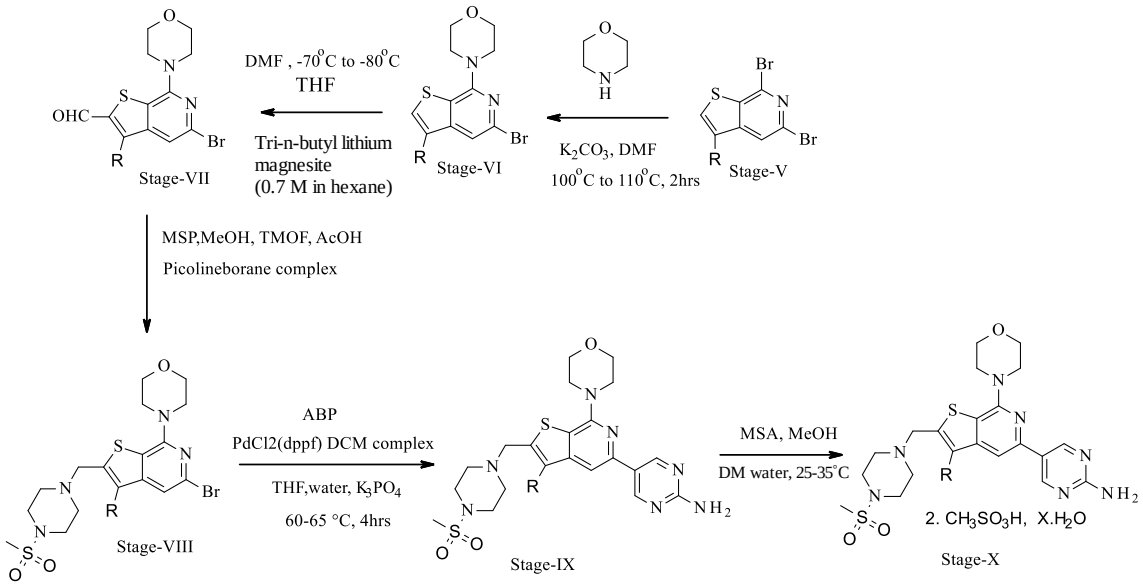
Scheme-2 (Second generation process):

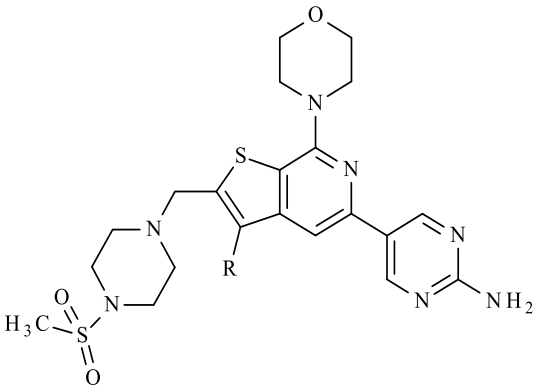


R = H for NRC-1111 and
R = CH_3 for NRC-1109

Summary:

Taking into consideration the above mentioned requirements, the aim of the present disclosure is to develop an improved process which is environmentally protective, safe, industrially applicable, devoid of the deficiencies of first generation process and makes possible the synthesis of highly pure (99.8%) desired compound of formula-I and in high yields (about 22% overall yield).

In one aspect, the present disclosure refers to an improved process for the preparation of 5-[3-substituted-2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*]pyridine-5-yl]-2-pyrimidinamine)dimethane sulfonate compound of Formula-(I),



.2CH3SO3H. xH2O

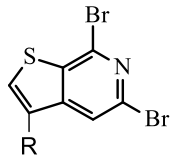
Formula (I)

Formula (I): R = H for NRC-1111 and

Formula (II): R = CH_3 for NRC-1109;

comprising the following steps of:

a) Reacting the compound offormula-(V)

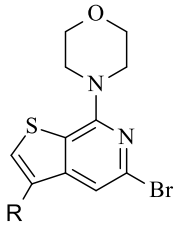


Formula (V)

Formula (V): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

with morpholine in presence of a suitable base and a solvent provides compound of formula-(VI),



Formula (VI)

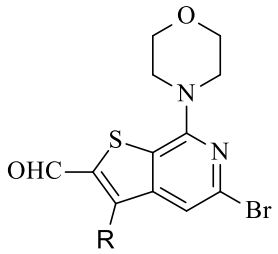
Formula (VI): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

b) treating the compound of formula-(VI) with a suitable base in a solvent followed by formylation with dimethylformamide provides compound of formula-(VII),

