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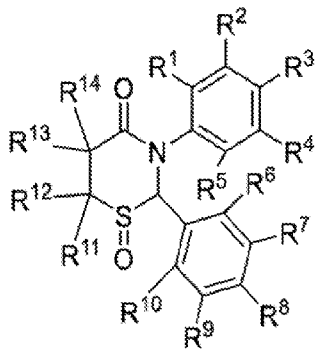

(57) Abstract: A compound with the following general formula and a general method of making this compound are provided: R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl.

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S-OXIDES OF 2,3-DIARYL-2,3-DIHYDRO-4*H*-1,3-THIAZIN-4-ONES AND 2,3-DIARYL-1,3-THIAZEPAN-4-ONES AND METHODS FOR MAKING

CROSS-REFERENCE TO RELATED APPLICATIONS

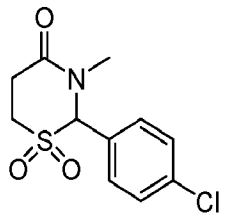
[0001] This application claims the benefit of United States Provisional Patent Application No. 62/846,046, filed on May 10, 2019, which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

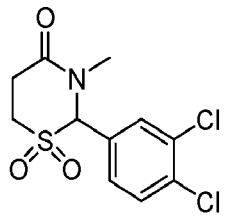
Field of the Invention

[0002] The present invention relates to *S*-oxides of a six-membered 1,3-thiazin-4-one system and *S*-oxides of a seven-membered 1,3-thiazapan-4-one ring system.

[0003] The 1,3-thiazin-4-ones are a group of six-membered heterocycles with a wide range of biological activity (Ryabukhin, Y. I., Korzhavina, O. B. & Suzdalev, K. F. *Adv. Heterocycl. Chem.* **1996**, *66*, 131–190). Surrey's research (Surrey, A. R., Webb, W. G.; Gesler, R. M. *J. Am. Chem. Soc.***1958**, *80*, 3469–3471; Surrey, A. R. *US Patent 3082209*, **1963**; Surrey, A. R. *US Patent 3093639*, **1963**) resulted in the discovery of two drugs, the antianxiety and muscle relaxant chlormezanone [2-(4-chlorophenyl)-3-methyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide] (O'Neil, M. J. Editor. The Merck Index, 14th ed., 2006, Whitehouse Station, NJ: Merck & Co. Inc., p. 349; Tanaka, R. & Horayama, N. *X-Ray Struct. Anal. Online*, **2005**, *21*, x57–x58) and muscle relaxant dichlormezanone [2-(3,4-dichlorophenyl)-3-methyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide] (Elks, J. & Ganellin, C. R. Editors. Dictionary of Drugs, **1990**, Cambridge, UK: Chapman and Hall, p. 382). These sulfones showed greater activity than the sulfides from which they were synthesized (Surrey, A. R., Webb, W. G.; Gesler, R. M. *J. Am. Chem. Soc.***1958**). Surrey also prepared a variety of other sulfoxides and sulfones of 3-alkyl-2-aryl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-ones (Surrey, A. R. *US Patent 3082209*, **1963**; Surrey, A. R. *US Patent 3093639*, **1963**). Surrey did not successfully synthesize any 2-aryl-3-aryl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-ones.

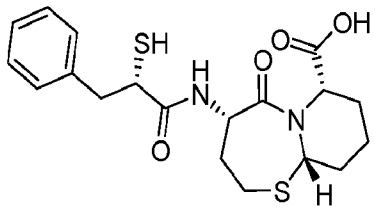


chlormezanone



dichlormezanone

The seven-membered 1,3-thiazepan-4-one ring system is also of biological interest, as exemplified by the investigational compound omapatrilat (Graul, A., Leeson, P.; Castañer, J. *Drugs Future*, **1999**, *24*, 269–277; Robl, J. A., et al. *J. Med. Chem.* **1997**, *40*, 1570–1577; Tabrizchi, R. *Curr. Opin. Investig. Drugs*, **2001**, *2*, 1414–1422).

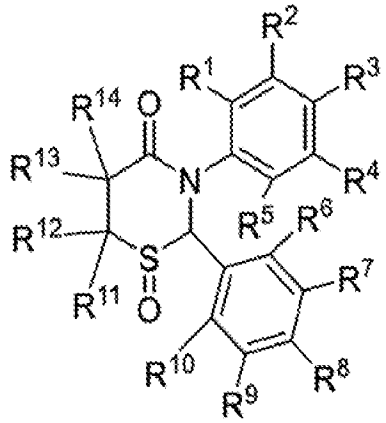


omapatrilat

[0004] Sulfoxides and sulfones of 2,3-diaryl-2,3-dihydro-4*H*-1,3-thiazin-4-ones and 2,3-diaryl-1,3-thiazepan-4-ones, along with methods for creating these compounds, can lead to new therapeutics due to their biological activity and potential medicinal properties.

