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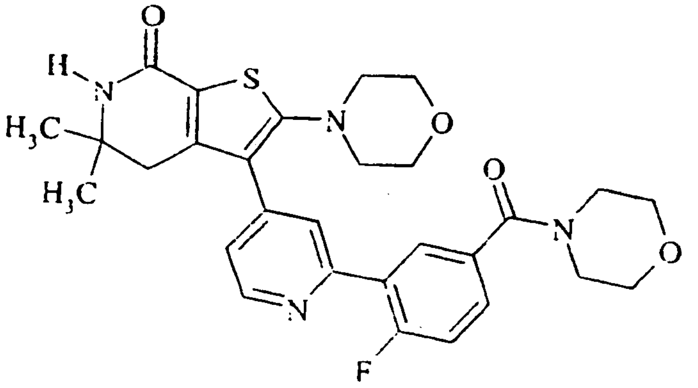
# (54) Title: A SUBSTITUTED THIENO-PYRIDINONE KINASE INHIBITOR



(I)

(57) **Abstract:** 3- {2-[2-Fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2.3-c]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof, being a selective inhibitor of PD kinase enzymes, is accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive or ophthalmic conditions. (I)

# A SUBSTITUTED THIENO-PYRIDINONE KINASE INHIBITOR

The present invention relates to a fused thiophene derivative, and to its use in therapy. More particularly, the invention provides a particular 5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one derivative, which is substituted in the 2-position of the thiophene ring by a morpholin-4-yl moiety, as well as pharmaceutically acceptable salts and solvates thereof. These compounds are selective inhibitors of phosphoinositide 3-kinase (PI3K) enzymes, and are accordingly of benefit as pharmaceutical agents, especially in the treatment of adverse inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The PI3K pathway is implicated in a variety of physiological and pathological functions that are believed to be operative in a range of human diseases. Thus, PI3Ks provide a critical signal for cell proliferation, cell survival, membrane trafficking, glucose transport, neurite outgrowth, membrane ruffling, superoxide production, actin reorganization and chemotaxis (cf. S. Ward *et al.*, *Chemistry & Biology*, 2003, **10**, 207-213; and S.G. Ward & P. Finan, *Current Opinion in Pharmacology*, 2003, **3**, 426-434); and are known to be involved in the pathology of cancer, and metabolic, inflammatory and cardiovascular diseases (cf. M.P. Wymann *et al.*, *Trends in Pharmacol. Sci.*, 2003, **24**, 366-376). Aberrant upregulation of the PI3K pathway is implicated in a wide variety of human cancers (cf. S. Brader & S.A. Eccles, *Tumori*, 2004, **90**, 2-8).

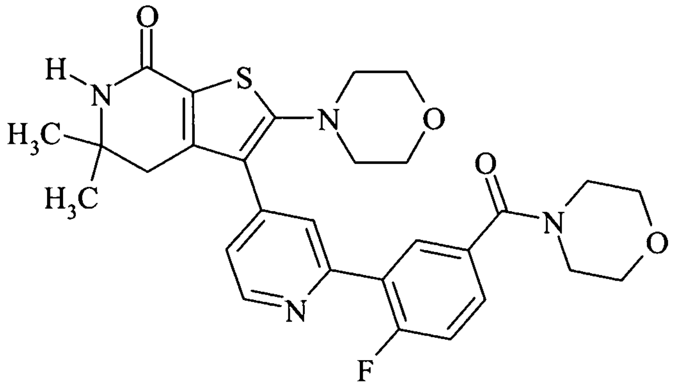
The compounds in accordance with the present invention, being potent and selective PI3K inhibitors, are therefore beneficial in the treatment and/or prevention of various human ailments. These include autoimmune and inflammatory disorders such as rheumatoid arthritis, multiple sclerosis, asthma, inflammatory bowel disease, psoriasis and transplant rejection; cardiovascular disorders including thrombosis, cardiac hypertrophy, hypertension, and irregular contractility of the heart (e.g. during heart failure); neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, amyotrophic lateral sclerosis, spinal cord injury, head trauma and seizures; metabolic disorders such as obesity and type 2 diabetes; oncological conditions including leukaemia, glioblastoma, lymphoma, melanoma, and human cancers of the liver, bone, skin, brain, pancreas, lung, breast, stomach, colon, rectum, prostate, ovary and cervix; pain and nociceptive disorders; and ophthalmic disorders including age-related macular degeneration (ARMD).

