial dysfunction causes changes in endothelial dependent vasodilatation. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. [Hurlimann, D. et al., Circulation 2002; 106(17): 2184-2187].

[0008] Medications commonly used to treat such diseases provide relief from pain and inflammation. Reduction of pain, swelling, and inflammation is reached by treatment with analgesics (e.g. acetaminophen) and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs, e.g. ibuprofen, celecoxib and rofecoxib). To alter the course of the disease, Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are used (e.g. gold (Myochrysine), antimalarials (Plaquenil), penicillamine (Depen)). Corticosteroids such as prednisone and methylprednisolone are also used because of their anti-inflammatory and immunosuppressive effects.

[0009] Several types of drugs currently utilized to treat patients with rheumatoid arthritis include analgesics, corticosteroids, uric acid-lowering drugs,

immunosuppressive drugs, non-steroidal anti-inflammatory drugs (“NSAIDs”), and disease-modifying anti-rheumatic drugs (“DMARDs”).

[0010] NSAIDs and DMARDs are the most commonly prescribed drugs. NSAIDs are usually the first drugs prescribed and the most commonly used. NSAIDs have a number of serious side effects, but compared to other alternatives are generally well-tolerated by patients at least on an acute basis. DMARDs such as gold and penicillamine are used in patients with more advanced disease and have a higher incidence of toxicity.

[0011] Although NSAIDs are efficacious in reducing pain, they have little or no effect on the underlying disease and therefore cannot prevent progression of joint destruction or organ damage. The effects of NSAIDs are relatively rapid, occurring over a period of a few hours. Once the drug is stopped, however, the benefits of its use rapidly fade. There are a number of side effects associated with use of NSAIDs and they are usually dose-related. Even with over-the-counter NSAIDs, problematic side effects which include the following: gastrointestinal tract irritation (including ulcers), skin reactions and rashes, increases in blood coagulation time, hepatocellular toxicity, and impaired renal function. Aspirin, a commonly prescribed NSAID for RA patients can induce other problems like hypersensitivity responses, tinnitus, and with overdoses may precipitate central nervous system disorders including coma.

[0012] Unlike NSAIDs, the DMARDs are thought to have some effect on altering the progression of RA. In general, DMARDs are employed prior to destructive changes in bones or joints. DMARDs include antimalarial drugs, gold compounds, penicillamine, and sulfasalazine and newer biologics. Further, in contrast to NSAIDs, DMARDs are slower acting and may take weeks or months for benefits of the drug to be noted. Because of this delayed action, some patients prematurely quit the drug because of the perception that the drug is not working. At the proper dosage and with continuous use, a significant reduction in the symptoms of RA may occur in some patients. In some instances, complete remission of RA may also occur. Generally, in the average RA patient, DMARDs are only somewhat effective in at least moderate suppression of symptoms. Unfortunately, some patients do not respond and have had continued active and progressive disease despite taking such drugs. On the contrary, if a particular patient experiences a clinical benefit but discontinues the DMARD, the symptoms of the disease are likely to return gradually. Due to the toxicity of DMARDs, patients receiving such medications need to be careful and frequently be

re-evaluated by their physicians. All of the DMARDs have significant side effects and include the following: retinal toxicity with the anti-malarial drugs, dermatitis or other skin rashes, nausea, diarrhea and various types of anemia.

[0013] Thus, the treatment options for patients with inflammatory joint diseases are limited, particularly so in the case of drugs that can have some effect on altering the progression of such diseases, as opposed to treating symptoms. Since RA is a heterogeneous disease, the patient responses to standard treatments are variable.

[0014] Most recent clinical trials of newer DMARDs alone and in combination with methotrexate have shown that ACR50 response – which includes reducing the signs and symptoms of disease by 50%, according to criteria established by the American College of Rheumatology (ACR) – was achieved in less than two-thirds of the patients.

[0015] Typically, clinicians have reserved biologics for those patients with severe disease who have failed other therapies. However, the emerging body of evidence suggests that practitioners should be moving toward treating early disease with these biologics.

SUMMARY OF THE INVENTION

[0016] In some embodiments, the invention provides a composition comprising: a) two or three of: i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; ii) an inhibitor of phosphodiesterase 5; and iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and b) optionally a pharmaceutically-acceptable excipient.

[0017] In some embodiments, the invention provides a kit comprising: two or three of: i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; ii) an inhibitor of phosphodiesterase 5; and iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and b) optionally a pharmaceutically-acceptable excipient, wherein the kit comprises one or a plurality of dosage forms.

[0018] In some embodiments, the invention provides a method for treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, the method comprising administering to the subject two or three of: a) a therapeutically-effective amount of an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response

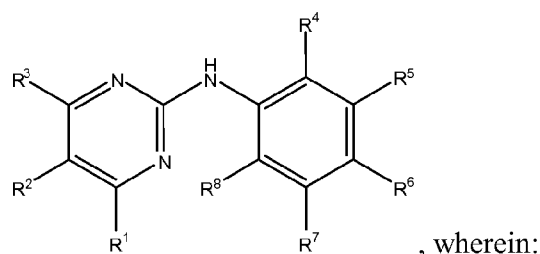
pathways; b) a therapeutically-effective amount of an inhibitor of phosphodiesterase 5; and c) a therapeutically-effective amount of an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, wherein the administration uses one or a plurality of dosage forms, each dosage form comprising one or more inhibitors, and wherein each dosage form optionally further comprises a pharmaceutically-acceptable excipient.

[0019] In some embodiments, the invention provides a use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[0020] In some embodiments, the invention provides a combination of compounds for use in the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[0021] In some embodiments, the invention provides a composition comprising: a) two or three of:

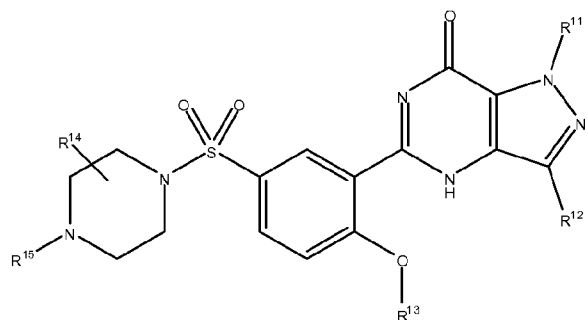
i) a compound of the formula (I):



- R^1 is a cyclic group that is substituted or unsubstituted; R^2 and R^3 are each independently hydrogen or alkyl; one or two of the groups R^4 , R^5 , R^6 , R^7 , and R^8 are each nitro, alkoxy, fluoro-substituted alkoxy, or a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein: R^9 is hydrogen or alkyl; X is oxo, thio, $=NH$, $=N(alkyl)$, $=NOH$, or $=NO(alkyl)$; Y is oxygen, NH , or $N(alkyl)$; n is 0 or 1; and R^{10} is an alkyl group or a cyclic group, and the remaining groups R^4 , R^5 , R^6 , R^7 , and R^8 are each independently: hydrogen; alkyl that is unsubstituted or substituted by amino, alkyl

amino, or dialkyl amino; a heterocycle; acyl; trifluoromethyl; hydroxyl; alkoxy; amino; alkyl amino; dialkyl amino; amido; carbamato; a carboxylic acid; or an ester group, or a pharmaceutically-acceptable salt thereof;

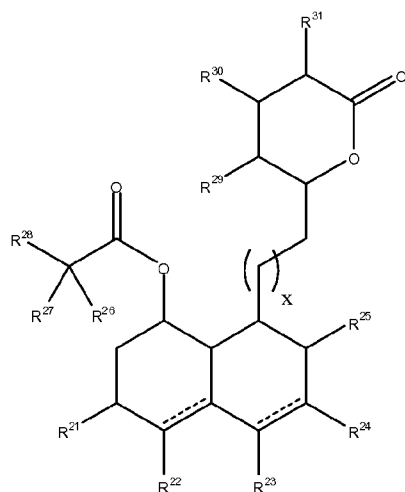
ii) a compound of the formula (II) or tautomer thereof:



, wherein:

R^{11} is H, C1-C3 alkyl, C3-C5 cycloalkyl or C1-C3 perfluoroalkyl; R^{12} is H, C1-C6 alkyl optionally substituted by OH, C1-C3 alkoxy or C3-C6 cycloalkyl, or C1-C3 perfluoroalkyl; R^{13} is C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, C3-C7 cycloalkyl, C1-C6 perfluoroalkyl or (C3-6 cycloalkyl)C1-C6 alkyl; R^{14} is H, C1-C4 alkyl, C1-C3 alkoxy, $NR^{16}R^{17}$, or $CONR^{16}R^{17}$; R^{15} is H, C1-C6 alkyl, (C1-C3 alkoxy)C2-C6 alkyl, hydroxy C2-C6 alkyl, $(R^{16}R^{17}N)C2-C6$ alkyl, $(R^{16}R^{17}NCO)C1-C6$ alkyl, $CONR^{16}R^{17}$, $CSNR^{16}R^{17}$ or $C(NH)NR^{16}R^{17}$; R^{16} and R^{17} are each independently H, C1-C4 alkyl, (C1-C3 alkoxy)C2-C4 alkyl or hydroxy C2-C4 alkyl, or a pharmaceutically-acceptable salt thereof;

iii) a compound of the formula (III):



, wherein:

each of R^{21} , R^{22} , R^{23} , R^{24} , and R^{25} is independently H, alkyl, hydroxyl, alkoxy, or an ester group; each of R^{26} , R^{27} , and R^{28} is independently H, alkyl, hydroxyl, alkoxy, amino, alkyl amino, dialkyl amino, or an ester group; each of R^{29} , R^{30} , and R^{31} is

independently H, alkyl, halogen, hydroxyl, alkoxy, amino, alkyl amino, dialkyl amino, or an ester group; x is 0, 1, 2, 3, 4, 5, or 6; and each  is independently either a single or double bond, or a pharmaceutically-acceptable salt thereof; and b) optionally a pharmaceutically-acceptable excipient.

BRIEF DESCRIPTION OF THE FIGURES

[0022] **Figure 1** illustrates schematics of scientific rationale.

[0023] **Figure 2** illustrates drugs of the present disclosure and their various biochemical targets.

[0024] **Figure 3** illustrates the efficacy of individual drugs CW299, CW305, and CW302 and the combination drug efficacy in terms of ACR Score in TNF responders.

[0025] **Figure 4** illustrates the efficacy of individual drugs CW299, CW305, and CW302 and the combination drug efficacy in terms of ACR score in a TNF resistive system (anti-TNF non responders).

[0026] **Figure 5** illustrates the comparison of the efficacy of combination of the compounds on clinical parameters of Swollen joints, Tender joints, CRP and Pain, of the present disclosure in TNF responders with two known/existing drugs. One is Etanercept (ENBREL®), which is approved and is currently a market leader. The other is CP-690,550 (also known as tofacitinib, or tasocitinib) a promising candidate in late phase clinical trials for Rheumatoid Arthritis.

[0027] **Figure 6** illustrates the comparison of the efficacies of two known drugs (Etanercept and CP-690,550) with those of combinations of compounds of the disclosure on clinical parameters of Swollen joints, Tender joints, CRP and Pain, in TNF non-responder system

[0028] **Figure 7** illustrates efficacy data of three individual drugs and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF responders.

[0029] **Figure 8** illustrates efficacy data of three individual drugs and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF responders.

[0030] **Figure 9** illustrates efficacy data of three individual drugs and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF responders.

[0031] **Figure 10** illustrates efficacy data of three individual drugs and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF non-responders.

[0032] **Figure 11** illustrates efficacy data of three individual drugs and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF non-responders.

[0033] **Figure 12** illustrates efficacy data of three individual drugs and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF non-responders.

[0034] **Figure 13** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain, in TNF responders.

[0035] **Figure 14** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain, in TNF responders.

[0036] **Figure 15** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain, in TNF responders.

[0037] **Figure 16** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain, in TNF responders.

[0038] **Figure 17** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF resistant (anti-TNF nonresponsive) system.

[0039] **Figure 18** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF resistant (anti-TNF nonresponsive) system.

[0040] **Figure 19** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF resistant (anti-TNF nonresponsive) system.

[0041] **Figure 20** compares the efficacy of individual drugs (CW299, CW305, CW302) and combinations thereof across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF resistant (anti-TNF nonresponsive) system.

[0042] **Figure 21** illustrates efficacy data of individual drugs (CW299 and CW305) and combinations thereof in terms of ACR Score in TNF responders.

[0043] **Figure 22** illustrates efficacy data of individual drugs (CW299 and CW305) and combinations thereof in terms of ACR Score in TNF resistive system (anti-TNF non responders).

[0044] **Figure 23** compares the efficacy of a combination of compounds (CW299 and CW305) across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF responders.

[0045] **Figure 24** compares the efficacy of a combination of compounds (CW299 and CW305) across clinical parameters of Swollen joints, Tender joints, CRP and Pain in a TNF resistive system (anti-TNF non responders).

[0046] **Figure 25** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF responders.

[0047] **Figure 26** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF responders.

[0048] **Figure 27** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF responders.

[0049] **Figure 28** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF resistive system (anti-TNF non responders).

[0050] **Figure 29** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF resistive system (anti-TNF non responders).

[0051] **Figure 30** compares the efficacy data of individual drugs (CW299 and CW305) and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF resistive system (anti-TNF non responders).

[0052] **Figure 31** illustrates efficacy data of individual drugs (CW305 and CW302) and combinations thereof in terms of ACR Score in TNF responders.

[0053] **Figure 32** illustrates efficacy data of individual drugs (CW305 and CW302) and combinations thereof in terms of ACR Score in TNF resistive system (anti-TNF non responders).

[0054] **Figure 33** compares the efficacy of a combination of CW305 and CW302 across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF responders.

[0055] **Figure 34** compares the efficacy of a combination of CW305 and CW302 across clinical parameters of Swollen joints, Tender joints, CRP and Pain in a TNF resistive system (anti-TNF non responders).

[0056] **Figure 35** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF responders.

[0057] **Figure 36** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF responders.

[0058] **Figure 37** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF responders.

[0059] **Figure 38** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF resistive system (anti-TNF non responders).

[0060] **Figure 39** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF resistive system (anti-TNF non responders).

[0061] **Figure 40** compares the efficacy data of individual drugs (CW305 and CW302) and combinations thereof for the chemokine biomarker CCL2 (otherwise called as MCP1 - monocyte chemotactic protein 1) in TNF resistive system (anti-TNF non responders).

[0062] **Figure 41** illustrates efficacy data of individual drugs (CW299 and CW302) and combinations thereof in terms of ACR Score in TNF responders.

[0063] **Figure 42** illustrates efficacy data of individual drugs (CW299 and CW302) and combinations thereof in terms of ACR Score in TNF resistive system (anti-TNF non responders).

[0064] **Figure 43** compares the efficacy of a combination of CW299 and CW302 across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF responders.

[0065] **Figure 44** compares the efficacy of a combination CW299 and CW302 across clinical parameters of Swollen joints, Tender joints, CRP and Pain in TNF resistive system (anti-TNF non responders).

[0066] **Figure 45** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF responders.

[0067] **Figure 46** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF responders.

[0068] **Figure 47** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in TNF responders.

[0069] **Figure 48** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the cytokine biomarker IL6 (Interleukin 6) in TNF resistive system (anti-TNF non responders).

[0070] **Figure 49** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the cytokine biomarker TNF- α (tumor necrosis factor alpha) in TNF resistive system (anti-TNF non responders).

[0071] **Figure 50** compares the efficacy data of individual drugs (CW299 and CW302) and combinations thereof for the chemokine biomarker CCL2 (also called as MCP1 - monocyte chemotactic protein 1) in a TNF resistive system (anti-TNF non responders).

[0072] **Figure 51** compares the efficacy data of drug combinations (CW299302, CW305302, and CW299305) with Etanercept and CP-690,550 in RA in TNF responders, across clinical parameters of Swollen joints, Tender joints, CRP and Pain.

[0073] **Figure 52** compares the efficacy data of drug combinations (CW299302, CW305302, CW299305) with Etanercept and CP-690,550 in RA in TNF resistive system (anti-TNF non responders), across clinical parameters of Swollen joints, Tender joints, CRP and Pain.

[0074] **Figure 53** compares the efficacy data in terms of Arthritis Mean Score for CW299305302 versus placebo (untreated animal) in a Collagen-Induced Arthritis (CIA) Animal Model with an Early-Mid Disease Therapeutic setting.

[0075] **Figure 54** compares the efficacy data in terms of Arthritis Mean Score for CW299305302 versus placebo (untreated animal) in a Collagen Induced Arthritis (CIA) Animal Model with a High bar - Advanced Disease Therapeutic setting.

[0076] **Figure 55** compares the efficacy data in terms of Predictive ACR score for CW299305302 versus CW299.

[0077] **Figure 56** compares the efficacy data in terms of Arthritis Mean score for CW299305302 versus CW299 in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0078] **Figure 57** compares the efficacy data in terms of Arthritis Mean score for CW299305302; CW299; and placebo (untreated animal) in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0079] **Figure 58** compares the efficacy data in terms of Predictive ACR score for CW299305302 versus CW299.

[0080] **Figure 59** compares the efficacy data in terms of Arthritis Mean score for CW299305302 versus CW299 in a Collagen Induced Arthritis Animal Model with a High bar - Advanced Disease Therapeutic setting.

[0081] **Figure 60** compares the efficacy data in terms of Arthritis Mean score CW299305302; CW299; and placebo (untreated animal) in a Collagen Induced Arthritis Animal Model with a High bar - Advanced Disease Therapeutic setting.

[0082] **Figure 61** compares the efficacy in terms of histo-pathological data regarding the effect of CW299305302 on Synovitis versus placebo (untreated animal) in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0083] **Figure 62** compares the efficacy in terms of histo-pathological data regarding the effect of CW299305302 on Pannus formation versus placebo (untreated animal) in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0084] **Figure 63** compares the efficacy in terms of histo-pathological data regarding the effect of CW299305302 on Cartilage degradation versus placebo (untreated animal) in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0085] **Figure 64** compares the efficacy in terms of histo-pathological data regarding the effect of CW299305302 on Bone degradation versus placebo (untreated animal) in

a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0086] **Figure 65** compares the efficacy in terms of predictive ACR Score of three combinations (CW299302, CW299305, and CW305302), each combination containing two drugs, versus that of CW299305302 in TNF responders.

[0087] **Figure 66** compares the efficacy in terms of Arthritis score of three combinations (CW299302, CW299305 & CW305302), each combination containing two drugs, versus that of CW299305302 in a Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0088] **Figure 67** compares the efficacy in terms of Arthritis score between CW299305302 with Standard of Care (SOC) Etanercept (ENBREL®) in Collagen Induced Arthritis Animal Model with an Early-Mid Disease Therapeutic setting.

[0089] **Figure 68** shows that the three drug combination showed comparable or higher percentage of efficacy in decreasing the disease than did Etanercept.

DETAILED DESCRIPTION OF DISCLOSURE

[0090] In some embodiments, the invention provides a composition comprising: a) two or three of: i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; ii) an inhibitor of phosphodiesterase 5; and iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and b) optionally a pharmaceutically-acceptable excipient.

[0091] In some embodiments, the invention provides a kit comprising: two or three of: i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; ii) an inhibitor of phosphodiesterase 5; and iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and b) optionally a pharmaceutically-acceptable excipient, wherein the kit comprises one or a plurality of dosage forms..

[0092] The invention disclosed herein provides combinations of three classes of drugs, which exhibit converging antagonistic effects on major pro-inflammatory transcription factors through different mechanisms of action. Inhibition of factors such as NFkB and AP1 causes a systemic reduction in the pro-inflammatory cytokines and chemokines that are involved in disease physiology and progression. In addition to targeting multiple pathways and nodes, the drug combinations target multiple cell

types. In some embodiments, the inhibition of multiple pathways in multiple cell types provides a systemic effect, even at low drug concentrations.

[0093] The drug combinations provided herein are effective in TNF resistive systems (anti-TNF non-responders), because the three drug compounds affect diverse (TNF independent) strategic signaling points distributed across three distinct pathways in the relevant cell systems. This phenomenon allows even minor inhibitory effects from each strategic point to produce an enhanced inhibitory effect upon convergence of the minor effects, thereby amplifying the effect on the pool of biomarkers secreted from the various cell types present in the synovium.

[0094] The CW299 class of drugs can inhibit multiple cell types, including, for example, Macrophages, B-Lymphocytes, T-Lymphocytes, Mast cells, Synovial Fibroblasts, Endothelial cells, Chondrocytes, Dendritic cells, Osteoclasts and Osteoblasts. CW299 can function by inhibiting one or more of macrophage colony stimulating factor (CSF1), platelet derived growth factor (PDGFR), T-cell response (TCR) and B-cell response (BCR) pathways. In some embodiments, CW299 inhibits all of colony stimulating factor (CSF1), platelet derived growth factor (PDGFR), T-cell response (TCR) and B-cell response (BCR) pathways. In some embodiments, CW299 is an inhibitor of colony stimulating factor (CSF1), platelet derived growth factor (PDGFR), T-cell response (TCR) and B-cell response (BCR) pathways.

[0095] The CW305 class of drugs can inhibit the enzyme phosphodiesterase 5 (PDE5). PDE5 degrades cyclic GMP (cGMP), and inhibition of PDE5 interferes with the degradation of cGMP, thereby increasing the levels of cyclic GMP (cGMP) in different cell systems. The increase in GMP can induce anti-inflammatory effects. In some embodiments, CW305 is an inhibitor of PDE5.

[0096] The CW302 class of drugs can inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, a rate-limiting enzyme in the cholesterol bio-synthesis pathway. Inhibition of HMG CoA reductase effects inhibition of the geranylation and farnesylation of the key kinase and regulatory proteins including MAP kinase family of enzymes. In some embodiments, CW302 is an inhibitor of HMG CoA reductase.

[0097] As used herein, the term, "CW299305302," refers to a combination of any CW299 compound, any CW305 compound, and any CW302 compound in any amount, ratio, concentration, or order thereof.

[0098] As used herein, the term, “CW299302,” refers to a combination of any CW299 compound, and any CW302 compound in any amount, ratio, concentration, or order thereof.

[0099] As used herein, the term, “CW299305,” refers to a combination of any CW299 compound and any CW305 compound in any amount, ratio, concentration, or order thereof.

[00100] As used herein, the term, “CW302305,” and the term, “CW305302,” refer to a combination of any CW305 compound and any CW302 compound in any amount, ratio, concentration, or order thereof.

[00101] Non-limiting examples of CW299 include: a) Imatinib or a pharmaceutically-acceptable salt thereof, such as Imatinib Mesylate; b) Sti-571 or a pharmaceutically-acceptable salt thereof; c) Nilotinib or a pharmaceutically-acceptable salt thereof; d) Dasatinib or a pharmaceutically-acceptable salt thereof; e) Sunitinib or a pharmaceutically-acceptable salt thereof, such as Sunitinib malate; f) Masitinib or a pharmaceutically-acceptable salt thereof, such as masitinib mesylate; g) Bosutinib or a pharmaceutically-acceptable salt thereof; h) Ponatinib or a pharmaceutically-acceptable salt thereof; i) Bafetinib or a pharmaceutically-acceptable salt thereof; j) CYC10268 or a pharmaceutically-acceptable salt thereof, and any combination thereof.

[00102] Non-limiting examples of CW305 include: a) Sildenafil or a pharmaceutically-acceptable salt thereof, such as Sildenafil Citrate; b) Udenafil or a pharmaceutically-acceptable salt thereof; c) Vardenafil or a pharmaceutically-acceptable salt thereof; d) Tadalafil or a pharmaceutically-acceptable salt thereof; e) Avanafil or a pharmaceutically-acceptable salt thereof, and any combination thereof.

[00103] Non-limiting examples of CW302 include: a) Fluvastatin or a pharmaceutically-acceptable salt thereof, such as Fluvastatin sodium; b) Atorvastatin or a pharmaceutically-acceptable salt thereof, such as Atorvastatin calcium; c) Simvastatin or a pharmaceutically-acceptable salt thereof; d) Lovastatin or a pharmaceutically-acceptable salt thereof; e) Mevastatin or a pharmaceutically-acceptable salt thereof; f) Pravastatin or a pharmaceutically-acceptable salt thereof, such as Pravastatin Sodium; g) Rosuvastatin or a pharmaceutically-acceptable salt thereof, such as Rosuvastatin calcium; h) Pitavastatin or a pharmaceutically-acceptable salt thereof; or i) Cerivastatin or a pharmaceutically-acceptable salt thereof, and any combination thereof.

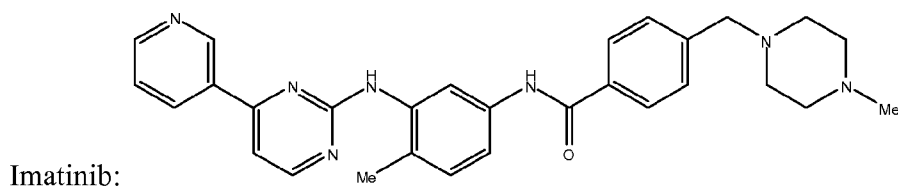
[00104] Non-limiting examples of CW299 include the compounds of Table 1.

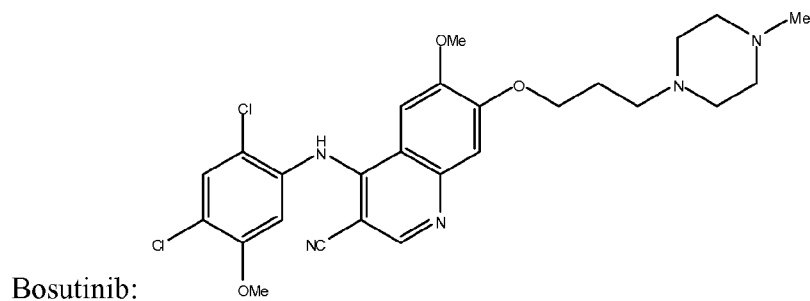
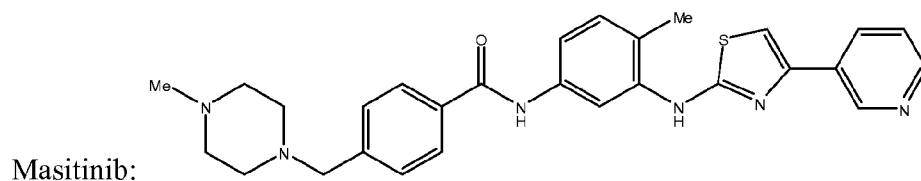
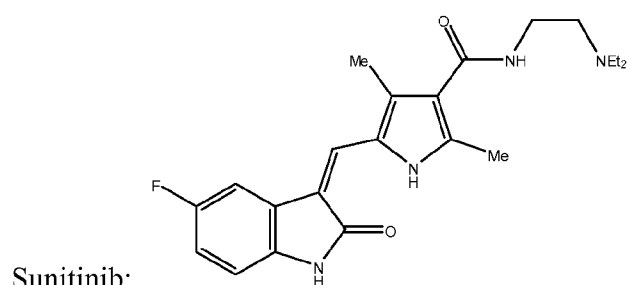
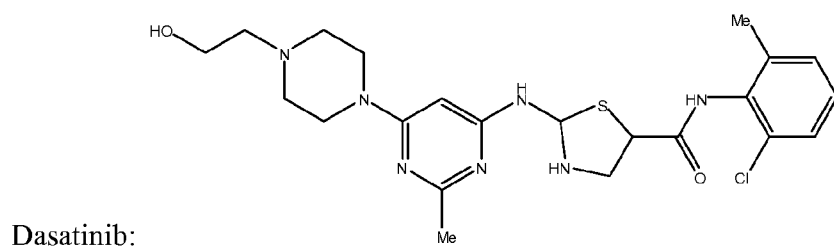
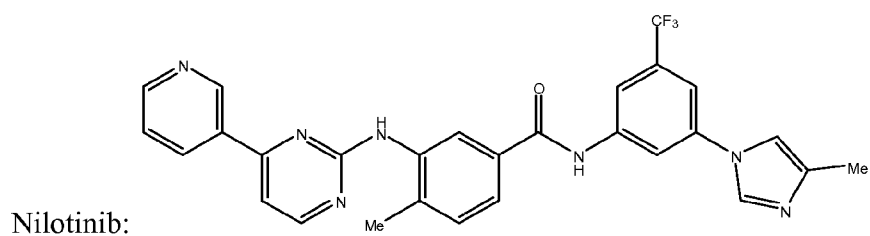
Table 1: CW299 Compound Names.

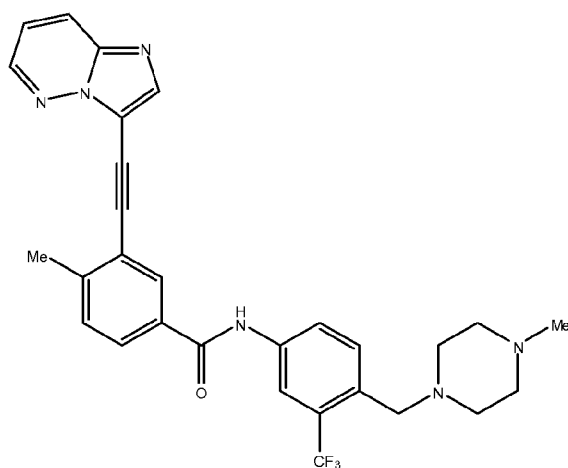
<u>Compound</u>	<u>Synonyms</u>	<u>Exemplary Salts</u>	<u>IUPAC Nomenclature</u>
Imatinib		Imatinib Mesylate (Imatinib Methansulfonate)	N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-4-[(4-methylpiperazin-1-yl)methyl]benzamide
Sti-571			N-(4-methyl-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}phenyl)-4-[(4-methylpiperazin-1-yl)methyl]benzamide
Nilotinib	AMN-107; AMN107		4-methyl-N-[3-(4-methyl-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl]-3-{[4-(pyridin-3-yl)pyrimidin-2-yl]amino}benzamide
Dasatinib	BMS-354825		N-(2-chloro-6-methylphenyl)-2-({6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-yl} amino)-1,3-thiazole-5-carboxamide
Sunitinib	SU11248; Sutent	Sunitinib malate	N-[2-(diethylamino)ethyl]-5-{[(3Z)-5-fluoro-2-oxo-2,3-dihydro-1H-indol-3-ylidene]methyl}-2,4-dimethyl-1H-pyrrole-3-carboxamide
Masitinib		masitinib mesylate	4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3ylthiazol-2-ylamino)phenyl]benzamide-

			mesylate methane sulfonic acid salt,
Bosutinib	SKI 606; SKI-606		4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile
Ponatinib	AP24534		3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-(4-((4-methylpiperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)benzamide
Bafetinib	CNS-9; Dual Bcr-Abl; Lyn Tyrosine Kinase Inhibitor INNO-406; INNO-406; NS-187		Benzamide, N-[3-([4,5'-bipyrimidin]-2-ylamino)-4-methylphenyl]-4-[[[(3S)-3-(dimethylamino)-1-pyrrolidinyl]methyl]-3-(trifluoromethyl)- benzamide
CYC10268			2-methoxy-4-(6-(1-phenylpropylamino)pyrazin-2-yl)phenol

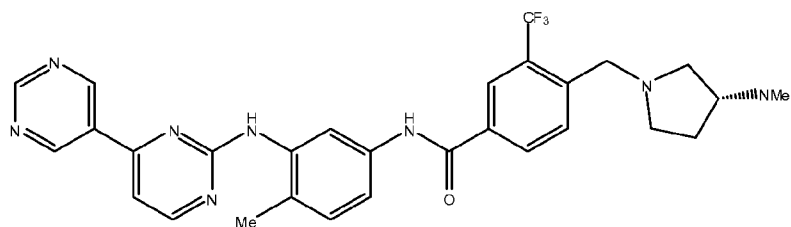
[00105] Chemical structures of the compounds of Table 1 are as follows.



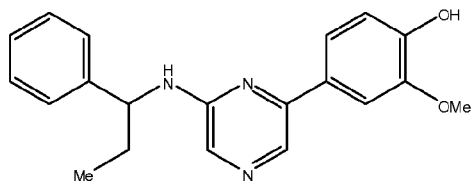




Ponatinib:

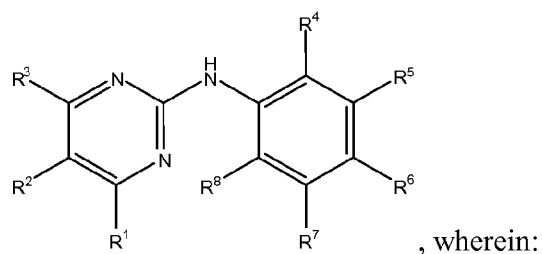


Bafetinib:



CYC10268:

[00106] In some embodiments, a compound of the invention is a compound of the formula (I):



- R^1 is a cyclic group that is substituted or unsubstituted;
- R^2 and R^3 are each independently hydrogen or alkyl;
- one or two of the groups R^4 , R^5 , R^6 , R^7 , and R^8 are each nitro, alkoxy, fluoro-substituted alkoxy, or a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:
 - R^9 is hydrogen or alkyl;
 - X is oxo, thio, $=NH$, $=N(alkyl)$, $=NOH$, or $=NO(alkyl)$;
 - Y is oxygen, NH , or $N(alkyl)$;

- n is 0 or 1; and

- R¹⁰ is an alkyl group or a cyclic group,

and the remaining groups R⁴, R⁵, R⁶, R⁷, and R⁸ are each independently:

hydrogen; alkyl that is unsubstituted or substituted by amino, alkyl amino, or dialkyl amino; a heterocycle; acyl; trifluoromethyl; hydroxyl; alkoxy; amino; alkyl amino; dialkyl amino; amido; carbamato; a carboxylic acid; or an ester group,

or a pharmaceutically-acceptable salt thereof.

[00107] In some embodiments, R¹ is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, phenyl; phenyl substituted with amino, alkyl amino, dialkyl amino, or acyl amino; phenyl substituted with aminoalkyl; phenyl substituted with alkyl; 1H-indolyl; 1H-imidazolyl; pyridyl; pyridyl substituted with alkyl; pyridyl *N*-oxide; or pyridyl *N*-oxide substituted with alkyl. R² and R³ are each independently hydrogen or alkyl. One or two of the groups R⁴, R⁵, R⁶, R⁷, and R⁸ are each nitro, fluoro-substituted alkoxy, or a group of the formula: -N(R⁹)-C(=X)-(Y)_n-R¹⁰, wherein:

- R⁹ is hydrogen or alkyl;

- X is oxo, thio, =NH, =N(alkyl), =NOH, or =NO(alkyl);

- Y is oxygen or NH;

- n is 0 or 1; and

- R¹⁰ is an aliphatic hydrocarbon group having 5-22 carbon atoms; a phenyl or naphthyl group each of which is unsubstituted or substituted by cyano, alkyl, alkoxy, (4-methyl-piperazinyl)-alkyl, trifluoromethyl, hydroxy, alkanoyloxy, halogen, amino, alkyl amino, dialkyl amino, alkanoyl amino, benzoyl amino, carboxy or by alkoxycarbonyl; or phenyl-alkyl wherein the phenyl group is unsubstituted or substituted as indicated above; a cycloalkyl or cycloalkenyl group having up to 30 carbon atoms; a cycloalkyl-alkyl or cycloalkenyl-alkyl group each having up to 30 carbon atoms; a heterocyclic group having 5 or 6 ring members and 1-3 ring heteroatoms selected from nitrogen, oxygen and sulfur, to which heterocyclic group one or two carbocyclic rings may be fused,

and the remaining groups R⁴, R⁵, R⁶, R⁷, and R⁸ are each independently: hydrogen; alkyl that is unsubstituted or substituted by amino, alkyl amino, or dialkyl amino; a

heterocycle; acyl; trifluoromethyl; hydroxyl; alkoxy; amino; alkyl amino; dialkyl amino; amido; carbamato; a carboxylic acid; or a carboxylic ester.