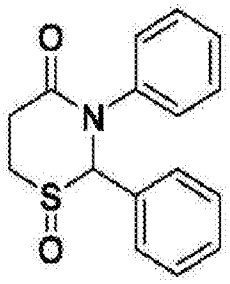
SUMMARY OF THE INVENTION

[0005] One embodiment of this invention is directed to a compound of Formula I:



I

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl. The pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups. Formula I is not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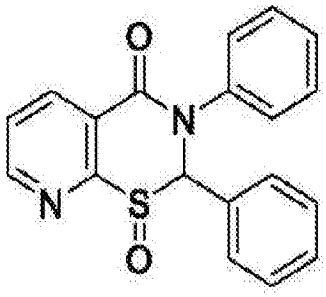
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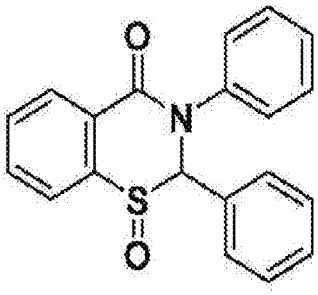
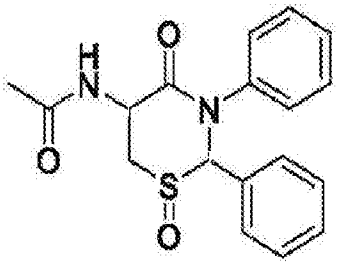

, or

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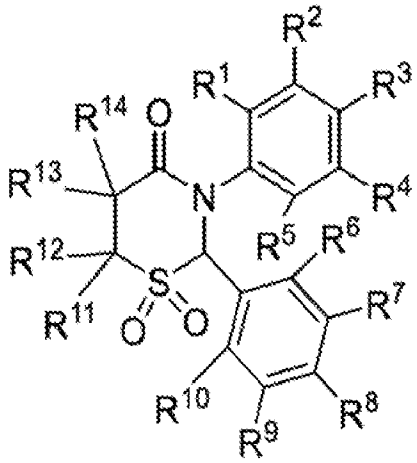
[0006] Another embodiment of this invention is directed to a compound of Formula II:

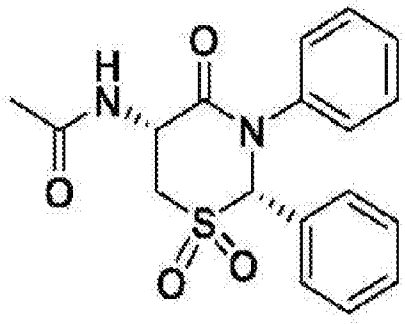


II

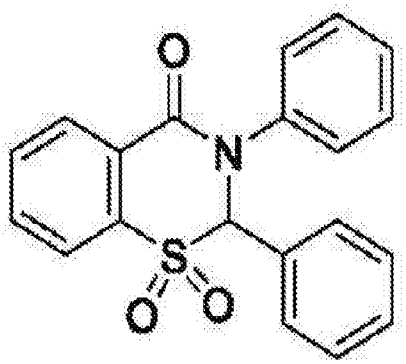
R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl. The pyridyl, alkyl,

aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups. And not all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are hydrogen.

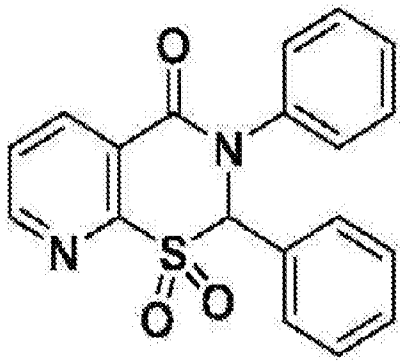
[0007] In another embodiment, the compound is



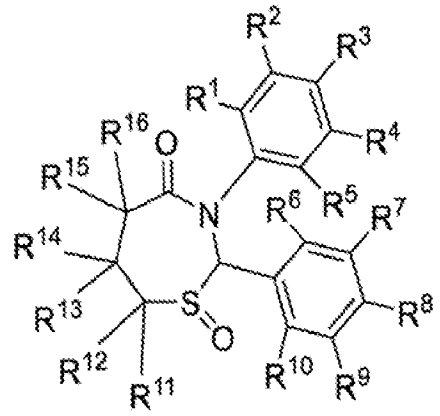
[0008] In another embodiment, the compound is



[0009] In another embodiment, the compound is



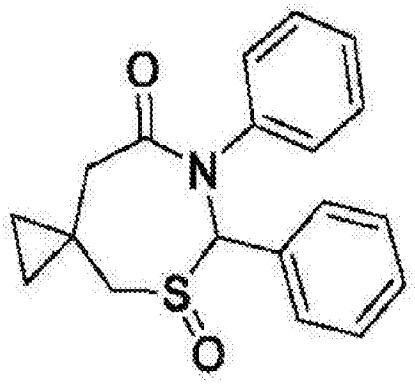
[0010] Another embodiment of this invention is directed to a compound of Formula III:



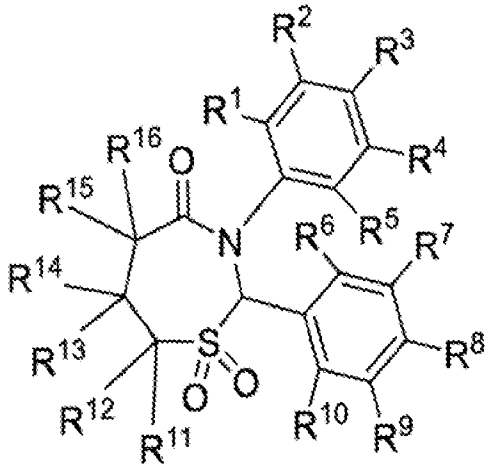
III

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl. The pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups.

