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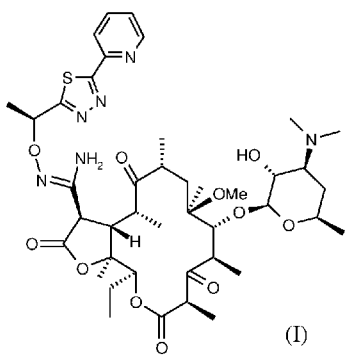
(54) Title: PHARMACEUTICAL COMPOSITIONS AND METHODS



(I)

(57) Abstract: Pharmaceutical compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof: Formula (I) for modulating one or more cytokines such as: Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF), and methods for modulating one or more cytokines and their use for modulating one or more cytokines is disclosed.

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PHARMACEUTICAL COMPOSITIONS AND METHODS

RELATED PATENT APPLICATIONS

This application claims the priority to and benefit of Indian Provisional Patent Application No. 201821028332 filed on July 27, 2018; the disclosures of which are incorporated herein by reference in its entirety as if fully rewritten herein.

FIELD OF THE INVENTION

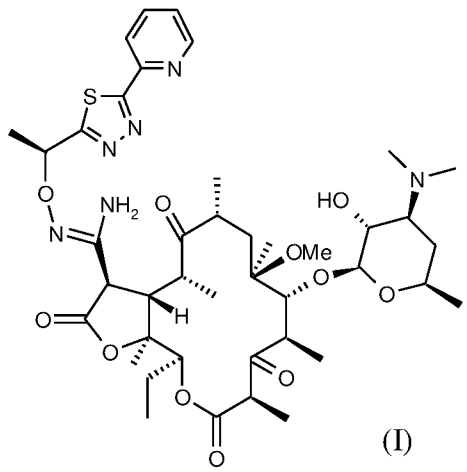
The invention relates to pharmaceutical compositions and their use in modulating one or more cytokines.

BACKGROUND OF THE INVENTION

Cytokines are important biological molecules that are involved in several biological functions. Cytokines are small proteins, and particularly play important role in the immune system. Cytokines may include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors. The modulation of cytokines, for example by increasing or decreasing their levels, can help in achieving outcome of many intended treatments (e.g. infections, allergies, inflammation).

SUMMARY OF THE INVENTION

Accordingly, there are provided pharmaceutical compositions for modulating one or more cytokines, said compositions comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



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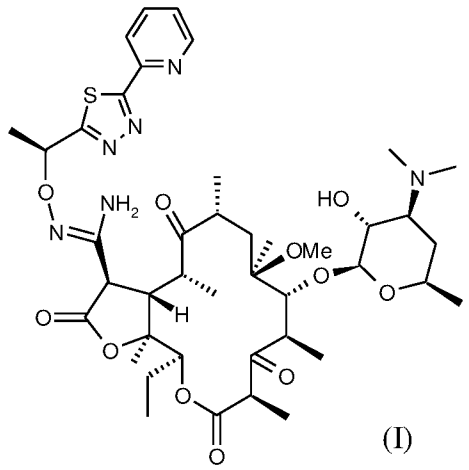
In another aspect, there is provided a method for modulating one or more cytokines in a subject, said method comprising administering to the subject a pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

In another general aspect, there is provided a method for modulating one or more cytokines in a subject, said method comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



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The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the following description including claims.

DETAILED DESCRIPTION OF THE INVENTION

Reference will now be made to the exemplary embodiments, and specific language will be used herein to describe the same. It should nevertheless be understood that no limitation of the scope of the invention is thereby intended. Alterations and further modifications of the inventive features illustrated herein, and additional applications of the principles of the invention as illustrated herein, which would occur to one of ordinary skills in the relevant art and having possession of this disclosure, are to be considered within the scope of the invention. It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise. All references including patents, patent applications, and literature cited in the specification are expressly incorporated herein by reference in their entirety.

The inventors have surprisingly discovered that certain compounds exhibit ability to modulate cytokines.

The term "pharmaceutically acceptable salt" as used herein refers to one or more salts of a given compound which possesses the desired pharmacological activity of the free compound and which are neither biologically nor otherwise undesirable. In general, the "pharmaceutically acceptable salts" refer to and include those salts that are suitable for use in contact with the tissues of human and animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. (J. Pharmaceutical Sciences, 66: 1-19 (1977)), incorporated herein by reference in its entirety, describes various pharmaceutically acceptable salts in details.

