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**NOTICE OF GRANT OF PATENT**

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**TAKE NOTICE** that the following Patent has been granted:

Title: **Heterocyclyl Compounds**

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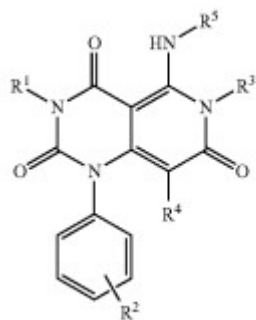
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**Abstract:** The present invention is related to heteroaryl compounds as MEK inhibitors. The invention includes heteroaryl compounds of formula I, their tautomers and pharmaceutically acceptable salts, combinations with suitable medicament and pharmaceutical compositions thereof. The present invention also includes process of preparation of the said compounds and intended use in therapy of them. (Formula I) (I)

## CLAIMS

1. A compound of formula I, its tautomeric forms, its pharmaceutically acceptable salts, their combinations with suitable medicament and pharmaceutical compositions containing them,



wherein,

R<sup>1</sup> is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted-heterocyclyl;

R<sup>2</sup> is selected from the group consisting of —R<sup>6</sup>-E, —SO<sub>2</sub>R<sup>7</sup>, and —C(O)R<sup>8</sup>;

R<sup>3</sup> is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted-cycloalkyl;

R<sup>4</sup> is selected from the group consisting of hydrogen, halogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted-cycloalkyl;

R<sup>5</sup> is substituted- or unsubstituted-aryl, wherein the substituents are selected from with R<sup>a</sup> and R<sup>b</sup>;

R<sup>a</sup> and R<sup>b</sup> are selected from the group consisting of hydrogen, halogen and haloalkyl;

R<sup>6</sup> is selected from the group consisting of direct bond, —[C(R<sup>c</sup>)R<sup>d</sup>]<sub>n</sub>NR<sup>9</sup>—, —[C(R<sup>c</sup>)R<sup>d</sup>]<sub>n</sub>O—, —NHC(=O)[C(R<sup>c</sup>)R<sup>d</sup>]<sub>p</sub>—, —S(O)<sub>2</sub>NH—, —NHC(=O)[C(R<sup>c</sup>)R<sup>d</sup>]<sub>n</sub>NR<sup>9</sup>—, —NHC(=O)[C(R<sup>c</sup>)R<sup>d</sup>]<sub>n</sub>O—, and —NHS(O)<sub>2</sub>—;

R<sup>c</sup> and R<sup>d</sup> are each independently selected from the group consisting of hydrogen and substituted- or unsubstituted-alkyl;

E is substituted- or unsubstituted-four membered heterocyclic ring, wherein the substituents are selected from the group consisting of alkyl, halogen,  $\text{—C(=O)OR}^e$ , and  $\text{—OR}^e$ ;

$\text{R}^e$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, and substituted or unsubstituted cycloalkyl;

$\text{R}^7$  is selected from the group consisting of substituted- or unsubstituted- cycloalkyl, and substituted- or unsubstituted-cycloalkenyl;

$\text{R}^8$  is selected from the group consisting of substituted- or unsubstituted- alkyl, substituted- or unsubstituted-alkenyl, substituted- or unsubstituted-alkynyl, substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted- cycloalkenyl;

$\text{R}^9$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted-alkenyl, substituted- or unsubstituted-alkynyl, substituted- or unsubstituted-cycloalkyl and substituted or unsubstituted-cycloalkenyl;

n is an integer selected from the group consisting of 0, 1 and 2;

p is an integer selected from the group consisting of 0 and 1;

when the alkyl group and alkenyl group is substituted, the alkyl group and alkenyl group is substituted with 1 to 4 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—OR}^{10a}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the cycloalkyl group and cycloalkenyl group is a substituted, the cycloalkyl group and cycloalkenyl group is substituted with 1 to 3 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl,

heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the aryl group is a substituted, the aryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O—alkyl}$ ,  $\text{—O—perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{—alkyl}$ ,  $\text{—SO}_2\text{—perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the heteroaryl group is a substituted, the heteroaryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O—alkyl}$ ,  $\text{O—perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{—alkyl}$ ,  $\text{—SO}_2\text{—perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the heterocyclyl group is a substituted, the heterocyclyl group is substituted with 1 to 3 substituents,

when the heterocyclic group is substituted on a ring carbon of the ‘heterocycle’, the substituents are

independently selected from the group consisting of halogen, nitro, cyano, oxo, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ;

