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ORIGINAL
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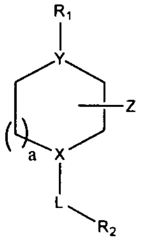
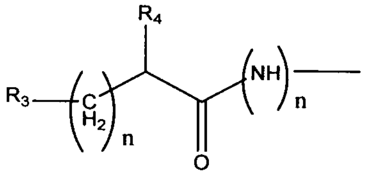
Abstract

NOVEL COMPOUNDS FOR INHIBITION OF AKT KINASE

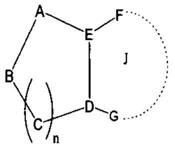
The present invention provides novel AKT inhibitor compounds of formula I



wherein
a=1 or 2
X and Y is each independently selected from C, O or N.
X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group
Z is H or Alkyl
R_1 = H or



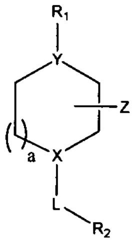
wherein
n=0 to 2
R_3= aryl optionally substituted by a halogen or an alkylene group;
R_4 is a group selected from hydrogen, amine, substituted amine or an amino alkyl group;
R_2 is



wherein A, B, C, D and E are independently selected from H, $-CH_2$, a heteroatom such as C, O, N or S;
n is 1 to 2;
with the proviso that:
A, B, C, D, E forms a 5 or 6 membered aromatic ring and at least one of A, B, C, D, E is Nitrogen;
AB C D E is optionally substituted by one or more groups selected from amino, N-alkyl amino oxo, alkoxy, hydroxyl or hydroxy alkyl group;
G and F are independently selected from the group comprising hydrogen, amino, alkoxy, hydroxyl-alkyl or an acetamide group or
G and F may be fused to form a 5 membered ring "J";
wherein the Ring J represents pyrrole ring or imidazole ring optionally substituted by one or more substituents independently selected from H, alkyl, hydroxyalkyl or halogen.
wherein the valency of fused heterocyclic ring is satisfied by corresponding double bonds as and where applicable.

We Claim:

1. A compound of general formula [I]



wherein

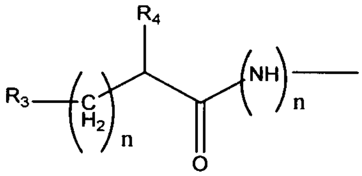
a=1or 2

X and Y is each independently selected from C, O or N;

X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group;

Z is H or Alkyl;

R_1 = H or



wherein

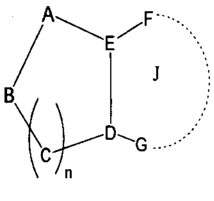
n=0 to 2

R_3= an alkylene group or an aryl optionally substituted by a halogen;

R_4 is a group selected from hydrogen, amine, substituted amine, an amino alkyl group or

$-CH_2-NH-CH(CH_3)_2$;

R_2 is



wherein A, B, C, D and E are independently selected from H, $-CH_2$, a heteroatom such as C, O, N or S;

n is 1 to 2;

with the proviso that:

A, B, C, D, E forms a 5 or 6 membered aromatic ring and at least one of A, B, C, D, E is Nitrogen;

A B C D E is optionally substituted by one or more groups selected from amino, oxo, N-alkyl amino, alkoxy or hydroxyl alkyl group;

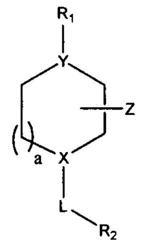
G and F are independently selected from the group comprising hydrogen, amino, alkoxy, hydroxyl-alkyl or an acetamide group or

G and F may be fused to form a 5 membered ring "J";

wherein the Ring J represents pyrrole ring or imidazole ring optionally substituted by one or more substituents independently selected from H, alkyl, hydroxyalkyl or halogen.

wherein the valency of fused heterocyclic ring is satisfied by corresponding double bonds as and where applicable.

2. The compound of general formula [I] as claimed in claim 1,



FORMULA I

wherein

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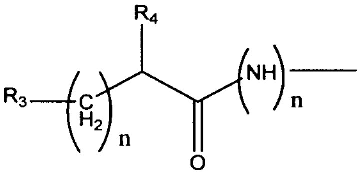
X and Y is each independently selected from C, O or N;

X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group;

Z is H or Alkyl;

R_1=H or

R_1 is



wherein

n= 0 to 2

R_3= halophenyl, phenyl group or alkylene group;

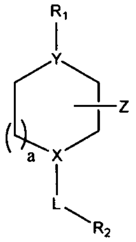
R_4 is a group selected from hydrogen, amine, substituted amine, an amino alkyl group or

-CH_2-NH-$CH(CH_3)_2$;

X and R_2 may be linked directly or indirectly through a linking group L, which may be selected from an Oxygen atom or a CO group

R_2 may be selected from aromatic or non-aromatic heterocyclic amines or fused heterocyclic amines optionally substituted by one or more groups selected from amines, substituted amines, alcohol and alkyl groups.

3. The compound of formula [I] as claimed in claim 1,



FORMULA I

wherein

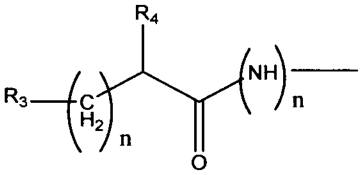
a=1or 2

X and Y is each independently selected from C, O or N;

X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group;

Z is H or Alkyl;

R_1=H; or



wherein

n= 0 to 2

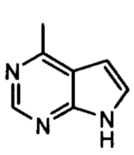
R_3= chlorophenyl, phenyl or methylene;

R_4 is a group selected from hydrogen, amine, isopropylamine , N-methyl amine, N-propyl amine or -CH_2-NH-$CH(CH_3)_2$;

X and R_2 may be linked directly or indirectly through a linking group L, which may be selected from an Oxygen atom or a CO group;

selected from an Oxygen atom or a CO group;

R_2 may be selected from optionally substituted heterocyclic amines selected from:



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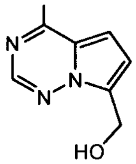

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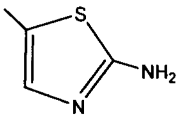

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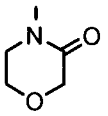

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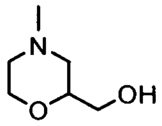

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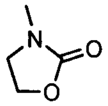

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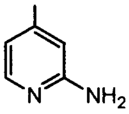

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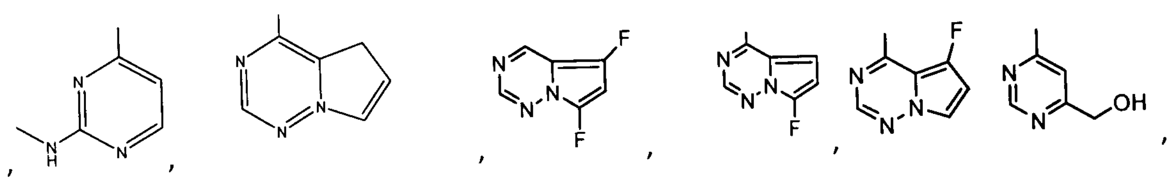
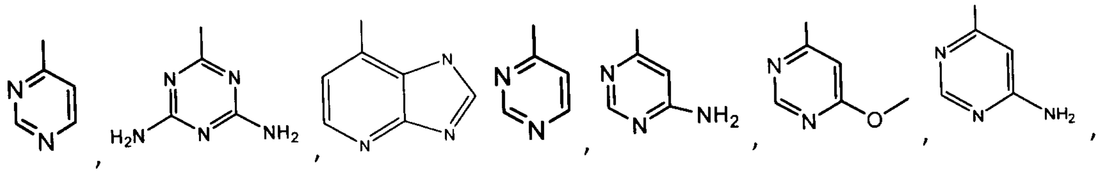
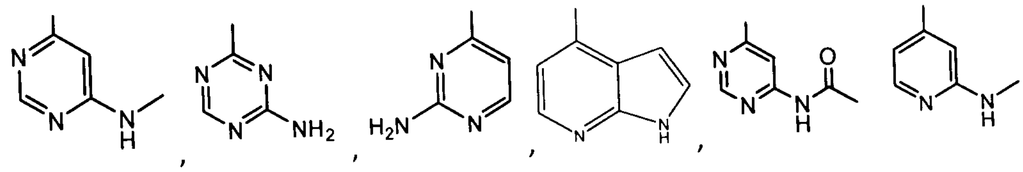






4. The compound as claimed in claim 1, wherein the compound is selected from the group comprising:

   i. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-3-phenylpropan-1-one
   ii. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-3-methylpiperazin-1-yl)-3-phenylpropan-1-one
   iii. 2-amino-1-(4-(4-amino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one
   iv. 1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one
   v. 2-amino-1-(4-(2,4-diamino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one
   vi. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-piperazin-1-yl)-3-phenylpropan-1-one
   vii. 1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)ethanone
   viii. 4-(piperazin-1-yl)pyrimidin-2-amine
   ix. (R)-1-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one

x. N-methyl-4-(piperazin-1-yl)pyrimidin-2-amine

xi. 6-(piperazin-1-yl)pyrimidin-4-amine

xii. 1-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xiii. 4-(piperazin-1-yl)pyrrolo[1,2-f][1,2,4]triazine

xiv. 1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xv. (R)-2-amino-1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xvi. (R)-1-(4-(1H-pyrrolo[2,3-b]pyridin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one

xvii. 2-amino-1-(4-(2-(methylamino) pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xviii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xix. 1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-amine

xx. (4-(piperazin-1-yl)pyrrolo[1,2-f][1,2,4]triazin-7-yl)methanol

xxi. (R)-N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-amino-3-phenylpropanamide

xxii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-methoxypyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxiii. 1-(4-(6-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxiv. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)propan-1-one

xxv. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(2-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxvi. (4-(piperazin-1-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)methanol

xxvii. 1-(4-(3H-imidazo[4,5-b]pyridin-7-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxviii. 2-(4-chlorophenyl)-1-(4-(7-(hydroxymethyl)pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxix. N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propanamide

xxx. 1-(4-(7,7a-dihydro-4aH-pyrrolo[2,3-d]pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxxi. 2-(4-chlorophenyl)-1-(4-(6-(hydroxymethyl)pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)-1,4-diazepan-1-yl)propan-1-one

xxxiii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxxiv. N-(6-(4-(2-(4-chlorophenyl)-3-(isopropylamino)propanoyl)piperazin-1-yl)pyrimidin-4-yl)acetamide

xxxv. 4-(piperidin-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

xxxvi. 2-(4-chlorophenyl)-1-(4-(7-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxvii. 2-(4-chlorophenyl)-1-(4-(5-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxviii. 2-(4-chlorophenyl)-1-(4-(2-(hydroxymethyl)morpholino)piperidin-1-yl)-3-(isopropylamino)propan-1-one

xxxix. 2-(4-chlorophenyl)-1-(4-(5,7-difluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xl. 1-(4-(6-(methylamino)pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino) propan-1-one

xli. 1-(4-(6-(methylamino)pyrimidin-4-ylamino)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xlii. (R)-2-amino-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xliii. 1-(4-(2-aminopyridin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xliv. 1-(4-(2-aminothiazole-5-carbonyl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xlv. 3-(N-isopropyl-N-methylamino)-2-(4-chlorophenyl)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

5. The compound of claim 1, when present as its stereoisomer or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant or vehicle.

6. A pharmaceutical composition comprising any compound as claimed in claims 1 to 5.

7. The compound as claimed in claim 1, for their use in ameliorating a disorder or condition by inhibition of AKT.
8. The compound as claimed in claims 1 to 5 when administered in a dose of 0.01 to 100mg/Kg of body weight of the mammal.

Dated, this 27th day of January, 2014.

CHITRA ARVIND
OF RAJESHWARI & ASSOCIATE
AGENT FOR THE APPLICANT(S)

FIELD OF THE INVENTION

The present invention relates to novel compounds having AKT kinase inhibitory activity and a process of preparation thereof.

BACKGROUND OF THE INVENTION

AKT is a serine/threonine protein kinase and is also known as Protein Kinase B (PKB) that plays a key role in multiple cellular processes such as glucose metabolism, cell proliferation, apoptosis, transcription and cell migration.

In mammals, there are three genes in the "AKT family": AKT1, AKT2, and AKT3. AKT1 is involved in cellular survival pathways, by inhibiting apoptotic processes. AKT1 is capable of inducing protein synthesis pathways, and is therefore a key signaling protein in the cellular pathways that lead to skeletal muscle hypertrophy, and general tissue growth. Since it can block apoptosis, and thereby promote cell survival, AKT1 has been implicated as a major factor in many pathways inducing cancer. AKT2 is an important signaling molecule in the Insulin signaling pathway. It is required to induce glucose transport. The role of AKT3 is less clear, though it appears to be predominantly expressed in the brain.

AKT is involved in the PI3K/AKT/mTOR pathway and other signaling pathways. AKT is directly activated by phosphorylation by its activating kinases at threonine 308 and at serine 473. Phosphorylation of both sites on AKT is necessary for activation, but phosphorylation at threonine 308 only stabilises the activation loop while the site at serine 473 is necessary for full activation (Alessi et al, (1996) EMBO J. 15 (23): 6541-51; Blume-Jensen et al, (2001) Nature 411(6835): 355-65). Activated AKT then proceeds to activate or deactivate its myriad substrates (e.g. mTOR) via its kinase activity. PI3K dependent AKT activation can be regulated through the tumor suppressor PTEN. PTEN acts as a phosphatase to dephosphorylate PtdIns (3,4,5)P3 back to PtdIns(4,5)P2. This removes the membrane-localization factor from the AKT signaling pathway. Without this localization, the rate of AKT activation decreases significantly, as do the all the downstream pathways that depend on AKT for activation.

AKT activation and signaling promotes cell survival, growth and proliferation. AKT regulates cellular survival and metabolism by binding and regulating many downstream effectors, e.g. Nuclear Factor-κB, Bcl-2 family proteins and murine double minute 2

(MDM2). Increased AKT activation has been implicated in a wide variety of cancers. AKT is believed to contribute to cancerous disease states by inhibiting apoptosis and promoting both angiogenesis and proliferation (Toker et al (2006) Cancer Res. 66(8):3963-3966).