[0011] In another embodiment, the compound is



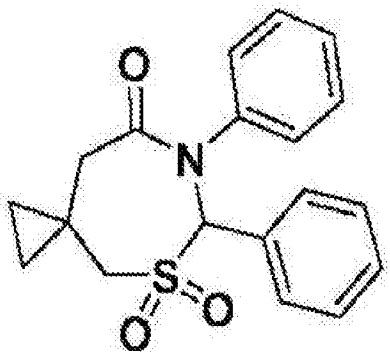
[0012] Another embodiment of this invention is directed to a compound of Formula IV:



IV

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl. The pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups.

[0013] In another embodiment, the compound is



[0014] Other aspects and advantages of the invention will be apparent from the following description and the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

[0015] Definitions

[0016] While the terms used herein are believed to be well understood by one of ordinary skill in the art, definitions are set forth herein to facilitate explanation of the subject matter disclosed herein.

[0017] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the subject matter disclosed herein belongs. Although any methods, devices, and materials similar or equivalent to those described herein can be used in the practice or testing of the presently disclosed subject matter, representative methods, devices, and materials are described herein.

[0018] The terms "a," "an," and "the" refer to "one or more" when used in this application, including the claims. The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

[0019] All references to singular characteristics or limitations of the present disclosure shall include the corresponding plural characteristic(s) or limitation(s) and vice versa, unless otherwise specified or clearly implied to the contrary by the context in which the reference is made.

[0020] All combinations of method or process steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0021] The methods and devices of the present disclosure, including components thereof, can comprise, consist of, or consist essentially of the essential elements and limitations of the embodiments described herein, as well as any additional or optional components or limitations described herein or otherwise useful.

[0022] Unless otherwise indicated, all numbers expressing physical dimensions, quantities of ingredients, properties such as reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about". Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and claims are approximations that can vary depending upon the desired properties sought to be obtained by the presently disclosed subject matter.

[0023] As used herein, ranges can be expressed as from "about" one particular value, and/or to "about" another particular value. It is also understood that there are a number of values

disclosed herein, and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units are also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

[0024] The term "alkyl" includes branched, straight chain and cyclic, substituted or unsubstituted saturated aliphatic hydrocarbon groups. Alkyl groups can comprise about 1 to about 24 carbon atoms ("C1-C24"), about 7 to about 24 carbon atoms ("C7-C24"), about 8 to about 24 carbon atoms ("C8-C24"), or about 9 to about 24 carbon atoms ("C9-C24"). Alkyl groups can also comprise about 1 to about 8 carbon atoms ("C1-C8"), about 1 to about 6 carbon atoms ("C1-C6"), or about 1 to about 3 carbon atoms ("C1-C3"). Examples of C1-C6 alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, cyclopropylmethyl and neohexyl radicals.

[0025] The term "aryl" includes a 6- to 14-membered monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring system. Examples of an aryl group include phenyl and naphthyl.

[0026] The term "aralkyl" refers to an aryl-alkyl group wherein aryl and alkyl are as previously described.

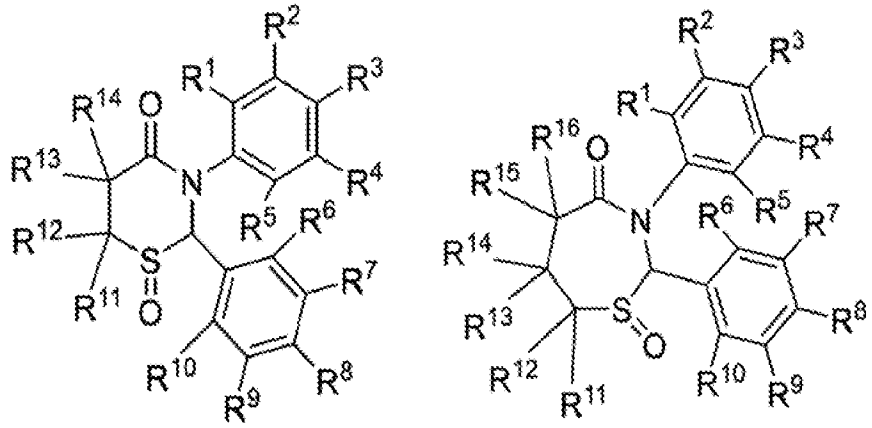
[0027] The term "heteroaryl" includes an aromatic heterocycle ring of 5 to 14 members and having at least one heteroatom selected from nitrogen, oxygen and sulfur, and containing at least 1 carbon atom, including monocyclic, bicyclic, and tricyclic ring systems. Representative heteroaryls are triazolyl, tetrazolyl, oxadiazolyl, pyridyl, furyl, benzofuranyl, thiophenyl, benzothiophenyl, quinolinyl, pyrrolyl, indolyl, oxazolyl, benzoxazolyl, imidazolyl, benzimidazolyl, thiazolyl, benzothiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, cinnolinyl, phthalazinyl, quinazolinyl, pyrimidyl, oxetanyl, azepinyl, piperazinyl, morpholinyl, dioxanyl, thietanyl and oxazolyl.