The term "treat", "treating" or "treatment" as used herein refers to administering a medicament, including a pharmaceutical composition, or one or more pharmaceutically active ingredients, for prophylactic and/or therapeutic purposes.

The term "pharmaceutically effective amount" or "therapeutically effective amount" or "effective amount" as used herein refers to an amount, which has a therapeutic effect or is the amount required to produce a therapeutic effect in a subject. The compounds and/or pharmaceutical compositions according to the invention are used in amounts that are effective in providing the desired therapeutic effect or result.

The term "administration" or "administering" includes delivery of a composition or one or more pharmaceutically active ingredients to a subject, including for example, by any appropriate methods, which serves to deliver the composition or its active ingredients or other pharmaceutically active ingredients to the desired site of action. The method of administration may vary depending on various factors, such as for example, the components of the pharmaceutical composition, nature of the pharmaceutically active or inert ingredients, the desired site of action, age and physical condition of the subject and a like. Some non-limiting examples of ways to administer a composition or a pharmaceutically active ingredient to a subject according to this invention includes oral, intravenous, topical, intra-respiratory, intra-peritoneal, intra-muscular, parenteral, sublingual, transdermal, intranasal, aerosol, intra-ocular, intra-tracheal, intra-rectal, vaginal, gene gun, dermal patch, eye drop, ear drop or mouthwash.

The term "synergistic" or "synergy" as used herein refers to the interaction of two or more agents so that their combined effect is greater than their individual effects.

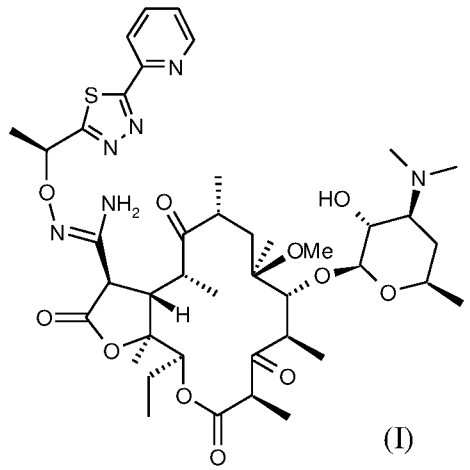
The term "pharmaceutically inert ingredient" or "carrier" or "excipient" refers to a compound or material used to facilitate administration of a compound, including for example, to increase the solubility of the compound. Typical, non-limiting examples of solid carriers include, starch, lactose, dicalcium phosphate, sucrose, and kaolin and so on. Typical, non-limiting examples of liquid carriers

include sterile water, saline, buffers, non-ionic surfactants, and edible oils such as oil, peanut and sesame oils and so on. In addition, various adjuvants commonly used in the art may be included. These and other such compounds are described in the literature, for example, in the Merck Index (Merck & Company, Rahway, N.J.). Considerations for inclusion of various components in pharmaceutical compositions are described, for example, in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press., which is incorporated herein by reference in its entirety.

The term "subject" as used herein refers to a vertebrate or invertebrate, including a mammal. The term "subject" includes human, animal, a bird, a fish, or an amphibian. Typical, non-limiting examples of a "subject" includes humans, cats, dogs, horses, sheep, bovine cows, pigs, lambs, rats, mice and guinea pigs.

The term "modulating" or "modulation" of cytokines refers to and includes increasing or decreasing level of cytokines. The term "modulating" or "modulation" also refers to and includes stimulating cytokines.

In one general aspect, there are provided pharmaceutical compositions for modulating one or more cytokines, said composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



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In some embodiments, the pharmaceutical composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof, for use in modulating one or more cytokines in a subject.

In some embodiments, the cytokine is one or more of Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF).

The pharmaceutical compositions according to the invention may include one or more pharmaceutically acceptable carriers or excipients or a like. Typical, non-limiting examples of such carriers or excipients include mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, sodium crosscarmellose, glucose, gelatine, sucrose, magnesium carbonate, wetting agents, emulsifying agents, solubilizing agents, pH buffering agents, lubricants, stabilizing agents, binding agents and a like.