[00108] In some embodiments, R^1 is pyridyl or pyridyl *N*-oxide; R^2 and R^3 are each hydrogen; R^4 is hydrogen or alkyl; R^5 is hydrogen or alkyl; R^6 is hydrogen; R^7 is a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:

- R^9 is hydrogen;
- X is oxo;
- n is 0; and
- R^{10} is a phenyl group that is unsubstituted or substituted by cyano, alkyl, (4-methyl-piperazinyl)methyl, or halogen,

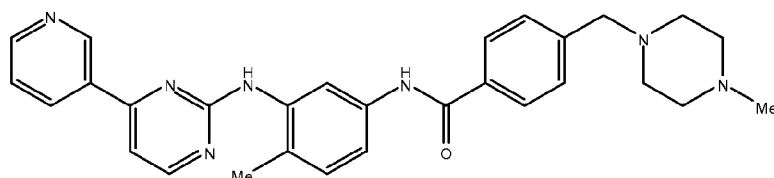
and R^8 is hydrogen.

[00109] In some embodiments, R^1 is 3-pyridyl; R^2 and R^3 are each hydrogen; R^4 is hydrogen or methyl; R^5 is hydrogen or methyl; R^6 is hydrogen; R^7 is a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:

- R^9 is hydrogen;
- X is oxo;
- n is 0; and
- R^{10} is a phenyl group that is unsubstituted or substituted by (4-methyl-piperazinyl)methyl,

and R^8 is hydrogen.

[00110] In some embodiments, the compound is:



[00111] In some embodiments, the compound is Imatinib. In some embodiments, the pharmaceutically-acceptable salt is a mesylate. In some embodiments, the compound is Imatinib mesylate.

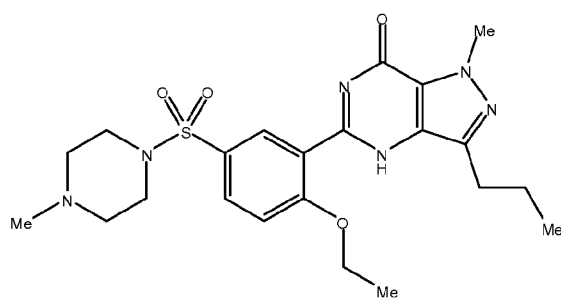
[00112] Non-limiting examples of CW305 include the compounds of Table 2 .

Table 2: CW305 Compound Names.

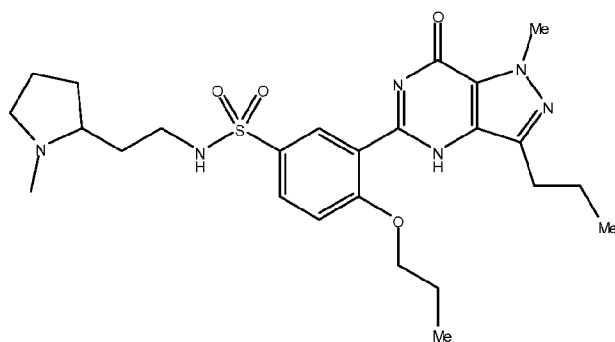
<u>Compound</u>	<u>Synonyms</u>	<u>Exemplary Salts</u>	<u>IUPAC Nomenclature</u>

Sildenafil		Sildenafil Citrate	5-[2-ethoxy-5-(4-methylpiperazine-1-sulfonyl)phenyl]-1-methyl-3-propyl-1H,4H,7H-pyrazolo[4,3-d]pyrimidin-7-one
Udenafil			3-{1-methyl-7-oxo-3-propyl-1H,4H,7H-pyrazolo[4,3-d]pyrimidin-5-yl}-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzene-1-sulfonamide
Vardenafil	VDN		2-[2-ethoxy-5-(4-ethylpiperazine-1-sulfonyl)phenyl]-5-methyl-7-propyl-1H,4H-imidazo[4,3-f][1,2,4]triazin-4-one
Tadalafil			(2R,8R)-2-(2H-1,3-benzodioxol-5-yl)-6-methyl-3,6,17-triazatetracyclo[8.7.0.0 ^{3,8} .0 ^{11,16}]heptadeca-1(10),11(16),12,14-tetraene-4,7-dione
Avanafil			4-[(3-Chloro-4-methoxybenzyl)amino]-2-[2-(hydroxymethyl)-1-pyrrolidinyl]-N-(2-pyrimidinylmethyl)-5-pyrimidinecarboxamide

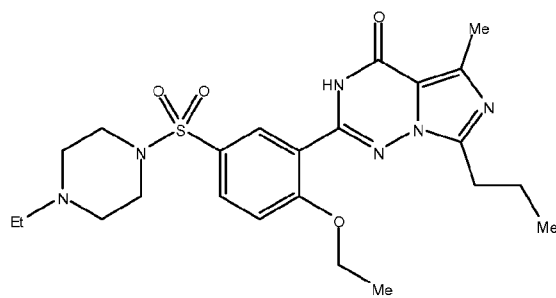
[00113] Chemical structures of the compounds of Table 2 are as follows.



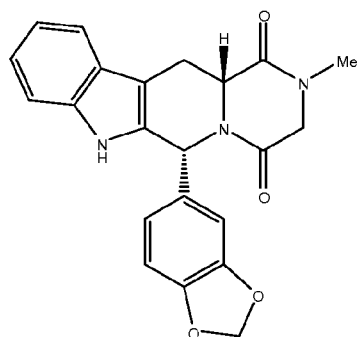
Sildenafil:



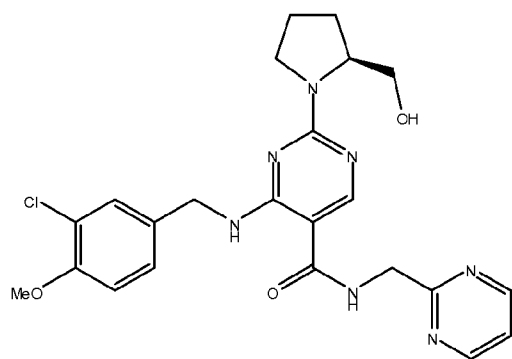
Udenafil:



Vardenafil:

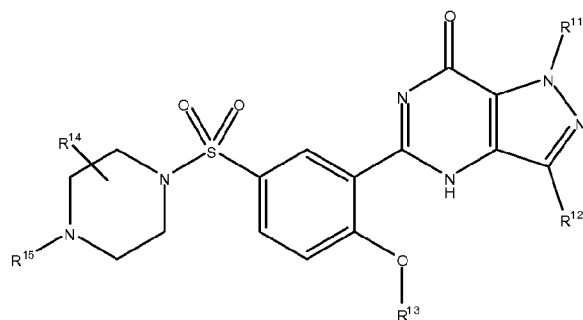


Tadalafil:



Avanafil:

[00114] In some embodiments, a compound of the invention is a compound of the formula (II) or tautomer thereof:



, wherein:

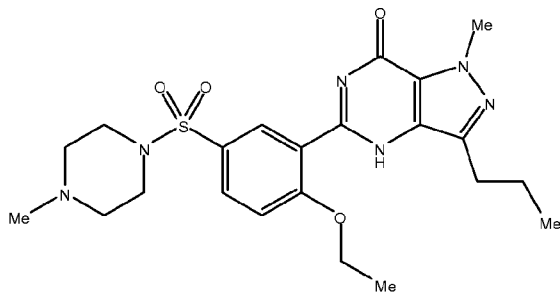
- R^{11} is H, C1-C3 alkyl, C3-C5 cycloalkyl or C1-C3 perfluoroalkyl;
- R^{12} is H, C1-C6 alkyl optionally substituted by OH, C1-C3 alkoxy or C3-C6 cycloalkyl, or C1-C3 perfluoroalkyl;
- R^{13} is C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, C3-C7 cycloalkyl, C1-C6 perfluoroalkyl or (C3-6 cycloalkyl)C1-C6 alkyl;
- R^{14} is H, C1-C4 alkyl, C1-C3 alkoxy, $NR^{16}R^{17}$, or $CONR^{16}R^{17}$;
- R^{15} is H, C1-C6 alkyl, (C1-C3 alkoxy)C2-C6 alkyl, hydroxy C2-C6 alkyl, $(R^{16}R^{17}N)C2-C6$ alkyl, $(R^{16}R^{17}NCO)C1-C6$ alkyl, $CONR^{16}R^{17}$, $CSNR^{16}R^{17}$ or $C(NH)NR^{16}R^{17}$;
- R^{16} and R^{17} are each independently H, C1-C4 alkyl, (C1-C3 alkoxy)C2-C4 alkyl or hydroxy C2-C4 alkyl,

or a pharmaceutically-acceptable salt thereof.

[00115] In some embodiments, R^{11} is H, methyl, or ethyl; R^{12} is C1-C3 alkyl optionally substituted by OH; R^{13} is C2-C3 alkyl or allyl; R^{14} is H, $NR^{16}R^{17}$ or $CONR^{16}R^{17}$; R^{15} is H, C1-C3 alkyl, hydroxy C2-C3 alkyl, $CONR^{16}R^{17}$, $CSNR^{16}R^{17}$ or $C(NH)NR^{16}R^{17}$; and R^{16} and R^{17} are each independently H or methyl.

[00116] In some embodiments, R^{11} is methyl; R^{12} is n-propyl; R^{13} is ethyl, n-propyl, or allyl; R^{14} is H, and R^{15} is H, C1-C3 alkyl or 2-hydroxyethyl.

[00117] In some embodiments, the compound is:



[00118] In some embodiments, the compound is Sildenafil. In some embodiments, the pharmaceutically-acceptable salt is a citrate. In some embodiments, the compound is Sildenafil citrate.

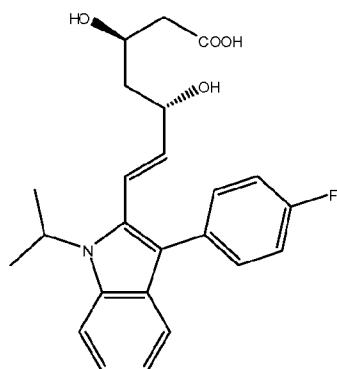
[00119] Non-limiting examples of CW302 include the compounds of Table 3.

Table 3: CW302 Compound Names.

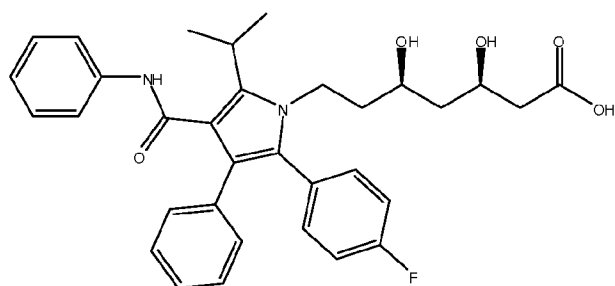
<u>Compound</u>	<u>Synonyms</u>	<u>Exemplary Salts</u>	<u>IUPAC Nomenclature</u>
Fluvastatin	Fluindostatin	Fluvastatin sodium	(3S,5R,6E)-7-[3-(4-fluorophenyl)-1-(propan-2-yl)-1H-indol-2-yl]-3,5-dihydroxyhept-6-enoic acid
Atorvastatin		Atorvastatin calcium	(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid
Simvastatin			(1S,3R,7S,8S,8aR)-8-{2-[(4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate
Lovastatin	6 alpha-Methylcompactin		(1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate
Mevastatin			(3R,5R)-7-[(1S,2S,8S,8aR)-2-methyl-8-[(2S)-2-methylbutanoyl]oxy]-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-

			dihydroxyheptanoic acid
Pravastatin		Pravastatin Sodium	(3R,5R)-7-[(1S,2S,6S,8S,8aR)-6-hydroxy-2-methyl-8-[[{(2S)-2-methylbutanoyl]oxy}-1,2,6,7,8,8a-hexahydronaphthalen-1-yl]-3,5-dihydroxyheptanoic acid
Rosuvastatin	ZD-4522	Rosuvastatin calcium	(3R,5R,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid
Pitavastatin			(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxyhept-6-enoic acid
Cerivastatin			(3R,5S,6E)-7-[4-(4-fluorophenyl)-5-(methoxymethyl)-2,6-bis(propan-2-yl)pyridin-3-yl]-3,5-dihydroxyhept-6-enoic acid

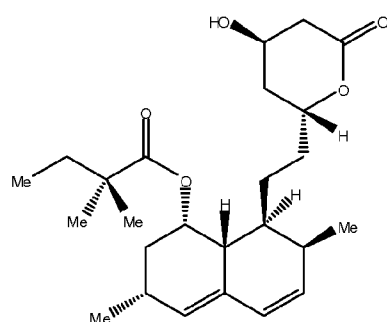
[00120] Chemical structures of the compounds of Table 3 are as follows.



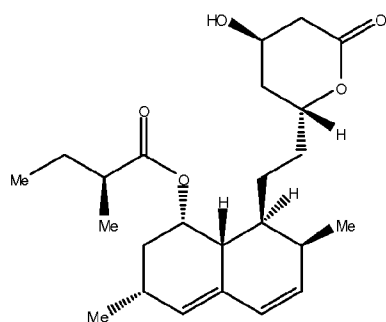
Fluvastatin:



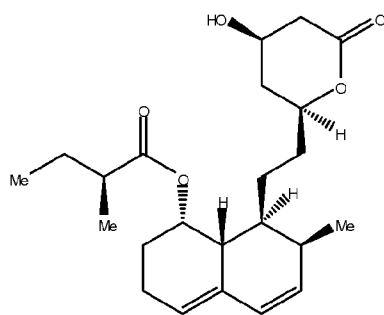
Atorvastatin:



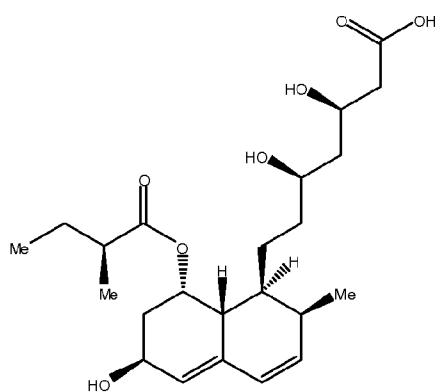
Simvastatin:



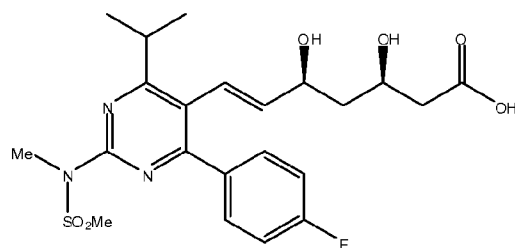
Lovastatin:



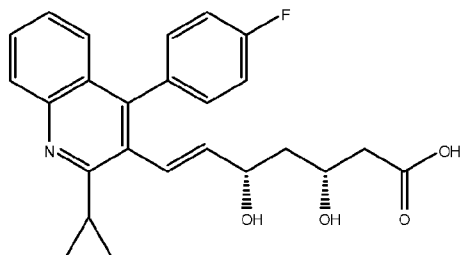
Mevastatin:



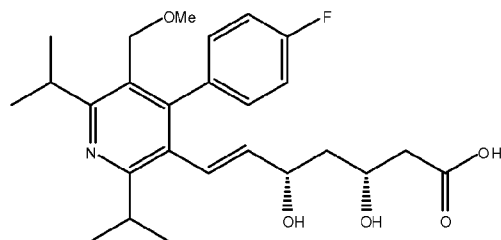
Pravastatin:



Rosuvastatin:

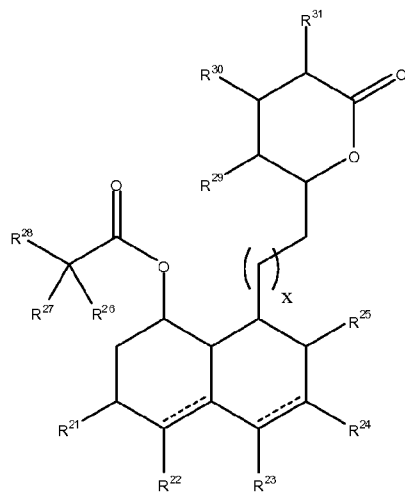


Pitavastatin:



Cerivastatin:

[00121] In some embodiments, a compound of the invention is a compound of the formula (III):



, wherein:

- each of R^{21} , R^{22} , R^{23} , R^{24} , and R^{25} is independently H, alkyl, hydroxyl, alkoxyl, or an ester group;
- each of R^{26} , R^{27} , and R^{28} is independently H, alkyl, hydroxyl, alkoxyl, amino, alkyl amino, dialkyl amino, or an ester group;
- each of R^{29} , R^{30} , and R^{31} is independently H, alkyl, halogen, hydroxyl, alkoxyl, amino, alkyl amino, dialkyl amino, or an ester group;

- x is 0, 1, 2, 3, 4, 5, or 6; and

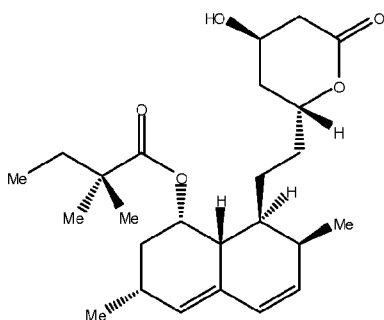
- each  is independently either a single or double bond,

or a pharmaceutically-acceptable salt thereof.

[00122] In some embodiments, each of R^{21} and R^{25} is independently alkyl or hydroxyl; each of R^{22} , R^{23} , R^{24} is H; each of R^{26} , R^{27} , and R^{28} is independently H, alkyl, or hydroxyl; each of R^{29} and R^{31} is H; R^{30} is H, alkyl, or hydroxyl; x is 0, 1, or 2; and each  is a double bond.

[00123] In some embodiments, each of R^{21} and R^{25} is alkyl; each of R^{22} , R^{23} , R^{24} is H; each of R^{26} , R^{27} , and R^{28} is independently alkyl; each of R^{29} and R^{31} is H; R^{30} hydroxyl; x is 1; and each  is a double bond.

[00124] In some embodiments, the compound is



[00125] In some embodiments, the compound is Simvastatin.

[00126] Non-limiting examples of optional substituents include hydroxyl groups, sulfhydryl groups, halogens, amino groups, nitro groups, nitroso groups, cyano groups, azido groups, sulfoxide groups, sulfone groups, sulfonamide groups, carboxyl groups, carboxaldehyde groups, imine groups, alkyl groups, halo-alkyl groups, alkenyl groups, halo-alkenyl groups, alkynyl groups, halo-alkynyl groups, alkoxy groups, aryl groups, aryloxy groups, aralkyl groups, arylalkoxy groups, heterocyclyl groups, acyl groups, acyloxy groups, carbamate groups, amide groups, urethane groups, and ester groups.

[00127] Non-limiting examples of alkyl groups include straight, branched, and cyclic alkyl groups. Non-limiting examples of straight alkyl groups include methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, and decyl.

[00128] Branched alkyl groups include any straight alkyl group substituted with any number of alkyl groups. Non-limiting examples of branched alkyl groups include isopropyl, isobutyl, sec-butyl, and t-butyl.

[00129] Non-limiting examples of cyclic alkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. Cyclic alkyl groups also include fused-, bridged-, and spiro-bicycles and higher fused-, bridged-, and spiro-systems. A cyclic alkyl group can be substituted with any number of straight, branched, or cyclic alkyl groups.

[00130] Non-limiting examples of alkenyl groups include straight, branched, and cyclic alkenyl groups. The olefin or olefins of an alkenyl group can be, for example, *E*, *Z*, *cis*, *trans*, terminal, or *exo*-methylene.

[00131] Non-limiting examples of alkynyl groups include straight, branched, and cyclic alkynyl groups. The triple bond of an alkynyl group can be internal or terminal.

[00132] A halo group can be any halogen atom, for example, fluorine, chlorine, bromine, or iodine.

[00133] A halo-alkyl group can be any alkyl group substituted with any number of halogen atoms, for example, fluorine, chlorine, bromine, and iodine atoms. A halo-alkenyl group can be any alkenyl group substituted with any number of halogen atoms. A halo-alkynyl group can be any alkynyl group substituted with any number of halogen atoms.

[00134] An alkoxy group can be, for example, an oxygen atom substituted with any alkyl, alkenyl, or alkynyl group. An ether or an ether group comprises an alkoxy group. Non-limiting examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, and isobutoxy.

[00135] An aryl group can be heterocyclic or non-heterocyclic. An aryl group can be monocyclic or polycyclic. An aryl group can be substituted with any number of substituents, for example, hydrocarbyl groups, alkyl groups, alkoxy groups, and halogen atoms. Non-limiting examples of aryl groups include phenyl, tolyl, naphthyl, pyrrolyl, pyridyl, imidazolyl, thiophenyl, and furyl.

[00136] An aryloxy group can be, for example, an oxygen atom substituted with any aryl group, such as phenoxy.

[00137] An aralkyl group can be, for example, any alkyl group substituted with any aryl group, such as benzyl.

[00138] An arylalkoxy group can be, for example, an oxygen atom substituted with any aralkyl group, such as benzyloxy.

[00139] A heterocycle can be any ring containing a ring atom that is not carbon. A heterocycle can be substituted with any number of substituents, for example, alkyl groups and halogen atoms. A heterocycle can be aromatic or non-aromatic. Non-limiting examples of heterocycles include pyrrole, pyrrolidine, pyridine, piperidine, succinamide, maleimide, morpholine, imidazole, thiophene, furan, tetrahydrofuran, pyran, and tetrahydropyran.

[00140] An acyl group can be, for example, a carbonyl group substituted with hydrocarbyl, alkyl, hydrocarbyloxy, alkoxy, aryl, aryloxy, aralkyl, arylalkoxy, or a heterocycle. Non-limiting examples of acyl include acetyl, benzoyl, benzyloxycarbonyl, phenoxycarbonyl, methoxycarbonyl, and ethoxycarbonyl.

[00141] An acyloxy group can be an oxygen atom substituted with an acyl group. An ester or an ester group comprises an acyloxy group. A non-limiting example of an acyloxy group, or an ester group, is acetate.

[00142] A carbamate group can be an oxygen atom substituted with a carbamoyl group, wherein the nitrogen atom of the carbamoyl group is unsubstituted, monosubstituted, or disubstituted with one or more of hydrocarbyl, alkyl, aryl, heterocyclyl, or aralkyl. When the nitrogen atom is disubstituted, the two substituents together with the nitrogen atom can form a heterocycle.

[00143] The invention provides the use of pharmaceutically-acceptable salts of any compound described herein. Pharmaceutically-acceptable salts include, for example, acid-addition salts and base-addition salts. The acid that is added to the compound to form an acid-addition salt can be an organic acid or an inorganic acid. A base that is added to the compound to form a base-addition salt can be an organic base or an inorganic base. In some embodiments, a pharmaceutically-acceptable salt is a metal salt. In some embodiments, a pharmaceutically-acceptable salt is an ammonium salt.

[00144] Metal salts can arise from the addition of an inorganic base to a compound of the invention. The inorganic base consists of a metal cation paired with a basic counterion, such as, for example, hydroxide, carbonate, bicarbonate, or phosphate. The metal can be an alkali metal, alkaline earth metal, transition metal, or main group metal. In some embodiments, the metal is lithium, sodium, potassium, cesium, cerium, magnesium, manganese, iron, calcium, strontium, cobalt, titanium, aluminum, copper, cadmium, or zinc.

[00145] In some embodiments, a metal salt is a lithium salt, a sodium salt, a potassium salt, a cesium salt, a cerium salt, a magnesium salt, a manganese salt, a iron salt, a calcium salt, a strontium salt, a cobalt salt, a titanium salt, an aluminum salt, a copper salt, a cadmium salt, or a zinc salt.

[00146] Ammonium salts can arise from the addition of ammonia or an organic amine to a compound of the invention. In some embodiments, the organic amine is triethyl amine, diisopropyl amine, ethanol amine, diethanol amine, triethanol amine, morpholine, N-methylmorpholine, piperidine, N-methylpiperidine, N-ethylpiperidine, dibenzylamine, piperazine, pyridine, pyrrazole, pipyrrazole, imidazole, pyrazine, or pipyrazine.

[00147] In some embodiments, an ammonium salt is a triethyl amine salt, a diisopropyl amine salt, an ethanol amine salt, a diethanol amine salt, a triethanol amine salt, a morpholine salt, an N-methylmorpholine salt, a piperidine salt, an N-methylpiperidine salt, an N-ethylpiperidine salt, a dibenzylamine salt, a piperazine salt, a pyridine salt, a pyrrazole salt, a pipyrrazole salt, an imidazole salt, a pyrazine salt, or a pipyrazine salt.

[00148] Acid addition salts can arise from the addition of an acid to a compound of the invention. In some embodiments, the acid is organic. In some embodiments, the acid is inorganic. In some embodiments, the acid is hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, nitrous acid, sulfuric acid, sulfurous acid, a phosphoric acid, isonicotinic acid, lactic acid, salicylic acid, tartaric acid, ascorbic acid, gentisinic acid, gluconic acid, glucaronic acid, saccharic acid, formic acid, benzoic acid, glutamic acid, pantothenic acid, acetic acid, propionic acid, butyric acid, fumaric acid, succinic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, oxalic acid, or maleic acid.

[00149] In some embodiments, the salt is a hydrochloride salt, a hydrobromide salt, a hydroiodide salt, a nitrate salt, a nitrite salt, a sulfate salt, a sulfite salt, a phosphate salt, isonicotinate salt, a lactate salt, a salicylate salt, a tartrate salt, an ascorbate salt, a gentisinate salt, a gluconate salt, a glucaronate salt, a saccharate salt, a formate salt, a benzoate salt, a glutamate salt, a pantothenate salt, an acetate salt, a propionate salt, a butyrate salt, a fumarate salt, a succinate salt, a methanesulfonate (mesylate) salt, an ethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a citrate salt, an oxalate salt, or a maleate salt.

Pharmaceutical Compositions.

[00150] A pharmaceutical composition of the invention can be a combination of any pharmaceutical compounds described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by any form and route known in the art including, for example, intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, and topical administration.

[00151] A pharmaceutical composition can be administered in a local or systemic manner, for example, via injection of the compound directly into an organ, optionally in a depot or sustained release formulation. Pharmaceutical compositions can be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. A rapid release form can provide an immediate release. An extended release formulation can provide a controlled release or a sustained delayed release.

[00152] For oral administration, pharmaceutical compositions can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers or excipients well known in the art. Such carriers can be used to formulate tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a subject.

[00153] Pharmaceutical preparations for oral use can be obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions can be used, which may optionally contain an excipient such as gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or to characterize different combinations of active compound doses.

[00154] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a

plasticizer, such as glycerol or sorbitol. In some embodiments, the capsule comprises a hard gelatin capsule comprising one or more of pharmaceutical, bovine, and plant gelatins. A gelatin can be alkaline processed. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. Stabilizers can be added. All formulations for oral administration are provided in dosages suitable for such administration.

[00155] For buccal or sublingual administration, the compositions can be tablets, lozenges, or gels.

[00156] Parental injections can be formulated for bolus injection or continuous infusion. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Suspensions of the active compounds can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. The suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

[00157] The active compounds can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00158] Formulations suitable for transdermal administration of the active compounds can employ transdermal delivery devices and transdermal delivery patches, and can be lipophilic emulsions or buffered aqueous solutions, dissolved

and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical compounds.

Transdermal delivery can be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches can provide controlled delivery. The rate of absorption can be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier can include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices can be in the form of a bandage comprising a backing member, a reservoir containing compounds and carriers, a rate controlling barrier to deliver the compounds to the skin of the subject at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[00159] For administration by inhalation, the active compounds can be in a form as an aerosol, a mist, or a powder. Pharmaceutical compositions are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, for example, gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compounds and a suitable powder base such as lactose or starch.

[00160] The compounds can also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as a mixture of fatty acid glycerides, optionally in combination with cocoa butter, is first melted.

[00161] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the compounds described herein are administered in pharmaceutical compositions to a subject having a disease or condition to be treated. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the

disease, the age and relative health of the subject, the potency of the compounds used, and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[00162] Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Formulation can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a compounds described herein can be manufactured in a conventional manner, for example, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00163] The pharmaceutical compositions can include at least one pharmaceutically acceptable carrier, diluent, or excipient and compounds described herein as free-base or pharmaceutically-acceptable salt form. The methods and pharmaceutical compositions described herein include the use crystalline forms (also known as polymorphs), and active metabolites of these compounds having the same type of activity.

[00164] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include, for example, solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, for example, gels, suspensions and creams. The compositions can be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

[00165] Compounds can be delivered via liposomal technology. The use of liposomes as drug carriers can increase the therapeutic index of the compounds. Liposomes are composed of natural phospholipids, and can contain mixed lipid chains with surfactant properties (e.g., egg phosphatidylethanolamine). A liposome design

can employ surface ligands for attaching to unhealthy tissue. Non-limiting examples of liposomes include the multilamellar vesicle (MLV), the small unilamellar vesicle (SUV), and the large unilamellar vesicle (LUV). Liposomal physicochemical properties can be modulated to optimize penetration through biological barriers and retention at the site of administration, and to prevent premature degradation and toxicity to non-target tissues. Optimal liposomal properties depend on the administration route: large-sized liposomes show good retention upon local injection, small-sized liposomes are better suited to achieve passive targeting. PEGylation reduces the uptake of the liposomes by liver and spleen, and increases the circulation time, resulting in increased localization at the inflamed site due to the enhanced permeability and retention (EPR) effect. Additionally, liposomal surfaces can be modified to achieve selective delivery of the encapsulated drug to specific target cells. Non-limiting examples of targeting ligands include monoclonal antibodies, vitamins, peptides, and polysaccharides specific for receptors concentrated on the surface of cells associated with the disease.

[00166] Non-limiting examples of dosage forms suitable for use in the invention include feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, geltab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, creams, drops, dispersible powders or granules, emulsion in hard or soft gel capsules, syrups, phytoceuticals, nutraceuticals, and any combination thereof.

[00167] Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the invention include granulating agents, binding agents, lubricating agents, disintegrating agents, sweetening agents, glidants, anti-adherents, anti-static agents, surfactants, anti-oxidants, gums, coating agents, coloring agents, flavouring agents, coating agents, plasticizers, preservatives, suspending agents, emulsifying agents, plant cellulosic material and spheronization agents, and any combination thereof.

[00168] A composition of the invention can be, for example, an immediate release form or a controlled release formulation. An immediate release formulation can be formulated to allow the compounds to act rapidly. Non-limiting examples of immediate release formulations include readily dissolvable formulations. A controlled release formulation can be a pharmaceutical formulation that has been adapted such that drug release rates and drug release profiles can be matched to physiological and

chronotherapeutic requirements or, alternatively, has been formulated to effect release of a drug at a programmed rate. Non-limiting examples of controlled release formulations include granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed through), granules within a matrix, polymeric mixtures, granular masses, and the like.

[00169] Compositions of the invention can be delivered via a time-controlled delivery system. An example of a suitable time-controlled delivery system is the PULSINCAP® system, or a variant thereof. The time-controlled delivery system can further comprise pH-dependent systems, microbially-triggered delivery systems, or a combination thereof. The time-controlled system may comprise a water insoluble capsule body enclosing a drug reservoir. The capsule body can be closed at one end with a hydrogel plug. The hydrogel plug can comprise swellable polymers, erodible compressed polymers, congealed melted polymers, enzymatically-controlled erodible polymers, or a combination thereof. The swellable polymers can include polymethacrylates. Non-limiting examples of erodible compressed polymers include hydroxypropyl methylcellulose, polyvinyl alcohol, polyvinyl acetate, polyethylene oxide, and combinations thereof. Non-limiting examples of congealed melted polymers include saturated polyglycolated glycerides, glyceryl monooleate, and combinations thereof. Non-limiting examples of enzymatically-controlled erodible polymers include polysaccharides; amylose; guar gum; pectin; chitosan; inulin; cyclodextrin; chondroitin sulphate; dextrans; locust bean gum; arabinogalactan; chondroitin sulfate; xylan; calcium pectinate; pectin/chitosan mixtures; amidated pectin; and combinations thereof.

[00170] The time-controlled delivery system can comprise a capsule, which further comprises an organic acid. The organic acid can be filled into the body of a hard gelatine capsule. The capsule can be coated with multiple layers of polymers. The capsule can be coated first with an acid soluble polymer, such as EUDRAGIT® E, then with a hydrophilic polymer, such as hydroxypropyl methylcellulose, and finally with an enteric coating, such as EUDRAGIT® L.

[00171] An additional example of a suitable time-controlled delivery system is the CHRONOTROPIC® system, or a variant thereof, which comprises a drug core that is coated with hydroxypropyl methylcellulose and an outer enteric film.

[00172] An additional example of a suitable time-controlled delivery system is the CODESTM system, or a variant thereof. The time-controlled delivery system can comprise a capsule body, which can house, for example, a drug-containing tablet, an erodible tablet, a swelling expulsion excipient, or any combination thereof. The capsule can comprise an ethyl cellulose coat. The time-controlled delivery system can comprise two different sized capsules, one inside the other. The space between the capsules can comprise a hydrophilic polymer. The drug-containing core can be housed within the inner capsule. The drug delivery system can comprise an impermeable shell, a drug-containing core, and erodible outer layers at each open end. When the outer layers erode, the drug is released.

[00173] Examples of suitable multiparticulate drug delivery systems include DIFFUCAPS®, DIFFUTAB®, ORBEXA®, EURAND MINITABS®, MICROCAPS®, and variants thereof. The drug delivery system can comprise multiparticulate beads, which are comprised of multiple layers of the drug compound, excipients, and release-controlling polymers. The multiparticulate beads can comprise an organic acid or alkaline buffer. The multiparticulate beads can comprise a solid solution of the drug compound and crystallization inhibitor. The drug delivery system can comprise a matrix tablet containing water-soluble particles and the drug compound. The matrix tablet can further comprise hydrophilic and hydrophobic polymers. In some multiparticulate delivery systems, particles in the micron size range are used. In some multiparticulate delivery systems, nanoparticle colloidal carriers composed of natural or synthetic polymers are used.

[00174] In some embodiments, a controlled release formulation is a delayed release form. A delayed release form can be formulated to delay a compound's action for an extended period of time. A delayed release form can be formulated to delay the release of an effective dose of one or more compounds, for example, for about 4, about 8, about 12, about 16, or about 24 hours.

[00175] A controlled release formulation can be a sustained release form. A sustained release form can be formulated to sustain, for example, the compound's action over an extended period of time. A sustained release form can be formulated to provide an effective dose of any compound described herein (e.g., provide a physiologically-effective blood profile) over about 4, about 8, about 12, about 16 or about 24 hours.