[0028] As used herein, the term "halogen" means F, Cl, Br or I.

[0029] The following description is of exemplary embodiments that are presently contemplated for carrying out the present invention. This description is not to be taken in a limiting sense, but is made merely for the purpose of describing the general principles and features of the present invention. The scope of the present invention is not limited by this description.

[0030] The present invention is directed to classes of 2,3-diaryl-2,3-dihydro-4*H*-1,3-thiazin-4-ones **I** and **II**, and 2,3-diaryl-1,3-thiazepan-4-ones **III** and **IV** and methods to make them.

[0031] General Synthetic Procedure for Sulfoxides Formulas I and III:



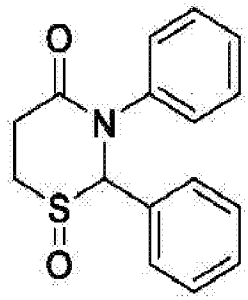
I **III**

[0032] In compound **I**, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl.

[0033] In compound **III,** R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl.

[0034] The heterocycle (1.0 equiv.) was dissolved in methanol (8 mL/mmol). An aqueous solution of Oxone® (3.0 equiv. calculated as $KHSO_5$, 152.2 g mol^{-1}), in water (4 mL/3 mmol) was added dropwise at room temperature with vigorous stirring. After the addition, the reaction mixture was stirred and the reaction was followed by TLC. Water was added to the mixture to dissolve precipitates, and the mixture was extracted with 4 times with CH_2Cl_2 or ethyl acetate. The organic layers were combined and washed with water and then saturated NaCl. The solution was dried over sodium sulfate and concentrated under vacuum to give a crude solid. Further purification is described below.

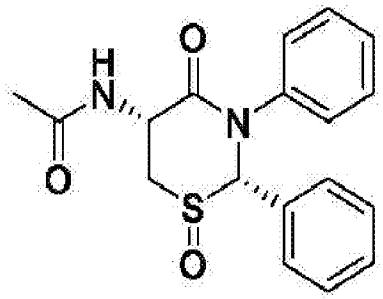
[0035] Example 1



1a

[0036] 2,3-diphenyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one 1-oxide **1a**: ^{1}H NMR of the crude product showed a diastereomeric ratio of 95:5. The product was purified by chromatography in a silica gel micro-column with mixtures of ethyl acetate and hexanes. 0.0251 g (45%). m.p.: 160-163 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 7.51 (m, 2H), 7.46 (m, 3H), 7.38 (m, 2H), 7.32 (m, 3H), 5.98 (d, 1H, J = 2.1Hz), 3.36 (m, 1H), 2.99 (m, 1H), 2.85 (m, 2H). Structure confirmed by X-Ray crystallography.

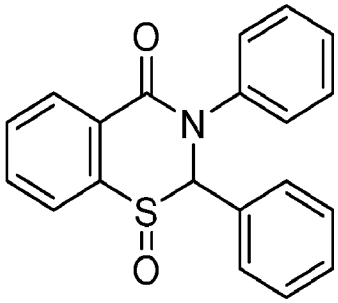
[0037] Example 2



1b

[0038] *N*-[(1*S*,2*S*,5*R*)-1,4-dioxo-2,3-diphenyl-1λ^4,3-thiazinan-5-yl]acetamide **1b**: ^{1}H NMR of the crude product showed a diastereomeric ratio of 37:63. The product was purified by chromatography in a silica gel micro-column with mixtures of ethyl acetate and hexanes. 0.0558 g (96%). m.p. 176-179 °C. Structure confirmed by X-Ray crystallography.

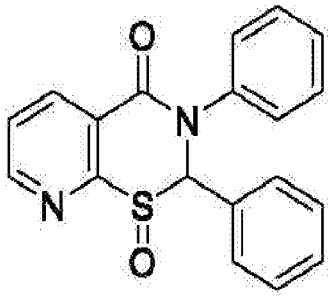
[0039] Example 3



1c

[0040] 2,3-diphenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-one 1-oxide **1c**: ^{1}H NMR of the crude product showed a diastereomeric ratio of 93:7. Recrystallized from CH_2Cl_2/hexanes. 0.0429 g (55%). m.p. 208-209 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 7.72 (m, 1H), 7.55, m, 2H), 7.46 (m, 5H), 7.36 (m, 1H), 7.29 (m, 6H), 6.28 (s, 1H). Structure confirmed by X-Ray crystallography.