The pharmaceutical compositions according to this invention can exist in various forms. In some embodiments, the pharmaceutical composition is in the form of a powder or a solution. In some other embodiments, the pharmaceutical compositions according to the invention are in the form of a powder that can be reconstituted by addition of a compatible reconstitution diluent prior to parenteral administration. Non-limiting example of such a compatible reconstitution diluent includes water.

In some other embodiments, the pharmaceutical compositions according to the invention are in the form of a frozen composition that can be diluted with a compatible diluent prior to parenteral administration.

In some other embodiments, the pharmaceutical compositions according to the invention are in the form ready to use for parenteral administration.

The pharmaceutical composition or the active ingredients according to the present invention may be formulated into a variety of dosage forms. Typical, non-limiting examples of dosage forms include solid, semi-solid, liquid and aerosol dosage forms; such as tablets, capsules, powders, solutions, suspensions, suppositories, aerosols, granules, emulsions, syrups, elixirs and a like.

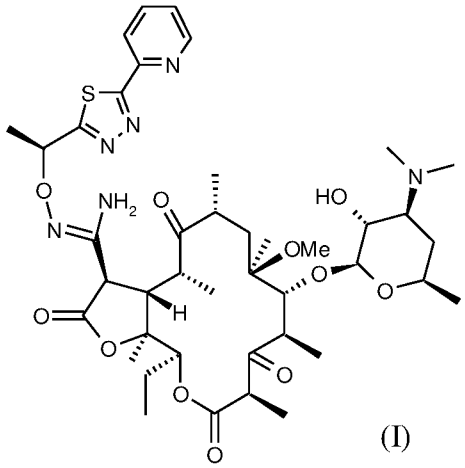
In the methods according to the invention, the pharmaceutical composition and/or other pharmaceutically active ingredients disclosed herein may be administered by any appropriate method, which serves to deliver the composition or its constituents or the active ingredients to the desired site. The method of administration can vary depending on various factors, such as for example, the components of the pharmaceutical composition, nature of the active ingredients, age and physical condition of the subject. Some non-limiting examples of administering the composition to a subject according to this invention include oral, intravenous, topical, intra-respiratory, intra-peritoneal, intra-muscular, parenteral, sublingual, transdermal, intranasal, aerosol, intraocular, intra-tracheal, intra-rectal, vaginal, gene gun, dermal patch, eye drop, ear drop or mouthwash.

The compositions according to the invention can be formulated into various dosage forms wherein the active ingredients and/or excipients may be present either together (e.g. as an admixture) or as separate components. When the various ingredients in the composition are formulated as a mixture, such composition can be delivered by administering such a mixture. The composition

or dosage form wherein the ingredients do not come as a mixture, but come as separate components, such composition/dosage form may be administered in several ways. In one possible way, the ingredients may be mixed in the desired proportions and the mixture is then administered as required. Alternatively, the components or the ingredients (active or inert) may be separately administered (simultaneously or one after the other) in appropriate proportion so as to achieve the same or equivalent therapeutic level or effect as would have been achieved by administration of the equivalent mixture.

In another general aspect, there are provided methods for modulating one or more cytokines in a subject, said method comprising administering to the subject a pharmaceutical composition disclosed herein.

In another general aspect, there are provided methods for modulating one or more cytokines in a subject, said method comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



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In the methods according to the invention, the active ingredients disclosed herein may be administered to a subject in several ways depending on the requirements. In some embodiments, the active ingredients are admixed in appropriate amounts and then the admixture is administered to a subject. In some other embodiments, the active ingredients are administered separately. Since the invention contemplates that the active ingredients agents may be administered separately, the invention further provides for combining separate pharmaceutical compositions in kit form. The kit may comprise one or more separate pharmaceutical compositions, each comprising one or more active ingredients. Each of such separate compositions may be present in a separate container such as a bottle, vial, syringes, boxes, bags, and the like. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably

administered in different dosage forms (e.g., oral and parenteral) ore are administered at different dosage intervals. When the active ingredients are administered separately, they may be administered simultaneously or sequentially.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention. For example, those skilled in the art will recognize that the invention may be practiced using a variety of different compounds within the described generic descriptions.

EXAMPLES

The following examples illustrate the embodiments of the invention that are presently best known. However, it is to be understood that the following are only exemplary or illustrative of the application of the principles of the present invention. Numerous modifications and alternative compositions, methods, and systems may be devised by those skilled in the art without departing from the spirit and scope of the present invention. The appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity, the following examples provide further detail in connection with what are presently deemed to be the most practical and preferred embodiments of the invention.