[00176] A tablet providing a sustained or controlled release can comprise a first layer containing one or two of the compounds described herein, and a tablet core containing one or two other compounds. The core can have a delayed or sustained dissolution rate. Other exemplary embodiments can include a barrier between the first layer and core, to limit drug release from the surface of the core. Barriers can prevent dissolution of the core when the pharmaceutical formulation is first exposed to gastric fluid. For example, a barrier can comprise a disintegrant, a dissolution-retarding coating (e.g., a polymeric material, for example, an enteric polymer such as a Eudragit polymer), or a hydrophobic coating or film, and can be selectively soluble in either the stomach or intestinal fluids. Such barriers permit the compounds to leach out slowly. The barriers can cover substantially the whole surface of the core.

[00177] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Dekker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999), each of which is incorporated by reference in its entirety.

Dosing.

[00178] Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for example, in combination with a preservative. Formulations for parenteral injection can be presented in unit dosage form, for example, in ampoules, or in multi-dose containers with a preservative.

[00179] A compound described herein can be present in a composition in a range of from about 1 mg to about 2000 mg; from about 5 mg to about 1000 mg, from about 10 mg to about 500 mg, from about 50 mg to about 250 mg, from about 100 mg

to about 200 mg, from about 1 mg to about 50 mg, from about 50 mg to about 100 mg, from about 100 mg to about 150 mg, from about 150 mg to about 200 mg, from about 200 mg to about 250 mg, from about 250 mg to about 300 mg, from about 300 mg to about 350 mg, from about 350 mg to about 400 mg, from about 400 mg to about 450 mg, from about 450 mg to about 500 mg, from about 500 mg to about 550 mg, from about 550 mg to about 600 mg, from about 600 mg to about 650 mg, from about 650 mg to about 700 mg, from about 700 mg to about 750 mg, from about 750 mg to about 800 mg, from about 800 mg to about 850 mg, from about 850 mg to about 900 mg, from about 900 mg to about 950 mg, or from about 950 mg to about 1000 mg.

[00180] A compound described herein can be present in a composition in an amount of about 1 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, or about 2000 mg.

[00181] In some embodiments, a dose can be expressed in terms of an amount of the drug divided by the mass of the subject, for example, milligrams of drug per kilograms of subject body mass. In some embodiments, CW299 is present in a composition in an amount ranging from about 5 mg/kg to about 1600 mg/kg, about 10 mg/kg to about 800 mg/kg, about 50 mg/kg to about 400 mg/kg, about 100 mg/kg to about 300 mg/kg, or about 150 mg/kg to about 200 mg/kg. In some embodiments, CW305 is present in a composition in an amount ranging from about 1 mg/kg to about 300 mg/kg, about 2 mg/kg to about 200 mg/kg, about 3 mg/kg to about 100 mg/kg, about 5 mg/kg to about 75 mg/kg, about 10 mg/kg to about 50 mg/kg or about 20 mg/kg to about 40 mg/kg. In some embodiments, CW302 is present in a composition in an amount ranging from about 1 mg/kg to about 900 mg/kg, about 5 mg/kg to about 600 mg/kg about 10 mg/kg to about 450 mg/kg, about 25 mg/kg to about 300 mg/kg, about 50 mg/kg to about 200 mg/kg, or about 100 mg/kg to about 150 mg/kg.

[00182] In some embodiments, a composition comprises from about 10 mg to about 800 mg of CW299, from about 3 mg to about 100 mg of CW305, and from about 10 mg to about 450 mg CW302.

[00183] In some embodiments, a compound described herein is present in a composition in an amount that is a fraction or percentage of the maximum tolerated amount. The maximum tolerated amount can be as determined in a subject, such as a mouse or human. The fraction can be expressed as a ratio of the amount present in the composition divided by the maximum tolerated dose. The ratio can be from about 1/20 to about 1/1. The ratio can be about 1/20, about 1/19, about 1/18, about 1/17, about 1/16, about 1/15, about 1/14, about 1/13, about 1/12, about 1/11, about 1/10, about 1/9, about 1/8, about 1/7, about 1/6, about 1/5, about 1/4, about 1/3, about 1/2, or about 1/1. The ratio can be 1/20, 1/19, 1/18, 1/17, 1/16, 1/15, 1/14, 1/13, 1/12, 1/11, 1/10, 1/9, 1/8, 1/7, 1/6, 1/5, 1/4, 1/3, 1/2, or 1/1.

[00184] For example, the maximum tolerated dose of Imatinib Mesylate is 100 mg/kg in mice. The maximum tolerated dose of Sildenafil is 8.5 mg/kg in mice. The maximum tolerated dose of Simvastatin is 25 mg/kg in mice.

[00185] The foregoing ranges are merely suggestive. Dosages can be altered depending on a number of variables, including, for example, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00186] A dose can be modulated to achieve a desired pharmacokinetic or pharmacodynamics profile, such as a desired or effective blood profile, as described herein.

Pharmacokinetic and Pharmacodynamic Measurements.

[00187] Pharmacokinetic and pharmacodynamic data can be obtained by techniques known in the art. Appropriate pharmacokinetic and pharmacodynamic profile components describing a particular composition can vary due to the inherent variation in pharmacokinetic and pharmacodynamic parameters of drug metabolism in human subjects. Pharmacokinetic and pharmacodynamic profiles can be based on the determination of the mean parameters of a group of subjects. The group of subjects includes any reasonable number of subjects suitable for determining a representative mean, for example, 5 subjects, 10 subjects, 16 subjects, 20 subjects, 25 subjects, 30 subjects, 35 subjects, or more. The mean is determined by calculating the average of all subject's measurements for each parameter measured.

[00188] The pharmacokinetic parameters can be any parameters suitable for describing a compound disclosed herein. For example, the $C_{\max}$ can be not less than about 100 ng/mL; not less than about 200 ng/mL; not less than about 300 ng/mL; not less than about 400 ng/mL; not less than about 500 ng/mL; not less than about 600 ng/mL; not less than about 700 ng/mL; not less than about 800 ng/mL; not less than about 900 ng/mL; not less than about 1000 ng/mL; not less than about 1250 ng/mL; not less than about 1500 ng/mL; not less than about 1750 ng/mL; not less than about 2000 ng/mL; or any other $C_{\max}$ appropriate for describing a pharmacokinetic profile of a compound described herein.

[00189] The $T_{\max}$ of a compound described herein can be, for example, not greater than about 0.5 hours, not greater than about 1.0 hours, not greater than about 1.5 hours, not greater than about 2.0 hours, not greater than about 2.5 hours, not greater than about 3.0 hours, or any other $T_{\max}$ appropriate for describing a pharmacokinetic profile of a compound described herein.

[00190] The $AUC_{(0-\infty)}$ of a compound described herein can be, for example, not less than about 250 ng•hr/mL, not less than about 500 ng•hr/mL, not less than about 1000 ng•hr/mL, not less than about 1500 ng•hr/mL, not less than about 2000 ng•hr/mL, not less than about 3000 ng•hr/mL, not less than about 3500 ng•hr/mL, not less than about 4000 ng•hr/mL, not less than about 5000 ng•hr/mL, not less than about 6000 ng•hr/mL, not less than about 7000 ng•hr/mL, not less than about 8000 ng•hr/mL, not less than about 9000 ng•hr/mL, or any other $AUC_{(0-\infty)}$ appropriate for describing a pharmacokinetic profile of a compound described herein.

[00191] The plasma concentration of a compound described herein about one hour after administration can be, for example, not less than about 25 ng/mL, not less than about 50 ng/mL, not less than about 75 ng/mL, not less than about 100 ng/mL, not less than about 150 ng/mL, not less than about 200 ng/mL, not less than about 300 ng/mL, not less than about 400 ng/mL, not less than about 500 ng/mL, not less than about 600 ng/mL, not less than about 700 ng/mL, not less than about 800 ng/mL, not less than about 900 ng/mL, not less than about 1000 ng/mL, not less than about 1200 ng/mL, or any other plasma concentration of a compound described herein.

[00192] The pharmacodynamic parameters can be any parameters suitable for describing compositions of the invention. For example, the pharmacodynamic profile can exhibit decreases in factors associated with inflammation after, for example, about 2 hours, about 4 hours, about 8 hours, about 12 hours, or about 24 hours.

[00193] For example, for Imatinib, the $T_{\max}$ is 1.2 hours; the $T_{1/2}$ is 13 hours (with a peak at 17.5 hours for an active metabolite), and the $C_{\max}$ is 0.925 $\mu\text{g/mL}$ (with a peak at 0.115 μL for an active metabolite). For Sildenafil, the $T_{\max}$ is 1 hour; the $T_{1/2}$ is 4-5 hours, and the $C_{\max}$ is 440 ng/mL. For Simvastatin, the $T_{\max}$ is 1.9 hours; the $T_{1/2}$ is 3 hours, and the $C_{\max}$ is 8.99 ng/mL.

Inflammatory Conditions and Methods of Treatment.

[00194] In some embodiments, the invention provides a process for preparing a composition, the composition comprising one or more compounds, wherein the compounds are CW299, CW305 and CW302, wherein the composition optionally further comprises a pharmaceutically-acceptable excipient, wherein the process comprises the step of combining the compounds and the optional; excipient in any order thereof.

[00195] The invention described herein provides therapeutic methods for the treatment of inflammatory joint diseases and chronic inflammatory connective tissue diseases, or combinations thereof.

[00196] In one embodiment of the present disclosure, the inflammatory joint diseases is selected from a group comprising but not limiting to rheumatoid arthritis, juvenile RA (JRA), osteoarthritis, polyarthritis, spondylitis, bursitis and gout or any combination of diseases thereof. The allied arthritic diseases also include psoriatic arthritis, ankylosing spondylitis, infectious arthritis including reactive arthritis; intestinal diseases including ulcerative colitis, inflammatory bowel disease (IBD) and the like or any combination of allied diseases thereof.

[00197] In one embodiment of the present disclosure, the chronic inflammatory connective tissue diseases are selected from a group comprising but not limiting to systemic lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis, mixed connective tissue disease (MCTD), tendonitis, synovitis, bacterial endocarditis, osteomyelitis and psoriasis or any combination of diseases thereof.

[00198] In some embodiments, the invention provides a method for treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, the method comprising administering to the subject: a) a therapeutically-effective amount of an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;

b) a therapeutically-effective amount of an inhibitor of phosphodiesterase 5; and c) a therapeutically-effective amount of an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00199] In some embodiments the invention provides a use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00200] In some embodiments the invention provides a use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory joint diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00201] In some embodiments the invention provides a use of a combination of compounds in the preparation of a medicament for the treatment of chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00202] In some embodiments the invention provides a use of a combination of compounds in the preparation of a kit for the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00203] In some embodiments the invention provides a use of a combination of compounds in the preparation of a kit for the treatment of inflammatory joint diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00204] In some embodiments the invention provides a use of a combination of compounds in the preparation of a kit for the treatment of chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00205] In some embodiments the invention provides a combination of compounds for use in the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00206] In some embodiments the invention provides a combination of compounds for use in the treatment of inflammatory joint diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00207] In some embodiments the invention provides a combination of compounds for use in the treatment of chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

[00208] Pharmaceutical compositions containing compounds described herein can be administered for prophylactic and/or therapeutic treatments. In therapeutic applications, the compositions are administered to a subject already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest the symptoms of the disease or condition, or to cure, heal, improve, or ameliorate the condition itself. Amounts effective for this use can vary based on the severity and course of the disease or condition, previous therapy, the subject's health status, weight, and response to the drugs, and the judgment of the treating physician. Pharmaceutically-acceptable amounts can be determined by routine experimentation, for example, by a dose escalation clinical trial.

[00209] Multiple therapeutic agents can be administered in any order or simultaneously. If simultaneously, the multiple therapeutic agents can be provided in a single, unified form, or in multiple forms, for example, as multiple separate pills. The compounds can be packed together or separately, in a single package or in a plurality of packages. One or all of the therapeutic agents can be given in multiple doses. If not simultaneous, the timing between the multiple doses may vary to as much as about a month.

[00210] In some embodiments, compounds of the invention are administered sequentially at a time interval. The time interval can range from about 1 second to about 600 minutes.

[00211] Compounds and compositions of the invention can be packaged as a kit. In some embodiments, a kit includes written instructions on the use of the compounds and compositions.

[00212] In some embodiments, therapeutics are combined with genetic or genomic testing to determine whether that individual is a carrier of a mutant gene that is known to be correlated with certain diseases or conditions. A personalized medicine approach can be used to provide companion diagnostic tests to discover a subject's predisposition to certain conditions and susceptibility to therapy. For example, a subject who is an anti-TNF non-responder could be identified via companion diagnostics. The companion diagnostic test can be performed on a tissue sample of the subject, such as blood, hair, or skin.

[00213] Instructions on the use of a companion diagnostic test can be provided on written material packaged with a compound, composition, or kit of the invention. The written material can be, for example, a label. The written material can suggest conditions or genetic features relevant to inflammation or the therapeutic compounds of the invention. The instructions provide the subject and the supervising physician with the best guidance for achieving the optimal clinical outcome from the administration of the therapy.

[00214] Compounds described herein can be administered before, during, or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound can vary. For example, the compounds can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions or diseases in order to prevent the occurrence of the disease or condition. The compounds and compositions can be administered to a subject

during or as soon as possible after the onset of the symptoms. The administration of the compounds can be initiated within the first 48 hours of the onset of the symptoms, within the first 24 hours of the onset of the symptoms, within the first 6 hours of the onset of the symptoms, or within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as by any route described herein using any formulation described herein. A compound can be administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. The length of treatment can vary for each subject, and the length can be determined using the known criteria.

[00215] In some embodiments, provided herein is a method of treating juvenile idiopathic arthritis using a therapeutically-effective amount of a composition provided herein. Juvenile idiopathic arthritis (JIA) (aka Juvenile Rheumatoid Arthritis JRA) is an autoimmune disorder. Onset is typically before age 16. The cardinal clinical feature is persistent swelling of the affected joint(s), which commonly include the knee, ankle, wrist and small joints of the hands and feet. Other joints affected can include spine, sacroiliac joints, shoulder, hip and jaw. JIA may be transient and self-limited or chronic, and differs significantly from arthritis commonly seen in adults.

[00216] In some embodiments, provided herein is a method of treating psoriatic arthritis using a therapeutically-effective amount of a composition provided herein. Psoriatic arthritis is a type of inflammatory arthritis. People who have the chronic skin condition psoriasis are likely to develop this type of arthritis. Psoriatic arthritis is said to be a seronegative spondyloarthropathy and therefore occurs more commonly in patients with tissue type HLA-B27.

[00217] In some embodiments, provided herein is a method of treating plaque psoriasis using a therapeutically-effective amount of a composition provided herein. Plaque psoriasis is an autoimmune disease that appears on the skin. It is one of the five known types of psoriasis. In psoriasis, immune cells move from the dermis to the epidermis, where they stimulate skin cells (keratinocytes) to proliferate. Immune cells, such as dendritic cells and T cells, move from the dermis to the epidermis, secreting chemical signals, such as tumor necrosis factor- α , interleukin-1 β , and interleukin-6, which cause inflammation, and interleukin-22, which causes keratinocytes to proliferate. In plaque psoriasis, skin rapidly accumulates at elbows

and knees, but can affect any area, including the scalp, palms of hands and soles of feet, and genitals which gives it a silvery-white appearance.

[00218] In some embodiments, provided herein is a method of treating osteoarthritis using a therapeutically-effective amount of a composition provided herein. Osteoarthritis also known as degenerative arthritis or degenerative joint disease or osteoarthrosis, is a group of mechanical abnormalities involving degradation of joints, including articular cartilage and subchondral bone. Symptoms may include joint pain, tenderness, stiffness, locking, and sometimes an effusion. When bone surfaces become less well protected by cartilage, bone may be exposed and damaged. As a result of decreased movement secondary to pain, regional muscles may atrophy, and ligaments may become more lax.

[00219] In some embodiments, provided herein is a method of treating polyarthritis using a therapeutically-effective amount of a composition provided herein. Polyarthritis is any type of arthritis which involves five or more joints simultaneously. It is usually associated with autoimmune conditions. Polyarthritis is most often caused by an auto-immune disorder such as Rheumatoid arthritis, Psoriatic arthritis, and Lupus erythematosus but can also be caused by infection with an alphavirus such as Chikungunya Virus and Ross River Virus.

[00220] In some embodiments, provided herein is a method of treating spondylitis using a therapeutically-effective amount of a composition provided herein. Spondylitis is an inflammation of the vertebra. It is a form of spondylopathy. In many cases, spondylitis involves one or more vertebral joint as well, which itself is called spondylarthritis.

[00221] In some embodiments, provided herein is a method of treating bursitis using a therapeutically-effective amount of a composition provided herein. Bursitis is the inflammation of one or more bursae (small sacs) of synovial fluid in the body. The bursae rest at the points where internal functionaries, such as muscles and tendons, slide across bone. Healthy bursae create a smooth, almost frictionless functional gliding surface making normal movement painless. When bursitis occurs, however, movement relying upon the inflamed bursa becomes difficult and painful. Moreover, movement of tendons and muscles over the inflamed bursa aggravates its inflammation, perpetuating the problem.

[00222] In some embodiments, provided herein is a method of treating gout using a therapeutically-effective amount of a composition provided herein. Gout is

characterized by recurrent attacks of acute inflammatory arthritis—a red, tender, hot, swollen joint. Gout is caused by elevated levels of uric acid in the blood which crystallizes and the crystals are deposited in joints, tendons, and surrounding tissues. The metatarsal-phalangeal joint at the base of the big toe is commonly affected. However, gout may also present as tophi, kidney stones, or urate nephropathy.

[00223] In some embodiments, provided herein is a method of treating arthritic diseases using a therapeutically-effective amount of a composition provided herein.

[00224] In some embodiments, provided herein is a method of treating ankylosing spondylitis (AS) using a therapeutically-effective amount of a composition provided herein. Ankylosing spondylitis (previously known as Bekhterev's disease) is a chronic inflammatory disease of the axial skeleton with variable involvement of peripheral joints and nonarticular structures. AS is a form of spondyloarthritis, a chronic, inflammatory arthritis and autoimmune disease. It mainly affects joints in the spine and the sacroiliac joint in the pelvis, and can cause eventual fusion of the spine results in a complete rigidity of the spine, a condition known as "bamboo spine". Both tumor necrosis factor-alpha (TNF α) and IL-1 are also implicated in ankylosing spondylitis.

[00225] In some embodiments, provided herein is a method of treating infectious arthritis including but not limited to osteomyelitis using a therapeutically-effective amount of a composition provided herein. *Staphylococcus aureus* is the most common organism seen in osteomyelitis, seeded from areas of contiguous infection. But anaerobes and Gram-negative organisms, including *Pseudomonas aeruginosa*, *E. coli*, and *Serratia marcescens*, are also common. Mixed infections are the rule rather than the exception. Septic arthritis is the purulent invasion of a joint by an infectious agent which produces arthritis. Systemic mycotic (fungal) infections may also cause osteomyelitis. The two most common are *Blastomyces dermatitidis* and *Coccidioides immitis*.

[00226] In some embodiments, provided herein is a method of treating reactive arthritis using a therapeutically-effective amount of a composition provided herein. Reactive arthritis is classified as an autoimmune condition that develops in response to an infection in another part of the body (cross-reactivity). Coming into contact with bacteria and developing an infection can trigger the disease. It is set off by a preceding infection, the most common of which would be a genital infection with *Chlamydia trachomatis*. Other bacteria known to cause reactive arthritis which are

more common worldwide are *Ureaplasma urealyticum*, *Salmonella spp.*, *Shigella spp.*, *Yersinia spp.*, and *Campylobacter spp.* Synovial fluid cultures are negative, suggesting that reactive arthritis is caused either by an over-stimulated autoimmune response or by bacterial antigens which have somehow become deposited in the joints.

[00227] In some embodiments, provided herein is a method of treating intestinal diseases including ulcerative colitis, inflammatory bowel disease (IBD) using a therapeutically-effective amount of a composition provided herein. IBD involves chronic inflammation of all or part of your digestive tract. IBD is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis.

[00228] In some embodiments, provided herein is a method of treating Systemic lupus erythematosus (SLE) using a therapeutically-effective amount of a composition provided herein. In SLE, the body's immune system produces antibodies against itself, particularly against proteins in the cell nucleus. SLE is triggered by environmental factors that are unknown. During an immune reaction to a foreign stimulus, such as bacteria, virus, or allergen, immune cells that would normally be deactivated due to their affinity for self tissues can be abnormally activated by signaling sequences of antigen-presenting cells. Thus triggers may include viruses, bacteria, allergens (both IgE and hypersensitivity), and can be aggravated by environmental stimulants such as ultraviolet light and certain drug reactions. These stimuli begin a reaction that leads to destruction of other cells in the body and exposure of their DNA, histones, and other proteins, particularly parts of the cell nucleus. The body's sensitized B-lymphocyte cells will now produce antibodies against these nuclear-related proteins. These antibodies clump into antibody-protein complexes which stick to surfaces and damage blood vessels in critical areas of the body, such as the glomeruli of the kidney; these antibody attacks are the cause of SLE. SLE is a chronic inflammatory disease believed to be a type III hypersensitivity response with potential type II involvement. HMGB1 may contribute to the pathogenesis of chronic inflammatory and autoimmune diseases due to its proinflammatory and immunostimulatory properties.

[00229] In some embodiments, provided herein is a method of treating Sjögren's syndrome using a therapeutically-effective amount of a composition provided herein. Sjögren's syndrome is a systemic autoimmune disease in which

immune cells attack and destroy the exocrine glands that produce tears and saliva. The hallmark symptom of Sjögren's syndrome is a generalized dryness, typically including xerostomia (dry mouth) and xerophthalmia (dry eyes), part of what are known as sicca symptoms. In addition, Sjögren's syndrome may cause skin, nose, and vaginal dryness, and may affect other organs of the body, including the kidneys, blood vessels, lungs, liver, pancreas, peripheral nervous system (distal axonal sensorimotor neuropathy) and brain. Sjögren's syndrome is associated with increased levels in Cerebrospinal fluid (CSF) of IL-1RA, an interleukin 1 antagonist. This suggests that the disease begins with increased activity in the interleukin 1 system, followed by an auto-regulatory up-regulation of IL-1RA to reduce the successful binding of interleukin 1 to its receptors. Sjögren's syndrome is also characterized by decreased levels of IL-1 RA in saliva.

[00230] In some embodiments, provided herein is a method of treating dermatomyositis using a therapeutically-effective amount of a composition provided herein. Dermatomyositis is a connective-tissue disease related to polymyositis (PM) and Bramaticosis that is characterized by inflammation of the muscles and the skin. The cause is unknown, but it may result from either a viral infection or an autoimmune reaction. Many people diagnosed with dermatomyositis were previously diagnosed with infectious mononucleosis and Epstein-Barr virus. In some cases of dermatomyositis onsets overlaps with other autoimmune diseases.

[00231] In some embodiments, provided herein is a method of treating vasculitis using a therapeutically-effective amount of a composition provided herein. Vasculitis refers to a heterogeneous group of disorders that are characterized by inflammatory destruction of blood vessels. Both arteries and veins are affected. Vasculitis is primarily due to leukocyte migration and resultant damage. There are many ways to classify vasculitis. It can be classified by the location of the affected or by the underlying cause. Vasculitides can be classified by the type or size of the blood vessels that they predominantly affect.

[00232] In some embodiments, provided herein is a method of treating mixed connective tissue disease (MCTD) using a therapeutically-effective amount of a composition provided herein. MCTD (also known as Sharp's syndrome), is an autoimmune disease, in which the body's defense system attacks itself. It is clinically characterized by presentation with overlapping features of primarily three connective

tissue diseases: lupus, scleroderma and polymyositis; and as a result, MCTD is considered an “overlap syndrome”.

[00233] In some embodiments, provided herein is a method of treating tendonitis using a therapeutically-effective amount of a composition provided herein. Tendonitis sometimes called chronic tendinitis, tendinosus, chronic tendinopathy or chronic tendon injury, is damage to a tendon. It is thought to be caused by microtears in the connective tissue in and around the tendon, leading to an increase in tendon repair cells. This may lead to reduced tensile strength, thus increasing the chance of tendon rupture. Classical characteristics of "tendinosis" include degenerative changes in the collagenous matrix, hypercellularity, hypervascularity and a lack of inflammatory cells.

[00234] In some embodiments, provided herein is a method of treating bacterial endocarditis using a therapeutically-effective amount of a composition provided herein. Bacterial endocarditis is a form of endocarditis, or inflammation, of the inner tissue of the heart, such as its valves, caused by infectious agents. The agents are usually bacterial, but other organisms can also be responsible. Historically, infective endocarditis has been clinically divided into acute and subacute presentations. Subacute bacterial endocarditis (SBE) is often due to *streptococci* of low virulence and mild to moderate illness which progresses slowly over weeks and months and has low propensity to hematogenously seed extracardiac sites. Acute bacterial endocarditis (ABE) is a fulminant illness over days to weeks, and is more likely due to *Staphylococcus aureus* which has much greater virulence, or disease-producing capacity and frequently causes metastatic infection.

[00235] In some embodiments, provided herein is a method of treating psoriasis using a therapeutically-effective amount of a composition provided herein. Psoriasis is common skin disease. It is characterized by cells to building up rapidly on the surface of the skin, forming thick silvery scales and itchy, dry, red patches that are sometimes painful. Psoriasis is a persistent, long-lasting (chronic) disease. You may have periods when your psoriasis symptoms improve or go into remission alternating with times your psoriasis worsens. The cause of psoriasis is not fully understood. There are two main hypotheses about the process that occurs in the development of the disease. The first considers psoriasis as primarily a disorder of excessive growth and reproduction of skin cells. The problem is simply seen as a fault of the epidermis and its keratinocytes. The second hypothesis sees the disease as being an immune-

mediated disorder in which the excessive reproduction of skin cells is secondary to factors produced by the immune system. T-cells become active by an unknown mechanism, and then migrate to the dermis where they trigger the release of cytokines such as tumor necrosis factor- α TNF α , in particular, This in turn, cause inflammation and the rapid production of skin cells.

[00236] In some embodiments, provided herein is a method of treating Rheumatic fever is using a therapeutically-effective amount of a composition provided herein. Rheumatic fever is a systemic inflammatory disease that occurs following a *Streptococcus pyogenes* infection. It believed to be caused by antibody cross-reactivity that can involve the heart, joints, skin, and brain. This cross-reactivity is a Type II hypersensitivity reaction. Usually, self reactive B-cells remain anergic in the periphery without T-cell costimulation. During a *Streptococcus* infection, mature antigen presenting cells such as B cells present the bacterial antigen to CD4-T cells which differentiate into helper T₂ cells. Helper T₂ cells subsequently activate the B-cells to become plasma cells and induce the production of antibodies against the cell wall of Streptococcus. However the antibodies may also react against the myocardium and joints producing the symptoms of rheumatic fever.

Virtual Cultures of Therapies of the Invention.

[00237] The compositions of the invention were analyzed on a virtual co-culture cell system designed to represent synovium, which can be triggered to represent inflammatory diseases such as Rheumatoid Arthritis (RA) conditions. These experiments have also been validated with *in-vivo* data as depicted in Examples 1 to 8.

[00238] The cell systems selected for the virtual co-culture included:

- a) macrophages responding to antigens or a bacterial insult thereby promoting an inflammatory response;
- b) B-Lymphocytes which recognize antigens and production of specific antibodies. In an autoimmune inflammatory disease the B-Lymphocytes are responsible for the recognition of self antigens and production of antibodies against them. In Rheumatoid Arthritis (RA), the antibodies against the self antigens are also known as Rheumatoid Factor or RA factor;
- c) T-Lymphocytes (CD4+ Cells), which recognize antigens presented by the macrophages and B-Lymphocytes and induce an inflammatory cytokine

response. In some inflammatory conditions, the interaction of T-Lymphocytes with macrophages and B-Lymphocytes is essential for the initiation of an inflammatory response; and,

d) the bone remodeling system cells (osteoclasts and osteoblasts) were selected to simulate their effect on the bone in response to the inflammatory cytokines.

[00239] In these virtual experiments, the system was first stimulated with high doses of antigen and then cultured for a minimum of about 18 hours. The culture time was selected to allow the system to attain severe RA conditions through all inflammatory mediators like cytokines, chemokines, and prostaglandins. After about 18 hours of antigen stimulation, an RA synovium-like environment was created, where the effect of the inflammatory cells (*i.e.* macrophages, T-Lymphocytes and B-Lymphocytes) could be analyzed for mediating a localized inflammation and modulating bone destruction.

[00240] As used in the virtual co-cultures, and throughout **Figures 3-52** and references to the same: CW299 is Imatinib Mesylate; CW302 is Simvastatin; CW305 is Sildenafil; CW299302 is a combination of Imatinib Mesylate and Simvastatin; CW299305 is a combination of Imatinib Mesylate and Sildenafil; CW305302 is a combination of Sildenafil and Simvastatin; and CW299305302 is a combination of Imatinib Mesylate, Sildenafil, and Simvastatin. The **Figures** reflect the simulated dosing for the virtual co-cultures.

[00241] The drug compounds CW299, CW305, and CW302 were administered concomitantly to the RA cell virtual co-culture system, and the cells were cultured for a minimum of about 12 hours. The drug administration was performed at multiple dosage ratios across an array of samples for each drugs. The effect of the multiple dosage ratios was evaluated after about 12 hours of culture by assaying the extent of decrease/increase in the cytokine population responsible for the swelling and tendering of joints. The major cytokines assayed included TNF α , IL6, IL1 β , IL17 and CCL2, which are responsible for joint swelling. Other proteins including matrix metalloproteinases (e.g. MMP9), cathepsin K, and other osteoclastogenesis-inducing factors, such as RANK ligand, were assayed to determine their effect. Other vital biomarkers including Prostaglandins (e.g. Prostaglandin E2) and C-Reactive Proteins (CRP) were assayed to estimate the levels of inflammation in the synovium.

[00242] Based on the assayed biomarkers, an ACR score was calculated using the ACR calculation criteria published by the American College of Rheumatology in 2010. *See* ARTHRITIS & RHEUMATISM; Vol. 62, No. 9, September 2010, pp 2569–2581, American College of Rheumatology.

[00243] “ACR score” is a scale to measure change in rheumatoid arthritis symptoms. It is named after the American College of Rheumatology. Different degrees of improvement are referred to as ACR20 (low), ACR50 (moderate), ACR70 (high). A level of improvement less than ACR20 is identified, “resist”. ACR50 response – which includes reducing the signs and symptoms of disease by 50%, according to criteria established by the American College of Rheumatology (ACR). The ACR score allows a 'common standard' between researchers.

[00244] The drugs were also tested on a TNF resistant (anti-TNF non-responders) cell co-culture system. This system was designed by desensitizing the TNF receptors by about 80% on all the cells in the co-culture system. The co-culture system was also populated with about 5 fold more B-Lymphocytes compared to the system described above. T-Lymphocyte co-stimulation was also enhanced by about 4 folds. Otherwise, the experiment followed the protocol described above.

[00245] The combinations of compounds described herein can provide therapeutic benefits at low dosage, including synergistic benefits. **Figures 1 and 2** illustrate the scientific rationale underlying the present disclosure, along with illustration the biochemical targets implicated in the relevant inflammatory pathways.

[00246] **Figure 3** illustrates the efficacies of individual drugs and combinations thereof in terms of ACR (American College of Rheumatology) score in TNF responders. The bars represent the efficacy of individual drugs CW299, CW305, CW302, and a combination thereof. Various drug ratios were used.

[00247] **Figure 4** illustrates the efficacies of individual drugs and combinations thereof in terms of ACR (American College of Rheumatology) score in a TNF resistive system (anti-TNF non responders). The bars represent the efficacy of individual drugs CW299, CW305, CW302, and a combination thereof. Various drug ratios were used. A comparison of the results illustrated in **Figures 3 and 4** reveal that the combination therapy is similarly effective in both TNF responders and anti-TNF non-responders.

[00248] The results illustrated in **Figure 3** and **Figure 4** indicate that CW299305302 exhibits better efficacy than CW299, CW305 and CW302

individually, as CW299305302 has a much higher ACR score than the individual drugs.

[00249] **Figure 5** compares the efficacy of combinations of the invention with two known/existing drugs. One is Etanercept, which is approved and currently a market leader in RA therapy, and the other, CP-690,550, is a promising candidate for RA in the late phase clinical trial . The comparison was done across clinically measurable parameters including Swollen joints, Tender Joints, CRP, and Pain.

[00250] **Figure 6** compares the efficacy of a drug combination in a TNF non-responders system with that of each of etanercept and CP-690,550. The comparison was done across clinically measurable parameters including Swollen joints, tender Joints, CRP, and Pain.

[00251] The results illustrated in **Figure 5** indicate that the three-drug combination of the invention exhibited efficacy similar to that of Etanercept and CP-690,550. The results illustrated in **Figure 6** demonstrate activity for three drug combination CW299305302 better than that of Etanercept and similar to that of CW299305302.

[00252] **Figures 7, 8 and 9** illustrate efficacy data for individual drugs and combinations thereof in TNF responders. The results are based on levels of TNF, IL6, and CCL2 biomarkers.

[00253] **Figures 10, 11 and 12** illustrate efficacy data for individual drugs and combinations thereof in TNF non-responders. The results are based on levels of TNF, IL6, CCL2 biomarkers.

[00254] The results illustrated in **Figures 7, 8, 9, 10, 11, and 12** indicate that the three drug combination CW299305302 was more effective than the individual drugs CW299, CW305 and CW302

[00255] **Figure 13** compares the efficacy of the individual drugs CW299, CW305 and CW302 with a combination thereof (CW299305) across parameters including Swollen joints, Tender Joints, CRP, and Pain in TNF responders.

[00256] **Figure 14** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF responders.

[00257] **Figure 15** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF responders.

[00258] **Figure 16** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF responders.

[00259] **Figure 17** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF resistant (anti-TNF non-responsive) system.

[00260] **Figure 18** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF resistant (anti-TNF non-responsive) system.

[00261] **Figure 19** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF resistant (anti-TNF non-responsive) system.

[00262] **Figure 20** compares the efficacy of the individual drugs CW299, CW305, and CW302 with a combination thereof (CW299305) across parameters including Swollen Joints, Tender Joints, CRP, and Pain in TNF resistant (anti-TNF non-responsive) system.

[00263] The results illustrated in **Figures 13, 14, 15, 16, 17, 18, 19, and 20** indicate that the three drug combination CW299305302 was more effective than the individual drugs CW299, CW305 and CW302 in TNF responders and TNF non-responders in measurements of Swollen Joints, Tender Joints, CRP, and Pain.

[00264] **Figure 21** illustrates efficacy data of the individual drugs CW299 and CW305 and a combination thereof (CW299305) in terms of ACR Score in TNF responders. The first two bars of **Figure 21** represent the efficacy of individual drugs CW299 and CW305, and the third bar represents the efficacy of the combination thereof.

[00265] **Figure 22** illustrates efficacy data of the individual drugs CW299 and CW305 and a combination thereof (CW299305) in terms of ACR Score in a TNF resistive system (anti-TNF non responders). The first two bars of **Figure 22** represent the efficacy of individual drugs, and the third bar represents the efficacy of the combination thereof.

[00266] The results illustrated in **Figures 21 and 22** indicate that the two drug combination CW299305 exhibited greater efficacy than the individual drugs CW299 and CW305 in TNF responders and TNF non-responders in measurements of Swollen Joints, Tender Joints, CRP and Pain.

