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(54) Title: FUNCTIONALIZED PYRANO[2,3-Z>]PYRIMIDIN-7-ONE DERIVATIVES AND METHODS FOR THEIR PREPARATION AND USE

(55) Fig. 3

Reagents and reaction condition: a) CH3ONa/CH3OH, 0, 1.5 h; b) A-S40, reflux, 40 min; c) DBDMH, DMF, rt, 70.5%; d) m-CPBA, CH3Cl, 12 hrs; rt; e) DMF, reflux, 1h. Pd2(dba)3, K2PdO4, S-Phos, toluene, 100 °C, 20 hrs; g) m-CPBA, CH3Cl, rt, 30 h; h) DMF, 110°C, 12 hrs; i) m-CPBA, DCM. 10 min; j) K2CO3, R-NH2, 110°C.

(57) Abstract: Functionalized pyranopyrimidine-7-one derivatives, methods for making the derivatives, and methods of using the derivatives as protein kinase inhibitors.

[Continued on next page]
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FUNCTIONALIZED PYRANO[2,3-ii]PYRIMIDIN-7-ONE DERIVATIVES AND
METHODS FOR THEIR PREPARATION AND USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of US Application No. 62/340,393, filed May 23, 2016, and US Application No. 62/508,958, filed May 19, 2017, each application expressly incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to functionalized pyrano[2,3-<i>]pyrimidin-7-one derivatives, to the preparation thereof and to the therapeutic use thereof, wherein said compounds are of general Formula (A). These compounds are potentially useful in treating disorders associated with aberrant protein kinase activities, including but not limited to, cancers, cardiovascular diseases, and certain central nervous system disorders.

BACKGROUND OF THE INVENTION

Pyrido[2,3-<i>]pyrimidin-7-one (I) (see FIGURE 1) belongs to an important family of pharmacophores, the purine- and ATP-related templates, which typically contain pyrimidine rings. Pharmaceutical exploration of the purine- and ATP-related templates have led to the discoveries of a number of drugs, such as Abacavia, Gleevec, Tarceva, and Iressa, and a few drug candidates in clinical trials. The structure of the pyrido[2,3-<i>]pyrimidin-7-one (I) has been previously identified as a privileged pharmacophore for the inhibition of ATP-dependent kinases. The kinase inhibitors derived from this pharmacophore are represented by Parke-Davis (now Pfizer) compounds PD0332991, PD173955 and PD180970. PD173955 and PD180970 (FIGURE 2) are two well-known Bcr-Abl inhibitors discovered following imatinib (Gleevec). They function as dual inhibitors of Src and Bcr-Abl, and can inhibit many imatinib (Gleevec)-resistant mutants of Bcr-Abl. PD0332991 is a selective inhibitor of cyclin dependent kinases (CDK) 4 and 6. It was recently proved by FDA and marketed as Palbociclib for the treatment of breast cancer. Notably, the structure of pyrido[2,3-<i>]pyrimidin-7-one 9 (I) was also proposed as a key pharmacophore for inhibiting other cyclin-dependent kinases (CDKs) such as the cyclin-dependent kinase 5 (CDK5) (V. Krystof, S. Uldrijan, Cyclin-dependent kinase inhibitors as anticancer drugs, Current Drug Targets, 11 (2010) 291-302; H. Galons, N. Oumata, L. Meijer, Cyclin-dependent kinase inhibitors: a survey of recent patent literature, Expert Opinion on Therapeutic Patents, 20 (2010) 377-404). CDK5 has been
implicated in the pathological processes that contribute to neurodegeneration in Alzheimer's disease (AD) (L.-H. Tsai, M.-S. Lee, J. Cruz, Cdk5, a therapeutic target for Alzheimer's disease? Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics, 1697 (2004) 137-142). Abnormal activation of CDK5 promotes hyperphosphorylation of the tau protein, a process well recognized as a key contributor in AD pathogenesis. Additionally, pyrido[2,3-<i>]<i>pyrimidin-7-one (I) pharmacophore has led to discovery of some PAK (p21-activated kinases) inhibitors, such as FRAX597 (FIGURE 2), which is a potent, ATP-competitive inhibitor of group I PAKs (Licciulli, J. Maksimoska, C. Zhou, S. Troutman, S. Kota, Q. Liu, S. Duron, D. Campbell, J. Chernoff, J. Field, FRAX597, a small molecule inhibitor of the p21-activated kinases, inhibits tumorigenesis of neurofibromatosis type 2 (NF2)-associated Schwannomas, Journal of Biological Chemistry, 288 (2013) 29105-29114). It has been suggested that PAK1 not only is involved in both cancer initiation and progression, but also plays a role in the pathology of Alzheimer's, Huntington's Disease, Neurofibromatosis, Autism, Schizophrenia, Fragile X mental retardations (J.V. Kichina, A. Goc, B. Al-Husein, P.R. Somanath, E.S. Kandel, PAK1 as a therapeutic target, Expert Opinion on Therapeutic Targets, 14 (2010) 703-725; and H. Maruta, PAKs, RAC/CDC42 (p21)-activated Kinases: Towards the Cure of Cancer and Other PAK-dependent Diseases, Newnes, 2013).

The synthesis of pyrido[2,3-<i>]<i>pyrimidin-7-one analogs typically requires fairly expensive starting materials that contains a pyrimidine ring, and often involves a tedious synthesis to build the pyridopyrimidinone core. Interestingly, the pharmacophore pyrano[2,3-<i>]<i>pyrimidin-7-one (II) (see FIGURE 1), which is a close structure of (I), has not yet been extensively studied in synthetic chemistry and pharmacology. Only a few syntheses of the pyrano[2,3-<i>]<i>pyrimidin-7-one ring system have been reported. Most of these syntheses employed functionalized pyrimidines or barbituric acid analogs as starting materials, which in most cases led to pyrano[2,3-<i>]<i>pyrimidin-7-one derivatives difficult to structurally modify for subsequent pharmaceutical applications. Presumably within the structure of pyrano[2,3-<i>]<i>pyrimidin-7-one (II), the 2- and 6-positions are pharmacologically important as was implicated by the class of pyrido[2,3-<i>]<i>pyrimidin-7-one (I) analogs.

Despite the advance noted above, there exists a need for new pyrido[2,3-<i>]<i>pyrimidin-7-one analogs and methods for their preparation. The present invention seeks to fulfill these needs and provides further related advantages.
SUMMARY OF THE INVENTION

The present invention relates to pyrano[2,3-i]pyrimidin-7-one compounds, processes for preparing said compounds and the intermediates thereof, pharmaceutical compositions comprising said compounds, and methods of their use.

In one aspect, provided herein is a pyrano[2,3-i]pyrimidin-7-one compound having the structure of Formula (A):

![Chemical Structure]

(A),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

- Z is selected from the group consisting of hydrogen, halogen, C(halogen)₃, a C₁₋C₉ alkyl, and C₃₋C₆ cycloalkyl;
- X¹ is selected from the group consisting of NH₂, NR¹, O, and S, provided when X¹ is O, R-(X³)ₙS₁ respectively is not methyl;
- R¹ is selected from the group consisting of hydrogen, C₁₋C₆ alkyl, and C₃₋C₆ cycloalkyl;
- X² is an optionally substituted aryl or optionally substituted heteroaryl;
- X³ is an optionally substituted heterocyclyl;
- R is H or alkyl;
- Y¹ is O or an optionally substituted group selected from the group consisting of an aryl, a heteroaryl, an alkenyl, an alkynyl, and an acyl group;
- Y² is an optionally substituted heteroaryl;
- S₁ is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, SQ¹, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ!C(=0)Q, C(=0)NQ!Q, N₃, NCS, NO₂, or NQ!Q, wherein Q¹ and Q² are independently selected from hydrogen and alkyl;
- m is 0 or 1;
- n is 0 or 1;
- p is 0 or 1;
q is 0 or 1; and
r is 0 or 1.

In certain group of embodiments, the compound of formula (A) has the structure of Formula (Al):

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

Z is selected from the group consisting of hydrogen, halogen, CF₃, CC1₃,

C₁-C₆ alkyl, and C₃-C₆ cycloalkyl;

Xᵢ is selected from the group consisting of NRᵢ, O, and S;

Arᵢ is an optionally substituted aryl or optionally substituted heteroaryl;

Arᵢ is an optionally substituted aryl or optionally substituted heteroaryl;

and

Rᵢ is hydrogen, C₁-C₆ alkyl or C₃-C₆ cycloalkyl.

In another aspect, provided herein are pharmaceutical compositions comprising pyrano[2,3-<i>]pyrimidin-7-one compounds of the present invention and a pharmaceutically acceptable carrier.

In an additional aspect, the invention provides a method of making 2 alkylsulfanylpyrano[2,3-<i>]pyrimidin-7-one comprising:

(i) contacting 2-alkylthiourea hemihydrate with a coumalate ester in a suitable solvent in the presence of a suitable base, thereby forming 3-(2-alkylsulfanyl-6-oxo-1,6-dihydro-pyrimidin-5-yl)acrylic acid; and

(ii) contacting the 3-(2-alkylsulfanyl-6-oxo-1,6-dihydro-pyrimidin-5-yl)acrylic acid of step (i) with an anhydride thereby forming 2-alkylsulfanylpyrano[2,3-<i>]pyrimidin-7-one.

In yet another aspect, the invention provides a method of making 6-bromo-2-(methylthio)-7<i>H</i>-pyrano[2,3-<i>]pyrimidin-7-one comprising contacting 2-methylsulfanylpyrano[2,3-<i>]pyrimidin-7-one with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in a suitable solvent wherein the contacting results in forming 6-bromo-2-(methylthio)-7<i>H</i>-pyrano[2,3-<i>]pyrimidin-7-one.
In another aspect, the invention provides a method for treating a disease or condition treatable by administering a protein kinase inhibitor, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of the present invention.

DEFINITIONS

Unless otherwise stated, the following terms used in the present invention have the meanings given below.

The term "halogen" means a fluorine, a chlorine, a bromine or an iodine atom.