Over expression or amplification of AKT has been associated with certain disorders. The PI3 kinase/AKT pathway is an attractive target for developing anticancer drugs to inhibit proliferation, reverse the repression of apoptosis and surmount resistance to cytotoxic agents in cancer cells. Effective and improved therapeutic agents which inhibit kinases such as AKT are continually needed for developing new and more effective formulations that are aimed at treating diseases associated with dysregulation of the pathways involving AKT.

"AKT inhibitor" refers to a compound which reduces and/or blocks the activity of AKT. The inhibitor may act directly on AKT, for example by preventing phosphorylation of AKT or de-phosphorylating AKT or alternatively, the inhibitor may act via the inhibition of an upstream activator (or multiple activators) of AKT in the PI3K/AKT/mTOR signaling pathway or other pathway involved in apoptosis, or via the activation of a upstream inhibitor of AKT. It is preferred that the AKT inhibitor acts to reduce and/or block the activity of AKT via multiple pathways such that effective inhibition is achieved. Such a compound may, for example, act by inhibition of up-stream effectors/activators of AKT in both the PI3K pathway and the mTOR pathway. Additionally, the inhibitor of AKT may act to prevent or reduce the transcription, translation, post-translational processing and/or mobilisation of AKT (i.e. reduce the expression of AKT), or an upstream activator of the expression of AKT. "AKT inhibitor" may also be a compound that counteracts the survival mechanism modulated by AKT activity by acting downstream of AKT to overcome the action of increased AKT activity.

Several classes of compounds have been disclosed in various prior art documents as AKT kinase inhibitors.

WO 2006/071819 (Exelixis) discloses a class of [lH-pyrazolo[3,4-d]pyrimidin-4-yl]piperidine compounds as inhibitors of AKTl, AKT2 and P70S6K. The compounds are stated to be useful for the treatment of immunological, inflammatory and proliferative diseases.

A series of substituted piperidine compounds having AKT inhibitory activity are disclosed in a number of patent applications such as US8377937, WO 2008/075109 and US2010120801. These compounds are disclosed for use in the treatment of conditions arising from abnormal cell growth or abnormally arrested cell death, including cancer.

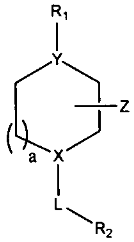
Despite the advances in developing AKT inhibitors, there still remains a need to provide alternative more selective and more potent AKT inhibitors which exhibit better pharmacokinetic properties and fewer side effects in the treatment of proliferative disorders such as cancer.

OBJECT OF THE INVENTION

An object of the invention is to provide novel AKT inhibitors and a process of preparation thereof.

SUMMARY OF THE INVENTION

The present invention provides novel AKT inhibitor compounds of formula I



FORMULA I

wherein

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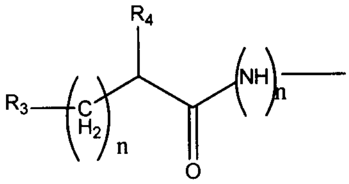

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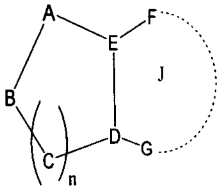
R_3= aryl optionally substituted by a halogen or an alkylene group;

R_4 is a group selected from hydrogen, amine, substituted amine or an amino alkyl group;

R_2 is



wherein A, B, C, D and E are independently selected from H, $-CH_2$, a heteroatom such as C, O, N or S;

n is 1 to 2;

with the proviso that:

A, B, C, D, E forms a 5 or 6 membered aromatic ring and at least one of A, B, C, D, E is Nitrogen;

AB C D E is optionally substituted by one or more groups selected from amino, N-alkyl amino oxo, alkoxy, hydroxyl or hydroxy alkyl group;

G and F are independently selected from the group comprising hydrogen, amino, alkoxy, hydroxyl-alkyl or an acetamide group or

G and F may be fused to form a 5 membered ring “J”;

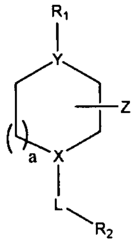
wherein the Ring J represents pyrrole ring or imidazole ring optionally substituted by one or more substituents independently selected from H, alkyl, hydroxyalkyl or halogen.

wherein the valency of fused heterocyclic ring is satisfied by corresponding double bonds as and where applicable.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds that have protein kinase (AKT) inhibiting or modulating activity, and which is envisaged will be useful in preventing or treating disease states or conditions mediated by AKT.

Accordingly, the present invention relates to the AKT inhibitor compounds of formula I



FORMULA I

wherein

a=1or 2

X and Y is each independently selected from C, O or N;

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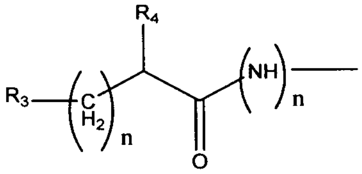
Z is H or Alkyl;

R_1 = H or



wherein

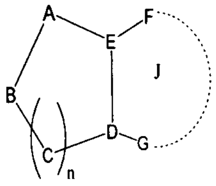
n=0 to 2

R_3= an alkylene group or an aryl optionally substituted by a halogen;

R_4 is a group selected from hydrogen, amine, substituted amine, an amino alkyl group or

$-CH_2-NH-CH(CH_3)_2$;

R_2 is



wherein A, B, C, D and E are independently selected from H, -CH_2, a heteroatom such as C, O, N or S;

n is 1 to 2;

with the proviso that:

A, B, C, D, E forms a 5 or 6 membered aromatic ring and at least one of A, B, C, D, E is Nitrogen;

A B C D E is optionally substituted by one or more groups selected from amino, oxo, N-alkyl amino, alkoxy or hydroxyl alkyl group;

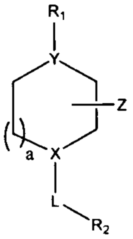
G and F are independently selected from the group comprising hydrogen, amino, alkoxy, hydroxyl-alkyl or an acetamide group or

G and F may be fused to form a 5 membered ring “J”;

wherein the Ring J represents pyrrole ring or imidazole ring optionally substituted by one or more substituents independently selected from H, alkyl, hydroxyalkyl or halogen.

wherein the valency of fused heterocyclic ring is satisfied by corresponding double bonds as and where applicable.

Particularly, the present invention provides AKT inhibitor compounds of formula I



FORMULA I

wherein

a=1or 2

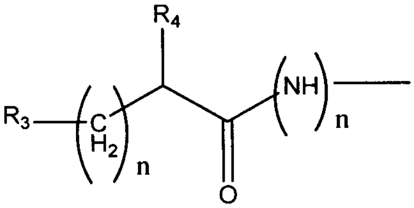
X and Y is each independently selected from C, O or N;

X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group;

Z is H or Alkyl;

R_1=H or

R_1 is



wherein

n= 0 to 2

R_3= halophenyl, phenyl group or alkylene group;

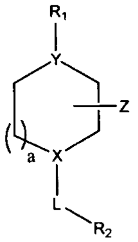
R_4 is a group selected from hydrogen, amine, substituted amine, an amino alkyl group or

$-CH_2-NH-CH(CH_3)_2$;

X and R_2 may be linked directly or indirectly through a linking group L, which may be selected from an Oxygen atom or a CO group

R_2 may be selected from aromatic or non-aromatic heterocyclic amines or fused heterocyclic amines optionally substituted by one or more groups selected from amines, substituted amines, alcohol and alkyl groups.

More particularly, the present invention relates to the AKT inhibitor compounds of formula I



FORMULA I

wherein

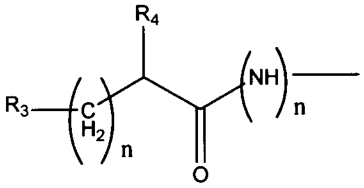
a=1or 2

X and Y is each independently selected from C, O or N;

X and R_2 may be directly attached or attached via a linking group L which may be selected from an Oxygen atom or a CO group;

Z is H or Alkyl;

R_1=H; or



wherein

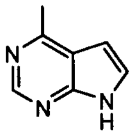
n= 0 to 2

R_3= chlorophenyl, phenyl or ethylene;

R_4 is a group selected from hydrogen, amine, isopropylamine , N-methyl amine, N-propyl amine or $-CH_2-NH-CH(CH_3)_2$;

X and R_2 may be linked directly or indirectly through a linking group L, which may be selected from an Oxygen atom or a CO group;

R_2 may be selected from optionally substituted heterocyclic amines selected from:



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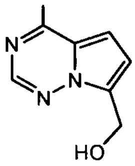

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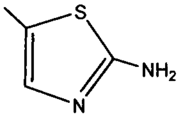

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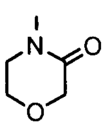

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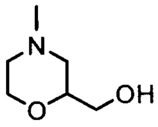

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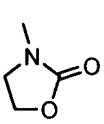

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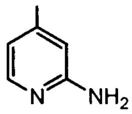

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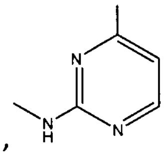

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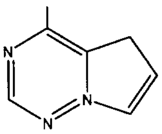

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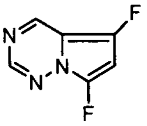

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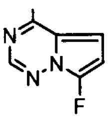

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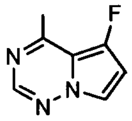

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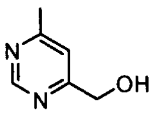

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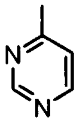

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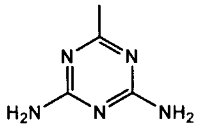

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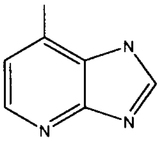

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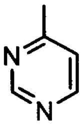

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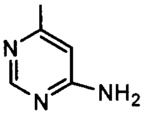

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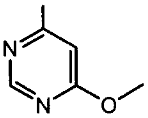

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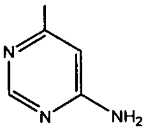

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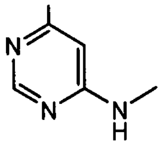

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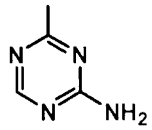

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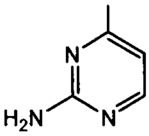

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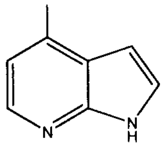

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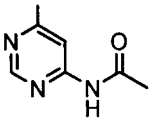

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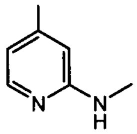

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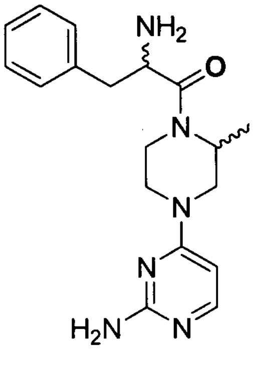
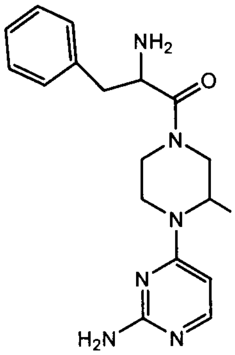
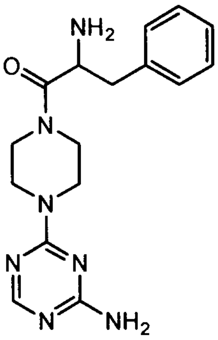
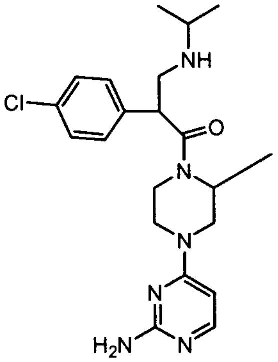
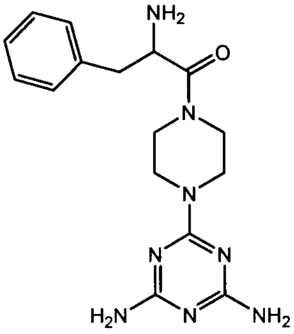
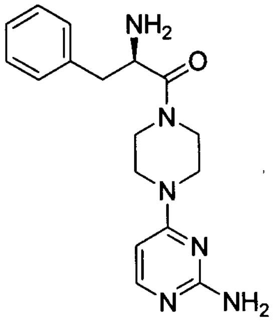
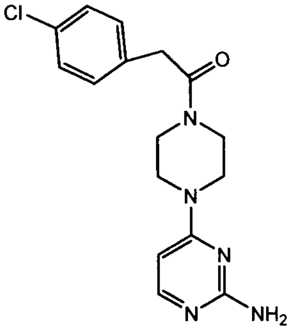
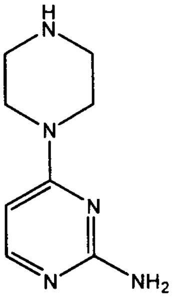
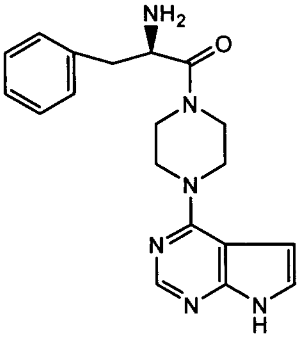
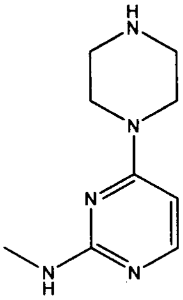
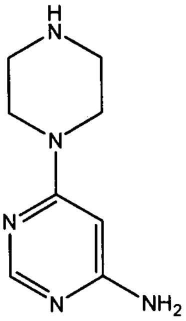
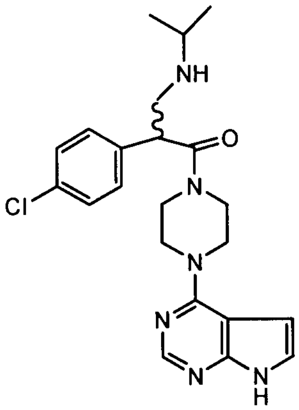
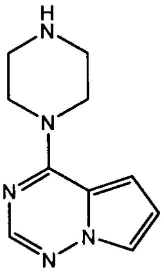
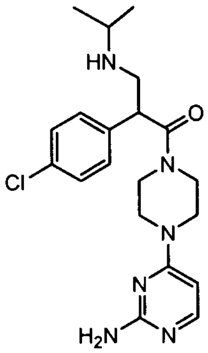
The compounds of the present invention may be illustrated but not limited to the examples as provided in Table 1.