[00267] **Figure 23** compares the efficacy of a combination of drugs (CW299 and CW305) with the efficacy of individual drugs having the same dosage. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in TNF responders.

[00268] **Figure 24** compares the efficacy of a combination of drugs (CW299 and CW305) with the efficacy of individual drugs having the same dosage. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in a TNF resistive system (anti-TNF non responders).

[00269] The results illustrated in **Figures 23 and 24** indicate that two drug combination CW299305 exhibited greater efficacy than the individual drugs CW299 and CW305 in TNF responders and TNF non-responders respectively in measurements of Swollen Joints, Tender Joints, CRP, and Pain.

[00270] **Figures 25, 26, and 27** compare the efficacies of individual drugs (CW299 and CW305) and a combination thereof (CW299305) by measurements of IL6, TNF and CCL2 biomarkers in TNF responders.

[00271] **Figures 28, 29, and 30** compare the efficacies of individual drugs (CW299 and CW305) and a combination thereof (CW299305) by measurements of IL6, TNF, and CCL2 biomarkers in a TNF resistive system (anti-TNF non responders).

[00272] The results illustrated in **Figures 25, 26, 27, 28, 29, and 30** indicate that the two drug combination CW299305 exhibited greater efficacy than the individual drugs CW299 and CW305 by measurements of IL6, TNF, and CCL2 biomarkers in TNF responders and TNF non-responders. The two drug combination exhibited higher efficacy with respect to the individual drugs as shown.

[00273] **Figure 31** compares efficacy data of the individual drugs CW305 and CW302 and a combination thereof in terms of ACR Score in TNF responders. The first two bars of **Figure 31** represent the efficacy of individual drugs, and the third bar represents the efficacy of the combination thereof.

[00274] **Figure 32** compares efficacy data of the individual drugs CW305 and CW302 and a combination thereof in terms of ACR Score in a TNF resistive system

(anti-TNF non responders). The first two bars of **Figure 32** represent the efficacy of individual drugs, and the third bar represents the efficacy of the combination thereof.

[00275] The results illustrated in **Figures 31 and 32** indicate that the two drug combination CW305302 exhibited greater efficacy than the individual drugs CW305 and CW302 in TNF responders and TNF non-responders as represented by ACR score.

[00276] **Figure 33** compares the efficacy of a combination of two drugs: (CW305 and CW302), with the individual drugs tested individually in the same doses. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in TNF responders.

[00277] **Figure 34** compares the efficacy of a combination of two drugs (CW305 and CW302), with the individual drugs tested individually in the same doses. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in TNF resistive system (anti-TNF non responders).

[00278] The results illustrated in **Figures 33 and 34** indicate that the two drug combination CW305302 exhibited greater efficacy than the individual drugs CW305 and CW302 in TNF responders and TNF non-responders across parameters including swollen joints, tender joints, CRP, and Pain.

[00279] **Figures 35, 36, and 37** compare the efficacy of individual drugs (CW305 and CW302) and a combination thereof by levels of IL6, TNF and CCL2 biomarkers in TNF responders.

[00280] **Figures 38, 39, and 40** compare the efficacy of individual drugs (CW302 and CW305) and a combination thereof by levels of IL6, TNF, and CCL2 biomarkers in a TNF resistive system (anti-TNF non responders).

[00281] The results illustrated in **Figures 35, 36, 37, 38, 39, and 40** indicate that the two drug combination CW305302 exhibited greater efficacy than the individual drugs CW305 and CW302 by measurements of IL6, TNF, and CCL2 biomarkers in TNF responders and TNF non-responders. The two drug combination drug has a much higher efficacy than the individual drugs as shown.

[00282] **Figure 41** illustrates efficacy data of the individual drugs CW299 and CW302 and a combination thereof (CW299302) in terms of ACR Score in TNF responders. The first two bars of **Figure 41** represent the efficacy of individual drugs; and the third bar represents the efficacy of the combination thereof.

[00283] **Figure 42** illustrates efficacy data of the individual drugs CW299 and CW302 and a combination thereof in terms of ACR Score in a TNF resistive system (anti-TNF non responders). The first two bars of **Figure 42** represent the efficacy of individual drugs, and the third bar represents the efficacy of the combination thereof.

[00284] The results illustrated in **Figures 41 and 42** indicate that the two drug combination CW299302 exhibited greater efficacy than the individual drugs CW299 and CW302 in TNF responders and TNF non-responders based on ACR score.

[00285] **Figure 43** compares the efficacy of a combination of two drugs (CW299 and CW302), with each of the individual drugs at the same dosage. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in TNF responders.

[00286] **Figure 44** compares the efficacy of a combination of two drugs (CW299 and CW302), with each of the individual drugs in the same dosage. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in a TNF resistive system (anti-TNF non responders).

[00287] The results illustrated in **Figures 43 and 44** indicate that the two drug combination CW299302 exhibited greater efficacy than the individual drugs CW299 and CW302 in TNF responders and TNF non-responders across parameter including swollen joints, tender joints, CRP, and Pain.

[00288] **Figures 45, 46, and 47** compare the efficacy of individual drugs (CW299 and CW302) and a combination thereof in measurements of IL6, TNF and CCL2 biomarkers in TNF responders.

[00289] **Figures 48, 49, and 50** compare the efficacy of individual drugs (CW299 and CW302) and a combination thereof by measurements of IL6, TNF, and CCL2 biomarkers in a TNF resistive system (anti-TNF non responders).

[00290] The results illustrated in **Figures 45, 46, 47, 48, 49, and 50** indicate that the two drug combination CW299302 exhibited greater efficacy than the individual drugs CW299 and CW302 by measurements of IL6, TNF, and CCL2 biomarkers in TNF responders and TNF non-responders. The two drug combination exhibited higher efficacy with respect to the individual drugs as shown.

[00291] **Figure 51** compares the efficacy of the two drug combinations CW299302, CW305302, and CW299305 with Etanercept and CP-690,550. The comparison was done across parameters including Swollen joints, Tender joints, CRP, and Pain in TNF responders.

[00292] **Figure 52** compares the efficacy of the two drug combinations CW299302, CW305302, and CW299305 with Etanercept and CP-690,550. The comparison was done across parameters including Swollen joints, Tender Joints, CRP, and Pain in a TNF resistive system (anti-TNF non responders).

[00293] The results illustrated in **Figure 51** indicates that the two drug combinations CW299302, CW305302 and CW299305, exhibited efficacies similar to those of Etanercept and CP-690,550 in TNF responders when compared across parameters including swollen joints, tender joints, CRP, and pain. **Figure 52** indicates that the two drug combinations CW299302, CW305302 and CW299305, exhibited efficacies greater than that of Etanercept and similar to that of CP-690,550 in TNF non-responders when compared across parameters including swollen joints, tender joints, CRP, and pain.

EXAMPLES

[00294] The present disclosure is further elucidated by the following illustrative, non-limiting examples.

Example	Description of the Example	Figures
Example 1	Effect of CW299305302 in collagen induced arthritis (CIA) mouse model with a high bar, early-mid disease stage therapeutic setting.	Figure 53
Example 2	Effect of CW299305302 in collagen induced arthritis (CIA) mouse model with a high bar, advanced disease stage therapeutic setting.	Figure 54
Example 3	Comparative analysis between mono (CW299) & combo (CW299305302) therapy in collagen induced arthritis model with a early-mid disease therapeutic setting.	Figure 55; Figure 56; Figure 57
Example 4	Comparative analysis between mono (CW299) & combo (CW299305302) therapy in collagen induced arthritis model with a high bar- advanced disease therapeutic setting.	Figure 58; Figure 59; Figure 60

Example 5	Histo-pathological analysis showing efficacy of CW299305302 therapy in collagen-induced arthritis model with a early -mid disease therapeutic setting.	Figure 61; Figure 62; Figure 63; Figure 64
Example 6	Comparative analysis between two drug combination (CW299305, CW305302, CW299302) and three drug combination (CW299305302) therapy in collagen-induced arthritis model with an early-mid disease therapeutic setting.	Figure 65; Figure 66
Example 7	Comparative analysis of efficacy between three drug combination (CW299305302) and etanercept therapy in collagen-induced arthritis model with an early-mid disease therapeutic setting.	Figure 67; Figure 68
Example 8	Toxicity / Tolerability Study of CW299305302	-

EXAMPLE 1

**EFFECT OF CW299305302 IN COLLAGEN INDUCED ARTHRITIS (CIA)
MOUSE MODEL WITH A HIGH BAR, EARLY-MID DISEASE STAGE
THERAPEUTIC SETTING**

Experimental Protocol

[00295] This study used DBA/1 mice (Taconic Farms 8 weeks old). Immunization agent was obtained from Hookes labs (Bovine collagen II/CFA, IIFA). All the mice were fed a standard Chow diet and provided a time of one week for acclimatization.

[00296] CIA induction was initiated at day 0 by injecting the mice with the immunization agent, one week after acclimatization. 95% of the immunized mice got at least a medium disease (score of 4), and 92% of mice got a score of approximately 10 by day 39.

[00297] A booster shot of collagen in IFA emulsion was administered subcutaneously into the tail on day 21, and subsequently the therapy administration was initiated on day 22, one day after the booster dose.

[00298] Starting at day 14, paws were scored daily using the following system:

0	Normal paw
1	One toe inflamed and swollen.
2	More than one toe, but not entire paw, inflamed and swollen, or Mild swelling of entire paw.
3	Entire paw inflamed and swollen.
4	Very inflamed and swollen paw or ankylosed paw.

[00299] Paw sores for each were added together to give a total score/ mouse (max =16).

Treatment Groups

[00300] The mice were divided into 2 groups (N = 10)

Group1: placebo (untreated)

Group2: A three drug combination was administered with a dosage composition of CW299 (Imatinib Mesylate) – 10 mg/kg (BID); CW305 (Sildenafil) – 3 mg/kg (BID); and CW302 (Simvastatin) – 12.5 mg/kg (QD).

[00301] The efficacy of the three drug combination was compared to placebo. The Sildenafil, and Simvastatin dosing in this study were equivalent to 1/3rd and 1/2 the approved therapeutic dosing, respectively. Imatinib Mesylate at 10 mg/kg is equivalent to 1/10th the approved therapeutic dosing.

Results

[00302] The three drug combination showed a 53% impact on disease progression 10 days after treatment, 39% after 14 days of treatment, and showed a significant statistical difference between placebo and treatment groups (**Figure 53**).

EXAMPLE 2

**EFFECT OF CW299305302 IN COLLAGEN INDUCED ARTHRITIS (CIA)
MOUSE MODEL WITH A HIGH BAR, ADVANCED DISEASE STAGE
THERAPEUTIC SETTING**

Experimental Protocol

[00303] This study used DBA/1 mice (Taconic Farms 8 weeks old). Immunization agent was obtained from Hookes Labs (Bovine collagen II/CFA, IIFA). All the mice were fed a standard Chow diet and provided a time of one week for acclimatization.

[00304] CIA induction was initiated at day 0 by injecting the mice with the immunization agent, one week after acclimatization. 95% of the immunized mice got at least a medium disease (score of 4) and 92% of mice got a score of approximately 10 by day 39.

[00305] A booster shot of collagen in IFA emulsion was administered subcutaneously into the tail on day 21 and subsequently the therapy administration was initiated on day 29, eight days after the booster dose when the average disease scores in all cohorts was around 3. Starting at day 14 paws were scored daily using the following system.

[00306] Paw sores were calculated as given in **Example 1**.

Treatment Groups

[00307] The mice were divided into 2 groups (N = 12)

Group1: placebo (untreated)

Group2: A three drug combination was administered with a dosage composition of CW299 (Imatinib Mesylate) – 5 mg/kg (BID); CW305 (Sildenafil) – 5 mg/kg (BID); and CW302 (Simvastatin) – 12.5 mg/kg (QD).

[00308] The efficacy of the three drug combination was compared to placebo. The Sildenafil and Simvastatin dosing in this study were equivalent to 2/3rd and 1/2 the approved therapeutic dosing, respectively. Imatinib Mesylate at 5 mg/kg is equivalent to 1/20th the approved therapeutic dosing.

Results

[00309] The three drug combination showed a 25% impact on disease progression 10 days after treatment, and showed a significant statistical difference between placebo and treatment groups (**Figure 54**).

EXAMPLE 3

COMPARATIVE ANALYSIS BETWEEN MONO (CW299) & COMBO (CW299305302) THERAPY IN COLLAGEN-INDUCED ARTHRITIS MODEL WITH AN EARLY-MID DISEASE THERAPEUTIC SETTING

Experimental Protocol

[00310] Experiments were conducted as per the protocol given in **Example 1**.

Treatment Groups:

[00311] The mice were divided into 4 groups (N = 10)

Group1: placebo (untreated)

Group2: CW299 (Imatinib Mesylate) – 30 mg/kg

Group3: CW299 (Imatinib Mesylate) – 10 mg/kg

Group4: A three drug combination was administered with a dosage composition of
CW299 (Imatinib Mesylate) – 10 mg/kg (BID);
CW305 (Sildenafil) – 3 mg/kg (BID); and
CW302 (Simvastatin) – 12.5 mg/kg (QD).

[00312] The efficacy of the three drug combination was compared to placebo. The Sildenafil and Simvastatin dosing in this study were equivalent to 1/3rd and 1/2 the approved therapeutic dosing, respectively. Imatinib Mesylate at 10mg/kg is equivalent to 1/10th the approved therapeutic dosing.

Results:

[00313] The three drug combination showed a significant impact on disease progression 10 days after treatment and showed a significant statistical difference between placebo and treatment groups (**Figures 56 and 57**), which could be attributed to synergy.

[00314] The results also showed a significant correlation to the predicted effect of the combination therapy for the data obtained from the Cellworks predictive technology (**Figure 55**).

EXAMPLE 4

COMPARATIVE ANALYSIS BETWEEN MONO (CW299) & COMBO (CW299305302) THERAPY IN COLLAGEN INDUCED ARTHRITIS MODEL WITH A HIGH BAR- ADVANCED DISEASE THERAPEUTIC SETTING

Experimental Protocol:

[00315] Experiments were conducted as per the protocol given in **Example 2**.

Treatment Groups:

[00316] The mice were divided in to 4 groups (N = 12)

Group1: placebo (untreated)

Group2: CW299 (Imatinib Mesylate) – 30 mg/kg

Group3: CW299 (Imatinib Mesylate) – 10 mg/kg

Group4: A three drug combination was administered with a dosage composition of
CW299 (Imatinib Mesylate) – 5 mg/kg (BID),
CW305 (Sildenafil) – 5 mg/kg (BID) and
CW302 (Simvastatin) – 12.5 mg/kg (QD).

[00317] The efficacy of the three drug combination was compared to placebo. The Sildenafil, and Simvastatin dosing in this study were equivalent to 2/3rd and 1/2 the approved therapeutic dosing, respectively. Imatinib Mesylate at 5 mg/kg is equivalent to 1/20th the approved therapeutic dosing.

Results:

[00318] The three drug combination showed a significant impact on disease progression 10 days after treatment and showed a significant statistical difference between placebo and treatment groups (**Figures 59 and 60**), which could be attributed to synergy.

[00319] The results also showed a significant correlation to the predicted effect of the combination therapy for the data obtained from the Cellworks predictive technology (**Figure 58**).

EXAMPLE 5

HISTOPATHOLOGICAL ANALYSIS SHOWING EFFICACY OF CW299305302 THERAPY IN COLLAGEN-INDUCED ARTHRITIS MODEL WITH AN EARLY-MID DISEASE THERAPEUTIC SETTING

Experimental Protocol:

[00320] Experiments were conducted as per the protocol given in **Example 1**. The following histo-pathological parameters are assessed.

Inflammation Scoring:

[00321] Inflammation consisted of infiltration by inflammatory cells (mononuclear cells and neutrophils) accompanied by edema and fibrosis.

Inflammation was scored as follows.

Grade 0	Within normal limits
Grade 1	Minimal scattered inflammatory cell infiltration.
Grade 2	Mild infiltration with small focal aggregates and diffuse peri-synovial infiltration and edema.
Grade 3	Moderate infiltration in the synovium and peri-synovial tissues.
Grade 4	More severe inflammatory cell infiltration with focal, diffuse and peri-synovial distribution.
Grade 5	Very severe inflammation with many large aggregates of inflammatory cells, intra-articular fibrin, and extensive peri-synovial infiltration and fibrosis.

Pannus Scoring:

[00322] Pannus is a tissue composed of proliferating synovial-lining cells admixed with inflammatory cells, granulation tissue and fibrous connective tissue that form villous fronds or plaques. Pannus was scored as follows.

Grade 0	Within normal limits.
Grade 1	A few relatively un-inflamed villi affecting the peripheral synovium.
Grade 2	More extensive formation of villous fronds.
Grade 3	Mild villous proliferation with some plaque formation.
Grade 4	Moderate plaque formation encroaching on the cartilage.
Grade 5	Marked plaque formation in the central joint space.

Cartilage Degeneration Scoring:

[00323] General cartilage degeneration included the important parameters of chondrocyte death/loss, proteoglycan loss, and collagen loss with replacement of cartilage by inflammation and pannus formation. Cartilage degeneration was scored as follows.

Grade 0	Within normal limits.
Grade 1	Minimal superficial cartilage degeneration and loss.
Grade 2	Mild cartilage loss extending up to 25% of the cartilage depth
Grade 3	Moderate cartilage loss extending well into the mid-zone and generally affecting > 25% of the total cartilage thickness and/or up to 25% of the total cartilage area
Grade 4	Marked degeneration and loss extending well into the mid-zone and generally affecting up to 50% of the total cartilage thickness and/or up to 50% of the total cartilage area.
Grade 5	Severe degeneration and loss generally affecting up to 75% of the total cartilage area.

Bone Resorption Scoring:

[00324] Cartilage erosion consists of destruction/resorption of bone as a consequence of inflammation. Bone resorption was scored as follows.

Grade 0	Within normal limits.
Grade 1	Minimal bone erosion with small foci.
Grade 2	Mild bone erosion with 1-4 focal areas of resorption.
Grade 3	Moderate bone erosion extending into the cortical bone.
Grade 4	Marked bone erosion extending partly through the cortical bone.
Grade 5	Extensive bone erosion with cortical penetration involving >25% of the entire bone length.

Treatment Groups:

[00325] The mice were divided in to 3 groups (N = 10)

Group1: Naïve (control)

Group2: Placebo (untreated)

Group3: A three drug combination was administered with a dosage composition of

CW299 (Imatinib Mesylate) – 10 mg/kg (BID),

CW305 (Sildenafil) – 3 mg/kg (BID) and

CW302 (Simvastatin) – 12.5 mg/kg (QD).

Results:

[00326] Three drug combination showed efficacy on the reduction of the histopathological parameters including Synovitis (**Figure 61**), Pannus formation (**Figure 62**), Cartilage Degradation (**Figure 63**), and Bone Degradation (**Figure 64**) by showing a significant statistical difference between placebo and the treatment group.

EXAMPLE 6

COMPARATIVE ANALYSIS BETWEEN TWO DRUG COMBINATION (CW299305, CW305302, CW299302) AND THREE DRUG COMBINATION (CW299305302) THERAPY IN COLLAGEN-INDUCED ARTHRITIS MODEL WITH AN EARLY-MID DISEASE THERAPEUTIC SETTING

Experimental Protocol

[00327] Experiments were conducted as per the protocol given in **Example 1**.

Treatment Groups:

[00328] The mice were divided in to 5 groups (N = 10)

Group1: placebo (untreated)

Group2: CW299305 (Imatinib Mesylate; Sildenafil)

Group3: CW305302 (Sildenafil; Simvastatin)

Group4: CW299302 (Imatinib Mesylate; Simvastatin)

Group5: CW299305302 (Imatinib Mesylate; Sildenafil; Simvastatin)

[00329] The drugs were administered in the following dosages: CW299 (Imatinib Mesylate) – 10 mg/kg (BID), CW305 (Sildenafil) – 3 mg/kg (BID), CW302 (Simvastatin) – 12.5 mg/kg (QD).

Results:

[00330] CW29930, CW305302, and CW299302 showed a significant statistical impact on disease progression 10 days after treatment. Three drug combination CW299305302 showed a higher impact on disease progression than did the two drug combinations, which could be attributed to synergy. All combinations tested showed a significant statistical difference between placebo and the treatment groups (**Figures 66**).

[00331] The results also showed a significant correlation to the predicted effect obtained from the Cellworks predictive technology (**Figure 65**).

EXAMPLE 7

COMPARATIVE ANALYSIS OF EFFICACY BETWEEN THREE DRUG COMBINATION (CW299305302) AND ETANERCEPT THERAPY IN COLLAGEN-INDUCED ARTHRITIS MODEL WITH AN EARLY-MID DISEASE THERAPEUTIC SETTING

Experimental Protocol

[00332] Experiments are conducted as per the protocol given in **Example 1**.

Treatment Groups:

[00333] The mice were divided into 3 groups (N = 10)

Group1: placebo (untreated)

Group2: Etanercept

Group3: Three drug combination

[00334] The three drug combination was administered with following dosage composition:

CW299 (Imatinib Mesylate) – 10 mg/kg (BID);

CW305 (Sildenafil) – 3 mg/kg (BID); and

CW302 (Simvastatin) – 12.5 mg/kg (QD).

Results:

[00335] The three drug combination showed a comparable or higher impact on disease progression than did Etanercept, and 10 days after treatment showed a significant statistical difference between placebo and treatment groups (**Figures 67**). The three drug combination showed comparable or higher percentage efficacy in decreasing the disease than did Etanercept (**Figure 68**).

[00336] The results also showed a significant correlation to the predicted effect obtained from the Cellworks predictive technology (**Figure 5**).

EXAMPLE 8

TOXICITY / TOLERABILITY STUDY OF CW299305302

Experimental Protocol:

[00337] Naive (non-induced) mice were dosed with either vehicle or CW299305302 (Imatinib Mesylate/Sildenafil/Simvastatin), PO, BID for 8 days, and toxicity and tolerability parameters were monitored.

Result

Tolerability Study:

[00338] A modest weight loss in the vehicle and therapy treatments groups was attributed solely to the stress of BID, PO dosing and not the study drugs. Furthermore, there was no evidence of drug effects on the appearance or behavior of the mice.

In-vivo Efficacy Studies:

[00339] As in the tolerability study, neither weight nor general health was compromised by CW299305302 therapy in either study. Furthermore, a liver enzyme and lipid profile panel of mice in study 1, treated for 18 days, showed no difference between the placebo and CW299305302 treated mice.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising:
 - a) two or three of:
 - i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;
 - ii) an inhibitor of phosphodiesterase 5; and
 - iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and
 - b) optionally a pharmaceutically-acceptable excipient.
2. The composition of claim 1, comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and optionally the pharmaceutically-acceptable excipient.
3. The composition of any one of claims 1-2, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is: Imatinib; Sti-571; Nilotinib; Dasatinib; Sunitinib; Masitinib; Bosutinib; Ponatinib; Bafetinib; CYC10268, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
4. The composition of any one of claims 1-3, wherein the inhibitor of phosphodiesterase 5 is: Sildenafil; Udenafil; Vardenafil; Tadalafil; or Avanafil, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
5. The composition of any one of claims 1-4, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is: Fluvastatin; Atorvastatin; Simvastatin; Lovastatin; Mevastatin; Pravastatin; Rosuvastatin; Pitavastatin; or Cerivastatin, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

6. The composition of claim 1, comprising: the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; the inhibitor of phosphodiesterase 5; and optionally the pharmaceutically-acceptable excipient.
7. The composition of claim 6, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is: Imatinib; Sti-571; Nilotinib; Dasatinib; Sunitinib; Masitinib; Bosutinib; Ponatinib; Bafetinib; CYC10268, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
8. The composition of any one of claims 6-7, wherein the inhibitor of phosphodiesterase 5 is: Sildenafil; Udenafil; Vardenafil; Tadalafil; or Avanafil, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
9. The composition of claim 1, comprising: the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and optionally the pharmaceutically-acceptable excipient.
10. The composition of claim 9, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is: Imatinib; Sti-571; Nilotinib; Dasatinib; Sunitinib; Masitinib; Bosutinib; Ponatinib; Bafetinib; CYC10268, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
11. The composition of any one of claims 9-10, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is: Fluvastatin; Atorvastatin; Simvastatin; Lovastatin; Mevastatin; Pravastatin; Rosuvastatin; Pitavastatin; or Cerivastatin, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

12. The composition of claim 1, comprising: the inhibitor of phosphodiesterase 5; the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and optionally the pharmaceutically-acceptable excipient.

13. The composition of claim 12, wherein the inhibitor of phosphodiesterase 5 is: Sildenafil; Udenafil; Vardenafil; Tadalafil; or Avanafil, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

14. The composition of any one of claims 12-13, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is: Fluvastatin; Atorvastatin; Simvastatin; Lovastatin; Mevastatin; Pravastatin; Rosuvastatin; Pitavastatin; or Cerivastatin, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

15. The composition of any one of claims 1 and 2, wherein: the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is Imatinib Mesylate; the inhibitor of phosphodiesterase 5 is Sildenafil; and the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is Simvastatin.

16. The composition of any one of claims 1-15, wherein each of the inhibitors is present in an amount from about 5% to about 100% of the maximum tolerated amount.

17. The composition of any one of claims 1-15, wherein each inhibitor is present in an amount from about 1 mg to about 2000 mg.

18. The composition of any one of claims 1-11, and 15, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is present in an amount from about 10 mg/kg to about 800 mg/kg.

19. The composition of any one of claims 1-8, and 12-15, wherein the inhibitor of phosphodiesterase 5 is present in an amount from about 3 mg/kg to about 100 mg/kg.

20. The composition of any one of claims 1-5, and 9-15, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is present in an amount from about 10 mg/kg to about 450 mg/kg.

21. The composition of any one of claims 1-20, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

22. The composition of any one of claims 1-21, wherein the composition is a dosage form that is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, geltab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

23. The composition of any one of claims 1-22, wherein the composition is a dosage form having an immediate release, a controlled release, or a sustained delayed release mechanism.

24. The composition of any one of claims 1-23, wherein the composition is a dosage form formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

25. The composition of any one of claims 1-24, wherein the composition is a dosage form formulated for oral administration.

26. A kit comprising:

a) two or three of:

- i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;
 - ii) an inhibitor of phosphodiesterase 5; and
 - iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and
- b) optionally a pharmaceutically-acceptable excipient,
- wherein the kit comprises one or a plurality of dosage forms.

27. The kit of claim 26, wherein the kit comprises:

- 1) a first dosage form comprising the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways, and optionally the pharmaceutically-acceptable excipient;
- 2) a second dosage form comprising the inhibitor of phosphodiesterase 5, and optionally the pharmaceutically-acceptable excipient; and
- 3) a third dosage form comprising the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and optionally the pharmaceutically-acceptable excipient.

28. The kit of claim 26, wherein the kit comprises:

- 1) a first dosage form comprising the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways, the inhibitor of phosphodiesterase 5, and optionally the pharmaceutically-acceptable excipient; and
- 2) a second dosage form comprising the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and optionally the pharmaceutically-acceptable excipient.

29. The kit of claim 26, wherein the kit comprises:

- 1) a first dosage form comprising the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways, the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and optionally the pharmaceutically-acceptable excipient; and
- 2) a second dosage form comprising the inhibitor of phosphodiesterase 5, and optionally the pharmaceutically-acceptable excipient.

30. The kit of claim 26, wherein the kit comprises:
- 1) a first dosage form comprising the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways, and optionally the pharmaceutically-acceptable excipient; and
 - 2) a second dosage form comprising the inhibitor of phosphodiesterase 5, the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and optionally the pharmaceutically-acceptable excipient.
31. The kit of claim 26, wherein the kit comprises:
- a single dosage form comprising the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways, the inhibitor of phosphodiesterase 5, the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and optionally the pharmaceutically-acceptable excipient.
32. The kit of any one of claims 26-31, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is: Imatinib; Sti-571; Nilotinib; Dasatinib; Sunitinib; Masitinib; Bosutinib; Ponatinib; Bafetinib; CYC10268, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
33. The kit of any one of claims 26-32, wherein the inhibitor of phosphodiesterase 5 is: Sildenafil; Udenafil; Vardenafil; Tadalafil; or Avanafil, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
34. The kit of any one of claims 26-33, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is: Fluvastatin; Atorvastatin; Simvastatin; Lovastatin; Mevastatin; Pravastatin; Rosuvastatin; Pitavastatin; or Cerivastatin, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.
35. The kit of any one of claims 26-34, wherein: the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is Imatinib Mesylate; the inhibitor of phosphodiesterase 5 is Sildenafil; and the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is Simvastatin.

36. The kit of any one of claims 26-35, wherein each of the inhibitors is present in an amount from about 5% to about 100% of the maximum tolerated amount.

37. The kit of any one of claims 26-35, wherein each inhibitor is present in an amount from about 1 mg to about 2000 mg.

38. The kit of any one of claims 26-35, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is present in an amount from about 10 mg/kg to about 800 mg/kg.

39. The kit of any one of claims 26-35, and 38, wherein the inhibitor of phosphodiesterase 5 is present in an amount from about 3 mg/kg to about 100 mg/kg.

40. The kit of any one of claims 26-35, and 38-39 wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is present in an amount from about 10 mg/kg to about 450 mg/kg.

41. The kit of claim 26, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

42. The kit of claim 26, wherein at least one of the dosage forms is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, gellab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

43. The kit of claim 26, wherein at least one of the dosage forms has an immediate release, a controlled release, or a sustained delayed release mechanism.

44. The kit of claim 26, wherein at least one of the dosage forms is formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

45. The kit of claim 26, wherein at least one of the dosage forms is formulated for oral administration.

46. A method for treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, the method comprising administering to the subject two or three of:

- a) a therapeutically-effective amount of an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;
- b) a therapeutically-effective amount of an inhibitor of phosphodiesterase 5; and
- c) a therapeutically-effective amount of an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase,

wherein the administration uses one or a plurality of dosage forms, each dosage form comprising one or more inhibitors, and wherein each dosage form optionally further comprises a pharmaceutically-acceptable excipient.

47. The method of claim 46, wherein:

- 1) all three inhibitors are administered to the subject in a single dosage form;
- 2) any two of the inhibitors are administered to the subject in a first dosage form, and the other inhibitor is administered to the subject in a second dosage form; or
- 3) three independent dosage forms are administered to the subject, each inhibitor being administered via one of the independent dosage forms.

48. The method of claim 46, wherein:

- 1) any two of the inhibitors are administered in a single dosage form; or

2) any two of the inhibitors are administered, each administered in separate dosage forms.

49. The method of any one of claims 46-48, wherein the inhibitors are administered simultaneously.

50. The method of any one of claims 46-48, wherein the inhibitors are administered sequentially.

51. The method of any one of claims 46-50, wherein the inflammatory joint disease is rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, polyarthritis, spondylitis, bursitis, gout, or any combination thereof.

52. The method of any one of claims 46-50, wherein the chronic inflammatory connective tissue disease is systemic lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis, mixed connective tissue disease, tendonitis, synovitis, bacterial endocarditis, osteomyelitis, psoriasis, or any combination thereof.

53. The method of any one of claims 46-52, wherein the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is: Imatinib; Sti-571; Nilotinib; Dasatinib; Sunitinib; Masitinib; Bosutinib; Ponatinib; Bafetinib; CYC10268, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

54. The method of any one of claims 46-53, wherein the inhibitor of phosphodiesterase 5 is: Sildenafil; Udenafil; Vardenafil; Tadalafil; or Avanafil, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

55. The method of any one of claims 46-54, wherein the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is: Fluvastatin; Atorvastatin; Simvastatin; Lovastatin; Mevastatin; Pravastatin; Rosuvastatin; Pitavastatin; or Cerivastatin, or a pharmaceutically-acceptable salt of any of the foregoing, or any combination thereof.

56. The method of any one of claims 46-55, wherein: the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is Imatinib Mesylate; the inhibitor of phosphodiesterase 5 is Sildenafil; and the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is Simvastatin.

57. The method of any one of claims 46-56, wherein the therapeutically-effective amount of each inhibitor is from about 5% to about 100% of the maximum tolerated dose.

58. The method of any one of claims 46-56, wherein the therapeutically-effective amount of each inhibitor is from about 1 mg to about 2000 mg.

59. The method of any one of claims 46-56, wherein:

a) the therapeutically-effective amount of the inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways is from about 10 mg/kg to about 800 mg/kg;

b) the therapeutically-effective amount of the inhibitor of phosphodiesterase 5 is from about 3 mg/kg to about 100 mg/kg; and

c) the therapeutically-effective amount of the inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase is from about 10 mg/kg to about 450 mg/kg.

60. The method of any one of claims 46-59, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

61. The method of any one of claims 46-60, wherein at least one of the dosage forms is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, gellab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion,

cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

62. The method of any one of claims 46-61, wherein at least one of the dosage forms has an immediate release, a controlled release, or a sustained delayed release mechanism.

63. The method of any one of claims 46-62, wherein at least one of the dosage forms is formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

64. The method of any one of claims 46-63, wherein at least one of the dosage forms is formulated for oral administration.

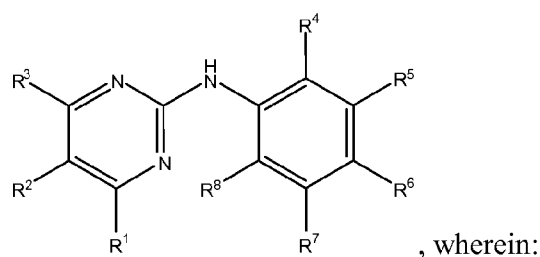
65. The method of any one of claims 50-64, wherein the sequential administration is at a time interval ranging from about 1 second to about 600 minutes.

66. A use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

67. A combination of compounds for use in the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways; an inhibitor of phosphodiesterase 5; and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase.