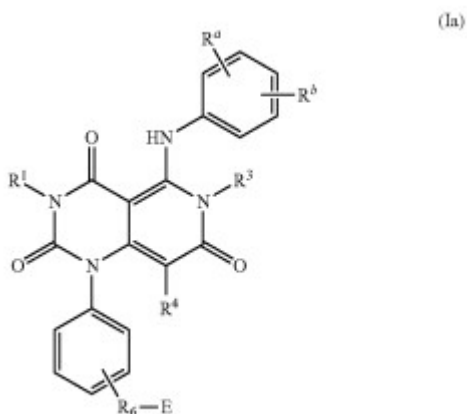
when the heterocyclic group is substituted on a ring nitrogen of the 'heterocycle', substituents are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{C(=O)OR}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

$\text{R}^{10}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

$\text{R}^{10a}$  is selected from the group consisting of alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

$\text{R}^{10b}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

2. A compound of the general formula Ia, its tautomeric forms, its pharmaceutically acceptable salts, their combinations with suitable medicament and pharmaceutical compositions containing them,



wherein,

$\text{R}^1$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted-heterocyclyl;

$R^3$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted-cycloalkyl;

$R^4$  is selected from the group consisting of hydrogen, halogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted- cycloalkyl;

$R^a$  and  $R^b$  are selected from the group consisting of hydrogen, halogen and haloalkyl;

$R^6$  is selected from the group consisting of direct bond,  $—[C(R^c)R^d]_nNR^9—$ ,  $—[C(R^c)R^d]_nO—$ ,  $—NHC(=O)[C(R^c)R^d]_p—$ ,  $—S(O)_2NH—$ ,  $—NHC(=O)[CR^c(R^d)]NR^9—$ ,  $—NHC(=O)[CR^c(R^d)]O—$ , and  $—NHS(O)_2—$ ;

$R^c$  and  $R^d$  are each independently selected from the group consisting of hydrogen and substituted- or unsubstituted-alkyl;

E is substituted- or unsubstituted-four membered heterocyclic ring, wherein the substituents are selected from the group consisting of alkyl, halogen,  $—C(=O)OR^e$ , and  $—OR^e$ ;

$R^e$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, and substituted or unsubstituted cycloalkyl;

$R^9$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted-alkenyl, substituted- or unsubstituted-alkynyl, substituted- or unsubstituted-cycloalkyl and substituted- or unsubstituted-cycloalkenyl;

n is an integer selected from the group consisting of 0, 1 and 2;

p is an integer selected from the group consisting of 0 and 1;

when the alkyl group and alkenyl group is substituted, the alkyl group and alkenyl group is substituted with 1 to 4 substituents independently selected from the group consisting of oxo,

halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—OR}^{10a}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the cycloalkyl group and cycloalkenyl group is a substituted, the cycloalkyl group and cycloalkenyl group is substituted with 1 to 3 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the aryl group is a substituted, the aryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O-alkyl}$ ,  $\text{—O-perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{-alkyl}$ ,  $\text{—SO}_2\text{-perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the heteroaryl group is a substituted, the heteroaryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O-alkyl}$ ,  $\text{O-perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{-alkyl}$ ,  $\text{—SO}_2\text{-perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;



when the heterocyclyl group is substituted, the heterocyclyl group is substituted with 1 to 3 substituents,

when the heterocyclic group is substituted on a ring carbon of the 'heterocycle', the substituents are independently selected from the group consisting of halogen, nitro, cyano, oxo, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ;

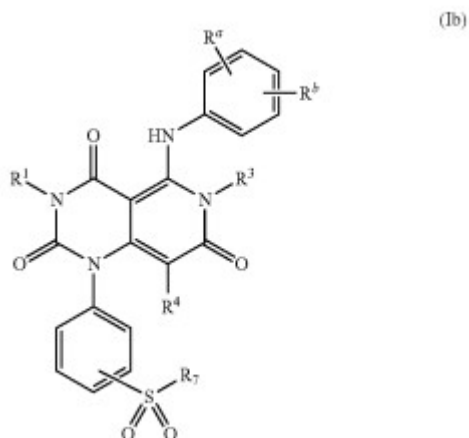
when the heterocyclic group is substituted on a ring nitrogen of the 'heterocycle', substituents are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{C(=O)OR}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

$\text{R}^{10}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

$\text{R}^{10a}$  is selected from the group consisting of alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