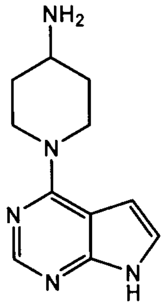
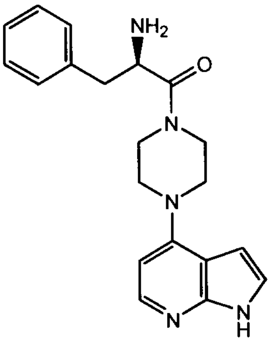
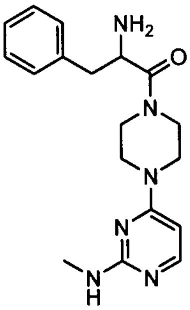
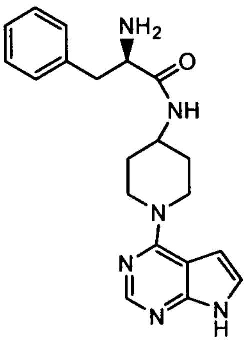
Table 1: Illustrative compounds of the present invention

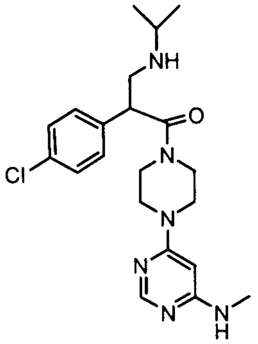
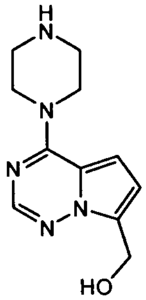
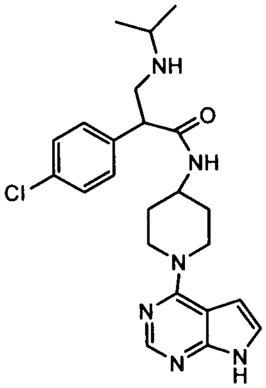
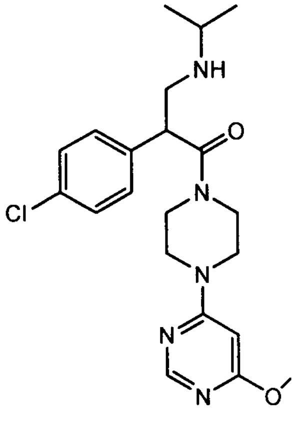
No.	IUPAC name	Structure	AKT1 % Inhib@0.1uM -PRELIM SCREEN HTRF (uM) (Inhibition)	AKT1 % Inhib@10uM -PRELIM SCREEN HTRF (uM) (Inhibition)
10713	2-amino-1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-3-phenylpropan-1-one			

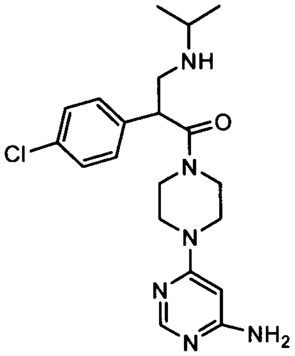
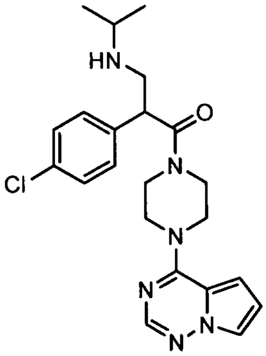
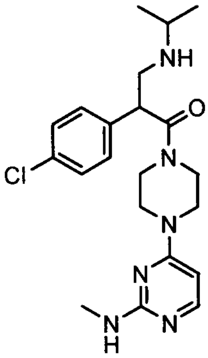
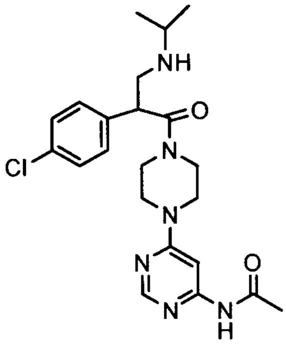
10714	2-amino-1-(4-(2-aminopyrimidin-4-yl)-3-methylpiperazin-1-yl)-3-phenylpropan-1-one			
10715	2-amino-1-(4-(4-amino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one		2	4
10720	1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		65	63
10723	2-amino-1-(4-(2,4-diamino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one			

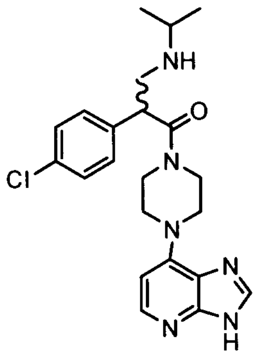
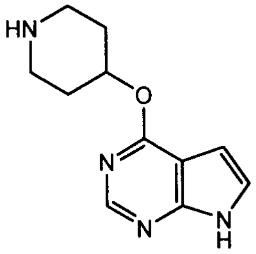
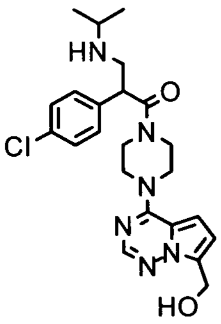
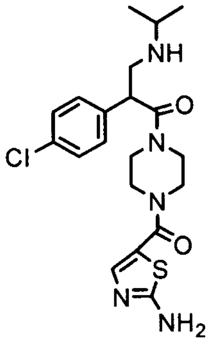
10724	(R)-2-amino-1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one			
10726	1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)ethanone			
10728	4-(piperazin-1-yl)pyrimidin-2-amine		26	77
10730	(R)-1-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one		29	87
10731	N-methyl-4-(piperazin-1-yl)pyrimidin-2-amine			

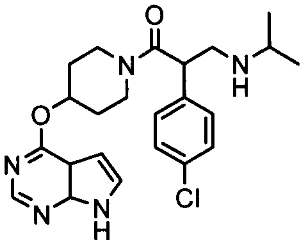
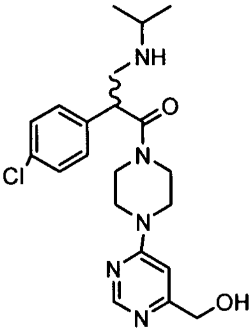
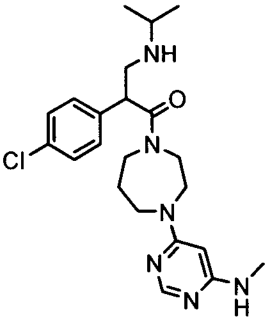
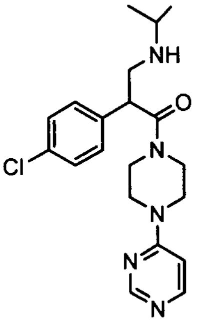
10732	6-(piperazin-1-yl)pyrimidin-4-amine			
10738	1-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one			
10742	4-(piperazin-1-yl)pyrrolo[1,2-f][1,2,4]triazine		0	37
10745	1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		5	50

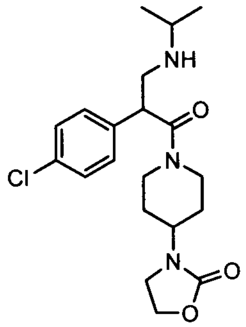
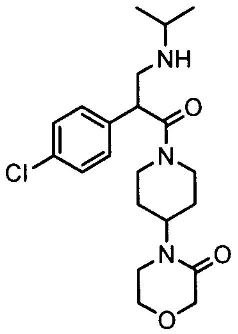
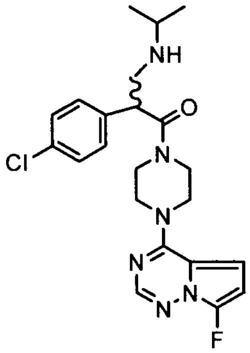
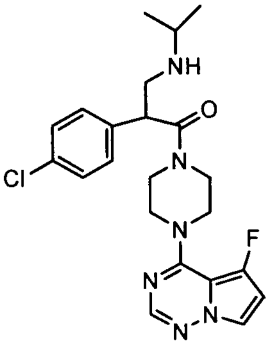
10751	1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-amine		26	77
10753	(R)-1-(4-(1H-pyrrolo[2,3-b]pyridin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one		43	80
10754	2-amino-1-(4-(2-(methylamino) pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one		10	17
10756	(R)-N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-amino-3-phenylpropanamide		12	48

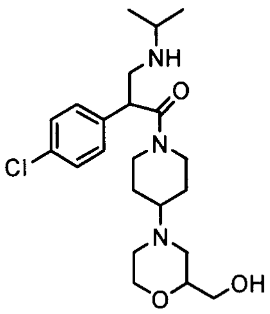
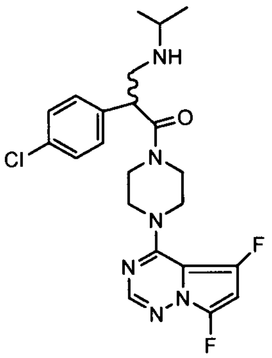
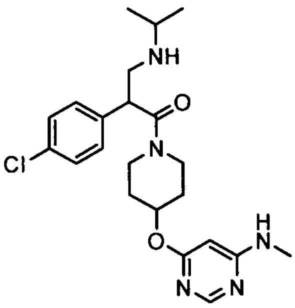
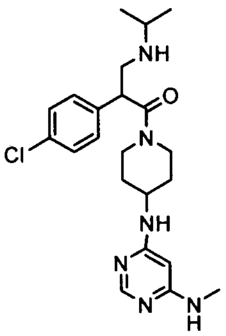
10759	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one		53	82
10760	(4-(piperazin-1-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)methanol		16	46
10761	N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propanamide		5	72
10764	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-methoxypyrimidin-4-yl)piperazin-1-yl)propan-1-one		11	39

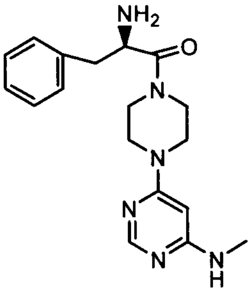
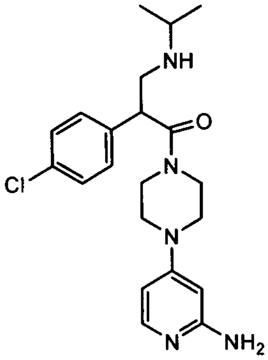
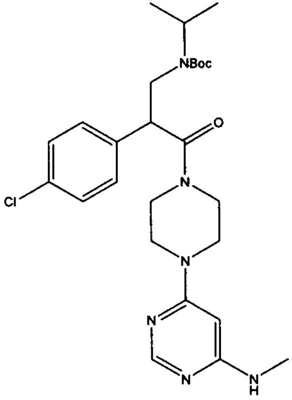
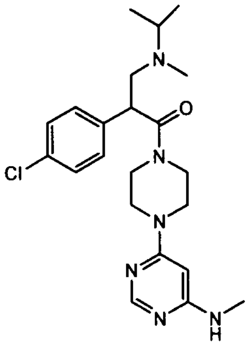
10766	1-(4-(6-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		25	76
10770	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)propan-1-one		31	78
10775	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(2-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one		15	71
10778	N-(6-(4-(2-(4-chlorophenyl)-3-(isopropylamino)propanoyl)piperazin-1-yl)pyrimidin-4-yl)acetamide		11	78

10780	1-(4-(3H-imidazo[4,5-b]pyridin-7-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		59	80
10781	4-(piperidin-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine		21	75
10783	2-(4-chlorophenyl)-1-(4-(7-(hydroxymethyl)pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one		0	63
10787	1-(4-(2-aminothiazole-5-carbonyl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		0	10

10789	1-(4-(7,7a-dihydro-4aH-pyrrolo[2,3-d]pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		58	86
10796	2-(4-chlorophenyl)-1-(4-(6-(hydroxymethyl)pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one		4	58
10814	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)-1,4-diazepan-1-yl)propan-1-one		0	56
10816	2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrimidin-4-yl)piperazin-1-yl)propan-1-one		10	24

10840	3-(1-(2-(4-chlorophenyl)-3-(isopropylamino)propanoyl)piperidin-4-yl)oxazolidin-2-one			
10842	4-(1-(2-(4-chlorophenyl)-3-(isopropylamino)propanoyl)piperidin-4-yl)morpholin-3-one			
10844	2-(4-chlorophenyl)-1-(4-(7-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one		0	34
10848	2-(4-chlorophenyl)-1-(4-(5-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one		33	70

10850	2-(4-chlorophenyl)-1-(4-(2-(hydroxymethyl)morpholino)piperidin-1-yl)-3-(isopropylamino)propan-1-one			
10865	2-(4-chlorophenyl)-1-(4-(5,7-difluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one			
10868	1-(4-(6-(methylamino)pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino) propan-1-one		0	36
10872	1-(4-(6-(methylamino)pyrimidin-4-ylamino)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		0	4

10912	(R)-2-amino-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one		0	44
10917	1-(4-(2-aminopyridin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one		0	36
10961	tert-butyl (2-(4-chlorophenyl)-3-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)-3-oxopropyl)(isopropyl)carbamate			
10992	3-(N-isopropyl-N-methylamino)-2-(4-chlorophenyl)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one			