The term "halo" means fluoro, chloro, bromo, or iodo, preferably fluoro and chloro.

The term "alkyl group" means a saturated, linear or branched, aliphatic group. Examples of an alkyl group include the methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylnpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methyl-propyl, 1-ethyl-2-methylpropyl, 1-ethylbutyl, 2-ethylbutyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 3,3-dimethylpentyl, 3,4-dimethylpentyl, 4,4-dimethylpentyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, 1,2,2-trimethylbutyl, 1,2,3-trimethylbutyl, 1,3,3-trimethylbutyl, 2,2,3-trimethylbutyl, 2,3,3-trimethylbutyl, 1,1,2,2-tetramethylpropyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 1-ethyl-1-methylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 2-ethyl-1-methylbutyl, 2-ethyl-2-methylbutyl, 2-ethyl-3-methylbutyl, 1-propylbutyl, 1-(1-methylethyl)butyl, and 1-(1-methylethyl)-2-methylpropyl groups.

The term "lower alkyl" means an alkyl group having 1 to 6 carbons linear or branched.

The term "alkenyl group" means a mono- or polyunsaturated, linear or branched, aliphatic group comprising, for example, one or two ethylenic unsaturations.

The term "alkynyl group" means a mono- or polyunsaturated, linear or branched, aliphatic group comprising, for example, one or two acetylenic unsaturations.
The term "cycloalkyl group" means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclooctyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl or adamantyl.

The term "acyl" means a radical — C(0)R', where R' is hydrogen, alkyl, alkenyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl wherein alkyl, cycloalkyl, cycloalkylalkyl, and phenyl-alkyl are as defined herein. Representative examples include, but are not limited to formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl, benzylcarbonyl, and the like.

The term "alkoxyl" means a radical —OR where R is an alkyl as defined above. Representative examples include, but are not limited to methoxy, ethoxy, propoxy, butoxy, t-butoxyl and the like.

The term "aryl" means a monovalent monocyclic or polycyclic aromatic hydrocarbon radical; it includes, but is not limited to, phenyl and naphthyl.

The term "heteroaryl" means a monovalent monocyclic or bicyclic radical of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms independently selected from N, O, or S, the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl radical will be on an aromatic ring. More specifically, the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofurany1, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoxothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, imidazo[1,2-a]-pyridinyl, and imidazo[2,1-b]thiazolyl.

The term "heterocyclic ring" or "heterocyclyl" means a saturated or unsaturated non-aromatic cyclic radical of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms independently selected from N, O, or S(0), where e is an integer from 0 to 2. More specifically, the term heterocyclic ring includes, but is not limited to, tetrahydropyranyl, piperidino, N-methylpiperidin-3-yl, 2-oxo-piperidinyl, piperazino, N-methylpyrrolidin-3-yl, 3-pyrrolidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 4-(1,1-dioxo-tetrahydro-2 H-thiopyranyl), pyrrolinyl, pyrrolidinyl, imidazolinyl, and N-methanesulfonyl-piperidin-4-yl.

The term "substituent" (e.g., group S1) means hydrogen, halogen, alkyl, alkoxy1, cycloalkyl, cyano, OH, SQ1, acyl, haloalkyl, heteroaryl, C(halogen)3, CN, C(=0)CH3,
NQ\(^1\)C(=O)Q\(^2\), C(=0)NQ\(^1\)Q\(^2\), N\(_3\), NCS, NO\(_2\), or NQiQ\(^2\), wherein Q\(^1\) and Q\(^2\) are independently selected from H and alkyl.

**DESCRIPTION OF THE DRAWINGS**

The foregoing aspects and many of the attendant advantages of this invention will become more readily appreciated as the same become better understood by reference to the following detailed description, when taken in conjunction with the accompanying drawings.

**FIGURE 1** illustrates the structures of pyrido[2,3-<i>1pyrimidin-7-one and pyrano[2,3-<i>1pyrimidin-7-one pharmacophores.

**FIGURE 2** illustrates the structures of protein kinase inhibitors PD173955, PD180970, PD0332991 (palbociclib) and FRAX597.

**FIGURE 3, 4, and 5** are schematic illustrations of the synthesis of representative functionalized pyrano[2,3-<i>1pyrimidin-7-one derivatives of the invention.

**FIGURE 6** is a schematic illustration of the synthetic routes for optimization of bromination of 4 to achieve the desired intermediate 5.

**FIGURES 7A and 7B** depict Compound 19a bound in its binding site of c-Abl (7A) and PD173955 and Compound IX superimposed in the binding site of c-Abl (7B).

**FIGURES 8A and 8B** depict PD173955 and Compound 12e bound in the binding site of c-Abl, respectively.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention relates to functionalized pyrano[2,3-<i>1pyrimidin-7-one derivatives, to the preparation thereof and to the therapeutic use thereof, wherein said compounds are of general Formulæ (A)-(A4). These compounds can interact with protein kinases, which include but are not limited to src-Abl, cyclin dependent kinases (CDKs), P21-activated kinases (PAKs), and mitogen-activated protein kinases (MAPK). Hence, they are potentially useful in treating disorders associated with aberrant protein kinase activities, including but not limited to, cancers, cardiovascular diseases, and certain central nervous system disorders.

In some embodiments, the compounds of Formulæ (A)-(A4) are inhibitors of ABL kinases. The Abelson (ABL) family of protein kinases comprises cytoplasmic ABL1 and ABL2, which link diverse extracellular stimuli to signaling pathways that control cell growth, survival, invasion, adhesion and migration. Inhibition of ABLs has
been implied in many types of hematopoietic malignancies and solid tumors. Increased ABL kinase activity has been reported in several types of invasive breast cancer and other solid tumors. PD173955 is a known potent ABL inhibitor developed from the scaffold pyrido[2,3-d]pyrimidine-7-one. The compounds of the present invention represent a new class of ABL inhibitors.

Compositions of Functionalized Pyrano|2,3-d|pyrimidin-7-one Derivatives

In one group of embodiments, the invention provides compounds having the structure of Formula (A):

![Formula Image]

(A),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein:
Z is hydrogen, halogen, C(halogen)_3, a lower alkyl, for example, C_1-C_6 alkyl, or lower cycloalkyl, for example, C_3-C_6 cycloalkyl;
X^1 is NH_2, NR^1, S, or O;
R^1 is hydrogen, a lower alkyl, for example, C^1-C_g alkyl, or lower cycloalkyl, for example, C_3-C_6 cycloalkyl;
X^2 is an optionally substituted aryl or optionally substituted heteroaryl; wherein if said group is substituted, it is substituted independently with one or more substituents; preferably one or two substituents S^1;
X^3 is an optionally substituted heterocyclic ring; wherein if the heterocyclic ring is substituted, it is substituted independently with one or more substituents; preferably one or two substituents S^1;
R is hydrogen or an alkyl;
Y^1 is an optionally substituted group selected from an aryl, a heteroaryl, an alkenyl, an alkynyl, an acyl group, and oxygen; wherein if the said group is substituted, it is substituted independently with one or more substituents; preferably one or two substituents S^1;
Y^2 is an optionally substituted heteroaryl; wherein if the heteroaryl is substituted, it is substituted independently with one or more substituents; preferably one or two substituents and the substituents are as defined;
S¹ is hydrogen, halogen, alkyl, alkoxyl, cycloalkyl, cyano, OH, SQ¹, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ¹C(=O)Q², C(=O)NQ¹Q², N₃, NCS, NO₂, or NQ¹Q², wherein Q¹ and Q² are independently selected from H and alkyl; and

the subscripts m, n, p, q, and r are independently 0 or 1.

In certain embeddings of Formula (A), when X¹ is O, R-(X³)r-(X²)q-(X¹)p - is not methyl. In other embeddings of Formula (A), when X¹ is O, R-(X³)r-(X²)q - is not methyl.

In a particular embodiment of Formula (A),

X¹ is NH where the subscript p is 1;

X² is a substituted aryl where the subscript q is 1;

the subscript r is 0;

Y¹ is a substituted aryl where the subscript n is 1;

the subscript m is 0.

In another particular embodiment of Formula (A),

X¹ is NH where the subscript p is 1;

X² is an optionally substituted aryl where the subscript q is 1;

X³ is an optionally substituted heterocyclic ring where the subscript r is 1;

Y¹ is a substituted aryl where the subscript n is 1; and

the subscript m is 0.

In yet another particular embodiment of Formula (A),

X¹ is NH where the subscript p is 1;

X² is an optionally substituted heteroaryl where the subscript q is 1;

X³ is an optionally substituted heterocyclic ring where the subscript r is 1;

Y¹ is a substituted aryl where the subscript n is 1; and

the subscript m is 0.

In a further particular embodiment of Formula (A),

X¹ is NH where the subscript p is 1;

Y¹ is an alkynyl where the subscript n is 1; and

the subscript m is 0.

In yet a further particular embodiment of Formula (A),

X¹ is NH where the subscript p is 1;

Y¹ is an acyl where the subscript n is 1; and
In another particular embodiment of Formula (A),

\( X^1 \) is NH where the subscript \( p \) is 1;

\( Y^1 \) is oxygen where the subscript \( n \) is 1; and

the subscript \( m \) is 0.

In a further particular embodiment of Formula (A),

\( X^1 \) is NH where the subscript \( p \) is 1;

\( Y^1 \) is optionally substituted aryl where the subscript \( n \) is 1; and

\( Y^2 \) is optionally substituted heteroaryl where the subscript \( m \) is 1.

In some embodiments of Formula (A), \( Z \) is selected from the group consisting of H, halogen, \( \text{CF}_3 \), \( \text{CCl}_3 \), \( \text{C}_1^\text{-C}_{10} \) alkyl, and \( \text{C}_3^\text{-C}_7 \) cycloalkyl. Preferably, \( Z \) is H or F. In other embodiments of Formula (A), \( S^1 \) is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, SQ\(^1\), acyl, haloalkyl, heteroaryl, C(halogen)\(_3\), CN, C(=0)CH\(_3\), NQ\(^1\)C(=O)Q\(^2\), C(=0)NQ\(^1\)Q\(^2\), N\(^3\), NCS, N0\(_2\), or NQ\(^1\)Q\(^2\), wherein \( Q^1 \) and \( Q^2 \) are independently selected from H and alkyl.