$\text{R}^{10b}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

3. A compound of formula Ib, its tautomeric forms, its pharmaceutically acceptable salts, their combinations with suitable medicament and pharmaceutical compositions containing them,



wherein,

$R^1$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted- cycloalkyl, and substituted- or unsubstituted-heterocyclyl;

$R^3$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted-cycloalkyl;

$R^4$  is selected from the group consisting of hydrogen, halogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted-cycloalkyl;

$R^a$  and  $R^b$  are selected from the group consisting of hydrogen, halogen and haloalkyl;

$R^7$  is selected from the group consisting of substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted-cycloalkenyl;

when the alkyl group and alkenyl group is substituted, the alkyl group and alkenyl group is substituted with 1 to 4 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,  $-\text{OR}^{10b}$ ,  $-\text{SO}_2\text{R}^{10a}$ ,  $-\text{C}(=\text{O})\text{OR}^{10a}$ ,  $-\text{OC}(=\text{O})\text{R}^{10a}$ ,  $-\text{C}(=\text{O})\text{N}(\text{H})\text{R}^{10}$ ,  $-\text{OR}^{10a}$ ,  $-\text{C}(=\text{O})\text{N}(\text{alkyl})\text{R}^{10}$ , —

$\text{N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the cycloalkyl group and cycloalkenyl group is a substituted, the cycloalkyl group and cycloalkenyl group is substituted with 1 to 3 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the aryl group is a substituted, the aryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O—alkyl}$ ,  $\text{—O—perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{—alkyl}$ ,  $\text{—SO}_2\text{—perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the heteroaryl group is substituted, the heteroaryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O—alkyl}$ ,  $\text{O—perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{—alkyl}$ ,  $\text{—SO}_2\text{—perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{—alkyl}$  and  $\text{—NH—SO}_2\text{—cycloalkyl}$ ;

when the heterocyclyl group is substituted, the heterocyclyl group is substituted with 1 to 3 substituents,

when the heterocyclic group is substituted on a ring carbon of the 'heterocycle', the substituents are independently selected from the group consisting of halogen, nitro, cyano, oxo, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ;

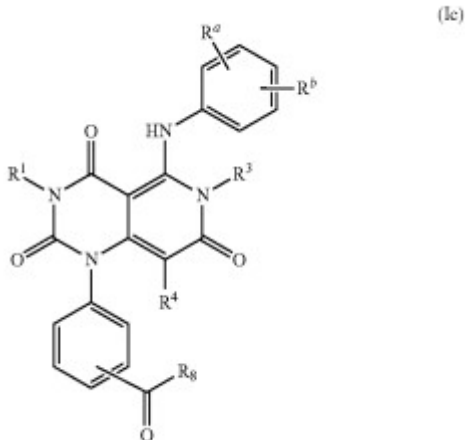
when the heterocyclic group is substituted on a ring nitrogen of the 'heterocycle', substituents are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{C(=O)OR}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

$\text{R}^{10}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

$\text{R}^{10a}$  is selected from the group consisting of alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

$\text{R}^{10b}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

4. A compound of formula Ic, its tautomeric forms, its pharmaceutically acceptable salts, their combinations with suitable medicament and pharmaceutical compositions containing them,



wherein,

$R^1$  is selected from the group consisting of hydrogen, substituted- or unsubstituted-alkyl, substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted- heterocyclyl;

$R^3$  is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted-cycloalkyl;

$R^4$  is selected from the group consisting of hydrogen, halogen, substituted- or unsubstituted-alkyl, and substituted- or unsubstituted- cycloalkyl;

$R^a$  and  $R^b$  are selected from the group consisting of hydrogen, halogen and haloalkyl;

$R^8$  is selected from the group consisting of substituted- or unsubstituted-alkyl, substituted- or unsubstituted-alkenyl, substituted- or unsubstituted-alkynyl, substituted- or unsubstituted-cycloalkyl, and substituted- or unsubstituted-cycloalkenyl;

when the alkyl group and alkenyl group is substituted, the alkyl group and alkenyl group is substituted with 1 to 4 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl,  $—OR^{10b}$ ,  $—SO_2R^{10a}$ ,  $—C(=O)OR^{10a}$ ,  $—OC(=O)R^{10a}$ ,  $—C(=O)N(H)R^{10}$ ,  $—OR^{10a}$ ,  $—C(=O)N(alkyl)R^{10}$ ,  $—$