(or)

treating the compound of formula-(VI) with a Grignard reagent and a suitable base in a solvent followed by formylation with dimethylformamide provides compound of formula-(VII),

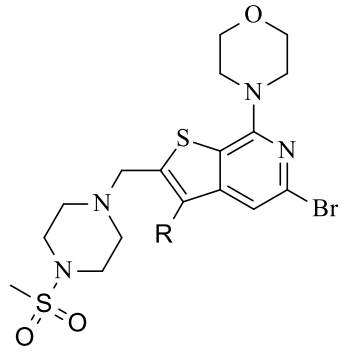


Formula (VII)

Formula (VII): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

c) reacting the compound of formula-(VII) with 1-methyl sulfonyl-piperazine in presence of 2-picoline borane complex, trimethyl orthoformate in a solvent provides compound of formula-(VIII),

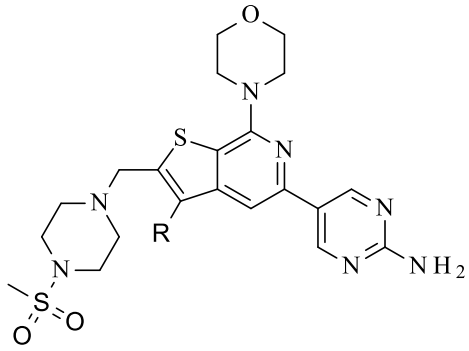


Formula (VIII)

Formula (VIII): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

d) reacting the compound of formula-(VIII) with 2-aminopyrimidine-5-boronic acid pinacol ester in presence of PdCl2(dppf)DCM complex, a suitable base and a solvent provides compound of formula-(IX),



Formula (IX)

Formula (IX): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

e) treating the compound of formula-(IX) with methane sulfonic acid in a solvent provides compound of formula-(I).

Therefore the main objective of the present disclosure is to develop an improved process for the preparation of NRC-1111 dimesylate hydrate which is 5-[2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*] pyridine-5-yl]-2-pyrimidinamine dimethane sulfonate hydrate having the formula-I would be to select the scheme-II as the working route and set all the five stages of the reaction conditions, work-ups and purifications.

Still another objective of the present disclosure is to develop an improved process 5-Bromo-7-(4-morpholinyl)-thieno[2,3-*c*]pyridine (Stage-VI) by avoiding sealed tube and excess moles of Morpholine.

Another objective of the present disclosure is to develop an improved process for the preparation of 5-Bromo-7-(4-morpholinyl)-thieno[2,3-*c*]pyridine-2-carboxaldehyde (Stage-VII) using Tri n-butyllithium magnesite (0.7M in hexane) reagent for lithiation to avoid scale up problems and to get high purity product consistently.

Another objective of the present disclosure is to develop an improved process for the preparation of 5-Bromo-2-[[4-(methylsulfonyl)-1-piperazinyl] methyl]-7-(4-morpholinyl)-thieno[2,3-*c*]pyridine (Stage-VIII) by substituting STAB with 2-picoline borane complex and modifying all the process parameters.

Yet another objective of the present disclosure is to develop an improved process for the preparation of 5-[2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*]pyridine-5-yl]-2-pyrimidinamine(Stage-IX; NRC-1111 base) by substituting bis(triphenylphosphine) palladium (II) dichloride with [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane to get high yielding and pure product in multi kilogram scale.

Still another objective of the present disclosure is to select dimesylate as acid addition salt of NRC-1111 and NRC-1109 and to make corresponding hydrates. Thus the polymorphic nature of both NRC-1111 dimesylate hydrate and NRC-1109 dimesylate hydrate are established on kilogram scale.

In another aspect, the present disclosure refers to 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate (NRC-1111).

In another aspect, the present disclosure refers to the crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl] pyrimidin-2-amine) (NRC-1111 base) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 9.31, 11.06, 18.64 and 20.05 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-1.

In another aspect, the present disclosure refers to 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1109).

In another aspect, the present disclosure refers to the crystal form of 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl]pyrimidin-2-amine) (NRC-1109 base) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 8.76, 9.45, 16.87, 18.39 and 19.50 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-3.

Another objective of the present disclosure is to provide crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl] pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1111) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 6.19, 15.11, 18.40, 18.65, 21.60, 22.56 and 25.13 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-5.

Another objective of the present disclosure is to provide crystal form of 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1109) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 7.67, 10.69, 18.39, 19.58, 21.93 and 25.83 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-7.