In a certain group of embodiments of the compounds of the present invention, the compound of Formula (A) has the structure of Formula (Al):

![Chemical structure](image)

(Al),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

\( Z \) is selected from the group consisting of hydrogen, halogen, \( \text{CF}_3 \), \( \text{CCl}_3 \), \( \text{C}_1^\text{-C}_6 \) alkyl, and \( \text{C}_3^\text{-C}_7 \) cycloalkyl;

\( X^1 \) is selected from the group consisting of NR\(^1\), O, and S;

\( Ar^1 \) is an optionally substituted aryl or optionally substituted heteroaryl;

\( Ar^2 \) is an optionally substituted aryl or optionally substituted heteroaryl; and

\( R^1 \) is H, \( \text{C}_1^\text{-C}_6 \) alkyl or \( \text{C}_3^\text{-C}_6 \) cycloalkyl.

In certain embodiments of Formula (A) or (Al), \( X^1 \) is NR\(^1\), wherein \( R^1 \) is H or \( \text{C}_1^\text{-C}_6 \) alkyl. In some embodiments of Formula (Al), \( Ar^2 \) is an optionally substituted phenyl, such as a mono- or di-substituted phenyl.
In some embodiments, the compound of Formula (A) or (Al) has the structure of Formula (A2):

![Chemical structure of (A2)](image)

(A2),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

\( R^x \) is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, aroyl, haloalkyl, heteroaryl, \( SQ^1, CF_3, CC1_3, CN, C(=O)Q \) \( \text{NHC}(=O)Q \), \( C(=O)NQ^1Q^2, N_3, NCS, NO_2, \) or \( NQ!Q \) where \( Q^1 \) and \( Q^2 \) are independently selected from \( H \) and \( C_1-C_1Q \) alkyl;

\( Z, Ar^1, \) and \( R^1 \) are as defined for Formula (A2); and

\( x \) is 0, 1, 2, 3, 4, or 5.

In some embodiments of Formula (A2), \( Ar^1 \) is an optionally substituted phenyl, preferably, a mono- or di-substituted phenyl.

In particular embodiments, the compound of Formula (A), (Al), or (A2) has the structure of Formula (A3):

![Chemical structure of (A3)](image)

(A3),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

\( R^y \) is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, aroyl, haloalkyl, heteroaryl, \( SQ^1, CF_3, CC1_3, CN, C(=O)OA \) \( \text{NHC}(=O)Q \), \( C^\!\!NQ!Q \), \( N_3, NCS, NO_2, \) or \( NQ!Q \) where \( Q^1 \) and \( Q^2 \) are independently selected from \( H \) and \( C_1-C_1Q \) alkyl;

\( Z, Ar^1, R^x, x, \) and \( R^1 \) are as defined for Formula A2; and

\( y \) is 0, 1, 2, 3, 4, or 5.
In certain embodiments of Formula (A3), \( R^1 \) is \( H \) or methyl. Preferably, \( R^1 \) is \( H \).

In other embodiments of Formula (A3), \( Z \) is \( H \), halogen, or methyl, or more preferably, \( Z \) is \( H \).

In particular embodiments, the compound of Formula (A), (A1), (A2), or (A3) has the structure of Formula (A4):

![Formula (A4)](image)

or a pharmaceutically acceptable salt, hydrate, or solvate thereof,

wherein:

\( R^{X1}, R^{X2}, R^{Y1}, \) and \( R^{Y2} \) are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, \( OH \), alkoxy, acyl, haloalkyl, heteroaryl, \( SQ^1, CF_3, CC1_3, CN, C(=O)Q^1, NH(=O)Q^1, C(=O)NO\)Q^2, N\( _3 \), NCS, N\( O \), and N\( O\)Q^2 wherein \( Q^1 \) and \( Q^2 \) are independently selected from \( H \) and C\( _1 \)\( -C_{10} \) alkyl.

In some embodiments of Formula (A4), \( R^{Y1} \) and \( R^{Y2} \) are independently selected from hydrogen, \( F, Cl, \) and \( CH_3 \). In other embodiments of Formula (A4), \( R^{X1} \) is selected from hydrogen, \( F, Cl, N(CH_3)_2, \) and \( CH_3 \). In yet other embodiments of Formula (A4), \( R^{X2} \) is selected from \( NH_2, OCH_3, CN, SCH_3, NHC(0)CH_3, \) and \( CH_3 \).

In some embodiments of the present invention, the compound of Formulae (A), (A1), (A2), (A3), or (A4) is a compound of Formulae 12a, 12b, 12c, 12d, 12e, 12f, 12g, 19a, or 19b of TABLE 1.

The activity of certain representative compounds of the present invention in comparison with the known ABL1 kinase inhibitor PD173955 is summarized in TABLE 1.

**Methods for Making Functionalized Pyrano[2,3-d]pyrimidin-7-one Derivatives**

In one aspect, the present invention provides methods for making functionalized pyrano[2,3-\( i \)]pyrimidin-7-one derivatives.

In one embodiment, the invention provides a method for making a key intermediate, 2-methylsulfanylpyrano[2,3-\( i \)]pyrimidin-7-one (4), which is useful for making functionalized pyrano[2,3-\( i \)]pyrimidin-7-one derivatives.
The method of making 2-methylsulfanylpyrano[2,3-<i>]pyrimidin-7-one (Compound 4) is shown below in Scheme 1.

Scheme 1

Reagents and reaction condition: a) CH₃ONa/CH₃OH, rt, 1.5 h; b) Ac₂O, reflux, 40 mins.

Referring to Scheme 1, 2-alkylthiourea hemihydrate (1) is treated with a coumalate ester (2) under basic conditions (e.g., reaction conditions a: sodium methoxide in anhydrous methanol) to provide 3-(2-methylsulfanyl-6-oxo-1,6-dihydro-pyrimidin-5-yl)acrylic acid (3), which was converted to 2-methylsulfanylpurano[2,3-<i>]pyrimidin-7-one (Compound 4) by treatment with an anhydride (e.g., reaction conditions b: acetic anhydride). A representative synthesis of Compound 4 is shown in FIGURE 3 and described in Example 1.

In another embodiment, the invention provides a method for making a functionalized pyrano[2,3-<i>]pyrimidin-7-one derivative, 6-bromo-2-(methylthio)-7<i>H</i>-pyrano[2,3-d]pyrimidin-7-one (compound 5).

The method of making 6-bromo-2-(methylthio)-7<i>H</i>-pyrano[2,3-d]pyrimidin-7-one (compound 5) from 2-methylsulfanylpurano[2,3-<i>]pyrimidin-7-one (Compound 4) is shown below in Scheme 2.

Scheme 2

Reagents and reaction condition: c) l,3-dibromo-5,5-dimethylhydantoin, DMF, rt, 70.5%.
Referring to Scheme 2, Compound 4 is treated with 1,3-dibromo-5,5-
dimethylhydantoin (DBDMH) in dimethylformaldehyde (DMF) to provide 6-bromo-2-
(methylthio)-7H-pyrano[2,3-i]pyrimidin-7-one (5).

In another embodiment, the present invention provides a facile synthesis of
6-bromo-2-methylsulfanyl-pyrano[2,3-i]pyrimidin-7-one from 2-methyl-2-
thiopseudourea and methyl coumalate. This dual functionalized pyranopyrimidin-7-one
serves as a new chemical entity to provide a potentially useful building block for
pharmaceutical applications.

In summary, a pyrano[2,3-i]pyrimidin-7-one template with a 2-SCH$_3$- and
6-bromo- functionality was prepared in three steps from easily accessible methyl
coumalate and inexpensive 2-methyl-2-thiopseudourea. The 2-methylsulfanyl group
allows for rapid and facile access to various substituents, such as amino analogs, alkyl
ether derivatives, and other functional groups via chemistry that is well-developed in the
class of pyrido[2,3-i]pyrimidin-7-one compounds. Additionally, the 6-bromo-
functionality offers a gateway to a wide range of structural modifications via palladium-
catalyzed coupling reactions, such as Suzuki coupling, Stille coupling, Heck reaction, and
palladium-catalyzed C-N coupling reaction, that are very well-exemplified in the
chemical classes of pyridopyrimidinones, chromen-2-ones and quinolin-2-ones. This
new template, having dual sites for functionalization (e.g. 5), provides new opportunities
for divergent syntheses in pharmaceutical applications as well as serve as a novel
pharmacophore for the class of ATP- and purine-related pharmaceutical compounds.

It will be appreciated that the functionalized pyrano[2,3-i]pyrimidin-7-one
derivatives of the invention can be provided in the form of a base or an acid addition salt
prepare from a pharmaceutically acceptable salt including those known in the art, or in
the form of a hydrate or solvate.

**Methods for Using Functionalized Pyranor2,3-i[pyrimidin-7-one Derivatives**

In a further aspect, the present invention provides methods for using
functionalized pyrano[2,3-d]pyrimidin-7-one derivatives. The functionalized pyrano[2,3-
d]pyrimidin-7-one derivatives described in Formula (A) can be used as therapeutic agents,
such as protein kinase inhibitors.

The functionalized pyrano[2,3-i]pyrimidin-7-one derivatives of the invention can
be used for the treatment of disorders associated with aberrant kinase activities, which
include but are not limited to, cancers, cardiovascular diseases, and certain central
nervous system disorders such as Alzheimer's, Huntington's Disease, neurofibromatosis,
autism, schizophrenia, and fragile X mental retardations.

For therapeutic applications, the functionalized pyrano[2,3-<i>]pyrimidin-7-one
derivatives of the invention can be formulated with a pharmaceutically acceptable carrier
suitable for the desired method of administration. Pharmaceutically acceptable carriers
are known in the art. The functionalized pyrano[2,3-<i>]pyrimidin-7-one derivatives of the
invention can be administered systemically by oral, intravenous, subcutaneous, or topical
administration.