In addition, the compounds in accordance with the present invention may be beneficial as pharmacological standards for use in the development of new biological tests and in the search for new pharmacological agents. Thus, the compounds of this invention may be useful as radioligands in assays for detecting compounds capable of binding to human PI3K enzymes.

Copending international patent application no. PCT/GB2007/002051, published on 13 December 2007 as WO 2007/141504, describes a class of fused bicyclic thiophene derivatives which are selective inhibitors of PI3 kinase enzymes and are accordingly of benefit in medicine, for example in the treatment of inflammatory, autoimmune, cardiovascular, neurodegenerative, metabolic, oncological, nociceptive and ophthalmic conditions.

The compounds in accordance with the present invention are potent and selective PI3K inhibitors having a binding affinity ($IC_{50}$) for at least one human PI3K isoform of less than 100 nM (the skilled person will appreciate that a *lower* $IC_{50}$ figure denotes a *more active* compound). The compounds of the invention possess at least a 100-fold selective affinity for at least one human PI3K isoform relative to at least one other human kinase. Moreover, the compounds of the invention display good efficacy in animal models of inflammation, and exhibit an exemplary toxicological profile.

The present invention provides 3-{2-[2-fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one of formula (I):



(I)

or a pharmaceutically acceptable salt or solvate thereof.

The compounds in accordance with the present invention are encompassed within the generic scope of copending international patent application no. PCT/GB2007/002051, published on 13 December 2007 as WO 2007/141504. There is, however, no specific disclosure therein of the compound of formula (I) as depicted above, or a pharmaceutically acceptable salt or solvate thereof.

For use in medicine, the salts of the compound of formula (I) above will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compound of formula (I) or of its pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compound of formula (I) include acid addition salts which may, for example, be formed by mixing a solution of the compound of formula (I) with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid or phosphoric acid.

The present invention includes within its scope solvates of the compound of formula (I) above. Such solvates may be formed with common organic solvents, e.g. hydrocarbon solvents such as benzene or toluene; chlorinated solvents such as chloroform or dichloromethane; alcoholic solvents such as methanol, ethanol or isopropanol; ethereal solvents such as diethyl ether or tetrahydrofuran; or ester solvents such as ethyl acetate. Alternatively, the solvates of the compound of formula (I) may be formed with water, in which case they will be hydrates.

Compounds of formula (I) may exist as tautomers including, by way of example, amide (NHC=O)↔hydroxyimine (N=COH) tautomers. Formula (I) and the formulae depicted hereinafter are intended to represent all individual tautomers and all possible mixtures thereof, unless stated or shown otherwise.

The present invention also provides a pharmaceutical composition which comprises a compound in accordance with the invention as described above, or a pharmaceutically acceptable salt or solvate thereof, in association with one or more pharmaceutically acceptable carriers.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical, ophthalmic or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogenphosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles or preservatives. The preparations may also contain buffer salts, flavouring agents, colouring agents or sweetening agents, as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compound of formula (I) may be formulated for parenteral administration by injection, e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoules or multi-dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compound of formula (I) may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds according to the present invention may be conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, fluorotrichloromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

For topical administration the compounds according to the present invention may be conveniently formulated in a suitable ointment containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, liquid petroleum, propylene glycol, polyoxyethylene, polyoxypropylene, emulsifying wax and water. Alternatively, the compounds according to the present invention may be formulated in a suitable lotion containing the active component suspended or dissolved in one or more pharmaceutically acceptable carriers. Particular carriers include, for example, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, benzyl alcohol, 2-octyldodecanol and water.

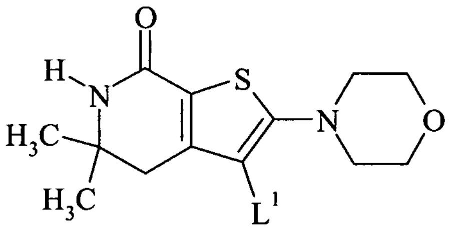
For ophthalmic administration the compounds according to the present invention may be conveniently formulated as microionized suspensions in isotonic, pH-adjusted sterile saline, either with or without a preservative such as a bactericidal or fungicidal agent, for example phenylmercuric nitrate, benzylalkonium chloride or chlorhexidine acetate. Alternatively, for ophthalmic administration compounds may be formulated in an ointment such as petrolatum.