The compounds of the present invention include:

i. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-3-phenylpropan-1-one

ii. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-3-methylpiperazin-1-yl)-3-phenylpropan-1-one

iii. 2-amino-1-(4-(4-amino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one

iv. 1-(4-(2-aminopyrimidin-4-yl)-2-methylpiperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

v. 2-amino-1-(4-(2,4-diamino-1,3,5-triazin-2-yl)piperazin-1-yl)-3-phenylpropan-1-one

vi. 2-amino-1-(4-(2-aminopyrimidin-4-yl)-piperazin-1-yl)-3-phenylpropan-1-one
vii. 1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)ethanone

viii. 4-(piperazin-1-yl)pyrimidin-2-amine

ix. (R)-1-(4-(7H-pyrrolo[2,3-d] pyrimidin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one

x. N-methyl-4-(piperazin-1-yl)pyrimidin-2-amine

xi. 6-(piperazin-1-yl)pyrimidin-4-amine

xii. 1-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xiii. 4-(piperazin-1-yl)pyrrolo[1,2-f][1,2,4]triazine

xiv. 1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xv. (R)-2-amino-1-(4-(2-aminopyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xvi. (R)-1-(4-(1H-pyrrolo[2,3-b]pyridin-4-yl)piperazin-1-yl)-2-amino-3-phenylpropan-1-one

xvii. 2-amino-1-(4-(2-(methylamino) pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xviii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xix. 1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-amine

xx. (4-(piperazin-1-yl)pyrrolo[1,2-f][1,2,4]triazin-7-yl)methanol

xxi. (R)-N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-amino-3-phenylpropanamide

xxii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-methoxypyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxiii. 1-(4-(6-aminopyrimidin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxiv. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)propan-1-one

xxv. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(2-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxvi. (4-(piperazin-1-yl)pyrrolo[2,1-f][1,2,4]triazin-7-yl)methanol

xxvii. 1-(4-(3H-imidazo[4,5-b]pyridin-7-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxviii. 2-(4-chlorophenyl)-1-(4-(7-(hydroxymethyl)pyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxix. N-(1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propanamide

xxx. 1-(4-(7,7a-dihydro-4aH-pyrrolo[2,3-d]pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xxxi. 2-(4-chlorophenyl)-1-(4-(6-(hydroxymethyl)pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(6-(methylamino)pyrimidin-4-yl)-1,4-diazepan-1-yl)propan-1-one

xxxiii. 2-(4-chlorophenyl)-3-(isopropylamino)-1-(4-(pyrimidin-4-yl)piperazin-1-yl)propan-1-one

xxxiv. N-(6-(4-(2-(4-chlorophenyl)-3-(isopropylamino)propanoyl)piperazin-1-yl)pyrimidin-4-yl)acetamide

xxxv. 4-(piperidin-4-yloxy)-7H-pyrrolo[2,3-d]pyrimidine

xxxvi. 2-(4-chlorophenyl)-1-(4-(7-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxvii. 2-(4-chlorophenyl)-1-(4-(5-fluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xxxviii. 2-(4-chlorophenyl)-1-(4-(2-(hydroxymethyl)morpholino)piperidin-1-yl)-3-(isopropylamino)propan-1-one

xxxix. 2-(4-chlorophenyl)-1-(4-(5,7-difluoropyrrolo[1,2-f][1,2,4]triazin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one

xl. 1-(4-(6-(methylamino)pyrimidin-4-yloxy)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino) propan-1-one

xli. 1-(4-(6-(methylamino)pyrimidin-4-ylamino)piperidin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one xlii. (R)-2-amino-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)-3-phenylpropan-1-one

xliii. 1-(4-(2-aminopyridin-4-yl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xliv. 1-(4-(2-aminothiazole-5-carbonyl)piperazin-1-yl)-2-(4-chlorophenyl)-3-(isopropylamino)propan-1-one

xlv. 3-(N-isopropyl-N-methylamino)-2-(4-chlorophenyl)-1-(4-(6-(methylamino)pyrimidin-4-yl)piperazin-1-yl)propan-1-one

The Compounds of the present invention may be present in their enantiomeric pure forms or their mixtures.

B. Salts and Isomers and counter ions

The present invention includes within its scope the salts and isomers. Compounds of the present invention after being novel may in some cases form salts which are also within the scope of this invention. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an basic moiety such as a amino group). Also included herein are quaternary ammonium salts such as alkyl ammonium salts. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are useful, for example, in isolation or purification steps which may be employed during preparation. Salts of the compounds may be formed, for example, by reacting a compound with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lypholization.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound, including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention.

The present invention also envisages within its scope the effect of selection of suitable counter ions. The present invention includes in its scope, the modification of deuterated compounds. Deuterated compounds are those wherein the compounds have selective incorporation of deuterium in place of hydrogen.

C. Synthesis of the compounds of the present invention.

The present invention also relates to a process of preparing the compounds of formula (I).

D. Composition containing the novel entities of the invention

The invention thus also provides the use of the novel entity as defined herein for use in human or veterinary medicine. The AKT kinase inhibitor compounds of the present invention may be used in the treatment of any disorder related to AKT kinase activity.

The compound for use as a pharmaceutical may be presented as a pharmaceutical formulation.

The invention therefore provides in a further aspect a pharmaceutical formulation comprising the novel compounds of the invention with a pharmaceutically acceptable carrier thereof and optionally other therapeutic and/or prophylactic ingredients. The carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formula and not deleterious to the recipient thereof. Suitably the pharmaceutical formulation will be in an appropriate unit dosage form.

The pharmaceutical formulations may be any formulation and include those suitable for oral, intranasal, intraocular or parenteral (including intramuscular and intravenous) administration. The formulations may, where appropriate, be conveniently presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active compound with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation.

For these purposes the compounds of the present invention may be administered orally, topically, intranasally, intraocularly, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasteral injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, dogs, cats, etc., the compounds of the invention are effective in the treatment of humans.

EXAMPLES

The following examples are representative of the disclosure, and provide detailed methods for preparing the compounds of the disclosure, including the preparation of the intermediate compounds. The preparation of particular compounds of the embodiments is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other agents of the various embodiments. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions.

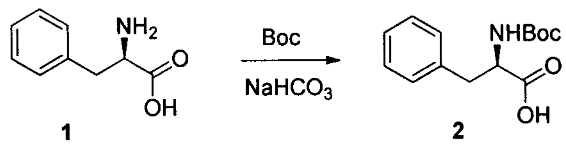
As used herein the symbols and conventions used in these process, schemes and examples, regardless of whether a particular abbreviation is specifically defined, are consistent with those used in the contemporary scientific literature, for example, the Journal of American Chemical Society or the Journal of Biological Chemistry. Specifically, but without limitation, the following abbreviationsmay be used in the examples and throughout the specification:

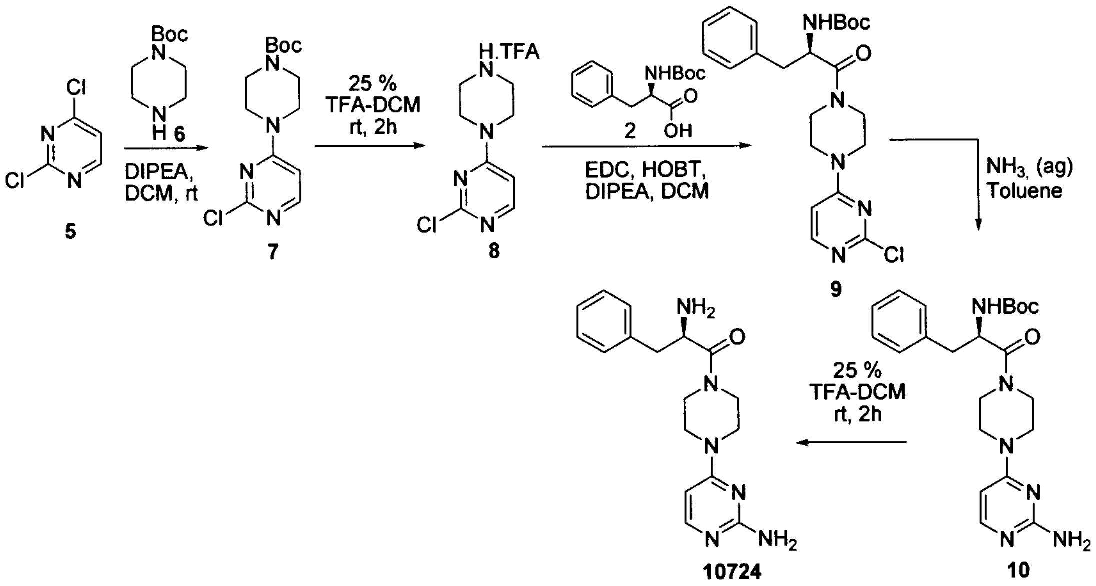
g(grams), mg (milligrams), mL(milli litres)RT or rt (room temperature), mmol (millimoles), DMF (dimethyl formamide), DMSO (dimethylsulfoxide), TLC (thin layer chromatography), EtOH (ethanol), MeOH (methanol), DCM (dichloromethane), THF (tetrahydrofuran), DIPEA(N,N-diisopropylethylamine), TFA(trifluoroacetic acid); TBDMSCI(tert-butylchlorodimethylsilane); TBAF(tetra-n-butylammonium fluoride); $PdCl_2$(dppf), (l,r-bis(diphenylphosphino)ferrocene) dichloropalladium (11)); EDTA(ethylenediaminetetraacetic acid); Me(methyl); Et(ethyl); tBu(tert-butyl); and Boc(Di-*tert*-butyl dicarbonate), HOBT (Hydroxybenzotriazole); EDC(Ethylene dichloride); ACN(Acetonitrile); EtOAc(ethyl acetate); i-PrOH(isopropanol),DMA(dimethyl amine), MNP (2-Methyl-2-nitrosopropane).

For all of the following examples, standard work-up and purification methods known to those skilled in the art may be utilized. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions conducted at room temperature unless otherwise noted. Synthetic methodologies illustrated herein are intended to exemplify the applicable chemistry through the use of specific examples and are not indicative of the scope of the disclosure.

Example 1: Synthesis of Compound 10724

Step 1:Preparation of compound 2 from compound 1:





Compound **1** (2.00 g, 12.12 mmol) was taken in water and $NaHCO_3$ (2.34 g, 24.24mmol) was added to it at 0°C. To this mixture boc anhydride (2.90 g, 13.33 mmol) in THF was added drop wise at 0°C and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction, THF was removed and the aqueous layer was washed with diethyl ether and acidified with citric acid solution (aq) up to PH 4-5. Then extracted with ethyl acetate and the organic layer were dried over Na_2SO_4 and evaporate the solvent to get the pure product **2**. (3.10 g, 97 %, M+1=266)

Step 2: Preparation of compound 7 from compound 5:

To a stirred solution of **5** (5.00 g, 33.78 mmol) in DCM, DIPEA (6.22 mL, 33.78 mmol) and Boc piperazine (6.28 gm, 33.78 mmol) were added and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using ethyl acetate hexane (10-30%) to get the pure product **7** (9.26 g, 92% M+1=299).

<u>Step 3:</u> Preparation of compound 8 from compound 7:

Compound **7** (2.00 g, 6.68 mmol) was taken in 25% TFA-DCM (10 mL) and stirred at for 2 h. Then the solvent was removed under vacuum to get an oily product **8** and used without purification.

<u>Step 4:</u> Preparation of compound 9 from compound 8:

Compound **2** (250.00 mg, 0.836 mmol) was taken in dry DCM, EDC.HCl (239.00 mg, 1.254 mmol), HOBT (124.00 mg, 0.919 mmol) were added under nitrogen and stirred for 30 min at room temperature. The Compound **8** (165 mg, 0.836 mmol) was taken in another round bottom flask and DIPEA (0.462mL, 2.51 mmol) was added. Then the second reaction mixture was added to first reaction mixture slowly and stirred for 12 h at r.t. After that the reaction was diluted with DCM and washed with water and extracted with ethyl acetate and the organic layer was dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using ethyl acetate hexane (20-50%) to get the pure product **9** (462 mg, 82%, M+1=447).

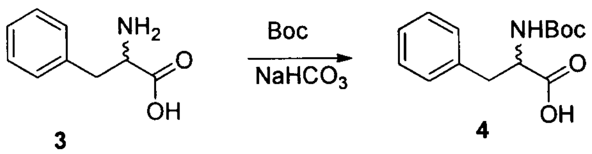
<u>Step 5:</u> Preparation of compound 10 from compound 9:

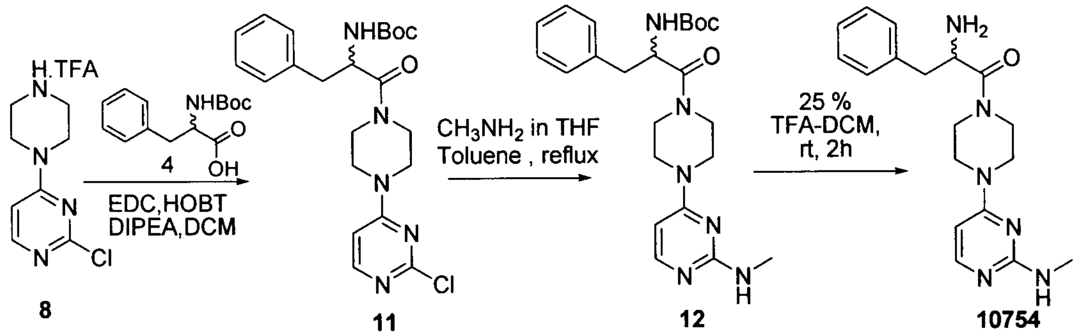
Compound **9** (150 mg, 0.336 mmol) was taken in toluene (10 mL) and aqueous ammonia (5 mL) was added in a sealed tube. Then the reaction mixture was heated up to 150 °C for 20 h. After that the reaction mixture was cooled down to r.t. and solvent was removed under vacuum to get crude product. The crude product was purified by column chromatography using Methanol-DCM (2-5%) to get the pure product **10** (51 mg, 52 %, M+1=427).

<u>Step 6:</u> Preparation of compound 10724 from compound 10:

Compound **10** (45 mg, 0.105 mmol) was taken in 25% TFA-DCM (2 mL) and stirred at rt for 2 h. Then the solvent was removed under vacuum to get an oily product and the oily product was washed with the diethyl ether to get the solid pure product **10724** (30 mg, 85%, M+1=327).

Example 2: Synthesis of Compound 10754.