The following examples are provided for the purpose of illustrating, not limiting
the invention.

EXAMPLE 1

The syntheses described below are illustrated in FIGURE 3.

3-(2-Methylsulfanyl-6-oxo-L6-dihydro-pyrimidin-5-yl)-acrylic acid (3). To a
solution of CH$_2$ONa (5.26 g, 97.32 mmol) in anhydrous methanol (65 mL) was added 2-
methyl-2-thiopseudourea hemisulfate 1 (13.5 g, 97.32 mmol). The reaction mixture was
stirred at room temperature for 10 mins, and methyl coumalate (10.0 g, 64.88 mmol) was
added. The reaction mixture was then stirred at room temperature for 1.5 h, and then
concentrated in vacuo to remove the methanol. The residue was then dissolved and
partitioned between chloroform (50 mL) and water (100 mL). The organic layer was
separated and extracted with water (20 mL) two times. The combined aqueous extract
was then treated with 12N aqueous HCl until pH 4 was reached. A light orange-colored
solid precipitated and was filtered and washed three times with ice-cold water (15 mL)
and three times with a acetone-hexane (1:1) mixture. The resulting solid was dried under
vacuum to afford 7.49 g of 3 (54.3%). Mp: 208-209 °C; H NMR (d$_6$-DMSO) δ 8.46 (s, 1H), 6.79 (d, J = 12.6 Hz, 1H), 5.93 (d, J = 12.6 Hz, 1H), 2.51 (s, 3H); MS mlz 211 (M+1). Elemental Analysis. (C$_9$H$_8$N$_2$O$_3$S) Calcd: C 45.28%, H, 3.80%, N, 13.20%; Found: C, 45.13%, H, 3.75%, N, 12.88%.

2-Methylsulfanyl-pyranor2,3-<i>]pyrimidin-7-one (4). A suspension of 3 (7.0 g, 33
mmol) in acetic anhydride (40 mL) was refluxed for 40 mins. The reaction mixture then
became homogeneous and was cooled to room temperature. Light greenish-colored
crystals precipitated and were filtered and washed with ice-cooled acetic anhydride (10 mL) and diethyl ether two times (15 mL). The resulting crystals were then treated with a solution of sodium carbonate solution with stirring to remove the trace amount of impurity from uncyclized acids. The resulted solid was filtered and dried in vacuum to afford 4.5 g of 4 (70.4%). Mp: 178-179 °C; H NMR (d₆-DMSO) δ 8.97 (s, 1H), 8.07 (d, J = 9.6 Hz, 1H), 6.54 (d, J = 9.6 Hz, 1H), 2.58 (s, 3H); MS m/z 195 (M+1). Elemental Analysis. (C₉H₆N₂O₂S) Calcd: C 49.47%, H, 3.11%, N, 14.42%; Found: C, 49.55%, H, 3.19%, N, 14.35%.

6-Bromo-2-methylsulfanyl-pyrano[2,3-i]pyrimidin-7-one (5). To a solution of 2-methylsulfanyl-pyrano[2,3-i]pyrimidin-7-one (4, 5.3 g, 27.2 mmol) in anhydrous DMF (42 mL) was added 1,3-dibromo-5,5-dimethyl-hydantoin (10.1 g, 35.4 mmol) in portions at room temperature. The resulting mixture was stirred at room temperature for 8 hours. The reaction mixture was slowly poured into a saturated aqueous NaHSO₃ solution (400 mL) and extracted with EtOAc (300 mL x 3). The combined organic phases were washed with water, brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was recrystallized from DCM (20 mL) to give the titled product (4.9 g, 72.3%) as pale yellow crystals. Rᵣ = 0.56, hexane/EtOAc = 3/2. mp: 174-175 °C. H NMR (300 MHz, DMSO-d₆) δ 8.92 (s, 1H), 8.58 (s, 1H), 2.58 (s, 3H); Elemental Analysis. (C₉H₆BrN₂O₂S) Calcd: C 35.18%, H, 1.85%, N, 10.26%; Found: C, 35.30%, H, 1.69%, N, 10.23%.

2-Methylsulfonyl-pyrano[2,3-i]pyrimidin-7-one (6). A suspension of 4 (97 mg, 0.5 mmol) in dichloromethane (5 mL) was stirred at room temperature for 10 mins until a homogenous solution resulted to which w-CPBA (246 mg, 1.1 mmol, 77% count) was then added. After stirring the reaction mixture for 16 h at room temperature, a white precipitate was formed and filtered (103 mg). This solid was washed with diethyl ether (1 mL) four times and acetone one time (1 mL) to afford 57 mg of 6 (50.4%). Mp: 180-182 °C; H NMR (d₆-DMSO) δ 9.39 (s, 1H), 8.22 (d, J = 9.6 Hz, 1H), 6.87 (d, J = 9.6 Hz, 1H), 3.46 (s, 3H); MS m/z 226 (M⁺); Elemental Analysis. (C₉H₇BrN₂O₄S-H₂O) Calcd: C 34.29%, H, 4.32%, N, 10.00%; found: C, 34.35%, H, 4.38%, N, 9.95%.

2-(4-Fluoro-3-methylphenylamino)-7 H-pyran-5,3-di-pyrano[2,3-id]pyrimidin-7-one (7a). 2-methyl-sulfonyl-pyrano [2, 3-d] pyrimidin-7-one (6, 0.2 g, 0.884 mmol) was taken in sealed tube and was added anhydrous diglyme (5.34 mL) under magnetic stirring. To this suspension 4-fluoro-methylaniline (0.243 g, 1.944 mmol) was added under room
temperature. The reaction mixture was heated up to 162 °C for one hour and homogeneous solution was observed at 140 °C. The reaction progress was monitored by TLC (80% ethyl acetate in hexane). After completion, reaction mixture was cooled to room temperature and mixed with water (40 mL), extracted with ethyl acetate for two times (35 mL). Combined organic layers was washed with water (40 mL) and brine (25 mL) and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated in vacuum to remove the solvent. The crude product was purified with Combiflash chromatography (0-80% ethyl acetate in hexane) and resulted 52 mg (21.75%) of 2-(4-fluoro-3-methylphenylamino)-7H-pyrazolo[2,3-d] pyrimidine-7-one as yellow solid. Mp: 233-234 °C; H NMR (<&-DMSO) δ 2.24 (s, 3H), 6.27 (d, J = 9.3 Hz, 1H), 7.12 (t, J = 9.4 Hz, 1H), 7.58 (m, 2H), 7.97 (d, J = 9.3 Hz, 1H), 8.82 (s, 1H), 10.32 (s, 1H); MS m/z 195 (M+).

2-(3-(Methylthio)phenylamino)-7H-pyranol 12, 3-<i>cf</i> pyrimidine-7-one (7b). 2-methyl-sulfonyl-pyranol [2, 3-<i>cf</i>] pyrimidine-7-one (6, 200 mg, 0.884 mmol) was taken in a sealed tube and was added anhydrous bis(2-methoxyethyl)ether (5.34 ml). To this magnetically stirred suspension, 3-(methylthio)aniline (270 mg, 1.944 mmol) was added dropwise at room temperature. The reaction mixture was stirred and heated to 162 °C for one hour. Homogeneous solution was observed at 120 °C. Reaction progress was monitored by TLC (80% ethyl acetate in hexane). After completion, reaction mixture was cooled to room temperature; water (10 ml) was added and extracted twice with ethyl acetate (2x20 mL). The combined organic layers were washed with water (10 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated in vacuum to remove the solvent. The resulted crude product was purified with Combiflash chromatography (0-80% ethyl acetate in hexane) and provided 76 mg (31%) of 2-(3-(methylthio)phenylamino)-7H-pyrazolo[2,3-<i>cf</i>] pyrimidine-7-one as light yellow solid. Mp: 201-203 °C; H NMR (<&-DMSO) δ 2.48 (s, 3H), 6.30 (d, J = 9.3 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.29 (t, J = 7.95 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 1.5 Hz, 1H), 7.98 (d, J = 9.3 Hz, 1H), 8.86 (s, 1H), 10.39 (s, 1H); MS m/z 285.32 (M+).

6-(2,6-Dichlorophenyl)-2-(methylthio)-7H-pyrazolo[2,3-d]pyrimidine-7-one (9). To a suspension of 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) (90 mg, 0.22 mmol), 2, 6-dichlorophenylboronic acid (314 mg, 1.65 mmol), K<sub>3</sub>P<sub>O</sub><sub>4</sub> (700.5 mg, 3.3 mmol) and Pd<sub>2</sub>(dba)<sub>3</sub> (100.7 mg, 0.11 mmol) in 30 mL toluene, reaction mixture was
degassed and 6-bromo-2-(methylthio)-7H-pyran[2,3-d]pyrimidin-7-one (5, 300 mg, 1.1 mmol) in toluene was added. Reaction mixture was degassed again and stirred at 100 °C under argon atmosphere for 20 h. Then it was cooled down to room temperature, and filtered through a layer of celite. Water (50 mL) and ethyl acetate (20 mL) were added to the filtrate solution and the two layers were separated by a separately funnel. After the water layer was extracted by ethyl acetate two times, the combined organic layer was washed with water to make pH at 7, then brine, and dried over anhydrous Na₂SO₄. Filtration and removal of solvent gave the crude product, which was purified by Combiflash chromatography (10-30% of ethyl acetate in hexane) to yield the title compound (250 mg, 67.3%) as a light-yellow solid; mp 187-188 °C. H NMR (300 MHz, DMSO-d₆): δ = 9.05 (s, 1H), 8.29 (s, 1H), 7.653 (d, J = 9.0 Hz, 1H), 7.652 (d, J = 7.5 Hz, 1H), 7.54 (dd, J = 7.5 Hz, 9.0 Hz, 1H), 2.62 (s, 3H). MS (EI): m/z = 416.2 (M⁺+1).