68. A composition comprising:

- a) two or three of:
 - i) a compound of the formula (I):



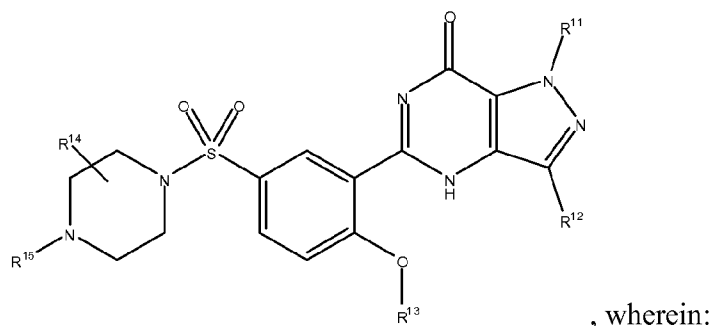
- R¹ is a cyclic group that is substituted or unsubstituted;
- R² and R³ are each independently hydrogen or alkyl;
- one or two of the groups R⁴, R⁵, R⁶, R⁷, and R⁸ are each nitro, alkoxy, fluoro-substituted alkoxy, or a group of the formula: -N(R⁹)-C(=X)-(Y)_n-R¹⁰, wherein:

- R⁹ is hydrogen or alkyl;
- X is oxo, thio, =NH, =N(alkyl), =NOH, or =NO(alkyl);
- Y is oxygen, NH, or N(alkyl);
- n is 0 or 1; and
- R¹⁰ is an alkyl group or a cyclic group,

and the remaining groups R⁴, R⁵, R⁶, R⁷, and R⁸ are each independently: hydrogen; alkyl that is unsubstituted or substituted by amino, alkyl amino, or dialkyl amino; a heterocycle; acyl; trifluoromethyl; hydroxyl; alkoxy; amino; alkyl amino; dialkyl amino; amido; carbamato; a carboxylic acid; or an ester group,

or a pharmaceutically-acceptable salt thereof;

ii) a compound of the formula (II) or tautomer thereof:



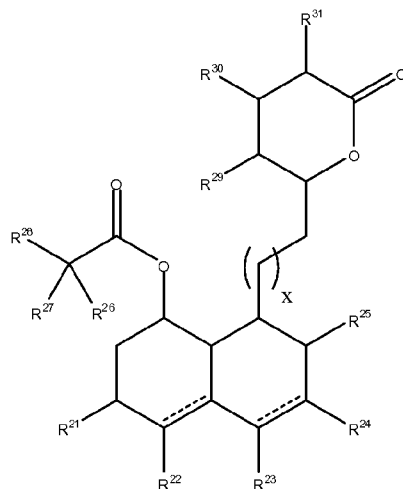
- R¹¹ is H, C1-C3 alkyl, C3-C5 cycloalkyl or C1-C3 perfluoroalkyl;
- R¹² is H, C1-C6 alkyl optionally substituted by OH, C1-C3 alkoxy or C3-C6 cycloalkyl, or C1-C3 perfluoroalkyl;
- R¹³ is C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, C3-C7 cycloalkyl, C1-C6 perfluoroalkyl or (C3-6 cycloalkyl)C1-C6 alkyl;
- R¹⁴ is H, C1-C4 alkyl, C1-C3 alkoxy, NR¹⁶R¹⁷, or CON¹⁶R¹⁷;

- R^{15} is H, C1-C6 alkyl, (C1-C3 alkoxy)C2-C6 alkyl, hydroxy C2-C6 alkyl, $(R^{16} R^{17} N)C2-C6$ alkyl, $(R^{16} R^{17} NCO)C1-C6$ alkyl, $CONR^{16} R^{17}$, $CSNR^{16} R^{17}$ or $C(NH)NR^{16} R^{17}$;

- R^{16} and R^{17} are each independently H, C1-C4 alkyl, (C1-C3 alkoxy)C2-C4 alkyl or hydroxy C2-C4 alkyl,

or a pharmaceutically-acceptable salt thereof; and

iii) a compound of the formula (III):



, wherein:

- each of R^{21} , R^{22} , R^{23} , R^{24} , and R^{25} is independently H, alkyl, hydroxyl, alkoxy, or an ester group;

- each of R^{26} , R^{27} , and R^{28} is independently H, alkyl, hydroxyl, alkoxy, amino, alkyl amino, dialkyl amino, or an ester group;

- each of R^{29} , R^{30} , and R^{31} is independently H, alkyl, halogen, hydroxyl, alkoxy, amino, alkyl amino, dialkyl amino, or an ester group;

- x is 0, 1, 2, 3, 4, 5, or 6; and

- each $\text{---}\text{---}\text{---}$ is independently either a single or double bond,

or a pharmaceutically-acceptable salt thereof; and

b) optionally a pharmaceutically-acceptable excipient.

69. The composition of claim 68, wherein: R^1 is 4-pyrazinyl, 1-methyl-1H-pyrrolyl, phenyl; phenyl substituted with amino, alkyl amino, dialkyl amino, or acyl amino; phenyl substituted with aminoalkyl; phenyl substituted with alkyl; 1H-indolyl; 1H-imidazolyl; pyridyl; pyridyl substituted with alkyl; pyridyl *N*-oxide; or pyridyl *N*-oxide substituted with alkyl. R^2 and R^3 are each independently hydrogen or alkyl.

One or two of the groups R^4 , R^5 , R^6 , R^7 , and R^8 are each nitro, fluoro-substituted alkoxy, or a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:

- R^9 is hydrogen or alkyl;
- X is oxo, thio, =NH, =N(alkyl), =NOH, or =NO(alkyl);
- Y is oxygen or NH;
- n is 0 or 1; and
- R^{10} is an aliphatic hydrocarbon group having 5-22 carbon atoms; a phenyl or naphthyl group each of which is unsubstituted or substituted by cyano, alkyl, alkoxy, (4-methyl-piperazinyl)-alkyl, trifluoromethyl, hydroxy, alkanoyloxy, halogen, amino, alkyl amino, dialkyl amino, alkanoyl amino, benzoyl amino, carboxy or by alkoxycarbonyl; or phenyl-alkyl wherein the phenyl group is unsubstituted or substituted as indicated above; a cycloalkyl or cycloalkenyl group having up to 30 carbon atoms; a cycloalkyl-alkyl or cycloalkenyl-alkyl group each having up to 30 carbon atoms; a heterocyclic group having 5 or 6 ring members and 1-3 ring heteroatoms selected from nitrogen, oxygen and sulfur, to which heterocyclic group one or two carbocyclic rings may be fused,

and the remaining groups R^4 , R^5 , R^6 , R^7 , and R^8 are each independently: hydrogen; alkyl that is unsubstituted or substituted by amino, alkyl amino, or dialkyl amino; a heterocycle; acyl; trifluoromethyl; hydroxyl; alkoxy; amino; alkyl amino; dialkyl amino; amido; carbamato; a carboxylic acid; or a carboxylic ester.

70. The composition of any one of claims 68-69, wherein: R^1 is pyridyl or pyridyl *N*-oxide; R^2 and R^3 are each hydrogen; R^4 is hydrogen or alkyl; R^5 is hydrogen or alkyl; R^6 is hydrogen; R^7 is a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:

- R^9 is hydrogen;
- X is oxo;
- n is 0; and
- R^{10} is a phenyl group that is unsubstituted or substituted by cyano, alkyl, (4-methyl-piperazinyl)methyl, or halogen, and

R^8 is hydrogen.

71. The composition of any one of claims 68-70, wherein: R^1 is 3-pyridyl; R^2 and R^3 are each hydrogen; R^4 is hydrogen or methyl; R^5 is hydrogen or methyl; R^6 is hydrogen; R^7 is a group of the formula: $-N(R^9)-C(=X)-(Y)_n-R^{10}$, wherein:

- R^9 is hydrogen;
- X is oxo;
- n is 0; and
- R^{10} is a phenyl group that is unsubstituted or substituted by (4-methyl-piperazinyl)methyl, and

R^8 is hydrogen.

72. The composition of any one of claims 68-71, wherein: R^{11} is H, methyl, or ethyl; R^{12} is C1-C3 alkyl optionally substituted by OH; R^{13} is C2-C3 alkyl or allyl; R^{14} is H, $NR^{16}R^{17}$ or $CONR^{16}R^{17}$; R^{15} is H, C1-C3 alkyl, hydroxy C2-C3 alkyl, $CONR^{16}R^{17}$, $CSNR^{16}R^{17}$ or $C(NH)NR^{16}R^{17}$; and R^{16} and R^{17} are each independently H or methyl.

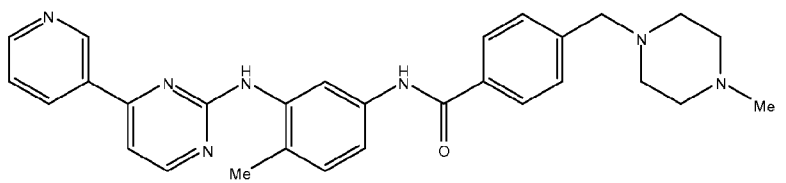
73. The composition of any one of claims 68-72, wherein: R^{11} is methyl; R^{12} is n-propyl; R^{13} is ethyl, n-propyl, or allyl; R^{14} is H, and R^{15} is H, C1-C3 alkyl or 2-hydroxyethyl.

74. The composition of any one of claims 68-73, wherein: each of R^{21} and R^{25} is independently alkyl or hydroxyl; each of R^{22} , R^{23} , R^{24} is H; each of R^{26} , R^{27} , and R^{28} is independently H, alkyl, or hydroxyl; each of R^{29} and R^{31} is H; R^{30} is H, alkyl, or hydroxyl; x is 0, 1, or 2; and each  is a double bond.

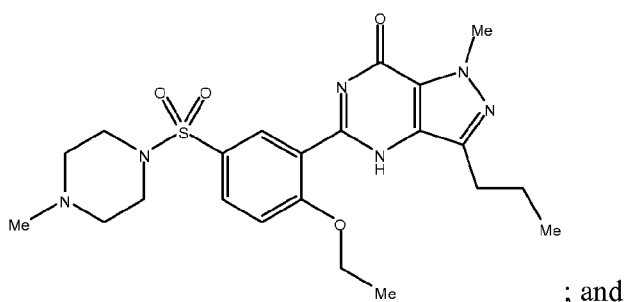
75. The composition of any one of claims 68-74, wherein: each of R^{21} and R^{25} is alkyl; each of R^{22} , R^{23} , R^{24} is H; each of R^{26} , R^{27} , and R^{28} is independently alkyl; each of R^{29} and R^{31} is H; R^{30} hydroxyl; x is 1; and each  is a double bond.

76. The composition of any one of claims 68-75, wherein:

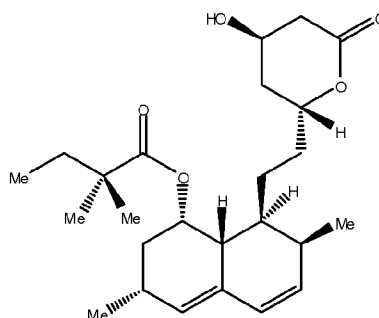
i) the compound of formula (I) is:



ii) the compound of formula (II) is:



; and



iii) the compound of formula (III) is:

77. The composition of any one of claims 68-76, wherein each of the compounds is present in an amount from about 5% to about 100% of the maximum tolerated amount.

78. The composition of any one of claims 68-76, wherein each compound is present in an amount from about 1 mg to about 2000 mg.

79. The composition of any one of claims 68-76, wherein the compound of formula (I) is present in an amount from about 10 mg/kg to about 800 mg/kg.

80. The composition of any one of claims 68-76, wherein the compound of formula (II) is present in an amount from about 3 mg/kg to about 100 mg/kg.

81. The composition of any one of claims 68-76, wherein the inhibitor of formula (III) is present in an amount from about 10 mg/kg to about 450 mg/kg.

82. The composition of any one of claims 68-81, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

83. The composition of any one of claims 68-82, wherein the composition is a dosage form that is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, gellab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

84. The composition of any one of claims 68-83, wherein the composition is a dosage form having an immediate release, a controlled release, or a sustained delayed release mechanism.

85. The composition of any one of claims 68-84, wherein the composition is a dosage form formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

86. The composition of any one of claims 68-85, wherein the composition is a dosage form formulated for oral administration.

87. A kit comprising:

a) two or three of:

i) the compound of formula (I), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76;

- ii) the compound of formula (II) or tautomer thereof, or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; and
 - iii) the compound of formula (III), a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; and
- b) optionally a pharmaceutically-acceptable excipient, wherein the kit comprises one or a plurality of dosage forms.

88. The kit of claim 87, wherein the kit comprises:

- 1) a first dosage form comprising the compound of formula (I), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient;
- 2) a second dosage form comprising the compound of formula (II) , or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient; and
- 3) a third dosage form comprising the compound of formula (III), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient.

89. The kit of claim 87, wherein the kit comprises:

- 1) a first dosage form comprising the compound of formula (I), or a pharmaceutically-acceptable salt thereof, the compound of formula (II) , or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient; and
- 2) a second dosage form comprising the compound of formula (III), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient.

90. The kit of claim 87, wherein the kit comprises:

- 1) a first dosage form comprising the compound of formula (I), or a pharmaceutically-acceptable salt thereof, the compound of formula (III), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient; and

2) a second dosage form comprising the compound of formula (II) , or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient.

91. The kit of claim 87, wherein the kit comprises:

1) a first dosage form comprising the compound of formula (I), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient; and

2) a second dosage form comprising the compound of formula (II) , or a pharmaceutically-acceptable salt thereof, the compound of formula (III), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient.

92. The kit of claim 87, wherein the kit comprises:

a single dosage form comprising the compound of formula (I), or a pharmaceutically-acceptable salt thereof, the compound of formula (II) , or a pharmaceutically-acceptable salt thereof, the compound of formula (III), or a pharmaceutically-acceptable salt thereof, and optionally the pharmaceutically-acceptable excipient.

93. The kit of any one of claims 87-92 wherein each of the compounds is present in an amount from about 5% to about 100% of the maximum tolerated amount.

94. The kit of any one of claims 87-92, wherein each compound is present in an amount from about 1 mg to about 2000 mg.

95. The kit of any one of claims 87-92, wherein the compound of formula (I) is present in an amount from about 10 mg/kg to about 800 mg/kg.

96. The kit of any one of claims 87-92, and 95 wherein the compound of formula (II) is present in an amount from about 3 mg/kg to about 100 mg/kg.

97. The kit of any one of claims 87-92, and 95-96 wherein the compound of formula (III) is present in an amount from about 10 mg/kg to about 450 mg/kg.

98. The kit of claim 87, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

99. The kit of claim 87, wherein at least one of the dosage forms is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, gellab, nanosuspension, nanoparticle, microgel, suppository troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

100. The kit of claim 87, wherein at least one of the dosage forms has an immediate release, a controlled release, or a sustained delayed release mechanism.

101. The kit of claim 87, wherein at least one of the dosage forms is formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

102. The kit of claim 87, wherein at least one of the dosage forms is formulated for oral administration.

103. A method for treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, the method comprising administering to the subject two or three of:

- a) a therapeutically-effective amount of the compound of formula (I), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76;
- b) a therapeutically-effective amount of the compound of formula (II) or tautomer thereof, or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; and

c) a therapeutically-effective amount of the compound of formula (III), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76, wherein the administration uses one or a plurality of dosage forms, each dosage form comprising one or more compounds, and wherein each dosage form optionally further comprises a pharmaceutically-acceptable excipient.

104. The method of claim 103, wherein:

- 1) all three compounds are administered to the subject in a single dosage form;
- 2) any two of the compounds are administered to the subject in a first dosage form, and the other compound is administered to the subject in a second dosage form; or
- 3) three independent dosage forms are administered to the subject, each compound being administered via one of the independent dosage forms.

105. The method of claim 103, wherein:

- 1) any two of the compounds are administered in a single dosage form; or
- 2) any two of the compounds are administered, each administered in separate dosage forms.

106. The method of claim 103-105, wherein the compounds are administered simultaneously.

107. The method of claim 103-105, wherein the compounds are administered sequentially.

108. The method of any one of claims 103-107, wherein the inflammatory joint disease is rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, polyarthritis, spondylitis, bursitis, gout, or any combination thereof.

109. The method of any one of claims 103-107, wherein the chronic inflammatory connective tissue disease is systemic lupus erythematosus, scleroderma, Sjorgen's syndrome, poly- and dermatomyositis, vasculitis, mixed connective tissue disease,

tendonitis, synovitis, bacterial endocarditis, osteomyelitis, psoriasis, or any combination thereof.

110. The method of any one of claims 103-109, wherein the therapeutically-effective amount of each compound is from about 5% to about 100% of the maximum tolerated dose.

111. The method of any one of claims 103-109, wherein the therapeutically-effective amount of each compound is from about 1 mg to about 2000 mg.

112. The method of any one of claims 103-109, wherein:

- a) the therapeutically-effective amount of the compound of formula (I) is from about 10 mg/kg to about 800 mg/kg;
- b) the therapeutically-effective amount of the compound of formula (II) is from about 3 mg/kg to about 100 mg/kg; and
- c) the therapeutically-effective amount of the compound of formula (III) is from about 10 mg/kg to about 450 mg/kg.

113. The method of any one of claims 103-112, wherein the pharmaceutically-acceptable excipient is a granulating agent, binding agent, lubricating agent, disintegrating agent, sweetening agent, glidant, anti-adherent, anti-static agent, surfactant, anti-oxidant, gum, coating agent, coloring agent, flavouring agent, coating agent, plasticizer, preservative, suspending agent, emulsifying agent, plant cellulosic material, spheronization agent, immediate release agent, controlled release agent, sustained delayed release agent, or any combination thereof.

114. The method of any one of claims 103-113, wherein at least one of the dosage forms is a feed, food, pellet, lozenge, liquid, elixir, aerosol, inhalant, spray, powder, tablet, pill, capsule, gel, gellab, nanosuspension, nanoparticle, microgel, suppository, troches, aqueous or oily suspensions, ointment, patch, lotion, dentifrice, emulsion, cream, drop, dispersible powder or granule, emulsion in hard or soft gel capsule, syrup, phytoceutical, nutraceutical, or any combination thereof.

115. The method of any one of claims 103-114, wherein at least one of the dosage forms has an immediate release, a controlled release, or a sustained delayed release mechanism.

116. The method of any one of claims 103-115, wherein at least one of the dosage forms is formulated for intravenous, subcutaneous, intramuscular, oral, rectal, aerosol, parenteral, ophthalmic, pulmonary, transdermal, vaginal, otic, nasal, or topical administration.

117. The method of any one of claims 103-116, wherein at least one of the dosage forms is formulated for oral administration.

118. The method of any one of claims 107-117, wherein the sequential administration is at a time interval ranging from about 1 second to about 600 minutes.

119. A use of a combination of compounds in the preparation of a medicament for the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: the compound of formula (I), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; the compound of formula (II) or tautomer thereof, or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; and the compound of formula (III), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76.

120. A combination of compounds for use in the treatment of inflammatory joint diseases and/or chronic inflammatory connective tissue diseases, the compounds comprising: the compound of formula (I), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; the compound of formula (II) or tautomer thereof, or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76; and the compound of formula (III), or a pharmaceutically-acceptable salt thereof, of any one of claims 68-76.

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FIGURE 1

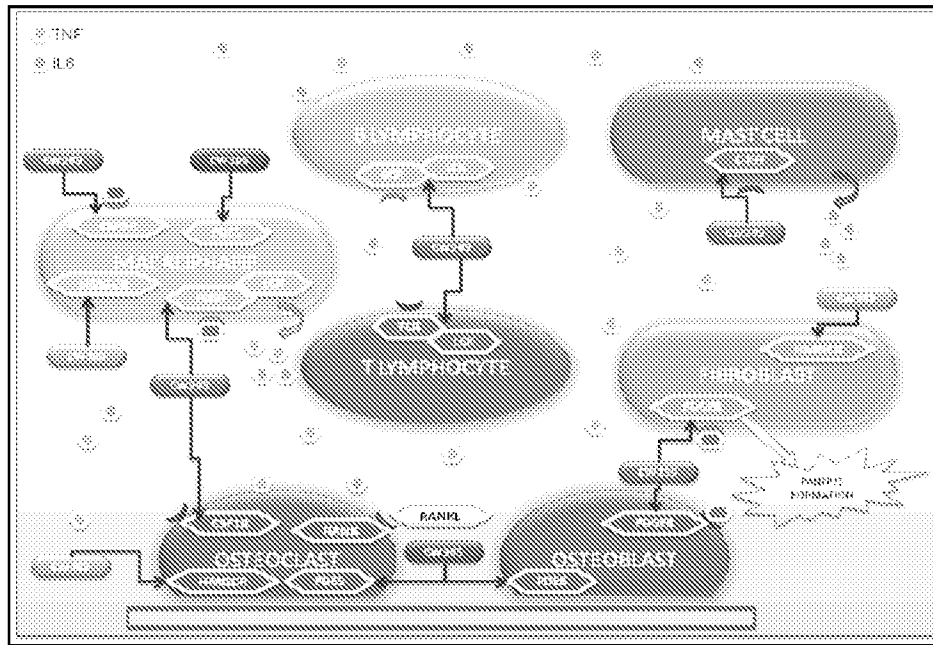
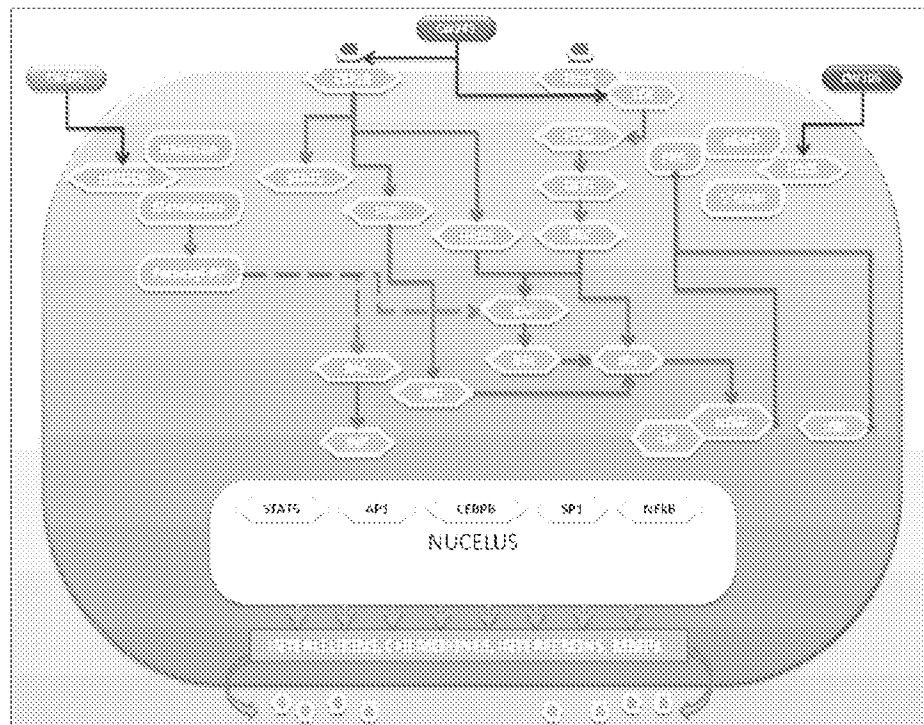
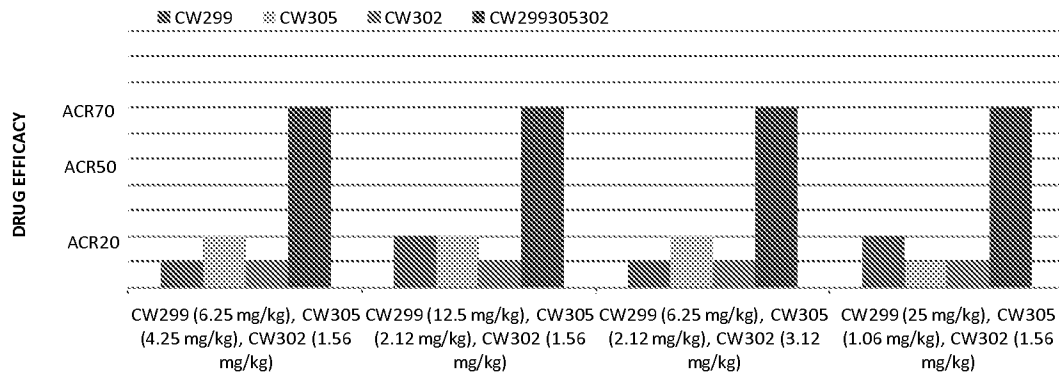
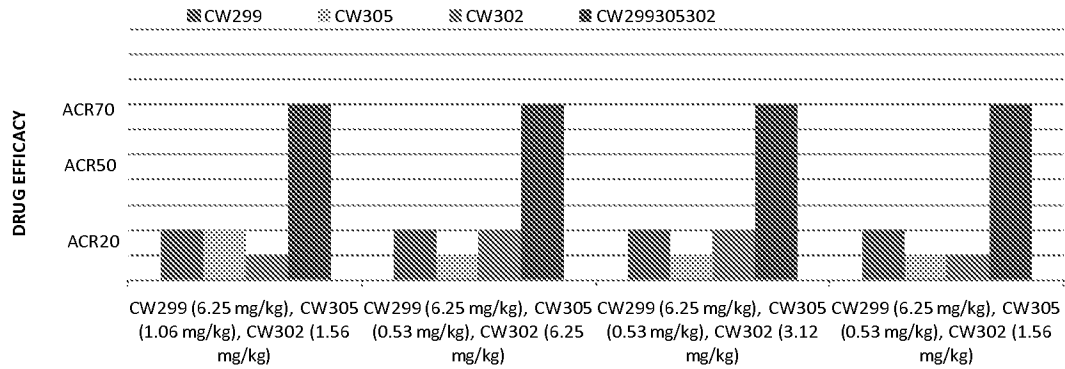


FIGURE 2



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FIG. 3 CW299305302 TNF RESPONDERS**ACR - EFFICACY BASED SYNERGY****FIG. 4 CW299305302 TNF NON-RESPONDERS****ACR - EFFICACY BASED SYNERGY**

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FIG. 5 COMPARISON OF ETANCERCEPT AND CP690550 VS. CW299302305 IN TNF RESPONDERS

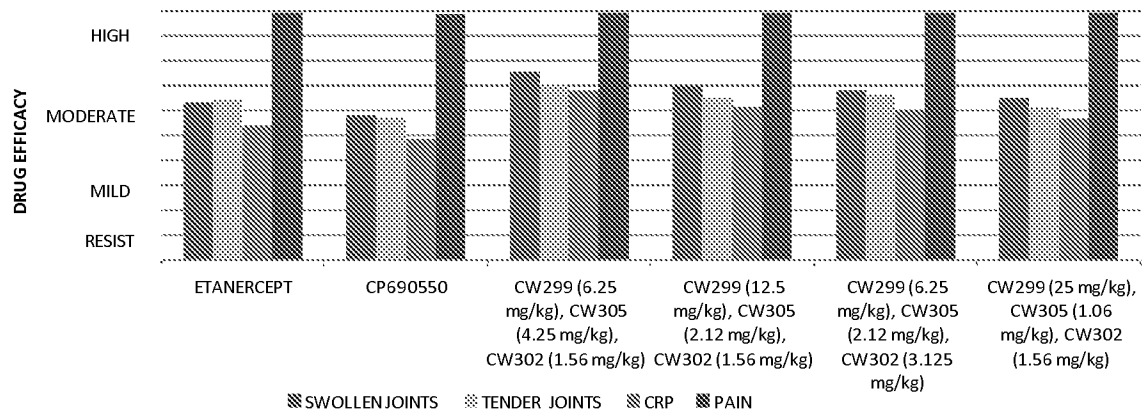


FIG. 6 COMPARISON OF ETANCERCEPT AND CP690550 VS. CW299302305 IN TNF NON-RESPONDERS

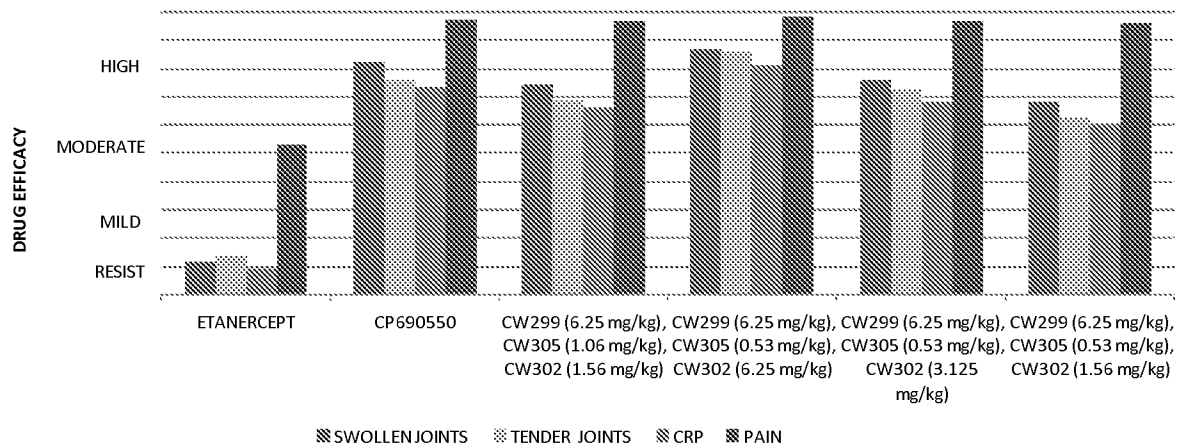


FIG. 7 CW299305302 - TNF RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs. COMBO

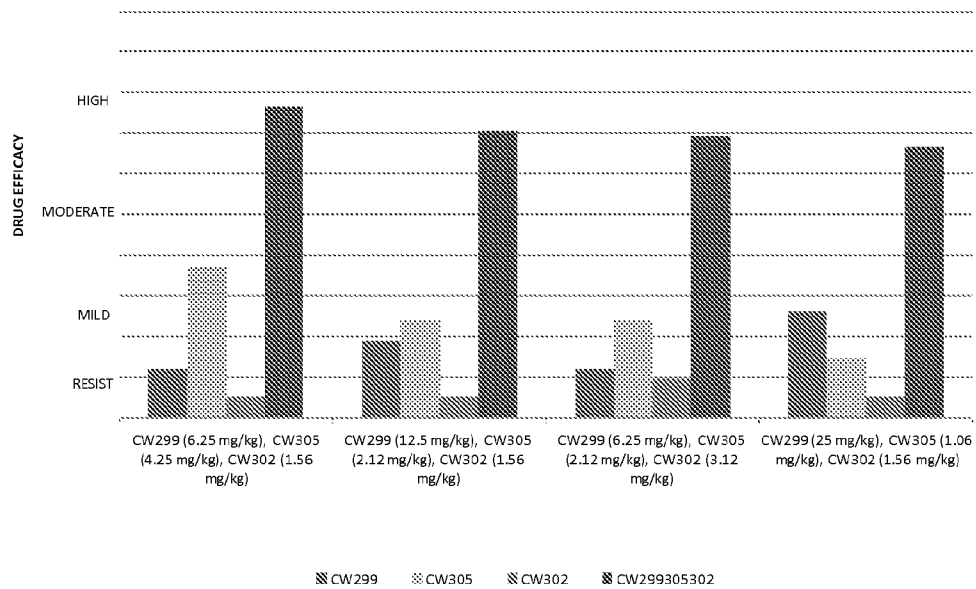
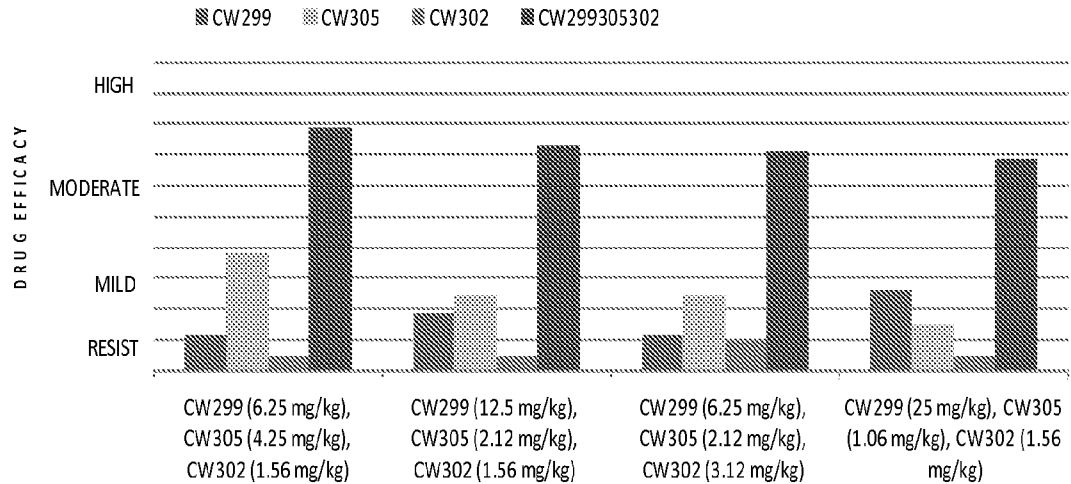


FIG. 8 CW299305302 - TNF RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs. COMBO



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FIG. 9 CW299305302 - TNF RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs. COMBO

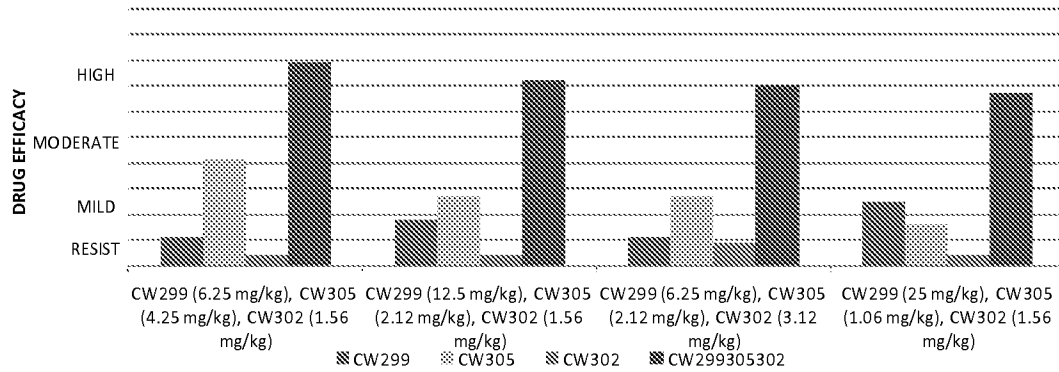


FIG . 10 CW299305302 - TNF NON-RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs. COMBO

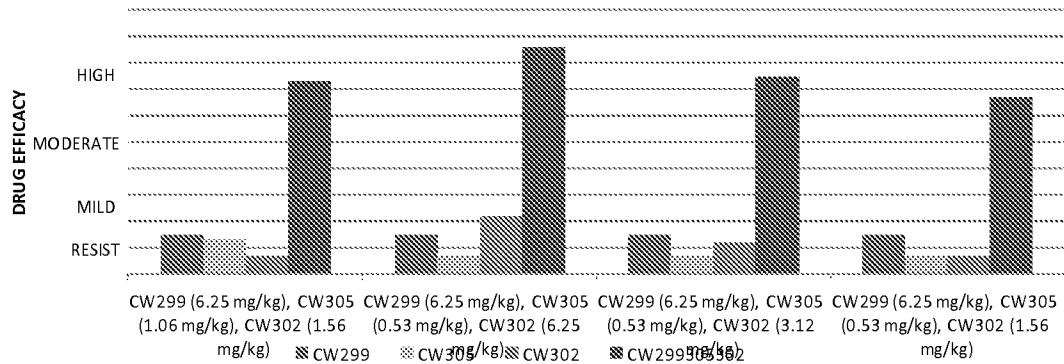


FIG. 11 CW299305302 - TNF NON-RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs. COMBO