Step 1: Preparation of compound 4 from compound 3:

Compound **3** (2.00 g, 12.12 mmol) was taken in water and $NaHCO_3$ (2.34 g, 24.24) was added to it at 0°C. To this mixture boc anhydride (2.90 g, 13.33 mmol) in THF was added drop wise at 0°C and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction, THF was removed and the aqueous layer was washed with diethyl ether and acidified with citric acid solution (aq) up to PH 4-5. Then extracted with ethyl acetate and the organic layer were dried over Na_2SO_4 and evaporate the solvent to get the pure product **4**. (3.00 gm, 96 %, M+1=266)

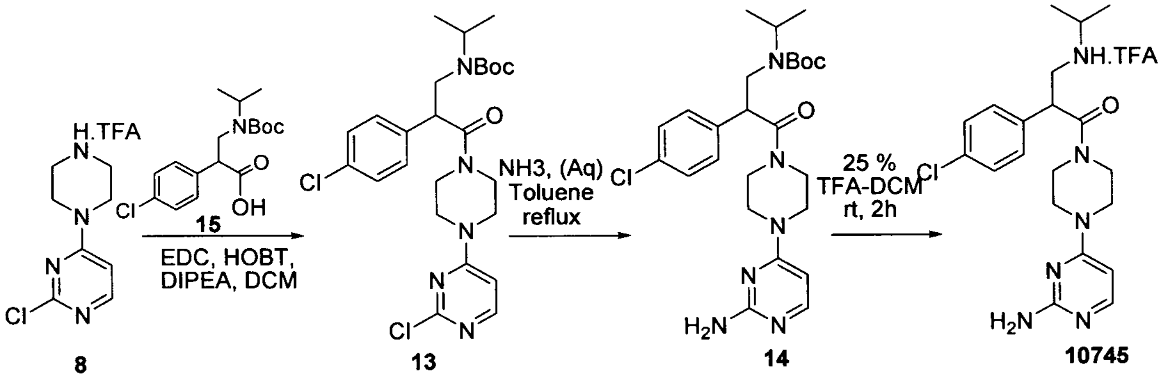
Step 2: Preparation of compound 11 from compound 8: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound 11 (87 %, M+1=447).

Step 3: Preparation of compound 12 from compound 11:

Compound **11** (120, 0.27 mmol) was taken in dry toluene (10 mL) and methylamine in THF (5 mL) was added in a seal tube. Then the reaction mixture was heated up to 150 °C for 20 h. After that the reaction mixture was cooled down to r.t. and solvent was removed under vacuum to get crude product. The crude product was purified by column chromatography using Methanol-DCM (2-5%) to get the pure product **12** (65 mg, 55%, M+1=441).

Step 4: Preparation of compound 10754 from compound 12: Compound **12** (45 mg, 0.105 mmol) was taken in 25% TFA-DCM (2 mL) and stirred at rt for 2 h. Then the solvent was removed under vacuum to get an oily product and the oily product was washed with the diethyl ether to get the solid pure product **10754** (90%, M+1=341), **SPI=10754.**

Example 3: Synthesis of Compound 10745.

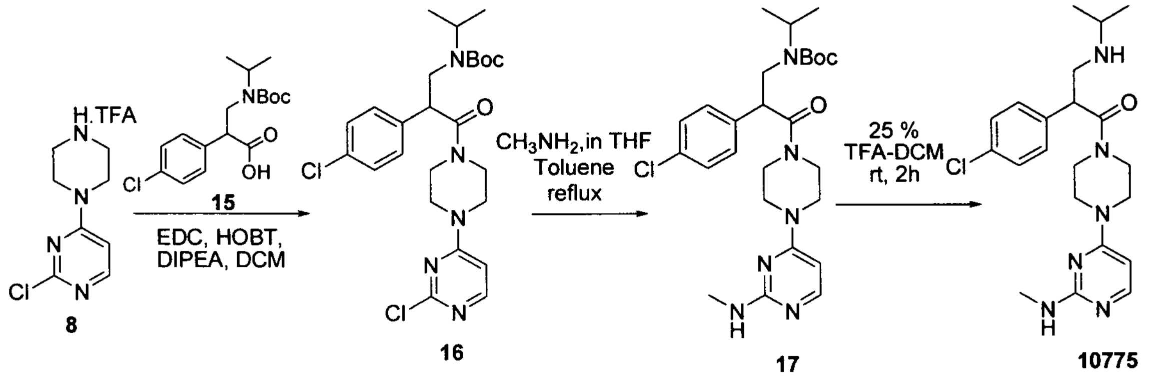


Step 1 : **Preparation of compound 13 from compound 8:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound 13 (85 %, M+1=522).

Step 2: **Preparation of compound 14 from compound 13:** The process employed for conversion of compound **10** from compound **9** may be suitably applied herein to obtain compound **14** (55%, M+1=503).

Step 3: **Preparation of compound 10745 from compound 14:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10745** (90%, M+1=403).

Example 4: Synthesis of Compound 10775.



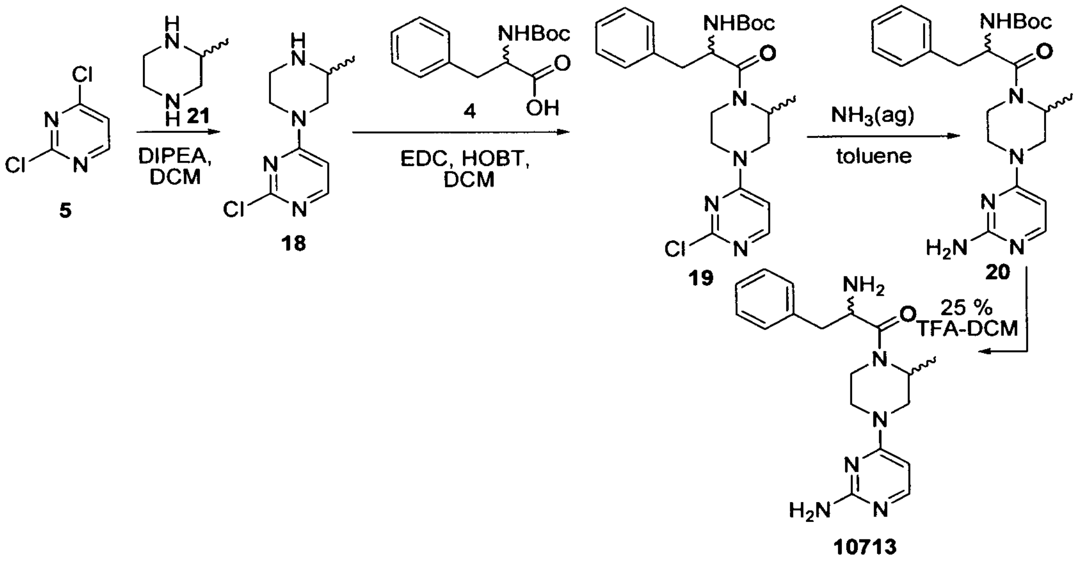
Step 1: **Preparation of compound 16 from compound 8:**

The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **16** (85%, M+1=522).

Step 2: Preparation of compound 17 from compound 16: The process employed for conversion of compound **12** from compound **11** may be suitably applied herein to obtain compound **17** (71%, M+1=518).

Step 3: Preparation of compound 10775 from compound 17: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10775** (90 %, M+1=418).

Example 5: Synthesis of Compound 10713



Step 1: **Preparation of compound 18 from compound 5:**

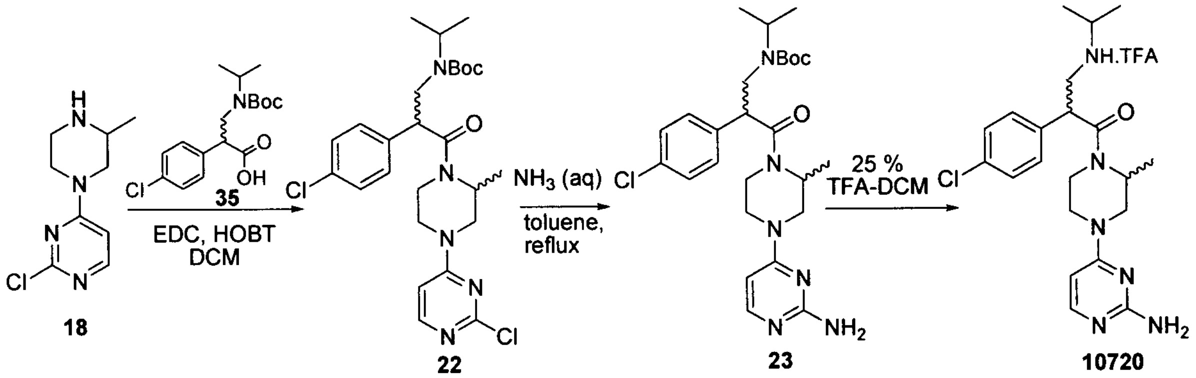
To a stirred solution of **5** (500.00 mg, 3.35 mmol) in DCM, methyl piperazine (335.00 mg, 3.35mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using ethyl acetate hexane (10-30%) to get the pure product **18** (243 mg, 35%, M+1=213).

Step 2: **Preparation of compound 19 from compound 18:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **19** (72 %, M+1=460).

Step 3: **Preparation of compound 20 from compound 19:** The process employed for conversion of compound **10** from compound **9** may be suitably applied herein to obtain compound **20** (56%, M+1=441).

Step 4: **Preparation of compound 10713 from compound 20:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound 10713 (90%, M+1=341).

Example 6: Synthesis of Compound 10720

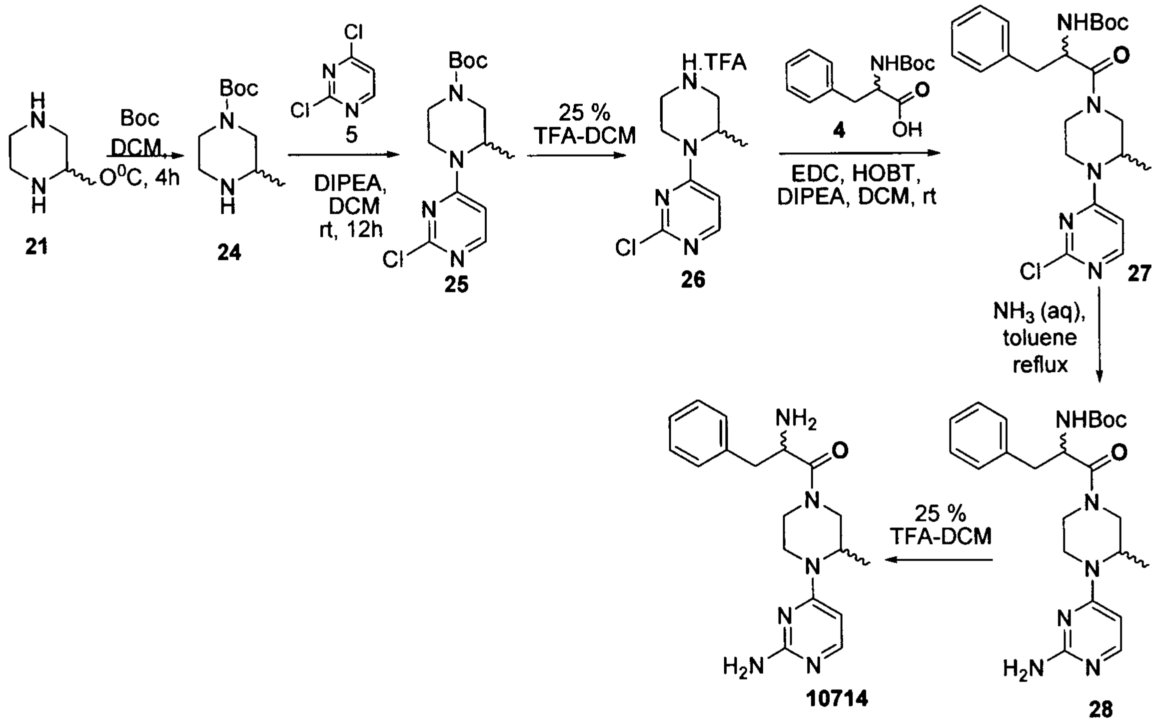


Step 1: **Preparation of compound 22 from compound 18:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **22** (70 %, M+1=536).

Step 2: **Preparation of compound 23 from compound 22:** The process employed for conversion of compound **10** from compound **9** may be suitably applied herein to obtain compound **23** (55%, M+1= 518).

Step 3: **Preparation of compound 10720 from compound 23:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10720** (90 %, M+1= 418).

Example 7: Synthesis of Compound 10714



Step 1: **Preparation of compound 24 from compound 21:** Compound **21** (2.50 g, 25.00 mmol) was taken in DCM and boc anhydride (4.90 gm, 22.50 mmol) was added to the mixture drop wise at 0 °C. Then the reaction mixture was stirred at r.t. for 4 h. After completion of reaction, the mixture was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4 and the solvent was evaporated to get a crude product **24.** The crude product was purified by column chromatography using ethyl acetate hexane (10-30%) to get the pure product **24** (2.10 g, 42 %, M+1= 201).

Step 2: **Preparation of compound 25 from compound 24:** The process employed for conversion of compound **7** from compound **5** may be suitably applied herein to obtain compound **25** (70 %, M+1= 314).

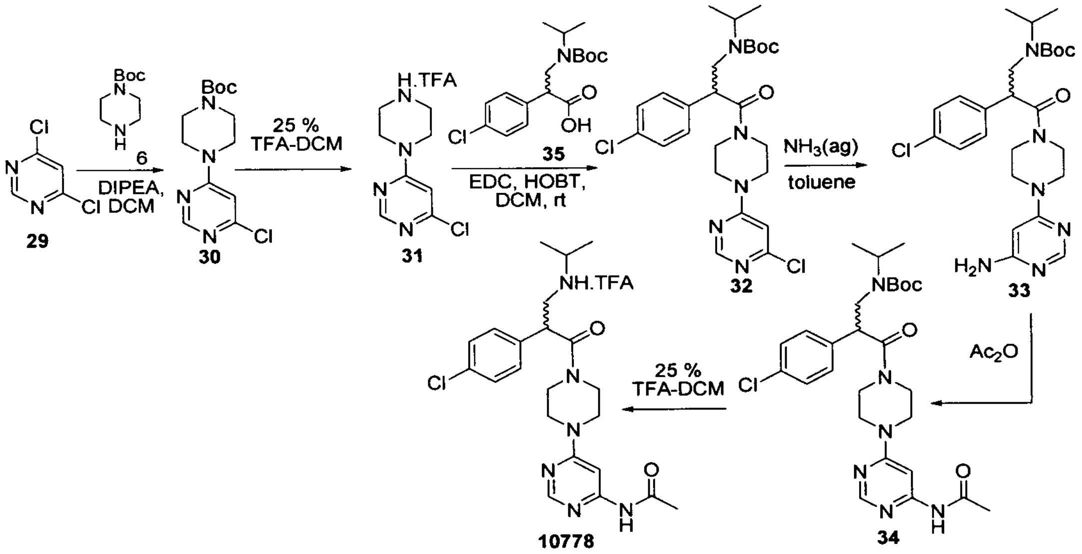
Step 3: **Preparation of compound 26 from compound 25:** The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound 26.