For rectal administration the compounds according to the present invention may be conveniently formulated as suppositories. These can be prepared by mixing the active component with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and so will melt in the rectum to release the active component. Such materials include, for example, cocoa butter, beeswax and polyethylene glycols.

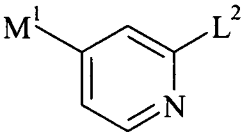
The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen and the condition of the patient to be treated. In general, however, daily dosages may range from around 10 ng/kg to 1000 mg/kg, typically from 100 ng/kg to 100 mg/kg, e.g. around 0.01 mg/kg to 40 mg/kg body weight, for oral or buccal administration, from around 10 ng/kg to 50 mg/kg body weight for parenteral administration, and from around 0.05 mg to around 1000 mg, e.g. from around 0.5 mg to around 1000 mg, for nasal administration or administration by inhalation or insufflation.

The compound of formula (I) as depicted above may be prepared by a process which comprises the following steps:

(i) reacting a compound of formula (III) with a compound of formula (IV):

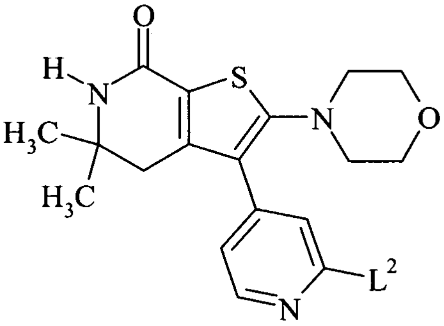


(III)



(IV)

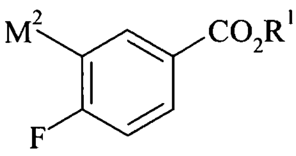
wherein $L^1$ and $L^2$ independently represent a suitable leaving group, and $M^1$ represents a boronic acid moiety -$B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol; in the presence of a transition metal catalyst; to provide a compound of formula (V):



(V)

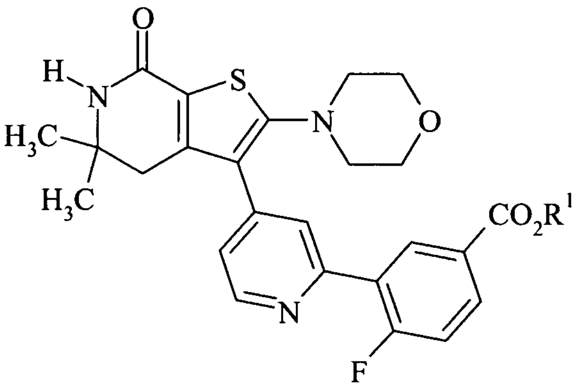
wherein $L^2$ is as defined above;

(ii) reaction of the compound of formula (V) with a compound of formula (VI):



(VI)

wherein $R^1$ represents $C_{1-6}$ alkyl, and $M^2$ represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol; in the presence of a transition metal catalyst; to provide a compound of formula (VII):



(VII)

wherein $R^1$ is as defined above;

(iii) saponification of the ester functionality $-CO_2R^1$ to provide a compound of formula (VII) as depicted above wherein $R^1$ represents hydrogen; and

(iv) reaction of the resulting carboxylic acid derivative with morpholine.

The leaving group $L^1$ is typically a halogen atom, e.g. iodo.

The leaving group $L^2$ is typically a halogen atom, e.g. chloro.

Suitably, $R^1$ represents methyl.

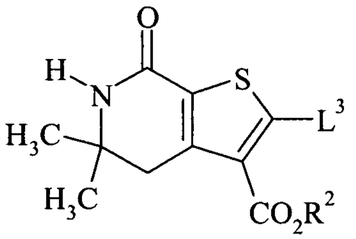
The transition metal catalyst of use in steps (i) and (ii) above is suitably tetrakis(triphenylphosphine)palladium(0), in which case the transformation may conveniently be effected at an elevated temperature in the presence of a base such as sodium carbonate, potassium carbonate or potassium phosphate, in an inert solvent such as 1,2-dimethoxyethane, tetrahydrofuran or 1,4-dioxane, optionally in the presence of tetra-*n*-butylammonium bromide.