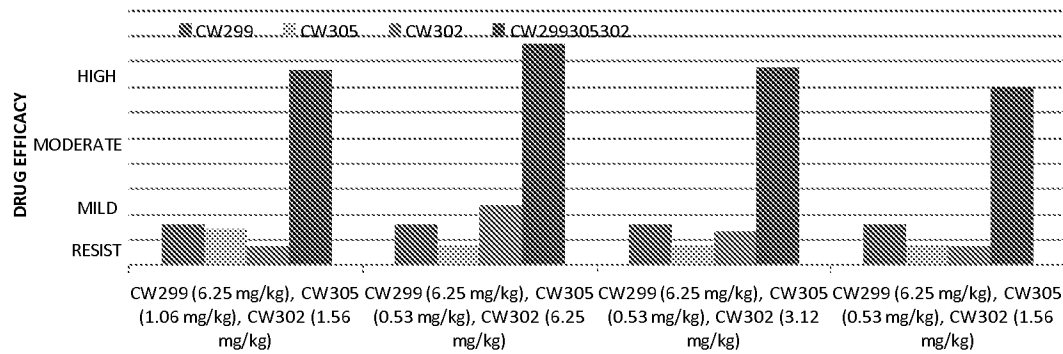
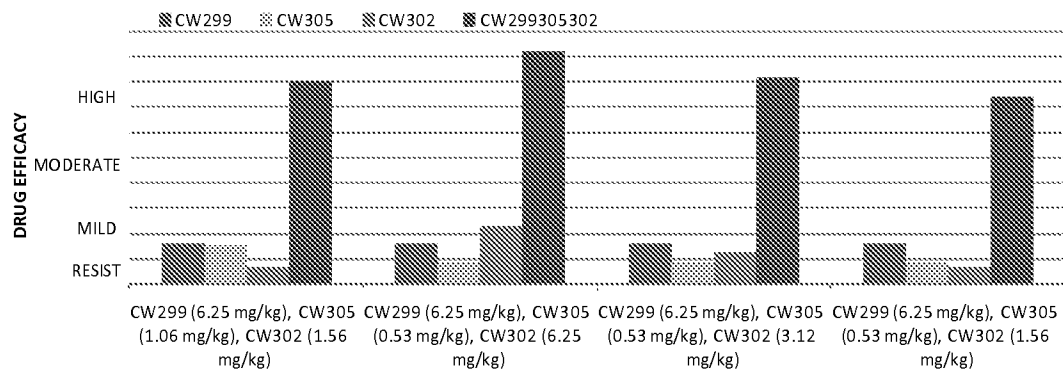


FIG. 12 CW299305302 - TNF NON-RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs. COMBO



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FIG. 13 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - MONO vs COMBO

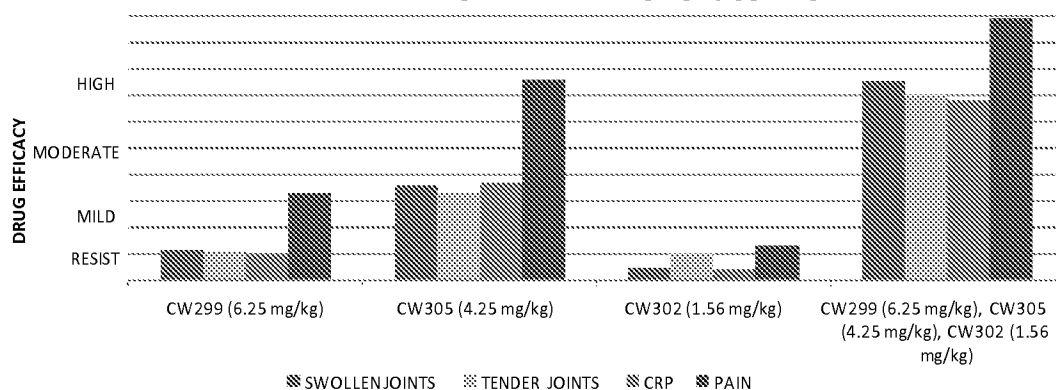
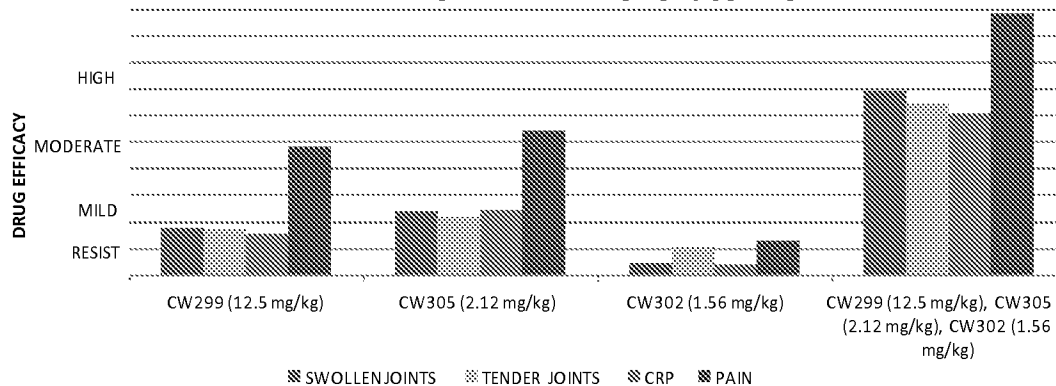


FIG. 14 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - MONO vs COMBO



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FIG. 15 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - MONO vs COMBO

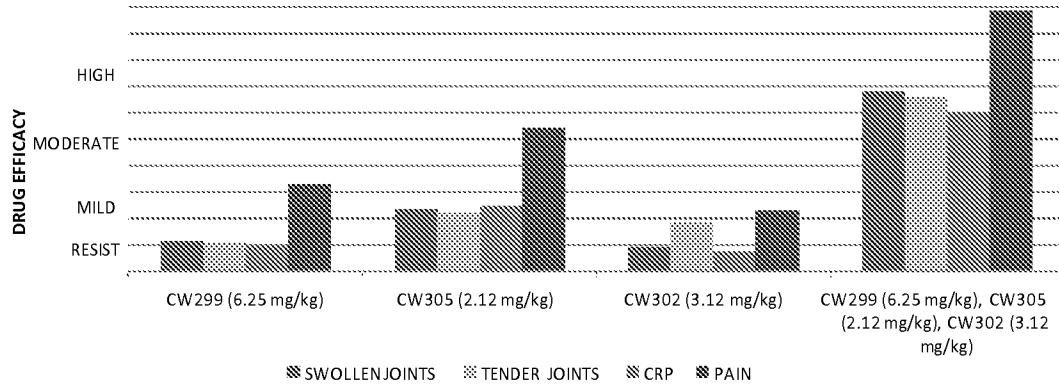
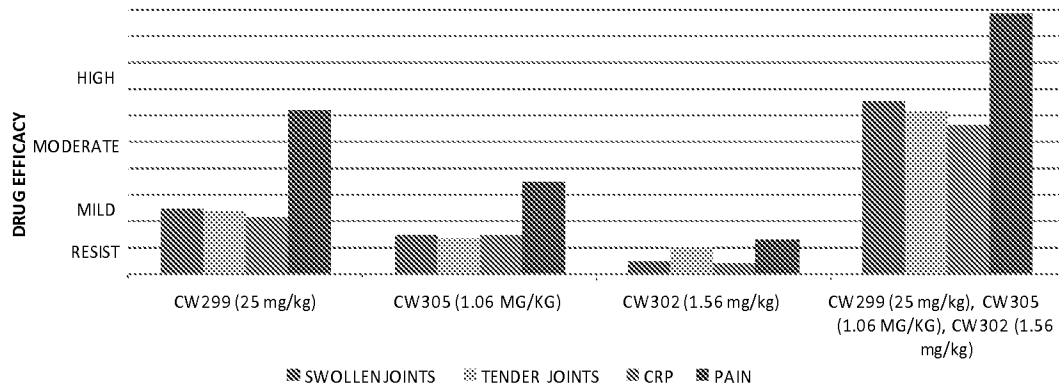


FIG. 16 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - MONO vs COMBO



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FIG. 17 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - MONO VS. COMBO

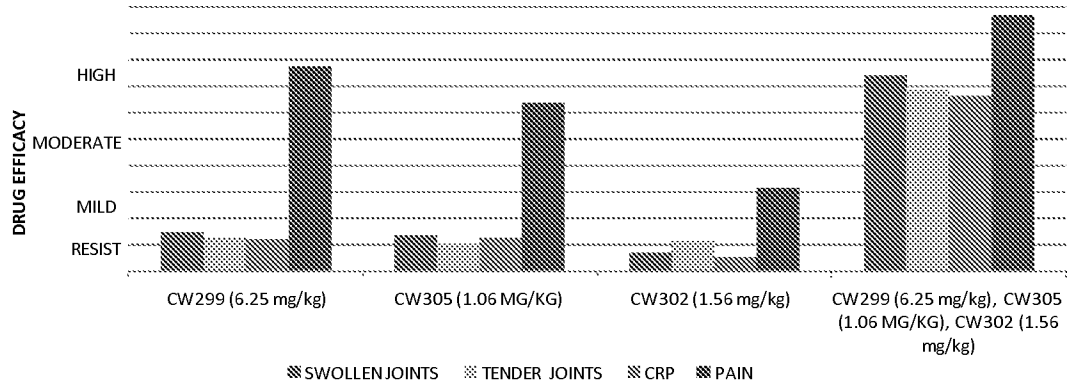
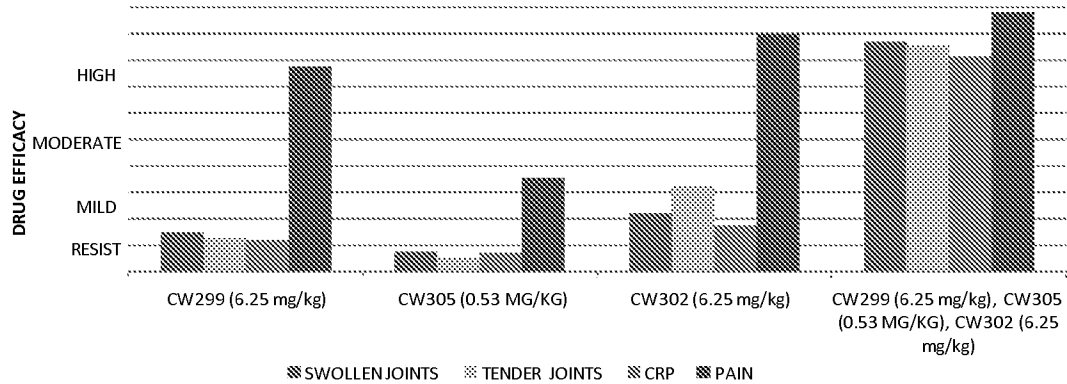


FIG. 18 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - MONO VS. COMBO



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FIG. 19 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - MONO vs COMBO

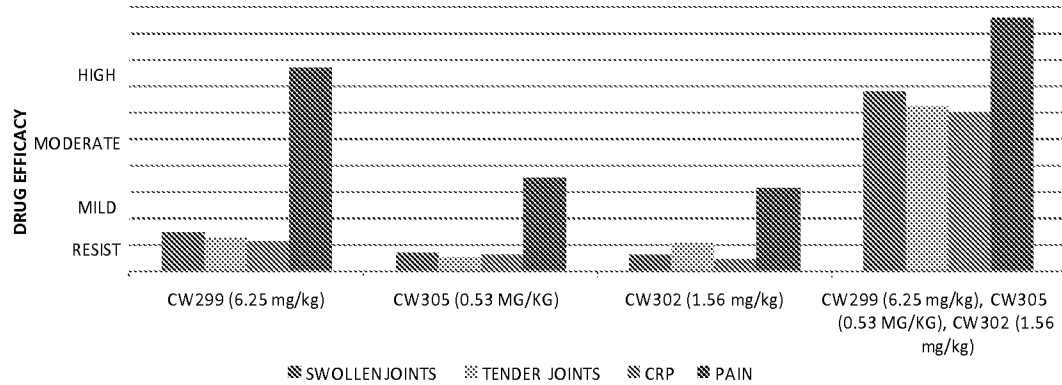
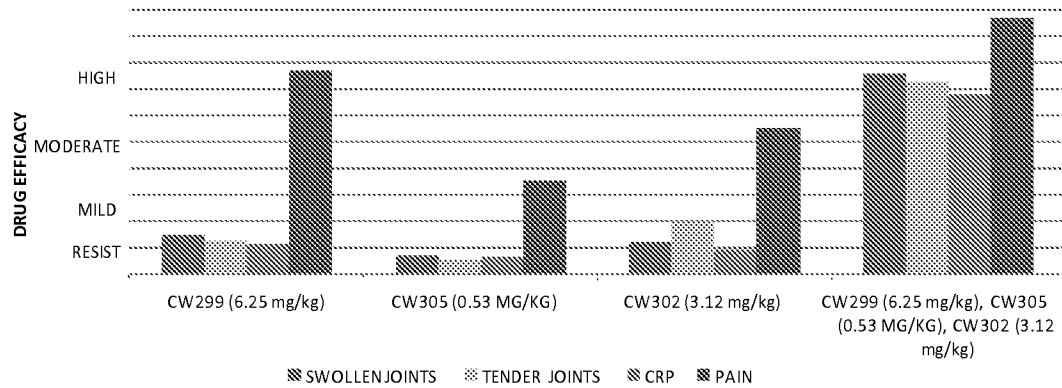
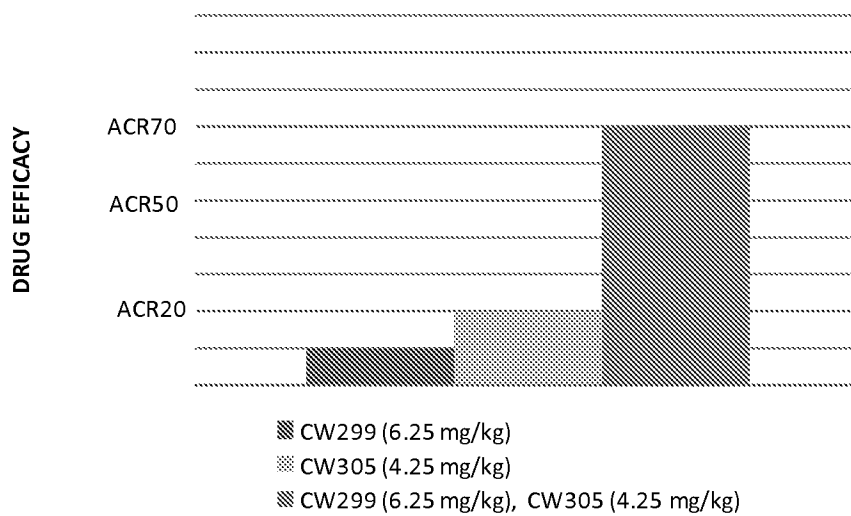
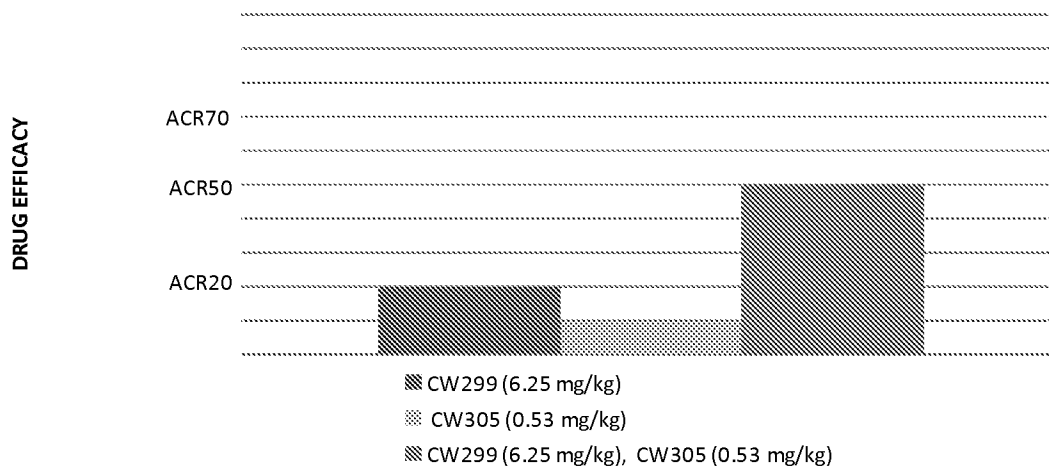


FIG. 20 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - MONO vs COMBO



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FIG. 21 CW299305 - TNF RESPONDERS**FIG. 22 CW299305 - TNF NON-RESPONDERS**

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FIG. 23 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - INDIVIDUAL vs COMBO

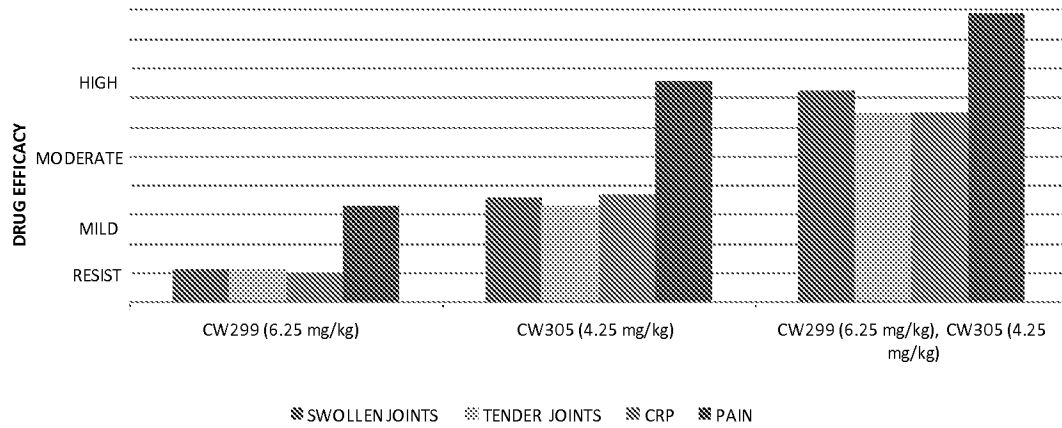
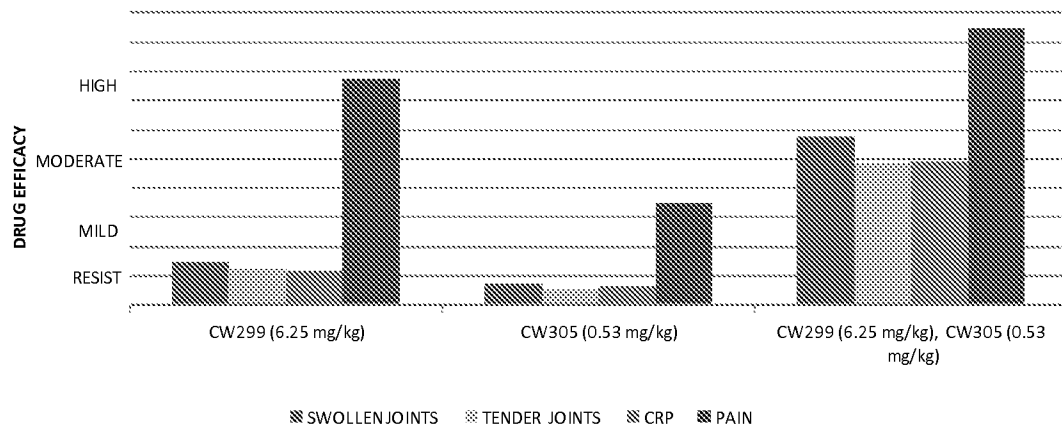


FIG. 24 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - INDIVIDUAL vs COMBO



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FIG. 25 CW299305 - TNF RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs COMBO

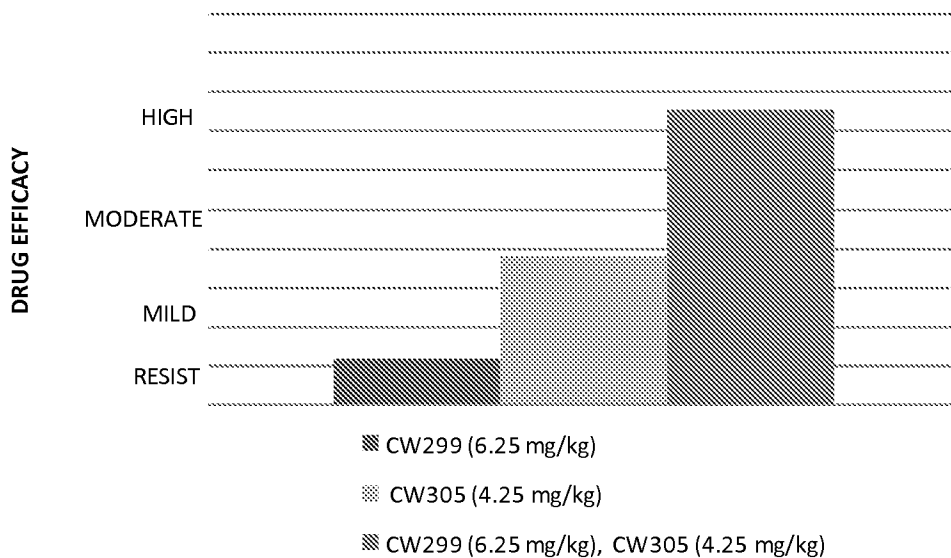
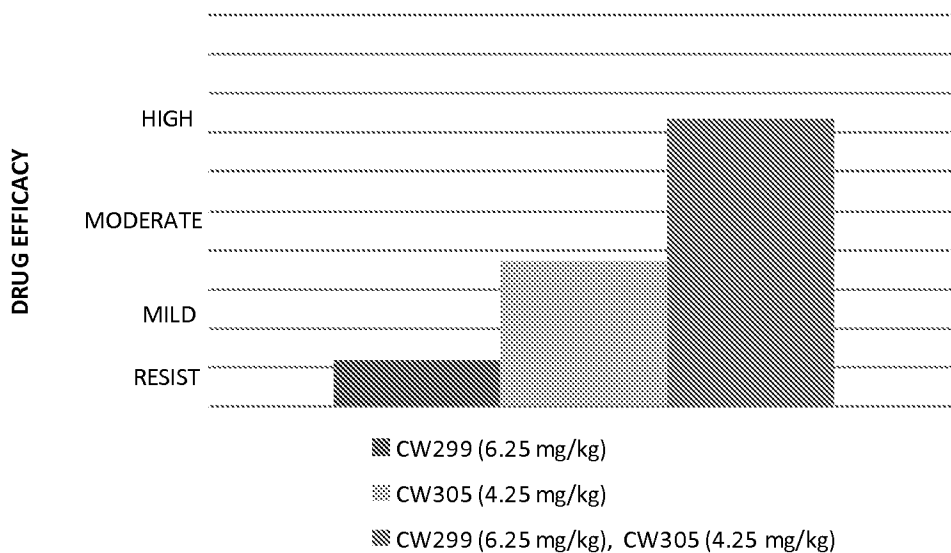


FIG. 26 CW299305 - TNF RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO



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FIG. 27 CW299305 - TNF RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs COMBO

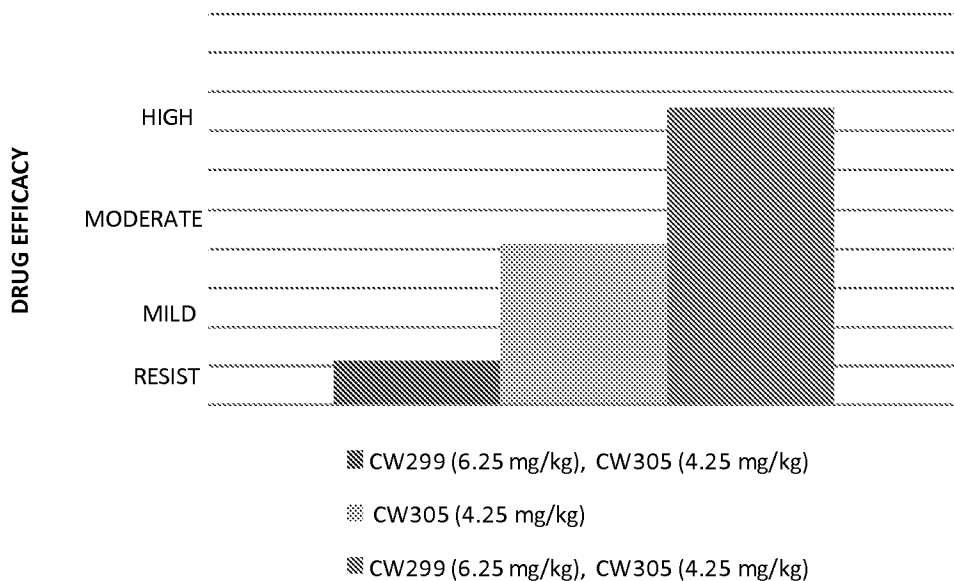
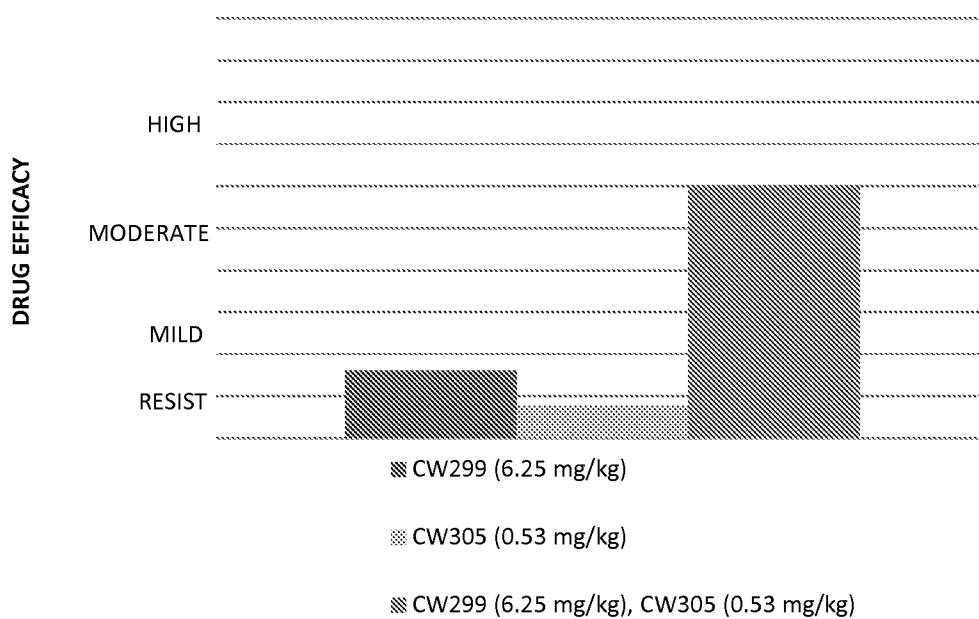


FIG. 28 CW299305 - TNF NON-RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs COMBO



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FIG. 29 CW299305 - TNF NON-RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO

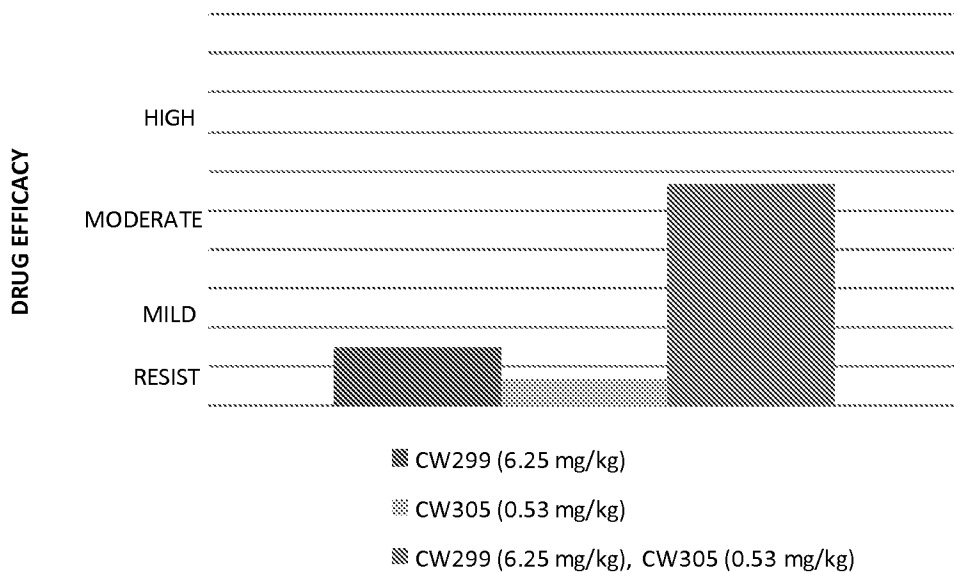
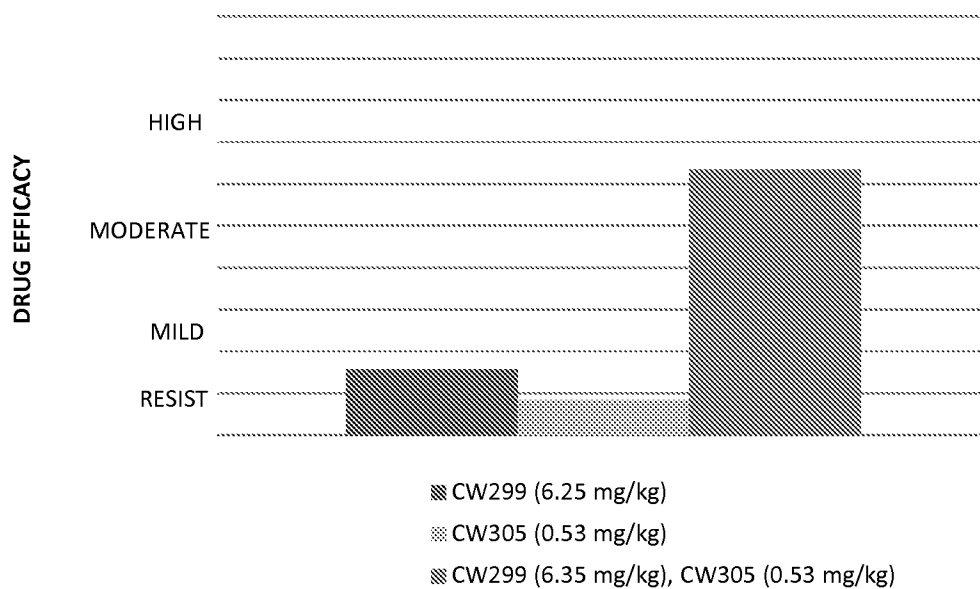
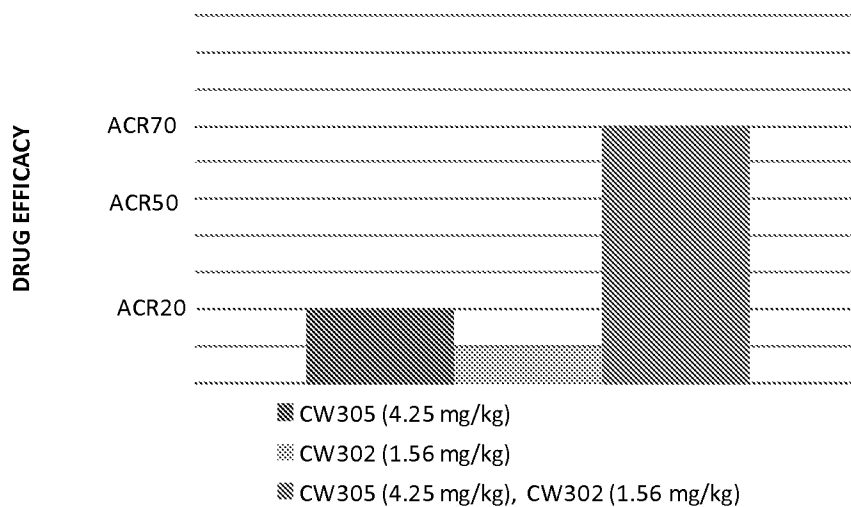
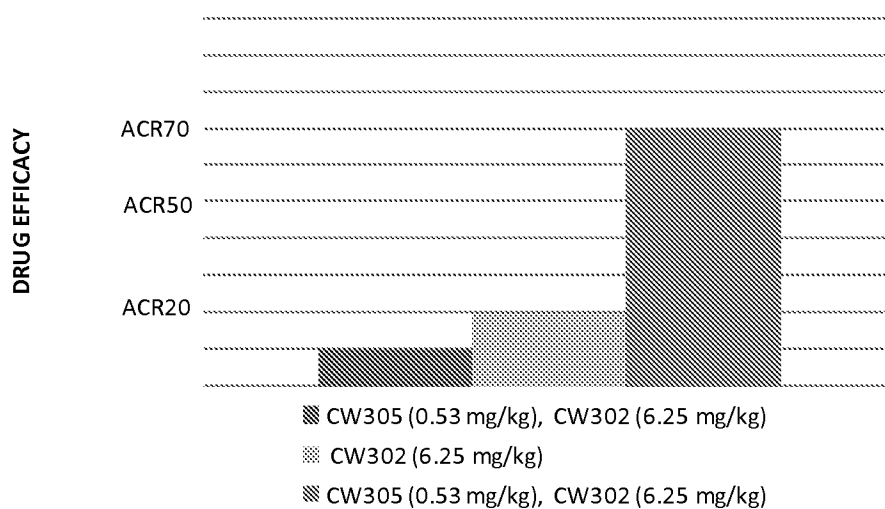
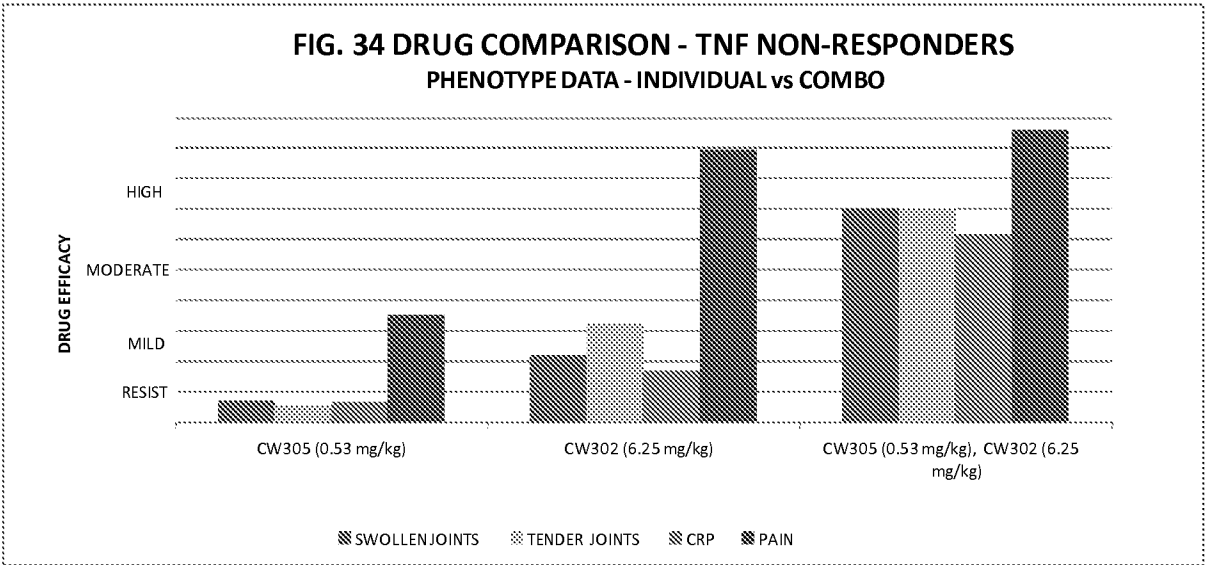
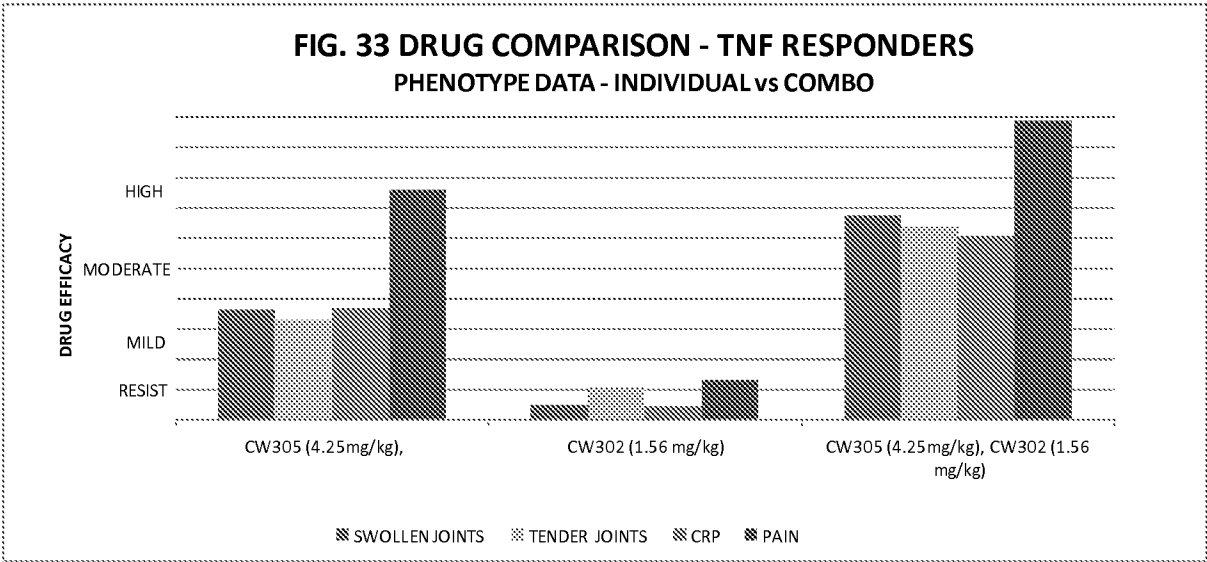