6-(2,6-Dichlorophenyl)-2-(methylsulfonyl)-7H-pyranor2,3-d1pyrimidin-7-one (10). To a solution of 6-dichlorophenyl)-2-(methylthio)-7H-pyranor2,3-<i>l</i>pyrimidin-7-one (9, 300 mg, 0.89 mmol) in dichloromethane (7 mL), m-CPBA in dichloromethane (8 mL) was slowly added at room temperature. The reaction mixture was stirred and monitored by TLC. After 3 h, the reaction was stopped just by filtration and washing with diethyl ether. Pure title compound (301 mg, 91.4%) was obtained as a white solid; mp decomposition at 245 °C. H NMR (300M, OMSO-d₆): δ = 9.46 (s, 1H), 8.48 (s, 1H), 7.686 (d, J = 9.0 Hz, 1H), 7.684 (d, J = 7.5 Hz, 1H), 7.58 (dd, J = 7.5 Hz, 9.0 Hz, 1H), 3.48 (s, 3H). MS (EI): m/z = 369.8 (M⁺).

2-(4-Fluoro-3-methylphenylamino)-6-(2,6-dichlorophenyl)-7H-pyranor2,3-d1pyrimidin-7-one (12a). The mixture of 6-(2,6-dichlorophenyl)-2-(methylsulfonyl)-7H-pyranor2,3-d1pyrimidin-7-one (197 mg, 0.53 mmol) and 4-fluoro-3-methylaniline (11a, 132.8 mg, 1.06 mmol) in DMF (6 mL) was heated to 110 °C and stirred overnight. Then the reaction mixture was cooled down to room temperature and quenched by adding water (60 mL). After the reaction mixture was extracted by ethyl acetate three times, the combined organic layer was washed by brine and then dried over anhydrous Na₂SO₄. Filtration and removal of solvent gave the crude product, which was purified by Combiflash chromatography (15-30%, of ethyl acetate in hexane) to yield the title compound 12a (44 mg, 19.6%) as a light-yellow solid; mp 255-256 °C. H NMR (300 MHz, chloroform-<i>d</i>): δ = 8.60 (s, 1H), 7.58 (s, 1H), 7.55-7.40 (m, 5H), 7.303 (dd, J = 7.5 Hz, 9.0 Hz, 1H), 7.02 (t, J = 8.7 Hz, 1H), 2.32 (s, 3H). MS (EI): m/z = 416.2 (M⁺+1).
Anal. Calcd for (C_{20}H_{12}Cl_{2}FN_{3}O_{2}): C, 57.71; H, 2.91; N, 10.10. Found: C, 57.79; H, 2.73; N, 9.97.

2-(3-(Methylthio)phenylamino)-6-(2,6-dichlorophenyl)-7H-pyrano[2,3-d]pyrimidin-7-one (12b). The mixture of 6-(2, 6-dichlorophenyl)-2-(methylsulfonyl)-7H-pyrano[2,3-d]pyrimidin-7-one (10, 200 mg, 0.54 mmol) and 3-(methylthio)aniline (lib, 150 mg, 1.08 mmol) in DMF (6 mL) was heated to 110 °C and stirred overnight. Then the reaction mixture was cooled down to room temperature and quenched by adding water (60 mL). After the reaction mixture was extracted by ethyl acetate three times, the combined organic layer was washed by brine and then dried over anhydrous Na_{2}SO_{4}.

Filtration and removal of solvent gave the crude product, which was purified by Combiflash chromatography (10-30% of ethyl acetate in hexane) to yield the title compound (59 mg, 25.5%) as a yellow solid; mp 229-230 °C. H NMR (300 MHz, chloroform-<f1>): δ = 8.63 (s, 1H), 7.66 (t, J = 1.8 Hz, 1H), 7.59 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.47-7.39 (m, 3H), 7.35-7.27 (m, 2H), 7.04 (d, J = 7.8 Hz, 1H), 2.53 (s, 3H). MS (EI): m/z = 430.3 (M+1). Anal. Calcd for (C_{20}H_{13}Cl_{2}N_{3}O_{2}S): C, 55.82; H, 3.05; N, 9.77. Found: C, 55.71; H, 3.07; N, 9.53.

2-(3-Aminophenylamino)-6-(2,6-dichlorophenyl)-7H-pyrano[2,3-d]pyrimidin-7-one (12c). A mixture of the sulfone 10 (700 mg, 1.88 mmol) and benzene-1,3-diamine (11c, 453 mg, 4.15 mmol) in diglyme (18.5 mL) was heated and stirred in a preheated oil bath at 150 °C for 1 h or till the complete consumption of the sulfone 10. The reaction mixture was cooled to rt. Then it was filtered through a celite paddled funnel. The filtered residue was washed with EtOAc (20 mL). The filtrate was concentrated and the resultant crude product was purified by Combiflash chromatography (40%-90% ethyl acetate in hexane) and preparative TLC (30% ethyl acetate in hexane) to yield the product 10 (220.6 mg, 29.4%) as a white solid; mp 259-260 °C. H NMR (500 MHz, DMSO-<f1>) : δ 10.32 (brs, 1H), 8.87 (s, 1H), 8.12 (s, 1H), 7.63 (d, J = 10 Hz, 2H), 7.52-7.49 (t, J = 10 Hz, 5Hz, 1H), 7.04-7.03 (t, J = 5 Hz, 1H), 6.99-6.96 (t, J = 10 Hz, 5Hz, 1H), 6.88 (d, J = 10 Hz, 1H), 6.31 (d, J = 5Hz, 1H), 5.41 (brs, 2H). ^{13}C NMR (75 MHz, DMSO-<f1>): δ 164.97, 160.27, 160.16, 158.09, 149.06, 142.69, 139.30, 134.93, 132.30, 132.30, 131.35, 128.92, 128.38, 118.72, 109.65, 108.47, 105.85. HRMS (ESI) m/z for C_{19}H_{13}Cl_{2}N_{4}O_{2} [M +H]^+: calcd, 399.0416; found, 399.0414. Anal. Calcd for (C_{19}H_{12}Cl_{2}N_{4}O_{2}): C, 57.00; H, 2.75; N, 13.63. Found: C, 57.16; H, 3.03; N, 14.03.
3-(6-(2,6-Dichlorophenyl)-7-oxo-7 H-pyrano[2,3-f]pyrimidin-2-ylamino)benzonitrile (12d). The title compound was prepared from the sulfone 10 (300 mg, 0.81 mmol) and 3-aminobenzonitrile (lil, 191 mg, 1.62 mmol) in 18 mL diglyme according to the procedure described for the synthesis of 12c. The crude product was purified by Combiflash chromatography (0-60% ethyl acetate in hexane) to yield the product 12d (76 mg, 22.9%) as a light yellow solid; mp 276-278 °C. H NMR (500 MHz, DMSO-d6): δ 10.88 (brs, 1H), 8.98 (s, 1H), 8.27 (t, J = 5Hz, 1H), 8.20 (s, 1H), 8.07-8.03 (m, 1H), 7.66-7.62 (m, 2H), 7.60-7.49 (m, 3H). 13C NMR (75 MHz, DMSO-d6): δ 165.01, 160.63, 159.93, 157.99, 142.70, 140.06, 134.98, 132.23, 131.62, 130.38, 128.56, 126.60, 124.69, 124.59, 122.65, 120.14, 119.01, 111.72. HRMS (ESI) m/z for C20H11ClN4O2 [M+H]+ calcd, 409.0251; found, 409.0251. Anal. Caled for (C20H11ClN4O2): C, 58.70; H, 2.46; N, 13.69. Found: C, 58.44; H, 2.63; N, 13.47.

6-(2,6-Dichlorophenyl)-2-(3-methoxyphenylamino)-7 H-pyrano[2,3-f]pyrimidin-7-one (12e). The title compound was prepared from the sulfone 10 (250 mg, 0.67 mmol) and 3-methoxybenzamine (lie, 182.5 mg, 1.48 mmol) in 8.3 mL diglyme (Rf = 0.37, hexane:ethyl acetate = 2:1) according to the procedure described for the synthesis of 12c. The crude product was purified by Combiflash chromatography (20-30% ethyl acetate in hexane) to obtain the product 12e (110 mg, 39.4%) as a white solid; mp 252-254 °C. H NMR (500 MHz, DMSO-d6): δ 10.53 (s, 1H), 8.92 (s, 1H), 8.15 (s, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.53-7.50 (t, J = 5.0 Hz, 1H), 7.49-7.48 (t, J = 5.0Hz, 1H), 7.36-7.35 (d, J = 5.0Hz, 1H), 7.28-7.26 (t, J = 5.0Hz, 1H), 6.69-6.67 (d, J = 5.0Hz, 1H), 3.77 (s, 1H). 13C NMR (75 MHz, DMSO-d6): δ 165.36, 160.79, 160.46, 159.98, 158.39, 143.08 140.45, 135.33, 132.66, 131.83, 129.94, 128.83, 19.69, 113.00, 108.81, 106.71, 55.51. HRMS (ESI) m/z for C20H14Cl2N3O3 [M+H]+: calcd, 414.0412; found, 414.0408. Anal. Caled for (C20H14Cl2N3O3): C, 57.99; H, 3.16; N, 10.04. Found: C, 57.93; H, 2.94; N, 9.94.

6-(2,6-Dichlorophenyl)-2-(4-(dimethylamino)phenylamino)-7 H-pyrano[2,3-f]pyrimidin-7-one (12f). The title compound was prepared from the sulfone 10 (200 mg, 0.540 mmol) and N,N-dimethyl-p-phenylenediamine (lifl, 110 mg, 0.810 mmol) in 12 mL diglyme (Rf= 0.67, hexane:ethyl acetate = 1:1) according to the procedure described for the synthesis of 12c. The crude product was purified by Combiflash chromatography (0-30% ethyl acetate in hexane) to yield the product 12f (145 mg, 62.8%) as a yellow solid; mp 276-278 °C. H NMR (500 MHz, DMSO-d6): δ 10.29 (brs, 1H), 8.81 (s, 1H), 8.07 (s, 1H), 7.61 (d, J = 5.0Hz), 7.54-7.49 (m, 3H), 6.75 (d, J = 15Hz, 2H), 2.88 (s, 6H).
\(^{13}\)C NMR (75 MHz, DMSO-\(\text{d}_4\)): \(\delta\) 160.16, 158.13, 147.38, 142.75, 134.98, 132.40, 131.28, 128.36, 128.03, 122.13, 112.57, ... heated in a preheated oil bath at 100 °C for 1 h. Upon the completion of the reaction, water (15 mL) was added. 