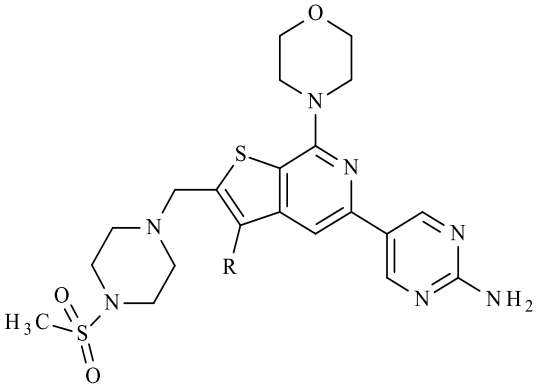
In another aspect, the present disclosure refers to the process for the preparation of crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1111) as defined above, comprising the steps of:

a) adding DM water to 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine (NRC-1111 base),
b) heating the reaction mixture to 90-100^{o}C,
c) cooling the reaction mixture and adding methanol,
d) adding methanesulfonic acid diluted in methanol to the reaction mixture,
e) stirring and filtering the mass to get the NRC-1111 dimethane sulfonate hydrate crystal form.

Another objective of the present disclosure is to provide a process for the preparation of crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1111), comprising the steps of:

WE CLAIM:

1. An improved process for the preparation of 5-[3-substituted-2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*]pyridine-5-yl]-2-pyrimidinamine)dimethane sulfonate compound of Formula-(I),



.2CH3SO3H. xH2O

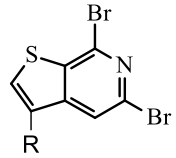
Formula (I)

Formula (I): R = H for NRC-1111 and

Formula (II): R = CH_3 for NRC-1109;

comprising the following steps of:

a) Reacting the compound offormula-(V)

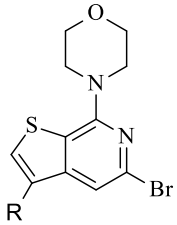


Formula (V)

Formula (V): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

with morpholine in presence of a suitable base and a solvent provides compound of formula-(VI),



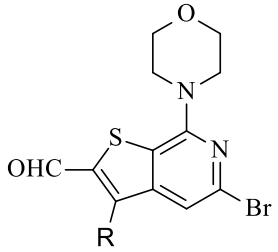
Formula (VI)

Formula (VI): R = H for NRC-1111 and
: R = CH_3 for NRC-1109;

b) treating the compound of formula-(VI) with a suitable base in a solvent followed by formylation with dimethylformamide provides compound of formula-(VII),

(or)

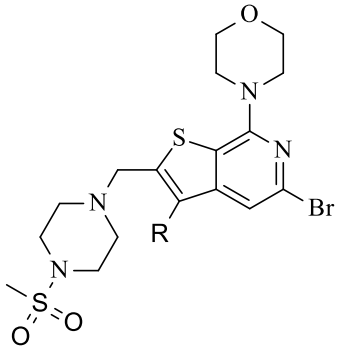
treating the compound of formula-(VI) with a Grignard reagent and a suitable base in a solvent followed by formylation with dimethylformamide provides compound of formula-(VII),



Formula (VII)

Formula (VII): R = H for NRC-1111 and
: R = CH_3 for NRC-1109;

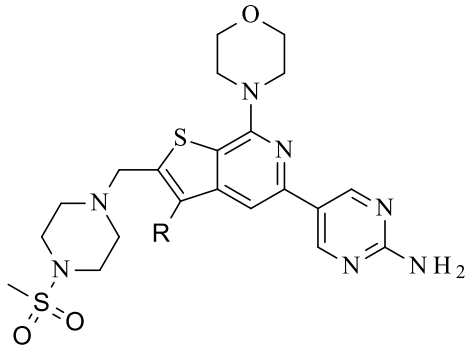
c) reacting the compound of formula-(VII) with 1-methyl sulfonyl-piperazine in presence of 2-picoline borane complex, trimethyl orthoformate in a solvent provides compound of formula-(VIII),



Formula (VIII)

Formula (VIII): R = H for NRC-1111 and
: R = CH_3 for NRC-1109;

d) reacting the compound of formula-(VIII) with 2-aminopyrimidine-5-boronic acid pinacol ester in presence of PdCl2(dppf)DCM complex, a suitable base and a solvent provides compound of formula-(IX),



Formula (IX)

Formula (IX): R = H for NRC-1111 and

: R = CH_3 for NRC-1109;

e) treating the compound of formula-(IX) with methane sulfonic acid in a solvent provides compound of formula-(I).