Step 4: **Preparation of compound 27 from compound 26:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **27**(82 %, M+1=461).

Step 5: Preparation of compound 28 from compound 27: The process employed for conversion of compound **10** from compound **9** may be suitably applied herein to obtain compound **28**(71 %, M+1=441).

Step 6: Preparation of compound 10714 from compound 28: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound d **10714** (90 %, M+1=341), **SPR10714.**

Example 8: Synthesis of Compound 10778



Step 1: Preparation of compound 30 from compound 29: The process employed for conversion of compound **7** from compound **5** may be suitably applied herein to obtain compound **30** (90%, M+1=299).

Step 2: Preparation of compound 31 from compound 30: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **31**.

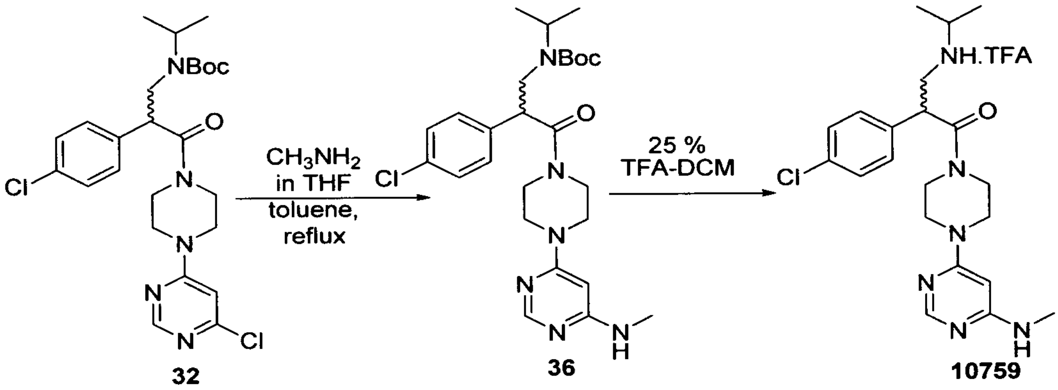
Step 3: Preparation of compound 32 from compound 31: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound (80 %, M+1=522).

<u>Step 4:</u> **Preparation of compound 33 from compound 32:** The process employed for conversion of compound **10** from compound **9** may be suitably applied herein to obtain compound **33** (49 %, M+1=503).

<u>Step 5</u>: **Preparation of compound 34 from compound 33:** Compound **33** (50 mg, 0.099 mmol) was taken in acetic anhydride (2.5 ml) under nitrogen and reflux for 1 h. TLC showed the completion of reaction, then the reaction mixture was cooled down to r.t. and diluted with ethyl acetate. The organic layer was washed with water and dried over Na_2SO_4 and the solvent was evaporated to get a crude product **34.** The crude product was purified by column chromatography using ethyl acetate hexane (30-50%) to get the pure product **34** (25 mg, 46%, M+1=545).

<u>Step 6:</u> **Preparation of compound 10778 from compound 34:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10778** (93%, M+1=445), **SPR10778.**

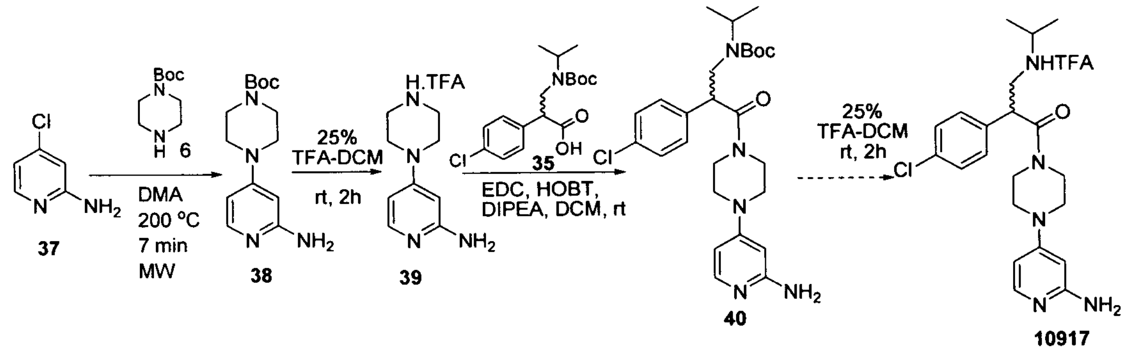
Example 9: Synthesis of Compound 10759



<u>Step 1</u>: **Preparation of compound 36 from compound 32** The process employed for conversion of compound **12** from compound **11** may be suitably applied herein to obtain compound **36** (71%, M+1=517).

<u>Step 2:</u> **Preparation of compound 10759 from compound 36:** the experiment is same as preparation of compound **10724** from compound **10** (88%, M+1=617), **SPR10759.**

Example 10: Synthesis of Compound 10917



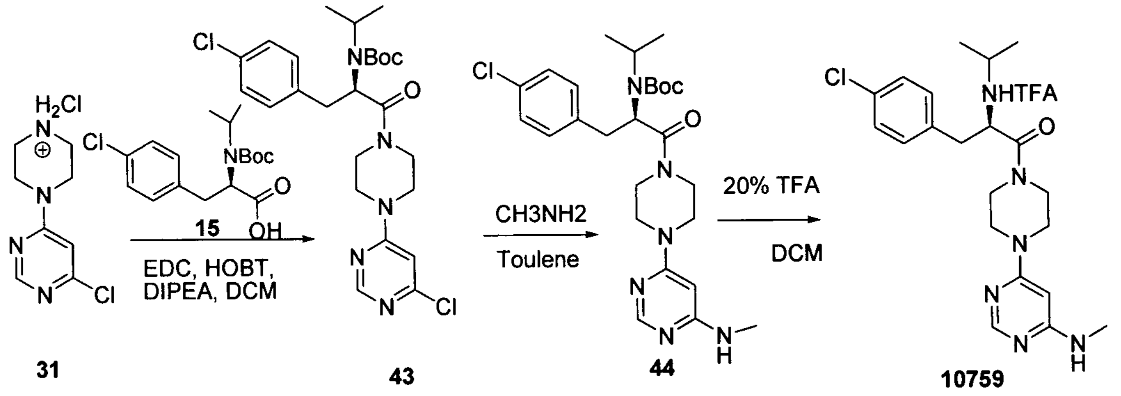
Step 1: Preparation of compound 38 from compound 37: Compound **37** (250 mg, 1.94 mmol) was taken in DMA (2 ml) and boc piperazine (1.20 g, 9.76 mmol) was added in microwave tube. The reaction mixture was run for 7 min at 200 °C. Then the reaction mixture was cooled down to r.t. and solid crystalline product was formed and filtered to get the pure product **38** (350 mg, 64%, M+1=279).

Step 2: Preparation of compound 39 from compound 38: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **39**.

Step 3: Preparation of compound 40 from compound 39 The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound (86%, M+1=502).

Step 4: Preparation of compound 10917 from compound 40: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10917, Yield :55%**

Example 11: Synthesis of Compound 10759



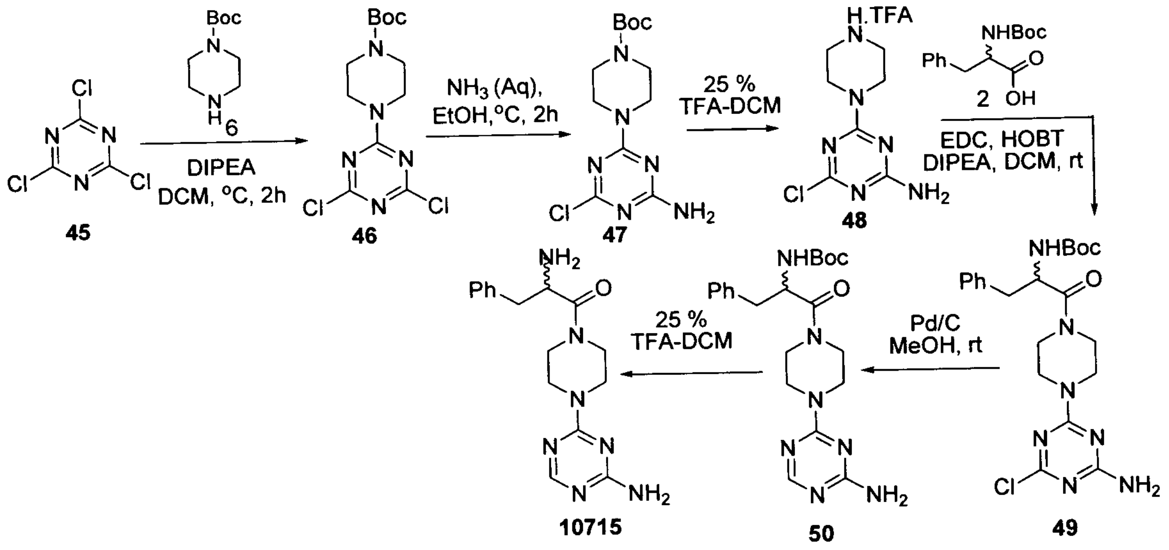
Step 1: Preparation of compound 43 from compound 31: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound (82%, M+1=446).

Step 2: Preparation of compound 44 from compound 43:

The process employed for conversion of compound **12** from compound **11** may be suitably applied herein to obtain compound **44** (71%, M+1=517).

Step 4: Preparation of compound 10759 from compound 44: The experiment is same as preparation of compound **10724** from compound **10** (88%, M+1=532), **SPR10759.**

Example 12: Synthesis of Compound 10715



Step 1: Preparation of compound 46 from compound 45: To a stirred solution of **45** (1.48 g, 8.05 mmol) in THF (20 mL), Boc piperazine (1.0 g, 5.37 mmol) was added and the reaction mixture was stirred at 0 °C for 2 h. Then the reaction mixture was diluted with DCM and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using ethyl acetate-hexane (20-30%) to get the pure product **46** (1.50 g, 55%, M+1=334).

Step 2: Preparation of compound 47 from compound 46: Compound **46** (500 mg, 1.49 mmol) was taken in acetone and aqueous ammonia (2ml) was added in a seal tube. Then the reaction mixture was stirred at 0 °C for 2 h. The solvent was removed under vacuum to get crude product. The crude product was purified by column chromatography using Methanol-DCM (2-5%) to get the pure product **47** (270 mg, 57%, M+1=315).

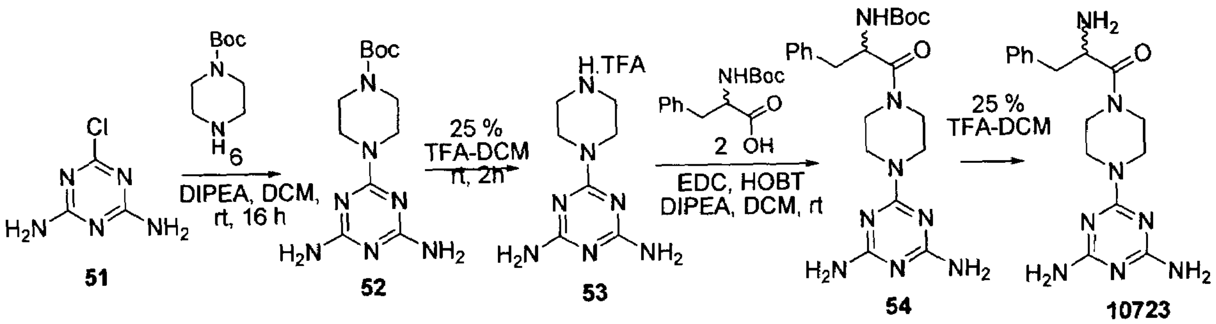
Step 3: Preparation of compound 48 from compound 47: Compound **47** (250 mg, 0.796 mmol) was taken in 25% TFA-DCM (2 mL) and stirred at for 2 h. Then the solvent was removed under vacuum to get an oily product **48** (240 mg, M+1= 215) and used without purification.

Step 4: Preparation of compound 49 from compound 48: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **49** (50 mg, M+1=462).

Step 5: Preparation of compound 50 from compound 48: Compound **49** (50 mg, 0.108 mmol) was taken in MeOH-ethyl acetate (1:1, 8 mL) under nitrogen and Pd/C (10 mg) was added to it under nitrogen. Then hydrogen balloon was introduced and stirred at r.t. for 16 h. After completion of reaction, the reaction mixture was filtered through celite, the filtrate was combined and the solvent was evaporated under vacuum to get a solid product. The crude product was purified by column chromatography using Methanol-DCM (2-5%) to get the pure product **50** (40 mg, 87%, M+1=428).

Step 6: Preparation of compound 10715 from compound 50: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **10715**(7 mg, 85%, M+1=328),SPR10715.

