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Novel process for the preparation of methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3 (methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino] propan-2yl}carbamate

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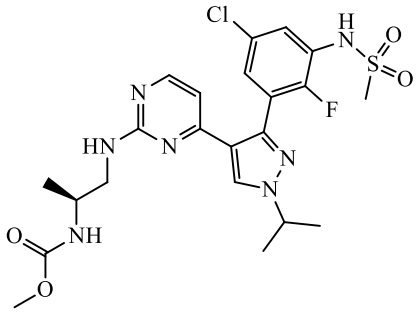
Novel process for the preparation of methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate

Abstract:

The present invention relates to a novel process for the preparation of methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate represented by the following structural formula.



Formula-1

The present invention also relates to amorphous Encorafenib and amorphous solid dispersions of Encorafenib.

Background of the Invention:

Encorafenib is a potent and highly selective ATP-competitive small molecule RAF kinase inhibitor. The half maximal inhibitory concentration (IC50) of Encorafenib against BRAFV600E, BRAF and CRAF enzymes was determined to be 0.35, 0.47 and 0.30 nM, respectively. The Encorafenib dissociation half-life was >30 hours and resulted in prolonged pERK inhibition. Encorafenib suppresses the RAF/MEK/ERK pathway in tumour cells expressing several mutated forms of BRAF kinase (V600E, D and K). Specifically, Encorafenib inhibits in vitro and in vivo BRAFV600E, D and K mutant melanoma cell growth. Encorafenib does not inhibit RAF/MEK/ERK signalling in cells expressing wild-type BRAF.

Encorafenib is approved by USFDA and Europe in combination with Binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test.

Methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl)amino]propan-2-yl}carbamate was disclosed in US8541575 B2 and in US8501758 B2 (herein described as US‘758).

US‘758 discloses process for the preparation of methyl N-{(2S)-1-[(4-{3-[5-chloro-2-fluoro-3-(methanesulfonamido)phenyl]-1-(propan-2-yl)-1H-pyrazol-4-yl}pyrimidin-2-yl) amino] propan-2-yl}carbamate.

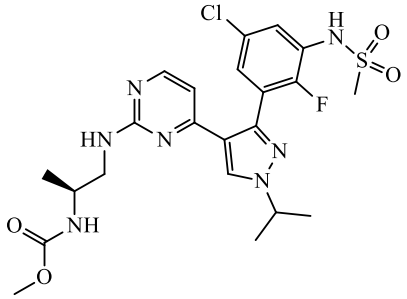
Detailed description of the Invention:

As used herein the term “suitable solvent” used in the present invention refers to “hydrocarbon solvents” such as n-hexane, n-heptane, cyclohexane, pet ether, toluene, pentane, cycloheptane, methyl cyclohexane, m-, o-, or p-xylene, and the like; “ether solvents” such as dimethoxy methane, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, diethyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, diethylene glycol diethyl ether, triethylene glycol dimethyl ether, anisole, t-butyl methyl ether, dimethoxy ethane and the like; “ester solvents” such as methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate and the like; “polar-aprotic solvents such as dimethylacetamide (DMA), dimethylformamide (DMF), dimethylsulfoxide (DMSO), N-methylpyrrolidone (NMP) and the like; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutylketone and the like; “nitrile solvents” such as acetonitrile, propionitrile, isobutyro nitrile and the like; “alcoholic solvents” such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, ethylene glycol, 2-methoxyethanol, l, 2-ethoxyethanol, diethylene glycol, 1, 2, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol, monoethyl ether, cyclohexanol, benzyl alcohol or glycerol and the like; “polar solvents” such as water or mixtures thereof.

The “suitable base” as used in the present invention is selected from inorganic bases like “alkali metal hydroxides” such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate and the like; “alkali metal hydrides” such as sodium hydride, potassium hydride, lithium hydride and the like; ammonia; and organic bases such as “alkali metal alkoxides” such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like;

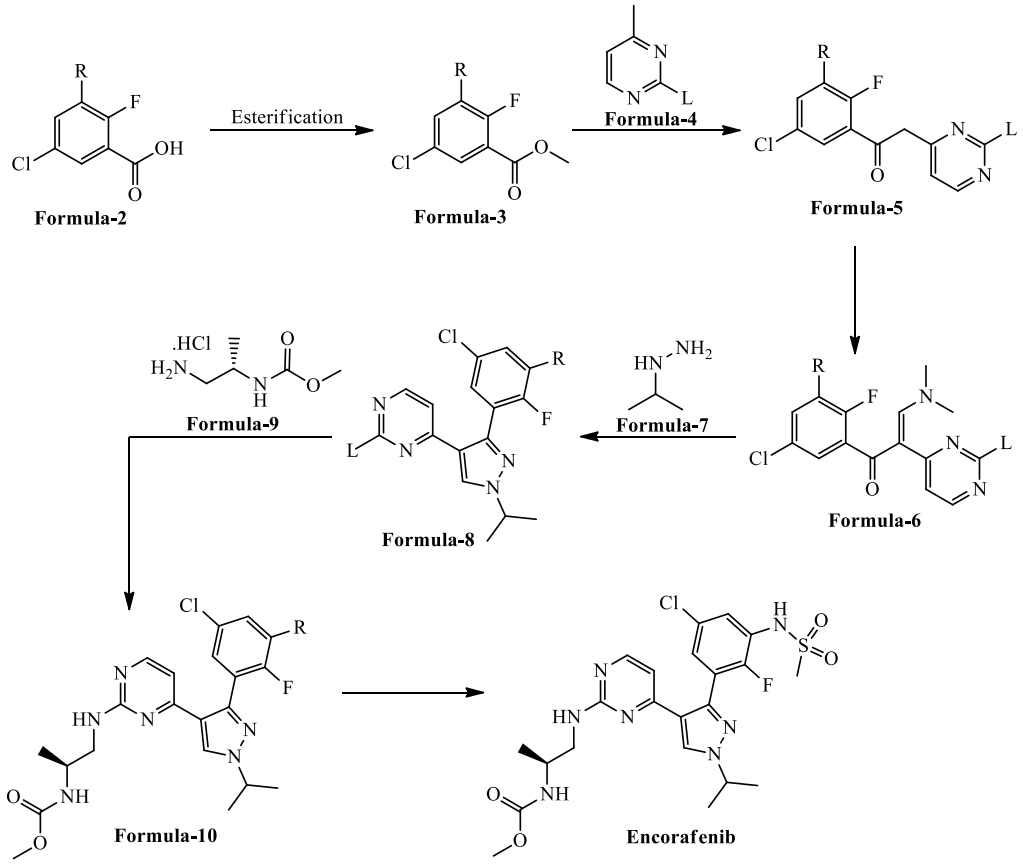
triethyl amine, methyl amine, ethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene (DBN), lithiumdiisopropylamide (LDA), n-butyl lithium, tribenzylamine, isopropylamine, diisopropylamine, diisopropylethylamine, N-methyl morpholine, N-ethylmorpholine, piperidine, dimethylaminopyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methyl imidazole, 1,2,4-triazole, 1,4-diazabicyclo [2.2.2]octane (DABCO) or mixtures thereof.

In the first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1



Formula-1

comprising one or more reaction steps of the following synthetic scheme.