The title compound was prepared from the sulfone 10 (301 mg, 0.81 mmol) and N-(3-aminophenyl)acetamide (11g, 253.5 mg, 1.66 mmol) in 8.3 mL diglyme (R/\(\text{hexane}=0.27\) hexane:ethyl acetate = 1:2) according to the procedure described for the synthesis of 12c. The crude product was purified by Combiflash chromatography (40-100% ethyl acetate in hexane) to obtain the product 12g (73.3 mg, 20.5%) as a white solid; mp 288-289 °C. \(^1\)H NMR (500 MHz, DMSO-\(\text{d}_6\)): \(\delta\) 10.57 (s, 1H), 10.01 (s, 1H), 8.90 (s, 1H), 8.15 (s, 1H), 7.99 (s, 1H), 7.64 (s, 1H), 7.63 (s, 1H), 7.53-7.50 (t, \(J=5.0\) Hz), 7.42-7.40 (m, 1H), 7.38-7.36 (m, 1H), 7.27-7.25 (t, \(J=5.0\) Hz), 2.05 (s, 1H). \(^{13}\)C NMR (75 MHz, DMSO-4): \(\delta\) 168.47, 165.11, 160.50, 160.26, 158.18, 142.80, 139.77, 139.16, 135.04, 132.38, 131.52, 128.90, 128.53, 124.73, 119.25, 115.58, 114.60, 111.41, 104.39, 24.19. HRMS (ESI) \(m/z\) for \(\text{C}_2\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_3\) [\(\text{M}+\text{H}\)]\(^+\): calcd, 414.0521; found, 414.0523.

6-Bromo-2-(methylsulfonyl)-7 \(H\)-pyranor2,3-d1pyrimidin-7-one (13). 6-Bromo-2-(methylsulfanyl)-7 \(H\)-pyranor2,3-\(\text{d}_1\)pyrimidin-7-one (5, 500 mg) was dissolved in anhydrous DCM (30 mL) and stirred for 10 mins until it becomes a homogeneous solution. w-CPBA (906 mg, 77%) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction was monitored by TLC. After completion of the reaction, the precipitated solid was filtered and washed with cold ether (3x 5 mL) and cold acetone (2 mL). The resultant compound was dried in vacuum oven to afford 320 mg of target compound. mp: 179-181 °C. \(^1\)HNMR (300 MHz, \(\text{CDCl}_3\)): \(\delta\) 9.33 (s, 1H), 8.75 (s, 1H), 3.48 (s, 3H).

\(\text{tert-Butyl-4-(6-6-bromo-7-oxo-7 \(H\)-pyranor2,3-tinpyrimidin-2-ylamino)pyridin-3-\(v\)Dpiperazine-1-carboxylate (14). The solution of 6-bromo-2-(methylsulfanyl)-7 \(H\)-pyranor2,3-\(\text{d}_1\)pyrimidin-7-one (13, 100 mg) in DMF (2 mL) in a sealed tube was added K\(_2\)CO\(_3\) (86 mg) with stirring for 5 mins. Then \(\text{tert-butyl-4-(6-aminopyridin-3-yl)}\)piperazine-l -carboxylate (109 mg) was added to the reaction mixture at room temperature. The reaction mixture in the sealed tube was heated in a preheated oil bath at 100 °C for 1 h. Upon the completion of the reaction, water (15 mL) was added and...
extracted organic compound with ethyl acetate (3x 10 mL). The combined organic layer
was washed with brine (15 mL) and then dried over sodium sulfate. Solvent was
removed under reduced pressure to obtain the crude product, which was purified by
Combiflash column chromatography (0-5% methanol in dichloromethane) to obtain the
target compound (18 mg). $^1$H NMR (300 MHz, CDC$_1$$_3$): δ 8.43 (d, J = 3.0 Hz, 1H ), 8.14
(d, J = 3.0 Hz, 1H ), 7.86 (d, J = 3.0 Hz, 1H ), 7.78 (d, J = 9.0 Hz, 1H), 7.35-7.29 (m, 1H),
3.63 (t, J = 4.9 Hz, 4H), 3.28 (t, J = 4.9 Hz, 4H), 1.49 (s, 9H). MS (EI): m/z = 502.0.

EXAMPLE 2

The syntheses described below are illustrated in FIGURE 4.

6-(2,6-Dimethylphenyl)-2-(methylthio)-7 H-pyrano[2,3-c]pyrimidin-7-one (16a).

To a 50 mL flask was added 6-bromo-2-(methylthio)-7 H-pyrano[2,3-c]pyrimidin-7-one
(5, 500 mg, 1.83 mmol), 2,6-dimethylphenylboronic acid (15a, 410 mg, 2.74 mmol),
Pd$_2$(dba)$_3$ (167 mg, 0.18 mmol), SPhos (147 mg, 0.36 mmol), K$_3$PO$_4$ (1.16 g, 5.49 mmol)
and dry toluene (10 mL). The resultant mixture was degassed with argon bubble for 2
minutes and stirred at 95°C for 5 hours. The reaction mixture was cooled and filtered
through a celite padded funnel. The cake was washed with EtOAc (200 mL) and the
filtrate was washed with water (50 mL) and brine (20 mL). The organic layer was dried
over anhydrous Na$_2$SO$_4$ and dried under reduced pressure. The residue was purified by
Combiflash chromatography (10-30% EtOAc in hexane) to give the titled product 16a
(295 mg, 54.0%) as a semisolid. (Rf = 0.72 (Hexane/EtOAc = 50/50) H NMR (300 MHz,
CDC$_1$$_3$) δ: 8.93 (s, 1H), 7.95 (s, 1H), 7.22 (m, 3H), 2.64 (s, 3H), 2.20 (s, 6H).

6-(2,6-Dimethylphenyl)-2-(methylsulfonyl)-7 H-pyrano[2,3-t]pyrimidin-7-one (17a).
To a solution of 6-(2,6-dimethylphenyl)-2-(methylthio)-7 H-pyrano[2,3-d]pyrimidin-7-one
(16a, 285 mg, 0.95 mmol) in DCM (14 mL) was added w-CPBA (515
mg, 70%, 2.1 mmol) in portions at room temperature. The resulting mixture was stirred at
room temperature for 3 hours. The precipitated solid was collected by filtration and
washed with hexane. The solid crude product was dissolved in EtOAc (100 mL), washed
with saturated aqueous NaHCO$_3$ solution (20 mL x 2) and brine (20 mL). The organic
layer was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated to give the titled
product (185 mg, 58.9%) as a yellow solid (Rf = 0.42, Hexane/EtOAc = 50/50). H NMR
(300 MHz, CDCl₃) δ: 9.07 (s, 1H), 7.66 (s, 1H), 7.24 (m, 1H), 7.13 (m, 2H), 3.41 (s, 3H), 2.16 (s, 6H).

2-(3-Aminophenylamino)-6-(2,6-dimethylphenyl)-7 H-pyranor2J-tf1pyrimidin-7-one (19a). To a suspension of 6-(2,6-dimethylphenyl)-2-(methylsulfonyl)-7H-pyano[2,3-d]pyrimidin-7-one (17a, 90 mg, 0.27 mmol) in diglyme (2.4 mL) was added w-phenylenediamine (18a, 63 mg, 0.59 mmol). The resulting mixture was stirred at 150°C under argon atmosphere for 1 hour. The reaction mixture was cooled, filtered through a celite padded funnel. The cake was washed with EtOAc (10 mL). The filtrate was concentrated and the resultant crude product was purified by preparative TLC (DCM/MeOH = 10/1) to give the titled product (22 mg, 22.7%) as a yellow solid (R₇ = 0.59, DCM/MeOH = 10/1). ¹H NMR (300 MHz, CDCl₃) δ: 8.59 (s, 1H), 7.56 (s, 1H), 7.46 (s, 1H), 7.36 (s, 1H), 7.21 (m, 1H), 7.15 (m, 3H), 6.90 (d, 1H, J = 7.8 Hz), 6.49 (d, 1H, J = 7.8 Hz), 2.21 (s, 6H). mp 223-226 °C. LRMS (ESI) m/z for C₂₂H₂₀N₄O₂ [M +H]^+: calcd, 358.1430; found, 359.1.

N-(3-(6-(2,6-Dimethylphenyl)-7-oxo-7 H-pyano[2,3-<f1pyrimidin-2-ylamino)phenyl)-acetamide (19b). To a suspension of 6-(2,6-dimethylphenyl)-2-(methylsulfonyl)-7 H-pyano[2,3-d]pyrimidin-7-one (17a, 90 mg, 0.27 mmol) in diglyme (2.4 mL) was added N-(3-aminophenyl)acetamide (18b, 88 mg, 0.6 mmol). The resulting mixture was heated and stirred at 150 °C under argon atmosphere for 1.5 hours. The reaction mixture was cooled, filtered through a celite padded funnel. The cake was washed with EtOAc (5 mL). The filtrate was concentrated and the residue was purified by Combiflash (10 -70% EtOAc in hexane) to give the titled product (40 mg, 37.9%) as a yellow solid (R₇ = 0.50, hexane/EtOAc = 1:3). ¹H NMR (300 MHz, CDCl₃) δ: 9.36 (s, 1H), 8.81 (s, 1H), 8.17 (s, 1H), 7.83 (s, 1H), 7.54 (t, 2H, J = 9.9 Hz), 7.29 (t, 1H, J = 8.1 Hz), 7.23-7.1 1 (m, 3H), 2.20 (s, 6H), 2.10 (s, 3H). mp 252-254 °C. HRMS (ESI) m/z for C₂₃H₂₇N₄O₃ [M +H]^+: calcd, 401.1614; found, 401.1609.