Example 13: Synthesis of Compound 10723



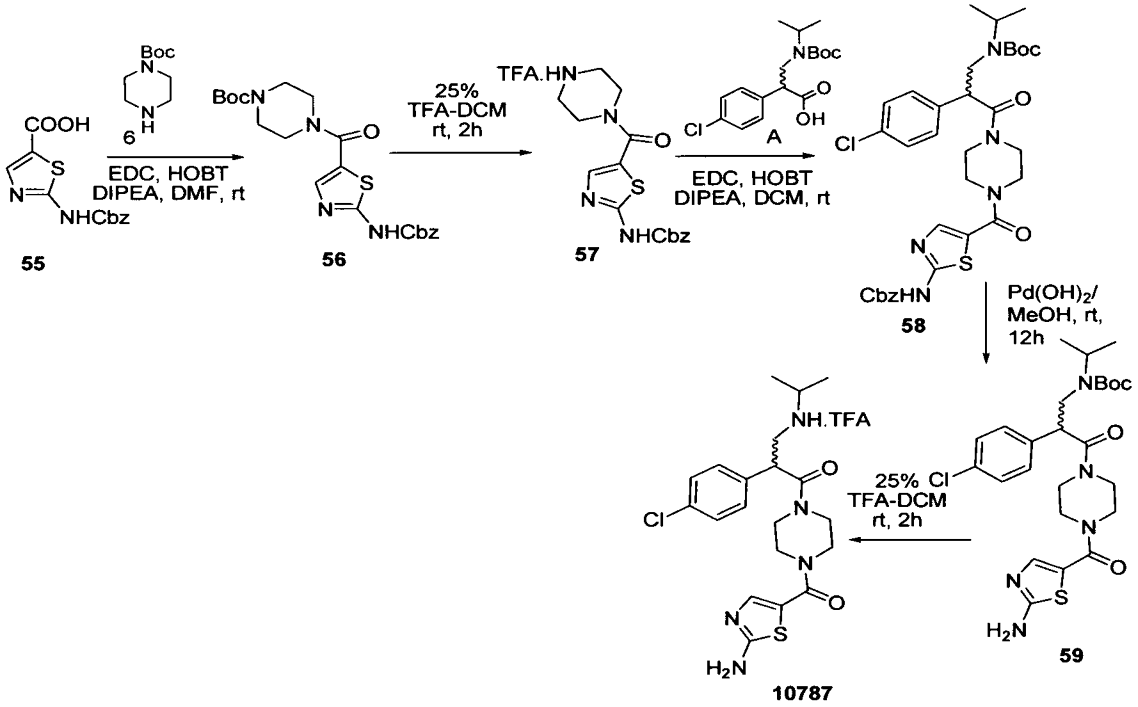
Step 1: Preparation of compound 52 from compound 51: To a stirred solution of **51** (500 mg, 2.73 mmol) in THF, TEA (0.4mL, 2.7 mmol) and Boc piperazine (200 mg, 2.70 mmol) were added and the reaction mixture was stirred at rt for 16 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using methanol-DCM (1-3%) to get the pure product **52** (70 mg, M+1=296).

Step 2: Preparation of compound 53 from compound 52: Compound **52** (70 mg, 0.23 mmol) was taken in 25% TFA-DCM (2 mL) and stirred at rt for 2 h. Then the solvent was removed under vacuum to get an oily product **53** (80 mg, M+1=196) and used without purification.

Step 3: **Preparation of compound 54 from compound 53:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **54**. The crude residue was purified by column chromatography using Methanol-DCM (2-5%) to get the pure product **54** (24 mg, 82%, M+1=443).

Step 4: **Preparation of compound 10723 from compound 54:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10723** (6 mg, 81%, M+1=343), SPR10723.

Example 14: Synthesis of Compound 10787



Step 1: **Preparation of compound 56 from compound 55:** Compound **55** (400 mg, 1.44 mmol) was taken in dry DMF and EDC.HCl (411 mg, 2.15 mmol), HOBT (208 mg, 1.58 mmol) were added under nitrogen and stirred for 30 min at rt. The Compound **6** (294.00 mg, 1.58 mmol) was taken in another round bottom flask and DIPEA (0.530 mL, 2.87 mmol) was added. Then the second reaction mixture was added to first reaction mixture slowly and stirred for 12 h at rt. After completion of reaction, the reaction was poured into cool water to

get a ppt of **56**, filtered out the ppt and dried. Next step is then proceeded without purification (410 mg, 82%, M+1=447).

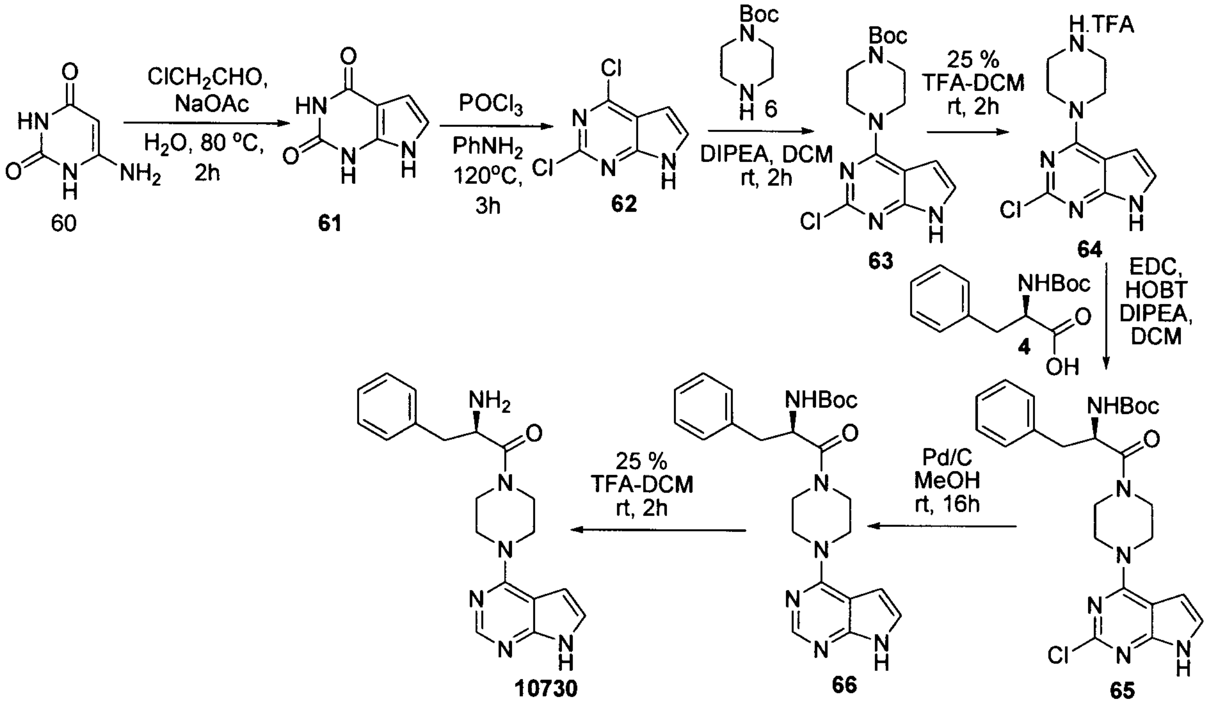
<u>Step 2:</u> **Preparation of compound 57 from compound 56:** The process employed for conversion of compound **48** from compound **47** may be suitably applied herein to obtain compound **57**.

<u>Step 3:</u> **Preparation of compound 58 from compound 57:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **58**. The crude residue was purified by column chromatography using ethyl acetate hexane (30-50%) to get the pure product **58** (64%, M+1=670).

<u>Step 4:</u> **Preparation of compound 59 from compound 58:** Compound **58** (40 mg was taken in MeOH under nitrogen and $Pd(OH)_2$ (20 mg) was added to it under nitrogen. Then hydrogen balloon was introduced and stirred at rt for 8 h. After completion of reaction, the reaction mixture was filtered through celite and the filtrate was combined and the solvent was evaporated under vacuum to get crude solid. The crude solid was purified by preparative TLC using 70% ethyl acetate–hexane to get the pure compound **59** (20 mg, 65%, M+1=534).

<u>Step 5:</u> **Preparation of compound 10787 from compound 59:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10787** (85%, M+1=434), **SPR10787**.

Example 14: Synthesis of Compound 10730



Step 1: Preparation of compound 61 from compound 60: To a stirred solution of **60** (5.00g, 39.37 mmol) in water (50 mL), chloroacetaldehyde (9.27 mL, 59.05 mmol) and sodium acetate (3.22 g, 39.37 mmol) were added and the reaction mixture was stirred at 80°C for 2 h. Then the reaction mixture was cooled down to rt and resulting solid was collected by filtration. The solid product was washed with water and acetone to get the pure product **61** (4.50g, 75% M+1=152).

Step 2: Preparation of compound 62 from compound 61: Compound **61** (5 gm. 33.11 mmol) was taken in N, N dimethylaniline (4.18 ml, 99.33 mmol) and $POCl_3$ (35 mL) was added to it at 0 °C in a seal tube. Then the resulting mixture was heated up to 120 °C for 3 h., cooled down to rt. and poured in ice cold water slowly to get a solid compound **62** (4.1 gm, 67%, M+1=187). The solid product was used without purification.

Step 3: Preparation of compound 63 from compound 62: The process employed for conversion of compound **7** from compound **5** may be suitably applied herein to obtain compound **63** (75%, M+1=338).

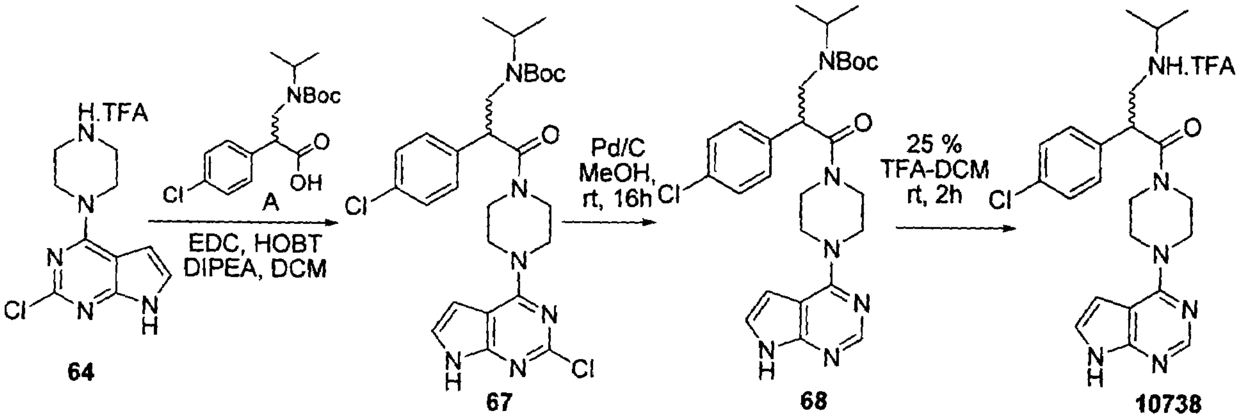
Step 4: **Preparation of compound 64 from compound 63:** The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **64**.

Step 5: **Preparation of compound 65 from compound 64:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **65**. The crude residue was purified by column chromatography using ethyl acetate hexane (30-50%) to get the pure product **65** (80%, M+1=485).

Step 6: **Preparation of compound 66 from compound 65:** The process employed for conversion of compound **50** from compound **49** may be suitably applied herein to obtain compound **66**. The crude residue was purified by column chromatography using methanol-DCM (3-5%) to get the pure product **66** (72%, M+1=451).

Step 7: **Preparation of compound 10730 from compound 66:** The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10730** (86%, M+1=351), **SPR10730.**

Example 15: Synthesis of Compound 10738

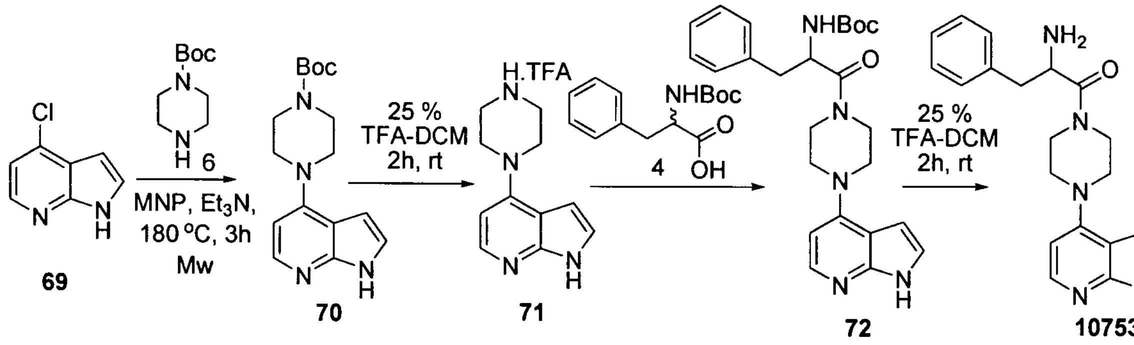


Step 1: **Preparation of compound 67 from compound 64:** The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **67**(83%, M+1=561).

Step 2: Preparation of compound 68 from compound 67: The process employed for conversion of compound **50** from compound **49** may be suitably applied herein to obtain compound **68** (76%, M+1=527).

Step 3: Preparation of compound 10738 from compound 68: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10738** (88%, M+1=427), **SPR10738.**

Example 16: Synthesis of Compound 10753



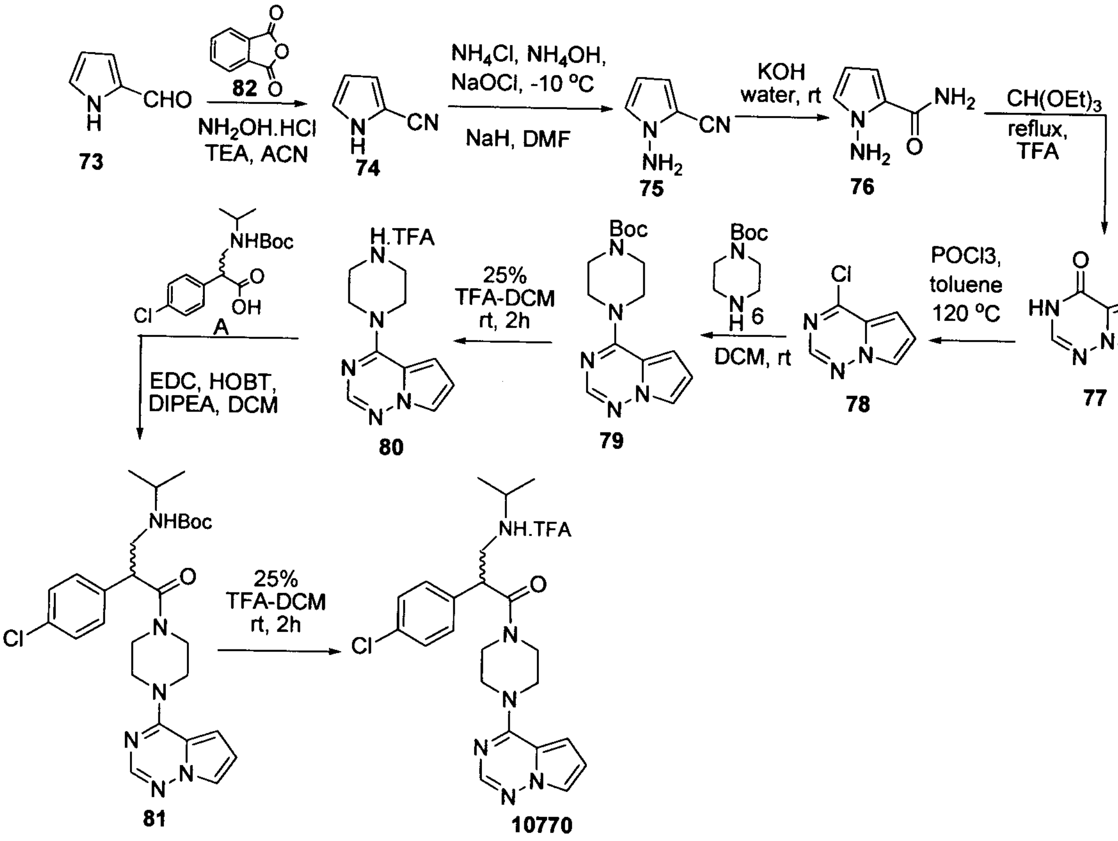
Preparation of compound 70 from compound 69: compound **69** (100 mg, 0.66 mmol), boc piperazine (615 mg, 3.31 mmol) MNP (2 mL) and triethylamine (0.47 mL, 3.31mmol) were taken in a microwave tube. This reaction mixture was run at 180 °C for 3h in microwave. After this the reaction mixture was cooled down to rt, poured into water and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent evaporates to get a crude residue. The crude residue was purified by column chromatography on silica gel using 50-100 % ethyl acetate-hexane to get the pure product **70** (25 mg, 13%, M+1=303).