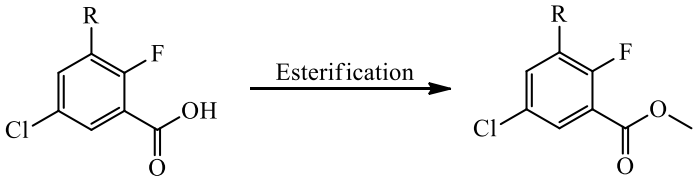


wherein "R" is selected from optionally protected amino group such as benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc), p-Methoxybenzyl ethers (PMB), methyloxycarbonyl, acetoxy carbonyl, propoxycarbonyl, tert-butyloxycarbonyl (Boc), acetyl, propanoyl, iso-butyryl, tert-butyryl, t-butylacetyl, pivaloyl, benzoyl, trimethylsilyl, ter-butyldimethylsilyl; nitro group or cyano group and "L" is selected from hydroxy, halogen (Cl, Br and I), tosylate, mesylate, esylate, nosylate or triflate.

The compounds of formulae 2, 4, 7 and 9 used in the present invention is synthesized from any of the known prior art processes.

In the first aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Esterification of compound of formula-2 with methanol in the presence of suitable acid to provide compound of formula-3,



Formula-2 **Formula-3**

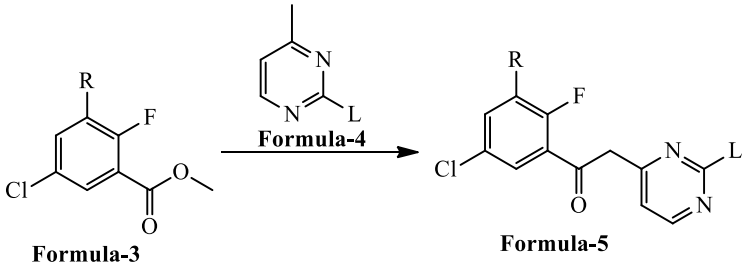
wherein "R" is defined above.

b) converting compound of formula-3 to Encorafenib compound of formula-1.

In the process of the first aspect of first embodiment, the suitable acid used in step-a) is selected from sulfuric acid, sulfonic acid, phosphoric acid, hydrochloric acid and the like.

In the second aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-3 with compound of formula-4 in the presence of suitable base and in a suitable solvent to provide compound of formula-5,



Formula-3 **Formula-5**

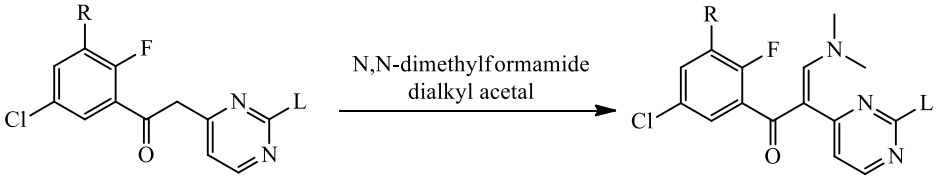
wherein “R” and “L” are defined above.

b) converting compound of formula-5 to Encorafenib compound of formula-1.

In the process of the second aspect of first embodiment, the suitable base used in step-a) is selected form sodium hexamethyldisilazane (NaHMDS), lithium hexamethyldisilazane (LiHMDS), lithium diisopropylamide (LDA), a Grignard reagent and the like; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the third aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-5 with N,N-dimethylformamide dialkyl acetal in the presence of suitable solvent to provide compound of formula-6,



Formula-5 **Formula-6**

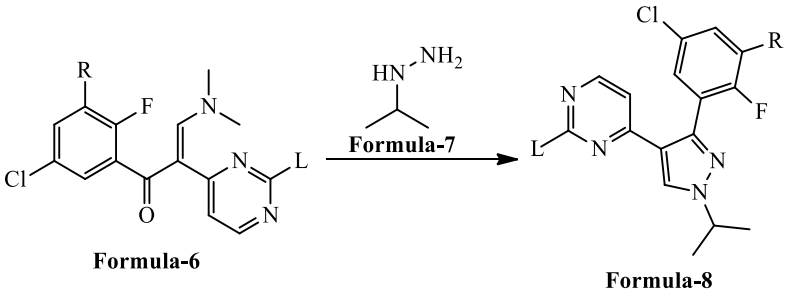
wherein “R” and “L” are defined above.

b) converting compound of formula-6 to Encorafenib compound of formula-1.

In the process of the third aspect of first embodiment, the N,N-dimethylformamide dialkyl acetal used in step-a) is selected from N,N-dimethylformamide dimethyl acetal, N,N-dimethylformamide ditertbutyl acetal and the like; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the fourth aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-6 with compound of formula-7 in the presence of suitable solvent to provide compound of formula-8,

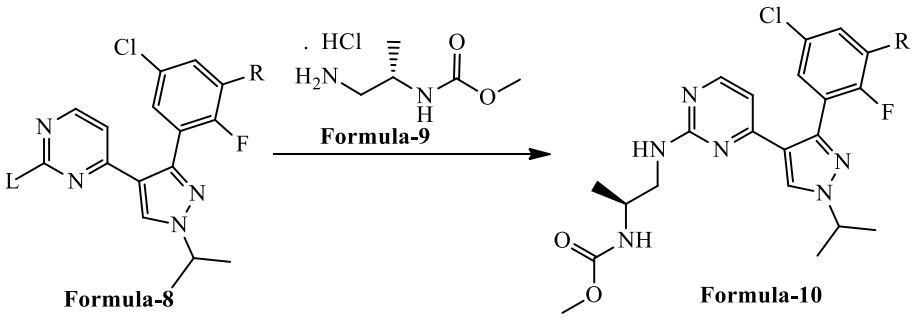


wherein "R" and "L" are defined above.

b) converting compound of formula-8 to Encorafenib compound of formula-1.

In the fifth aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-8 with compound of formula-9 in the presence of suitable base in a suitable solvent to provide compound of formula-10,



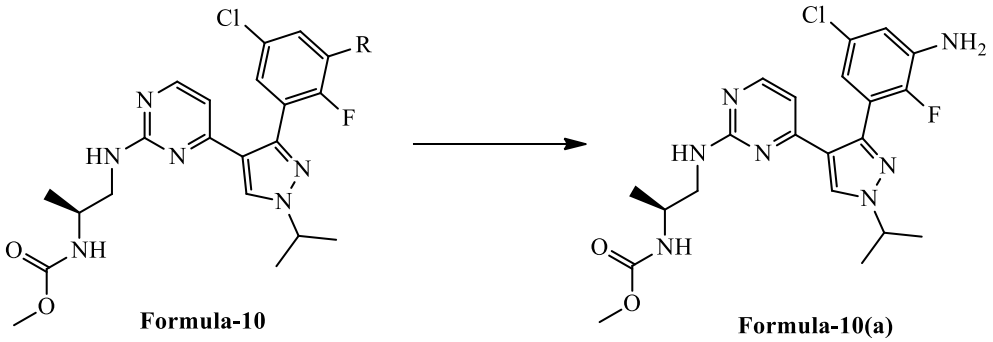
wherein "R" and "L" are defined above.

b) converting compound of formula-10 to Encorafenib compound of formula-1.