2-(Methylthio)-6-phenyl-7 H-pyranor2,3-tinpyrimidin-7-one (16b). To a 50 mL flask was added 6-bromo-2-(methylthio)-7 H-pyano[2,3-<i>pyrimidin-7-one (5, 1.36 g, 5 mmol), phenylboronic acid (914 mg, 7.5 mmol), Pd₂(dba)₃ (457 mg, 0.5 mmol), SPhos (410 mg, 1 mmol), K₃PO₄ (3.18 g, 15 mmol) and dry toluene (25 mL). The resulting suspension was degassed with argon for 2 minutes and stirred at 95°C for 5 hours. The reaction mixture was cooled to room temperature and the solids were removed by filtration. The filtrate was concentrated and the residue was purified by Combiflash
chromatography (10-50% of EtOAc in hexane) and ether (50 mL) trituration to give the
titled product 16b (860 mg, 63.7%) as a yellow solid. (Rf = 0.50, Hexane/EtOAc = 50/50) H NMR (300 MHz, DMSO-<i>d</i><sub>6</sub>) δ: 8.99 (s, 1H), 8.26 (s, 1H), 7.69 (m, 2H), 7.47 (m, 3H), 2.60 (s, 3H).

2-(Methylsulfonyl)-6-phenyl-7 H-pyranor2,3-tinpyrimidin-7-one (17b). To a solution of 2-(methylthio)-6-phenyl-7 H-pyranor2,3-tinpyrimidin-7-one (16b, 860 mg, 3.18 mmol) in DCM (20 mL) was added w-CPBA (1.73 g, 70%, 7.0 mmol) in portions at room temperature. The resulting mixture was stirred at room temperature for 5 hours. The precipitated solid was collected by filtration, washed with DCM (20 mL) and ether (20 mL), and dried under vacuum to give the titled product 17b (410 mg, 42.7%) as a pale yellow solid. (Rf = 0.25, Hexane/EtOAc = 50/50). H NMR (300 MHz, DMSO-<i>d</i><sub>6</sub>) δ: 9.39 (s, 1H), 8.41 (s, 1H), 7.76 (m, 2H), 7.52 (m, 3H), 3.48 (s, 3H).

2-(3-Aminophenylamino)-6-phenyl-7 H-pyranor2,3-tinpyrimidin-7-one (19c). To a suspension of 2-(methylsulfonyl)-6-phenyl-7 H-pyranor2,3-tinpyrimidin-7-one (17b, 100 mg, 0.33 mmol) in diglyme (2.4 mL) was added w-phenylenediamine (78.5 mg, 0.73 mmol). The resulting mixture was stirred at 150°C for 1 hour under argon atmosphere. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated and the residue was purified by Combiflash chromatography (5-50% of EtOAc in hexane) to give the titled product 19c (17 mg, 15.6%) as a yellow solid. (Rf = 0.55, Hexane/EtOAc = 50/50). H NMR (300 MHz, DMSO-<i>d</i><sub>6</sub>) δ: 10.15 (s, 1H), 8.84 (s, 1H), 8.18 (s, 1H), 7.68 (d, 2H, J = 6.9 Hz), 7.44 (m, 3H), 7.05 (s, 1H), 6.94 (m, 2H), 6.28 (d, 1H, J = 7.8 Hz), 5.11 (s, 2H).

EXAMPLE 3
The syntheses described below are illustrated in FIGURE 5.

6-Bromo-2-chloro-7 H-pyranor2,3-tinpyrimidin-7-one (20). To a solution of 6-bromo-2-(methylthio)-7 H-pyranor2,3-tinpyrimidin-7-one (5, 2.4 g, 8.7 mmol) in anhydrous acetonitrile (5.4 mL) was added SO<sub>2</sub>Cl<sub>2</sub> (8.3 mL, 86.8 mmol) dropwise at room temperature. The resulting mixture was stirred and refluxed for 2 hours and then cooled to room temperature. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL). The solution was washed with saturated NaHCO<sub>3</sub> (50 mL x 2), water and brine. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The residue was triturated with hexane (30
mL) to provide the titled product (1.8 g, 83.3%) as a white solid. Rf = 0.32,
hexane/EtOAc = 2/1. mp 225-226 °C. H NMR (300 MHz, DMSO-4): δ 9.06 (s, 1H),
8.67 (s, 1H). MS (ESI) m/z for C17H12BrClN2O2 [M +H]+: calcd, 260.9; found,260.9; |M
+H+2|: 262.9; found, 262.9.

2-Chloro-6-(1-ethoxyvinyl)-7 H-pyranor2,3-tinpyrimidin-7-one (21). To a solution
of 6-bromo-2-chloro-7 H-pyano [2, 3-<i>ilpyrimidin-7-one (20, 2.1 g, 8.0 mmol) in 1,4-
dioxane (20 mL) was added 1-ethoxyvinyltributyltin (2.8 mL, 8.0 mmol) and Pd(PPh3)4.
The resulting mixture was degassed with argon for 3 minutes and stirred and refluxed for
2 hours. The reaction mixture was cooled to room temperature and filtered through a pad
of celite. The filtrate was concentrated and the residue was purified by Comiflash
chromatography (0-20% of EtOAc in hexane) to give the titled product (831.4 mg,
41.1%). Rf = 0.63 (hexane/EtOAc = 2/1). mp 190-192 °C. H NMR (300 MHz, CDCl3): δ
8.85(s, 1H), 8.17(s, 1H), 5.81(d, J = 2.8 Hz, 1H), 4.74(d, J = 2.8 Hz, 1H), 3.96(q, J =
7.0Hz, 2H), 1.47(t, J = 7.0Hz, 3H). MS (APCI) m/z for C17H12ClN2O [M -H]+: calcd,
251.1; found, 251.1; [M -H+2] +: calcd, 253.0; found, 253.1.

6-Acetyl-2-chloro-7 H-pyranor2,3-<ianpyrimidin-7-one (22). To a solution of 2-
chloro-6-(1-ethoxyvinyl)-7 H-pyano[2,3-<i>ilpyrimidin-7-one (21, 916.8 mg, 3.6 mmol) in
1,4-dioxane (7.2 mL) was added aqueous HCl solution (2N, 9.0 mL, 18 mmol) at room
temperature. The resulting solution was stirred at room temperature for 30 minutes and
concentrated. The residue was partitioned with EtOAc (50 mL) and saturated NaHCO3
solution (20 mL). The organic layer was dried over anhydrous Na2SO4. Filtration and
concentration provided the titled product (753.1 mg, 92.4%) as an off-white solid. Rf =
0.26 (hexane/EtOAc = 2/1). mp 171-173 °C. H NMR (300 MHz, CDCl3): δ 8.94 (s, 1H),
8.51(s, 1H), 2.73(s, 1H). MS (APCI) m/z for C19H16ClN2O3 [M +H]+: calcd, 225.0; found,
224.8; [M +H+2]+: calcd, 227.0; found, 226.8.

2-(4-(4-Methylpiperazin-1-yl)phenylamino)-6-acetyl-7 H-pyranor2,3-tinpyrimidin-
7-one (23). To a solution of 6-acetyl-2-chloro-7 H-pyano[2,3-<i>ilpyrimidin-7-one (22, 200
mg, 0.9 mmol) in 2-butanol (7.2 mL) was added 4-(4-methyl-piperazino)aniline (176 mg,
0.9 mmol) and TFA (66 µL, 0.9 mmol). The resulting mixture was stirred at reflux
overnight and then cooled to room temperature. The reaction mixture was concentrated
and the residue was partitioned with EtOAc (200 mL) and saturated aqueous NaHCO3
solution (20 mL). The organic layer was washed with water, brine, dried over anhydrous
Na2SO4, filtered and concentrated. The resultant residue was purified by Comiflash
chromatography (DCM/MeOH/Et_3N = 1000/100/1) to give the titled product (99 mg, 29.2%) as a red solid. R_f = 0.24 (hexane/EtOAc/Et_3N = 100:300:1). Mp >240 °C. H NMR (300 MHz, DMSO-d_6): δ 10.63 (brs, 1H), 8.96 (s, 1H), 8.60 (s, 1H), 7.56 (d, J = 8.1Hz), 6.94 (d, J = 8.1Hz), 3.11 (t, J = 4.6 Hz, 4H), 2.53(s, 3H), 2.45 (t, J = 4.6 Hz, 4H), 2.22 (s, 3H). HRMS (ESI) m/z for (C_20H_22N_3O_3) [M+H]^+ calcd, 380.1723; found, 380.1721. Anal. Calcd for (C_20H_22N_3O_3H_2O): C, 60.44; H, 5.83; N, 17.62. Found: C, 60.60; H, 5.56; N, 17.34.

EXAMPLE 4

The pharmacological activities of some invented compounds as protein kinase modulators are illustrated in TABLE 1.

TABLE 1. Biological activities of selected compounds against Abelson kinase 1 (ABL1)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>K_d (nM)^a</th>
<th>IC_{50} (nM)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD173955</td>
<td><img src="image" alt="PD173955 Structure" /></td>
<td>0.58</td>
<td>Lit^c</td>
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<td>17.5</td>
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<td>12b</td>
<td><img src="image" alt="12b Structure" /></td>
<td>3.3</td>
<td>18.7</td>
</tr>
<tr>
<td>12c</td>
<td><img src="image" alt="12c Structure" /></td>
<td>0.4</td>
<td>2.13</td>
</tr>
<tr>
<td>12d</td>
<td><img src="image" alt="12d Structure" /></td>
<td>2.6</td>
<td>42.6</td>
</tr>
<tr>
<td>12e</td>
<td><img src="image" alt="12e Structure" /></td>
<td>1.5</td>
<td>16.1</td>
</tr>
<tr>
<td>12f</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>1.5</td>
<td>15.7</td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>12g</td>
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<td>0.91</td>
<td>3.51</td>
</tr>
<tr>
<td>19a</td>
<td><img src="#" alt="Chemical Structure" /></td>
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<tr>
<td>19b</td>
<td><img src="#" alt="Chemical Structure" /></td>
<td>0.66</td>
<td>2.09</td>
</tr>
</tbody>
</table>

*K_{d} for Abelson kinase ABL1 was determined by DiscoverX corporation though the KINOMEscan™ competition binding assay ([https://www.discoverx.com/kinase-datasheets/abl1-nonphosphorylated](https://www.discoverx.com/kinase-datasheets/abl1-nonphosphorylated)). IC_{50} against Abelson kinase ABL1 was determined by Life Technologies corporation though the Z'-LITE biochemical assay. See Wang, J.; Pendergast, A.M. *Trans Cancer*, 2015, 1, 110-123 and Nagar, B.; et al; *Cancer Res*, 2002, 62, 4236-4243.