Experimental Procedure

The activity of test compounds in modulating one or more cytokines was evaluated using a whole blood cytokine secretion assay, using the following general procedure. Peripheral venous blood was collected with consent from healthy adult volunteers between 25 to 40 years of age and stored in tubes containing heparin. All volunteers confirmed that they did not take any concomitant medication within the last 2 weeks prior to the start of study and also that they had no known hypersensitivity to any antibacterial drugs. All blood collections were in accordance to protocols approved by the Institutional Review Board of Wockhardt Ltd, India. Written informed consent was obtained from study participants. Lipopolysaccharide (Sigma, USA) was used as stimulating agent for immune cells. Quantikine ELISA human cytokine kits were purchased from, R & D Systems, Inc, USA. Test compounds were prepared using literature procedures.

Heparinised whole blood samples were kept at room temperature and processed within 2 hours of collection. Blood was diluted 1:3 with sterile RPMI 1640 with L-glutamine and 25 mM HEPES (Gibco, Life Technologies; USA) and a final volume of 1 mL was added to each well of 24-well tissue culture treated flat-bottom polystyrene plates (eppendorf, Germany). Samples were stimulated

with LPS (Lipopolysaccharide) reagent (10 ng/mL) with or without test compounds or their respective vehicle control, and cultured for the 6 hours under each experiment at 37°C in a humidified incubator at 5% CO_2. After incubation, the blood was centrifuged at 8000 rpm for 8 minutes at 4°C and supernatants were collected at 6 hour intervals. The supernatants were stored at -80°C prior to the detection of cytokines.

The supernatants were analysed for IL-6 and TNF-α sandwich immunoassay using a BioTek 96 well Plate Reader. The assay was performed according to the manufacturer's instructions (R & D Systems, Inc, USA) and analysed with the BioTek 96 well Plate Reader software. The sensitivity of TNF-α method was 1.6 pg/mL and the assay could accurately detect cytokines in the range of 15.6 – 1,000 pg/ml. The sensitivity of IL-6 method was 0.7 pg/mL and the assay could accurately detect cytokines in the range of 3.13 – 200 pg/ml.

Supernatant cytokine concentrations of samples treated with test compounds were expressed as a percentage compared to cytokine concentrations induced by LPS alone, which were defined as 100%. Linear mixed models, which take into account the possible dependence among measurements from the same sample under different drug concentrations, were employed to analyse drug concentration response data for each cytokine, stimulation condition and antibacterial agent independently. Data were expressed as means ± standard error of mean (SEM).The results were analysed via a one-way ANOVA with Graph pad Prism 5 software, and Tukey's post hoc test was used to compare the differences between groups.

Example 1

Activity of **Compound of formula (I),** Azithromycin, Clarithromycin and Telithromycin in modulating LPS-simulated cytokine release in whole blood assay was evaluated using the above experimental procedure. In general, the activity was evaluated with respect to Interleukin-6 (IL-6) and Tumor necrosis factor α (TNF-α). The results are presented in Table 1 and 2, below.

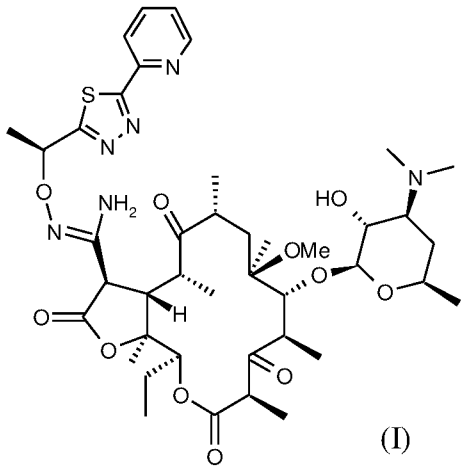

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Table 1. Effect of Compound of Formula (I), Azithromycin, Clarithromycin and Telithromycin on interleukin-6 (IL-6) release in whole blood assay after 6 hours of incubation