In the process of the fifth aspect of first embodiment, the suitable base used in step-a) is selected form inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the sixth aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Deprotection of compound of formula-10 in the presence of suitable deprotecting agent to provide compound of formula-10(a),



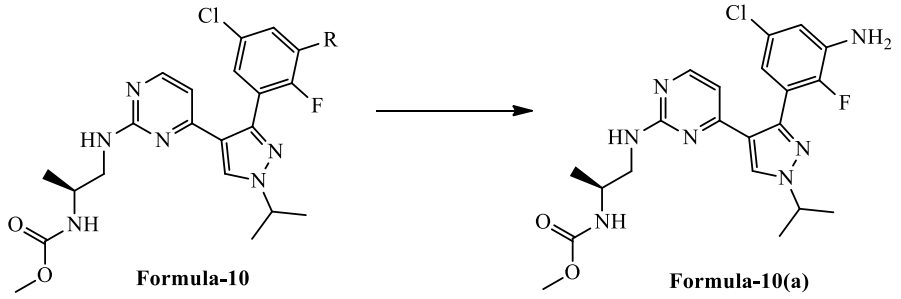
wherein "R" is selected from protected amino group such as benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc), p-Methoxybenzyl ethers (PMB), methyloxycarbonyl, acetoxy carbonyl, propoxycarbonyl, acetyl, propanoyl, iso-butyryl, tert-butyryl, t-butylacetyl, pivaloyl, benzoyl, trimethylsilyl, ter-butyldimethylsilyl, with a proviso that the protected amino group is not tert-butyloxycarbonyl (Boc).

b) converting compound of formula-10(a) to Encorafenib compound of formula-1.

In the process of the sixth aspect of first embodiment, the suitable deprotecting agent used in step-a) is selected from trifluoroacetic acid, methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, hydrogen chloride, hydrogen bromide, acetic acid and mixtures thereof.

In the seventh aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reduction of compound of formula-10 in the presence of suitable reducing agent to provide compound of formula-10(a),



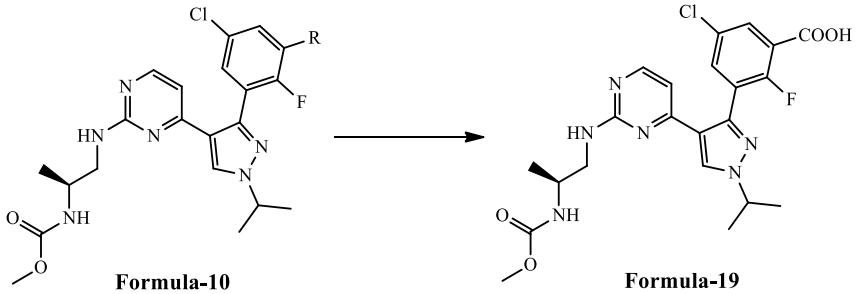
wherein "R" is selected from nitro group.

b) converting compound of formula-10(a) to Encorafenib compound of formula-1.

In the process of the seventh aspect of first embodiment, the suitable reducing agent used in step-a) is selected from hydrogen sulfide, sodium sulfide, potassium sulfide, sodium hydrogen sulfide, Zn/Magnesium, Ni, Raney Ni, H_2/Pd, Zinc dust, PtO_2 or Fe.

In the eighth aspect of first embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

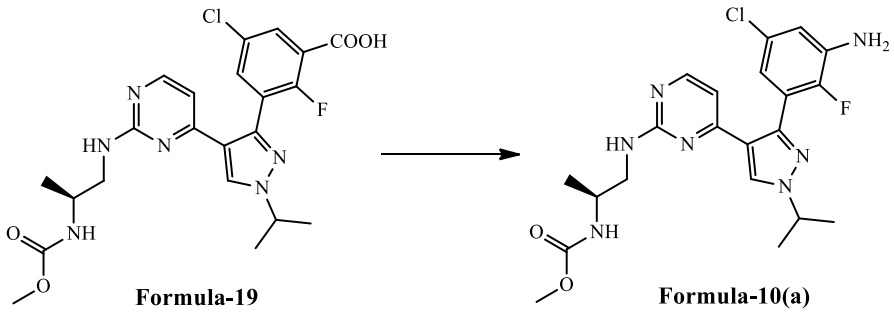
a) Hydrolysis of compound of formula-10 in the presence of suitable base in a suitable solvent to provide compound of formula-19,



Formula-10 **Formula-19**

wherein "R" is selected from CN group.

b) converting compound of formula-19 to compound of formula-10(a),

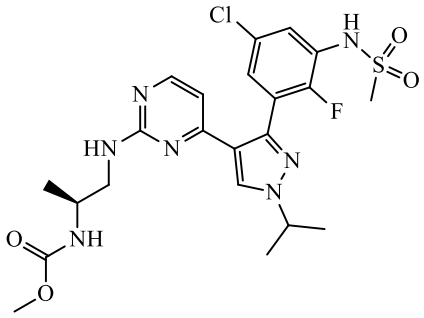


Formula-19 **Formula-10(a)**

c) converting compound of formula-10(a) to Encorafenib compound of formula-1.

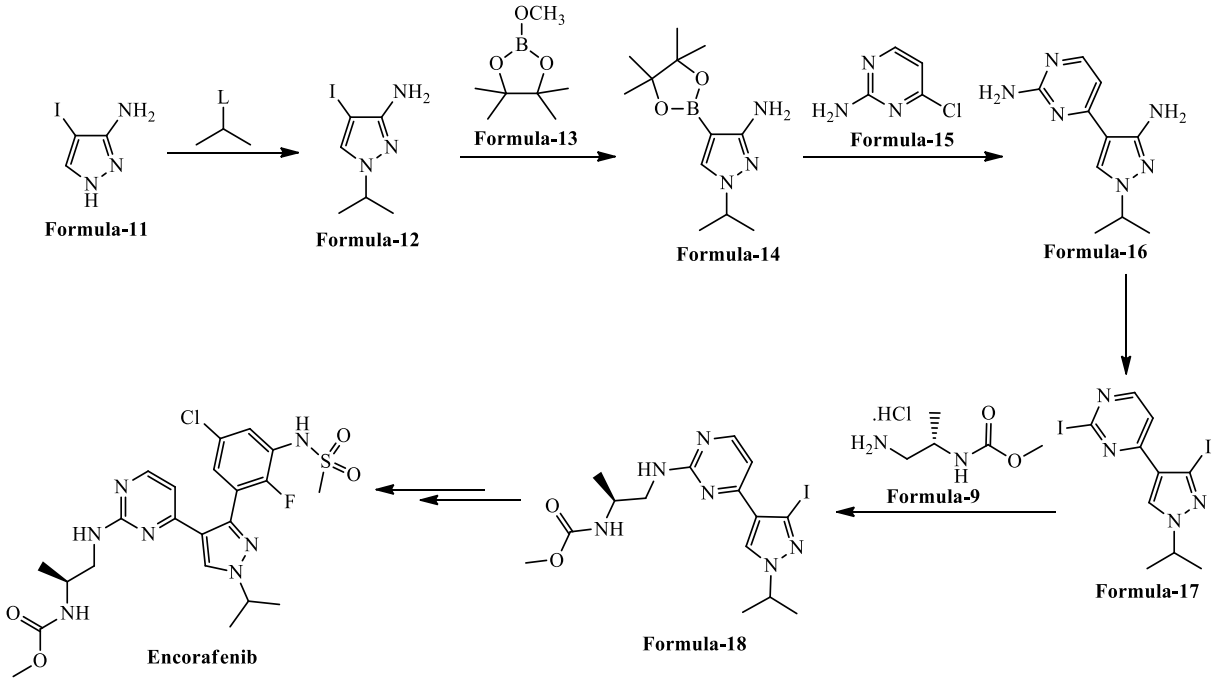
In the process of the eighth aspect of first embodiment, the suitable base used in step-a) is selected from inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1



Formula-1

comprising one or more reaction steps of the following synthetic scheme.