Saponification of the compound of formula (VII) in step (iii) above may suitably be accomplished by treatment with a base such as lithium hydroxide. The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. an ethereal solvent such as aqueous tetrahydrofuran.

Reaction of the resulting carboxylic acid derivative with morpholine in step (iv) above is suitably effected in the presence of a condensing agent such as *O*-(benzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate (HBTU). The reaction is conveniently carried out at ambient temperature in a suitable solvent, e.g. a chlorinated organic solvent such as dichloromethane.

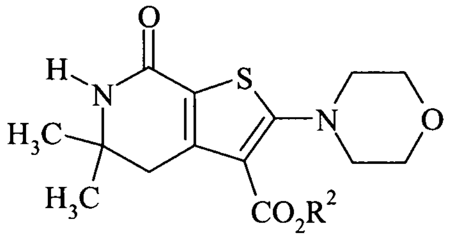
The intermediates of formula (III) above wherein $L^1$ represents iodo may be prepared by a process which comprises the following steps:

(v) reacting a compound of formula (VIII):



(VIII)

wherein $R^2$ represents $C_{1-6}$ alkyl, and $L^3$ represents a suitable leaving group; with morpholine; to provide a compound of formula (IX):



(IX)

wherein $R^2$ is as defined above;

(vi) saponification and decarboxylation to remove the $-CO_2R^2$ functionality; and

(vii) iodination of the product thereby obtained.

The leaving group $L^3$ is typically a halogen atom, e.g. bromo.

Suitably, $R^2$ represents ethyl.

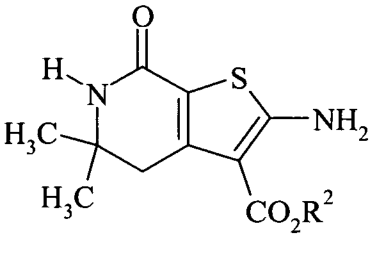
The reaction between compound (VIII) and morpholine in step (v) is conveniently effected at an elevated temperature in a suitable solvent, e.g. acetonitrile, dimethylsulphoxide, a lower alkanol such as isopropanol, a cyclic ether such as tetrahydrofuran, or a dipolar aprotic solvent such as *N,N*-dimethylformamide, optionally under basic conditions, e.g. in the presence of an organic base such as *N,N*-diisopropylethylamine or 2,6-lutidine.

Alternatively, the reaction may be effected at an elevated temperature in a solvent such as 2-ethoxyethanol in the presence of a catalytic quantity of a mineral acid, e.g. concentrated hydrochloric acid.

Saponification and decarboxylation of compound (IX) in step (vi) above may suitably be accomplished by treatment with a base such as lithium hydroxide. The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. an ethereal solvent such as aqueous tetrahydrofuran.

Iodination of the resulting product in accordance with step (vii) may suitably be accomplished by treatment with an iodinating agent such as *N*-iodosuccinimide. The reaction is conveniently effected at ambient temperature in a suitable solvent, e.g. an ethereal solvent such as aqueous tetrahydrofuran.

The intermediates of formula (VIII) above wherein $L^3$ is bromo may be prepared from a compound of formula (X):

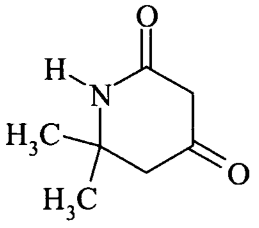


(X)

wherein $R^2$ is as defined above; by diazotization/bromination.

The reaction is conveniently effected by stirring compound (X) with *tert*-butyl nitrite and copper(II) bromide in a suitable solvent, e.g. acetonitrile.

The intermediates of formula (X) above may be prepared by reacting a compound of formula $R^2O_2C\text{-}CH_2\text{-}CN$ with the compound of formula (XI):



(XI)

wherein $R^2$ is as defined above; in the presence of sulphur.

The reaction is conveniently effected at an elevated temperature in a suitable solvent, e.g. a lower alkanol such as ethanol, typically under basic conditions, e.g. in the presence of morpholine.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at any convenient subsequent stage utilising methods known from the art.