2. The process as claimed in claim 1, wherein,

In step (a), the base is inorganic base. Wherein, the inorganic base is selected from alkali and alkaline metal carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, cesium carbonate, or any other equivalent base.

In step (b), the base is selected from n-butyl lithium, Tri n-butyllithium magnesate; And the Grignard regent is alkylmagnesuim halide, preferably isopropylmagnesium bromide.

In step (d), the base is inorganic base selected from Potassium phosphate, Potassium acetate or potassium carbonate Preferably Potassium phosphate.

In step-a, b, c, d & e) the suitable solvent is selected from alcoholic solvents, polar-aprotic solvents, ether solvents, hydrocarbon solvents, nitrile solvents and polar solvents such as water or mixtures thereof;

3. The process as claimed in claim 1, wherein in step-a) the number of moles of Morpholine to formula-(V) is in the range of 2.0-3.0 preferably in the range of 2.25-2.50 moles. And the number of moles of Potassium Carbonate to formula-V is in the range of 2.0-4.0 preferably in the range of 2.0-3.0.

4. The process as claimed in claim 1, wherein in step-b) the number of moles of formula-(VI) to Tri-n butyllithum magnesate in hexane is in the range of 0.9 - 1.3 preferably in the range of 1.1-1.2 moles. And the number of moles of dimethyl formamide to formula-(VI) is in the range of 1.8-2.2 preferably 1.9-2.1 moles.

5. The process as claimed in claim 1, wherein in step-c) the number of moles of formula-(VII) to 1-methane sulfonylpiperazine is in the range of 1.4 - 1.8 preferably in the range of 1.2-1.6. And the number of moles of formula-(VII) to trimethyl orthoformate is in the range of 14-18 moles preferably in the range of 15-17. The number of moles of formula-(VII) to 2-Picoline borane complex is in the range of 2.5-3.5 moles preferably in the range of 2.8-3.2.

6. The process as claimed in claim 1, wherein in step-d) the number of moles of formula-(VIII) to [1,1′-Bis(diphenylphosphino)ferrocene] dichloropalladium (II), complex with dichloromethane is in the range of 0.01 to 0.05 moles, preferably 0.05 moles.

7. The process as claimed in claim-1, wherein the compound of formula-(VI) is prepared by reacting the compound of formula-(V) with morpholine in presence of a suitable inorganic base selected from alkali and alkaline metal carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, cesium carbonate and a solvent is polar-aprotic solvents such as dimethylformamide.

8. The process as claimed in claim-1, wherein compound of formula-(VII) is prepared by treating the compound of formula-(VI) with Tri n-butyllithium magnesate in tetrahydrofuran followed by formylation with dimethylformamide provides compound of formula-(VII).

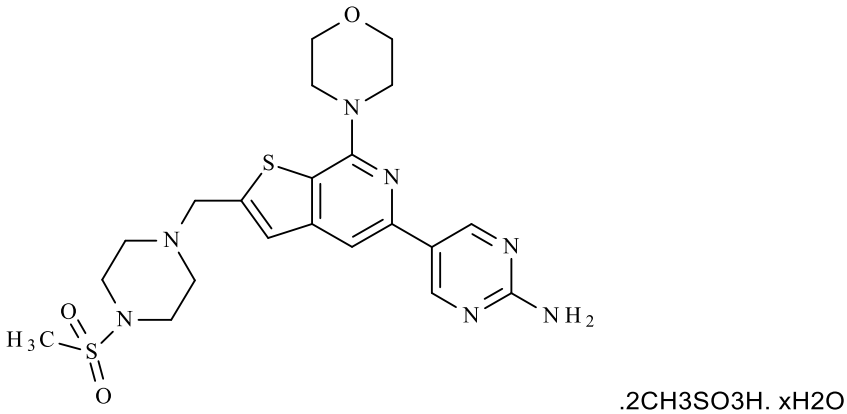
9. The process as claimed in claim-1, wherein compound of formula-(VII) is prepared by treating the compound of formula-(VI) with isopropylmagnesium bromide and n-butyl lithium in tetrahydrofuran followed by formylation with dimethylformamide provides compound of formula-(VII).

10. The process as claimed in claim-1, wherein compound of formula-(VIII) is prepared by reacting the compound of formula-(VII) with 1-methyl sulfonyl-piperazine in presence of 2-picoline borane complex, trimethyl orthoformate and acetic acid in methanol provides compound of formula-(VIII).