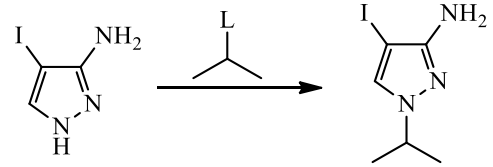


wherein "L" is selected from halogen (Cl, Br and I).

The compounds of formulae 11, 13, 15 and 9 used in the present invention is synthesized from any of the known prior art processes.

In the first aspect of second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-11 with 2-halopropane in the presence of suitable base and in a suitable solvent to provide compound of formula-12,



Formula-11 **Formula-12**

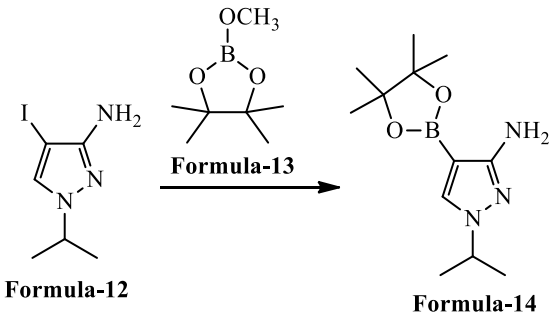
wherein "L" is selected from halogen (Cl, Br and I).

b) converting compound of formula-12 to Encorafenib compound of formula-1.

In the process of the first aspect of second embodiment, the suitable base used in step-a) is selected form inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the second aspect of second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-12 with compound of formula-13 in the presence of suitable base and in a suitable solvent to provide compound of formula-14,



Formula-12 **Formula-14**

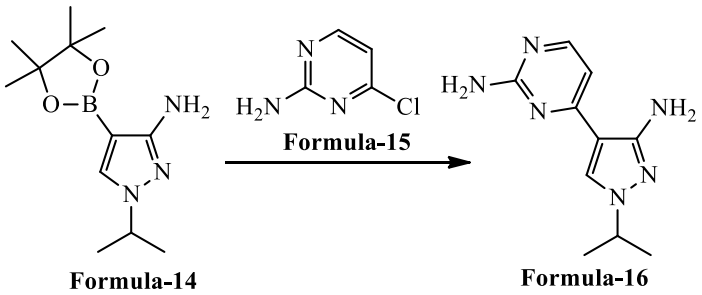
b) converting compound of formula-14 to Encorafenib compound of formula-1.

In the process of second aspect of second embodiment, the suitable base used in step-a) is selected form inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the third aspect of second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-14 with compound of formula-15 in the presence of

suitable palladium catalyst, suitable base and in a suitable solvent to provide compound of formula-16,



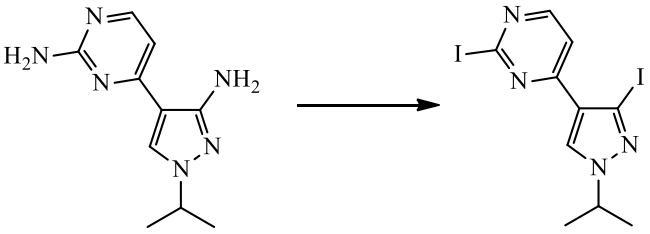
Formula-14 Formula-16

b) converting compound of formula-16 to Encorafenib compound of formula-1.

In the process of the third aspect of second embodiment, the suitable palladium catalyst used in step-a) is selected from $PdCl_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$ or $[(cinnamyl)PdCl]_2$; the suitable base is selected form inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the fourth aspect of second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Iodination compound of formula-16 in the presence of suitable iodinating agent to compound of formula-17,



Formula-16 Formula-17

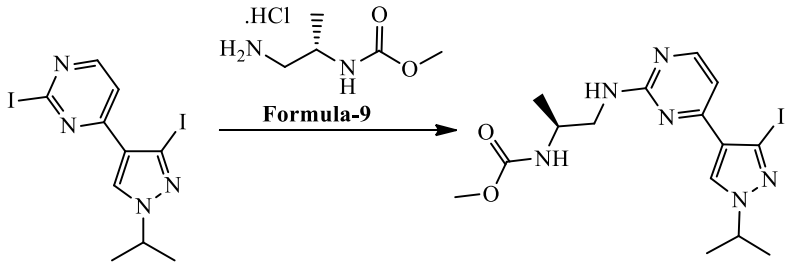
b) converting compound of formula-17 to Encorafenib compound of formula-1.

In the process of the fourth aspect of second embodiment, the suitable iodinating agent used in step-a) is selected from KI, I_2, HI and the like.

In the fifth aspect of second embodiment, the present invention provides a process for the preparation of Encorafenib compound of formula-1, which comprises:

a) Reacting compound of formula-17 with compound of formula-9 in the presence of

suitable base and in a suitable solvent to provide compound of formula-18,

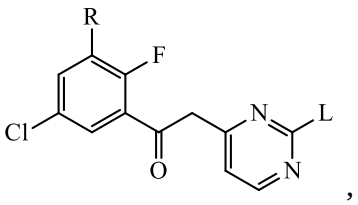


Formula-17 Formula-18

b) converting compound of formula-18 to Encorafenib compound of formula-1.

In the process of fifth aspect of second embodiment, the suitable base used in step-a) is selected form inorganic base or organic base; and the suitable solvent is selected form alcohol solvents, ester solvents, hydrocarbon solvents, nitrile solvents, polar-aprotic solvents, ketone solvents, ether solvents, chloro solvents, and water or mixture thereof.

In the third embodiment, the present invention provides novel intermediate compounds of Encorafenib compound of formula-1 represented by the following structural formulae.



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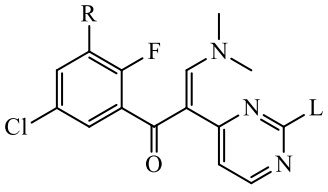

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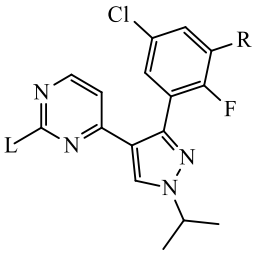
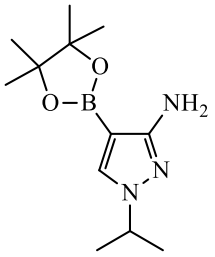


Formula-5 Formula-6 Formula-8



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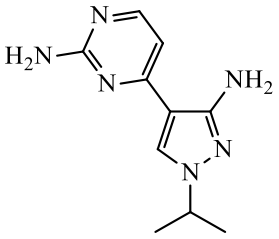

Formula-14 Formula-16

wherein “R” is selected from optionally protected amino group such as benzyloxycarbonyl (Cbz), fluorenylmethoxycarbonyl (Fmoc), p-Methoxybenzyl ethers (PMB), methyloxycarbonyl, acetoxy carbonyl, propoxycarbonyl, tert-butyloxycarbonyl (Boc),

acetyl, propanoyl, iso-butyryl, tert-butyryl, t-butylacetyl, pivaloyl, benzoyl, trimethylsilyl, ter-butyldimethylsilyl; nitro group or cyano group and "L" is selected from hydroxy, halogen (Cl, Br and I), tosylate, mesylate, esylate, nosylate or triflate.

The above mentioned novel intermediate compounds of the present invention are useful in the preparation of Encorafenib compound of formula-1.

In the fourth embodiment, the present invention provides a process for the preparation of an amorphous form of Encorafenib of formula-1, which comprises:

a) Providing a solution of Encorafenib of formula-1 in a suitable solvent or mixtures thereof; and
b) isolating the amorphous form of Encorafenib of formula-1.