FIG. 30 CW299305 - TNF NON-RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs COMBO



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**FIG. 31 ACR SCORE CW305302
TNF RESPONDERS****FIG. 32 ACR SCORE CW305302
TNF NON-RESPONDERS**



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FIG. 35 CW305302 - TNF RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL VS. COMBO

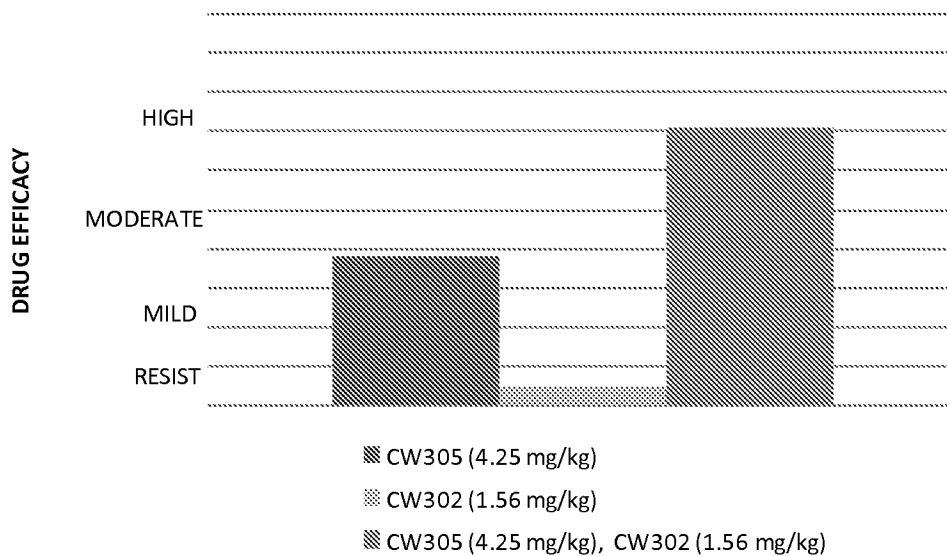
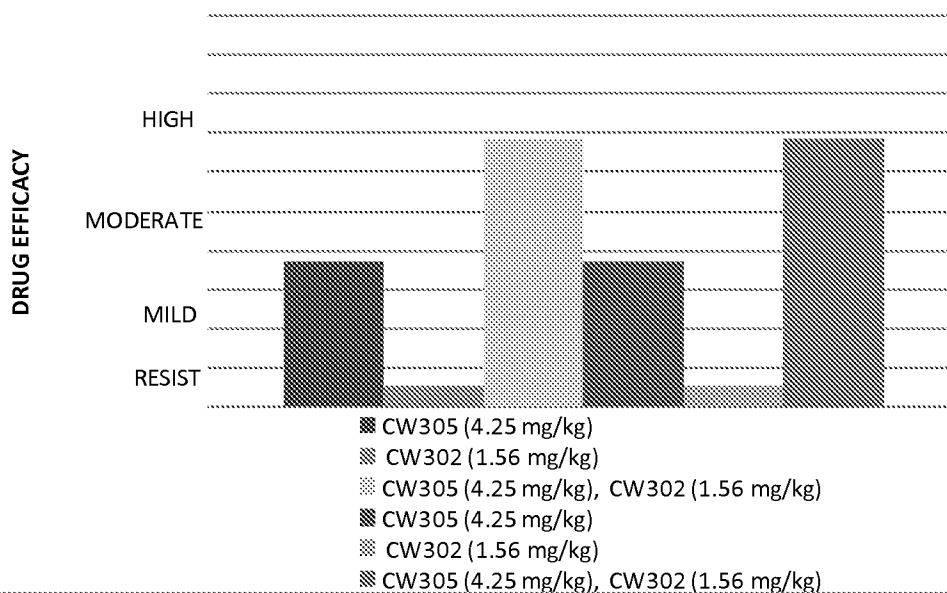


FIG. 36 CW305302 - TNF RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO



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FIG. 37 CW305302 - TNF RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs COMBO

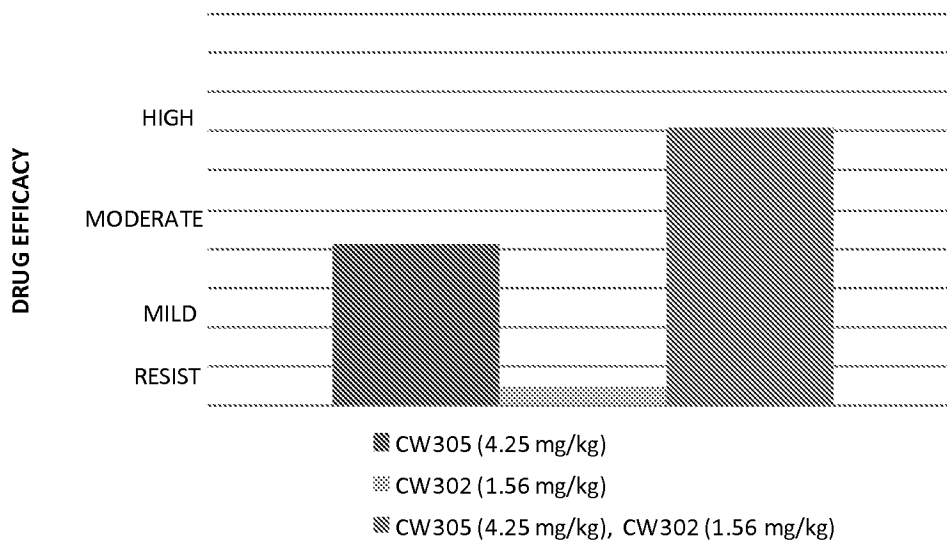
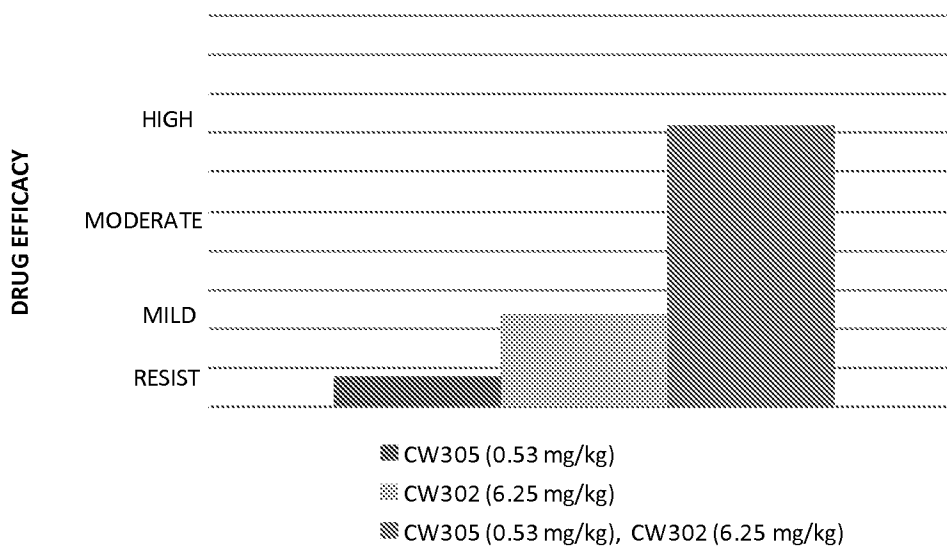


FIG. 38 CW305302 - TNF NON-RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs COMBO



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FIG. 39 CW305302 - TNF NON-RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO

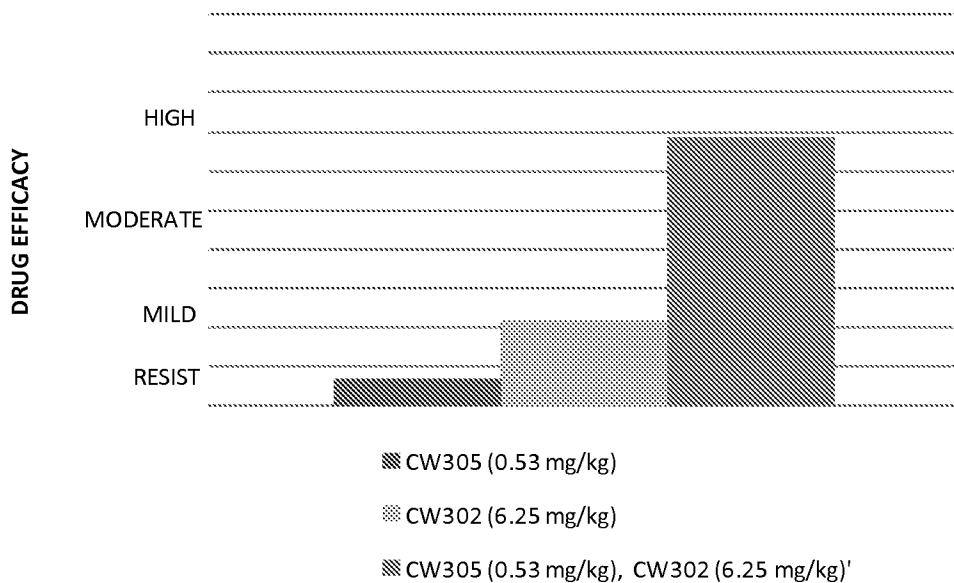
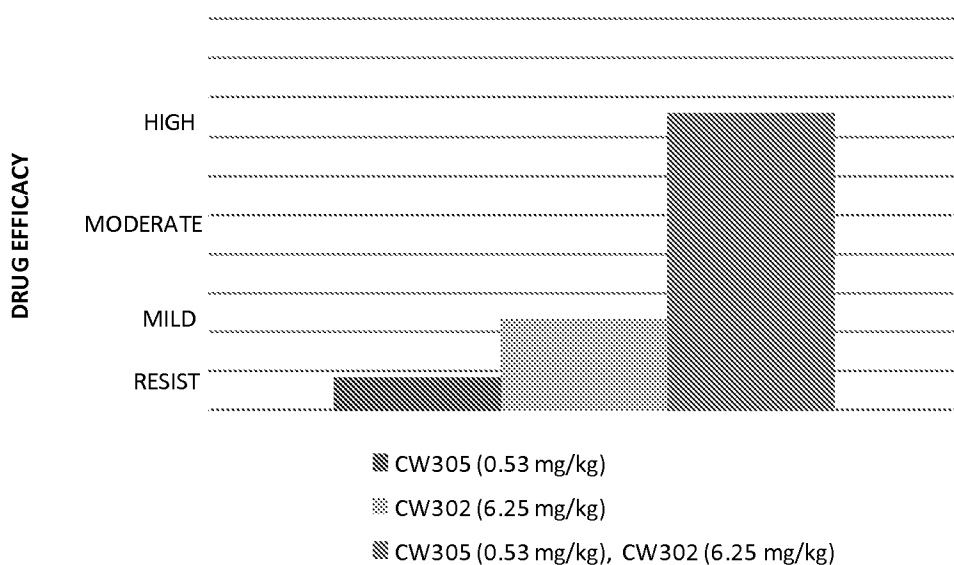
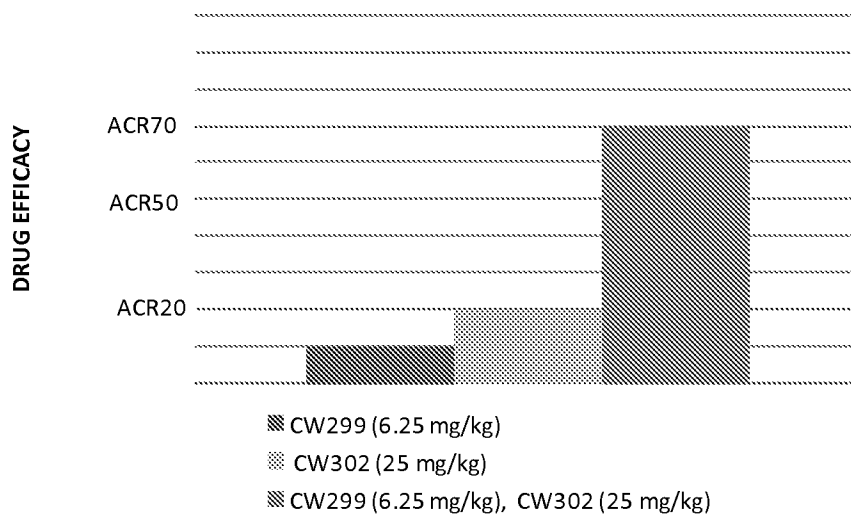
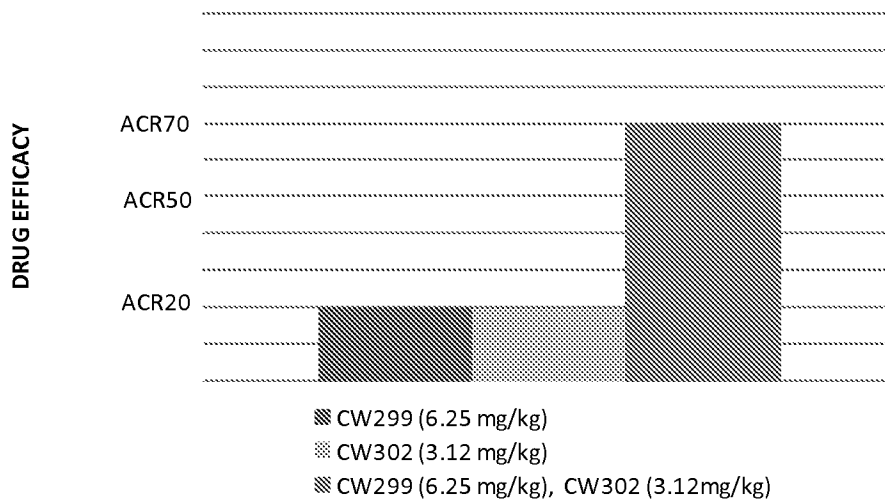


FIG. 40 CW305302 - TNF NON-RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL vs COMBO



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**FIG. 41 ACR SCORE CW299302
TNF RESPONDERS****FIG. 42 ACR SCORE CW299302
TNF NON-RESPONDERS**

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FIG. 43 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - INDIVIDUAL vs COMBO

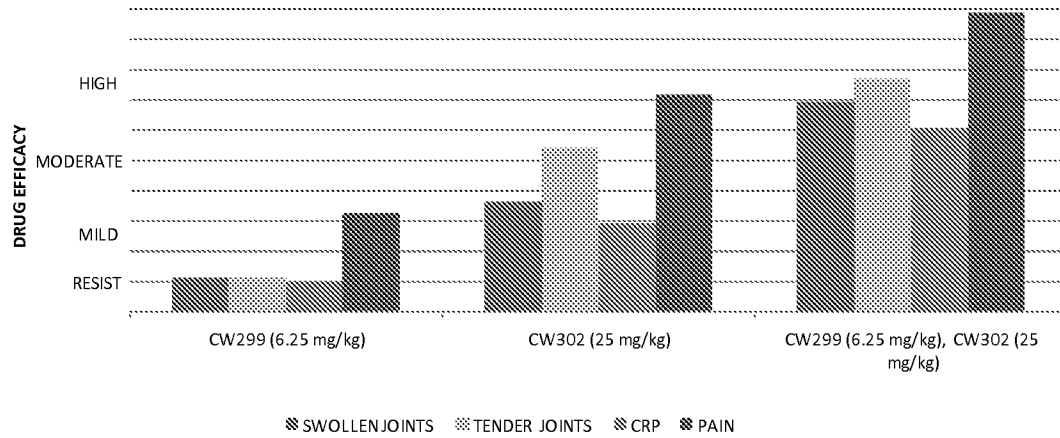
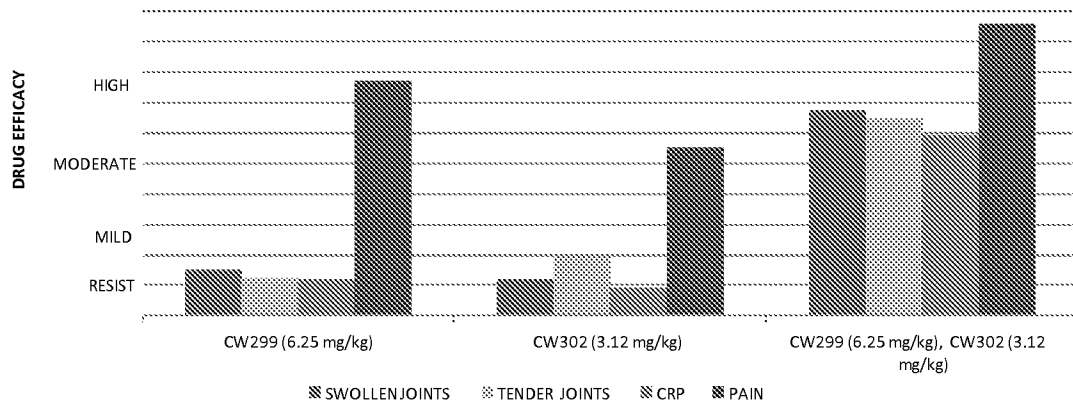


FIG. 44 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - INDIVIDUAL vs COMBO



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FIG. 45 CW299302 - TNF RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL vs COMBO

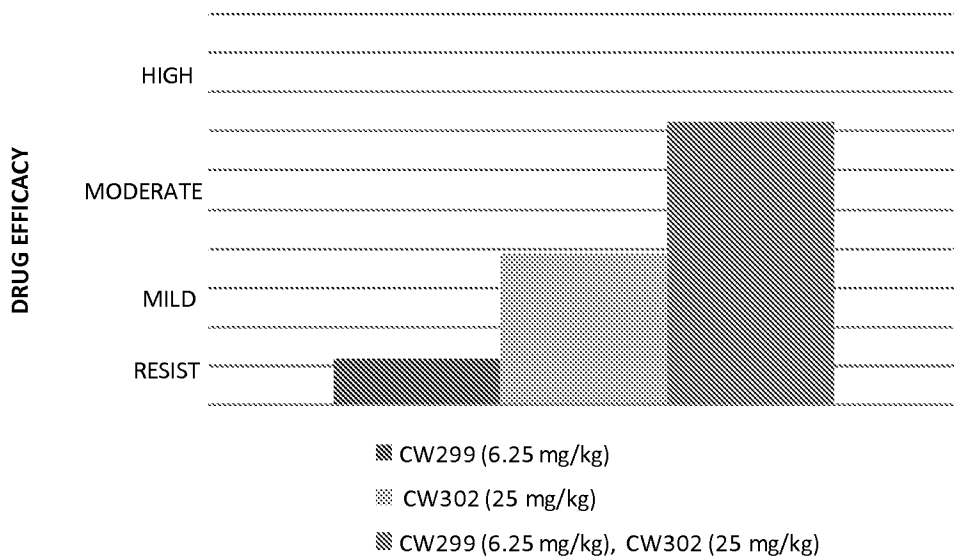
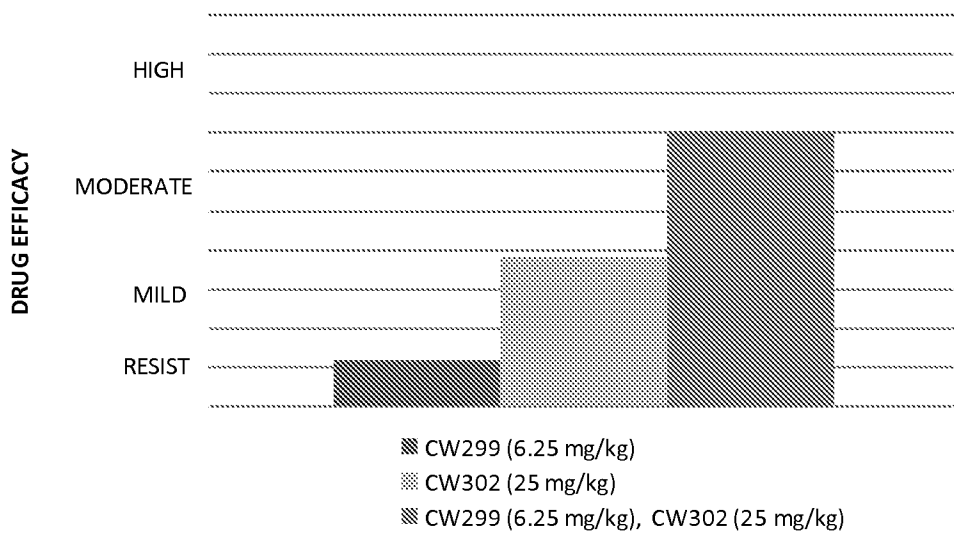


FIG. 46 CW299302 - TNF RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO



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FIG. 47 CW299302 - TNF RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL VS. COMBO

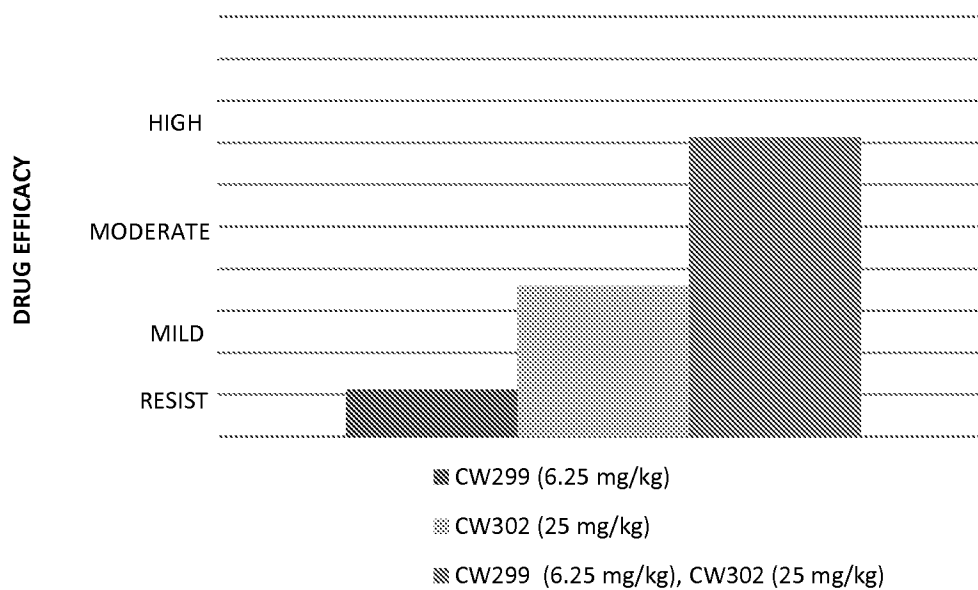
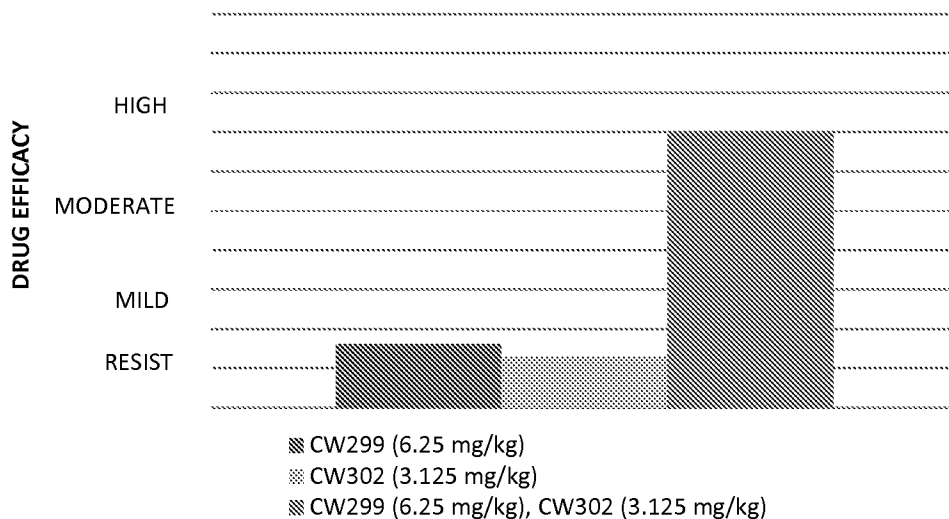


FIG. 48 CW299302 - TNF NON-RESPONDERS
IL6 - EFFICACY DATA - INDIVIDUAL VS. COMBO



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FIG. 49 CW299302 - TNF NON-RESPONDERS
TNF-alpha - EFFICACY DATA - INDIVIDUAL vs COMBO

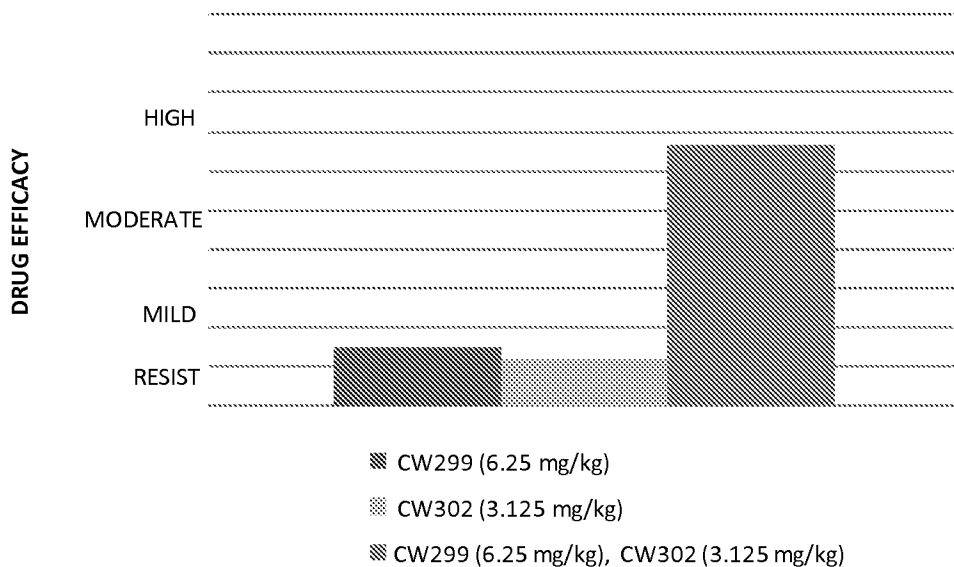
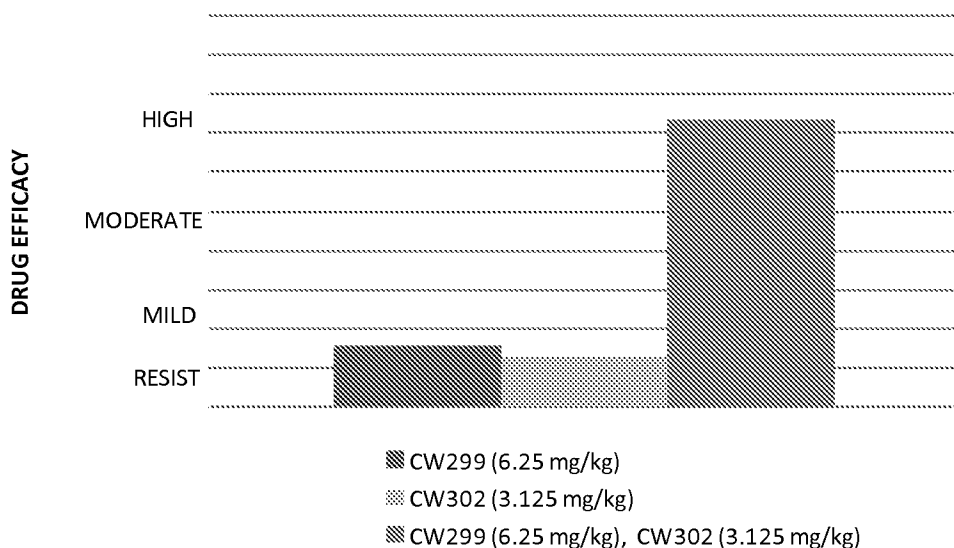


FIG. 50 CW299302 - TNF NON-RESPONDERS
CCL2 - EFFICACY DATA - INDIVIDUAL VS.COMBO



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FIG. 51 DRUG COMPARISON - TNF RESPONDERS
PHENOTYPE DATA - 2D COMBO

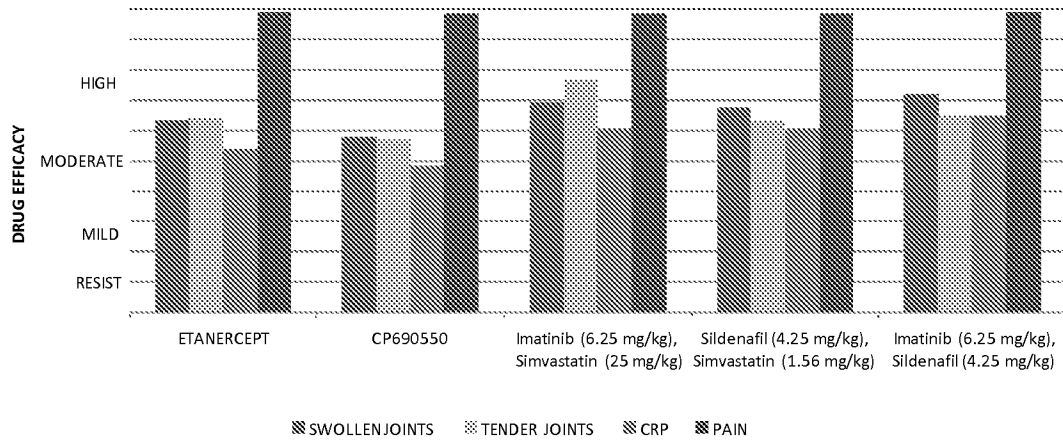
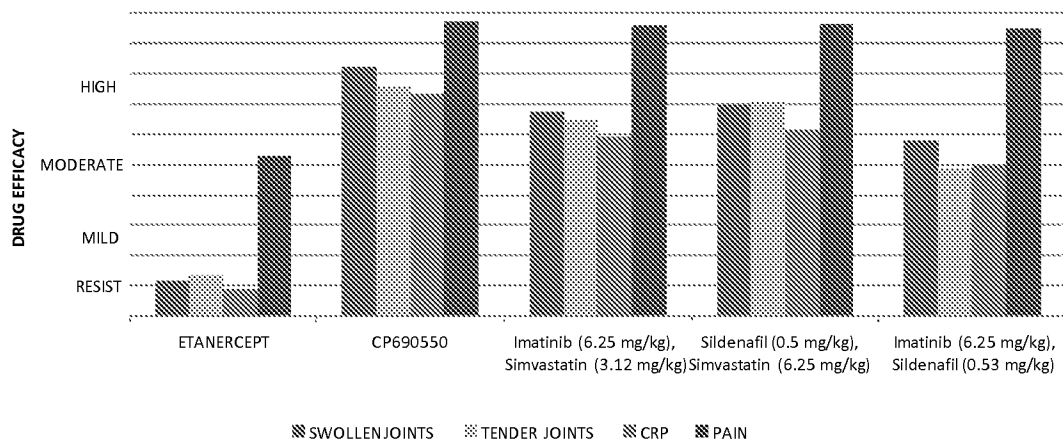


FIG. 52 DRUG COMPARISON - TNF NON-RESPONDERS
PHENOTYPE DATA - 2D COMBO



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**FIG. 53 EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
EARLY - MID DISEASE THERAPEUTIC SETTING**

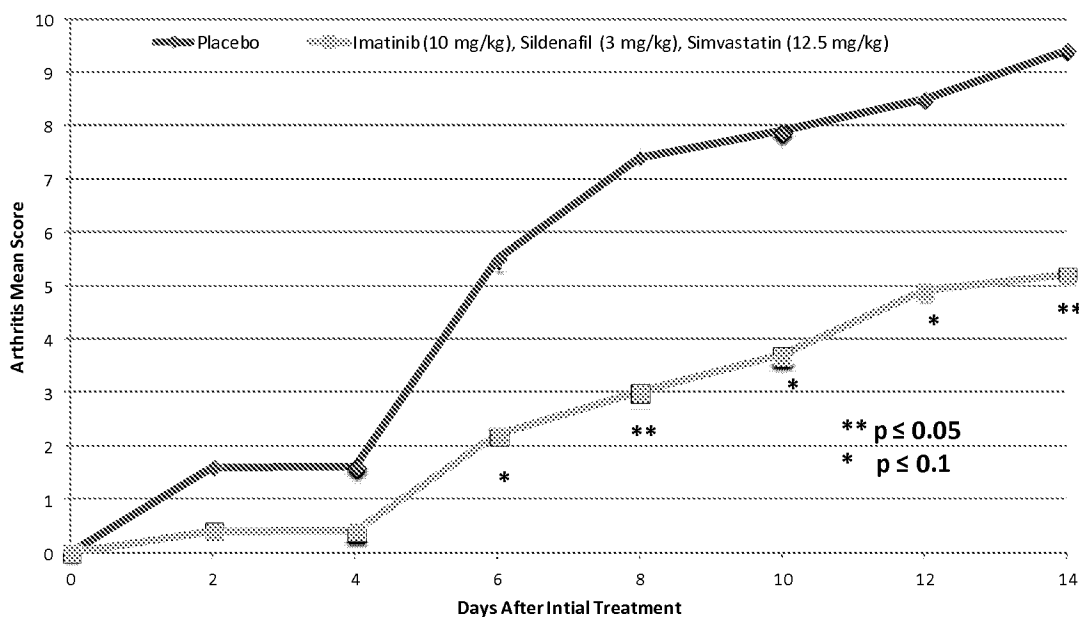
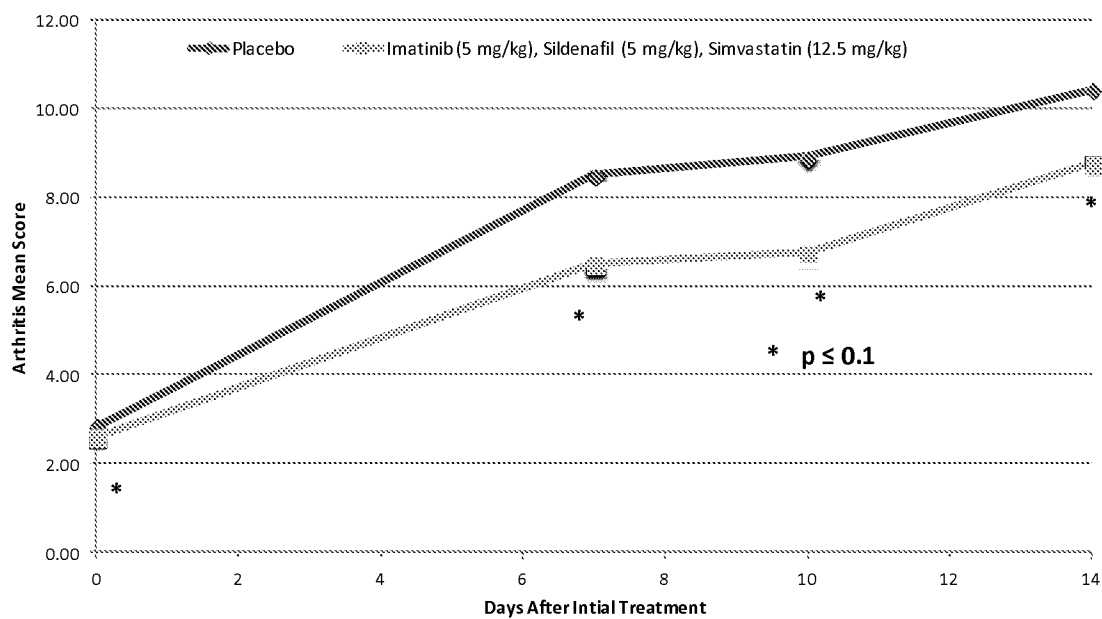