[0041] Example 4

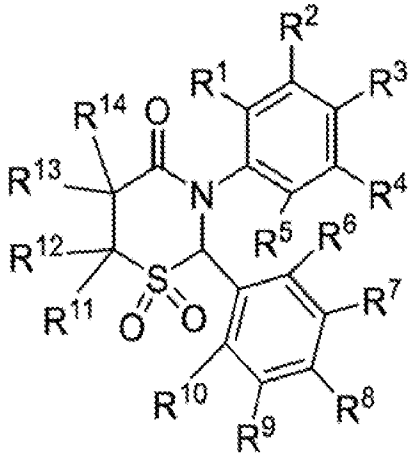


1d

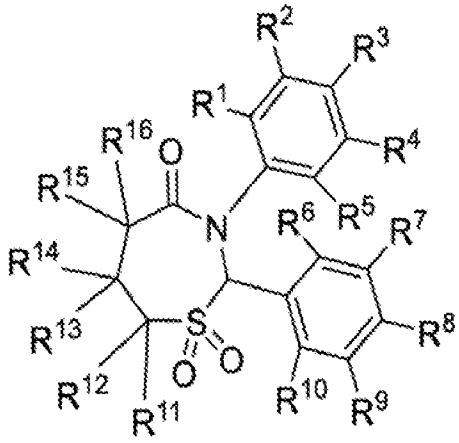
[0042] 2,3-diphenyl-2,3-dihydro-4*H*-pyrido[3,2-e]-[1,3]thiazin-4-one 1-oxide **1d**: ^{1}H NMR of the crude product showed a diastereomeric ratio of 84:16. The product was purified by chromatography in a silica gel micro-column with mixtures of ethyl acetate and hexanes. 0.0226 g (43%). m.p. 177-179 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 8.70 (m, 2H), 7.63 (s, 1H), 7.48 (s, 4H), 7.36 (m, 6H), 6.34 (s, 1H). Structure confirmed by X-Ray crystallography.

[0043] Example 5

[0044] General Synthetic Procedure for Sulfones Formulas **II** and **IV**:



II



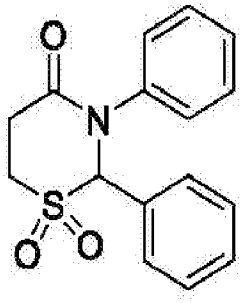
IV

[0045] In compound **II**, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group that includes hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl.

[0046] In compound **IV,** R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that includes H, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl.

[0047] The heterocycle (0.267 mmol) was dissolved in glacial acetic acid (1.2 mL). An aqueous solution of $KMnO_4$ (0.535 mmol in 1.45 mL water was added dropwise at room temperature with vigorous stirring. The reaction was followed by TLC. Solid sodium bisulfite ($NaHSO_3/Na_2S_2O_5$) was added until the solution remained colorless. 1.45 mL of water was added and stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 x 5 mL). The organics were combined and washed once with sat. NaCl. The solution was dried over Na_2SO_4 and filtered. The product was purified by chromatography in a silica gel micro-column.

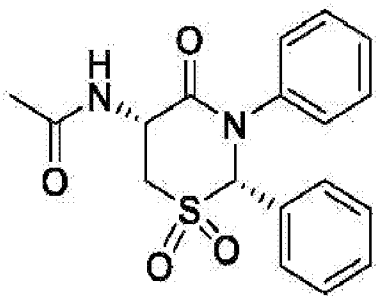
[0048] Example 6



2a

[0049] 2,3-diphenyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one 1,1-dioxide **2a**: 0.0534 g (70%). m.p. 145-148 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 7.58 (m, 2H), 7.50 (m, 3H), 7.36 (m, 3H), 7.30 (m, 1H), 7.23 (m, 2H), 5.61 (s, 1H), 3.48 (m, 1H), 3.99 (m, 3H).

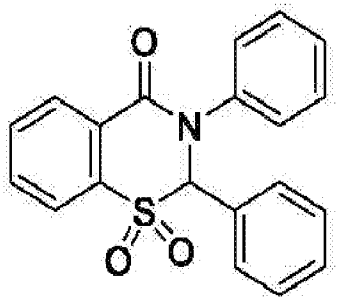
[0050] Example 7



2b

[0051] *N*-[(2*S*,5*R*)-1,1,4-trioxo-2,3-diphenyl-1λ^6,3-thiazinan-5-yl]acetamide **2b**: 0.0762 g (80%). m.p. 170-194 °C (decomposition). ^{1}H NMR ($CDCl_3$): δ(ppm): 7.37 (m, 2H), 7.30 (m, 1H), 7.24 (m, 2H), 7.17 (m, 3H), 6.95 (m, 2H), 5.81 (s, 1H), 5.12 (dt, 1H, J = 12, 6.1 Hz), 3.92 (m, 1H), 3.54 (m, 1H), 2.03 (d, 1H, J = 1.8 Hz). Structure confirmed by X-Ray crystallography.