The following Example illustrates the preparation of a compound according to the invention.

The compounds in accordance with this invention potently inhibit the activity of at least one human PI3K isoform.

*Enzyme Inhibition Assays*

Measurement of the ability of compounds to inhibit the lipid kinase activity of the four class 1 PI3 kinase isoforms (α, β, γ and δ) was performed using a commercially available homogeneous time-resolved fluorescence assay as described by Gray *et al.*, *Anal. Biochem.*, 2003, **313**, 234-245, according to the manufacturer's instructions (Upstate). All assays were performed at 2 μM ATP and a concentration of purified class 1 PI3 kinase known to generate product within the linear range of the assay. Dilutions of inhibitor in DMSO were added to the assay and compared with assays run in the presence of 2% (v/v) DMSO alone (100% activity). The concentration of inhibitor required to inhibit the enzyme activity by 50% is quoted as the $IC_{50}$.

When tested in the above assay, the compound of accompanying Example 1 was found to possess an $IC_{50}$ value for inhibition of activity of at least one human PI3K isoform of better than 100 nM.

## EXAMPLES

### Abbreviations

EtOAc: ethyl acetate
DMSO: dimethylsulphoxide
$Et_2O$: diethyl ether
MeCN: acetonitrile
IPA: isopropyl alcohol
Me: methyl
DCM: dichloromethane
DME: ethylene glycol dimethyl ether
EtOH: ethanol
THF: tetrahydrofuran
NIS: *N*-iodoosuccinimide
AcOH: acetic acid
HBTU: *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
sat.: saturated
$SiO_2$: silica
M: mass
r.t.: room temperature
h: hour
brine: saturated aqueous sodium chloride solution
HPLC: High Performance Liquid Chromatography
LCMS: Liquid Chromatography Mass Spectrometry
ES+: Electrospray Positive Ionisation

### Analytical Conditions

All NMRs were obtained either at 300 MHz or 400 MHz.

Compounds were named with the aid of ACD Labs Name (v. 9.0 or 10.0) supplied by Advanced Chemical Development, Toronto, Canada.

All reactions involving air- or moisture-sensitive reagents were performed under a nitrogen atmosphere using dried solvents and glassware. Degassing was performed by bubbling nitrogen through the reaction mixture.

Compounds that required preparative HPLC were purified using *Method 1* below.

*Method 1*: Phenomenex Luna C18(2) 250 × 21.2 mm, 5 µm column. Mobile phase A: 99.92% water, 0.08% formic acid. Mobile phase B: 99.92% MeCN, 0.08%

formic acid. Gradient program (flow rate 25.0 mL/min), column temperature: ambient, variable gradient.

## INTERMEDIATE 1

Ethyl 2-amino-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a stirred solution of sulphur (1.0 g, 31.0 mmol), 6,6-dimethylpiperidine-2,4-dione (4.0 g, 28.0 mmol) and ethyl cyanoacetate (3.7 g, 3.5 mL, 29.0 mmol) in EtOH (20 mL) at 45°C was added morpholine (2.9 g, 2.9 mL, 33.0 mmol) dropwise over 15 minutes. The reaction mixture was stirred at this temperature for 15 minutes and then at 65°C for 48 h before it was cooled and concentrated *in vacuo.* To the residue was added water, and the resulting solid was filtered and washed with water to give the *title compound* (4.1 g, 54%) as a pale brown solid. $\delta_H$ (DMSO-$d_6$) 7.86 (s, 2H), 7.28 (s, 1H), 4.21 (q, *J* 7.0 Hz, 2H), 2.88 (s, 2H), 1.27 (t, *J* 7.1 Hz, 3H), 1.23 (s, 6H). LCMS (ES+) 269.1 $(M+H)^+$.

## INTERMEDIATE 2

Ethyl 2-bromo-5,5-dimethyl-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a stirred suspension of *Intermediate 1* (0.20 g, 0.75 mmol) in MeCN (5 mL) at 0-5°C was added copper(II) bromide (0.20 g, 0.90 mmol) followed by *tert*-butyl nitrite (0.10 mL, 0.80 mmol) dropwise. The reaction mixture was stirred at this temperature for 10 minutes before it was partitioned between EtOAc (50 mL) and water (50 mL). The organics were separated, washed with water (3 x 20 mL) and brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo.* The crude residue was washed with $Et_2O$ to give the *title compound* (0.15 g, 61%) as a pale brown solid. $\delta_H$ (DMSO-$d_6$) 8.53 (s, 1H), 4.32 (q, *J* 7.0 Hz, 2H), 3.10 (s, 2H), 1.33 (t, *J* 7.1 Hz, 3H), 1.26 (s, 6H). LCMS (ES+) 332.0, 334.0 $(M+H)^+$.