11. The process as claimed in claim-1, wherein compound of formula-(IX) is prepared by reacting the compound of formula-(VIII) with 2-aminopyrimidine-5-boronic acid pinacol ester in presence of PdCl2(dppf)DCM complex, potassium phosphate in tetrahydrofuran provides compound of formula-(IX).

12. The process as claimed in claim-1, wherein compound (NRC-1111) of formula-(I) is prepared by treating the compound of formula-(IX) with methane sulfonic acid in aqueous methanol provides (NRC-1111) dimethane sulfonate compound of formula-(I).

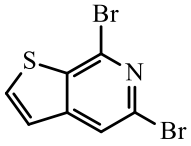
13. The process as claimed in claim 1 for the preparation of 5-[2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*] pyridine-5-yl]-2-pyrimidinamine) dimethane sulfonate (NRC-1111),



Formula (I)

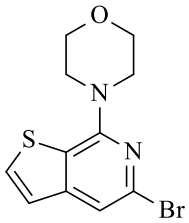
comprising the following steps of:

a) Reacting the compound of formula-(V)



Formula (V)

with morpholine in presence of potassium carbonate base in dimethylformamide solvent provides compound of formula-(VI),

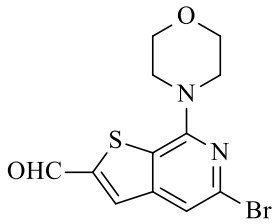


Formula (VI)

b) treating the compound of formula-(VI) with Tri n-butyllithium magnesate reagent in tetrahydrofuran solvent followed by formylation with dimethylformamide provides compound of formula-(VII),

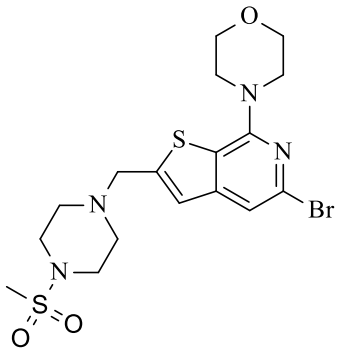
(or)

treating the compound of formula-(VI) with reagents isopropylmagnesium bromide and n-butyl lithium in tetrahydrofuran solvent followed by formylation with dimethylformamide provides compound of formula-(VII),



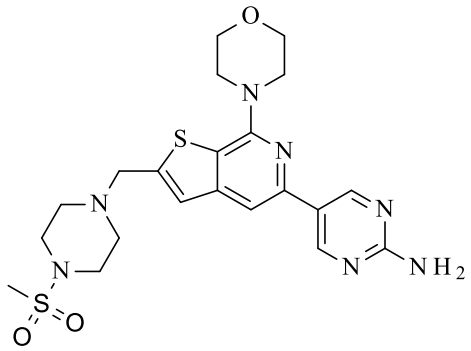
Formula (VII)

c) reacting the compound of formula-(VII) with 1-methyl sulfonyl-piperazine in presence of reagents 2-picoline borane complex, trimethyl orthoformate and acetic acid in methanol solvent provides compound of formula-(VIII),



Formula (VIII)

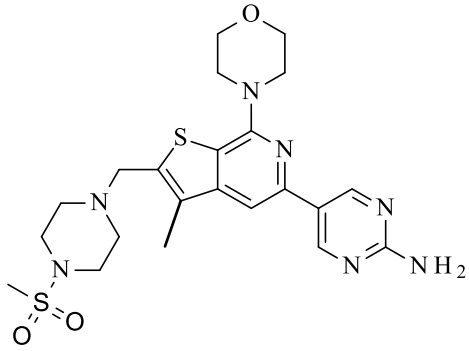
d) reacting the compound of formula-(VIII) with 2-aminopyrimidine-5-boronic acid pinacol ester in presence of the catalyst PdCl2(dppf)DCM complex and potassium phosphate base in tetrahydrofuran solvent provides compound of formula-(IX),



Formula (IX)

e) treating the compound of formula-(IX) with methane sulfonic acid in aqueous methanol provides (NRC-1111) compound of formula-(I).