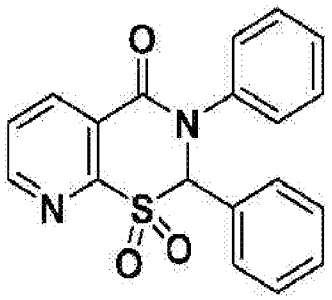
[0052] Example 8



2c

[0053] 2,3-diphenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-one 1,1-dioxide **2c**: 0.050 g (54%). m.p. 163-165 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 8.29 (d, 1H, J = 7.7 Hz), 7.70 (m, 2H), 7.60 (m, 1H), 7.32 (m, 2H), 7.25 (m, 8H), 5.79 (m, 1H).

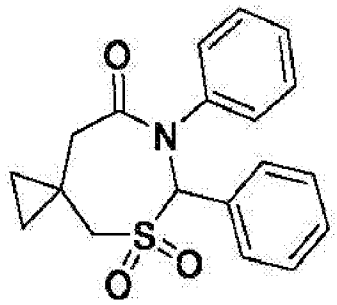
[0054] Example 9



2d

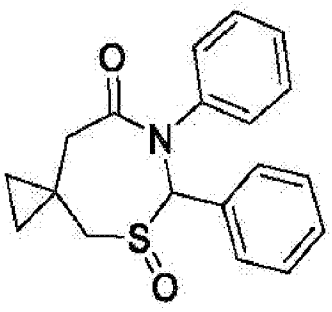
[0055] 2,3-diphenyl-2,3-dihydro-4*H*-pyrido[3,2-e]-[1,3]thiazin-4-one 1-oxide **2d**: 0.0691g (74%). m.p.: 210-211 °C (decomposition). ^{1}H NMR ($CDCl_3$): δ(ppm): 8.77 (d, J = 4.7 Hz, 1H), 8.62 (d, J = 7.9 Hz, 1H), 7.67 (dd, J = 8.0, 4.7 Hz, 1H), 7.31 (m, 9H), 5.88 (s, 1H).

[0056] Example 10



2e

[0057] 6,7-diphenyl-5λ^6-thia-7-azaspiro[2.6]nonane-5,5,8-trione **2e**: 70% yield. m.p. 186.6-187.7 °C (decomposition). ^{1}H NMR ($CDCl_3$): δ(ppm): 7.72 (s, 3H), 7.44 (m, 3H), 7.35 (m, 4H), 7.29 (m, 1H), 6.05 (s, 1H), 3.50 (d, 1H, J = 14.6 Hz), 2.93 (d, 1H, J = 14.6 Hz), 2.86 (m, 1H), 2.56 (bs, 1H), 1.02 (m, 2H), 0.77 (t, 2H, J = 7.8 Hz). Structure confirmed by X-Ray crystallography.



1e

[0058] 6,7-diphenyl-5λ^4-thia-7-azaspiro[2.6]nonane-5,8-dione **1e**: In one experiment, this was isolated along with **2e** from the $KMnO_4$ reaction. m.p. 193-194 °C. ^{1}H NMR ($CDCl_3$): δ(ppm): 7.40-7.10 (m, 7H), 7.27 (m, 2H), 7.19 (d, 1H, J = 7.0 Hz), 6.33 (s, 1H), 3.18 (d, 1H, J =14.0 Hz), 3.04 (d, 1H, J = 13.4 Hz), 2.74 (bs, 2H), 1.08-0.98 (m, 2H), 0.71 (m, 1H), 0.60 (m, 1H).

[0059] Although the present invention has been described in terms of specific exemplary embodiments and examples, it will be appreciated that the embodiments disclosed herein are for illustrative purposes only and various modifications and alterations might be made by those skilled in the art without departing from the spirit and scope of the invention as set forth in the following claims.

[0060] References

[0061] All references cited herein including those below are hereby incorporated by reference in their entirety.

[0062] H. P. Yennawar, Z. Yang, and L. J. Silverberg, "Crystal structure of *rac*-2,3-diphenyl-2,3,5,6-tetrahydro-4*H*-1,3-thiazin-4-one 1-oxide," *Acta Cryst., Sect. E: Crystallogr. Commun.* **2016**, E72, 1541-1543.

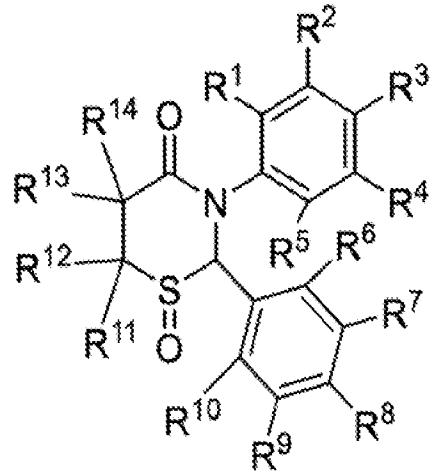
[0063] H. P. Yennawar, D. J. Noble, and L. J. Silverberg, "Crystal structure of (1*S*,2*S*,5*R*)-5-(acetylamino)-4-oxo-2,3-diphenyl-1,3-thiazinan-1-ium-1-olate," *Acta Cryst., Sect. E: Crystallogr. Commun.* **2017,** E73, 1417-1420.