Treatment	Conc. (µg/mL)	IL-6 (n=5)	
		Absolute levels (pg/mL)	% Inhibition vs. positive control
Lipopolysaccharide (LPS)	0.01	6599 ± 1236	-
Compound of Formula (I)	2.5	6030 ± 1221	10 ± 3
	5	5628 ± 1103	15 ± 4
	10	5284 ± 1026	20 ± 4
	20	4283 ± 866	35 ± 4
	40	3734 ± 810	44 ± 4
Telithromycin	2.5	6240 ± 1066	4 ± 6
	5	5949 ± 996	8 ± 3
	10	5498 ± 892	15 ± 3
	20	5174 ± 787	19 ± 4
	40	4236 ± 737	33 ± 8
Azithromycin	2.5	6228 ± 1321	7 ± 6
	5	6721 ± 1353	-1 ± 6
	10	6489 ± 1253	2 ± 5
	20	6453 ± 1198	0 ± 9
	40	5372 ± 1051	17 ± 7
Clarithromycin	2.5	6404 ± 1057	2 ± 5
	5	6742 ± 1267	-3 ± 7
	10	6713 ± 1097	-4 ± 6
	20	5670 ± 907	7 ± 13
	40	6229 ± 1019	3 ± 6

As can be seen, Compound of Formula (I) and Telithromycin showed concentration-dependent inhibition of LPS-stimulated IL-6 release with 44% and 33% inhibition at highest concentration, respectively. Compound of Formula (I) showed statistically non-significant higher inhibition of IL-6 release compared to Telithromycin at all the tested concentrations. Azithromycin and Clarithromycin did not show any effect on LPS-stimulated IL-6 release. Thus, Compound of Formula (I) was found to be more potent modulator when compared to Telithromycin, Azithromycin and Clarithromycin.

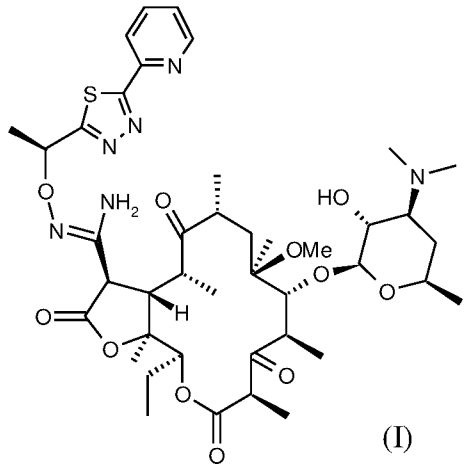
Table 2. Effect of Compound of Formula (I), Azithromycin, Clarithromycin and Telithromycin on Tumor necrosis factor α (TNF-α) release in whole blood assay after 6 hours of incubation

Treatment	**Conc. (µg/mL)**	**TNF-α (n=5)**	
		Absolute levels (pg/mL)	**% Inhibition vs. positive control**
LPS	0.01	3622 ± 733	-
Compound of Formula (I)	2.5	2866 ± 673	23 ± 4
	5	2638 ± 568	28 ± 4
	10	2326 ± 549	38 ± 4
	20	1869 ± 426	50 ± 3
	40	1367 ± 348	64 ± 3
Telithromycin	2.5	3228 ± 699	12 ± 5
	5	2915 ± 596	20 ± 4
	10	2765 ± 534	23 ± 4
	20	2312 ± 403	35 ± 4
	40	1648 ± 254	52 ± 3
Azithromycin	2.5	3400 ± 767	8 ± 5
	5	3462 ± 750	6 ± 4
	10	3681 ± 727	-2 ± 4
	20	4030 ± 662	-15 ± 8
	40	3452 ± 602	2 ± 7
Clarithromycin	2.5	3422 ± 706	6 ± 5
	5	3686 ± 648	-4 ± 5
	10	4270 ± 815	-19 ± 6
	20	4367 ± 611	-27 ± 10
	40	3959 ± 567	-15 ± 10

As can be seen, Compound of Formula (I) and Telithromycin showed concentration-dependent inhibition of LPS- stimulated TNF–α release with 64 and 52% inhibition at highest concentration, respectively. Compound of Formula (I) showed statistically non-significant higher inhibition of TNF–α release compared to Telithromycin at all the tested concentrations. Azithromycin and Clarithromycin did not show any effect on LPS-stimulated TNF–α release. Thus, Compound of Formula (I) was found to be more potent modulator when compared to Telithromycin, Azithromycin and Clarithromycin.