## INTERMEDIATE 3

Ethyl 5,5-dimethyl-2-(morpholin-4-yl)-7-oxo-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3-carboxylate

To a stirred solution of *Intermediate 2* (1.40 g, 4.10 mmol) in IPA (25 mL) at r.t. was added morpholine (1.0 mL, 11.50 mmol) and the reaction mixture was heated at 60°C for 48 h. After cooling, the mixture was partitioned between EtOAc (100 mL) and water (50 mL). The organics were separated, washed with water (2 x 20 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. The residue was then purified by column chromatography ($SiO_2$, EtOAc) to give the *title compound* (1.0 g, 76%) as an off-white solid. $\delta_H$ (DMSO-$d_6$) 7.58 (s, 1H), 4.23 (q, *J* 7.2 Hz, 2H), 3.71-3.78 (m, 4H), 3.14-3.21 (m, 4H), 2.89 (s, 2H), 1.28 (t, *J* 7.0 Hz, 3H), 1.23 (s, 6H). LCMS (ES+) 339.0 $(M+H)^+$.

## INTERMEDIATE 4

5,5-Dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

To a stirred solution of *Intermediate 3* (0.86 g, 2.50 mmol) in THF (9 mL) and water (8 mL) at r.t. was added LiOH (0.16 g, 3.80 mmol). The reaction mixture was then heated at 60°C for 48 h before it was cooled and concentrated *in vacuo*. To the residue was added aqueous 2M HCl (8 mL) and the reaction mixture was stirred at r.t. for 6 h before it was cooled and basified to pH 10 by the addition of aqueous sat. $Na_2CO_3$. The resulting solid was filtered and dried to give the *title compound* (0.52 g, 80%) as a white powder. $\delta_H$ (DMSO-$d_6$) 7.18 (s, 1H), 6.08 (s, 1H), 3.69-3.77 (m, 4H), 3.12-3.19 (m, 4H), 2.63 (s, 2H), 1.21 (s, 6H). LCMS (ES+) 267.0 $(M+H)^+$.

## INTERMEDIATE 5

3-Iodo-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

To a stirred solution of *Intermediate 4* (0.45 g, 1.67 mmol) in THF (20 mL) at r.t. was added NIS (0.39 g, 1.76 mmol). After stirring for 2 h, $Na_2CO_3$ (2.00 g, 18.87 mmol) was added and the reaction mixture was stirred for a further minute, prior to the addition of sat. aqueous $Na_2CO_3$ (10 mL). The resulting solid was filtered and washed with water and $Et_2O$ to give the *title compound* (0.35 g, 53%) as a white solid. $\delta_H$ (DMSO-$d_6$) 7.65 (s, 1H), 3.72-3.79 (m, 4H), 3.04-3.10 (m, 4H), 2.65 (s, 2H), 1.25 (s, 6H). LCMS (ES+) 393.0 $(M+H)^+$.

## INTERMEDIATE 6

3-(2-Chloropyridin-4-yl)-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

A mixture of *Intermediate 5* (1.0 g, 2.55 mmol), 2-chloropyridine-4-boronic acid (0.41 g, 2.61 mmol), potassium phosphate (0.55 g, 2.59 mmol) and tetra-*n*-butyl-ammonium bromide (0.82 g, 2.55 mmol) in DME (30 mL) and water (9 mL) was degassed for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.3 g, 2.60 mmol) was added and the reaction mixture was heated to 90°C for 24 h. Sat. $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The solvent was removed *in vacuo* and the residue purified by column chromatography ($SiO_2$, 30-75% EtOAc in heptane) to give the *title compound* (220 mg, 23%) as a cream solid. $\delta_H$ ($CD_3OD$) 8.41-8.47 (m, 1H), 7.44-7.70 (m, 3H), 3.69-3.77 (m, 4H), 2.94-3.02 (m, 4H), 2.75 (s, 3H), 1.32 (s, 6H). LCMS (ES+) 378.2, 380.2 $(M+H)^+$.