In the process of fourth embodiment, the suitable solvent used in step-a) is selected form alcohol solvents and chloro solvents.

In the process of fourth embodiment, a solution of Encorafenib compound of formula-1 can be prepared at any suitable temperatures, such as about 0°C to about the reflux temperature of the solvent used. Stirring and heating may be used to reduce the time required for the dissolution process.

In the process of fourth embodiment, the Encorafenib compound of formula-1 dissolved in suitable solvent. Optionally, the solution may be filtered to make it particle free.

In the process of fourth embodiment, isolating describes removal of solvent by suitable techniques which may be used for the removal of solvent from the reaction mixture includes but not limited to evaporation optionally under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, distillation under reduced pressure, distillation by using a rotational distillation device such as a Buchi Rotavapor, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying, adding a suitable anti-solvent to the reaction mixture followed by filtration of the precipitated solid, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction mixture or by any other suitable techniques known in the art.

In the fifth embodiment, the present invention provides a process for the preparation of an amorphous solid dispersion of Encorafenib compound of formula-1, which comprises:

a) Providing a solution of Encorafenib compound of formula-1 and at least one pharmaceutically acceptable excipient in a suitable solvent or mixtures thereof; and
b) isolating the amorphous solid dispersion of Encorafenib compound of formula-1.

In the process of fifth embodiment, the suitable solvent used in step-a) is selected form alcohol solvents and chloro solvents.

In the process of fifth embodiment, the suitable pharmaceutically acceptable excipient used in step-a) selected from but not limited to polyvinylpyrrolidone (povidone or PVP; PVP of different grades like K-15, K-30, K-60, K-90 and K-120 may be used), co-povidone, cros-polyvinylpolypyrrolidone, polysorbate, cross linked polyvinyl pyrrolidone (crospovidone), cros-copovidone, Eudragit, polyethylene glycol (macrogol or PEG), polyvinyl alcohol, polyvinyl chloride, polyvinyl acetate, propylene glycol, cellulose, cellulose acetate phthalate (CAP), methyl cellulose, carboxymethyl cellulose (CMC, its sodium and calcium salts), carboxymethylethyl cellulose (CMEC), ethyl cellulose, hydroxymethylcellulose, ethyl hydroxyethyl cellulose, hydroxyethylcellulose, hydroxypropylcellulose (HPC), hydroxy propyl cellulose acetate succinate, hydroxypropylmethyl cellulose (hypromellose or HPMC), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), hydroxyethyl methyl cellulose succinate (HEMCS), hydroxypropylcellulose acetate succinate (HPCAS), hydroxypropyl methylcellulose phthalate (HPMC-P), hydroxypropylmethylcellulose acetate phthalate, microcrystalline cellulose (MCC), cross linked sodium carboxymethyl cellulose (croscarmellose sodium), cross linked calcium carboxymethyl cellulose, magnesium stearate, aluminium stearate, calcium stearate, magnesium carbonate, talc, iron oxide (red, yellow, black), stearic acid, dextrates, dextrin, dextrose, sucrose, glucose, xylitol, lactitol, sorbitol, mannitol, maltitol, maltose, raffinose, fructose, maltodextrin, anhydrous lactose, lactose monohydrate, starches such as maize starch or corn starch, sodium starch glycolate, sodium carboxymethyl starch, pregelatinized starch, gelatin, sodium dodecyl sulfate, edetate disodium, sodium phosphate, sodium lauryl sulfate, triacetin, sucralose, calcium phosphate, polydextrose, α-, β-, γ-cyclodextrins, sulfobutylether beta-cyclodextrin, sodium stearyl fumarate, fumaric acid, alginic acid, sodium alginate, propylene glycol alginate, citric acid, succinic acid,

carbomer, docusate sodium, glyceryl behenate, glyceryl stearate, meglumine, arginine, polyethylene oxide, polyvinyl acetate phthalates and the like.

In the process of fifth embodiment, a solution of Encorafenib compound of formula-1 and the excipient may be prepared at any suitable temperatures, such as about 0°C to about the reflux temperature of the solvent used. Stirring and heating may be used to reduce the time required for the dissolution process.

In the process of fifth embodiment, removal of solvent at step b) suitable techniques which may be used for the removal of solvent from the reaction mixture includes but not limited to evaporation optionally under reduced pressure, flash evaporation, vacuum drying, concentrating the reaction mixture, atmospheric distillation, distillation under reduced pressure, distillation by using a rotational distillation device such as a Buchi Rotavapor, agitated thin film drying (ATFD), melt extrusion, spray drying, freeze drying (lyophilization), spray-freeze drying, adding a suitable anti-solvent to the reaction mixture followed by filtration of the precipitated solid, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction mixture or by any other suitable techniques known in the art.

In yet another embodiment, isolating the amorphous form or amorphous solid dispersion of Encorafenib compound of formula-1 is carried out by any methods known in the art or may be isolated by employing any of the techniques, but not limited to: decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In the process of the present invention, the amorphous form or amorphous solid dispersion of Encorafenib compound of formula-1 produced according to the present invention is dried using suitable drying equipment such as tray dryer, vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying can be carried out at atmospheric pressure or under reduced pressure at temperature of less than about 100ºC, less than about 60ºC, less than about 40ºC, or any other suitable temperature. The drying can be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

The sixth embodiment of the present invention provides a process for the preparation of crystalline form-M of Encorafenib compound of formula-1, which comprises:

a) combining Encorafenib of formula-1 with a solvent and stirring,
b) providing crystalline form-M of Encorafenib of formula-1.

In an aspect, the suitable solvent used in step-a) is selected from alcohol solvents, ester solvents water or mixtures thereof.

In an aspect, heating the mixture obtained in step-a) to a temperature ranging from 30°C to 150°C and optionally the solution may be filtered to make it particle free.

In an aspect of the sixth embodiment, isolating the crystalline form-M of Encorafenib can be carried out by any methods known in the art or can be isolated by employing any of the techniques, but not limited to cooling, decantation, filtration by gravity or suction, centrifugation, adding solvent to make slurry followed by filtration, or other techniques specific to the equipment used and the like, and optionally washing with a solvent.

In an aspect of the sixth embodiment, the crystalline form-M of Encorafenib may be dried in a suitable drying equipment such as tray dryer, vacuum oven, rotatory cone dryer, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 100°C, less than about 60°C, less than about 40°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to 10 hours or longer.

The seventh embodiment of the present invention relates to crystalline form-M of Encorafenib is characterized by its X-ray powder diffraction (XRD) pattern as illustrated in figure-8.

The eighth embodiment of the present invention provides a process for the preparation of crystalline form-M of Encorafenib compound of formula-1, which comprises:

a) adding ethanol to Encorafenib of formula-1,
b) heating the mixture to 80-85°C,
c) cooling the mixture to 70-75°C,
d) adding water to the mixture at 70-75°C,
e) filtering the mixture through hyflow bed,

f) cooling the mixture to a suitable temperature,
g) providing crystalline form-M of Encorafenib of formula-1.

In an aspect, cooling the mixture obtained in step-f) to a temperature ranging from 0°C to 35°C.

In yet another embodiment, pharmaceutical composition comprising amorphous form of Encorafenib compound of formula-1 and one or more pharmaceutically acceptable excipients is formulated in a manner suitable for the route of administration to be used.

As used herein, the term "pharmaceutical compositions" include tablets, pills, powders, liquids, suspensions, emulsions, granules, capsules, suppositories, or injection preparations.