**FIG. 54 EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN
IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
ADVANCED DISEASE**



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**FIG. 55 CW299305302 - N-ACR - PREDICTIVE PROFILES
COMPARISON OF MONO THERAPY VS COMBO THERAPY**

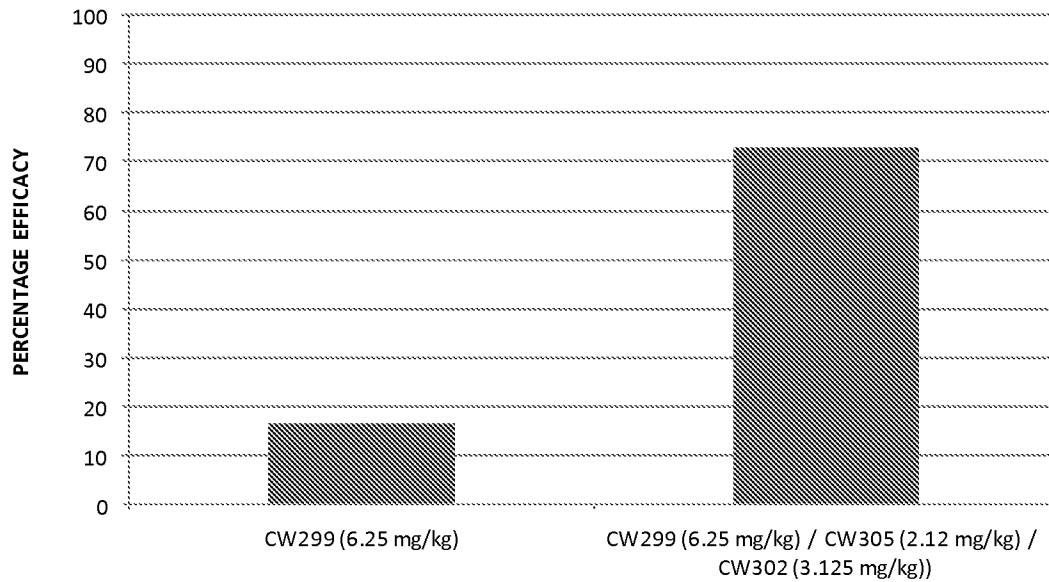
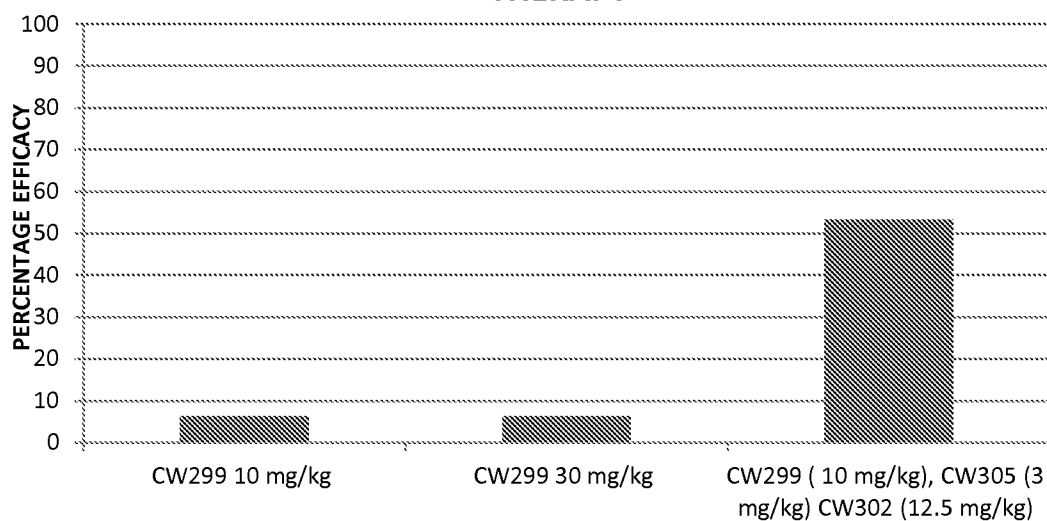


**FIG. 56 EFFECT OF OF IMATINIB/SILDENAFIL/SIMVASTATIN IN
THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
COMPARISON BETWEEN MONO THERAPY VS COMBINATION
THERAPY**



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**FIG. 57 EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
EARLY - MID DISEASE THERAPEUTIC SETTING**

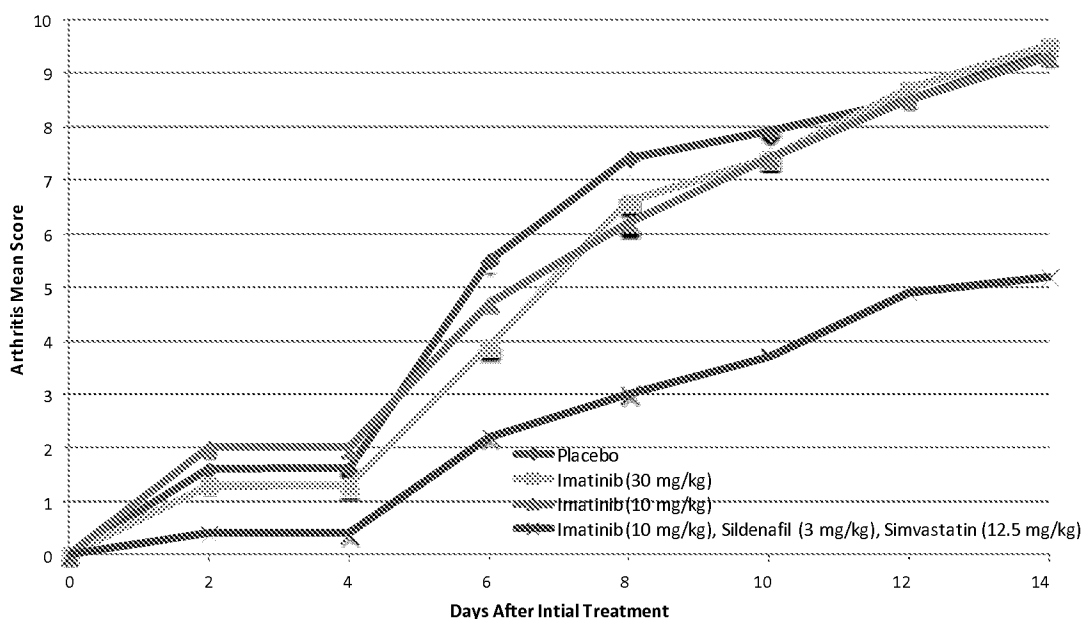
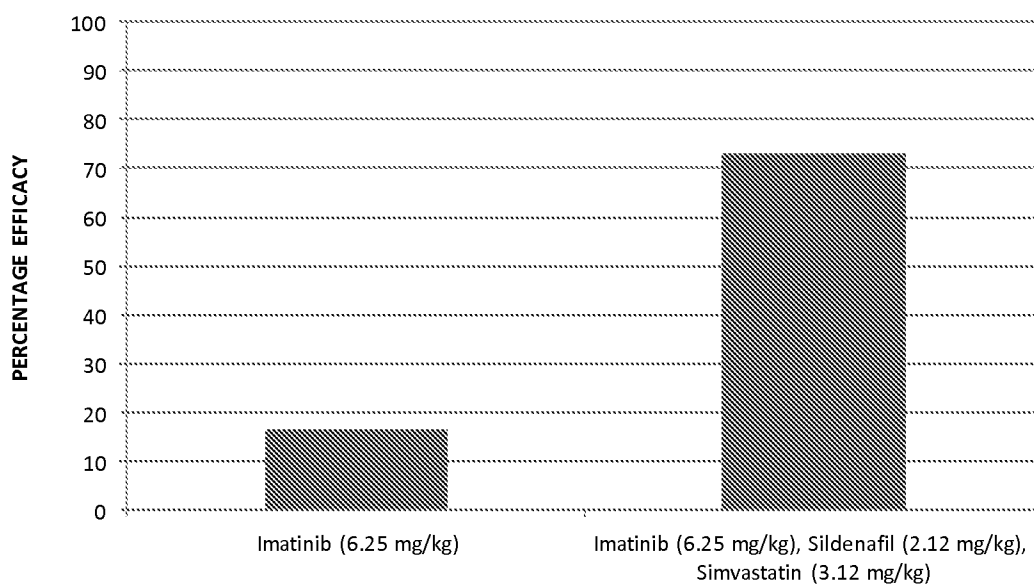


**FIG. 58 CW299305302 - N-ACR - Predictive Profiles
Comparison of Mono Therapy vs Combo Therapy**



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FIG. 59 EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN IN COLLAGEN INDUCED ARTHRITIS ANIMAL COMPARISON BETWEEN MONO VS COMBINATION THERAPY

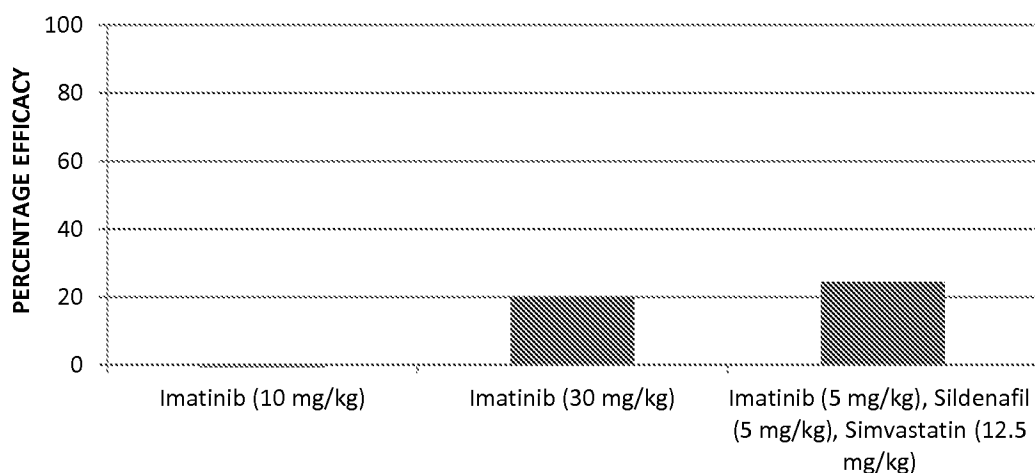
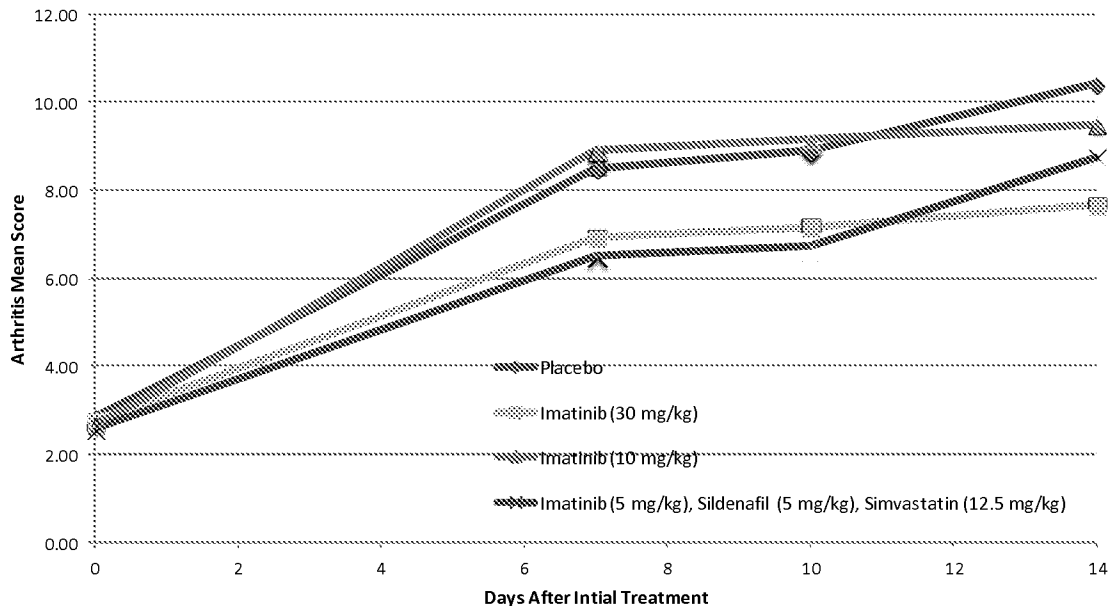
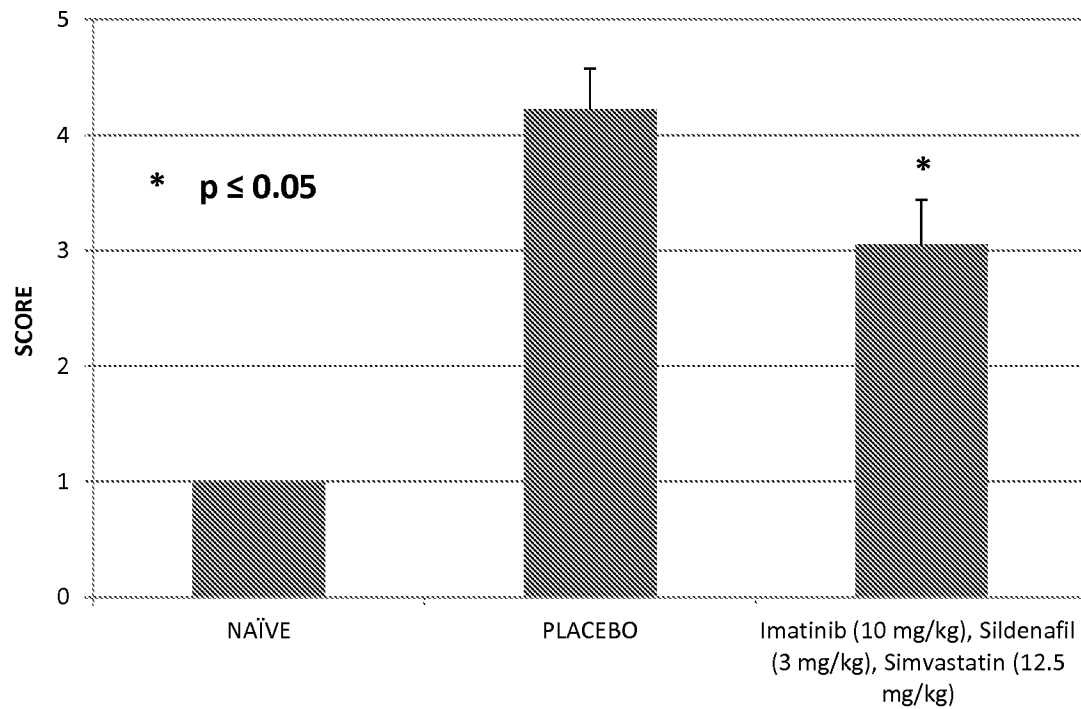


FIG. 60 Effect OF IMATINIB/SILDENAFIL/SIMVASTATIN IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL HIGH BAR - ADVANCED DISEASE THERAPEUTIC SETTING



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**FIG. 61 HISTOPATHOLOGICAL DATA
EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN
ON SYNOVITIS**



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**FIG. 62 HISTOPATHOLOGICAL DATA
EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN
ON PANNUS FORMATION**

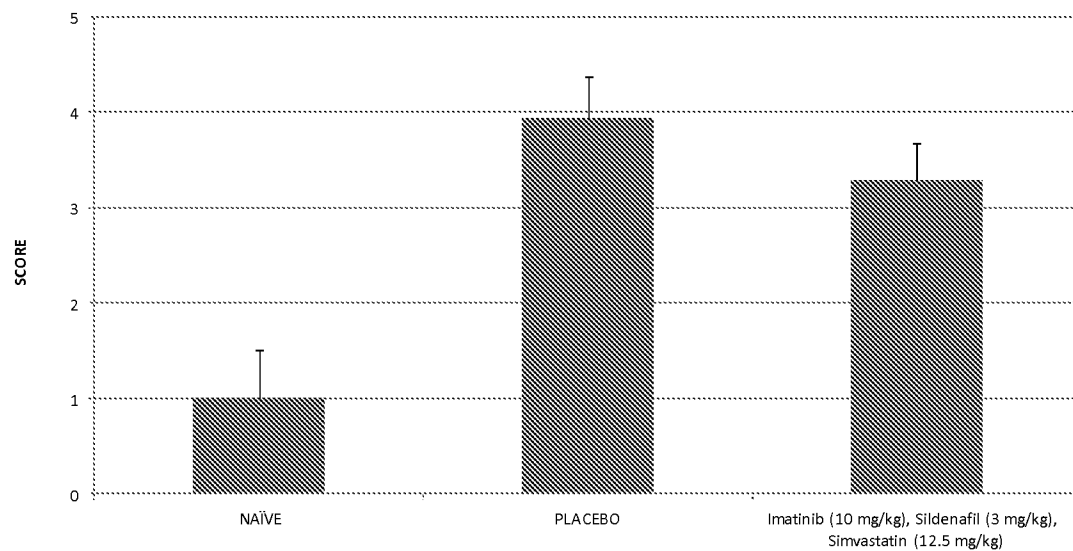


**FIG. 63 HISTOPATHOLOGICAL DATA
EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN ON CARTILAGE
DEGRADATION**

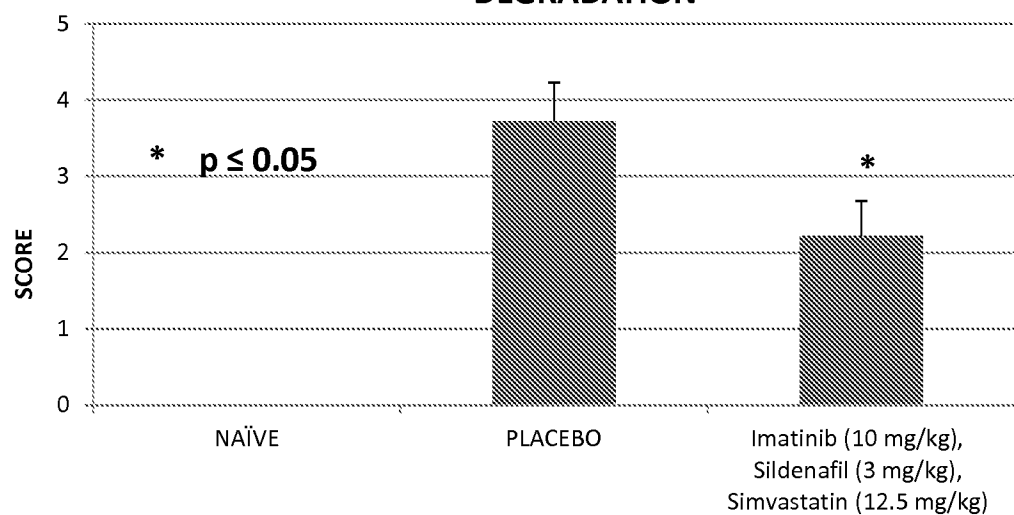


**FIG. 64 HISTOPATHOLOGICAL DATA
EFFECT OF IMATINIB/SILDENAFIL/SIMVASTATIN ON BONE
DEGRADATION**

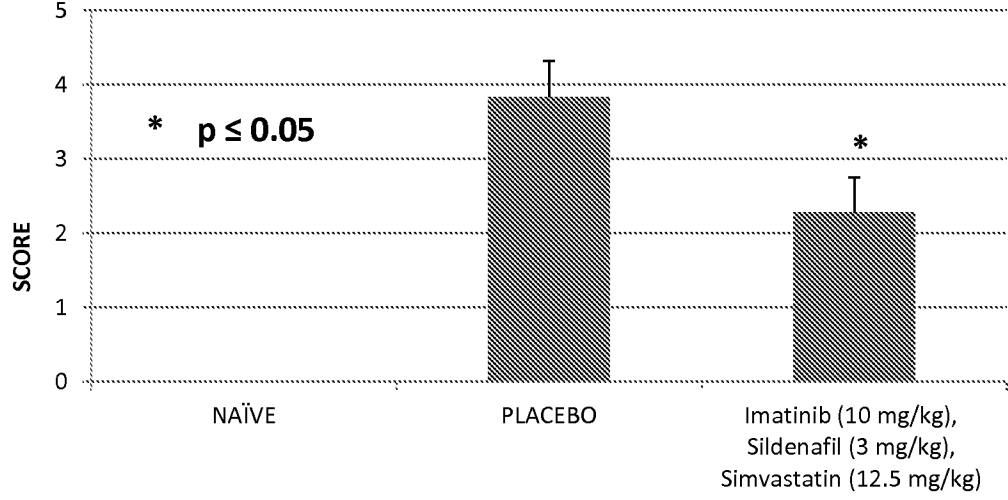


**FIG. 65 PREDICTED ACR SCORE OF DRUG COMBINATIONS
IN THE IN SILICO TNF RESPONDER MODEL**

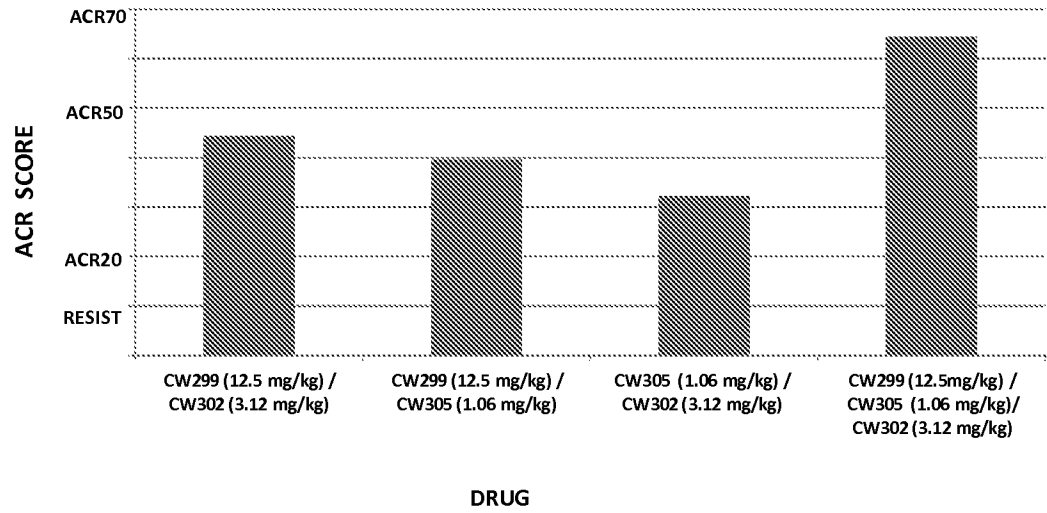
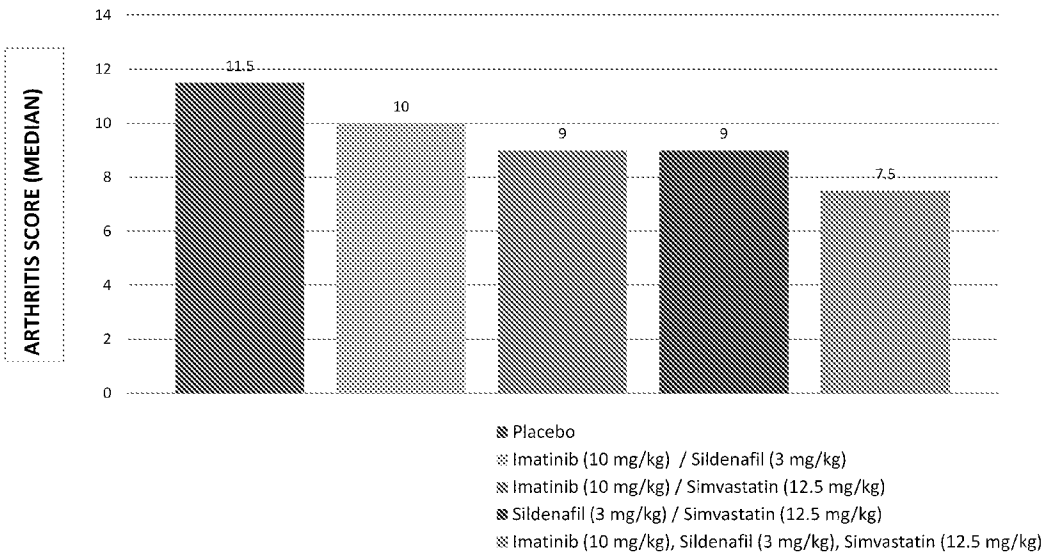
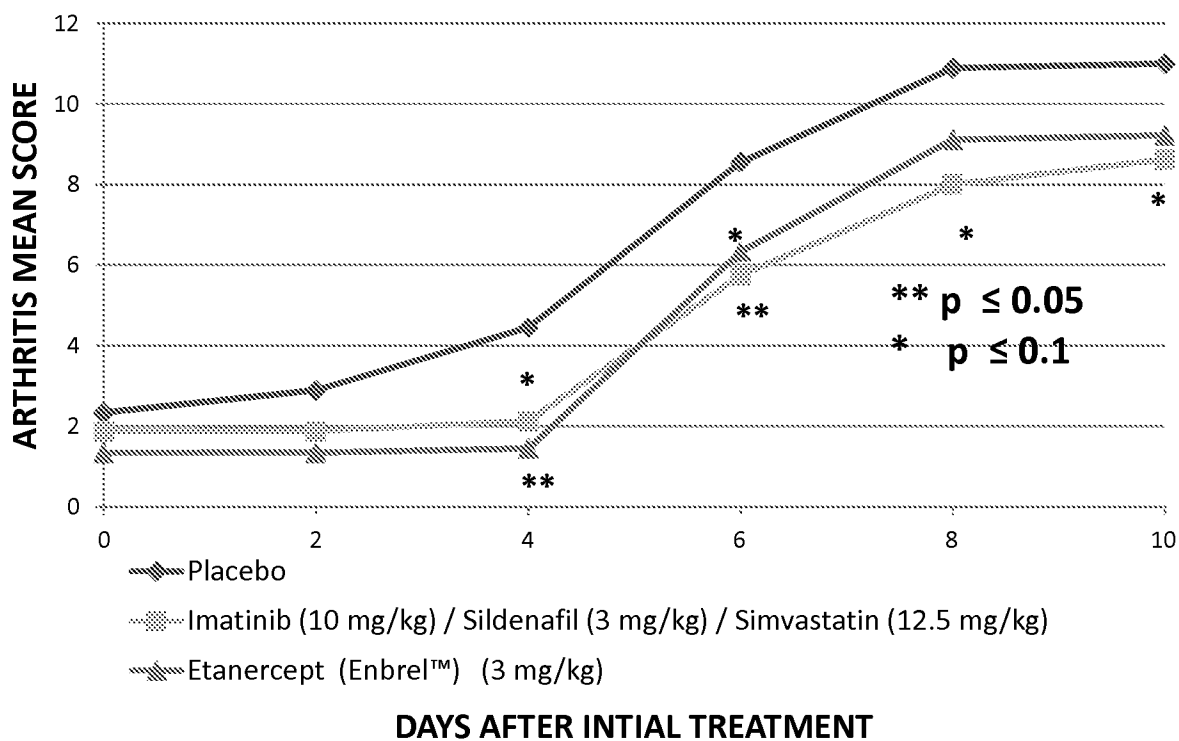


FIG. 66 COMPARISON OF DRUG COMBINATIONS
IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
EARLY - MID DISEASE THERAPEUTIC SETTING



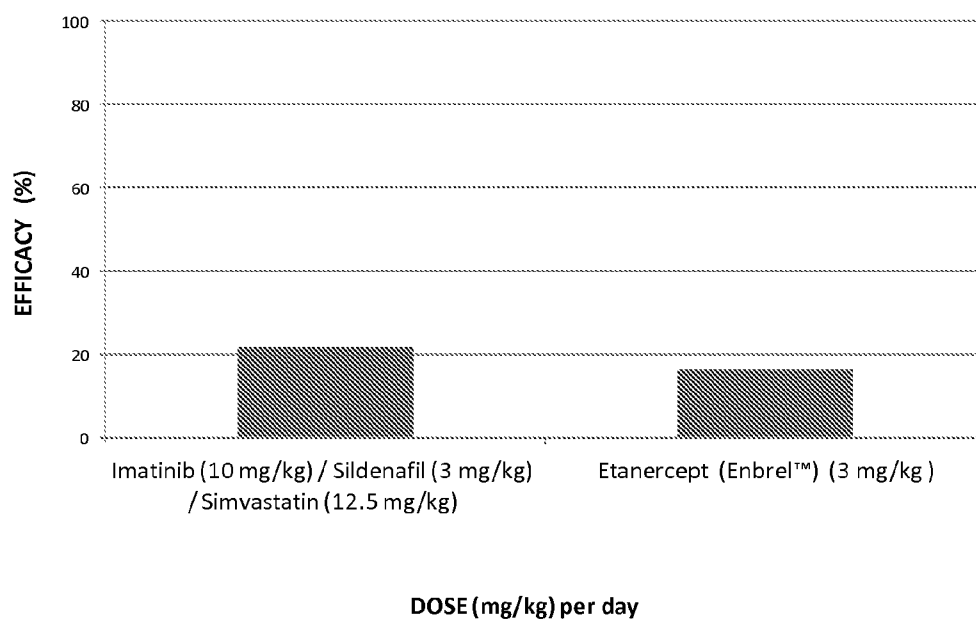
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**FIG. 67 COMPARISON OF OF IMATINIB/SILDENAFIL/SIMVASTATIN
VS. ETANERCEPT IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL
EARLY - MID DISEASE THERAPEUTIC SETTING**



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**FIG. 68 EFFICACY COMPARISON OF IMATINIB/SILDENAFIL/SIMVASTATIN VS. ETANERCEPT IN THE COLLAGEN INDUCED ARTHRITIS ANIMAL MODEL
EARLY - MID DISEASE THERAPEUTIC SETTING**



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/28143

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C12N 15/09 (2012.01)

USPC - 435/69.2

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)

USPC: 435/69.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/6.17, 336 (keyword limited; terms below)

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

PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar

Search Terms Used: Imatinib, sildenafil, simvastatin, PDGF, CSF, PDE5, combination therapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010/0035888 A1 (SANDNER et al.) 11 February 2010 (11.02.2010) para [0001]-[0002], [0007], [0027], [0031], [0034], [0038], [0047], [0048], [0050], [0052], [0058]	1-3, 6-15, 26-32, 41-45, 68-70
A	US 2009/0291958 A1 (GANT et al.) 26 November 2009 (26.11.2009) abstract, para [0218]	1
A	SCHERMULY et al. 'Reversal of experimental pulmonary hypertension by PDGF inhibition' J Clin Invest., October 2005, Vol. 115, pp 2811-2821. Entire document.	1
A, P	US 2011/0104137 A1 (RICHARDSON et al.) 05 May 2011 (05.05.2011) abstract	1

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" 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

"X" 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

"Y" 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

Date of the actual completion of the international search

08 August 2012 (08.08.2012)

Date of mailing of the international search report

23 AUG 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/28143

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
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:
3. ☒ Claims Nos.: 4-5, 16-25, 33-40, 51-65 and 71-120
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:
-see extra sheet-

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 claims 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 claims Nos.:
1-3, 6-15, 25-32, 41-45, 68-70

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.

Attachment to Box No. III:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-3, 6-15, 26-32, 41-45, 68-70, drawn to a composition comprising:

a) two or three of:

- i) an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;
 - ii) an inhibitor of phosphodiesterase 5; and
 - iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase; and
- b) optionally a pharmaceutically-acceptable excipient.

Group II: claims 46-50, 66-67, drawn to a method for treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, the method comprising administering to the subject two or three of:

- a) a therapeutically-effective amount of an inhibitor of colony stimulating factor, platelet derived growth factor, T-cell response and B-cell response pathways;
 - b) a therapeutically-effective amount of an inhibitor of phosphodiesterase 5; and
 - c) a therapeutically-effective amount of an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase,
- wherein the administration uses one or a plurality of dosage forms, each dosage form comprising one or more inhibitors, and wherein each dosage form optionally further comprises a pharmaceutically-acceptable excipient.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I do not include the inventive concept of treating inflammatory joint diseases and/or chronic inflammatory connective tissue diseases in a subject in need or want of relief thereof, as required by Group II.

The inventions of Groups I and II share the technical feature of the composition of Claim 1. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2010/0035888 A1 to Sandner et al. (hereinafter 'Sandner'). Sandner discloses Claim 1, a composition comprising:

a) two or three of:

- i) an inhibitor of platelet derived growth factor pathway (para [0001]-[0002] and [0007], formula 1 is an inhibitor of PDGFR kinase; para [0038], imatinib is an inhibitor of PDGF);
 - ii) an inhibitor of phosphodiesterase 5 (para [0027] and [0031]); and
 - iii) an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (para [0027] and [0034]); and
- b) optionally a pharmaceutically-acceptable excipient (para [0052], pharmaceutically-acceptable carrier). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Groups I and II is the administration of one or a plurality of dosage forms, each dosage form comprising one or more inhibitors. The inventions do not share a special technical feature, because Sandner teaches that the compounds can be administered as a single composition or dosage unit, e.g., a pill or liquid containing both compositions; or they can be administered as separate compositions (para [0050]). Without a shared special technical feature, the inventions lack unity with one another.

Groups I and II therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.

Continuation of Section 4:

Claims 4-5, 16-25, 33-40, 51-65 and 71-120 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).