[0064] H. P. Yennawar, D. J. Noble, Z. Yang, and L. J. Silverberg, "*rac*-2,3-Diphenyl-2,3-dihydro-4*H*-pyrido[3,2-e][1,3]thiazin-4-one 1-oxide," *IUCrData* **2017,** 2**,** x171112.

[0065] H. P. Yennawar, R. F. Fox, Q. J. Moyer, Z. Yang, and L. J. Silverberg, "Crystal structure of 2,3-diphenyl-2,3-dihydro-4*H*-1,3-benzothiazin-4-one 1-oxide," *Acta Cryst., Sect. E: Crystallogr. Commun.* **2017**, E73, 1189-1191.

WE CLAIM:

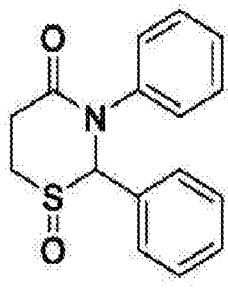
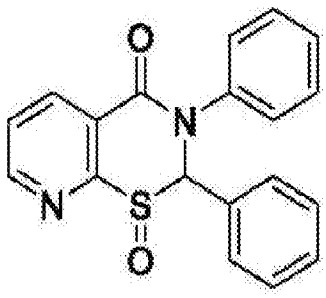
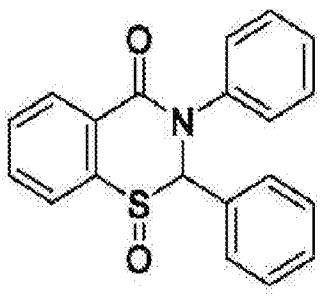
1. A compound of Formula I:

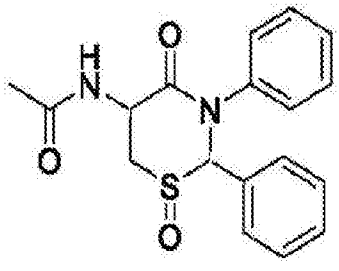


I

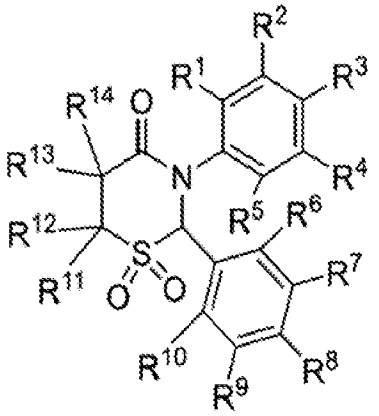
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl, wherein the pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups, and

wherein Formula I is not

 ,  ,  , or

 .

2. A compound of Formula II:



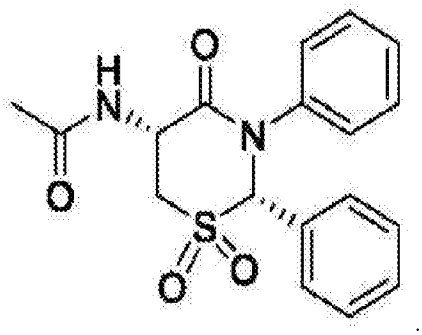
II

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are each independently selected from the group consisting of hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl,

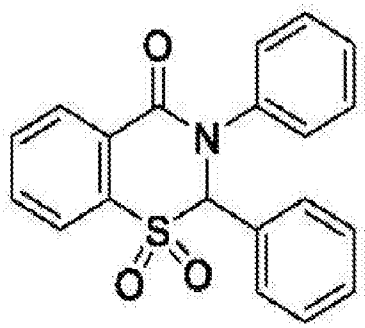
wherein the pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups, and

wherein not all of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13} and R^{14} are hydrogen.

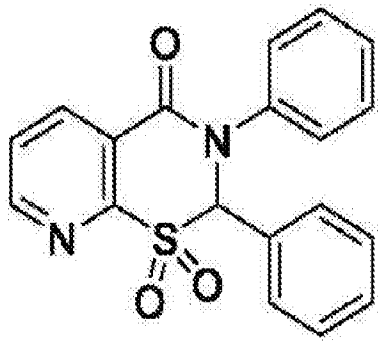
3. The compound of claim 2, wherein the compound is



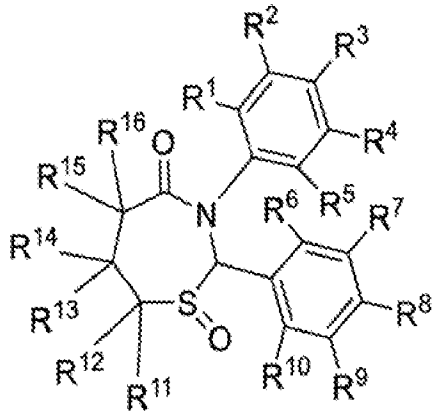
4. The compound of claim 2, wherein the compound is