P-XRD Method of Analysis:

PXRD analysis of compound of formula-1 was carried out by using BRUKER/D8 ADVANCE diffractometer using Cu Kα radiation of wavelength 1.5406 A° and continuous scan speed of 0.03°/min.

The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

Examples:

Example-1: Preparation of amorphous form of Encorafenib.

Encorafenib (250.0 mg) was dissolved in dichloromethane (20.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 180.0 mg.

The PXRD pattern of the obtained compound is shown in figure-1.

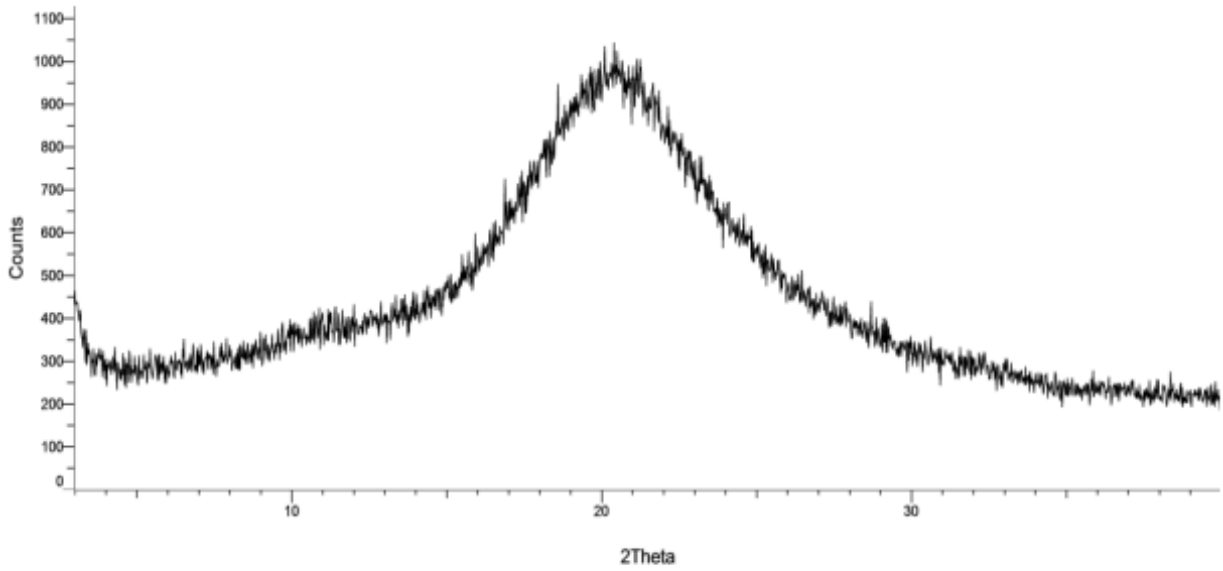

Figure-01

Example-2: Preparation of amorphous form of Encorafenib

Encorafenib (500.0 mg) was dissolved in methanol (20.0 ml) at 25-30ºC and stirred for 15-20 minutes and filtered the solution to make it particle free. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

Example-3: Preparation of amorphous form of Encorafenib

Encorafenib (500.0 mg) was dissolved in a mixture of dichloromethane (10.0 ml) and methanol (10.0 ml) and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

Example-4: Preparation of amorphous solid dispersion of Encorafenib with co-povidone.

Encorafenib (250.0 mg) and co-povidone (250.0 mg) were dissolved in a mixture of dichloromethane (5.0 ml) and methanol (5.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-2.

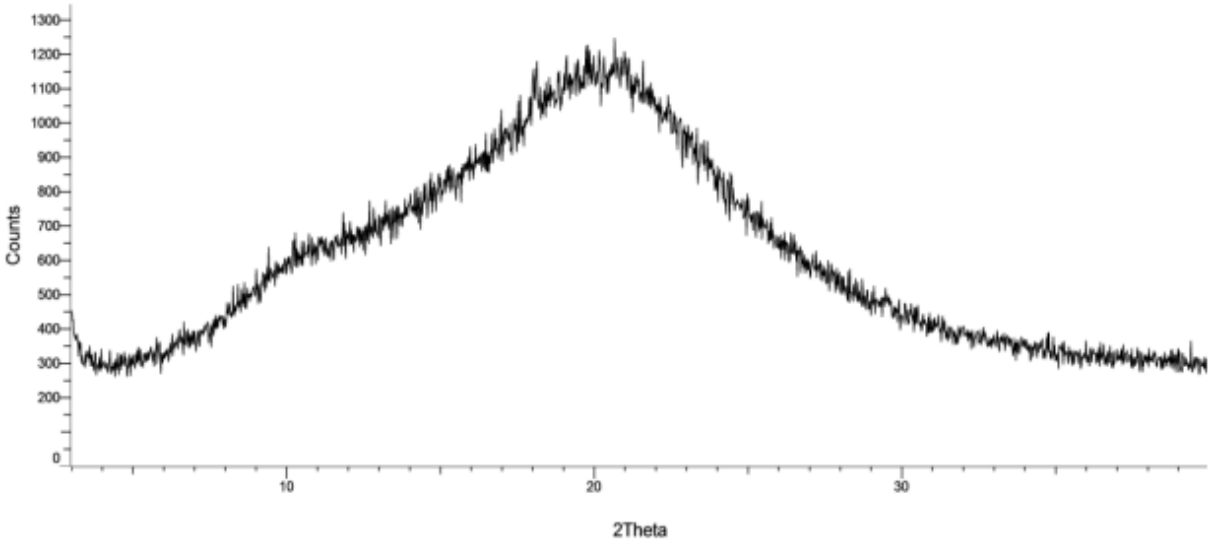

Figure-02

Example-5: Preparation of amorphous solid dispersion of Encorafenib with microcrystalline cellulose.

Encorafenib (250.0 mg) and microcrystalline cellulose (250.0 mg) were dissolved in a mixture of dichloromethane (5.0 ml) and methanol (5.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-3.

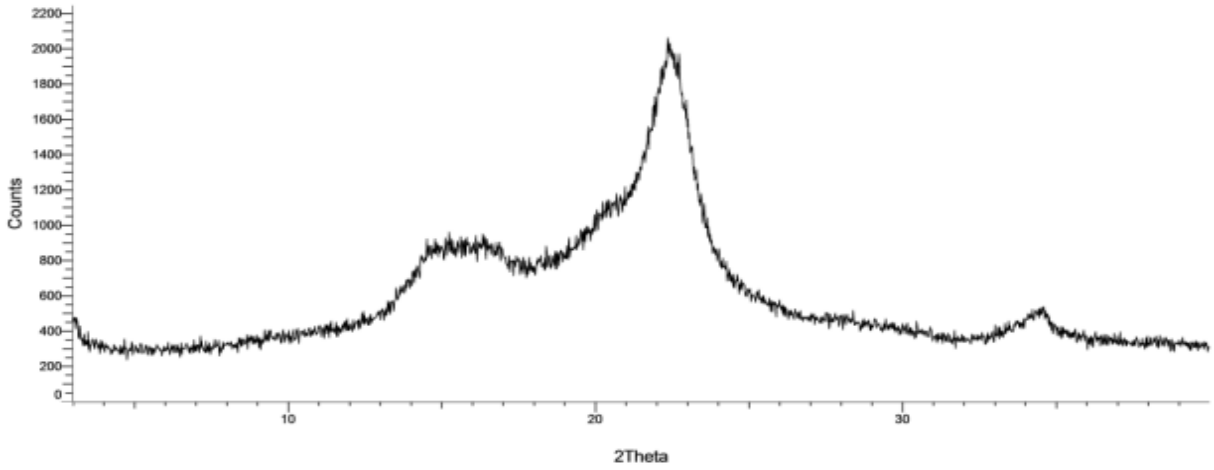

Figure-03

Example-6: Preparation of amorphous solid dispersion of Encorafenib with cros-copovidone.