$\text{N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the cycloalkyl group and cycloalkenyl group is a substituted, the cycloalkyl group and cycloalkenyl group is substituted with 1 to 3 substituents independently selected from the group consisting of oxo, halogen, nitro, cyano, alkyl, alkenyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the aryl group is a substituted, the aryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O-alkyl}$ ,  $\text{—O-perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{-alkyl}$ ,  $\text{—SO}_2\text{-perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the heteroaryl group is a substituted, the heteroaryl group is substituted with 1 to 3 substituents independently selected from the group consisting of halogen, nitro, cyano, hydroxy, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, heterocycle,  $\text{—O-alkyl}$ ,  $\text{O-perhaloalkyl}$ ,  $\text{—N(alkyl)alkyl}$ ,  $\text{—N(H)alkyl}$ ,  $\text{—NH}_2$ ,  $\text{—SO}_2\text{-alkyl}$ ,  $\text{—SO}_2\text{-perhaloalkyl}$ ,  $\text{—N(alkyl)C(=O)alkyl}$ ,  $\text{—N(H)C(=O)alkyl}$ ,  $\text{—C(=O)N(alkyl)alkyl}$ ,  $\text{—C(=O)N(H)alkyl}$ ,  $\text{—C(=O)NH}_2$ ,  $\text{—SO}_2\text{N(alkyl)alkyl}$ ,  $\text{—SO}_2\text{N(H)alkyl}$ ,  $\text{—SO}_2\text{NH}_2$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

when the heterocyclyl group is substituted, the heterocyclyl group is substituted with 1 to 3 substituents, when the heterocyclic group is substituted on a ring carbon of the ‘heterocycle’, the

substituents are independently selected from the group consisting of halogen, nitro, cyano, oxo, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl,  $\text{—OR}^{10b}$ ,  $\text{—C(=O)OR}^{10a}$ ,  $\text{—OC(=O)R}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)R}^{10a}$ ,  $\text{—N(H)R}^{10}$ ,  $\text{—N(alkyl)R}^{10}$ ,  $\text{—N(H)C(=O)N(H)R}^{10}$ ,  $\text{—N(H)C(=O)N(alkyl)R}^{10}$ ;

when the heterocyclic group is substituted on a ring nitrogen of the 'heterocycle', substituents are independently selected from the group consisting of alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl,  $\text{—SO}_2\text{R}^{10a}$ ,  $\text{—C(=O)R}^{10a}$ ,  $\text{C(=O)OR}^{10a}$ ,  $\text{—C(=O)N(H)R}^{10}$ ,  $\text{—C(=O)N(alkyl)R}^{10}$ ,  $\text{—NH—SO}_2\text{-alkyl}$  and  $\text{—NH—SO}_2\text{-cycloalkyl}$ ;

$\text{R}^{10}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl;

$\text{R}^{10a}$  is selected from the group consisting of alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl; and

$\text{R}^{10b}$  is selected from the group consisting of hydrogen, alkyl, alkenyl, perhaloalkyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocyclyl.

5. The compound of claim 1, wherein  $\text{R}^1$  is selected from the group consisting of hydrogen, alkyl, and cycloalkyl.

6. The compound of claim 5, wherein  $\text{R}^1$  is selected from the group consisting of hydrogen, methyl and cyclopropyl.