14. The process as claimed in claim 1 for the preparation of 5-[3-methyl-2-[[4-(methylsulfonyl)-1-piperazinyl]methyl]-7-(4-morpholinyl)thieno[2,3-*c*] pyridine-5-yl]-2-pyrimidinamine) dimethane sulfonate (NRC-1109),

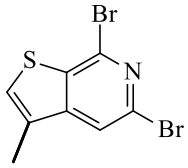


.2CH3SO3H. xH2O

Formula (II)

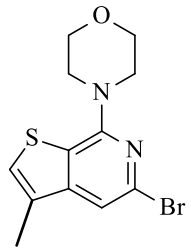
comprising the following steps of:

a) Reacting the compound of formula-(V)



Formula (V)

with morpholine in presence of potassium carbonate base in dimethylformamide solvent provides compound of formula-(VI),

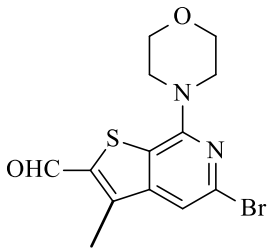


Formula (VI)

b) treating the compound of formula-(VI) with Tri n-butyllithium magnesate reagent in tetrahydrofuran solvent followed by formylation with dimethylformamide provides compound of formula-(VII),

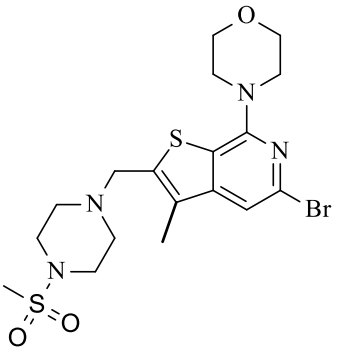
(or)

treating the compound of formula-(VI) with reagents isopropylmagnesium bromide and n-butyl lithium in tetrahydrofuran solvent followed by formylation with dimethylformamide provides compound of formula-(VII),



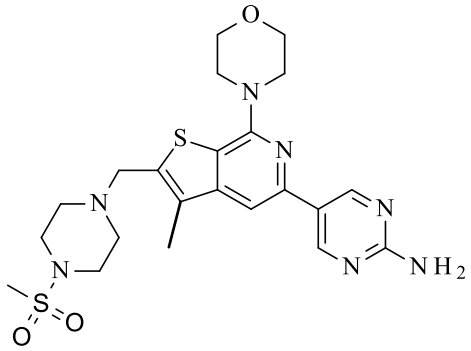
Formula (VII)

c) reacting the compound of formula-(VII) with 1-methyl sulfonyl-piperazine in presence of reagents 2-picoline borane complex, trimethyl orthoformate and acetic acid in methanol solvent provides compound of formula-(VIII),



Formula (VIII)

d) reacting the compound of formula-(VIII) with 2-aminopyrimidine-5-boronic acid pinacol ester in presence of the catalyst PdCl2(dppf)DCM complex and potassium phosphate base in tetrahydrofuran solvent provides compound of formula-(IX),



Formula (IX)

e) treating the compound of formula-(IX) with methane sulfonic acid in aqueous methanol provides (NRC-1109) compound of formula-(II).

15. 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate (NRC-1111).

16. The compound as claimed in claim-15 is hydrate.

17. The crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) (NRC-1111 base) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 9.31, 11.06, 18.64 and 20.05 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-1.

18. The compound as claimed in claim 15, which is a crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1111) and is characterized by:

i) Its powder X-ray diffractogram having peaks at about 6.19, 15.11, 18.40, 18.65, 21.60, 22.56 and 25.13 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-5.

19. 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c] pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1109).

20. The crystal form of 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) (NRC-1109 base) is characterized by:

i) Its powder X-ray diffractogram having peaks at about 8.76, 9.45, 16.87, 18.39 and 19.50 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-3.

21. The compound as claimed in claim 19, which is a crystal form of 5-[3-methyl-2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1109) and is characterized by:

i) Its powder X-ray diffractogram having peaks at about 7.67, 10.69, 18.39, 19.58, 21.93 and 25.83 ± 0.2 degrees 2-theta.

ii) powdered X-ray diffraction pattern as shown in figure-7.

22. The process for the preparation of crystal form of 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine) dimethane sulfonate hydrate (NRC-1111) as claimed in claim 18, comprising the steps of:

a) adding DM water to 5-[2-[(4-methylsulfonylpiperazin-1-yl)methyl]-7-morpholino-thieno [2,3-c]pyridin-5-yl]pyrimidin-2-amine (NRC-1111 base),

b) heating the reaction mixture to 90-100^{o}C,

c) cooling the reaction mixture and adding methanol,

d) adding methanesulfonic acid diluted in methanol to the reaction mixture,

e) stirring and filtering the mass to get the NRC-1111 dimethane sulfonate hydrate crystal form.