Encorafenib (250.0 mg) and cros-copovidone (250.0 mg) were dissolved in a mixture of dichloromethane (10.0 ml) and methanol (10.0 ml) at 25-30ºC and stirred for 15-20 minutes.

Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-4.

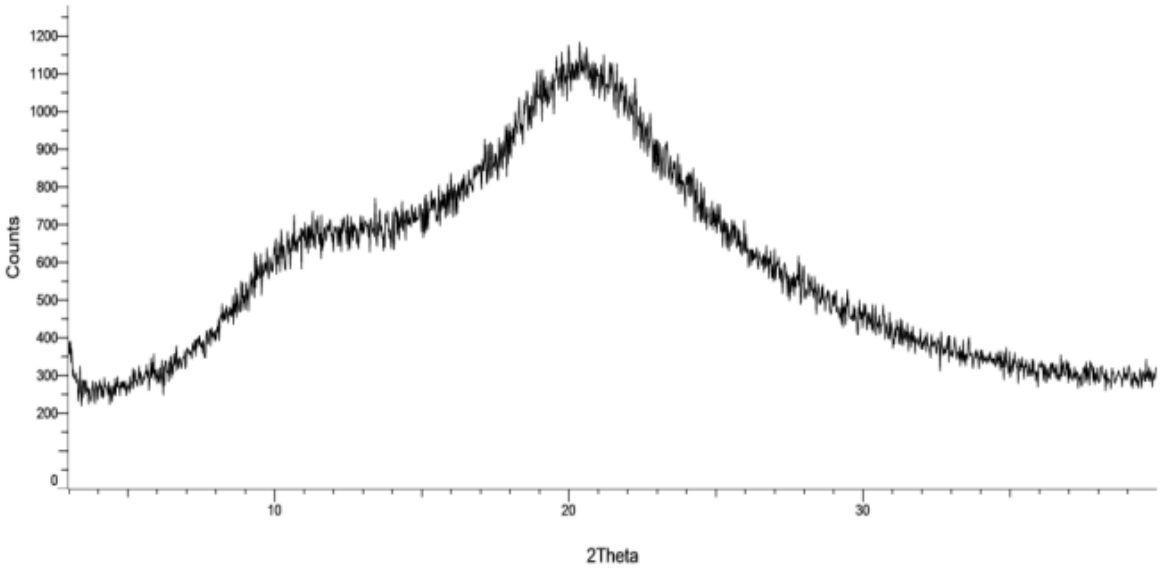

Figure-04

Example-7: Preparation of amorphous solid dispersion of Encorafenib with povidone k-30.

Encorafenib (250.0 mg) and povidone k-30 (250.0 mg) were dissolved in a mixture of dichloromethane (10.0 ml) and methanol (10.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-5.

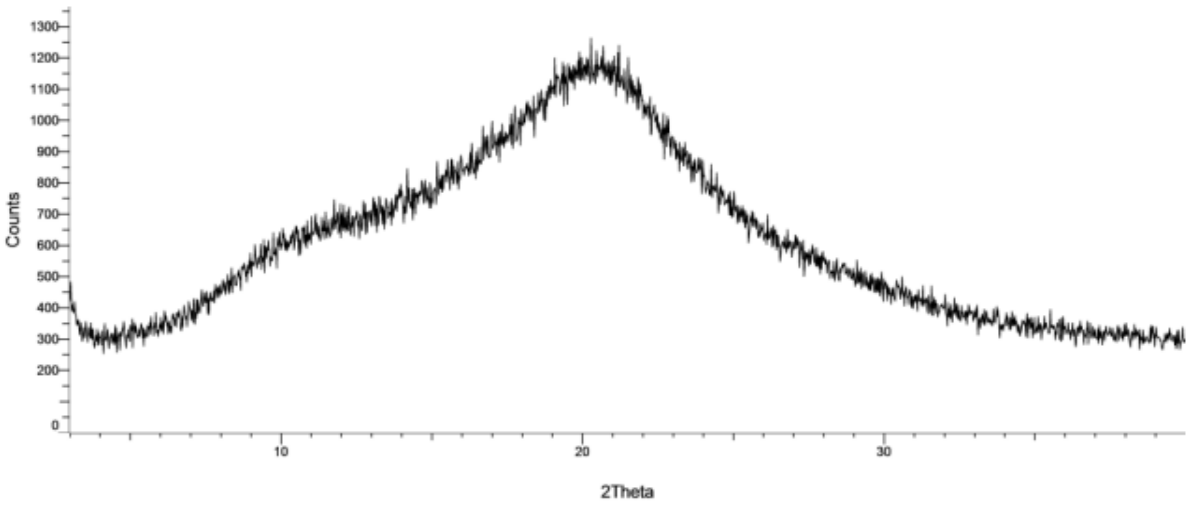

Figure-05

Example-8: Preparation of amorphous solid dispersion of Encorafenib with HPMC-E5

Encorafenib (250.0 mg) and HPMC-E5 (250.0 mg) were dissolved in a mixture of dichloromethane (5.0 ml) and methanol (5.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-6.

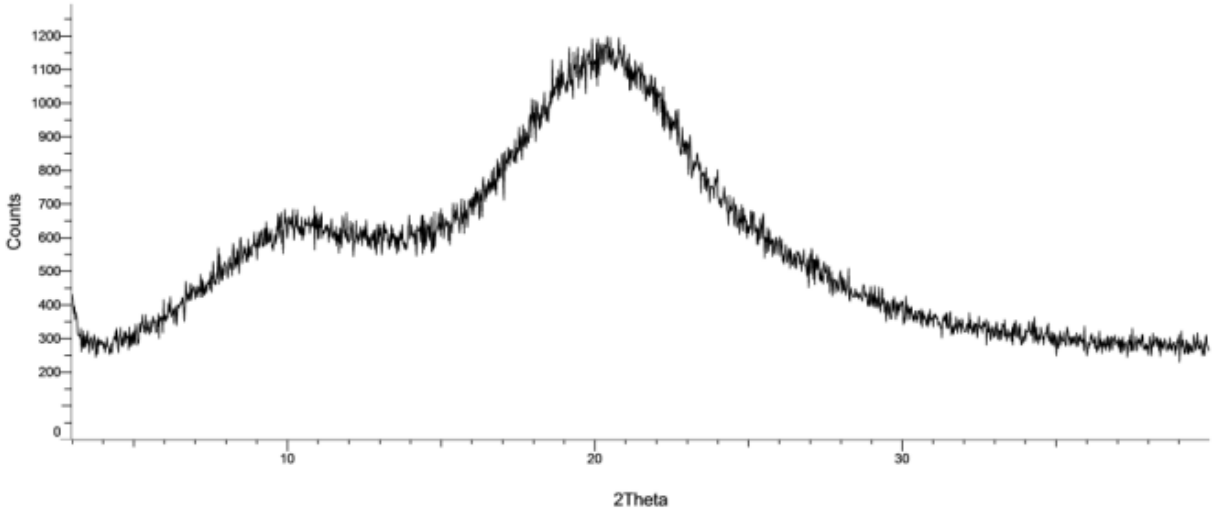

Figure-06

Example-9: Preparation of amorphous solid dispersion of Encorafenib with HPMC-AS

Encorafenib (250.0 mg) and HPMC-AS (250.0 mg) were dissolved in a mixture of dichloromethane (5.0 ml) and methanol (5.0 ml) at 25-30ºC and stirred for 15-20 minutes. Distilled the solvent completely under reduced pressure and dried to get the title compound. Yield: 400.0 mg.