5. The compound of claim 2, wherein the compound is



6. A compound of Formula III:

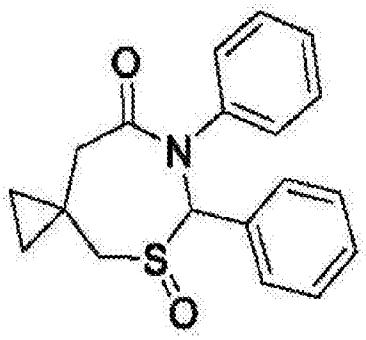


III

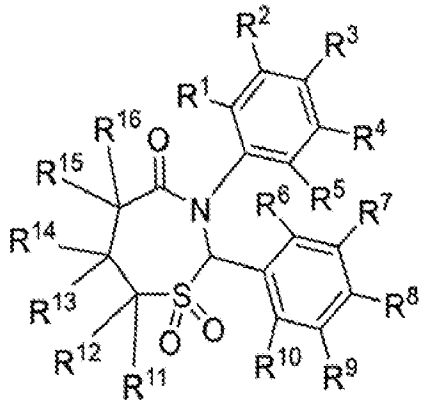
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that consists of hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl, and

wherein the pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups.

7. The compound of claim 6, wherein the compound is



8. A compound of Formula IV:

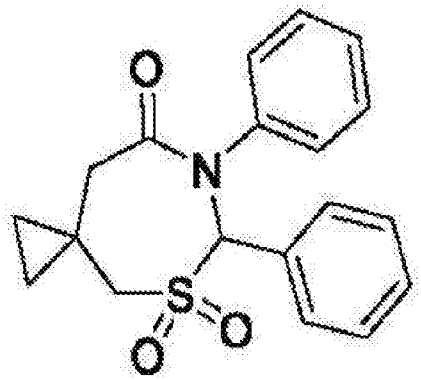


IV

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15} and R^{16} are each independently selected from the group that consists of hydrogen, halogen, nitro, cyano, amido, pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl, and

wherein the pyridyl, alkyl, aryl, alkoxy, cycloalkyl, heteroalkyl, heterocyclyl, aralkyl, heteroaryl and heteroaralkyl may be optionally substituted with one or more of methyl, ethyl, halogen, nitro, methoxy, or cyano groups.

9. The compound of claim 8, wherein the compound is



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/32249

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/519; A61K 31/53; A61K 31/553 (2020.01)

CPC - A61K 31/519; A61K 31/53; A61K 31/553; A61K 9/0019

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)
See Search History document

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Silverberg et al., "Synthesis and Spectroscopic Properties of 2,3-Diphenyl-1,3-thiaza-4-one Heterocycles", International Journal of Chemistry; Vol. 7, No. 2; 2015, 150-162	1
A	PubChem CID 44517771, create date, 28 December 2009 (28.12.2009) page 2 formula	1
A	PubChem CID 22090046, create date, 05 December 2007 (05.12.2007) page 2 formula	1
P/A	PubChem CID: 139088178, create date, 03 September 2019 (03.09.2019)	1
A	US 3,082,209 A (Surry et al.) 19 March 1963 (19.03.1963) entire document	1

☐ 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
"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	Date of mailing of the international search report
01 September 2020	05 OCT 2020
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. 571-273-8300	Authorized officer Lee Young Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 20/32249

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.:
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:
--please see supplemental box ---

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.:
claim 1

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.

lack of unity Box 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 searched, the appropriate additional search fees must be paid.

Group I: Claim 1 directed towards a compound of formula 1

Group II: Claims 2-5 directed towards a compound of formula II

Group III: Claims 6-7 directed towards a compound of formula III

Group IV: Claims 8-9 directed towards a compound of formula IV

The inventions listed as Groups I-IV 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:

Special Technical Features:

Group I requires a compound of formula I, not required by groups II-IV

Group II requires a compound of formula II, not required by groups I and III-IV

Group III requires a compound of formula III, not required by groups I-II and IV

Group IV requires a compound of formula IV, not required by groups I-III

Shared Technical Features:

Groups I-II share the common feature of core structure of formula diaryl-2,3-dihydro-4h-1,3-thiazine. However, this shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by the document entitled "PubChem CID 44517771" (hereinafter "Pubchem44517771") which discloses the core structure diaryl-2,3-dihydro-4h-1,3-thiazine (page 2 formula).

Groups III-IV share the technical feature of 7-membered thiazolidinone. However, this shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by the document entitled "PubChem CID: 22090046" (hereinafter "PubChem 22090046") teaches a 7-membered thiazolidinone compound (page 1 formula).

As the shared technical features were known in the art at the time of the invention, they cannot be considered special technical features that would otherwise unify the groups. Therefore, Groups I-IV lack unity under PCT Rule 13.