Preparation of compound 71 from compound 70: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **71.**

Preparation of compound 72 from compound 71: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **72**(72%, M+1=450).

Preparation of compound 10753 from compound 75: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10753** (87%, M+1=350), **SPR10753.**

Example 16: Synthesis of Compound 10770



Preparation of compound 74 from compound 73: To a solution of hydroxyamine hydrochloride (14.50 g, 210.5 mmol) in ACN, triethyl amine (29.1 mL, 210.5 mmol) was added at 0 °C and stirred for 30 min. Then compound **73** (10.00 g, 105.26 mmol) was added and stirred for another 1h. After that phthalic anhydride was added and heated for reflux for 6h. then cooled down to rt. and solvent was removed under vacuum to get solid material. To this solid material DCM was added and filtered. The combined filtrate was collected and the solvent was removed under vacuum to get crude product. The crude product was purified by column chromatography on silica gel using 5-10 % ethyl acetate-hexane to get the pure product **74** (7.50 g, %, M+1=93).

Preparation of compound 75 from compound 74:

Step1:-Preparation of NH_2Cl: Ammonium chloride (18 gm) was taken in diethyl ether (600 ml) and cooled down to -5 °C and NH_4OH (28 mL) was added slowly then commercial bleach (NaOCl, 432mL) was added using dropping funnel (45 min). The reaction mixture was stirred for 15 min at-5 °C and the organic layer was separated out, washed with brine and dried over $CaCl_2$, and stored at -40 °C.

Step 2: To a solution of compound **74** (6 gm, 65.21 mmol) in DMF, NaH was added slowly at rt and stirred for 45 min. NH_2Cl solution was then added *via* syringe under nitrogen atmosphere. After this the reaction mixture was stirred at rt for 4h. and the reaction mixture was quenched with $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent evaporates to get a pure compound **75** (6.20 gm, M+1= 108).

Preparation of compound 76 from compound 75: Compound **75** (6 gm, 56.07mmol) was taken in 1L RB, then pre cold KOH aqueous solution (56 gm, 1000 mmol) was added slowly and stirred for 12h. After this, solid was formed and filtered, dried under vacuum to get the pure product **76** (6.1 g, M+1=126).

Preparation of compound 77 from compound 76: Compound **76** (1 gm, mmol) was taken in triethyl ortho formate and head to 90 °C for 6 h. then cooled down to rt and few drops of (0.5ml) TFA was added and again heated to 80 °C for 1 h. Then the reaction mixture was cooled down to rt and solid was formed slowly. The solid was filtered out and dried to get pure product 77 (700 mg, M+1=136).

Preparation of compound 78 from compound 77: Compound 77 (450 gm. 3.30 mmol) was taken in $POCl_3$ (5 mL, 30 mmol) and DIPEA (0.6 ml, 3.3 mmol) was added to it at 0 °C in a seal tube. Then the resulting mixture was heated to 120 °C for 3 h. and cooled down to rt. and poured in ice cold water slowly to get a solid compound **78** (gm, M+1=154). The solid product was used without purification and immediately after synthesis.

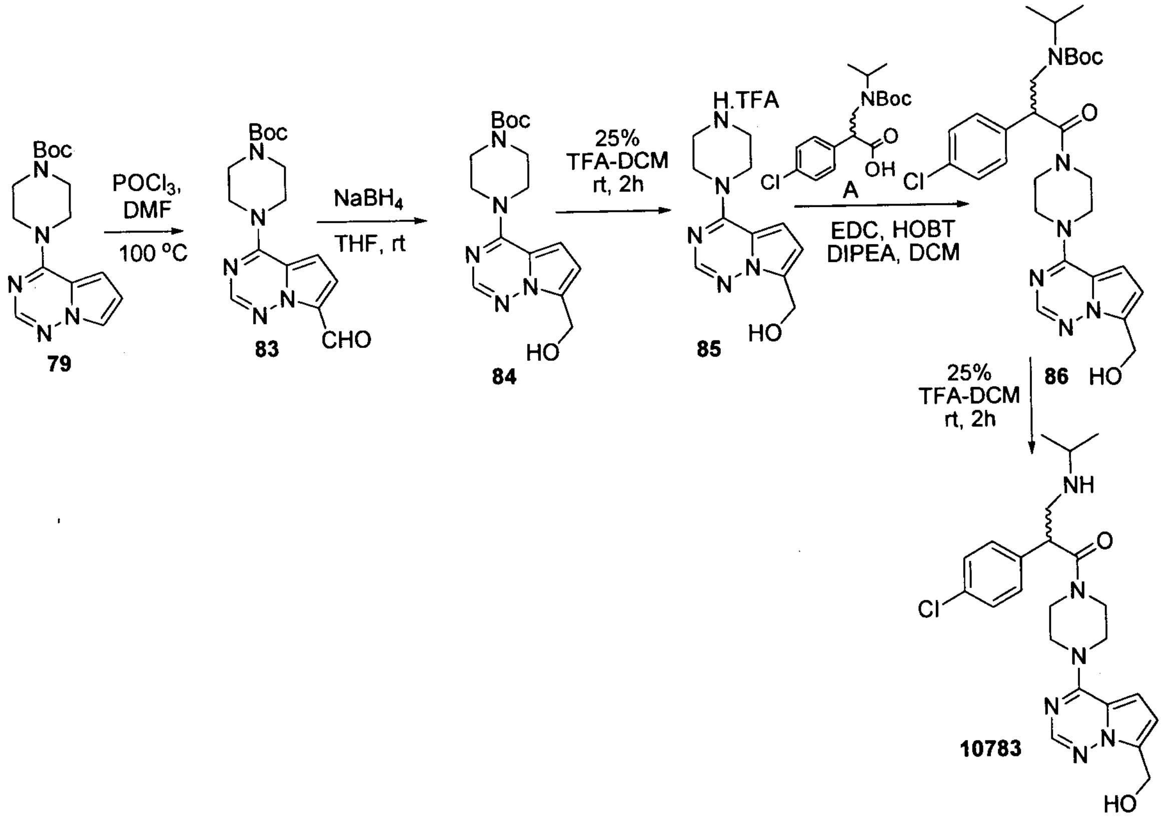
Preparation of compound 79 from compound 78: To a stirred solution of **78** (200 mg, 1.31 mmol) in DCM, DIPEA (0.361 mL, 1.96 mmol) and Boc piperazine (323 mg, 1.31 mmol) were added and the reaction mixture was stirred at rt for 2 h. The reaction mixture was diluted with DCM and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get a crude residue. The crude residue was purified by column chromatography using ethyl acetate hexane (10-30%) to get the pure product **79** (330 mg, M+1=304).

Preparation of compound 80 from compound 79: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **80**.

Preparation of compound 81 from compound 80: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **81** (85%, M+1=528).

Preparation of compound 10770 from compound 81: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10770** (92%, M+1=428), **SPR10770**.

Example 18: Synthesis of Compound 10783



Preparation of compound 83 from compound 79: Compound **79** (300 mg, 0.90 mmol) was taken in $POCl_3$ (0.946 mL, 9.9 mmol) and DMF (0.346 mL, 4.5 mmol) at 0 °C in a sealed tube. Then the resulting mixture was heated up to 100 °C for 3 h. and cooled down to rt. and poured in ice cold water slowly to get a solid compound **83** (200 mg, M+1= 332). The solid product was used without purification and immediately after synthesis.

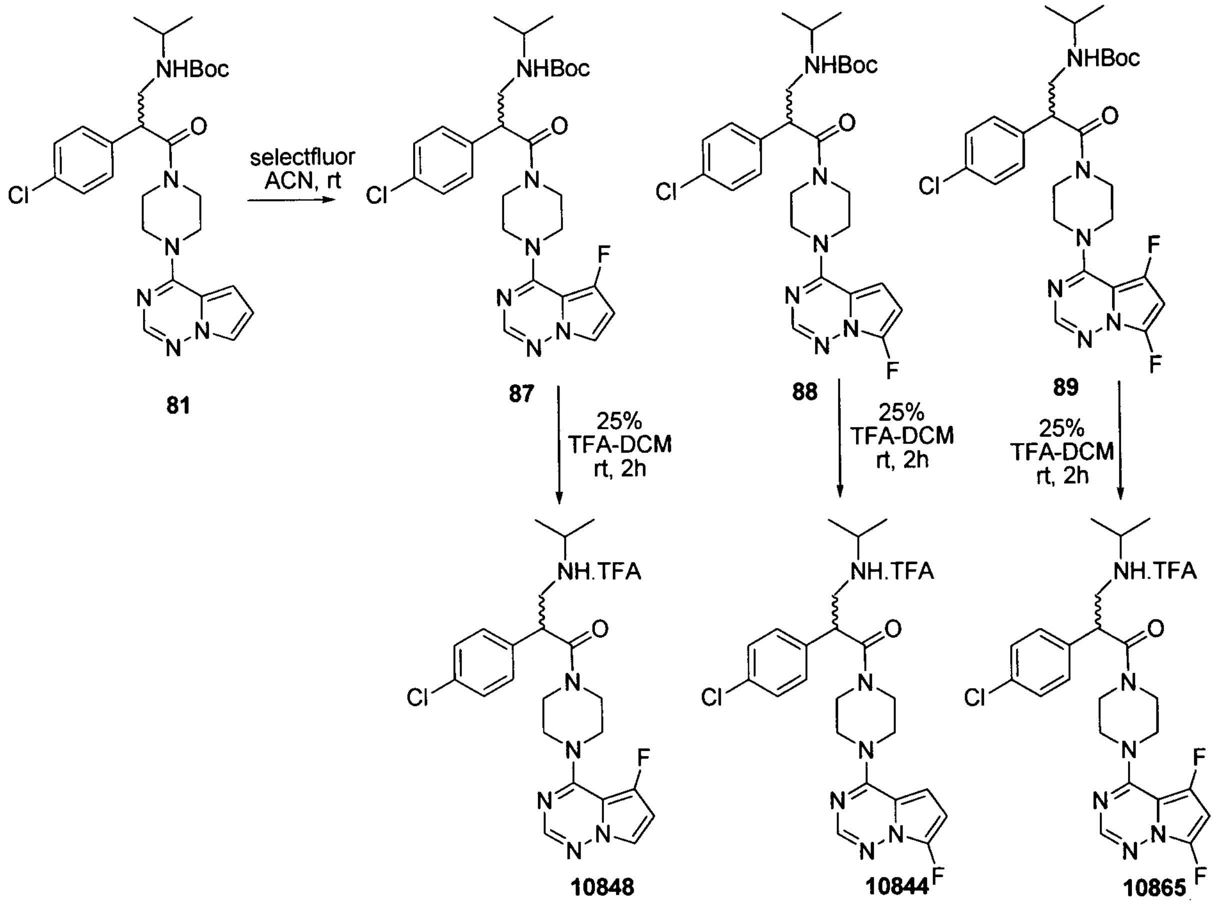
Preparation of compound 84 from compound 83: Compound **83** (30 mg, 0.12 mmol) was taken in THF and sodium borohydride (14 mg, 0.38 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 4h. After this, the reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was separated out, dried over Na_2SO_4 and the solvent was evaporated to get the compound **84**. (20 mg, M+1= 334)

Preparation of compound 85 from compound 84: The process employed for conversion of compound **8** from compound **7** may be suitably applied herein to obtain compound **85**.

Preparation of compound 86 from compound 85: The process employed for conversion of compound **9** from compound **8** may be suitably applied herein to obtain compound **86** (15 mg, M+1= 557).

Preparation of compound 10783 from compound 86: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10783** (10 mg, M+1= 457), **SPR10783.**

Example 19: Synthesis of Compound 10844, 10848 and 10865



Preparation of compound 87 from compound 81: Compound **81** (50 mg, 0.095 mmol) was taken in ACN and selectfluor (33 mg, 0.095 mmol) was added at 0 °C. The reaction mixture was stirred at rt for 24 h. then solvent was removed under vacuum and ethyl acetate was added. The organic layer was washed with water and separated out, dried over Na_2SO_4 and evaporate the solvent to get the mixture of compound **87, 88** & **89**. All the compound were separated by preparative TLC using 50 % ethyl acetate- hexane (**87**, 25%, M+1=546; **88**, 25%, M+1=546; **89**, 20%, M+1=564).

Example 19-20: Synthesis of Compounds 10848

Preparation of compound 10848 from compound 87: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10848** (90%, M+1= 446).

Preparation of compound 10844 from compound 88: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10844** (92%, M+1=446).

Preparation of compound 10865 from compound 89: The process employed for conversion of compound **10724** from compound **10** may be suitably applied herein to obtain compound **10865.**