The PXRD pattern of the obtained compound is shown in figure-7.

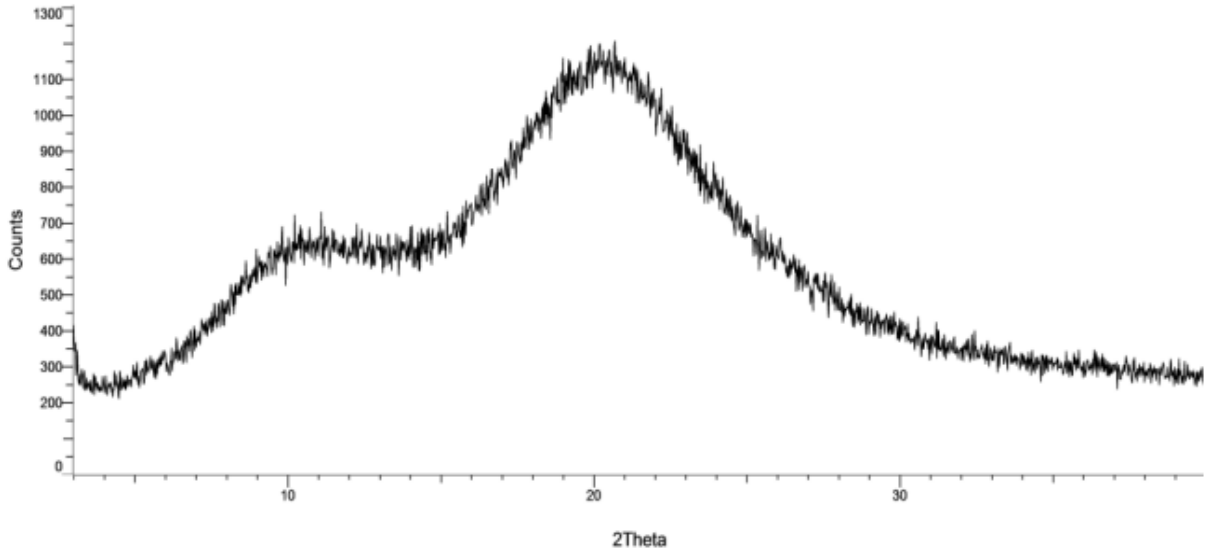

Figure-07

Example-10: Preparation of crystalline form-M of Encorafenib

A mixture of Encorafenib (25.0 gms) and ethanol (125 ml) were stirred for 10 minutes at 25-30°C. Heated the mixture to 80-85°C and stirred for 30 minutes at the same temperature. Cooled the mixture to 25-30°C and stirred for 1 hour at the same temperature. Filtered the precipitated solid, washed with ethanol and dried to get the title compound.

Yield: 16 gms.

The PXRD pattern of the obtained compound is shown in figure-8.

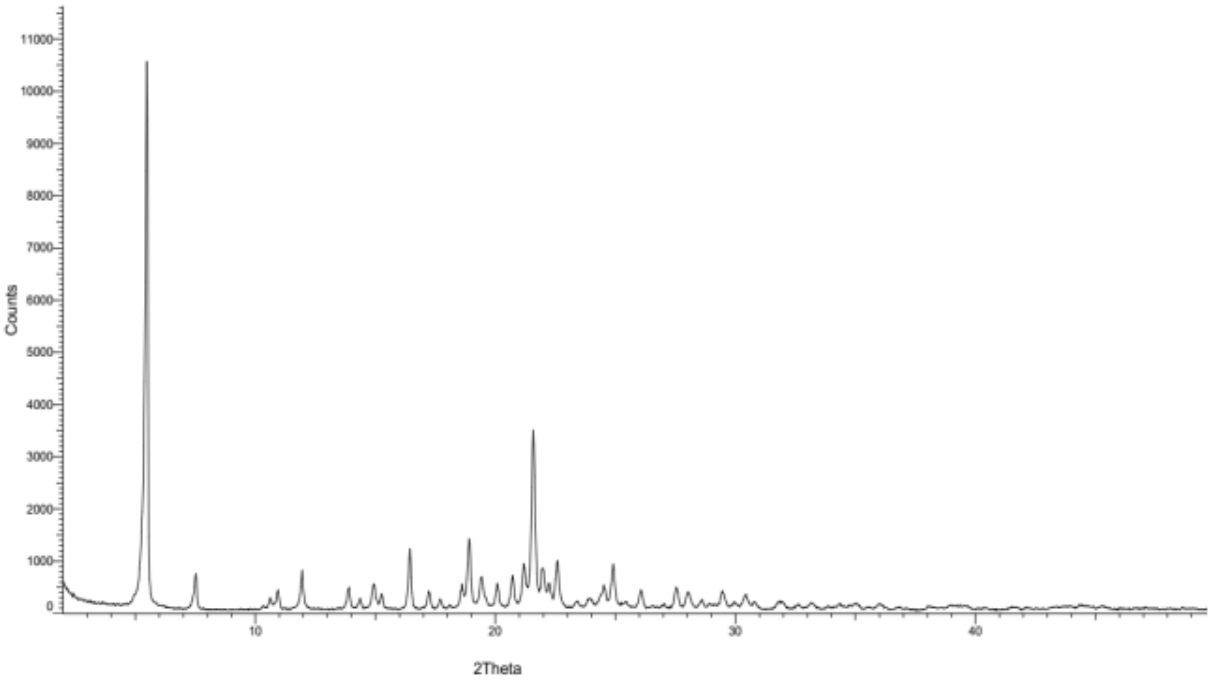

Figure-08

Example-11: Preparation of crystalline form-M of Encorafenib

A mixture of Encorafenib (650 gms) and n-butyl acetate (3900 ml) were stirred for 10 minutes at 25-30°C. Heated the mixture to 120-125°C and stirred for 30 minutes at the same temperature. Filtered the mixture through hyflow bed. Cooled the mixture to 25-30°C and stirred for 2 hour at the same temperature. Filtered the precipitated solid, washed with n-butyl acetate and dried to get the title compound.

Yield: 630 gms. The PXRD pattern of the obtained compound is shown in figure-8.

Example-12: Preparation of crystalline form-M of Encorafenib

A mixture of Encorafenib (65.0 gms) and ethanol (520 ml) were stirred for 10 minutes at 25-30°C. Heated the mixture to 80-85°C and stirred for 30 minutes. Cooled the mixture to 70-75°C and stirred for 30 minutes. Water (65.0 ml) was slowly added to the mixture at 70-75°C and stirred for 30 minutes. Cooled the mixture to 60-65°C. Filtered the mixture through hyflow bed and washed the bed with ethanol. Cooled the mixture to 30-35°C. Further cooled the mixture to 0-5°C and stirred for 1 hour. Filtered the precipitated solid, washed with ethanol and dried to get the title compound.

Yield: 60.0 gms. M.R: 180-185°C. Purity by HPLC: 99.49%

The PXRD pattern of the obtained compound is shown in figure-8.

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