Claims

1. A pharmaceutical composition for modulating one or more cytokines, said composition comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



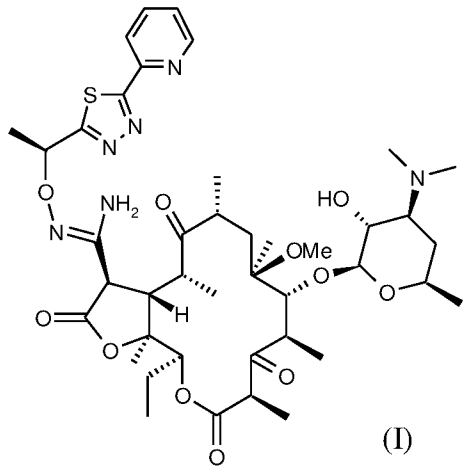
(I)

2. The pharmaceutical composition according to Claim 1, wherein the cytokine is one or more of Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF).

3. A method for modulating one or more cytokines in a subject, said method comprising administering to the subject a pharmaceutical composition according to Claim 1.

4. The method according to Claim 3, wherein the cytokine is one or more of Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF).

5. A method for modulating one or more cytokines in a subject, said method comprising administering to the subject a compound of Formula (I) or a pharmaceutically acceptable salt thereof:



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6. The method according to Claim 5, wherein the cytokine is one or more of Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF).

7. The pharmaceutical composition according to any one of the claims 1-2, for use in modulating one or more cytokines in a subject, wherein the cytokine is one or more of Tumor necrosis factor-α (TNF-α), Interleukin-1 (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Interleukin-10 (IL-10), Interleukin-1β (IL-1β), Interferon-g (IFN-g), and Granulocyte-macrophage colony stimulating factor (GM-CSF).

8. The pharmaceutical composition for modulating one or more cytokines, comprising a compound of Formula (I) or a pharmaceutically acceptable salt thereof according to Claim 1 and one or more pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050546

A. CLASSIFICATION OF SUBJECT MATTER
A61K9/00,A61K31/7048,A61K38/19,A61K38/20,A61K38/21,C07H17/00,C07H17/08,C07K14/52,C07K14/525,C12N15/19,C12N15/24,C12N15/25,C12N15/26,C12N15/28
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)
A61K, C07H, C07K, C12N

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US20050037983 A1 (NEUROCURE LTD. [IE]); 17 Feruary 2005 Abstract, paragraphs [0014],[0040-0041], [0051], [0077]	1-2, 7-8
Y	US20100209357 A1 (LEVITT ROY C.); 19 August 2010 Abstract, paragraphs [0002],[0005-0006],[0028-0035],[0080], claims 27, 35-36, 38, 42	1-2, 7-8
Y	Kristina Lotter et al. "In vivo efficacy of telithromycin on cytokine and nitric oxide formation in lipopolysaccharide-induced acute systemic inflammation in mice", Journal of Antimicrobial Chemotherapy 58(3): 615-21, October 2006, DOI: 10.1093/jac/dkl270 The whole document	1-2, 7-8
Y	WO2006090067 A1 (AVENTIS PHARMA S. A. [FR]); 31 August 2006 Abstract, claims	1-2, 7-8
Y	WO2008072034 A1 (ZAMBON S. P. A. [IT]); 19 June	

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
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"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	Date of mailing of the international search report
18-10-2019	18-10-2019
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Sateesh Kumar Meena Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050546

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	2008 Pages 1; line 25 - page 2 line 1	1-2, 7-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050546

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.: 3-6
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claims 3-6 relates to a method for treatment of
the human or animal body, which does not require an international search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].

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.:
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:

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.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2019/050546

Citation	Pub.Date	Family	Pub.Date
US 20050037983 A1	17-02-2005	WO 2005087207 A1	22-09-2005
US 20100209357 A1	19-08-2010	WO 2008021237 A1	21-02-2008
		EP 2068889 A1	17-06-2009
		JP 2010500360 A	17-01-2010
WO 2006090067 A1	31-08-2006	CN 101180064 A	14-05-2008
		EP 1855695 A1	21-11-2007
		JP 2008531529 A	14-08-2008
		KR 20070106581 A	01-11-2007
WO 2008072034 A1	19-06-2008	EP 2102226 A1	23-09-2009
		CN 101558078 A	14-10-2009
		US 2010099634 A1	22-04-2010
		DK 2102226 T3	10-12-2012