While the preferred embodiments of the invention have been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.
CLAIMS

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of Formula (A):

   \[
   \text{R} - (\text{x}^3) - (\text{x}^2) - (\text{x}^1) - (\text{y}^1) - (\text{y}^2) - \text{S}^1
   \]

   (A),

   or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

   Z is selected from the group consisting of hydrogen, halogen, C(halogen)₃, a C₃-Cg alkyl, and C₃-Cc cycloalkyl;

   X¹ is selected from the group consisting of N, R, O, and S, wherein when X¹ is O, R-(X³)₁-(X²)ᵱ is not methyl;

   R¹ is selected from the group consisting of hydrogen, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl;

   X² is an optionally substituted aryl or optionally substituted heteroaryl;

   X³ is an optionally substituted heterocyclyl;

   R is hydrogen or alkyl;

   Y¹ is O or an optionally substituted group selected from the group consisting of an aryl, a heteroaryl, an alkenyl, an alkynyl, and an acyl group;

   Y² is an optionally substituted heteroaryl;

   S¹ is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, SQ¹, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ¹C(=0)Q², C(=0)NQ¹Q², N₃, NCS, NO₂, or NQ¹Q², wherein Q¹ and Q² are independently selected from hydrogen and alkyl;

   m is 0 or 1;

   n is 0 or 1;

   p is 0 or 1;

   q is 0 or 1; and

   r is 0 or 1.
2. The compound of Claim 1, wherein the compound of formula (A) has the structure of Formula (A1):

![Chemical structure](attachment:image)

(A1),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

- Z is selected from the group consisting of hydrogen, halogen, CF₃, CC1₃, C₁-C₆ alkyl, and C₃-C₆ cycloalkyl;
- X¹ is selected from the group consisting of NR¹, O, and S;
- Ar¹ is an optionally substituted aryl or optionally substituted heteroaryl;
- Ar² is an optionally substituted aryl or optionally substituted heteroaryl;

and

- R¹ is hydrogen, C₁-C₆ alkyl or C₃-C₆ cycloalkyl.

3. The compound of Claim 1 or Claim 2, wherein X¹ is NR¹.

4. The compound of Claim 3, wherein Ar² is an optionally substituted phenyl.

The compound of Claim 4, wherein the compound has the structure of Formula (A2):

![Chemical structure](attachment:image)

(A2),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

- R² is hydrogen, halogen, alkyl, alkoxyalkyl, cycloalkyl, cyano, OH, SQ¹, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ¹C(=0)Q², C(=0)NQ₁Q², N₃, NCS, NO₂, or NO^Q₂ whereby Q¹ and Q² are independently selected from H and C₁-C₁₀ alkyl; and
- x is 0, 1, 2, 3, 4, or 5.

5. The compound of Claim 5, wherein the Ar¹ is an optionally substituted phenyl.

6. The compound of Claim 5, wherein the Ar¹ is a phenyl.
7. The compound of Claim 6, wherein the compound has the structure of Formula (A3):

(A3),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

\[ R_Y \] is hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, SQ, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ!C(=0)Q², C(=0)NQ¹Q², N₃, NCS, NO₂, or NQiQ², wherein Q¹ and Q² are independently selected from H and C₁-C₁₀ alkyl; and

\[ y \] is 0, 1, 2, 3, 4, or 5.

8. The compound of Claim 7, wherein \[ R_I \] is hydrogen or methyl.

9. The compound of Claim 8, wherein \[ R_I \] is hydrogen.

10. The compound of Claim 9, wherein \[ Z \] is hydrogen, halogen, or methyl.

11. The compound of Claim 10, wherein \[ Z \] is hydrogen.

12. The compound of Claim 11, wherein the compound has the structure of Formula (A4):

(A4),

or a pharmaceutically acceptable salt, hydrate, or solvate thereof, wherein

\[ R_{X1}, R_{X2}, R_{Y1}, \] and \[ R_{Y2} \] are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, cycloalkyl, cyano, OH, SQ, acyl, haloalkyl, heteroaryl, C(halogen)₃, CN, C(=0)CH₃, NQ!C(=0)Q², C(=0)NQ¹Q², N₃, NCS, NO₂, and NQiQ², wherein Q¹ and Q² are independently selected from H and C₁-C₁₀ alkyl.
13. The compound of Claim 12, wherein RY1 and RY2 are independently selected from H, F, Cl, and CH₃.

14. The compound of Claim 12, wherein RX1 is selected from H, F, Cl, N(CH₃)₂, and CH₃.

15. The compound of Claim 12, wherein RX2 is selected from NH₂, OCH₃, CN, SCH₃, NHC(0)CH₃, and CH₃.

16. The compound of any one of Claims 1, 2, 5, 7, or 12, wherein the compound is Compound 12a, 12b, 12c, 12d, 12e, 12f, 12g, 19a, or 19b.

17. A pharmaceutical composition comprising a compound of any one of Claims 1-16 and a pharmaceutically acceptable carrier.

18. A method of making 2-alkylsulfanylpyrano[2,3-<i>l</i>]pyrimidin-7-one comprising:

   (i) contacting 2-alkylthiourea hemihydrate with a coumalate ester in a suitable solvent in the presence of a suitable base, thereby forming 3-(2-alkylsulfanyl-6-oxo-1,6-dihydro-pyrimidin-5-yl)acrylic acid; and

   (ii) contacting the 3-(2-alkylsulfanyl-6-oxo-1,6-dihydro-pyrimidin-5-yl)acrylic acid of step (i) with an anhydride thereby forming 2-alkylsulfanylpyrano[2,3-<i>l</i>]pyrimidin-7-one.

19. The method of Claim 18, wherein 2-alkylthiourea hemihydrate is 2-methylthiourea hemihydrate.

20. A method of making 6-bromo-2-(methylthio)-7-<i>H</i>pyrano[2,3-<i>l</i>]pyrimidin-7-one comprising contacting 2-methylsulfanylpyrano[2,3-<i>l</i>]pyrimidin-7-one with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in a suitable solvent wherein the contacting results in 6-bromo-2-(methylthio)-7-<i>H</i>pyrano[2,3-<i>l</i>]pyrimidin-7-one.

21. The method of Claim 20, wherein the solvent is DMF.
22. A method for treating a disease or condition treatable by administering a protein kinase inhibitor, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of Claim 1-16.

23. A method for treating a disease or condition characterized by aberrant kinase activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of Claim 1-16.

24. The method of Claim 23, wherein the disease or condition is selected from the group consisting of cancer, cardiovascular disease, and a central nervous system disorder.
Fig. 1

$8H$-Pyrido[2,3-$d$]pyrimidin-7-one

Pyrido[2,3-$d$]pyrimidin-7-one

Fig. 2

PD17399

PD180970

PD0332991 (Palbociclib)

FRAX597
Fig. 3

Reagents and reaction condition: a) CH₃ONa/CH₃OH, rt, 1.5 h; b) Ac₂O, reflux, 40 mins; c) DBDMH, DMF, rt, 70.5%; d) m-CPBA, CH₂Cl₂, 12 hrs, rt; e) DMF, reflux; f) Pd₂(db₃), K₂PO₄, S-Phos, toluene, 100 °C, 20 hrs; g) m-CPBA, CH₂Cl₂, rt, 30 h; h) DMF, 110°C, 12 hrs; i) m-CPBA, DCM, 10 min; j) K₂CO₃, R-NH₂, 110°C.
Reagents and reaction condition: 

a) Pd$_2$(dba)$_3$, K$_3$PO$_4$, S-Phos, toluene, 95 °C, 4-5 h; 
b) m-CPBA, CH$_2$Cl$_2$, 2-3 h, rt; 
c) diglyme, 150 °C, 1h.

Fig. 4
Reagents and reaction conditions: 1) SO$_2$Cl$_2$, MeCN, reflux, 2h; 2) Pd(Ph$_3$)$_2$, dioxane, reflux, 2h; 3) dioxane, HCl, 30 min; 4) 2-butanol, TFA, reflux, overnight.
Fig. 6
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 47/04 (2017.01)
CPC - C07D 47/04, A61 K 9/0056, A61 K 9/0031, A61 K 45/06, A61 K 9/06

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

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
| A         | US 2006/0264489 A1 (Palani et al.) 23 November 2006 (23.11.2006); p42 | 2-3, 4A, 4B, 6-15
| A         | US 7,244,727 B2 (Fox et al.) 17 July 2007 (17.07.2007); col 75 | 2-3, 4A, 4B, 6-15
| A         | WO 2010/071846 A2 (Afraxis, Inc.) 24 June 2010 (24.06.2010); para[00401] | 20-21
| A         | CN 105481858 A (Li et al.) 13 April 2016 (13.04.2016); para[0176] | 20-21
| A         | US 201/0257207 A1 (Backes et al.) 20 October 2011 (20.10.2011); entire document | 1-3, 4A, 4B, 6-15, 18-21

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
- "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
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- "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
- "Q" member of the same patent family

Date of the actual completion of the international search: 24 July 2017
Date of mailing of the international search report: 29 AUG 2017

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PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)
# INTERNATIONAL SEARCH REPORT

## 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.: 16-17, 22-24 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.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2015)