## EXAMPLE 1

3-{2-[2-Fluoro-5-(morpholin-4-ylcarbonyl)phenyl]pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one

A mixture of *Intermediate 6* (1.0 g, 2.65 mmol), (2-fluoro-5-methoxycarbonyl-phenyl)boronic acid (524 mg, 2.65 mmol), tetrakis(triphenylphosphine)palladium(0) (152 mg, 0.13 mmol) and a solution of potassium phosphate tribasic (1.13 g, 5.32 mmol) in water (1.7 mL) was degassed. DME (8 mL) was added and the mixture was degassed further. The reaction mixture was heated at 130°C under microwave irradiation for 2 h. The solvent was removed *in vacuo* and the residue purified by column chromatography ($SiO_2$, 0-100% EtOAc in heptane). The product obtained was combined with lithium hydroxide monohydrate (329 mg, 7.88 mmol) in THF (30 mL) and water (5 mL) and stirred at r.t. overnight. The solvent was removed *in vacuo* and the residue was extracted with DCM (3 x 30 mL). The aqueous phase was acidified to pH 4 and extracted with further DCM (3 x 30 mL). The combined organic phases were dried ($MgSO_4$) and evaporated *in vacuo*. A sample of the residue was purified by preparative HPLC (*Method 1*). A sample of the purified material (38 mg, 0.08 mmol) was dissolved in DCM (4 mL). HBTU (60 mg, 0.16 mmol) and morpholine (0.01 mL, 0.16 mmol) were added and the reaction mixture stirred at r.t. overnight. It was then diluted with water and extracted with DCM (2 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by preparative HPLC (*Method 1*) to give the *title compound* (44 mg, 18%) as a yellow-orange solid. $\delta_H$ (DMSO-$d_6$) 8.80 (d, *J* 5.1 Hz, 1H), 8.05 (dd, *J* 7.5, 2.3 Hz, 1H), 7.95 (s, 1H), 7.43-7.62 (m, 4H), 3.52-3.73 (m, 12H), 2.86-2.95 (m, 4H), 2.71 (s, 2H), 1.20 (s, 6H). LCMS (ES+) 551.3 $(M+H)^+$.

## Claims:

1. 3-{2-[2-Fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof.

2. A pharmaceutical composition comprising 3-{2-[2-fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof, in association with a pharmaceutically acceptable carrier.

3. 3-{2-[2-Fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

4. 3-{2-[2-Fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

5. The use of 3-{2-[2-fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated.

6. A method for the treatment and/or prevention of a disorder for which the administration of a selective PI3K inhibitor is indicated which comprises administering to a patient in need of such treatment an effective amount of 3-{2-[2-fluoro-5-(morpholin-4-ylcarbonyl)phenyl]-pyridin-4-yl}-5,5-dimethyl-2-(morpholin-4-yl)-5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one, or a pharmaceutically acceptable salt or solvate thereof.

## INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/004018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D495/04 A61K31/4365 A61P29/00

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)
C07D A61K A61P

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

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

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 2007/141504 A (UCB PHARMA SA [BE]; ALEXANDER RIKKI PETER [GB]; BAILEY STUART [GB]; BR) 13 December 2007 (2007-12-13)<br>cited in the application<br>Claim 2, formula (IA); claims 1,8<br>----- | 1-6 |
| A | WO 2007/127175 A (PIRAMED LTD [GB]; GENENTECH INC [US]; GOLDSMITH RICHARD [US]; FOLKES A)<br>8 November 2007 (2007-11-08)<br>page 2, line 17 - line 20; claim 1<br>----- | 1-6 |

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

☒ See patent family annex.

* Special categories of cited documents :

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

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|---|---|
| Date of the actual completion of the international search<br>23 January 2009 | Date of mailing of the international search report<br>02/02/2009 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Authorized officer<br>Johnson, Claire |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2008/004018

| Patent document cited in search report | | Publication date | Patent family member(s) | | | Publication date |
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| WO 2007127175 | A | 08-11-2007 | AR | 060633 | A1 | 02-07-2008 |
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