7. The compound of claim 5, wherein  $\text{R}^3$  is methyl.

8. The compound of claim 5, wherein  $\text{R}^4$  is selected as methyl.

9. The compound of claim 5, wherein  $\text{R}^a$  and  $\text{R}^b$  are halogen.

10. The compound of claim 9, wherein  $\text{R}^a$  and  $\text{R}^b$  are independently fluorine and iodine.

11. The compound of claim 5, wherein  $R^6$  is selected from the group consisting of direct bond, —  
 $[C(R^c)R^d]_nNR^9$ —, — $[C(R^c)R^d]_nO$ —, and — $NHC(=O)[C(R^c)R^d]_p$ —.
12. The compound of claim 5, wherein  $R^6$  is selected from the group selected from direct bond, —NH—,  
—O—, —CH<sub>2</sub>O—, and —NHC(=O)—.
13. The compound of claim 1, wherein E is selected from the group consisting of 3-oxetane, 1-azetidine,  
1-azetidine-2-one and 3-azetidine substituted- or unsubstituted-with methyl, fluoro, —C(=O)OR<sup>e</sup> and —  
OR<sup>e</sup>; wherein R<sup>e</sup> is hydrogen, tert-butyl, and —CH<sub>2</sub>C(=O)NH<sub>2</sub>.
14. The compound of claim 5, wherein  $R^7$  is cyclopropyl.
15. The compound of claim 5, wherein  $R^8$  is cyclopropyl.
16. The compound of claim 1,  
wherein  
 $R^1$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl;  
 $R^3$  is alkyl;  
 $R^4$  is alkyl;  
 $R^a$  and  $R^b$  are halogen;  
 $R^6$  is selected from the group consisting of direct bond, — $[C(R^c)R^d]_nNR^9$ —, — $[C(R^c)R^d]_nO$ — and —  
NHC(=O)[C(R<sup>c</sup>)R<sup>d</sup>]<sub>p</sub>—;  
E is substituted- or unsubstituted-four membered heterocyclic ring;  
 $R^7$  is substituted- or unsubstituted-cycloalkyl;  
 $R^8$  is substituted- or unsubstituted-cycloalkyl.
17. The compound of claim 1,  
wherein  
 $R^1$  is selected from the group consisting of hydrogen, methyl, cyclopropyl;



R<sup>3</sup> is methyl;

R<sup>4</sup> is methyl;

R<sup>a</sup> and R<sup>b</sup> are independently fluoro and iodo;

R<sup>6</sup> is direct bond, —NH—, —O—, —CH<sub>2</sub>O— and —NHC(=O)—;

E is 3-oxetane, 1-azetidine, 1-azetidine-2-one and 3-azetidine substituted- or unsubstituted-with methyl, fluoro, tert-butoxy carbonyl, —OH and —OCH<sub>2</sub>C(=O)NH<sub>2</sub>;

R<sup>7</sup> is cyclopropyl and

R<sup>8</sup> is cyclopropyl.

18. A compound, its tautomeric forms, or its pharmaceutically acceptable salt thereof, wherein the compound is selected from the group consisting of:

1-(3-(cyclopropylsulfonyl)phenyl)-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 1);

3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(3-(3-hydroxyazetidin-1yl)phenyl)-6,8-dimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 2);

3-cyclopropyl-1-(3-(cyclopropylsulfonyl)phenyl)-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 3);

3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(3-(2-oxoazetidin-1-yl)phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 4);

3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(3-(oxetan-3-ylamino)phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 5);

3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(3-(oxetan-3-yloxy)phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 7);

1-(3-(azetidin-1-yl)phenyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl pyrido[4,3-d]pyrimidine-2,4,7(1H,II,II)-trione (Compound 8);

3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(3-(3-hydroxyoxetan-3-yl)phenyl)-6,8-dimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 9);

N-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)-3-methyloxetane-3-carboxamide (Compound 10);

1-(3-(cyclopropanecarbonyl)phenyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 11);

1-(3-(cyclopropylsulfonyl)phenyl)-5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 12);

5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl-1-(3-((oxetan-3-yloxy)methyl) phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 13);

5-((2-fluoro-4-iodophenyl)amino)-1-(3-(3-hydroxyoxetan-3-yl)phenyl)-3,6,8-trimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 14);

5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl-1-(3-(oxetan-3-yloxy)phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 15);

1-(3-(azetidin-1-yl)phenyl)-5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethylpyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 16);

5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl-1-(3-(oxetan-3-ylamino)phenyl)pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 17);

N-(3-(5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydro pyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)-3-methyloxetane-3-carboxamide (Compound 18);

2-((1-(3-(5-((2-fluoro-4-iodophenyl)amino)-3,6,8-trimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)azetidin-3-yl)oxy)acetamide (Compound 19);

5-((2-fluoro-4-iodophenyl)amino)-1-(3-(3-fluorooxetan-3-yl)phenyl)-3,6,8-trimethyl pyrido[4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 20); and

N-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)azetidine-3-carboxamide (Compound 21).

19. A pharmaceutical composition comprising the compound, its tautomeric forms, or its pharmaceutically acceptable salt thereof, as claimed in claim 1, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

20. A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt of claim 2 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

21. A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt of claim 3 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

22. A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt of claim 4 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

23. A pharmaceutical composition comprising the compound or a pharmaceutically acceptable salt of claim 18 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

24. 1-(3-(cyclopropylsulfonyl)phenyl)-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl pyrido [4,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (Compound 1).

25. A pharmaceutical composition comprising the compound of claim 24 and one or more pharmaceutically acceptable carriers, diluents, or excipients.

V/C/A/2014/0005

Lekeicha Caesar-Toney  
Registrar, CIPO  
8<sup>th</sup> April, 2019

